

Integrative Functions of the Nervous System

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CHAPTER OUTLINE

- THE HYPOTHALAMUS
- THE RETICULAR FORMATION

- THE FOREBRAIN

KEY CONCEPTS

1. Homeostatic functions are regulated by the hypothalamus.
2. Homeostatically regulated functions fluctuate in a daily pattern.
3. The reticular formation serves as the activating system of the forebrain.
4. Sleep occurs in stages that exhibit different EEG patterns.
5. The limbic system receives distributed monoaminergic and cholinergic innervation.

6. Limbic structures play a role in the brain's reward system.
7. The limbic system regulates aggression and sexual activity.
8. Affective disorders and schizophrenia are disruptions in limbic function.
9. The cerebral cortex and hippocampus are involved in learning and memory.
10. Language is a lateralized function of association cortex.

The **central nervous system (CNS)** receives sensory stimuli from the body and the outside world and processes that information in neural networks or centers of integration to mediate an appropriate response or learned experience. Centers of integration are hierarchical in nature. In a caudal-to-rostral sequence, the more rostral it is placed, the greater the complexity of the neural network. This chapter considers functions integrated within the diencephalon and telencephalon, where emotionally motivated behavior, appetitive drive, consciousness, sleep, language, memory, and cognition are coordinated.

THE HYPOTHALAMUS

The **hypothalamus** coordinates autonomic reflexes of the brainstem and spinal cord. It also activates the endocrine and somatic motor systems when responding to signals generated either within the hypothalamus or brainstem or in higher centers, such as the **limbic system**, where the emotions and motivations are generated. The hypothalamus can accomplish this by virtue of its unique location at the interface between the limbic system and the endocrine and autonomic nervous systems.

As a major regulator of homeostasis, the hypothalamus receives input about the internal environment of the body

via signals in the blood. In most of the brain, capillary endothelial cells are connected by tight junctions that prevent substances in the blood from entering the brain. These tight junctions are part of the **blood-brain barrier**. The blood-brain barrier is missing in several small regions of the brain called **circumventricular organs**, which are adjacent to the fluid-filled ventricular spaces. Several circumventricular organs are in the hypothalamus. Capillaries in these regions, like those in other organs, are fenestrated ("leaky"), allowing the cells of hypothalamic nuclei to sample freely, from moment to moment, the composition of the blood. Neurons in the hypothalamus then initiate the mechanisms necessary to maintain levels of constituents at a given set point, fixed within narrow limits by a specific hypothalamic nucleus. Homeostatic functions regulated by the hypothalamus include body temperature, water and electrolyte balance, and blood glucose levels.

The hypothalamus is the major regulator of endocrine function because of its connections with the pituitary gland, the master gland of the endocrine system. These connections include direct neuronal innervation of the posterior pituitary lobe by specific hypothalamic nuclei and a direct hormonal connection between specific hypothalamic nuclei and the anterior pituitary. **Hypothalamic hormones**, designated as **releasing factors**, reach the anterior

pituitary lobe by a portal system of capillaries. Releasing factors then regulate the secretion of most hormones of the endocrine system.

The Hypothalamus Is Composed of Anatomically Distinct Nuclei

The **diencephalon** includes the hypothalamus, thalamus, and subthalamus (Fig. 7.1). The rostral border of the hypothalamus is at the optic chiasm, and its caudal border is at the mammillary body.

On the basal surface of the hypothalamus, exiting the median eminence, the pituitary stalk contains the **hypothalamo-hypophyseal portal blood vessels** (see Fig. 32.3). Neurons within specific nuclei of the hypothalamus secrete releasing factors into these portal vessels. The releasing factors are then transported to the anterior pituitary, where they stimulate secretion of hormones that are trophic to other glands of the endocrine system (see Chapter 32).

The pituitary stalk also contains the axons of magnocellular neurons whose cell bodies are located in the supraoptic and paraventricular hypothalamic nuclei. These axons form the **hypothalamo-hypophyseal tract** within the pituitary stalk and represent the efferent limbs of neuroendocrine reflexes that lead to the secretion of the hormones vasopressin and oxytocin into the blood. These hormones are made in the magnocellular neurons and released by their axon terminals next to the blood vessels within the posterior pituitary.

The nuclei of the hypothalamus have ill-defined boundaries, despite their customary depiction (Fig. 7.2). Many are named according to their anatomic location (e.g., anterior hypothalamic nuclei, ventromedial nucleus) or for the structures they lie next to (e.g., the periventricular nucleus surrounds the third ventricle, the suprachiasmatic nucleus lies above the optic chiasm).

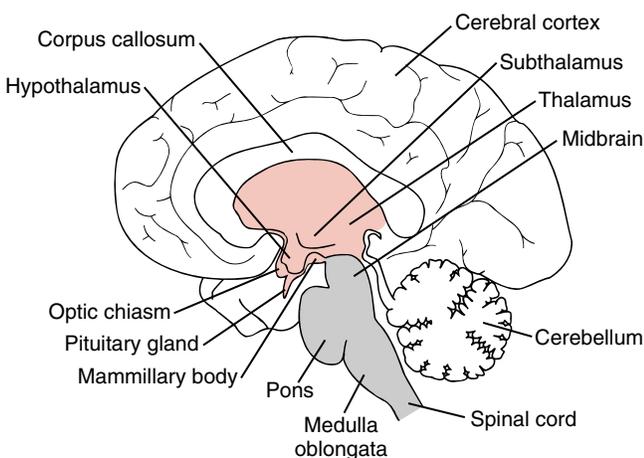


FIGURE 7.1 A midsagittal section through the human brain, showing the most prominent structures of the brainstem (gray), diencephalon (red), and forebrain (white). The cerebellum is also shown. (Modified from Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*. 3rd Ed. New York: Elsevier, 1991.)

The hypothalamus receives afferent inputs from all levels of the CNS. It makes reciprocal connections with the limbic system via fiber tracts in the **fornix**. The hypothalamus also makes extensive reciprocal connections with the brainstem, including the reticular formation and the medullary centers of cardiovascular, respiratory, and gastrointestinal regulation. Many of these connections travel within the **medial forebrain bundle**, which also connects the brainstem with the cerebral cortex.

Several major connections of the hypothalamus are one-way rather than reciprocal. One of these, the **mammillothalamic tract**, carries information from the mammillary bodies of the hypothalamus to the anterior nucleus of the **thalamus**, from where information is relayed to limbic regions of the cerebral cortex. A second one-way pathway carries visual information from the retina to the **suprachiasmatic nucleus** of the hypothalamus via the optic nerve. Through this retinal input, the light cues of the day/night cycle entrain or synchronize the "biological clock" of the brain to the external clock. A third one-way connection is the hypothalamo-hypophyseal tract from the supraoptic and paraventricular nuclei to the posterior pituitary gland. The hypothalamus also projects directly to the spinal cord to activate sympathetic and parasympathetic preganglionic neurons (see Chapter 6).

Hypothalamic Nuclei Are Centers of Physiological Regulation

The nuclei of the hypothalamus contain groups of neurons that regulate several important physiological functions:

- 1) Water and electrolyte balance in magnocellular cells of the supraoptic and paraventricular nuclei (see Chapter 32)
- 2) Secretion of hypothalamic releasing factors in the arcuate and periventricular nuclei and in parvocellular cells of the paraventricular nucleus (see Chapters 32 and 33)
- 3) Temperature regulation in the anterior and posterior hypothalamic nuclei (see Chapter 29)
- 4) Activation of the sympathetic nervous system and adrenal medullary hormone secretion in the dorsal and posterior hypothalamus (see Chapter 34)
- 5) Thirst and drinking regulation in the lateral hypothalamus (see Chapter 24)
- 6) Hunger, satiety, and the regulation of eating behavior in the arcuate nucleus, ventromedial nucleus, and lateral hypothalamic area
- 7) Regulation of sexual behavior in the anterior and preoptic areas
- 8) Regulation of circadian rhythms in the suprachiasmatic nucleus

The Hypothalamus Regulates Eating Behavior

Classically, the hypothalamus has been considered a grouping of regulatory centers governing homeostasis. With respect to eating, the ventromedial nucleus of the hypothalamus serves as a **satiety center** and the lateral hypothalamic area serves as a **feeding center**. Together, these areas coordinate the processes that govern eating behavior and the subjective perception of satiety. These hypothalamic areas also influence the secretion of hormones, partic-

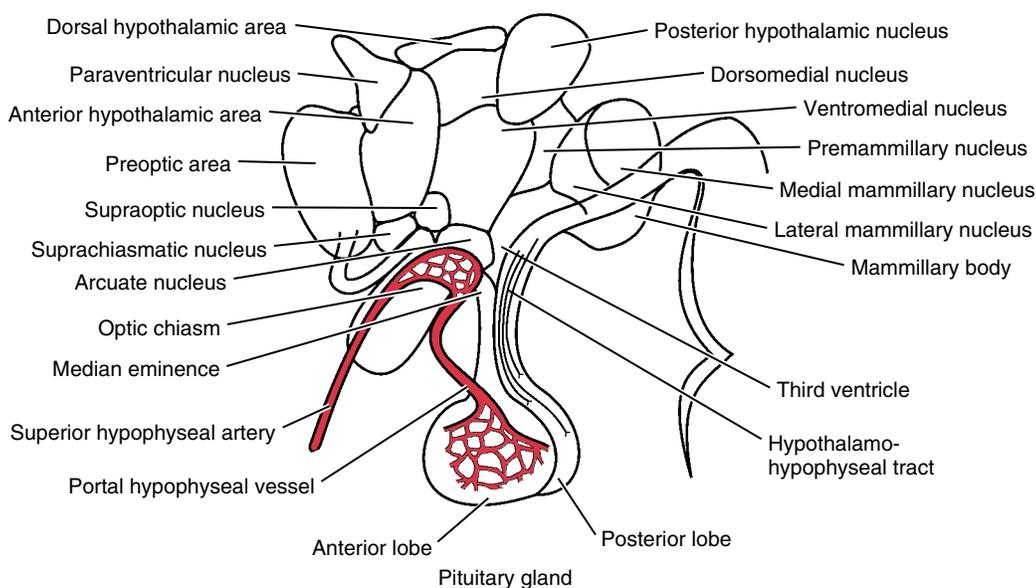


FIGURE 7.2 The hypothalamus and its nuclei. The connections between the hypothalamus and the pituitary gland are also shown. (Modified from Ganong WF.

Review of Medical Physiology. 16th Ed. Norwalk, CT: Appleton & Lange, 1993.)

ularly from the thyroid gland, adrenal gland, and pancreatic islet cells, in response to changing metabolic demands.

Lesions in the ventromedial nucleus in experimental animals lead to morbid obesity as a result of unrestricted eating (hyperphagia). Conversely, electrical stimulation of this area results in the cessation of eating (hypophagia). Destructive lesions in the lateral hypothalamic area lead to hypophagia, even in the face of starvation; electrical stimulation of this area initiates feeding activity, even when the animal has already eaten.

The regulation of eating behavior is part of a complex pathway that regulates food intake, energy expenditure, and reproductive function in the face of changes in nutritional state. In general, the hypothalamus regulates caloric intake, utilization, and storage in a manner that tends to maintain the body weight in adulthood. The presumptive set point around which it attempts to stabilize body weight, however, is poorly defined or maintained, as it changes readily with changes in physical activity, composition of the diet, emotional states, stress, pregnancy, and so on.

A key player in the regulation of body weight is the hormone **leptin**, which is released by white fat cells (adipocytes). As fat stores increase, plasma leptin levels increase; conversely, as fat stores are depleted, leptin levels decrease. Cells in the arcuate nucleus of the hypothalamus appear to be the sensors for leptin levels. Physiological responses to low leptin levels (starvation) are initiated by the hypothalamus to increase food intake, decrease energy expenditure, decrease reproductive function, decrease body temperature, and increase parasympathetic activity. Physiological responses to high leptin levels (obesity) are initiated by the hypothalamus to decrease food intake, increase energy expenditure, and increase sympathetic activity. Hypothalamic pathways involving neuropeptide Y are important for the starvation response, while pathways involving the melanocyte-stimulating hormone are important for the obesity response.

In addition to long-term regulation of body weight, the hypothalamus also regulates eating behavior more acutely. Factors that limit the amount of food ingested during a single feeding episode originate in the gastrointestinal tract and influence the hypothalamic regulatory centers. These include sensory signals carried by the vagus nerve that signify stomach filling and chemical signals giving rise to the sensation of satiety, including absorbed nutrients (glucose, certain amino acids, and fatty acids) and gastrointestinal hormones, especially cholecystokinin.

The Hypothalamus Controls the Gonads and Sexual Activity

The anterior and preoptic hypothalamic areas are sites for regulating gonadotropic hormone secretion and sexual behavior. Neurons in the preoptic area secrete gonadotropin-releasing hormone (GnRH), beginning at puberty, in response to signals that are not understood. These neurons contain receptors for gonadal steroid hormones, testosterone and/or estradiol, which regulate GnRH secretion in either a cyclic (female) or a continual (male) pattern following the onset of puberty.

At a critical period in fetal development, circulating testosterone secreted by the testes of a male fetus changes the characteristics of cells in the preoptic area that are destined later in life to secrete GnRH. These cells, which would secrete GnRH *cyclically* at puberty, had they not been exposed to androgens prenatally, are transformed into cells that secrete GnRH *continually* at a homeostatically regulated level. As a result, males exhibit a steady-state secretion rate for gonadotropic hormones and, consequently, for testosterone (see Chapter 37).

In the absence of androgens in fetal blood during development, the preoptic area remains unchanged, so that at puberty the GnRH-secreting cells begin to secrete in a

cyclic pattern. This pattern is reinforced and synchronized throughout female reproductive life by the cyclic feedback of ovarian steroids, estradiol and progesterone, on secretion of GnRH by the hypothalamus during the menstrual cycle (see Chapter 38).

Steroid levels during prenatal and postnatal development are known to mediate differentiation of sexually dimorphic regions of the brain of most vertebrate species. Sexually dimorphic brain anatomy, behavior, and susceptibility to neurological and psychiatric illness are evident in humans; however, with the exception of the GnRH-secreting cells, it has been difficult to definitively show a steroid dependency for sexually dimorphic differentiation in the human brain.

The Hypothalamus Contains the “Biological Clock”

Many physiological functions, including body temperature and sleep/wake cycles, vary throughout the day in a pattern that repeats itself daily. Others, such as the female menstrual cycle, repeat themselves approximately every 28 days. Still others, such as reproductive function in seasonal breeders, repeat annually. The hypothalamus is thought to play a major role in regulating all of these biological rhythms. Furthermore, these rhythms appear to be endogenous (within the body) because they persist even in the absence of time cues, such as day/night cycles for light and dark periods, lunar cycles for monthly rhythms, or changes in temperature and day length for seasonal change. Accordingly, most organisms, including humans, are said to possess an endogenous timekeeper, a so-called **biological clock** that times the body's regulated functions.

Most homeostatically regulated functions exhibit peaks and valleys of activity that recur approximately daily. These are called **circadian rhythms** or diurnal rhythms. The circadian rhythms of the body are driven by the **suprachiasmatic nucleus (SCN)**, a center in the hypothalamus that serves as the brain's biological clock. The SCN, which influences many hypothalamic nuclei via its efferent connections, has the properties of an oscillator whose spontaneous firing patterns change dramatically during a day/night cycle. This diurnal cycle of activity is maintained *in vitro* and is an internal property of SCN cells. The molecular basis of the cellular rhythm is a series of transcriptional/translational feedback loops. The genes involved in these loops are apparently conserved from prokaryotes to humans. An important pathway influencing the SCN is the afferent **retinohypothalamic tract** of the optic nerve, which originates in the retina and enters the brain through the optic chiasm and terminates in the SCN. This pathway is the principal means by which light signals from the outside world transmit the day/night rhythm to the brain's internal clock, thereby entraining the endogenous oscillator to the external clock.

Figure 7.3 illustrates some of the circadian rhythms of the body. One of the most vivid is alertness, which peaks in the afternoon and is lowest in the hours preceding and following sleep. Another, body temperature, ranges approximately 1°C (about 2°F) throughout the day, with the low point occurring during sleep. Plasma levels of growth hor-

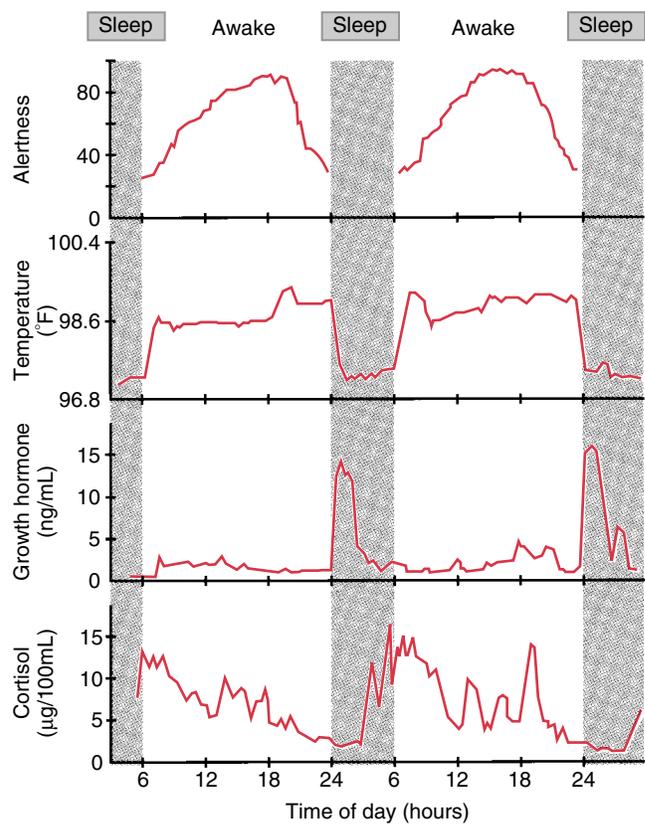


FIGURE 7.3 Circadian rhythms in some homeostatically regulated functions during two 24-hour periods. Alertness is measured on an arbitrary scale between sleep and most alert. (Modified from Coleman RM. *Wide Awake at 3:00 AM*. New York: WH Freeman, 1986.)

more increase greatly during sleep, in keeping with this hormone's metabolic role as a glucose-sparing agent during the nocturnal fast. Cortisol, on the other hand, has its highest daily plasma level prior to arising in the morning. The mechanism by which the SCN can regulate diverse functions is related to its control of the production of **melatonin** by the **pineal gland**. Melatonin levels increase with decreasing light as night ensues.

Other homeostatically regulated functions exhibit diurnal patterns as well; when they are all in synchrony, they function harmoniously and impart a feeling of well-being. When there is a disruption in rhythmic pattern, such as by sleep deprivation or when passing too rapidly through several time zones, the period required for reentrainment of the SCN to the new day/night pattern is characterized by a feeling of malaise and physiological distress. This is commonly experienced as jet lag in travelers crossing several time zones or by workers changing from day shift to night shift or from night shift to day shift. In such cases, the hypothalamus requires time to “reset its clock” before the regular rhythms are restored and a feeling of well-being ensues. The SCN uses the new pattern of light/darkness, as perceived in the retina, to entrain its firing rate to a pattern consistent with the external world. Resetting the clock may

be facilitated by the judicious use of exogenous melatonin and by altering exposure to light.

THE RETICULAR FORMATION

The brainstem contains anatomic groupings of cell bodies clearly identified as the nuclei of cranial sensory and motor nerves or as relay cells of ascending sensory or descending motor systems. The remaining cell groups of the brainstem, located in the central core, constitute a diffuse-appearing system of neurons with widely branching axons, known as the **reticular formation**.

Neurons of the Reticular Formation Exert Widespread Modulatory Influence in the CNS

As neurochemistry and cytochemical localization techniques improve, it is becoming increasingly clear that the reticular formation is not a diffuse, undefined system; it contains highly organized clusters of transmitter-specific cell groups that influence functions in specific areas of the CNS. For example, the nuclei of monoaminergic neuronal systems are located in well-defined cell groups throughout the reticular formation.

A unique characteristic of neurons of the reticular formation is their widespread system of axon collaterals, which make extensive synaptic contacts and, in some cases, travel over long distances in the CNS. A striking example is the demonstration, using intracellular labeling of individual cells and their processes, that one axon branch descends all the way into the spinal cord, while the collateral branch projects rostrally all the way to the forebrain, making myriad synaptic contacts along both axonal pathways.

The Ascending Reticular Activating System Mediates Consciousness and Arousal

Sensory neurons bring peripheral sensory information to the CNS via specific pathways that ascend and synapse with specific nuclei of the thalamus, which, in turn, innervate primary sensory areas of the cerebral cortex. These pathways involve three to four synapses, starting from a receptor that responds to a specific sensory modality—such as touch, hearing, or vision. Each modality has, in addition, a nonspecific form of sensory transmission, in that axons of the ascending fibers send collateral branches to cells of the reticular formation (Fig. 7.4). The latter, in turn, send their axons to the **intralaminar nuclei of thalamus**, which innervate wide areas of the cerebral cortex and limbic system. In the cerebral cortex and limbic system, the influence of the nonspecific projections from the reticular formation is arousal of the organism. This series of connections from the reticular formation through the intralaminar nuclei of the thalamus and on to the forebrain is termed the **ascending reticular activating system**.

The reticular formation also houses the neuronal systems that regulate sleep/wake cycles and consciousness. So important is the ascending reticular activating system to the state of arousal that a malfunction in the reticular formation, particularly the rostral portion, can lead to a loss of consciousness and coma.

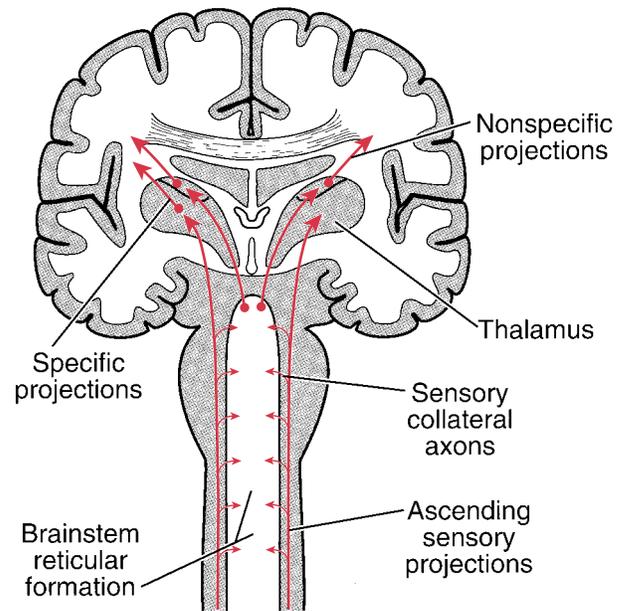


FIGURE 7.4 The brainstem reticular formation and reticular activating system. Ascending sensory tracts send axon collateral fibers to the reticular formation. These give rise to fibers synapsing in the intralaminar nuclei of the thalamus. From there, these nonspecific thalamic projections influence widespread areas of the cerebral cortex and limbic system.

An Electroencephalogram Records Electrical Activity of the Brain's Surface

The influence of the ascending reticular activating system on the brain's activity can be monitored via **electroencephalography**. The electroencephalograph is a sensitive recording device for picking up the electrical activity of the brain's surface through electrodes placed on designated sites on the scalp. This noninvasive tool measures simultaneously, via multiple leads, the electrical activity of the major areas of the cerebral cortex. It is also the best diagnostic tool available for detecting abnormalities in electrical activity, such as in epilepsy, and for diagnosing sleep disorders.

The detected electrical activity reflects the extracellular recording of the myriad postsynaptic potentials in cortical neurons underlying the electrode. The summated electrical potentials recorded from moment to moment in each lead are influenced greatly by the input of sensory information from the thalamus via specific and nonspecific projections to the cortical cells, as well as inputs that course laterally from other regions of the cortex.

EEG Waves. The waves recorded on an **electroencephalogram** (EEG) are described in terms of frequency, which usually ranges from less than 1 to about 30 Hz, and amplitude or height of the wave, which usually ranges from 20 to 100 μV . Since the waves are a summation of activity in a complex network of neuronal processes, they are highly variable. However, during various states of consciousness, EEG waves have certain characteristic patterns. At the highest state of alertness, when sensory input is greatest, the waves are of high frequency and low amplitude, as many

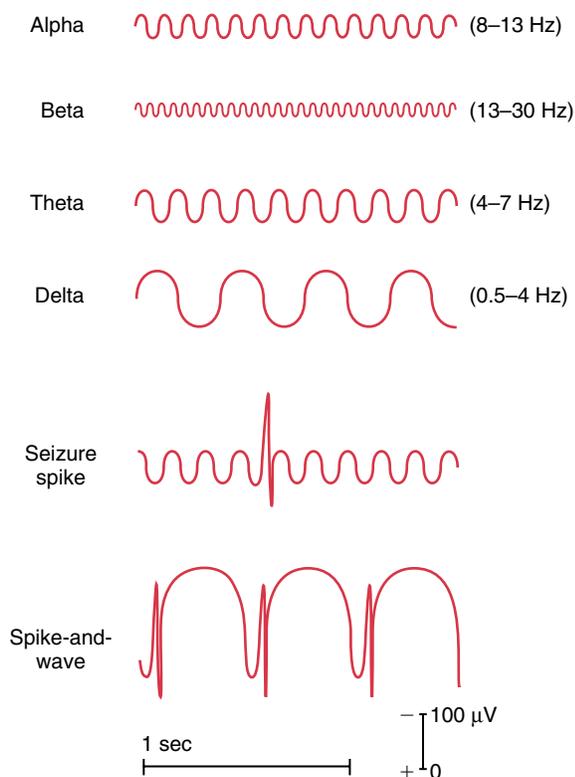


FIGURE 7.5 Patterns of brain waves recorded on an EEG. Wave patterns are designated alpha, beta, theta, or delta waves, based on frequency and relative amplitude. In epilepsy, abnormal spikes and large summated waves appear as many neurons are activated simultaneously.

units discharge asynchronously. At the opposite end of the alertness scale, when sensory input is at its lowest, in deep sleep, a synchronized EEG has the characteristics of low frequency and high amplitude. An absence of EEG activity is the legal criterion for death in the United States.

EEG wave patterns are classified according to their frequency (Fig. 7.5). **Alpha waves**, a rhythm ranging from 8 to 13 Hz, are observed when the person is awake but relaxed with the eyes closed. When the eyes are open, the added visual input to the cortex imparts a faster rhythm to the EEG, ranging from 13 to 30 Hz and designated **beta waves**. The slowest waves recorded occur during sleep: **theta waves** at 4 to 7 Hz and **delta waves** at 0.5 to 4 Hz, in deepest sleep.

Abnormal wave patterns are seen in **epilepsy**, a neurological disorder of the brain characterized by spontaneous discharges of electrical activity, resulting in abnormalities ranging from momentary lapses of attention, to seizures of varying severity, to loss of consciousness if both brain hemispheres participate in the electrical abnormality. The characteristic waveform signifying seizure activity is the appearance of spikes or sharp peaks, as abnormally large numbers of units fire simultaneously. Examples of spike activity occurring singly and in a spike-and-wave pattern are shown in Figure 7.5.

Sleep and the EEG. Sleep is regulated by the reticular formation. The ascending reticular activating system is periodically shut down by influences from other regions of the reticular formation. The EEG recorded during sleep reveals a persistently changing pattern of wave amplitudes and frequencies, indicating that the brain remains continually active even in the deepest stages of sleep. The EEG pattern recorded during sleep varies in a cyclic fashion that repeats approximately every 90 minutes, starting from the time of falling asleep to awakening 7 to 8 hours later (Fig. 7.6). These cycles are associated with two different forms of sleep, which follow each other sequentially:

1. **Slow-wave sleep:** four stages of progressively deepening sleep (i.e., it becomes harder to wake the subject)
2. **Rapid eye movement (REM) sleep:** back-and-forth movements of the eyes under closed lids, accompanied by autonomic excitation

EEG recordings of sleeping subjects in laboratory settings reveal that the brain's electrical activity varies as the

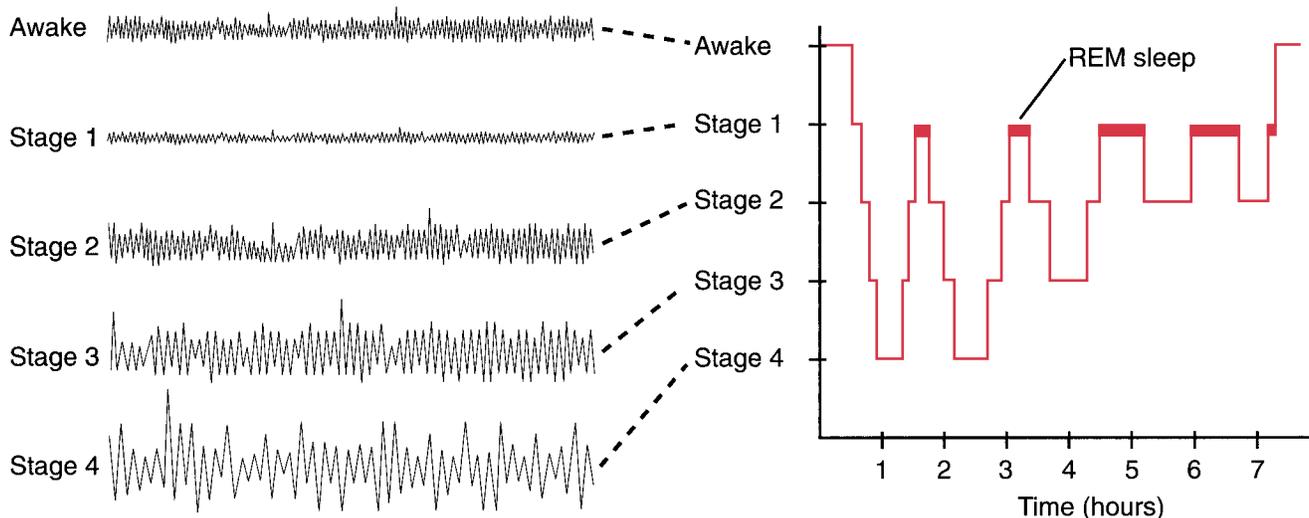


FIGURE 7.6 The brain wave patterns during a normal sleep cycle. (See text for details.) (Modified

from Kandel ER, Schwartz JH, Jessel TM. Principles of Neural Science. 3rd Ed. New York: Elsevier, 1991.)

subject passes through cycles of slow-wave sleep, then REM sleep, on through the night.

A normal sleep cycle begins with slow-wave sleep, four stages of increasingly deep sleep during which the EEG becomes progressively slower in frequency and higher in amplitude. Stage 4 is reached at the end of about an hour, when delta waves are observed (see Fig. 7.6). The subject then passes through the same stages in reverse order, approaching stage 1 by about 90 minutes, when a REM period begins, followed by a new cycle of slow-wave sleep. Slow-wave sleep is characterized by decreased heart rate and blood pressure, slow and regular breathing, and relaxed muscle tone. Stages 3 and 4 occur only in the first few sleep cycles of the night. In contrast, REM periods increase in duration with each successive cycle, so that the last few cycles consist of approximately equal periods of REM sleep and stage 2 slow-wave sleep.

REM sleep is also known as **paradoxical sleep**, because of the seeming contradictions in its characteristics. First, the EEG exhibits unsynchronized, high-frequency, low-amplitude waves (i.e., a beta rhythm), which is more typical of the awake state than sleep, yet the subject is as difficult to arouse as when in stage 4 slow-wave sleep. Second, the autonomic nervous system is in a state of excitation; blood pressure and heart rate are increased and breathing is irregular. In males, autonomic excitation in REM sleep includes penile erection. This reflex is used in diagnosing impotence, to determine whether erectile failure is based on a neurological or a vascular defect (in which case, erection does not accompany REM sleep).

When subjects are awakened during a REM period, they usually report dreaming. Accordingly, it is customary to consider REM sleep as dream sleep. Another curious characteristic of REM sleep is that most voluntary muscles are temporarily paralyzed. Two exceptions, in addition to the muscles of respiration, include the extraocular muscles, which contract rhythmically to produce the rapid eye movements, and the muscles of the middle ear, which protect the inner ear (see Chapter 4). Muscle paralysis is caused by an active inhibition of motor neurons mediated by a group of neurons located close to the locus ceruleus in the brainstem. Many of us have experienced this muscle paralysis on waking from a bad dream, feeling momentarily incapable of running from danger. In certain sleep disorders in which skeletal muscle contraction is not temporarily paralyzed in REM sleep, subjects act out dream sequences with disturbing results, with no conscious awareness of this happening.

Sleep in humans varies with developmental stage. Newborns sleep approximately 16 hours per day, of which about 50% is spent in REM sleep. Normal adults sleep 7 to 8 hours per day, of which about 25% is spent in REM sleep. The percentage of REM sleep declines further with age, together with a loss of the ability to achieve stages 3 and 4 of slow-wave sleep.

THE FOREBRAIN

The forebrain contains the **cerebral cortex** and the **subcortical structures** rostral to the diencephalon. The cortex, a few-millimeters-thick outer shell of the cerebrum, has a rich, multilayered array of neurons and their processes forming

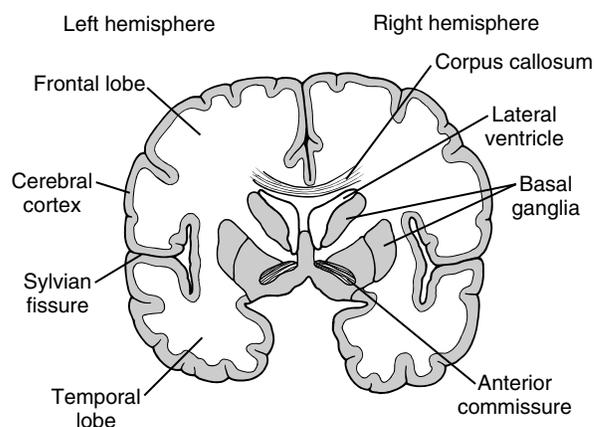


FIGURE 7.7 The cerebral hemispheres and some deep structures in a coronal section through the rostral forebrain.

The corpus callosum is the major commissure that interconnects the right and left hemispheres. The anterior commissure connects rostral components of the right and left temporal lobes. The cortex is an outer rim of gray matter (neuronal cell bodies and dendrites); deep to the cortex is white matter (axonal projections) and then subcortical gray matter.

columns perpendicular to the surface. The axons of cortical neurons give rise to descending fiber tracts and intrahemispheric and interhemispheric fiber tracts, which, together with ascending axons coursing toward the cortex, make up the prominent white matter underlying the outer cortical gray matter. A deep sagittal fissure divides the cortex into a right and left hemisphere, each of which receives sensory input from and sends its motor output to the opposite side of the body. A set of **commissures** containing axonal fibers interconnects the two hemispheres, so that processed neural information from one side of the forebrain is transmitted to the opposite hemisphere. The largest of these commissures is the **corpus callosum**, which interconnects the major portion of the hemispheric regions (Fig. 7.7).

Among the subcortical structures located in the forebrain are the components of the limbic system, which regulates emotional response, and the **basal ganglia** (caudate, putamen, and globus pallidus), which are essential for coordinating motor activity (see Chapter 5).

The Cerebral Cortex Is Functionally Compartmentalized

In the human brain, the surface of the cerebral cortex is highly convoluted, with **gyri** (singular, *gyrus*) and **sulci** (singular, *sulcus*), which are akin to hills and valleys, respectively. Deep sulci are also called **fissures**. Two deep fissures form prominent landmarks on the surface of the cortex; the **central sulcus** divides the **frontal lobe** from the **parietal lobe**, and the **sylvian fissure** divides the parietal lobe from the **temporal lobe** (Fig. 7.8). The **occipital lobe** has less prominent sulci separating it from the parietal and temporal lobes.

Topographically, the cerebral cortex is divided into areas of specialized functions, including the primary sensory areas for vision (occipital cortex), hearing (temporal cortex), somatic sensation (postcentral gyrus), and primary

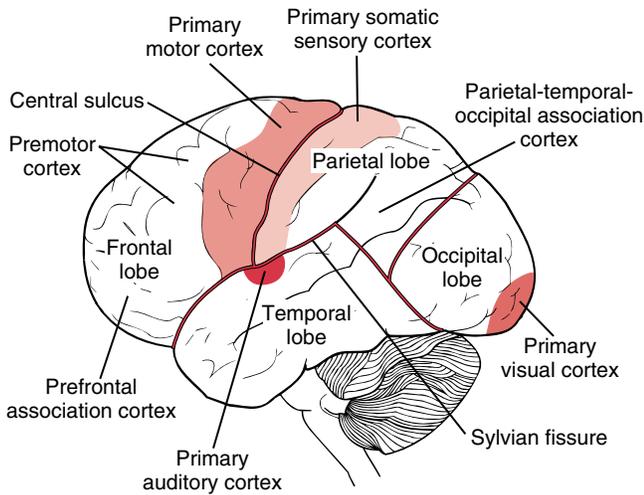


FIGURE 7.8 The four lobes of the cerebral cortex, containing primary sensory and motor areas and major association areas. The central sulcus and sylvian fissure are prominent landmarks used in defining the lobes of the cortex. Imaginary lines are drawn in to indicate the boundaries between the occipital, temporal, and parietal lobes. (Modified from Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*. 3rd Ed. New York: Elsevier, 1991.)

motor area (precentral gyrus) (see Chapters 4 and 5). As shown in Figure 7.8, these well-defined areas comprise only a small fraction of the surface of the cerebral cortex. The majority of the remaining cortical area is known as **association cortex**, where the processing of neural information is performed at the highest levels of which the organism is capable; among vertebrates, the human cortex contains the most extensive association areas. The association areas are also sites of long-term memory, and they control such human functions as language acquisition, speech, musical ability, mathematical ability, complex motor skills, abstract thought, symbolic thought, and other cognitive functions.

Association areas interconnect and integrate information from the primary sensory and motor areas via intrahemispheric connections. The **parietal-temporal-occipital association cortex** integrates neural information contributed by visual, auditory, and somatic sensory experiences. The **prefrontal association cortex** is extremely important as the coordinator of emotionally motivated behaviors, by virtue of its connections with the limbic system. In addition, the prefrontal cortex receives neural input from the other association areas and regulates motivated behaviors by direct input to the **premotor area**, which serves as the association area of the motor cortex.

Sensory and motor functions are controlled by cortical structures in the contralateral hemisphere (see Chapters 4 and 5). Particular cognitive functions or components of these functions may be lateralized to one side of the brain (see Clinical Focus Box 7.1).

The Limbic System Is the Seat of the Emotions

The limbic system comprises large areas of the forebrain where the emotions are generated and the responses to

emotional stimuli are coordinated. Understanding its functions is particularly challenging because it is a complex system of numerous and disparate elements, most of which have not been fully characterized. A compelling reason for studying the limbic system is that the major psychiatric disorders—including bipolar disorder, major depression, schizophrenia, and dementia—involve malfunctions in the limbic system.

Anatomy of the Limbic System. The limbic system comprises specific areas of the cortex and subcortical structures interconnected via circuitous pathways that link the cerebrum with the diencephalon and brainstem (Fig. 7.9). Originally the limbic system was considered to be restricted to a ring of structures surrounding the corpus callosum, including the olfactory system, the **cingulate gyrus**, **parahippocampal gyrus**, and **hippocampus**, together with the fiber tracts that interconnect them with the diencephalic components of the limbic system, the hypothalamus and anterior thalamus. Current descriptions of the limbic system also include the **amygdala** (deep in the temporal lobe), **nucleus accumbens** (the limbic portion of the basal ganglia), **septal nuclei** (at the base of the forebrain), the **prefrontal cortex** (anterior and inferior components of the frontal lobe) and the **habenula** (in the diencephalon).

Circuitous loops of fiber tracts interconnect the limbic structures. The main circuit links the hippocampus to the mammillary body of the hypothalamus by way of the fornix, the hypothalamus to the anterior thalamic nuclei via the mammillothalamic tract, and the anterior thalamus to the cingulate gyrus by widespread, anterior thalamic projections (Fig. 7.10). To complete the circuit, the cingulate gyrus connects with the hippocampus, to enter the circuit again. Other structures of the limbic system form smaller loops within this major circuit, forming the basis for a wide range of emotional behaviors.

The fornix also connects the hippocampus to the base of the forebrain where the septal nuclei and nucleus accumbens reside. Prefrontal cortex and other areas of association cortex provide the limbic system with information based on previous learning and currently perceived needs. Inputs from the brainstem provide visceral and somatic sensory signals, including tactile, pressure, pain, and temperature information from the skin and sexual organs and pain information from the visceral organs.

At the caudal end of the limbic system, the brainstem has reciprocal connections with the hypothalamus (see Fig. 7.10). As noted above, all ascending sensory systems in the brainstem send axon collaterals to the reticular formation, which, in turn, innervates the limbic system, particularly via monoaminergic pathways. The reticular formation also forms the ascending reticular activating system, which serves not only to arouse the cortex but also to impart an emotional tone to the sensory information transmitted nonspecifically to the cerebral cortex.

Monoaminergic Innervation. Monoaminergic neurons innervate all parts of the CNS via widespread, divergent pathways starting from cell groups in the reticular formation. The limbic system and basal ganglia are richly innervated by catecholaminergic (noradrenergic and dopaminergic)

CLINICAL FOCUS BOX 7.1

The Split Brain

Patients with life-threatening, intractable epileptic seizures were treated in the past by surgical commissurotomy or cutting of the corpus callosum (see Fig. 7.7). This procedure effectively cut off most of the neuronal communication between the left and right hemispheres and vastly improved patient status because seizure activity no longer spread back and forth between the hemispheres.

There was a remarkable absence of overt signs of disability following commissurotomy; patients retained their original motor and sensory functions, learning and memory, personality, talents, emotional responding, and so on. This outcome was not unexpected because each hemisphere has bilateral representation of most known functions; moreover, those ascending (sensory) and descending (motor) neuronal systems that crossed to the opposite side were known to do so at levels lower than the corpus callosum.

Notwithstanding this appearance of normalcy, following commissurotomy, patients were shown to be impaired to the extent that one hemisphere literally did not know what the other was doing. It was further shown that each hemisphere processes neuronal information differently from the other, and that some cerebral functions are confined exclusively to one hemisphere.

In an interesting series of studies by Nobel laureate Roger Sperry and colleagues, these patients with a so-called split-brain were subjected to psychophysiological testing in which each disconnected hemisphere was examined independently. Their findings confirmed what was already known: Sensory and motor functions are controlled by cortical structures in the contralateral hemisphere. For example, visual signals from the left visual field were perceived in the right occipital lobe, and there were contralateral controls for auditory, somatic sensory, and motor functions. (Note that the olfactory system is an exception, as odorant chemicals applied to one nostril are perceived in the olfactory lobe on the same side.) However, the scientists were surprised to find that language

ability was controlled almost exclusively by the left hemisphere. Thus, if an object was presented to the left brain via any of the sensory systems, the subject could readily identify it by the spoken word. However, if the object was presented to the right hemisphere, the subject could not find words to identify it. This was not due to an inability of the right hemisphere to perceive the object, as the subject could easily identify it among other choices by nonverbal means, such as feeling it while blindfolded. From these and other tests it became clear that the right hemisphere was mute; it could not produce language.

In accordance with these findings, anatomic studies show that areas in the temporal lobe concerned with language ability, including Wernicke's area, are anatomically larger in the left hemisphere than in the right in a majority of humans, and this is seen even prenatally. Corroborative evidence of language ability in the left hemisphere is shown in persons who have had a stroke, where aphasias are most severe if the damage is on the left side of the brain. Analysis of people who are deaf who communicated by sign language prior to a stroke has shown that sign language is also a left-hemisphere function. These patients show the same kinds of grammatical and syntactical errors in their signing following a left-hemisphere stroke as do speakers.

In addition to language ability, the left hemisphere excels in mathematical ability, symbolic thinking, and sequential logic. The right hemisphere, on the other hand, excels in visuospatial ability, such as three-dimensional constructions with blocks and drawing maps, and in musical sense, artistic sense, and other higher functions that computers seem less capable of emulating. The right brain exhibits some ability in language and calculation, but at the level of children ages 5 to 7. It has been postulated that both sides of the brain are capable of all of these functions in early childhood, but the larger size of the language area in the left temporal lobe favors development of that side during language acquisition, resulting in nearly total specialization for language on the left side for the rest of one's life.

ergic) and serotonergic nerve terminals emanating from brainstem nuclei that contain relatively few cell bodies compared to their extensive terminal projections. From neurochemical manipulation of monoaminergic neurons in the limbic system, it is apparent that they play a major role in determining emotional state.

Dopaminergic neurons are located in three major pathways originating from cell groups in either the midbrain (the substantia nigra and ventral tegmental area) or the hypothalamus (Fig. 7.11). The **nigrostriatal system** consists of neurons with cell bodies in the substantia nigra (pars compacta) and terminals in the neostriatum (caudate and putamen) located in the basal ganglia. This dopaminergic pathway is essential for maintaining normal muscle tone and initiating voluntary movements (see Chapter 5). The **tuberoinfundibular system** of dopaminergic neurons is located entirely within the hypothalamus, with cell bodies in the arcuate nucleus and periventricular nuclei and terminals in the median eminence on the ventral surface of the hypothalamus. The tuberoinfundibular system is responsible for

the secretion of hypothalamic releasing factors into a portal system that carries them through the pituitary stalk into the anterior pituitary lobe (see Chapter 32).

The **mesolimbic/mesocortical system** of dopaminergic neurons originates in the ventral tegmental area of the mid-brain region of the brainstem and innervates most structures of the limbic system (olfactory tubercles, septal nuclei, amygdala, nucleus accumbens) and limbic cortex (frontal and cingulate cortices). This dopaminergic system plays an important role in motivation and drive. For example, dopaminergic sites in the limbic system, particularly the more ventral structures such as the septal nuclei and nucleus accumbens, are associated with the brain's **reward system**. Drugs that increase dopaminergic transmission, such as cocaine, which inhibits dopamine reuptake, and amphetamine, which promotes dopamine release and inhibits its reuptake, lead to repeated administration and abuse presumably because they stimulate the brain's reward system. The mesolimbic/mesocortical dopaminergic system is also the site of action of **neuroleptic drugs**, which

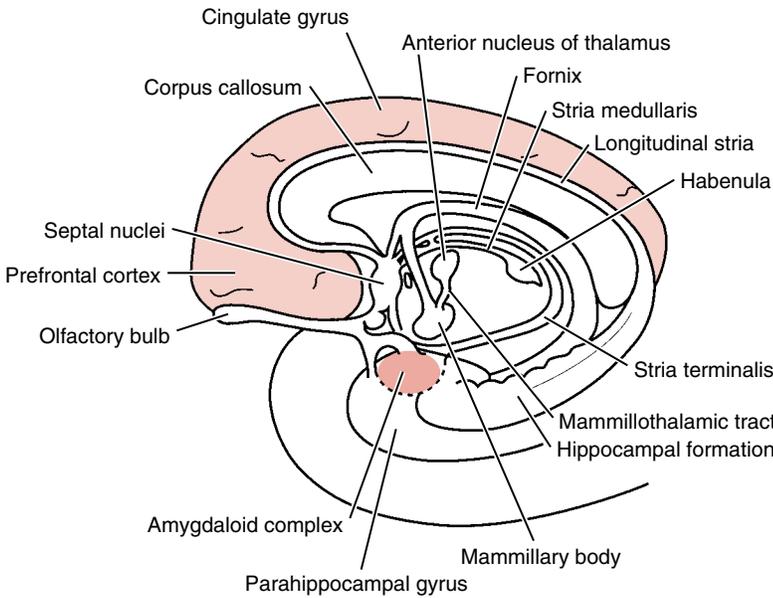


FIGURE 7.9 The cortical and subcortical structures of the limbic system extending from the cerebral cortex to the diencephalon. The fiber tracts that interconnect the structures of the limbic system are also shown. (Modified from Truex RC, Carpenter MB. Strong and Elwyn's Human Neuroanatomy. 5th Ed. Baltimore: Williams & Wilkins, 1964.)

are used to treat schizophrenia (discussed later) and other psychotic conditions.

Noradrenergic neurons (containing norepinephrine) are located in cell groups in the medulla and pons (Fig. 7.12). The medullary cell groups project to the spinal cord, where they influence cardiovascular regulation and other autonomic functions. Cell groups in the pons include the **lateral system**, which innervates the basal forebrain and hy-

pothalamus, and the **locus ceruleus**, which sends efferent fibers to nearly all parts of the CNS.

Noradrenergic neurons innervate all parts of the limbic system and the cerebral cortex, where they play a major role in setting **mood** (sustained emotional state) and **affect** (the emotion itself; e.g., euphoria, depression, anxiety). Drugs that alter noradrenergic transmission have profound effects on mood and affect. For example, reserpine, which depletes brain norepinephrine (NE), induces a state of depression. Drugs that enhance NE availability, such as monoamine oxidase inhibitors (MAOIs) and inhibitors of reuptake, reverse this depression. Amphetamines and cocaine have effects on boosting noradrenergic transmission similar to those described for dopaminergic transmission; they inhibit reuptake and/or promote the release of norepinephrine. Increased noradrenergic transmission results in an elevation of mood, which further contributes to the po-

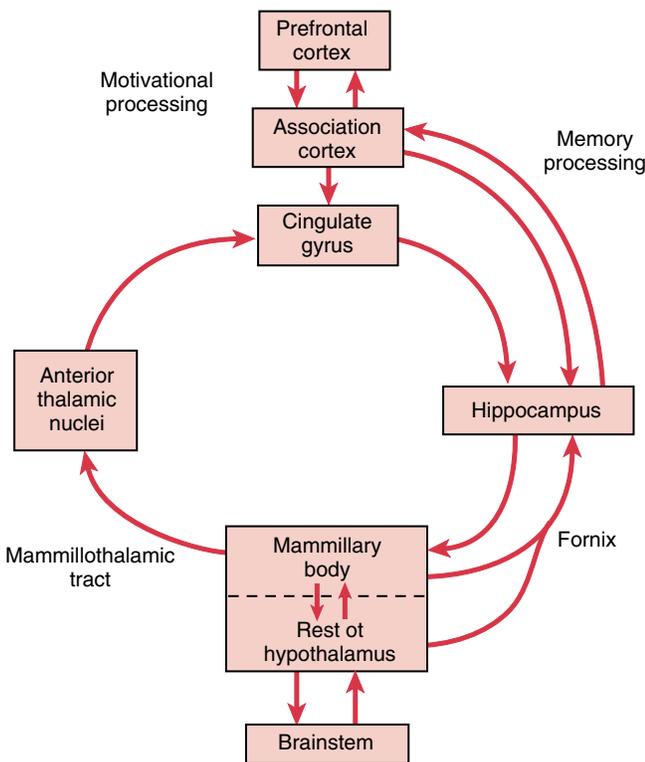


FIGURE 7.10 The main circuit of the limbic system.

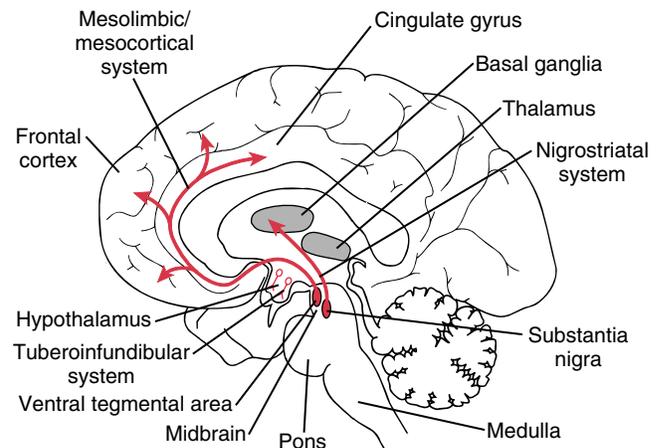


FIGURE 7.11 The origins and projections of the three major dopaminergic systems. (Modified from Heimer L. The Human Brain and Spinal Cord. New York: Springer-Verlag, 1983.)

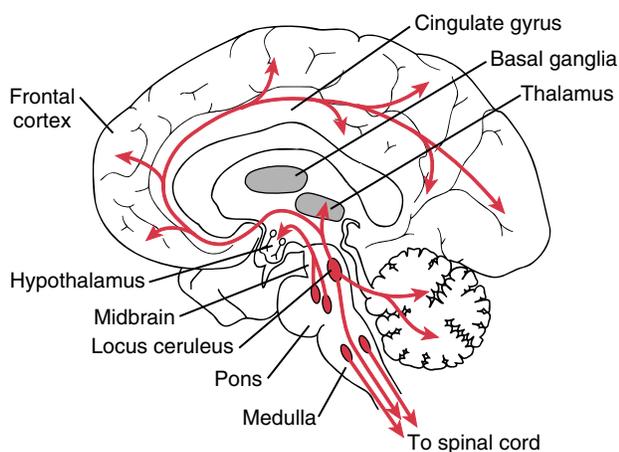


FIGURE 7.12 The origins and projections of five of seven cell groups of noradrenergic neurons of the brain. The depicted groups originate in the medulla and pons. Among the latter, the locus ceruleus in the dorsal pons innervates most parts of the CNS. (Modified from Heimer L. *The Human Brain and Spinal Cord*. New York: Springer-Verlag, 1983.)

tential for abusing such drugs, despite the depression that follows when drug levels fall. Some of the unwanted consequences of cocaine or amphetamine-like drugs reflect the increased noradrenergic transmission, in both the periphery and the CNS. This can result in a hypertensive crisis, myocardial infarction, or stroke, in addition to marked swings in affect, starting with euphoria and ending with profound depression.

Serotonergic neurons also innervate most parts of the CNS. Cell bodies of these neurons are located at the midline of the brainstem (the raphe system) and in more laterally placed nuclei, extending from the caudal medulla to the midbrain (Fig. 7.13). Serotonin plays a major role in the defect underlying affective disorders (discussed later). Drugs

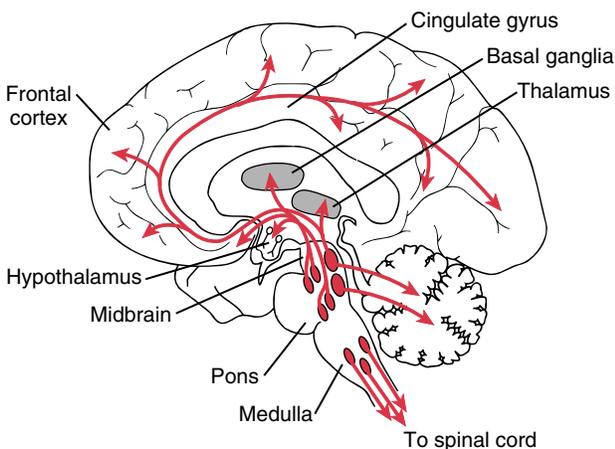


FIGURE 7.13 The origins and projections of the nine cell groups of the serotonergic system of the brain. The depicted groups originate in the caudal medulla, pons, and midbrain and send projections to most regions of the brain. (Modified from Heimer L. *The Human Brain and Spinal Cord*. New York: Springer-Verlag, 1983.)

that increase serotonin transmission are effective antidepressant agents.

The Brain's Reward System. Experimental studies beginning early in the last century demonstrated that stimulating the limbic system or creating lesions in various parts of the limbic system can alter emotional states. Most of our knowledge comes from animal studies, but emotional feelings are reported by humans when limbic structures are stimulated during brain surgery. The brain has no pain sensation when touched, and subjects awakened from anesthesia during brain surgery have communicated changes in emotional experience linked to electrical stimulation of specific areas.

Electrical stimulation of various sites in the limbic system produces either pleasurable (rewarding) or unpleasant (aversive) feelings. To study these findings, researchers use electrodes implanted in the brains of animals. When electrodes are implanted in structures presumed to generate rewarding feelings and the animals are allowed to deliver current to the electrodes by pressing a bar, repeated and prolonged self-stimulation is seen. Other needs—such as food, water, and sleep—are neglected. The sites that provoke the highest rates of electrical self-stimulation are in the ventral limbic areas, including the septal nuclei and nucleus accumbens. Extensive studies of electrical self-stimulatory behavior indicate that dopaminergic neurons play a major role in mediating reward. The nucleus accumbens is thought to be the site of action of addictive drugs, including opiates, alcohol, nicotine, cocaine, and amphetamine.

Aggression and the Limbic System. A fight-or-flight response, including the autonomic components (see Chapter 6) and postures of rage and aggression characteristic of fighting behavior, can be elicited by electrical stimulation of sites in the hypothalamus and amygdala. If the frontal cortical connections to the limbic system are severed, rage postures and aggressiveness become permanent, illustrating the importance of the higher centers in restraining aggression and, presumably, in invoking it at appropriate times. By contrast, bilateral removal of the amygdala results in a placid animal that cannot be provoked.

Sexual Activity. The biological basis of human sexual activity is poorly understood because of its complexity and because findings derived from nonhuman animal studies cannot be extrapolated. The major reason for this limitation is that the cerebral cortex, uniquely developed in the human brain, plays a more important role in governing human sexual activity than the instinctive or olfactory-driven behaviors in nonhuman primates and lower mammalian species. Nevertheless, several parallels in human and nonhuman sexual activities exist, indicating that the limbic system, in general, coordinates sex drive and mating behavior, with higher centers exerting more or less overriding influences.

Copulation in mammals is coordinated by reflexes of the sacral spinal cord, including male penile erection and ejaculation reflexes and engorgement of female erectile tissues, as well as the muscular spasms of the orgasmic response. Copulatory behaviors and postures can be elicited in animals by stimulating parts of the hypothalamus, olfactory

system, and other limbic areas, resulting in mounting behavior in males and lordosis (arching the back and raising the tail) in females. Ablation studies have shown that sexual behavior also requires an intact connection of the limbic system with the frontal cortex.

Olfactory cues are important in initiating mating activity in seasonal breeders. Driven by the hypothalamus' endogenous seasonal clock, the anterior and preoptic areas of the hypothalamus initiate hormonal control of the gonads. Hormonal release leads to the secretion of odorants (pheromones) by the female reproductive tract, signaling the onset of estrus and sexual receptivity to the male. The odorant cues are powerful stimulants, acting at extremely low concentrations to initiate mating behavior in males. The olfactory system, by virtue of its direct connections with the limbic system, facilitates the coordination of behavioral, endocrine, and autonomic responses involved in mating.

Although human and nonhuman primates are not seasonal breeders (mating can occur on a continual basis), vestiges of this pattern remain. These include the importance of the olfactory and limbic systems and the role of the hypothalamus in cyclic changes in female ovarian function and the continuous regulation of male testicular function. More important determinants of human sexual activity are the higher cortical functions of learning and memory, which serve to either reinforce or suppress the signals that initiate sexual responding, including the sexual reflexes coordinated by the sacral spinal cord.

Psychiatric Disorders Involve the Limbic System

The major psychiatric disorders, including affective disorders and schizophrenia, are disabling diseases with a genetic predisposition and no known cure. The biological basis for these disorders remains obscure, particularly the role of environmental influences on individuals with a genetic predisposition to developing a disorder. Altered states of the brain's monoaminergic systems have been a major focus as possible underlying factors, based on extensive human studies in which neurochemical imbalances in catecholamines, acetylcholine, and serotonin have been observed. Another reason for focusing on the monoaminergic systems is that the most effective drugs used in treating psychiatric disorders are agents that alter monoaminergic transmission.

Affective Disorders. The affective disorders include **major depression**, which can be so profound as to provoke suicide, and **bipolar disorder** (or **manic-depressive disorder**), in which periods of profound depression are followed by periods of mania, in a cyclic pattern. Biochemical studies indicate that depressed patients show decreased use of brain NE. In manic periods, NE transmission increases. Whether in depression or in mania, all patients seem to have decreased brain serotonergic transmission, suggesting that serotonin may exert an underlying permissive role in abnormal mood swings, in contrast with norepinephrine, whose transmission, in a sense, titrates the mood from highest to lowest extremes.

The most effective treatments for depression, including antidepressant drugs such as MAOIs and selective serotonin

reuptake inhibitors (SSRIs) and electroconvulsive therapy, have in common the ability to stimulate both noradrenergic and serotonergic neurons serving the limbic system. A therapeutic response to these treatments ensues only after treatment is repeated over time. Similarly, when treatment stops, symptoms may not reappear for several weeks. This time lag in treatment response is presumably due to alterations in the long-term regulation of receptor and second messenger systems in relevant regions of the brain.

The most effective long-term treatment for mania is lithium, although antipsychotic (neuroleptic) drugs, which block dopamine receptors, are effective in the acute treatment of mania. The therapeutic actions of lithium remain unknown, but the drug has an important action on a receptor-mediated second messenger system. Lithium interferes with regeneration of phosphatidylinositol in neuronal membranes by blocking the hydrolysis of inositol-1-phosphate. Depletion of phosphatidylinositol in the membrane renders it incapable of responding to receptors that use this second messenger system.

Schizophrenia. **Schizophrenia** is the collective name for a group of psychotic disorders that vary greatly in symptoms among individuals. The features most commonly observed are thought disorder, inappropriate emotional response, and auditory hallucinations. While the biochemical imbalance resulting in schizophrenia is poorly understood, the most troubling symptoms of schizophrenia are ameliorated by neuroleptic drugs, which block dopamine receptors in the limbic system.

Current research is focused on finding the subtype of dopamine receptor that mediates mesocortical/mesolimbic dopaminergic transmission but does not affect the nigrostriatal system, which controls motor function (see Fig. 7.12). So far, neuroleptic drugs that block one pathway almost always block the other as well, leading to unwanted neurological side effects, including abnormal involuntary movements (tardive dyskinesia) after long-term treatment or parkinsonism in the short term. Similarly, some patients with Parkinson's disease who receive L-DOPA to augment dopaminergic transmission in the nigrostriatal pathway must be taken off the medication because they develop psychosis.

Memory and Learning Require the Cerebral Cortex and Limbic System

Memory and learning are inextricably linked because part of the learning process involves the assimilation of new information and its commitment to memory. The most likely sites of learning in the human brain are the large association areas of the cerebral cortex, in coordination with subcortical structures deep in the temporal lobe, including the hippocampus and amygdala. The association areas draw on sensory information received from the primary visual, auditory, somatic sensory, and olfactory cortices and on emotional feelings transmitted via the limbic system. This information is integrated with previously learned skills and stored memory, which presumably also reside in the association areas.

The learning process itself is poorly understood, but it can be studied experimentally at the synaptic level in iso-

lated slices of mammalian brain or in more simple invertebrate nervous systems. Synapses subjected to repeated presynaptic neuronal stimulation show changes in the excitability of postsynaptic neurons. These changes include the facilitation of neuronal firing, altered patterns of neurotransmitter release, second messenger formation, and, in intact organisms, evidence that learning occurred. The phenomenon of increased excitability and altered chemical state on repeated synaptic stimulation is known as **long-term potentiation**, a persistence beyond the cessation of electrical stimulation, as is expected of learning and memory. An early event in long-term potentiation is a series of protein phosphorylations induced by receptor-activated second messengers and leading to activation of a host of intracellular proteins and altered excitability. In addition to biochemical changes in synaptic efficacy associated with learning at the cellular level, structural alterations occur. The number of connections between sets of neurons increases as a result of experience.

Much of our knowledge about human memory formation and retrieval is based on studies of patients in whom stroke, brain injury, or surgery resulted in memory disorders. Such knowledge is then examined in more rigorous experiments in nonhuman primates capable of cognitive functions. From these combined approaches, we know that the prefrontal cortex is essential for coordinating the formation of memory, starting from a learning experience in the cerebral cortex, then processing the information and communicating it to the subcortical limbic structures. The prefrontal cortex receives sensory input from the parietal, occipital, and temporal lobes and emotional input from the limbic system. Drawing on skills such as language and mathematical ability, the prefrontal cortex integrates these inputs in light of previously acquired learning. The prefrontal cortex can thus be considered the site of **working memory**, where new experiences are processed, as opposed to sites that consolidate the memory and store it. The processed information is then transmitted to the hippocampus, where it is consolidated over several hours into a more permanent form that is stored in, and can be retrieved from, the association cortices.

Declarative and Procedural Memory. A remarkable finding from studies of surgical patients who had bilateral resections of the medial temporal lobe is that there are two fundamentally different memory systems in the brain. **Declarative memory** refers to memory of events and facts and the ability to consciously access them. Patients with bilateral medial temporal lobectomies lose their ability to form any new declarative memories. However, they retain their ability to learn and remember new skills and procedures. This type of memory is called **procedural memory** and involves several different regions of the brain, depending on the type of procedure. In contrast to declarative memory, structures in the medial temporal lobe are not involved in procedural memory. Learning and remembering new motor skills and habits requires the striatum, motor areas of the cortex, and the cerebellum. Emotional associations require the amygdala. Conditioned reflexes require the cerebellum.

An early demonstration of the dichotomy between declarative and procedural memory came from studies by Dr. Brenda Milner on a patient of Dr. Wilder Penfield in the mid-1950s. This patient (H.M.) had received a bilateral medial temporal lobectomy to treat severe epilepsy and, since that time, has been unable to form any new declarative memories. This deficit is called **anterograde amnesia**. Dr. Milner was quite surprised to learn that H.M. could learn a relatively difficult mirror-drawing task, in which (like anyone else) he got better with repeated trials and retained the skill over time. However, he could not remember ever having done the task before.

Short-Term Memory. Declarative memory can be divided into that which can be recalled for only a brief period (seconds to minutes), and that which can be recalled for weeks to years. Newly acquired learning experiences can be readily recalled for only a few minutes or more using **short-term memory**. An example of short-term memory is looking up a telephone number, repeating it mentally until you finish dialing the number, then promptly forgetting it as you focus your attention on starting the conversation. Short-term memory is a product of working memory; the decision to process information further for permanent storage is based on judgment as to its importance or on whether it is associated with a significant event or emotional state. An active process involving the hippocampus must be employed to make a memory more permanent.

Long-Term Memory. The conversion of short-term to **long-term memory** is facilitated by repetition, by adding more than one sensory modality to learn the new experience (e.g., writing down a newly acquired fact at the same time one hears it spoken) and, even more effective, by tying the experience (through the limbic system) to a strong, meaningful emotional context. The role of the hippocampus in consolidating the memory is reinforced by its participation in generating the emotional state with which the new experience is associated. As determined by studying patients such as H.M., the most important regions of the medial temporal lobe for long-term declarative memory formation are the hippocampus and parahippocampal cortex.

Once a long-term memory is formed, the hippocampus is not required for subsequent retrieval of the memory. Thus, H.M. showed no evidence of a loss of memories laid down prior to surgery; this type of memory loss is known as **retrograde amnesia**. Nor was there loss of intellectual capacity, mathematical skills, or other cognitive functions. An extreme example of H.M.'s memory loss is that Dr. Milner, who worked with him for years, had to introduce herself to her patient every time they met, even though he could readily remember people and events that had occurred before his surgery.

Cholinergic Innervation. The primacy of the hippocampus and its connections with the base of the forebrain for memory formation implicates acetylcholine as a major transmitter in cognitive function and learning and memory. The basal forebrain region contains prominent populations of cholinergic neurons that project to the hippocampus and to all regions of the cerebral cortex

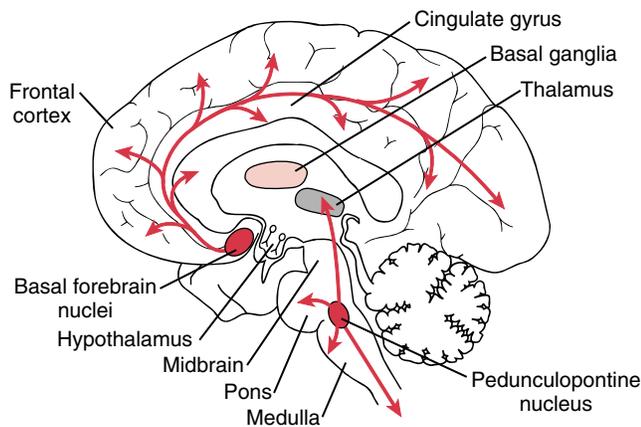


FIGURE 7.14 The origins and projections of major cholinergic neurons. Cholinergic neurons in the basal forebrain nuclei innervate all regions of the cerebral cortex. Cholinergic neurons in the brainstem's pedunculopontine nucleus provide a major input to the thalamus and also innervate the brainstem and spinal cord. Cholinergic interneurons are found in the basal ganglia. Not shown are peripherally projecting neurons, the somatic motor neurons, and autonomic preganglionic neurons, which also are cholinergic.

(Fig. 7.14). These cholinergic neurons are known generically as **basal forebrain nuclei** and include the septal nuclei, the nucleus basalis, and the nucleus accumbens. Another major cholinergic projection derives from a region of the brainstem reticular formation known as the **pedunculopontine nucleus**, which projects to the thalamus, spinal cord, and other regions of the brainstem. Roughly 90% of brainstem inputs to all nuclei of the thalamus are cholinergic.

Cortical cholinergic connections are thought to control selective attention, a function congruent with the cholinergic brainstem projections through the ascending reticular activating system. Loss of cholinergic function is associated with **dementia**, an impairment of memory, abstract thinking, and judgment (see Clinical Focus Box 7.2). Other cholinergic neurons include motor neurons and autonomic preganglionic neurons, as well as a major interneuronal pool in the striatum.

Language and Speech Are Coordinated in Specific Areas of Association Cortex

The ability to communicate by language, verbally and in writing, is one of the most difficult cognitive functions to study because only humans are capable of these skills. Thus, our knowledge of language processing in the brain has been inferred from clinical data by studying patients with **aphasias**—disturbances in producing or understanding the meaning of words—following brain injury, surgery, or other damage to the cerebral cortex.

Two areas appear to play an important role in language and speech: **Wernicke's area**, in the upper temporal lobe, and **Broca's area**, in the frontal lobe (Fig. 7.15). Both of these areas are located in association cortex, adjacent to cortical areas that are essential in language communication. **Wernicke's area** is in the parietal-temporal-occipital association cortex, a major association area for processing sensory information from the somatic sensory, visual, and auditory cortices. **Broca's area** is in the prefrontal association cortex, adjacent to the portion of the motor cortex that regulates movement of the muscles of the mouth, tongue, and throat (i.e., the structures used in the mechanical production of speech). A fiber tract, the **arcuate fasciculus**, connects Wernicke's area with Broca's area to

CLINICAL FOCUS BOX 7.2

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia in older adults. The cause of the disease still is unknown and there is no cure. In 1999, an estimated 4 million people in the United States suffered from AD. While the disease usually begins after age 65, and risk of AD goes up with age, it is important to note that AD is not a normal part of aging. The aging of the baby boom population has made AD one of the fastest growing diseases; estimates indicate that by the year 2040, some 14 million people in the United States will suffer from AD.

Cognitive deficits are the primary symptoms of AD. Early on, there is mild memory impairment; as the disease progresses, memory problems increase and difficulties with language are generally observed, including word-finding problems and decreased verbal fluency. Many patients also exhibit difficulty with visuospatial tasks. Personality changes are common, and patients become disoriented as the memory problems worsen. A progres-

sive deterioration of function follows and, at late stages, the patient is bedridden, nearly mute, unresponsive, and incontinent. A definitive diagnosis of AD is not possible until autopsy, but the constellation of symptoms and disease progression allows a reasonably certain diagnosis.

Gross pathology consistent with AD is mild to severe cortical atrophy (depending on age of onset and death). Microscopic pathology indicates two classic signs of the disease even at the earliest stages: the presence of senile plaques (SPs) and neurofibrillary tangles (NFTs). As the disease progresses, synaptic and neuronal loss or atrophy and an increase in SPs and NFTs occur.

While many neurotransmitter systems are implicated in AD, the most consistent pathology is the loss or atrophy of cholinergic neurons in the basal forebrain. Medications that ameliorate the cognitive symptoms of AD are cholinergic function enhancers. These observations emphasize the importance of cholinergic systems in cognitive function.

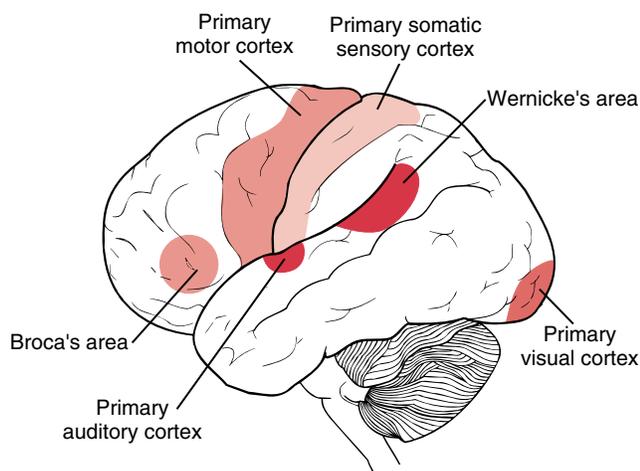


FIGURE 7.15 Wernicke's and Broca's areas and the primary motor, visual, auditory, and somatic sensory cortices.

coordinate aspects of understanding and executing speech and language skills.

Clinical evidence indicates that Wernicke's area is essential for the comprehension, recognition, and construction of words and language, whereas Broca's area is essential for the mechanical production of speech. Patients with a defect in Broca's area show evidence of comprehending a spoken or written word but they are not able to say the word. In contrast, patients with damage in Wernicke's area can produce speech, but the words they put together have little meaning.

Language is a highly lateralized function of the brain residing in the left hemisphere (see Clinical Focus Box 7.1). This dominance is observed in left-handed as well as right-handed individuals. Moreover, it is language that is lateralized, not the reception or production of speech. Thus native signers (individuals who use sign language) that have been deaf since birth still show left-hemisphere language function.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

- An EEG technician can look at an electroencephalogram and tell that the subject was awake, but relaxed with eyes closed, during generation of the recording. She can tell this because the EEG recording exhibits
 - Alpha rhythm
 - Beta rhythm
 - Theta rhythm
 - Delta rhythm
 - Variable rhythm
- A patient's wife complains that, several times during the last few weeks, her husband struck her as he flailed around violently during sleep. The husband indicates that when he wakes up during one of these sessions, he has been dreaming. What is the likely cause of his problem?
 - Increased muscle tone during stage 4 sleep
 - Increased drive to the motor cortex during REM sleep
 - Lack of behavioral inhibition by the prefrontal cortex during sleep
 - Lack of abolished muscle tone during REM sleep
 - Abnormal functioning of the amygdala during paradoxical sleep
- The hormone secreted by the pineal gland under control of the suprachiasmatic nucleus is
 - Adrenaline
 - Leptin
 - Melanocyte-stimulating hormone
 - Melatonin
 - Vasopressin
- The basal forebrain nuclei and the pedunclopontine nuclei are similar in that neurons within them
 - Are major inputs to the striatum
 - Receive innervation from the cingulate gyrus
 - Process information related to language construction
 - Utilize acetylcholine as their neurotransmitter
 - Are atrophied in patients with schizophrenia
- A scientist develops a reagent that allows identification of leptin-sensing neurons in the CNS. The reagent is a fluorescent compound that binds to the plasma membrane of cells that sense leptin. Application of this reagent to sections of the brain would result in fluorescent staining located in the
 - Arcuate nucleus of the hypothalamus
 - Mammillary nuclei of the hypothalamus
 - Paraventricular nucleus of the hypothalamus
 - Preoptic nucleus of the hypothalamus
 - Ventromedial nucleus of the thalamus
- The hypothalamus receives cues concerning the cycle of sunlight and darkness in a 24-hour day. Following removal of a tumor and concomitant destruction of surrounding tissue, a patient's hypothalamus no longer received this information. The most likely location of this tumor was in
 - The body's internal clock
 - A direct neural pathway from the optic nerve to the suprachiasmatic nucleus
 - The reticular formation
 - A projection from the occipital lobe of the cerebral cortex to the hypothalamus
 - The pineal gland
- Posterior pituitary hormone secretion is mediated by
 - A portal capillary system from the hypothalamus to the posterior pituitary
 - The fight-or-flight response
 - The hypothalamo-hypophyseal tract originating from magnocellular neurons in the supraoptic and paraventricular nuclei
 - The reticular activating system's input to the hypothalamus
 - The emotional state (i.e., mood and affect)
- Language and speech require the participation of both Wernicke's area and Broca's area. These two regions of the brain communicate with each other via a fiber bundle called
 - The thalamocortical tract
 - The reticular activating system
 - The prefrontal lobe
 - The fornix
 - The arcuate fasciculus
- A chemist is trying to produce a new neuroleptic drug. To be an effective

(continued)

- neuroleptic, the new compound must target
- (A) Acetylcholine receptors
 - (B) Dopamine receptors
 - (C) Neuropeptide Y receptors
 - (D) Norepinephrine receptors
 - (E) Serotonin receptors
10. A patient suffered a stroke that destroyed the intralaminar nuclei of the thalamus. The location of the stroke was confirmed by magnetic resonance imaging of the brain; however, an indication that the stroke affected these nuclei was provided prior to imaging by an alteration in arousal in the patient. Which of the following alterations in arousal is most likely following destruction of these nuclei?
- (A) Loss of consciousness
 - (B) Increased time spent in beta rhythm
 - (C) Increased attention to specific sensory inputs
 - (D) Alterations in paradoxical, but not slow-wave sleep
 - (E) Alteration in the period of the biological clock
11. A blindfolded subject is asked to verbally identify a common object presented to her left hand. She is not allowed to touch the object with her right hand. Which of the following structures must be intact for her to complete this task?
- (A) The primary somatic sensory cortex on the left side of her brain
 - (B) The primary visual cortex on the right side of her brain
 - (C) The fornix
 - (D) The corpus callosum
 - (E) The hippocampus
12. A viral infection causes damage to both hippocampi in a patient. This damage would cause the patient to exhibit functional deficits in
- (A) Recalling an old declarative memory
 - (B) Recalling an old procedural memory
 - (C) Forming a new short-term memory
 - (D) Forming a new long-term memory
 - (E) Forming a new procedural memory
13. An older gentleman is brought to the emergency department (ED) by his daughter. She had gone to his house for lunch, which she did on a daily basis. During her visit that day, she was alarmed because his speech did not make sense to her even though he talked a lot and the words themselves were clear. The physician in the ED informed the daughter that her father had most likely suffered a stroke that damaged
- (A) Broca's area
 - (B) The corpus callosum
 - (C) The hippocampus
 - (D) The arcuate fasciculus
 - (E) Wernicke's area
14. A woman agreed to visit her physician because her husband was very worried about her behavior. She told the doctor she felt great and that she was going to run for governor of the state because she was smarter than the current governor and people would immediately agree to her plans. Her husband said she had been sleeping very little the last several days and had spent several thousand dollars in a shopping spree the day before. This was not typical behavior and had significantly affected their ability to meet their obligations for household expenses. The physician indicated a diagnosis of mania and started her on a course of a drug that would decrease neurotransmission in
- (A) Cholinergic pathways
 - (B) Dopaminergic pathways
 - (C) Glutamatergic pathways
 - (D) Noradrenergic pathways
 - (E) Serotonergic pathways
15. Persons with mild cognitive impairments who smoke may experience a worsening of symptoms if they stop smoking. This worsening of symptoms is because nicotine acts as an agonist for receptors of a particular neurotransmitter. That neurotransmitter is
- (A) Acetylcholine
 - (B) Dopamine
 - (C) Neuropeptide Y
 - (D) Nitric oxide
 - (E) Serotonin

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CASE STUDIES FOR PART II ● ● ●

CASE STUDY FOR CHAPTER 4

Dizziness

A 35-year-old man consulted his family physician because of some recent episodes of what he described as dizziness. He was concerned that this complaint might be related to a fall from a stepladder that had occurred the previous month, although his symptoms did not begin immediately after the incident. At the time of his visit to the doctor, his symptoms are minimal, and he appears to be in good general health. He states that the feeling of dizziness, which also included sensations of nausea (without vomiting) and “ringing in the ears,” make him feel as though his surroundings were spinning around him. The episodes, which could last for several days at a time, are quite annoying and sufficiently severe to cause him concern for his safety on the job. When questioned,

he indicates that he also may not be hearing as well as he should, but at other times he does not notice any hearing problems. He further indicates that he may have had occasional dizzy spells before the ladder incident, but that they now appear to be much more frequent. The only medication he takes is aspirin for an occasional headache. He has no difficulty in following a moving finger with his head held stationary, and on the day of the visit he walks with a normal gait. He reports no light-headedness with moderate and continued exertion.

Gentle irrigation of his external ear canals with warm water (at approximately 39°C) produces a feeling of dizziness and nausea accompanied by nystagmus. The subjective sensations appeared to be the same for each ear. He is further evaluated with the Dix-Hallpike maneuver, and no sensations of vertigo are elicited during the positional maneuvers. However, when he is rapidly rotated

(continued)

in a swivel chair, he reports dizziness that was more severe than his usual symptoms. Rotation in the opposite direction produced similar symptoms. His physician advises him that there may be some appropriate specific medications for his condition, but he would first like him to try a salt-restricted diet for the next 4 weeks. He also prescribes a mild diuretic.

Upon his return visit 4 weeks later, the patient reports a gradual lessening of the frequency and duration of his spells of dizziness and accompanying symptoms.

Questions

1. What features of this case would indicate that trauma from the stepladder incident was not the precipitating cause of the symptoms?
2. What factors would tend to rule out a diagnosis of benign paroxysmal positional vertigo?
3. Would the use of water at body temperature yield the same diagnostic information as warmer or cooler water?
4. Is the patient's lack of light-headedness with moderate exercise relevant to the diagnosis of this problem?
5. Is it likely that the sensations produced by rapid rotation are mimicking those produced by his underlying disorder?
6. What is the purpose of the salt-restricted diet and diuretic therapy? Why was this tried before prescribing medication for his problem?

Answers to Case Study Questions for Chapter 4

1. Several features of this case suggest that trauma from the stepladder incident was not the precipitating cause. The caloric stimulation test and the rotation in the swivel chair indicate that his vestibular function is bilaterally symmetrical and of normal sensitivity. A defect arising from trauma would likely be localized to the injured side. His uncertainty of the timing of the onset of the symptoms indicates that the problem may have preceded the accident (and, perhaps, led to it), and the lack of immediate appearance of symptoms also tends to rule out trauma.
2. The relatively young age of the patient and the negative findings from the Dix-Hallpike test argue against positional vertigo and lend support to a tentative diagnosis of Ménière's disease, as would the presence of tinnitus and the fluctuating hearing loss. The patient's positive response to salt restriction and diuretic therapy is also indicative of this syndrome. (See answer to Question 6.)
3. The purpose of the application of water is to provide a thermal stimulus that will heat or cool the endolymph in the semicircular canals and cause convection currents that would stimulate the ampullae. Use of water at body temperature would not produce this effect, and no symptoms would be elicited. Warmer or cooler water would each produce symptoms of vertigo.
4. This observation tends to rule out cerebral ischemia as a result of circulatory (vascular) or heart problems, factors that would also be more likely in an older patient.
5. The symptoms produced by the rotation are severe because of the simultaneous involvement of both sets of vestibular apparatus and the resulting heavy neural input, which is likely to be greater than that produced by his underlying condition.
6. The use of salt restriction and diuretics would reduce the overall hydration state of his body and tend to reduce abnormal pressure within the labyrinthine system. The use of antimotion sickness drugs would interfere with the natural neural compensation that would, it is hoped, reduce the severity of the symptoms with time.

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CASE STUDY FOR CHAPTER 5

Upper Motor Neuron Lesion

A 50-year-old man comes for evaluation of persistent difficulty using his right arm and leg. The patient was well until one month previously when he had abrupt onset of weakness on the right side of his body while watching a television show. He was taken to the hospital by ambulance within one hour of onset of symptoms. The initial evaluation in the hospital emergency department shows elevated blood pressure with values of 200 mm Hg systolic and 150 mm Hg diastolic. The right arm and leg are severely weak. Activity of the myotatic reflexes on the right side is very reduced in comparison with the left side, where they are normal. Right side limb movements are slightly improved by 12 hours after onset, but are still moderately impaired on the fourth hospital day.

A magnetic resonance imaging study (MRI) of the brain performed on the second day of hospitalization shows a stroke involving the left cerebral hemisphere in the region of the internal capsule. The blood pressure remains elevated, and medication to lower it is begun during the hospital stay. The patient is transferred to a rehabilitation hospital on the fourth day for extensive physical therapy to assist further recovery of neurological function.

At follow-up examination one month after onset of the stroke, the blood pressure remains normal on the medication that was started in the hospital. Neurological examination demonstrates mild weakness of the right arm and leg. There is still a slight but obvious delay between asking the patient to move those limbs and the movement actually beginning. Passive movement of the right arm and leg by the physician provokes involuntary contraction of the muscles in those limbs that seem to counteract the attempted movement. Right side myotatic reflexes are very hyperactive compared with those obtained on the left. When the skin over the lateral plantar area of the right foot is stroked, the first toe extends involuntarily. When this maneuver is performed on the left, the toes flex.

Questions

1. Explain the neurophysiology of the muscular weakness, slowness of movement initiation, increased muscle resistance to passive movement, and overactive myotatic reflexes on the right side one month after stroke onset.
2. Explain why the toes extend on the right side and flex on the left in response to plantar stimulation.

Answers to Case Study Questions for Chapter 5

1. The motor pathways that descend to the spinal cord from higher CNS levels initiate voluntary muscle action and also regulate the sensitivity of the muscle stretch (myotatic) reflex. Impairment of corticospinal tract input to the alpha motor neuron pools results in weakness and slowness of initiation of voluntary movement. The corticospinal tract deficit also produces an increased sensitivity of the spinal reflex pathways, resulting in overly vigorous muscle stretch reflexes. Muscle tone, the normal slight resistance to passive movement that is detectable in a relaxed muscle, becomes greatly increased and demonstrates a pattern that is called **spasticity**. Spastic tone is most evident in the flexor muscles of the arm and the extensor muscles of the leg.
2. The extensor movement of the first toe in response to stroking the plantar aspect of the foot, termed **Babinski sign**, is thought to occur because of modification of flexor withdrawal reflexes secondary to the impaired input of the

corticospinal tract. The normal response is for the toes to flex when the plantar surface is stimulated.

The neurophysiological details of how the deficit in corticospinal input actually produces these commonly encountered abnormalities in muscle tone and reflex patterns are still not well understood. A current theory is that the disturbance of central control reduces the threshold of the stretch reflex but does not alter its gain.

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CASE STUDY FOR CHAPTER 6

Autonomic Dysfunction as a Result of CNS Disease

A 30-year-old patient came to the hospital emergency department because of a terrible headache that began several hours ago and did not improve. Previously he had experienced only mild, infrequent tension headaches associated with stressful days. Because of the intensity of this new headache, he is treated with injectable analgesics and is admitted to the hospital for further observation.

During the next several hours, the patient's level of consciousness declines to the point of responding only to painful stimuli. An emergency computed tomography (CT) scan of the brain demonstrates the presence of blood diffusely in the subarachnoid space. The source of the blood is thought to be a ruptured cerebral artery aneurysm.

During the next 24 hours, the patient's ECG begins to show abnormalities consisting of both tachycardia and changes in the configuration of the waves suggestive of a heart attack. The patient has no risk factors for premature cardiac disease. A cardiology consultation is requested.

Questions

1. What is the explanation for the cardiac abnormalities in this situation?
2. Describe two other scenarios in which there are prominent manifestations of autonomic activation produced by abnormalities in the central nervous system.

Answers to Case Study Questions for Chapter 6

1. The consulting cardiologist reviewed the situation and stated that the ECG abnormalities were all a result of subarachnoid blood and that an adrenergic antagonist medication should be administered.

Blood released into the subarachnoid space by rupture of blood vessels or direct trauma to the brain can stimulate excessive activity of the sympathetic nervous system. Although a full explanation is still lacking, it is postulated that the subarachnoid blood irritates the hypothalamus and autonomic regulatory areas in the medulla, resulting in excessive activation of the sympathetic pathways. This activation causes the secretion of norepinephrine from sympathetic nerve endings and epinephrine by the adrenal medulla. Direct stimulation of the sympathetic pathways that supply the heart can produce the same ECG abnormalities in experimental animals as were found in this patient. The heightened release of norepinephrine and epinephrine stimulates the cardiac conducting system and may also produce direct damage of the myocardium. Treatment with medications that attenuate the effects of sympathetic neurotransmitters can be lifesaving.

2. The Cushing response (described by famous neurosurgeon Harvey Cushing) consists of the development of hypertension, bradycardia, and apnea in patients with increased intracranial pressure most often a result of tumors or other lesions, such as hemorrhage, that compress the brain. The pressure is transmitted downward to the brainstem and distorts the medulla, where the centers for blood pressure, heart rate, and respiratory drive originate. Correct interpretation of these abnormalities in vital signs permits beginning treatments that reduce intracranial pressure. These include elevating the head of the bed, placing the patient on an artificial respirator, and then instituting hyperventilation to lower the blood P_{CO_2} to produce cerebral vasoconstriction and giving mannitol to reduce the fluid content of the brain temporarily.

Another autonomic reaction from the CNS that is utilized daily in hospitals is the response of fetal heart rate to compression of the head during labor. During uterine contractions, the fetal head is temporarily compressed. As the fetal skull is still malleable because the bones of the cranium are not yet fused, the pressure of the contraction is transmitted to the brain. The same mechanism of cardiac slowing as cited for the Cushing response is presumed to cause the temporary bradycardia. Slowing of greater than established normal limits indicates the fetus is suffering significant physiological distress. Additional factors, such as umbilical cord compression, may also produce patterns of slowing outside of the normal range.

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CASE STUDY FOR CHAPTER 7

Stroke

A 67-year-old man was taken to see his physician by his wife. For the preceding 2 days, the patient's wife had noticed that he did not seem to make sense when he spoke. She also indicated that he seemed a little disoriented and did not respond appropriately to her questions. He has no obvious motor or somatic sensory deficits.

On examination, the physician concludes that the man had a stroke in a region of one of his cerebral hemispheres. As part of the diagnosis, the physician tests the man's visual fields and notices a decreased awareness of stimuli presented to one visual field.

Questions

1. Which side of the brain most likely suffered the stroke?
2. Which regions of the hemisphere suffered the stroke?
3. What information from the case history gives the answers to questions 1 and 2?
4. Which visual field is affected by the stroke?

Answers to Case Study Questions for Chapter 7

1. The stroke occurred on the left side of the brain.
2. The stroke involved the superior posterior temporal lobe encompassing Wernicke's area and the occipital lobe encompassing the primary visual cortex.
3. Language deficits indicate involvement of the left hemisphere. The fluent but nonsensical speech indicates involvement of Wernicke's area. The visual field deficit indicates a loss in the visual cortex. The lack of motor or somatic sensory deficits excludes the posterior frontal and anterior parietal lobes.
4. The right visual field would be affected, because visual fields are represented in the contralateral hemispheres.