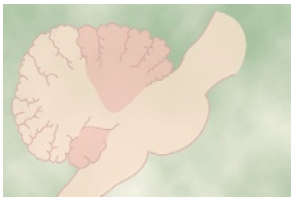
Contributions of the Cerebellum and Basal Ganglia to Overall Motor Control



Aside from the areas in the cerebral cortex that stimulate muscle contraction, two other brain structures are also essential for normal motor function. They are the *cerebellum* and the *basal ganglia*. Yet neither of these two can control muscle function by themselves. Instead, *they always function in association with other systems of motor control.*

The cerebellum plays major roles in the timing of motor activities and in rapid, smooth progression from one muscle movement to the next. It also helps to control the intensity of muscle contraction when the muscle load changes and controls the necessary instantaneous interplay between agonist and antagonist muscle groups.

The basal ganglia help to plan and control complex patterns of muscle movement, controlling relative intensities of the separate movements, directions of movements, and sequencing of multiple successive and parallel movements for achieving specific complicated motor goals. This chapter explains the basic functions of the cerebellum and basal ganglia and discusses the overall brain mechanisms for achieving intricate coordination of total motor activity.

Cerebellum and Its Motor Functions

The cerebellum, illustrated in Figures 56-1 and 56-2, has long been called a *silent area* of the brain, principally because electrical excitation of the cerebellum does not cause any conscious sensation and rarely causes any motor movement. Removal of the cerebellum, however, causes body movements to become highly abnormal. The cerebellum is especially vital during rapid muscular activities such as running, typing, playing the piano, and even talking. Loss of this area of the brain can cause almost total incoordination of these activities even though its loss causes paralysis of no muscles.

But how is it that the cerebellum can be so important when it has no direct ability to cause muscle contraction? The answer is that it helps to *sequence the motor activities* and also *monitors and makes corrective adjustments in the body's motor activities while they are being executed so that they will conform to the motor signals directed by the cerebral motor cortex and other parts of the brain.*

The cerebellum receives continuously updated information about the desired sequence of muscle contractions from the brain motor control areas; it also receives continuous sensory information from the peripheral parts of the body, giving sequential changes in the status of each part of the body—its position, rate of movement, forces acting on it, and so forth. The cerebellum then *compares* the actual movements as depicted by the peripheral sensory feedback information with the movements intended by the motor system. If the two do not compare favorably, then instantaneous subconscious corrective signals are transmitted back into the motor system to increase or decrease the levels of activation of specific muscles.

The cerebellum also aids the cerebral cortex in planning the next sequential movement a fraction of a second in advance while the current movement is still being executed, thus helping the person to progress smoothly from one movement to the next. Also, it learns by its mistakes—that is, if a movement does not occur exactly as intended, the cerebellar circuit learns to make a stronger or weaker movement the next time. To do this, *changes occur in the excitability of appropriate cerebellar neurons, thus bringing subsequent muscle contractions into better correspondence with the intended movements.*

Anatomical Functional Areas of the Cerebellum

Anatomically, the cerebellum is divided into three lobes by two deep fissures, as shown in Figures 56-1 and 56-2: (1) the *anterior lobe,* (2) the *posterior lobe,* and (3) the *flocculonodular lobe.* The flocculonodular lobe is the oldest of all portions of the cerebellum; it developed along with (and functions with) the vestibular system in controlling body equilibrium, as discussed in Chapter 55.

Longitudinal Functional Divisions of the Anterior and Posterior Lobes. From a functional point of view, the anterior and posterior lobes are organized not by lobes but along

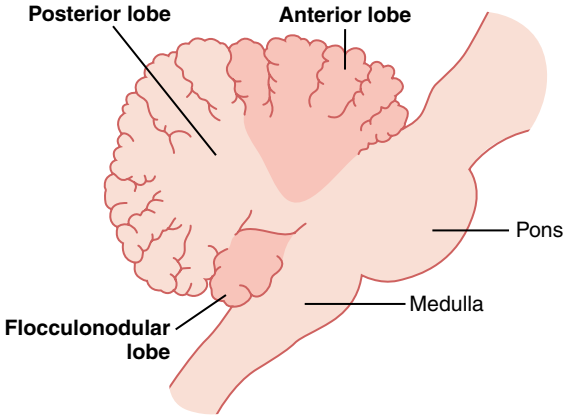


Figure 56-1 Anatomical lobes of the cerebellum as seen from the lateral side.

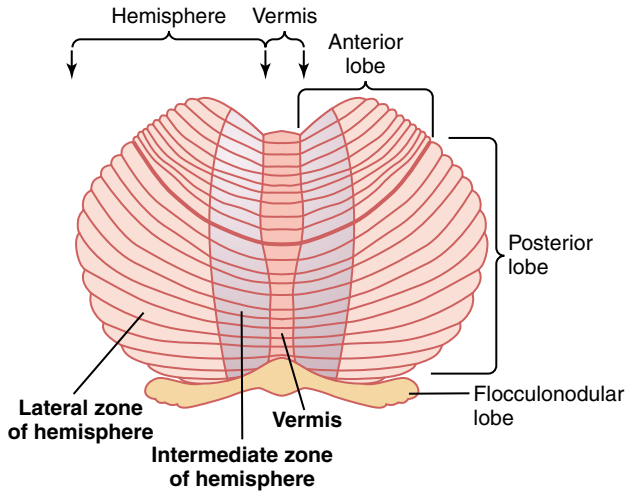


Figure 56-2 Functional parts of the cerebellum as seen from the posteroinferior view, with the inferiormost portion of the cerebellum rolled outward to flatten the surface.

the longitudinal axis, as demonstrated in Figure 56-2, which shows a posterior view of the human cerebellum after the lower end of the posterior cerebellum has been rolled downward from its normally hidden position. Note down the center of the cerebellum a narrow band called the *vermis,* separated from the remainder of the cerebellum by shallow grooves. In this area, most cerebellar control functions for muscle movements of the *axial body, neck, shoulders, and hips* are located.

To each side of the vermis is a large, laterally protruding *cerebellar hemisphere,* and each of these hemispheres is divided into an *intermediate zone* and a *lateral zone.*

The intermediate zone of the hemisphere is concerned with controlling muscle contractions in the distal portions of the upper and lower limbs, especially the hands and fingers and feet and toes.

The lateral zone of the hemisphere operates at a much more remote level because this area joins with the cerebral cortex in the overall planning of sequential motor movements. Without this lateral zone, most discrete motor activities of the body lose their appropriate timing and sequencing and therefore become incoordinate, as we discuss more fully later.

Topographical Representation of the Body in the Vermis and Intermediate Zones. In the same manner that the cerebral sensory cortex, motor cortex, basal ganglia, red nuclei, and reticular formation all have topographical representations of the different parts of the body, so also is this true for the vermis and intermediate zones of the cerebellum. Figure 56-3 shows two such representations. Note that the axial portions of the body lie in the vermis part of the cerebellum, whereas the limbs and facial regions lie in the intermediate zones. These topographical representations receive afferent nerve signals from all the respective parts of the body, as well as from corresponding topographical motor areas in the cerebral cortex and brain stem. In turn, they send motor signals back to the same respective topographical areas of the cerebral motor cortex, as well as to topographical areas of the red nucleus and reticular formation in the brain stem.

Note that the large lateral portions of the cerebellar hemispheres *do not* have topographical representations of the body. These areas of the cerebellum receive their input signals almost exclusively from the cerebral cortex, especially from the premotor areas of the frontal cortex and from the somatosensory and other sensory association areas of the parietal cortex. It is believed that this connectivity with the cerebral cortex allows the lateral portions of the cerebellar hemispheres to play important roles in planning and coordinating the body's *rapid* sequential muscular activities that occur one after another within fractions of a second.

Neuronal Circuit of the Cerebellum

The human cerebellar cortex is actually a large folded sheet, about 17 centimeters wide by 120 centimeters long, with the folds lying crosswise, as shown in Figures 56-2 and 56-3. Each fold is called a *folium.* Lying deep beneath the folded mass of cerebellar cortex are *deep cerebellar nuclei.*

Input Pathways to the Cerebellum

Afferent Pathways from Other Parts of the Brain. The basic input pathways to the cerebellum are shown in Figure 56-4. An extensive and important afferent pathway is the *corticopontocerebellar pathway,* which originates in the *cerebral motor* and *premotor cortices* and also in the *cerebral somatosensory cortex.* It passes by way of the *pontile nuclei* and *pontocerebellar tracts* mainly to the lateral divisions of the cerebellar hemispheres on the opposite side of the brain from the cerebral areas.

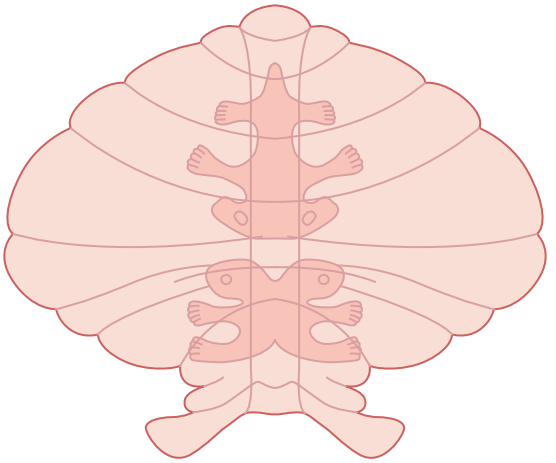


Figure 56-3 Somatosensory projection areas in the cerebellar cortex.

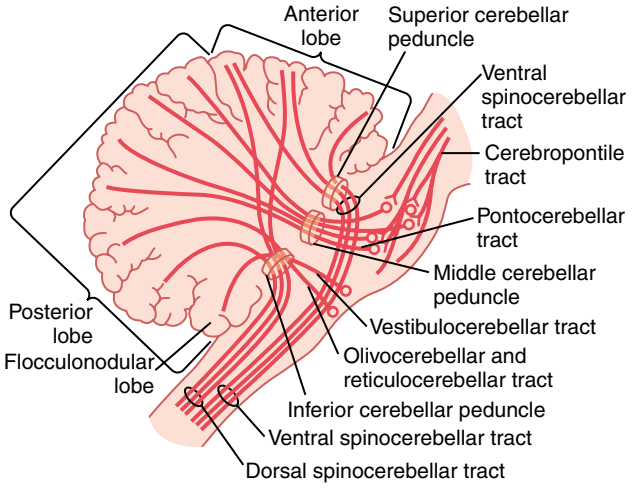


Figure 56-4 Principal *afferent* tracts to the cerebellum.

In addition, important afferent tracts originate in each side of the brain stem; they include (1) an extensive *olivocerebellar tract,* which passes from the *inferior olive* to all parts of the cerebellum and is excited in the olive by fibers from the *cerebral motor cortex, basal ganglia,* widespread areas of the *reticular formation,* and *spinal cord;* (2) *vestibulocerebellar fibers,* some of which originate in the vestibular apparatus itself and others from the brain stem vestibular nuclei—almost all of these terminate in the *flocculonodular lobe* and *fastigial nucleus* of the cerebellum; and (3) *reticulocerebellar fibers*, which originate in different portions of the brain stem reticular formation and terminate in the midline cerebellar areas (mainly in the vermis).

Afferent Pathways from the Periphery. The cerebellum also receives important sensory signals directly from the peripheral parts of the body mainly through four tracts on each side, two of which are located dorsally in the cord and two ventrally. The two most important of these tracts are shown in Figure 56-5: the *dorsal spinocerebellar tract* and the *ventral spinocerebellar tract.* The dorsal tract enters the cerebellum through the inferior cerebellar peduncle and terminates in the vermis and intermediate zones of the cerebellum on the same side as its origin. The ventral tract enters the cerebellum through the superior cerebellar peduncle, but it terminates in both sides of the cerebellum.

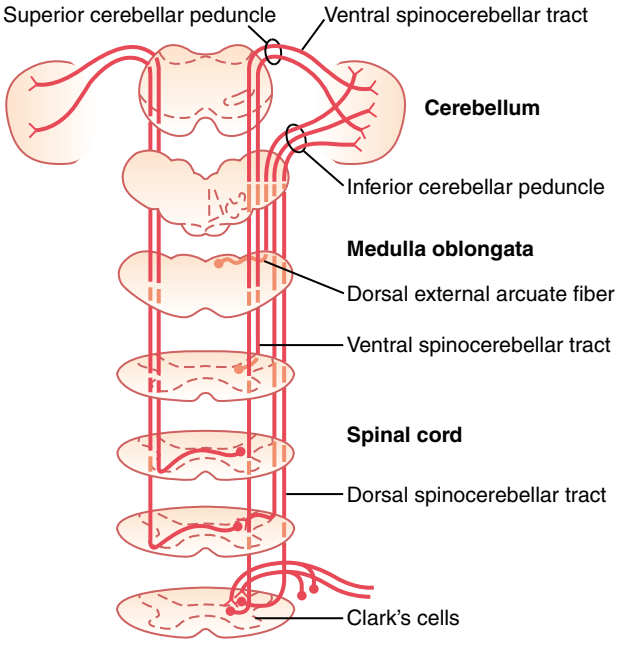


Figure 56-5 Spinocerebellar tracts.

The signals transmitted in the dorsal spinocerebellar tracts come mainly from the muscle spindles and to a lesser extent from other somatic receptors throughout the body, such as Golgi tendon organs, large tactile receptors of the skin, and joint receptors. All these signals apprise the cerebellum of the momentary status of (1) muscle contraction, (2) degree of tension on the muscle tendons, (3) positions and rates of movement of the parts of the body, and (4) forces acting on the surfaces of the body.

The ventral spinocerebellar tracts receive much less information from the peripheral receptors. Instead, they are excited mainly by motor signals arriving in the anterior horns of the spinal cord from (1) the brain through the corticospinal and rubrospinal tracts and (2) the internal motor pattern generators in the cord itself. Thus, this ventral fiber pathway tells the cerebellum which motor signals have arrived at the anterior horns; this feedback is called the *efference copy* of the anterior horn motor drive.

The spinocerebellar pathways can transmit impulses at velocities up to 120 m/sec, which is the most rapid conduction in any pathway in the central nervous system. This extremely rapid conduction is important for instantaneous apprisal of the cerebellum of changes in peripheral muscle actions.

In addition to signals from the spinocerebellar tracts, signals are transmitted into the cerebellum from the body periphery through the spinal dorsal columns to the dorsal column nuclei of the medulla and then relayed to the cerebellum. Likewise, signals are transmitted up the spinal cord through the *spinoreticular pathway* to the reticular formation of the brain stem and also through the *spino-olivary pathway* to the inferior olivary nucleus. Then signals are relayed from both of these areas to the cerebellum. Thus, the cerebellum continually collects information about the movements and positions of all parts of the body even though it is operating at a subconscious level.

Output Signals from the Cerebellum

Deep Cerebellar Nuclei and the Efferent Pathways. Located deep in the cerebellar mass on each side are three *deep cerebellar nuclei*—the *dentate, interposed,* and *fastigial.* (The *vestibular nuclei* in the medulla also function in some respects as if they were deep cerebellar nuclei because of their direct connections with the cortex of the flocculonodular lobe.) All the deep cerebellar nuclei receive signals from two sources: (1) the cerebellar cortex and (2) the deep sensory afferent tracts to the cerebellum.

Each time an input signal arrives in the cerebellum, it divides and goes in two directions: (1) directly to one of the cerebellar deep nuclei and (2) to a corresponding area of the cerebellar cortex overlying the deep nucleus. Then, a fraction of a second later, the cerebellar cortex relays an *inhibitory* output signal to the deep nucleus. Thus, all input signals that enter the cerebellum eventually end in the deep nuclei in the form of initial excitatory signals followed a fraction of a second later by inhibitory signals. From the deep nuclei, output signals leave the cerebellum and are distributed to other parts of the brain.

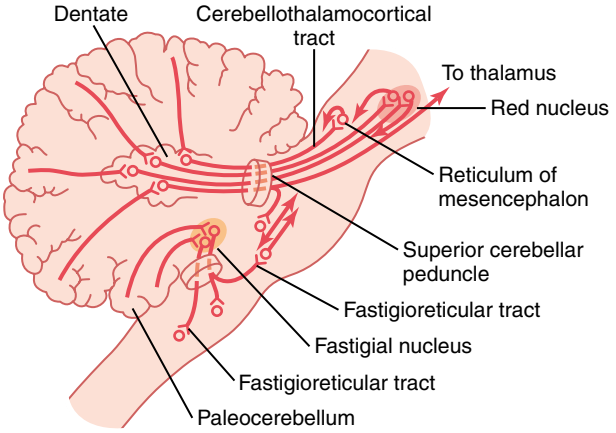


Figure 56-6 Principal *efferent* tracts from the cerebellum.

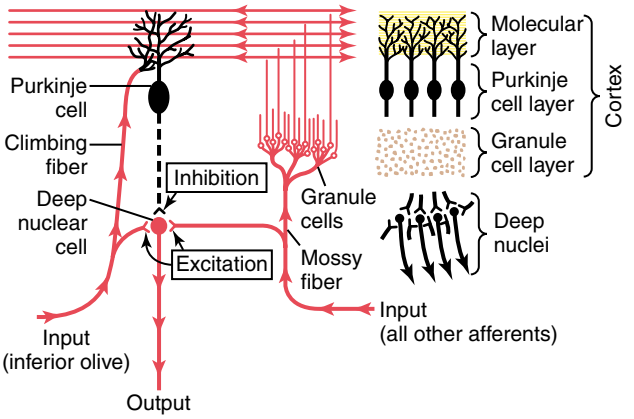


Figure 56-7 The left side of this figure shows the basic neuronal circuit of the cerebellum, with excitatory neurons shown in *red* and the Purkinje cell (an inhibitory neuron) shown in *black*. To the right is shown the physical relationship of the deep cerebellar nuclei to the cerebellar cortex with its three layers.

The general plan of the major efferent pathways leading out of the cerebellum is shown in Figure 56-6 and consists of the following:

1. A pathway that originates in the *midline structures of the cerebellum* (the *vermis*) and then passes through the *fastigial nuclei* into the *medullary* and *pontile regions of the brain stem.* This circuit functions in close association with the equilibrium apparatus and brain stem vestibular nuclei to control equilibrium, as well as in association with the reticular formation of the brain stem to control the postural attitudes of the body. It was discussed in detail in Chapter 55 in relation to equilibrium.
2. A pathway that originates in (1) the intermediate zone of the cerebellar hemisphere and then passes through (2) the interposed nucleus to (3) the ventrolateral and ventroanterior nuclei of the thalamus and then to (4) the cerebral cortex, to (5) several midline structures of the thalamus and then to (6) the basal ganglia and (7) the red nucleus and reticular formation of the upper portion of the brain stem. This complex circuit helps to coordinate mainly the reciprocal contractions of agonist and antagonist muscles in the peripheral portions of the limbs, especially in the hands, fingers, and thumbs.
3. A pathway that begins in the cerebellar cortex of the lateral zone of the cerebellar hemisphere and then passes to the dentate nucleus, next to the ventrolateral and ventroanterior nuclei of the thalamus, and, finally, to the cerebral cortex. This pathway plays an important role in helping coordinate sequential motor activities initiated by the cerebral cortex.

Functional Unit of the Cerebellar Cortex—the Purkinje Cell and the Deep Nuclear Cell

The cerebellum has about 30 million nearly identical functional units, one of which is shown to the left in Figure 56-7. This functional unit centers on a single, very large *Purkinje cell* and on a corresponding *deep nuclear cell.*

To the top and right in Figure 56-7, the three major layers of the cerebellar cortex are shown: the *molecular layer, Purkinje cell layer,* and *granule cell layer.* Beneath these cortical layers, in the center of the cerebellar mass, are the deep cerebellar nuclei that send output signals to other parts of the nervous system.

Neuronal Circuit of the Functional Unit. Also shown in the left half of Figure 56-7 is the neuronal circuit of the functional unit, which is repeated with little variation 30 million times in the cerebellum. The output from the functional unit is from a *deep nuclear cell.* This cell is continually under both excitatory and inhibitory influences. The excitatory influences arise from direct connections with afferent fibers that enter the cerebellum from the brain or the periphery. The inhibitory influence arises entirely from the Purkinje cell in the cortex of the cerebellum.

The afferent inputs to the cerebellum are mainly of two types, one called the *climbing fiber type* and the other called the *mossy fiber type.*

The climbing fibers *all originate from the inferior olives of the medulla.* There is one climbing fiber for about 5 to 10 Purkinje cells. After sending branches to several deep nuclear cells, the climbing fiber continues all the way to the outer layers of the cerebellar cortex, where it makes about 300 synapses with the soma and dendrites of each Purkinje cell. This climbing fiber is distinguished by the fact that a single impulse in it will always cause a single, prolonged (up to 1 second), peculiar type of action potential in each Purkinje cell with which it connects, beginning with a strong spike and followed by a trail of weakening secondary spikes. This action potential is called the *complex spike.*

The mossy fibers are all the other fibers that enter the cerebellum from multiple sources: from the higher brain, brain stem, and spinal cord. These fibers also send collaterals to excite the deep nuclear cells. Then they proceed to the granule cell layer of the cortex, where they, too, synapse with hundreds to thousands of *granule cells.* In turn, the granule cells send extremely small axons, less than 1 micrometer in diameter, up to the molecular layer on the outer surface of the cerebellar cortex. Here the axons divide into two branches that extend 1 to 2 millimeters in each direction parallel to the folia. There are many millions of these *parallel nerve fibers* because there are some 500 to 1000 granule cells for every 1 Purkinje cell. It is into

this molecular layer that the dendrites of the Purkinje cells project and 80,000 to 200,000 of the parallel fibers synapse with each Purkinje cell.

The mossy fiber input to the Purkinje cell is quite different from the climbing fiber input because the synaptic connections are weak, so large numbers of mossy fibers must be stimulated simultaneously to excite the Purkinje cell. Furthermore, activation usually takes the form of a much weaker short-duration Purkinje cell action potential called a *simple spike,* rather than the prolonged complex action potential caused by climbing fiber input.

Purkinje Cells and Deep Nuclear Cells Fire Continuously Under Normal Resting Conditions. One characteristic of both Purkinje cells and deep nuclear cells is that normally both of them fire continuously; the Purkinje cell fires at about 50 to 100 action potentials per second, and the deep nuclear cells at much higher rates. Furthermore, the output activity of both these cells can be modulated upward or downward.

Balance Between Excitation and Inhibition at the Deep Cerebellar Nuclei. Referring again to the circuit of Figure 56-7, note that direct stimulation of the deep nuclear cells by both the climbing and the mossy fibers excites them. By contrast, signals arriving from the Purkinje cells inhibit them. Normally, the balance between these two effects is slightly in favor of excitation so that under quiet conditions, output from the deep nuclear cell remains relatively constant at a moderate level of continuous stimulation.

In execution of a rapid motor movement, the initiating signal from the cerebral motor cortex or brain stem at first greatly increases deep nuclear cell excitation. Then, another few milliseconds later, feedback inhibitory signals from the Purkinje cell circuit arrive. In this way, there is first a rapid excitatory signal sent by the deep nuclear cells into the motor output pathway to enhance the motor movement, but this is followed within another small fraction of a second by an inhibitory signal. This inhibitory signal resembles a "delay-line" negative feedback signal of the type that is effective in providing *damping.* That is, when the motor system is excited, a negative feedback signal occurs after a short delay to stop the muscle movement from overshooting its mark. Otherwise, oscillation of the movement would occur.

Other Inhibitory Cells in the Cerebellum. In addition to the deep nuclear cells, granule cells, and Purkinje cells, two other types of neurons are located in the cerebellum: *basket cells* and *stellate cells.* These are inhibitory cells with short axons. Both the basket cells and the stellate cells are located in the molecular layer of the cerebellar cortex, lying among and stimulated by the small parallel fibers. These cells in turn send their axons at right angles across the parallel fibers and cause *lateral inhibition* of adjacent Purkinje cells, thus sharpening the signal in the same manner that lateral inhibition sharpens contrast of signals in many other neuronal circuits of the nervous system.

Turn-On/Turn-Off and Turn-Off/Turn-On Output Signals from the Cerebellum

The typical function of the cerebellum is to help provide rapid turn-on signals for the agonist muscles and simultaneous reciprocal turn-off signals for the antagonist muscles at the onset of a movement. Then on approaching termination of the movement, the cerebellum is mainly responsible for timing and executing the turn-off signals to the agonists and turn-on signals to the antagonists. Although the exact details are not fully known, one can speculate from the basic cerebellar circuit of Figure 56-7 how this might work, as follows.

Let us suppose that the turn-on/turn-off pattern of agonist/antagonist contraction at the onset of movement begins with signals from the cerebral cortex. These signals pass through noncerebellar brain stem and cord pathways directly to the agonist muscle to begin the initial contraction.

At the same time, parallel signals are sent by way of the pontile mossy fibers into the cerebellum. One branch of each mossy fiber goes directly to deep nuclear cells in the dentate or other deep cerebellar nuclei; this instantly sends an excitatory signal back into the cerebral corticospinal motor system, either by way of return signals through the thalamus to the cerebral cortex or by way of neuronal circuitry in the brain stem, to support the muscle contraction signal that had already been begun by the cerebral cortex. As a consequence, the turn-on signal, after a few milliseconds, becomes even more powerful than it was at the start because it becomes the sum of both the cortical and the cerebellar signals. This is the normal effect when the cerebellum is intact, but in the absence of the cerebellum, the secondary extra supportive signal is missing. This cerebellar support makes the turn-on muscle contraction much stronger than it would be if the cerebellum did not exist.

Now, what causes the turn-off signal for the agonist muscles at the termination of the movement? Remember that all mossy fibers have a second branch that transmits signals by way of the granule cells to the cerebellar cortex and eventually, by way of "parallel" fibers, to the Purkinje cells. The Purkinje cells in turn *inhibit* the deep nuclear cells. This pathway passes through some of the smallest, slowest-conducting nerve fibers in the nervous system: that is, the parallel fibers of the cerebellar cortical molecular layer, which have diameters of only a fraction of a millimeter. Also, the signals from these fibers are weak, so they require a finite period of time to build up enough excitation in the dendrites of the Purkinje cell to excite it. But once the Purkinje cell is excited, it in turn sends a strong *inhibitory signal* to the same deep nuclear cell that had originally turned on the movement. Therefore, this helps *to turn off* the movement after a short time.

Thus, one can see how the complete cerebellar circuit could cause a rapid turn-on agonist muscle contraction at the beginning of a movement and yet cause also a *precisely timed* turn-off of the same agonist contraction after a given time period.

Now let us speculate on the circuit for the antagonist muscles. Most important, remember that throughout the spinal cord there are reciprocal agonist/antagonist circuits for virtually every movement that the cord can initiate. Therefore, these circuits are part of the basis for antagonist turn-off at the onset of movement and then turn-on at termination of movement, mirroring whatever occurs in the agonist muscles. But we must remember, too, that the cerebellum contains several other types of inhibitory cells besides Purkinje cells. The functions of some of these are still to be determined; they, too, could play roles in the initial inhibition of the antagonist muscles at onset of a movement and subsequent excitation at the end of a movement.

All these mechanisms are still partly speculation. They are presented here especially to illustrate ways by which the cerebellum could cause exaggerated turn-on and turn-off signals, controlling the agonist and antagonist muscles, as well as the timing.

The Purkinje Cells "Learn" to Correct Motor Errors—Role of the Climbing Fibers

The degree to which the cerebellum supports onset and offset of muscle contractions, as well as timing of contractions, must be learned by the cerebellum. Typically, when a person first performs a new motor act, the degree of motor enhancement by the cerebellum at the onset of contraction, the degree or inhibition at the end of contraction, and the timing of these are almost always incorrect for precise performance of the movement. But after the act has been performed many times, the individual events become progressively more precise, sometimes requiring only a few movements before the desired result is achieved, but at other times requiring hundreds of movements.

How do these adjustments come about? The exact answer is not known, although it is known that sensitivity levels of cerebellar circuits themselves progressively adapt during the training process, especially the sensitivity of the Purkinje cells to respond to the granule cell excitation. Furthermore, this sensitivity change is brought about by signals from the climbing fibers entering the cerebellum from the inferior olivary complex.

Under resting conditions, the climbing fibers fire about once per second. But they cause extreme depolarization of the entire dendritic tree of the Purkinje cell, lasting for up to a second, each time they fire. During this time, the Purkinje cell fires with one initial strong output spike followed by a series of diminishing spikes. When a person performs a new movement for the first time, feedback signals from the muscle and joint proprioceptors will usually denote to the cerebellum how much the actual movement fails to match the intended movement. And the climbing fiber signals in some way alter long-term sensitivity of the Purkinje cells. Over a period of time, this change in sensitivity, along with other possible "learning" functions of the cerebellum, is believed to make the timing and other aspects of cerebellar control of movements approach perfection. When this has been achieved, the climbing fibers no longer need to send "error" signals to the cerebellum to cause further change.

Function of the Cerebellum in Overall Motor Control

The nervous system uses the cerebellum to coordinate motor control functions at three levels, as follows:

1. The *vestibulocerebellum*. This consists principally of the small flocculonodular cerebellar lobes that lie under the posterior cerebellum and adjacent portions of the vermis. It provides neural circuits for most of the body's equilibrium movements.
2. The *spinocerebellum*. This consists of most of the vermis of the posterior and anterior cerebellum plus the adjacent intermediate zones on both sides of the vermis. It provides the circuitry for coordinating mainly movements of the distal portions of the limbs, especially the hands and fingers.
3. The *cerebrocerebellum*. This consists of the large lateral zones of the cerebellar hemispheres, lateral to the intermediate zones. It receives virtually all its input from the cerebral motor cortex and adjacent premotor and somatosensory cortices of the cerebrum. It transmits its output information in the upward direction back to the brain, functioning in a feedback manner with the cerebral cortical sensorimotor system to plan sequential voluntary body and limb movements, planning these as much as tenths of a second in advance of the actual movements. This is called development of "motor imagery" of movements to be performed.

Vestibulocerebellum Functions in Association with the Brain Stem and Spinal Cord to Control Equilibrium and Postural Movements

The vestibulocerebellum originated phylogenetically at about the same time that the vestibular apparatus in the inner ear developed. Furthermore, as discussed in Chapter 55, loss of the flocculonodular lobes and adjacent portions of the vermis of the cerebellum, which constitute the vestibulocerebellum, causes extreme disturbance of equilibrium and postural movements.

We still must ask the question, what role does the vestibulocerebellum play in equilibrium that cannot be provided by other neuronal machinery of the brain stem? A clue is the fact that in people with vestibulocerebellar dysfunction, equilibrium is far more disturbed *during performance of rapid motions* than during stasis, especially when these movements involve *changes in direction* of movement and stimulate the semicircular ducts. This suggests that the vestibulocerebellum is important in controlling balance between agonist and antagonist muscle contractions of the spine, hips, and shoulders during *rapid changes* in body positions as required by the vestibular apparatus.

One of the major problems in controlling balance is the amount of time required to transmit position signals and velocity of movement signals from the different parts of the body to the brain. Even when the most rapidly conducting sensory pathways are used, up to 120 m/sec in the spinocerebellar afferent tracts, the delay for transmission from the feet to the brain is still 15 to 20 milliseconds. The feet of a person running rapidly can move as much as 10 inches during that time. Therefore, it is never possible for return signals from the peripheral parts of the body to reach the brain at the same time that the movements actually occur. How, then, is it possible for the brain to know when to stop a movement and to perform the next sequential act when the movements are performed rapidly? The answer is that the signals from the periphery tell the brain how rapidly and in which directions the body parts are moving. It is then the function of the vestibulocerebellum to *calculate in advance* from these rates and directions where the different parts will be during the next few milliseconds. The results of these calculations are the key to the brain's progression to the next sequential movement.

Thus, during control of equilibrium, it is presumed that information from both the body periphery and the vestibular apparatus is used in a typical feedback control circuit to provide *anticipatory correction* of postural motor signals necessary for maintaining equilibrium even during extremely rapid motion, including rapidly changing directions of motion.

Spinocerebellum—Feedback Control of Distal Limb Movements by Way of the Intermediate Cerebellar Cortex and the Interposed Nucleus

As shown in Figure 56-8, the intermediate zone of each cerebellar hemisphere receives two types of information when a movement is performed: (1) information from the cerebral motor cortex and from the midbrain red nucleus, telling the cerebellum the *intended sequential plan of movement* for the next few fractions of a second, and (2) feedback information from the peripheral parts of the body, especially from the distal proprioceptors of the limbs, telling the cerebellum what *actual movements* result.

After the intermediate zone of the cerebellum has compared the intended movements with the actual movements, the deep nuclear cells of the interposed nucleus send *corrective* output signals (1) back to the *cerebral motor cortex* through relay nuclei in the *thalamus* and (2) to the *magnocellular portion* (the lower portion) *of the red nucleus* that gives rise to the *rubrospinal tract.* The rubrospinal tract in turn joins the corticospinal tract in innervating the lateral most motor neurons in the anterior horns of the spinal cord gray matter, the neurons that control the distal parts of the limbs, particularly the hands and fingers.

This part of the cerebellar motor control system provides smooth, coordinate movements of the agonist and antagonist muscles of the distal limbs for performing

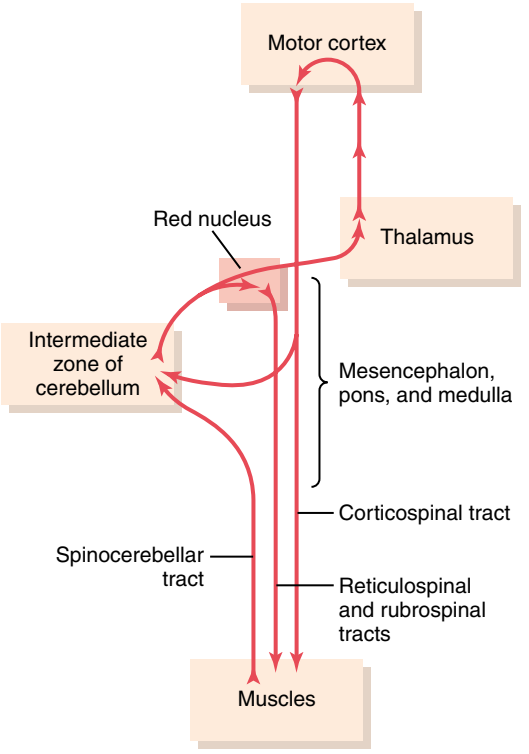


Figure 56-8 Cerebral and cerebellar control of voluntary movements, involving especially the intermediate zone of the cerebellum.

acute purposeful patterned movements. The cerebellum seems to compare the "intentions" of the higher levels of the motor control system, as transmitted to the intermediate cerebellar zone through the corticopontocerebellar tract, with the "performance" by the respective parts of the body, as transmitted back to the cerebellum from the periphery. In fact, the ventral spinocerebellar tract even transmits back to the cerebellum an "efference" copy of the actual motor control signals that reach the anterior motor neurons, and this is also integrated with the signals arriving from the muscle spindles and other proprioceptor sensory organs, transmitted principally in the dorsal spinocerebellar tract. Similar comparator signals also go to the inferior olivary complex; if the signals do not compare favorably, the olivary-Purkinje cell system along with possibly other cerebellar learning mechanisms eventually corrects the motions until they perform the desired function.

Function of the Cerebellum to Prevent Overshoot of Movements and to "Damp" Movements. Almost all movements of the body are "pendular." For instance, when an arm is moved, momentum develops, and the momentum must be overcome before the movement can be stopped. Because of momentum, all pendular movements have a tendency to *overshoot*. If overshooting does occur in a person whose cerebellum has been destroyed, the conscious centers of the cerebrum eventually recognize this and initiate a movement in the reverse direction attempting to bring the arm to its intended position. But the arm, by virtue of its momentum, overshoots once more in the opposite direction, and appropriate corrective

signals must again be instituted. Thus, the arm oscillates back and forth past its intended point for several cycles before it finally fixes on its mark. This effect is called an *action tremor,* or *intention tremor.*

But, if the cerebellum is intact, appropriate learned, subconscious signals stop the movement precisely at the intended point, thereby preventing the overshoot and the tremor. *This is the basic characteristic of a damping system.* All control systems regulating pendular elements that have inertia must have damping circuits built into the mechanisms. For motor control by the nervous system, the cerebellum provides most of this damping function.

Cerebellar Control of Ballistic Movements. Most rapid movements of the body, such as the movements of the fingers in typing, occur so rapidly that it is not possible to receive feedback information either from the periphery to the cerebellum or from the cerebellum back to the motor cortex before the movements are over. These movements are called *ballistic movements,* meaning that the entire movement is preplanned and set into motion to go a specific distance and then to stop. Another important example is the saccadic movements of the eyes, in which the eyes jump from one position to the next when reading or when looking at successive points along a road as a person is moving in a car.

Much can be understood about the function of the cerebellum by studying the changes that occur in these ballistic movements when the cerebellum is removed. Three major changes occur: (1) The movements are slow to develop and do not have the extra onset surge that the cerebellum usually provides, (2) the force developed is weak, and (3) the movements are slow to turn off, usually allowing the movement to go well beyond the intended mark. Therefore, in the absence of the cerebellar circuit, the motor cortex has to think extra hard to turn ballistic movements on and again has to think hard and take extra time to turn the movement off. Thus, the automatism of ballistic movements is lost.

Considering once again the circuitry of the cerebellum, one sees that it is beautifully organized to perform this biphasic, first excitatory and then delayed inhibitory function that is required for preplanned rapid ballistic movements. One also sees that the built-in timing circuits of the cerebellar cortex are fundamental to this particular ability of the cerebellum.

Cerebrocerebellum—Function of the Large Lateral Zone of the Cerebellar Hemisphere to Plan, Sequence, and Time Complex Movements

In human beings, the lateral zones of the two cerebellar hemispheres are highly developed and greatly enlarged. This goes along with human abilities to plan and perform intricate sequential patterns of movement, especially with the hands and fingers, and to speak. Yet the large lateral zones of the cerebellar hemispheres have no direct input of information from the peripheral parts of the body. Also, almost all communication between these lateral cerebellar areas and the cerebral cortex is not with the primary cerebral motor cortex itself but instead with the *premotor area* and *primary* and *association somatosensory areas*.

Even so, destruction of the lateral zones of the cerebellar hemispheres along with their deep nuclei, the dentate nuclei, can lead to extreme incoordination of complex purposeful movements of the hands, fingers, and feet and of the speech apparatus. This has been difficult to understand because of lack of direct communication between this part of the cerebellum and the primary motor cortex. However, experimental studies suggest that these portions of the cerebellum are concerned with two other important but indirect aspects of motor control: (1) the planning of sequential movements and (2) the "timing" of the sequential movements.

Planning of Sequential Movements. The planning of sequential movements requires that the lateral zones of the hemispheres communicate with both the premotor and the sensory portions of the cerebral cortex, and it requires two-way communication between these cerebral cortex areas with corresponding areas of the basal ganglia. It seems that the "plan" of sequential movements actually begins in the sensory and premotor areas of the cerebral cortex, and from there the plan is transmitted to the lateral zones of the cerebellar hemispheres. Then, amid much two-way traffic between cerebellum and cerebral cortex, appropriate motor signals provide transition from one sequence of movements to the next.

An interesting observation that supports this view is that many neurons in the cerebellar dentate nuclei display the activity pattern for the sequential movement that is yet to come while the present movement is still occurring. Thus, the lateral cerebellar zones appear to be involved not with what movement is happening at a given moment but with *what will be happening during the next sequential movement* a fraction of a second or perhaps even seconds later.

To summarize, one of the most important features of normal motor function is one's ability to progress smoothly from one movement to the next in orderly succession. In the absence of the large lateral zones of the cerebellar hemispheres, this capability is seriously disturbed for rapid movements.

Timing Function. Another important function of the lateral zones of the cerebellar hemispheres is to provide appropriate timing for each succeeding movement. In the absence of these cerebellar zones, one loses the subconscious ability to predict how far the different parts of the body will move in a given time. Without this timing capability, the person becomes unable to determine when the next sequential movement needs to begin. As a result, the succeeding movement may begin too early or, more likely, too late. Therefore, lesions in the lateral zones of the cerebellum cause complex movements (such as those required for writing, running, or even talking) to become incoordinate and lacking ability to progress in orderly sequence from one movement to the next. Such cerebellar lesions are said to cause *failure of smooth progression of movements*.

Extramotor Predictive Functions of the Cerebrocerebellum. The cerebrocerebellum (the large lateral lobes) also helps to "time" events other than movements of the body. For instance, the rates of progression of both auditory and visual phenomena can be predicted by the brain, but both of these require cerebellar participation. As an example, a person can predict from the changing visual scene how rapidly he or she is approaching an object. A striking experiment that demonstrates the importance of the cerebellum in this ability is the effects of removing the large lateral portions of the cerebellum in monkeys. Such a monkey occasionally charges the wall of a corridor and literally bashes its brains because it is unable to predict when it will reach the wall.

We are only now beginning to learn about these extramotor predictive functions of the cerebellum. It is quite possible that the cerebellum provides a "time-base," perhaps using time-delay circuits, against which signals from other parts of the central nervous system can be compared; it is often stated that the cerebellum is particularly helpful in interpreting *rapidly changing spatiotemporal relations* in sensory information.

Clinical Abnormalities of the Cerebellum

Destruction of small portions of the lateral cerebellar *cortex* seldom causes detectable abnormalities in motor function. In fact, several months after as much as one half of the lateral cerebellar cortex on one side of the brain has been removed, if the deep cerebellar nuclei are not removed along with the cortex, the motor functions of the animal appear to be almost normal *as long as the animal performs all movements slowly*. Thus, the remaining portions of the motor control system are capable of compensating tremendously for loss of parts of the cerebellum.

To cause serious and continuing dysfunction of the cerebellum, the cerebellar lesion usually must involve one or more of the deep cerebellar nuclei—the *dentate, interposed,* or *fastigial nuclei.*

Dysmetria and Ataxia. Two of the most important symptoms of cerebellar disease are *dysmetria* and *ataxia.* In the absence of the cerebellum, the subconscious motor control system cannot predict how far movements will go. Therefore, the movements ordinarily overshoot their intended mark; then the conscious portion of the brain overcompensates in the opposite direction for the succeeding compensatory movement. This effect is called *dysmetria,* and it results in uncoordinated movements that are called *ataxia.* Dysmetria and ataxia can also result from *lesions in the spinocerebellar tracts* because feedback information from the moving parts of the body to the cerebellum is essential for cerebellar timing of movement termination.

Past Pointing. *Past pointing* means that in the absence of the cerebellum, a person ordinarily moves the hand or some other moving part of the body considerably beyond the point of intention. This results from the fact that normally the cerebellum initiates most of the motor signal that turns off a movement after it is begun; if the cerebellum is not available to do this, the movement ordinarily goes beyond the intended mark. Therefore, past pointing is actually a manifestation of dysmetria.

Failure of Progression

Dysdiadochokinesia—Inability to Perform Rapid Alternating Movements. When the motor control system fails to predict where the different parts of the body will be at a given time, it "loses" perception of the parts during rapid motor movements. As a result, the succeeding movement may begin much too early or much too late, so no orderly "progression of movement" can occur. One can demonstrate this readily by having a patient with cerebellar damage turn one hand upward and downward at a rapid rate. The patient rapidly "loses" all perception of the instantaneous position of the hand during any portion of the movement. As a result, a series of stalled attempted but jumbled movements occurs instead of the normal coordinate upward and downward motions. This is called *dysdiadochokinesia.*

Dysarthria—Failure of Progression in Talking. Another example in which failure of progression occurs is in talking because the formation of words depends on rapid and orderly succession of individual muscle movements in the larynx, mouth, and respiratory system. Lack of coordination among these and inability to adjust in advance either the intensity of sound or duration of each successive sound causes jumbled vocalization, with some syllables loud, some weak, some held for long intervals, some held for short intervals, and resultant speech that is often unintelligible. This is called *dysarthria.*

Intention Tremor. When a person who has lost the cerebellum performs a voluntary act, the movements tend to oscillate, especially when they approach the intended mark, first overshooting the mark and then vibrating back and forth several times before settling on the mark. This reaction is called an *intention tremor* or an *action tremor,* and it results from cerebellar overshooting and failure of the cerebellar system to "damp" the motor movements.

Cerebellar Nystagmus—Tremor of the Eyeballs. *Cerebellar nystagmus* is tremor of the eyeballs that occurs usually when one attempts to fixate the eyes on a scene to one side of the head. This off-center type of fixation results in rapid, tremulous movements of the eyes rather than steady fixation, and it is another manifestation of failure of damping by the cerebellum. It occurs especially when the flocculonodular lobes of the cerebellum are damaged; in this instance it is also associated with loss of equilibrium because of dysfunction of the pathways through the flocculonodular cerebellum from the semicircular ducts.

Hypotonia—Decreased Tone of the Musculature. Loss of the deep cerebellar nuclei, particularly of the dentate and interposed nuclei, causes decreased tone of the peripheral body musculature on the side of the cerebellar lesion. The hypotonia results from loss of cerebellar facilitation of the motor cortex and brain stem motor nuclei by tonic signals from the deep cerebellar nuclei.

Basal Ganglia—Their Motor Functions

The basal ganglia, like the cerebellum, constitute another *accessory motor system* that functions usually not by itself but in close association with the cerebral cortex and corticospinal motor control system. In fact, the basal ganglia receive most of their input signals from the cerebral cortex itself and also return almost all their output signals back to the cortex.

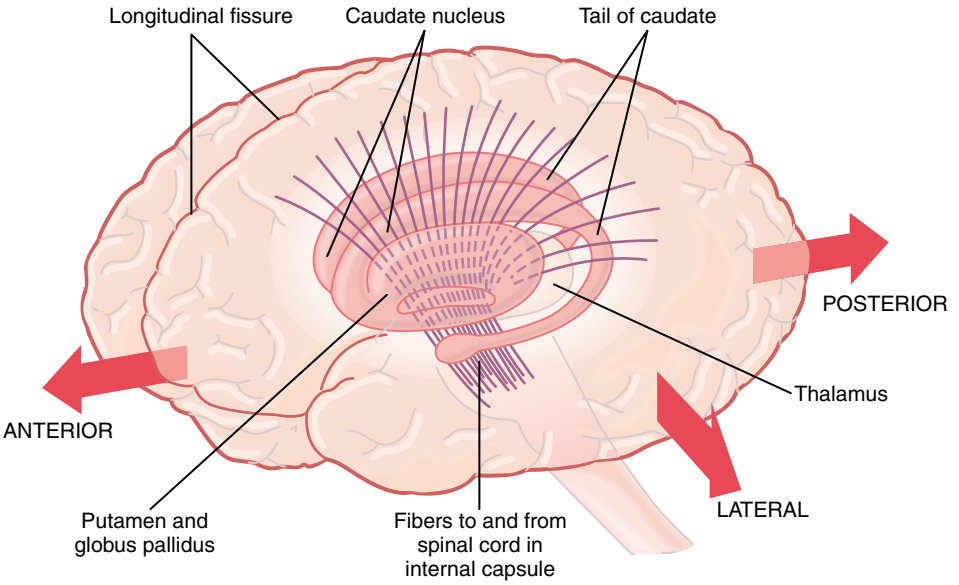


Figure 56-9 Anatomical relations of the basal ganglia to the cerebral cortex and thalamus, shown in three-dimensional view. (Redrawn from Guyton AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders, 1992.)

Figure 56-9 shows the anatomical relations of the basal ganglia to other structures of the brain. On each side of the brain, these ganglia consist of the *caudate nucleus, putamen, globus pallidus, substantia nigra,* and *subthalamic nucleus.* They are located mainly lateral to and surrounding the thalamus, occupying a large portion of the interior regions of both cerebral hemispheres. Note also that almost all motor and sensory nerve fibers connecting the cerebral cortex and spinal cord pass through the space that lies between the major masses of the basal ganglia, the *caudate nucleus* and the *putamen*. This space is called the *internal capsule* of the brain. It is important for our current discussion because of the intimate association between the basal ganglia and the corticospinal system for motor control.

Neuronal Circuitry of the Basal Ganglia. The anatomical connections between the basal ganglia and the other brain elements that provide motor control are complex, as shown in Figure 56-10. To the left is shown the motor cortex, thalamus, and associated brain stem and cerebellar circuitry. To the right is the major circuitry of the basal ganglia system, showing the tremendous interconnections among the basal ganglia themselves plus extensive input and output pathways between the other motor regions of the brain and the basal ganglia.

In the next few sections we concentrate especially on two major circuits, the *putamen circuit* and the *caudate circuit.*

Function of the Basal Ganglia in Executing Patterns of Motor Activity—the Putamen Circuit

One of the principal roles of the basal ganglia in motor control is to function in association with the corticospinal system to control *complex patterns of motor activity.* An example is the writing of letters of the alphabet. When there is serious damage to the basal ganglia, the cortical system of motor control can no longer provide these patterns. Instead, one's writing becomes crude, as if one were learning for the first time how to write.

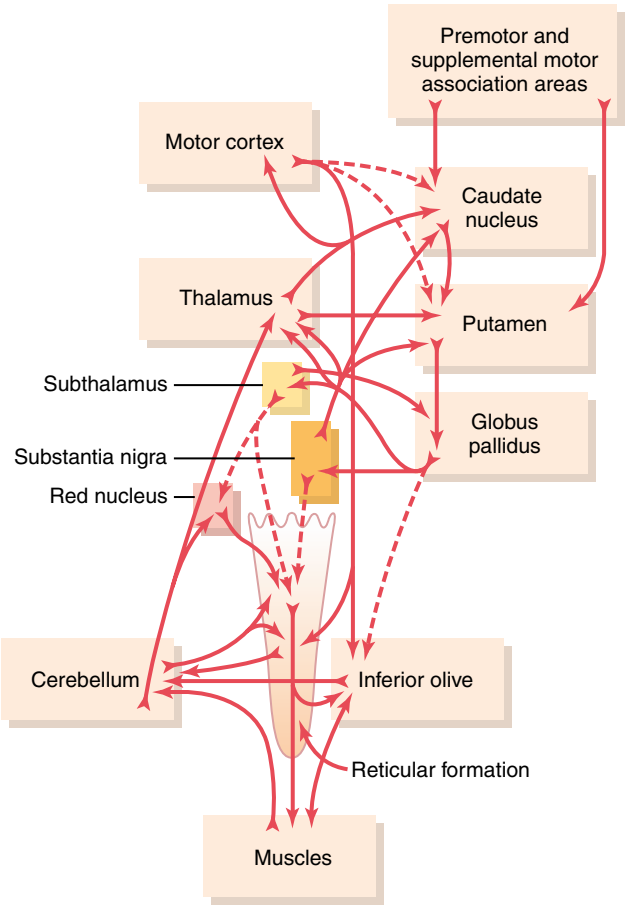


Figure 56-10 Relation of the basal ganglial circuitry to the corticospinal-cerebellar system for movement control.

Other patterns that require the basal ganglia are cutting paper with scissors, hammering nails, shooting a basketball through a hoop, passing a football, throwing a baseball, the movements of shoveling dirt, most aspects of vocalization, controlled movements of the eyes, and virtually any other of our skilled movements, most of them performed subconsciously.

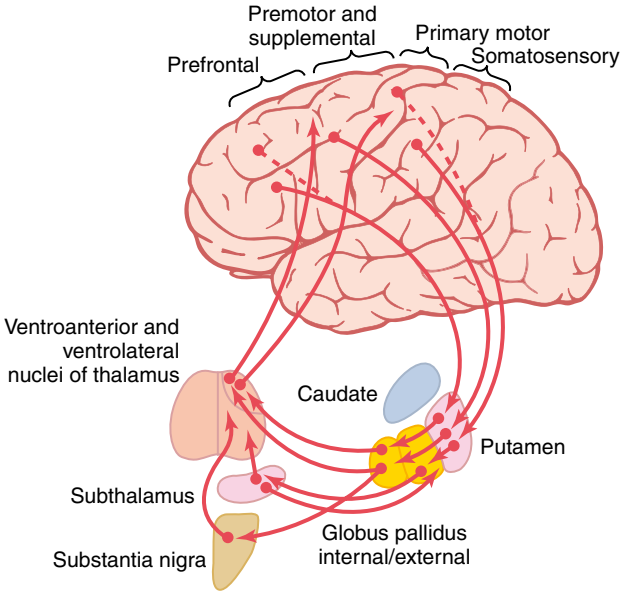


Figure 56-11 Putamen circuit through the basal ganglia for subconscious execution of learned patterns of movement.

Neural Pathways of the Putamen Circuit. Figure 56-11 shows the principal pathways through the basal ganglia for executing learned patterns of movement. They begin mainly in the premotor and supplementary areas of the motor cortex and in the somatosensory areas of the sensory cortex. Next they pass to the putamen (mainly bypassing the caudate nucleus), then to the internal portion of the globus pallidus, next to the ventroanterior and ventrolateral relay nuclei of the thalamus, and finally return to the cerebral primary motor cortex and to portions of the premotor and supplementary cerebral areas closely associated with the primary motor cortex. Thus, the putamen circuit has its inputs mainly from those parts of the brain adjacent to the primary motor cortex but not much from the primary motor cortex itself. Then its outputs do go mainly back to the primary motor cortex or closely associated premotor and supplementary cortex. Functioning in close association with this primary putamen circuit are ancillary circuits that pass from the putamen through the external globus pallidus, the subthalamus, and the substantia nigra—finally returning to the motor cortex by way of the thalamus.

Abnormal Function in the Putamen Circuit: Athetosis, Hemiballismus, and Chorea. How does the putamen circuit function to help execute patterns of movement? The answer is poorly known. However, when a portion of the circuit is damaged or blocked, certain patterns of movement become severely abnormal. For instance, lesions in the *globus pallidus* frequently lead to spontaneous and often continuous *writhing movements* of a hand, an arm, the neck, or the face—movements called *athetosis.*

A lesion in the *subthalamus* often leads to sudden *flailing movements* of an entire limb, a condition called *hemiballismus.*

Multiple small lesions in the *putamen* lead to *flicking movements* in the hands, face, and other parts of the body, called *chorea.*

Lesions of the *substantia nigra* lead to the common and extremely severe disease of *rigidity, akinesia,* and *tremors* known as *Parkinson's disease,* which we discuss in more detail later.

Role of the Basal Ganglia for Cognitive Control of Sequences of Motor Patterns—the Caudate Circuit

The term *cognition* means the thinking processes of the brain, using both sensory input to the brain plus information already stored in memory. Most of our motor actions occur as a consequence of thoughts generated in the mind, a process called *cognitive control of motor activity.* The caudate nucleus plays a major role in this cognitive control of motor activity.

The neural connections between the caudate nucleus and the corticospinal motor control system, shown in Figure 56-12, are somewhat different from those of the putamen circuit. Part of the reason for this is that the caudate nucleus, as shown in Figure 56-9, extends into all lobes of the cerebrum, beginning anteriorly in the frontal lobes, then passing posteriorly through the parietal and occipital lobes, and finally curving forward again like the letter "C" into the temporal lobes. Furthermore, the caudate nucleus receives large amounts of its input from the *association areas* of the cerebral cortex overlying the caudate nucleus, mainly areas that also integrate the different types of sensory and motor information into usable thought patterns.

After the signals pass from the cerebral cortex to the caudate nucleus, they are next transmitted to the internal globus pallidus, then to the relay nuclei of the

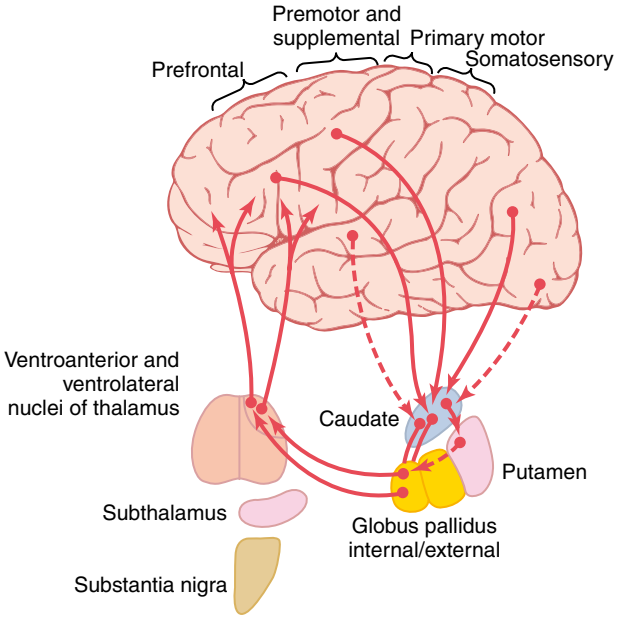


Figure 56-12 Caudate circuit through the basal ganglia for cognitive planning of sequential and parallel motor patterns to achieve specific conscious goals.

ventroanterior and ventrolateral thalamus, and finally back to the prefrontal, premotor, and supplementary motor areas of the cerebral cortex, but with almost none of the returning signals passing directly to the primary motor cortex. Instead, the returning signals go to those accessory motor regions in the premotor and supplementary motor areas that are concerned with putting together sequential patterns of movement lasting 5 or more seconds instead of exciting individual muscle movements.

A good example of this would be a person seeing a lion approach and then responding instantaneously and automatically by (1) turning away from the lion, (2) beginning to run, and (3) even attempting to climb a tree. Without the cognitive functions, the person might not have the instinctive knowledge, without thinking for too long a time, to respond quickly and appropriately. Thus, cognitive control of motor activity determines subconsciously, and within seconds, which patterns of movement will be used together to achieve a complex goal that might itself last for many seconds.

Function of the Basal Ganglia to Change the Timing and to Scale the Intensity of Movements

Two important capabilities of the brain in controlling movement are (1) to determine how rapidly the movement is to be performed and (2) to control how large the movement will be. For instance, a person may write the letter "a" slowly or rapidly. Also, he or she may write a small "a" on a piece of paper or a large "a" on a chalkboard. Regardless of the choice, the proportional characteristics of the letter remain nearly the same.

In patients with severe lesions of the basal ganglia, these timing and scaling functions are poor; in fact, sometimes they are nonexistent. Here again, the basal ganglia do not function alone; they function in close association with the cerebral cortex. One especially important cortical area is the posterior parietal cortex, which is the locus of the spatial coordinates for motor control of all parts of the body, as well as for the relation of the body and its parts to all its surroundings. Damage to this area does not produce simple deficits of sensory perception, such as loss of tactile sensation, blindness, or deafness. Instead, lesions of the posterior parietal cortex produce an inability to accurately perceive objects through normally functioning sensory mechanisms, a condition called *agnosia.* Figure 56-13 shows the way in which a person with a lesion in the right posterior parietal cortex might try to copy drawings. In these cases, the patient's ability to copy the left side of the drawings is severely impaired. Also, such a person will always try to avoid using his or her left arm, left hand, or other portions of his or her left body for the performance of tasks, or even wash this side of the body *(personal neglect syndrome),* almost not knowing that these parts of his or her body exist.

Because the caudate circuit of the basal ganglial system functions mainly with association areas of the cerebral cortex such as the posterior parietal cortex, presumably

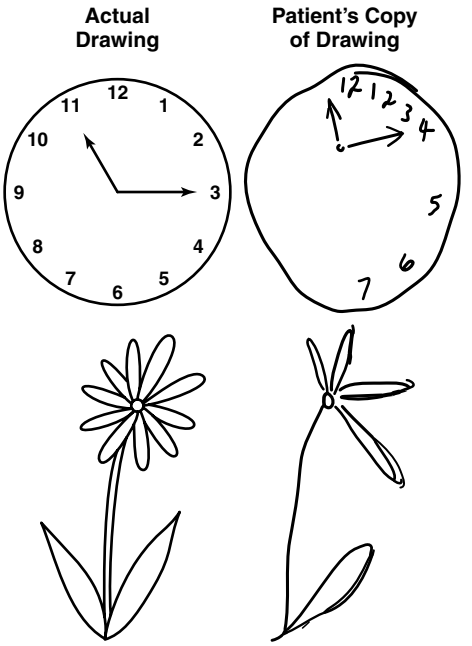


Figure 56-13 Illustration of drawings that might be made by a person who has *neglect syndrome* caused by severe damage in his or her right posterior parietal cortex compared with the actual drawing the patient was requested to copy. Note that the person's ability to copy the left side of the drawings is severely impaired.

the timing and scaling of movements are functions of this caudate cognitive motor control circuit. However, our understanding of function in the basal ganglia is still so imprecise that much of what is conjectured in the last few sections is analytical deduction rather than proven fact.

Functions of Specific Neurotransmitter Substances in the Basal Ganglial System

Figure 56-14 demonstrates the interplay of several specific neurotransmitters that are known to function within the

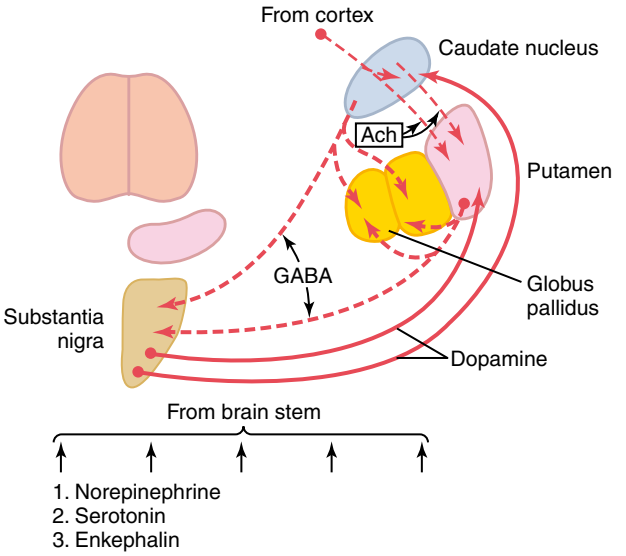


Figure 56-14 Neuronal pathways that secrete different types of neurotransmitter substances in the basal ganglia. Ach, acetylcholine; GABA, gamma-aminobutyric acid.

basal ganglia, showing (1) *dopamine* pathways from the substantia nigra to the caudate nucleus and putamen, (2) *gamma-aminobutyric acid (GABA)* pathways from the caudate nucleus and putamen to the globus pallidus and substantia nigra, (3) *acetylcholine* pathways from the cortex to the caudate nucleus and putamen, and (4) multiple general pathways from the brain stem that secrete *norepinephrine, serotonin, enkephalin,* and several other neurotransmitters in the basal ganglia, as well as in other parts of the cerebrum. In addition to all these are *multiple glutamate pathways* that provide most of the excitatory signals (not shown in the figure) that balance out the large numbers of inhibitory signals transmitted especially by the dopamine, GABA, and serotonin inhibitory transmitters. We have more to say about some of these neurotransmitter and hormonal systems in subsequent sections when we discuss diseases of the basal ganglia, as well as in subsequent chapters when we discuss behavior, sleep, wakefulness, and functions of the autonomic nervous system.

For the present, it should be remembered that the neurotransmitter GABA always functions as an inhibitory agent. Therefore, GABA neurons in the feedback loops from the cortex through the basal ganglia and then back to the cortex make virtually all these loops *negative feedback loops,* rather than positive feedback loops, thus lending stability to the motor control systems. Dopamine also functions as an inhibitory neurotransmitter in most parts of the brain, so it also functions as a stabilizer under some conditions.

Clinical Syndromes Resulting from Damage to the Basal Ganglia

Aside from *athetosis* and *hemiballismus,* which have already been mentioned in relation to lesions in the globus pallidus and subthalamus, two other major diseases result from damage in the basal ganglia. These are Parkinson's disease and Huntington's disease.

Parkinson's Disease

Parkinson's disease, known also as *paralysis agitans,* results from widespread destruction of that portion of the substantia nigra (the pars compacta) that sends dopamine-secreting nerve fibers to the caudate nucleus and putamen. The disease is characterized by (1) rigidity of much of the musculature of the body; (2) involuntary tremor of the involved areas even when the person is resting at a fixed rate of three to six cycles per second; and (3) serious difficulty in initiating movement, called *akinesia;* (4) postural instability caused by impaired postural reflexes, leading to poor balance and falls; and (5) other motor symptoms including dysphagia (impaired ability to swallow), speech disorders, gait disturbances, and fatigue.

The causes of these abnormal motor effects are unknown. However, the dopamine secreted in the caudate nucleus and putamen is an inhibitory transmitter; therefore, destruction of the dopaminergic neurons in the substantia nigra of the parkinsonian patient theoretically would allow the caudate nucleus and putamen to become overly active and possibly cause continuous output of excitatory signals to the corticospinal motor control system. These signals could overly excite many or all of the muscles of the body, thus leading to *rigidity.*

Some of the feedback circuits might easily *oscillate* because of high feedback gains after loss of their inhibition, leading to the *tremor* of Parkinson's disease. This tremor is quite different from that of cerebellar disease because it occurs during all waking hours and therefore is an *involuntary tremor,* in contradistinction to cerebellar tremor, which occurs only when the person performs intentionally initiated movements and therefore is called *intention tremor.*

The *akinesia* that occurs in Parkinson's disease is often much more distressing to the patient than are the symptoms of muscle rigidity and tremor, because to perform even the simplest movement in severe parkinsonism, the person must exert the highest degree of concentration. The mental effort, even mental anguish, that is necessary to make the desired movements is often at the limit of the patient's willpower. Then, when the movements do occur, they are usually stiff and staccato in character instead of smooth. The cause of this akinesia is still speculative. However, dopamine secretion in the limbic system, especially in the *nucleus accumbens,* is often decreased along with its decrease in the basal ganglia. It has been suggested that this might reduce the psychic drive for motor activity so greatly that akinesia results.

Treatment with L-Dopa. Administration of the drug *L-dopa* to patients with Parkinson's disease usually ameliorates many of the symptoms, especially the rigidity and akinesia. The reason for this is believed to be that L-dopa is converted in the brain into dopamine, and the dopamine then restores the normal balance between inhibition and excitation in the caudate nucleus and putamen. Administration of dopamine itself does not have the same effect because dopamine has a chemical structure that will not allow it to pass through the blood-brain barrier, even though the slightly different structure of L-dopa does allow it to pass.

Treatment with L-Deprenyl. Another treatment for Parkinson's disease is the drug L-deprenyl. This drug inhibits monoamine oxidase, which is responsible for destruction of most of the dopamine after it has been secreted. Therefore, any dopamine that is released remains in the basal ganglial tissues for a longer time. In addition, for reasons not understood, this treatment helps to slow destruction of the dopamine-secreting neurons in the substantia nigra. Therefore, appropriate combinations of L-dopa therapy along with L-deprenyl therapy usually provide much better treatment than use of one of these drugs alone.

Treatment with Transplanted Fetal Dopamine Cells. Transplantation of dopamine-secreting cells (cells obtained from the brains of aborted fetuses) into the caudate nuclei and putamen has been used with some short-term success to treat Parkinson's disease. However, the cells do not live for more than a few months. If persistence could be achieved, perhaps this would become the treatment of the future.

Treatment by Destroying Part of the Feedback Circuitry in the Basal Ganglia. Because abnormal signals from the basal ganglia to the motor cortex cause most of the abnormalities in Parkinson's disease, multiple attempts have been made to treat these patients by blocking these signals surgically. For a number of years, surgical lesions were made in the ventrolateral and ventroanterior nuclei of the thalamus, which blocked part of the feedback circuit from the basal ganglia to the cortex; variable degrees of success were achieved, as well as sometimes serious neurological damage. In monkeys with Parkinson's disease, lesions placed in the subthalamus have been used, sometimes with surprisingly good results.

Huntington's Disease (Huntington's Chorea)

Huntington's disease is a hereditary disorder that usually begins causing symptoms at age 30 to 40 years. It is characterized at first by flicking movements in individual muscles and then progressive severe distortional movements of the entire body. In addition, severe dementia develops along with the motor dysfunctions.

The abnormal movements of Huntington's disease are believed to be caused by loss of most of the cell bodies of the GABA-secreting neurons in the caudate nucleus and putamen and of acetylcholine-secreting neurons in many parts of the brain. The axon terminals of the GABA neurons normally inhibit portions of the globus pallidus and substantia nigra. This loss of inhibition is believed to allow spontaneous outbursts of globus pallidus and substantia nigra activity that cause the distortional movements.

The dementia in Huntington's disease probably does not result from the loss of GABA neurons but from the loss of acetylcholine-secreting neurons, perhaps especially in the thinking areas of the cerebral cortex.

The abnormal gene that causes Huntington's disease has been found; it has a many-times-repeating codon, CAG, that codes for multiple extra *glutamine* amino acids in the molecular structure of an abnormal neuronal cell protein called *huntington* that causes the symptoms. How this protein causes the disease effects is now the question for major research effort.

Integration of the Many Parts of the Total Motor Control System

Finally, we need to summarize as best we can what is known about overall control of movement. To do this, let us first give a synopsis of the different levels of control.

Spinal Level

Programmed in the spinal cord are local patterns of movement for all muscle areas of the body—for instance, programmed withdrawal reflexes that pull any part of the body away from a source of pain. The cord is the locus also of complex patterns of rhythmical motions such as to-and-fro movement of the limbs for walking, plus reciprocal motions on opposite sides of the body or of the hindlimbs versus the forelimbs in four-legged animals.

All these programs of the cord can be commanded into action by higher levels of motor control, or they can be inhibited while the higher levels take over control.

Hindbrain Level

The hindbrain provides two major functions for general motor control of the body: (1) maintenance of axial tone of the body for the purpose of standing and (2) continuous modification of the degrees of tone in the different muscles in response to information from the vestibular apparatuses for the purpose of maintaining body equilibrium.

Motor Cortex Level

The motor cortex system provides most of the activating motor signals to the spinal cord. It functions partly by issuing sequential and parallel commands that set into motion various cord patterns of motor action. It can also change the intensities of the different patterns or modify their timing or other characteristics. When needed, the corticospinal system can bypass the cord patterns, replacing them with higher-level patterns from the brain stem or cerebral cortex. The cortical patterns are usually complex; also, they can be "learned," whereas cord patterns are mainly determined by heredity and are said to be "hard wired."

Associated Functions of the Cerebellum. The cerebellum functions with all levels of muscle control. It functions with the spinal cord especially to enhance the stretch reflex, so when a contracting muscle encounters an unexpectedly heavy load, a long stretch reflex signal transmitted all the way through the cerebellum and back again to the cord strongly enhances the load-resisting effect of the basic stretch reflex.

At the brain stem level, the cerebellum functions to make the postural movements of the body, especially the rapid movements required by the equilibrium system, smooth and continuous and without abnormal oscillations.

At the cerebral cortex level, the cerebellum operates in association with the cortex to provide many accessory motor functions, especially to provide extra motor force for turning on muscle contraction rapidly at the start of a movement. Near the end of each movement, the *cerebellum* turns on antagonist muscles at exactly the right time and with proper force to stop the movement at the intended point. Furthermore, there is good physiologic evidence that all aspects of this turn-on/turn-off patterning by the cerebellum can be learned with experience.

The cerebellum functions with the cerebral cortex at still another level of motor control: it helps to program in advance muscle contractions that are required for smooth progression from a present rapid movement in one direction to the next rapid movement in another direction, all this occurring in a fraction of a second. The neural circuit for this passes from the cerebral cortex to the large lateral zones of the cerebellar hemispheres and then back to the cerebral cortex.

The cerebellum functions mainly when muscle movements have to be rapid. Without the cerebellum, slow and calculated movements can still occur, but it is difficult for the corticospinal system to achieve rapid and changing intended movements to execute a particular goal or especially to progress smoothly from one rapid movement to the next.

Associated Functions of the Basal Ganglia. The basal ganglia are essential to motor control in ways entirely different from those of the cerebellum. Their most important functions are (1) to help the cortex execute subconscious but *learned patterns of movement* and (2) to help plan multiple parallel and sequential patterns

of movement that the mind must put together to accomplish a purposeful task.

The types of motor patterns that require the basal ganglia include those for writing all the different letters of the alphabet, for throwing a ball, and for typing. Also, the basal ganglia are required to modify these patterns for writing small or writing very large, thus controlling dimensions of the patterns.

At a still higher level of control is another combined cerebral and basal ganglia circuit, beginning in the thinking processes of the cerebrum to provide overall sequential steps of action for responding to each new situation, such as planning one's immediate motor response to an assailant who hits the person in the face or one's sequential response to an unexpectedly fond embrace.

What Drives Us to Action?

What is it that arouses us from inactivity and sets into play our trains of movement? We are beginning to learn about the motivational systems of the brain. Basically, the brain has an older core located beneath, anterior, and lateral to the thalamus—including the hypothalamus, amygdala, hippocampus, septal region anterior to the hypothalamus and thalamus, and even old regions of the thalamus and cerebral cortex themselves—all of which function together to initiate most motor and other functional activities of the brain. These areas are collectively called the *limbic system* of the brain. We discuss this system in detail in Chapter 58.

Bibliography

Bastian AJ: Learning to predict the future: the cerebellum adapts feedforward movement control, *Curr Opin Neurobiol* 16:645, 2006.

Bloom F, Lazerson A: *Brain, Mind and Behavior*, ed 2, New York, 1988, W.H. Freeman, p 300.

Breakefield XO, Blood AJ, Li Y, et al: The pathophysiological basis of dystonias, *Nat Rev Neurosci* 9:222, 2008.

Cheron G, Servais L, Dan B: Cerebellar network plasticity: from genes to fast oscillation, *Neuroscience* 153:1, 2008.

DeKosky ST, Marek K: Looking backward to move forward: early detection of neurodegenerative disorders, *Science* 302:830, 2003.

Fuentes CT, Bastian AJ: 'Motor cognition'—what is it and is the cerebellum involved? *Cerebellum* 6:232, 2007.

Gibson AR, Horn KM, Pong M: Inhibitory control of olivary discharge, *Ann N Y Acad Sci* 978:219, 2002.

Hasnain M, Vieweg WV, Baron MS, et al: Pharmacological management of psychosis in elderly patients with parkinsonism, *Am J Med* 122:614, 2009.

Ito M: Cerebellar long-term depression: characterization, signal transduction, and functional roles, *Physiol Rev* 81:1143, 2001.

Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, ed 4, New York, 2000, McGraw-Hill.

Kreitzer AC, Malenka RC: Striatal plasticity and basal ganglia circuit function, *Neuron* 60:543, 2008.

Lees AJ, Hardy J, Revesz T: Parkinson's disease, *Lancet* 373:2055, 2009.

Li JY, Plomann M, Brundin P: Huntington's disease: a synaptopathy? *Trends Mol Med* 9:414, 2003.

Mustari MJ, Ono S, Das VE: Signal processing and distribution in cortical-brainstem pathways for smooth pursuit eye movements, *Ann N Y Acad Sci* 1164:147, 2009.

Nambu A: Seven problems on the basal ganglia, *Curr Opin Neurobiol* 18:595, 2008.

Pugh JR, Raman IM: Nothing can be coincidence: synaptic inhibition and plasticity in the cerebellar nuclei, *Trends Neurosci* 32:170, 2009.

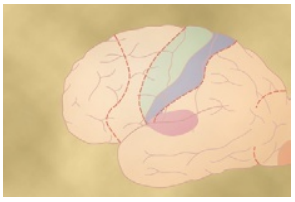
Ramnani N: The primate cortico-cerebellar system: anatomy and function, *Nat Rev Neurosci* 7:511, 2006.

Rosas HD, Salat DH, Lee SY, et al: Complexity and heterogeneity: what drives the ever-changing brain in Huntington's disease? *Ann N Y Acad Sci* 1147:196, 2008.

Spruston N: Pyramidal neurons: dendritic structure and synaptic integration, *Nat Rev Neurosci* 9:206, 2008.

Sethi KD: Tremor, *Curr Opin Neurol* 16:481, 2003.

Cerebral Cortex, Intellectual Functions of the Brain, Learning, and Memory



It is ironic that of all the parts of the brain, we know the least about the functions of the cerebral cortex, even though it is by far the largest portion of the nervous system. But we do know the effects of damage or specific stimulation in various portions of the cortex. In the first part of this chapter, the known cortical functions are discussed; then basic theories of neuronal mechanisms involved in thought processes, memory, analysis of sensory information, and so forth are presented briefly.

Physiologic Anatomy of the Cerebral Cortex

The functional part of the cerebral cortex is a thin layer of neurons covering the surface of all the convolutions of the cerebrum. This layer is only 2 to 5 millimeters thick, with a total area of about one quarter of a square meter. The total cerebral cortex contains about 100 *billion* neurons.

Figure 57-1 shows the typical histological structure of the neuronal surface of the cerebral cortex, with its successive layers of different types of neurons. Most of the neurons are of three types: (1) *granular* (also called *stellate*), (2) *fusiform,* and (3) *pyramidal,* the last named for their characteristic pyramidal shape.

The *granular* neurons generally have short axons and, therefore, function mainly as interneurons that transmit neural signals only short distances within the cortex itself. Some are excitatory, releasing mainly the excitatory neurotransmitter *glutamate;* others are inhibitory and release mainly the inhibitory neurotransmitter *gamma-aminobutyric acid* (GABA). The sensory areas of the cortex, as well as the association areas between sensory and motor areas, have large concentrations of these granule cells, suggesting a high degree of intracortical processing of incoming sensory signals within the sensory areas and association areas.

The *pyramidal* and *fusiform cells* give rise to almost all the output fibers from the cortex. The pyramidal cells are larger and more numerous than the fusiform cells. They are the source of the long, large nerve fibers that go all the way to the spinal cord. They also give rise to most of the large subcortical association fiber bundles that pass from one major part of the brain to another.

To the right in Figure 57-1 is shown the typical organization of nerve fibers within the different layers of the cerebral cortex. Note particularly the large number of

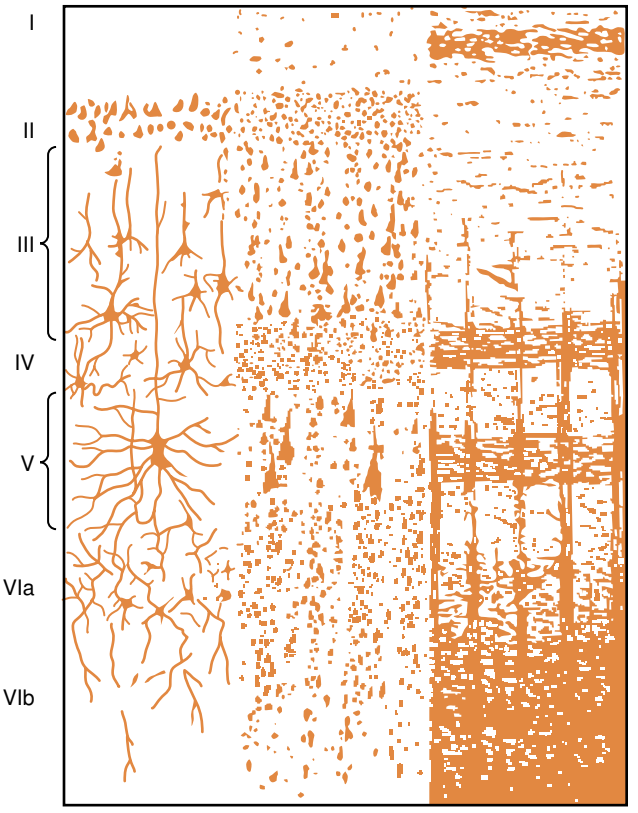


Figure 57-1 Structure of the cerebral cortex, showing: *I,* molecular layer; *II,* external granular layer; *III,* layer of pyramidal cells; *IV,* internal granular layer; *V,* large pyramidal cell layer; and *VI,* layer of fusiform or polymorphic cells. (Redrawn from Ranson SW, Clark SL [after Brodmann]: Anatomy of the Nervous System. Philadelphia: WB Saunders, 1959.)

horizontal fibers that extend between adjacent areas of the cortex, but note also the *vertical fibers* that extend to and from the cortex to lower areas of the brain and some all the way to the spinal cord or to distant regions of the cerebral cortex through long association bundles.

The functions of the specific layers of the cerebral cortex are discussed in Chapters 47 and 51. By way of review, let us recall that most incoming specific sensory signals from the body terminate in cortical layer IV. Most of the output signals leave the cortex through neurons located in layers V and VI; the very large fibers to the brain stem and cord arise generally in layer V; and the tremendous numbers of fibers to the thalamus arise in layer VI. Layers I, II, and III perform most of the intracortical association functions, with especially large numbers of neurons in layers II and III making short horizontal connections with adjacent cortical areas.

Anatomical and Functional Relations of the Cerebral Cortex to the Thalamus and Other Lower Centers. All areas of the cerebral cortex have extensive to-and-fro efferent and afferent connections with deeper structures of the brain. It is important to emphasize the relation between the cerebral cortex and the thalamus. When the thalamus is damaged along with the cortex, the loss of cerebral function is far greater than when the cortex alone is damaged because thalamic excitation of the cortex is necessary for almost all cortical activity.

Figure 57-2 shows the areas of the cerebral cortex that connect with specific parts of the thalamus. These connections act in *two* directions, both from the thalamus to the cortex and then from the cortex back to essentially the same area of the thalamus. Furthermore, when the thalamic connections are cut, the functions of the corresponding cortical area become almost entirely lost. Therefore, the cortex operates in close association with the thalamus and can almost be considered both anatomically and functionally a unit with the thalamus: for this reason, the thalamus and the cortex together are sometimes called the *thalamocortical system*. Almost all pathways from the sensory receptors and sensory organs to the cortex pass through the thalamus, with the principal exception of some sensory pathways of olfaction.

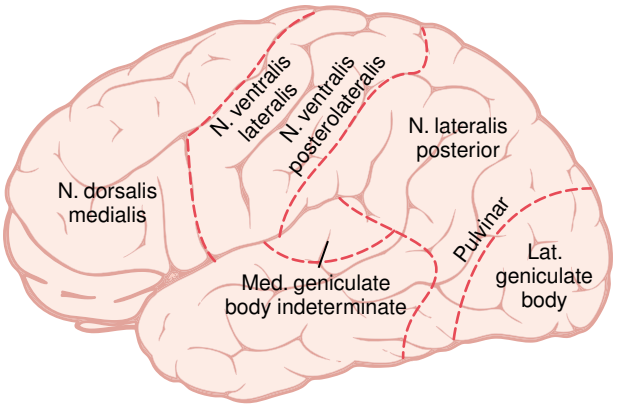


Figure 57-2 Areas of the cerebral cortex that connect with specific portions of the thalamus.

Functions of Specific Cortical Areas

Studies in human beings have shown that different cerebral cortical areas have separate functions. Figure 57-3 is a map of some of these functions as determined from electrical stimulation of the cortex in awake patients or during neurological examination of patients after portions of the cortex had been removed. The electrically stimulated patients told their thoughts evoked by the stimulation, and sometimes they experienced movements. Occasionally they spontaneously emitted a sound or even a word or gave some other evidence of the stimulation.

Putting large amounts of information together from many different sources gives a more general map, as shown in Figure 57-4. This figure shows the major primary and secondary premotor and supplementary motor areas of the cortex, as well as the major primary and secondary sensory areas for somatic sensation, vision, and hearing, all of which are discussed in earlier chapters. The primary motor areas have direct connections with specific muscles for causing discrete muscle movements. The primary sensory areas detect specific sensations—visual, auditory, or somatic—transmitted directly to the brain from peripheral sensory organs.

The secondary areas make sense out of the signals in the primary areas. For instance, the supplementary and premotor areas function along with the primary motor cortex and basal ganglia to provide "patterns" of motor activity. On the sensory side, the secondary sensory areas, located within a few centimeters of the primary areas, begin to analyze the meanings of the specific sensory signals, such as (1) interpretation of the shape or texture of an object in one's hand; (2) interpretation of color, light intensity, directions of lines and angles, and other aspects of vision; and (3) interpretations of the meanings of sound tones and sequence of tones in the auditory signals.

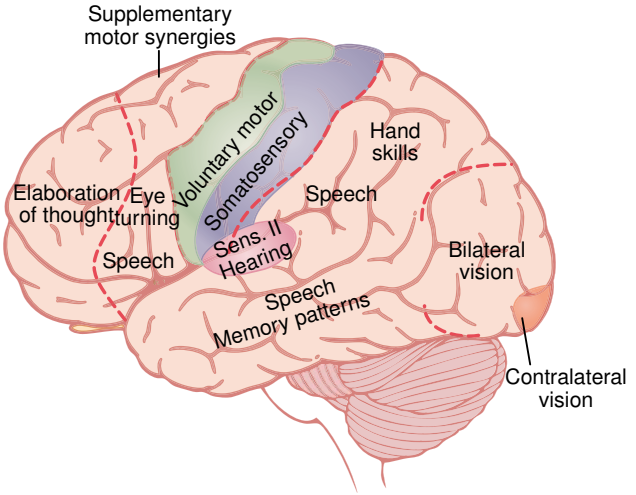


Figure 57-3 Functional areas of the human cerebral cortex as determined by electrical stimulation of the cortex during neurosurgical operations and by neurological examinations of patients with destroyed cortical regions. (Redrawn from Penfield W, Rasmussen T: The Cerebral Cortex of Man: A Clinical Study of Localization of Function. New York: Hafner, 1968.)

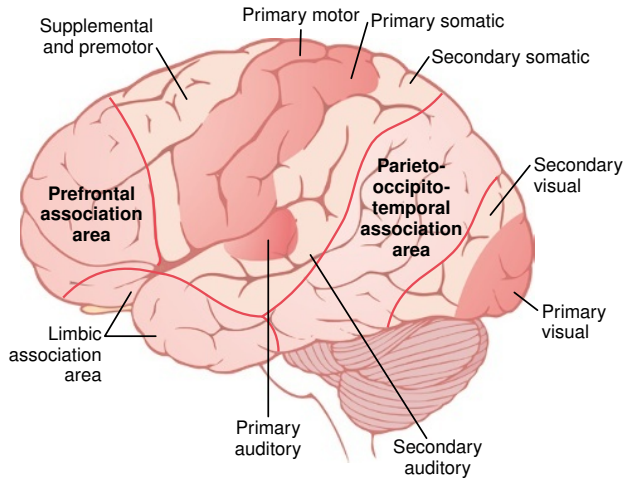


Figure 57-4 Locations of major association areas of the cerebral cortex, as well as primary and secondary motor and sensory areas.

Association Areas

Figure 57-4 also shows several large areas of the cerebral cortex that do not fit into the rigid categories of primary and secondary motor and sensory areas. These areas are called *association areas* because they receive and analyze signals simultaneously from multiple regions of both the motor and sensory cortices, as well as from subcortical structures. Yet even the association areas have their specializations. Important association areas include (1) the *parieto-occipitotemporal association area,* (2) the *prefrontal association area,* and (3) the *limbic association area.* Following are explanations of the functions of these areas.

Parieto-occipitotemporal Association Area. This association area lies in the large parietal and occipital cortical space bounded by the somatosensory cortex anteriorly, the visual cortex posteriorly, and the auditory cortex laterally. As would be expected, it provides a high level of interpretative meaning for signals from all the surrounding sensory areas. However, even the parieto-occipitotemporal association area has its own functional subareas, which are shown in Figure 57-5.

1. Analysis of the Spatial Coordinates of the Body. An area beginning in the posterior parietal cortex and extending into the superior occipital cortex provides continuous analysis of the spatial coordinates of all parts of the body, as well as of the surroundings of the body. This area receives visual sensory information from the posterior occipital cortex and simultaneous somatosensory information from the anterior parietal cortex. From all this information, it computes the coordinates of the visual, auditory, and body surroundings.

2. Wernicke's Area Is Important for Language Comprehension. The major area for language comprehension, called *Wernicke's area,* lies behind *the primary auditory cortex in the posterior part of the superior gyrus of the temporal lobe.* We discuss this area much more fully later; it is the most important region of the entire brain for higher intellectual function because almost all such intellectual functions are language based.

3. Angular Gyrus Area Is Needed for Initial Processing of Visual Language (Reading). Posterior to the language comprehension area, lying mainly in the anterolateral region of the occipital lobe, is a visual association area that feeds visual information conveyed by words read from a book into Wernicke's area, the language comprehension area. This so-called *angular gyrus area* is needed to make meaning out of the visually perceived words. In its absence, a person can still have excellent language comprehension through hearing but not through reading.

4. Area for Naming Objects. *In the most lateral portions of the anterior occipital lobe and posterior temporal lobe is an area for naming objects.* The names are learned mainly through auditory input, whereas the physical

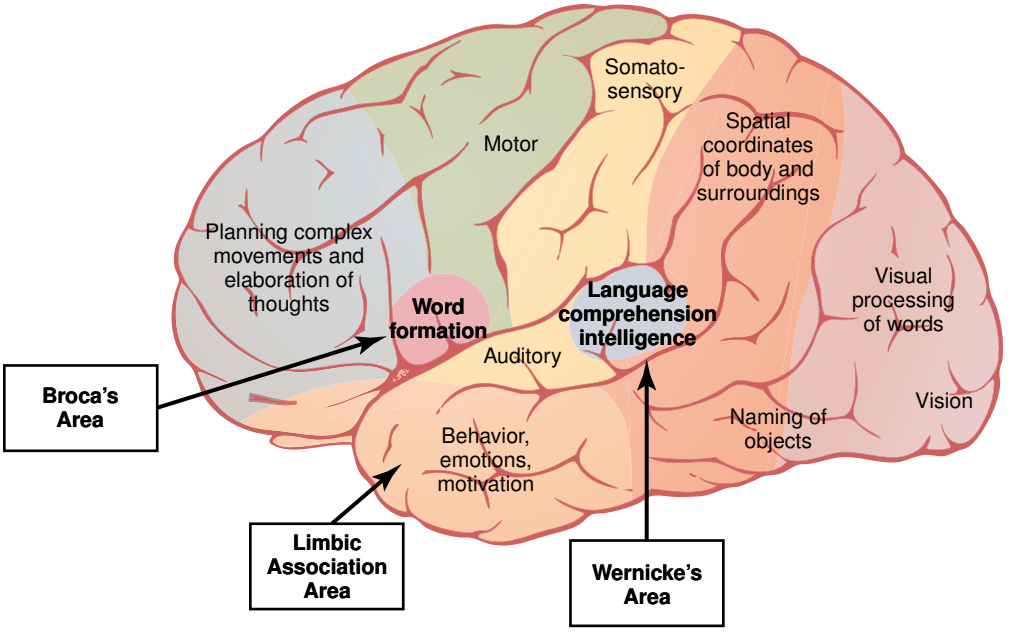


Figure 57-5 Map of specific functional areas in the cerebral cortex, showing especially Wernicke's and Broca's areas for language comprehension and speech production, which in 95 percent of all people are located in the left hemisphere.

natures of the objects are learned mainly through visual input. In turn, the names are essential for both auditory and visual language comprehension (*functions performed in Wernicke's area* located immediately superior to the auditory "names" region and anterior to the visual word processing area).

Prefrontal Association Area. As discussed in Chapter 56, the prefrontal association area functions in close association with the motor cortex to plan complex patterns and sequences of motor movements. To aid in this function, it receives strong input through a massive subcortical bundle of nerve fibers connecting the parieto-occipitotemporal association area with the prefrontal association area. Through this bundle, the prefrontal cortex receives much preanalyzed sensory information, especially information on the spatial coordinates of the body that is necessary for planning effective movements. Much of the output from the prefrontal area into the motor control system passes through the caudate portion of the basal ganglia–thalamic feedback circuit for motor planning, which provides many of the sequential and parallel components of movement stimulation.

The *prefrontal association area* is also *essential to carrying out "thought" processes in the mind.* This presumably results from some of the same capabilities of the prefrontal cortex that allow it to plan motor activities. It seems to be capable of processing nonmotor and motor information from widespread areas of the brain and therefore to achieve nonmotor types of thinking, as well as motor types. In fact, the prefrontal association area is frequently described simply as important for *elaboration of thoughts,* and it is said to store on a short-term basis"working memories" that are used to combine new thoughts while they are entering the brain.

Broca's Area Provides the Neural Circuitry for Word Formation. *Broca's area,* shown in Figure 57-5, is located partly in the posterior lateral prefrontal cortex and partly in the premotor area. It is here that plans and motor patterns for expressing individual words or even short phrases are initiated and executed. This area also works in close association with the Wernicke's language comprehension center in the temporal association cortex, as we discuss more fully later in the chapter.

An especially interesting discovery is the following: When a person has already learned one language and then learns a new language, the area in the brain where the new language is stored is slightly removed from the storage area for the first language. If both languages are learned simultaneously, they are stored together in the same area of the brain.

Limbic Association Area. Figures 57-4 and 57-5 show still another association area called the *limbic association area.* This area is found in the anterior pole of the temporal lobe, in the ventral portion of the frontal lobe, and in the cingulate gyrus lying deep in the longitudinal fissure on the midsurface of each cerebral hemisphere. It is concerned primarily with *behavior, emotions,* and *motivation.* We discuss in Chapter 58 that the limbic cortex is part of a much more extensive system, the *limbic system,* that includes a complex set of neuronal structures in the midbasal regions of the brain. This limbic system provides most of the emotional drives for activating other areas of the brain and even provides motivational drive for the process of learning itself.

Area for Recognition of Faces

An interesting type of brain abnormality called *prosopagnosia* is inability to recognize faces. This occurs in people who have extensive damage on the medial undersides of both occipital lobes and along the medioventral surfaces of the temporal lobes, as shown in Figure 57-6. Loss of these face recognition areas, strangely enough, results in little other abnormality of brain function.

One wonders why so much of the cerebral cortex should be reserved for the simple task of face recognition. Most of our daily tasks involve associations with other people, and one can see the importance of this intellectual function.

The occipital portion of this facial recognition area is contiguous with the visual cortex, and the temporal portion is closely associated with the limbic system that has to do with emotions, brain activation, and control of one's behavioral response to the environment, as we see in Chapter 58.

Comprehensive Interpretative Function of the Posterior Superior Temporal Lobe—"Wernicke's Area" (a General Interpretative Area)

The somatic, visual, and auditory association areas all meet one another in the posterior part of the superior temporal lobe, shown in Figure 57-7, where the temporal, parietal, and occipital lobes all come together. This area of confluence of the different sensory interpretative areas

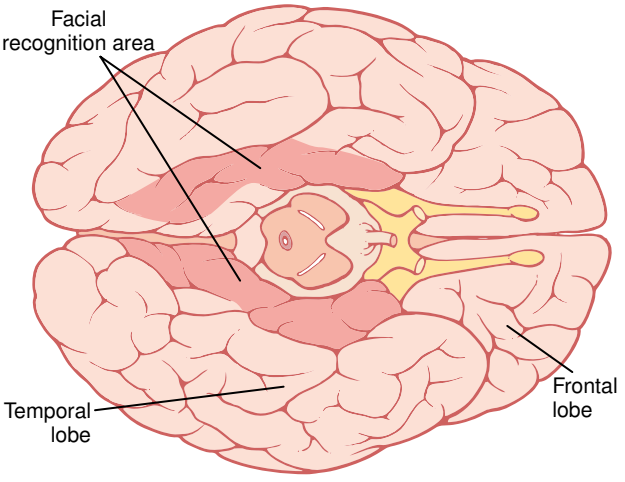


Figure 57-6 Facial recognition areas located on the underside of the brain in the medial occipital and temporal lobes. (Redrawn from Geschwind N: Specializations of the human brain. Sci Am 241:180, 1979. ® 1979 by Scientific American, Inc. All rights reserved.)

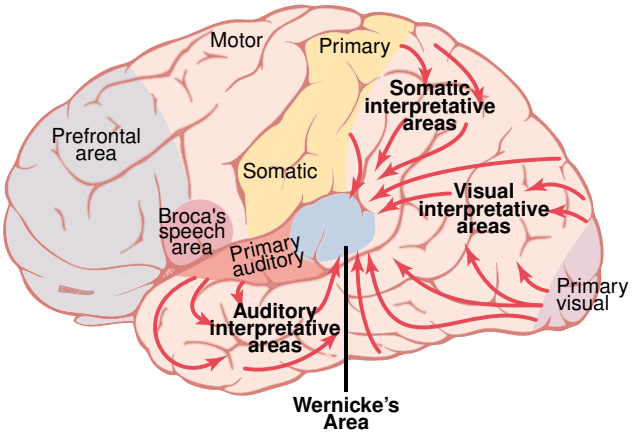


Figure 57-7 Organization of the somatic auditory and visual association areas into a general mechanism for interpretation of sensory experience. All of these feed also into *Wernicke's area,* located in the posterosuperior portion of the temporal lobe. Note also the prefrontal area and *Broca's speech area* in the frontal lobe.

is especially highly developed in the *dominant* side of the brain—the *left side* in almost all right-handed people—and it plays the greatest single role of any part of the cerebral cortex for the higher comprehension levels of brain function that we call *intelligence.* Therefore, this region has been called by different names suggestive of an area that has almost global importance: the *general interpretative area,* the *gnostic area,* the *knowing* area, the *tertiary association area,* and so forth. It is best known as *Wernicke's area* in honor of the neurologist who first described its special significance in intellectual processes.

After severe damage in Wernicke's area, a person might hear perfectly well and even recognize different words but still be unable to arrange these words into a coherent thought. Likewise, the person may be able to read words from the printed page but be unable to recognize the thought that is conveyed.

Electrical stimulation in Wernicke's area of a conscious person occasionally causes a highly complex thought. This is particularly true when the stimulation electrode is passed deep enough into the brain to approach the corresponding connecting areas of the thalamus. The types of thoughts that might be experienced include complicated visual scenes that one might remember from childhood, auditory hallucinations such as a specific musical piece, or even a statement made by a specific person. For this reason, it is believed that activation of Wernicke's area can call forth complicated memory patterns that involve more than one sensory modality even though most of the individual memories may be stored elsewhere. This belief is in accord with the importance of Wernicke's area in interpreting the complicated meanings of different patterns of sensory experiences.

Angular Gyrus—Interpretation of Visual Information. The *angular gyrus* is the most inferior portion of the posterior parietal lobe, lying immediately behind Wernicke's area and fusing posteriorly into the visual areas of the occipital lobe as well. If this region is destroyed while Wernicke's area in the temporal lobe is still intact, the person can still interpret auditory experiences as usual, but the stream of visual experiences passing into Wernicke's area from the visual cortex is mainly blocked. Therefore, the person may be able to see words and even know that they are words but not be able to interpret their meanings. This is the condition called *dyslexia,* or *word blindness.*

Let us again emphasize the global importance of Wernicke's area for processing most intellectual functions of the brain. Loss of this area in an adult usually leads thereafter to a lifetime of almost demented existence.

Concept of the Dominant Hemisphere

The general interpretative functions of Wernicke's area and the angular gyrus, as well as the functions of the speech and motor control areas, are usually much more highly developed in one cerebral hemisphere than in the other. Therefore, this hemisphere is called the *dominant hemisphere.* In about 95 percent of all people, the left hemisphere is the dominant one.

Even at birth, the area of the cortex that will eventually become Wernicke's area is as much as 50 percent larger in the left hemisphere than in the right in more than one half of neonates. Therefore, it is easy to understand why the left side of the brain might become dominant over the right side. However, if for some reason this left side area is damaged or removed in very early childhood, the opposite side of the brain will usually develop dominant characteristics.

A theory that can explain the capability of one hemisphere to dominate the other hemisphere is the following. The attention of the"mind" seems to be directed to one principal thought at a time. Presumably, because the left posterior temporal lobe at birth is usually slightly larger than the right, the left side normally begins to be used to a greater extent than the right. Thereafter, because of the tendency to direct one's attention to the better developed region, the rate of learning in the cerebral hemisphere that gains the first start increases rapidly, whereas in the opposite, less-used side, learning remains slight. Therefore, the left side normally becomes dominant over the right.

In about 95 percent of all people, the left temporal lobe and angular gyrus become dominant, and in the remaining 5 percent, either both sides develop simultaneously to have dual function or, more rarely, the right side alone becomes highly developed, with full dominance.

As discussed later in the chapter, the premotor speech area (Broca's area), located far laterally in the intermediate frontal lobe, is also almost always dominant on the left side of the brain. This speech area is responsible for formation of words by exciting simultaneously the laryngeal muscles, respiratory muscles, and muscles of the mouth.

The motor areas for controlling hands are also dominant in the left side of the brain in about 9 of 10 persons, thus causing right-handedness in most people.

Although the interpretative areas of the temporal lobe and angular gyrus, as well as many of the motor areas, are usually highly developed in only the left hemisphere, these areas receive sensory information from both hemispheres and are capable also of controlling motor activities in both hemispheres. For this purpose, they use mainly fiber pathways in the *corpus callosum* for communication between the two hemispheres. This unitary, cross-feeding organization prevents interference between the two sides of the brain; such interference could create havoc with both mental thoughts and motor responses.

Role of Language in the Function of Wernicke's Area and in Intellectual Functions

A major share of our sensory experience is converted into its language equivalent before being stored in the memory areas of the brain and before being processed for other intellectual purposes. For instance, when we read a book, we do not store the visual images of the printed words but instead store the words themselves or their conveyed thoughts often in language form.

The sensory area of the dominant hemisphere for interpretation of language is Wernicke's area, and this is closely associated with both the primary and secondary hearing areas of the temporal lobe. This close relation probably results from the fact that the first introduction to language is by way of hearing. Later in life, when visual perception of language through the medium of reading develops, the visual information conveyed by written words is then presumably channeled through the angular gyrus, a visual association area, into the already developed Wernicke's language interpretative area of the dominant temporal lobe.

Functions of the Parieto-occipitotemporal Cortex in the Nondominant Hemisphere

When Wernicke's area in the dominant hemisphere of an adult person is destroyed, the person normally loses almost all intellectual functions associated with language or verbal symbolism, such as the ability to read, the ability to perform mathematical operations, and even the ability to think through logical problems. Many other types of interpretative capabilities, some of which use the temporal lobe and angular gyrus regions of the opposite hemisphere, are retained.

Psychological studies in patients with damage to the nondominant hemisphere have suggested that this hemisphere may be especially important for understanding and interpreting music, nonverbal visual experiences (especially visual patterns), spatial relations between the person and their surroundings, the significance of "body language" and intonations of people's voices, and probably many somatic experiences related to use of the limbs and hands. Thus, even though we speak of the "dominant" hemisphere, this is primarily for language-based intellectual functions; the so-called nondominant hemisphere might actually be dominant for some other types of intelligence.

Higher Intellectual Functions of the Prefrontal Association Areas

For years, it has been taught that the prefrontal cortex is the locus of "higher intellect" in the human being, principally because the main difference between the brains of monkeys and of human beings is the great prominence of the human prefrontal areas. Yet efforts to show that the prefrontal cortex is more important in higher intellectual functions than other portions of the brain have not been successful. Indeed, destruction of the language comprehension area in the posterior superior temporal lobe (Wernicke's area) and the adjacent angular gyrus region in the dominant hemisphere causes much more harm to the intellect than does destruction of the prefrontal areas. The prefrontal areas do, however, have less definable but nevertheless important intellectual functions of their own. These functions can best be explained by describing what happens to patients in whom the prefrontal areas have become damaged, as follows.

Several decades ago, before the advent of modern drugs for treating psychiatric conditions, it was found that some patients could receive significant relief from severe psychotic depression by severing the neuronal connections between the prefrontal areas of the brain and the remainder of the brain, that is, by a procedure called *prefrontal lobotomy.* This was done by inserting a blunt, thin-bladed knife through a small opening in the lateral frontal skull on each side of the head and slicing the brain at the back edge of the prefrontal lobes from top to bottom. Subsequent studies in these patients showed the following mental changes:

1. The patients lost their ability to solve complex problems.
2. They became unable to string together sequential tasks to reach complex goals.
3. They became unable to learn to do several parallel tasks at the same time.
4. Their level of aggressiveness was decreased, sometimes markedly, and, in general, they lost ambition.
5. Their social responses were often inappropriate for the occasion, often including loss of morals and little reticence in relation to sexual activity and excretion.
6. The patients could still talk and comprehend language, but they were unable to carry through any long trains of thought, and their moods changed rapidly from sweetness to rage to exhilaration to madness.
7. The patients could also still perform most of the usual patterns of motor function that they had performed throughout life, but often without purpose.

From this information, let us try to piece together a coherent understanding of the function of the prefrontal association areas.

Decreased Aggressiveness and Inappropriate Social Responses. These two characteristics probably result from loss of the ventral parts of the frontal lobes on the underside of the brain. As explained earlier and shown in Figures 57-4 and 57-5, this area is part of the limbic association cortex, rather than of the prefrontal association cortex. This limbic area helps to control behavior, which is discussed in detail in Chapter 58.

Inability to Progress Toward Goals or to Carry Through Sequential Thoughts. We learned earlier in this chapter that the prefrontal association areas have the capability of calling forth information from widespread areas of the brain and using this information to achieve deeper thought patterns for attaining goals.

Although people without prefrontal cortices can still think, they show little concerted thinking in logical sequence for longer than a few seconds or a minute or so at most. One of the results is that people without prefrontal cortices are *easily distracted from their central theme of thought,* whereas people with functioning prefrontal cortices can drive themselves to completion of their thought goals irrespective of distractions.

Elaboration of Thought, Prognostication, and Performance of Higher Intellectual Functions by the Prefrontal Areas—Concept of a "Working Memory." Another function that has been ascribed to the prefrontal areas is *elaboration of thought.* This means simply an increase in depth and abstractness of the different thoughts put together from multiple sources of information. Psychological tests have shown that prefrontal lobectomized lower animals presented with successive bits of sensory information fail to keep track of these bits even in temporary memory, probably because they are distracted so easily that they cannot hold thoughts long enough for memory storage to take place.

This ability of the prefrontal areas to keep track of many bits of information simultaneously and to cause recall of this information instantaneously as it is needed for subsequent thoughts is called the brain's "working memory." This may explain the many functions of the brain that we associate with higher intelligence. In fact, studies have shown that the prefrontal areas are divided into separate segments for storing different types of temporary memory, such as one area for storing shape and form of an object or a part of the body and another for storing movement.

By combining all these temporary bits of working memory, we have the abilities to (1) prognosticate; (2) plan for the future; (3) delay action in response to incoming sensory signals so that the sensory information can be weighed until the best course of response is decided; (4) consider the consequences of motor actions before they are performed; (5) solve complicated mathematical, legal, or philosophical problems; (6) correlate all avenues of information in diagnosing rare diseases; and (7) control our activities in accord with moral laws.

Function of the Brain in Communication—Language Input and Language Output

One of the most important differences between human beings and lower animals is the facility with which human beings can communicate with one another. Furthermore, because neurological tests can easily assess the ability of a person to communicate with others, we know more about the sensory and motor systems related to communication than about any other segment of brain cortex function. Therefore, we will review, with the help of anatomical maps of neural pathways in Figure 57-8, function of the cortex in communication. From this, one will see immediately how the principles of sensory analysis and motor control apply to this art.

There are two aspects to communication: first, the *sensory aspect* (language input), involving the ears and eyes, and, second, the *motor aspect* (language output), involving vocalization and its control.

Sensory Aspects of Communication. We noted earlier in the chapter that destruction of portions of the *auditory* or *visual association areas* of the cortex can result in inability to understand the spoken word or the written word. These effects are called, respectively, *auditory receptive aphasia* and *visual receptive aphasia* or, more commonly, *word deafness* and *word blindness* (also called *dyslexia*).

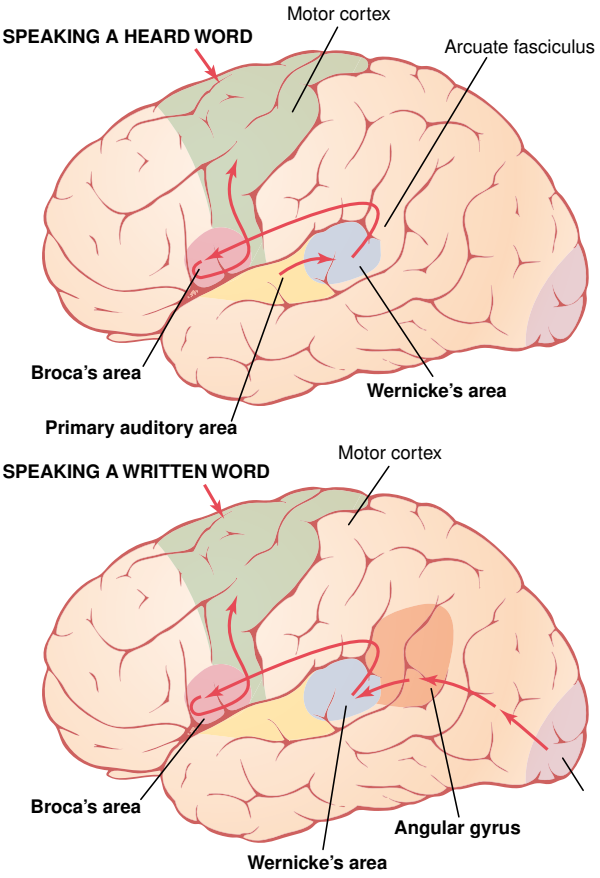


Figure 57-8 Brain pathways for (*top*) perceiving a heard word and then speaking the same word and (*bottom*) perceiving a written word and then speaking the same word. (Redrawn from Geschwind N: Specializations of the human brain. Sci Am 241:180, 1979. ® 1979 by Scientific American, Inc. All rights reserved.)

Wernicke's Aphasia and Global Aphasia. Some people are capable of understanding either the spoken word or the written word but are *unable to interpret the thought* that is expressed. This results most frequently when *Wernicke's area* in the *posterior superior temporal gyrus in the dominant hemisphere* is damaged or destroyed. Therefore, this type of aphasia is called *Wernicke's aphasia.*

When the lesion in Wernicke's area is widespread and extends (1) backward into the angular gyrus region, (2) inferiorly into the lower areas of the temporal lobe, and (3) superiorly into the superior border of the sylvian fissure, the person is likely to be almost totally demented for language understanding or communication and therefore is said to have *global aphasia.*

Motor Aspects of Communication. The process of speech involves two principal stages of mentation: (1) formation in the mind of thoughts to be expressed, as well as choice of words to be used, and then (2) motor control of vocalization and the actual act of vocalization itself.

The formation of thoughts and even most choices of words are the function of sensory association areas of the brain. Again, it is Wernicke's area in the posterior part of the superior temporal gyrus that is most important for this ability. Therefore, a person with either Wernicke's aphasia or global aphasia is unable to formulate the thoughts that are to be communicated. Or, if the lesion is less severe, the person may be able to formulate the thoughts but unable to put together appropriate sequences of words to express the thought. The person sometimes is even fluent with words but the words are jumbled.

Loss of Broca's Area Causes Motor Aphasia. Sometimes a person is capable of deciding what he or she wants to say but cannot make the vocal system emit words instead of noises. This effect, called *motor aphasia,* results from damage to *Broca's speech area,* which lies in the *prefrontal* and *premotor* facial region of the cerebral cortex—about 95 percent of the time in the left hemisphere, as shown in Figures 57-5 and 57-8. Therefore, the *skilled motor patterns* for control of the larynx, lips, mouth, respiratory system, and other accessory muscles of speech are all initiated from this area.

Articulation. Finally, we have the act of articulation, which means the muscular movements of the mouth, tongue, larynx, vocal cords, and so forth that are responsible for the intonations, timing, and rapid changes in intensities of the sequential sounds. The *facial and laryngeal regions of the motor cortex* activate these muscles, and the *cerebellum, basal ganglia,* and *sensory cortex* all help to control the sequences and intensities of muscle contractions, making liberal use of basal ganglial and cerebellar feedback mechanisms described in Chapters 55 and 56. Destruction of any of these regions can cause either total or partial inability to speak distinctly.

Summary. Figure 57-8 shows two principal pathways for communication. The upper half of the figure shows the pathway involved in hearing and speaking. This sequence is the following: (1) reception in the primary auditory area of the sound signals that encode the words; (2) interpretation of the words in Wernicke's area; (3) determination, also in Wernicke's area, of the thoughts and the words to be spoken; (4) transmission of signals from Wernicke's area to Broca's area by way of the *arcuate fasciculus;* (5) activation of the skilled motor programs in Broca's area for control of word formation; and (6) transmission of appropriate signals into the motor cortex to control the speech muscles.

The lower figure illustrates the comparable steps in reading and then speaking in response. The initial receptive area for the words is in the primary visual area rather than in the primary auditory area. Then the information passes through early stages of interpretation in the *angular gyrus region* and finally reaches its full level of recognition in Wernicke's area. From here, the sequence is the same as for speaking in response to the spoken word.

Function of the Corpus Callosum and Anterior Commissure to Transfer Thoughts, Memories, Training, and Other Information Between the Two Cerebral Hemispheres

Fibers in the *corpus callosum* provide abundant bidirectional neural connections between most of the respective cortical areas of the two cerebral hemispheres except for the anterior portions of the temporal lobes; these temporal areas, including especially the *amygdala,* are interconnected by fibers that pass through the *anterior commissure.*

Because of the tremendous number of fibers in the corpus callosum, it was assumed from the beginning that this massive structure must have some important function to correlate activities of the two cerebral hemispheres. However, when the corpus callosum was destroyed in laboratory animals, it was at first difficult to discern deficits in brain function. Therefore, for a long time, the function of the corpus callosum was a mystery.

Properly designed experiments have now demonstrated extremely important functions for the corpus callosum and anterior commissure. These functions can best be explained by describing one of the experiments: A monkey is first prepared by cutting the corpus callosum and splitting the optic chiasm longitudinally so that signals from each eye can go only to the cerebral hemisphere on the side of the eye. Then the monkey is taught to recognize different objects with its right eye while its left eye is covered. Next, the right eye is covered and the monkey is tested to determine whether its left eye can recognize the same objects. The answer to this is that the left eye *cannot* recognize the objects. However, on repeating the same experiment in another monkey with the optic chiasm split but the corpus callosum intact, it is found invariably that recognition in one hemisphere of the brain creates recognition in the opposite hemisphere.

Thus, one of the functions of the corpus callosum and the anterior commissure is to make information stored in the cortex of one hemisphere available to corresponding cortical areas of the opposite hemisphere. Important examples of such cooperation between the two hemispheres are the following.

1. Cutting the corpus callosum blocks transfer of information from Wernicke's area of the dominant hemisphere to the motor cortex on the opposite side of the brain. Therefore, the intellectual functions of Wernicke's area, located in the left hemisphere, lose control over the right

motor cortex that initiates voluntary motor functions of the left hand and arm, even though the usual subconscious movements of the left hand and arm are normal.

2. Cutting the corpus callosum prevents transfer of somatic and visual information from the right hemisphere into Wernicke's area in the left dominant hemisphere. Therefore, somatic and visual information from the left side of the body frequently fails to reach this general interpretative area of the brain and therefore cannot be used for decision making.
3. Finally, people whose corpus callosum is completely sectioned have two entirely separate conscious portions of the brain. For example, in a teenage boy with a sectioned corpus callosum, only the left half of his brain could understand both the written word and the spoken word because the left side was the dominant hemisphere. Conversely, the right side of the brain could understand the written word but not the spoken word. Furthermore, the right cortex could elicit a motor action response to the written word without the left cortex ever knowing why the response was performed.

The effect was quite different when an emotional response was evoked in the right side of the brain: In this case, a subconscious emotional response occurred in the left side of the brain as well. This undoubtedly occurred because the areas of the two sides of the brain for emotions, the anterior temporal cortices and adjacent areas, were still communicating with each other through the anterior commissure that was not sectioned. For instance, when the command "kiss" was written for the right half of his brain to see, the boy immediately and with full emotion said, "No way!" This response required function of Wernicke's area and the motor areas for speech in the left hemisphere because these left-side areas were necessary to speak the words "No way!" But when questioned why he said this, the boy could not explain. Thus, the two halves of the brain have independent capabilities for consciousness, memory storage, communication, and control of motor activities. The corpus callosum is required for the two sides to operate cooperatively at the superficial subconscious level, and the anterior commissure plays an important additional role in unifying the emotional responses of the two sides of the brain.

Thoughts, Consciousness, and Memory

Our most difficult problem in discussing consciousness, thoughts, memory, and learning is that we do not know the neural mechanisms of a thought and we know little about the mechanisms of memory. We know that destruction of large portions of the cerebral cortex does not prevent a person from having thoughts, but it does reduce the *depth* of the thoughts and also the *degree* of awareness of the surroundings.

Each thought certainly involves simultaneous signals in many portions of the cerebral cortex, thalamus, limbic system, and reticular formation of the brain stem. Some basic thoughts probably depend almost entirely on lower centers; the thought of pain is probably a good example because electrical stimulation of the human cortex seldom elicits anything more than mild pain, whereas stimulation of certain areas of the hypothalamus, amygdala, and mesencephalon can cause excruciating pain. Conversely, a type of thought pattern that does require large involvement of the cerebral cortex is that of vision because loss of the visual cortex causes complete inability to perceive visual form or color.

We might formulate a provisional definition of a thought in terms of neural activity as follows: A thought results from a "pattern" of stimulation of many parts of the nervous system at the same time, probably involving most importantly the cerebral cortex, thalamus, limbic system, and upper reticular formation of the brain stem. This is called the *holistic theory* of thoughts. The stimulated areas of the limbic system, thalamus, and reticular formation are believed to determine the general nature of the thought, giving it such qualities as pleasure, displeasure, pain, comfort, crude modalities of sensation, localization to gross areas of the body, and other general characteristics. However, specific stimulated areas of the cerebral cortex determine discrete characteristics of the thought, such as (1) specific localization of sensations on the surface of the body and of objects in the fields of vision, (2) the feeling of the texture of silk, (3) visual recognition of the rectangular pattern of a concrete block wall, and (4) other individual characteristics that enter into one's overall awareness of a particular instant. *Consciousness* can perhaps be described as our continuing stream of awareness of either our surroundings or our sequential thoughts.

Memory—Roles of Synaptic Facilitation and Synaptic Inhibition

Memories are stored in the brain by changing the basic sensitivity of synaptic transmission between neurons as a result of previous neural activity. The new or facilitated pathways are called *memory traces.* They are important because once the traces are established, they can be selectively activated by the thinking mind to reproduce the memories.

Experiments in lower animals have demonstrated that memory traces can occur at all levels of the nervous system. Even spinal cord reflexes can change at least slightly in response to repetitive cord activation, and these reflex changes are part of the memory process. Also, long-term memories result from changed synaptic conduction in lower brain centers. However, most memory that we associate with intellectual processes is based on memory traces in the cerebral cortex.

Positive and Negative Memory—"Sensitization" or "Habituation" of Synaptic Transmission. Although we often think of memories as being *positive* recollections of previous thoughts or experiences, probably the greater share of our memories is *negative,* not positive. That is, our brain is inundated with sensory information from all

our senses. If our minds attempted to remember all this information, the memory capacity of the brain would be rapidly exceeded. Fortunately, the brain has the capability to learn to ignore information that is of no consequence. This results from *inhibition* of the synaptic pathways for this type of information; the resulting effect is called *habituation.* This is a type of *negative* memory.

Conversely, for incoming information that causes important consequences such as pain or pleasure, the brain has a different automatic capability of enhancing and storing the memory traces. This is *positive* memory. It results from *facilitation* of the synaptic pathways, and the process is called *memory sensitization*. We discuss later that special areas in the basal limbic regions of the brain determine whether information is important or unimportant and make the subconscious decision whether to store the thought as a *sensitized* memory trace or to suppress it.

Classification of Memories. We know that some memories last for only a few seconds, whereas others last for hours, days, months, or years. For the purpose of discussing these, let us use a common classification of memories that divides memories into (1) *short-term memory,* which includes memories that last for seconds or at most minutes unless they are converted into longer-term memories; (2) *intermediate long-term memories,* which last for days to weeks but then fade away; and (3) *long-term memory,* which, once stored, can be recalled up to years or even a lifetime later.

In addition to this general classification of memories, we also discussed earlier (in connection with the prefrontal lobes) another type of memory, called"working memory," which includes mainly short-term memory that is used during the course of intellectual reasoning but is terminated as each stage of the problem is resolved.

Memories are frequently classified according to the type of information that is stored. One of these classifications divides memory into *declarative memory* and *skill memory,* as follows:

1. *Declarative memory* basically means memory of the various details of an integrated thought, such as memory of an important experience that includes (1) memory of the surroundings, (2) memory of time relationships, (3) memory of causes of the experience, (4) memory of the meaning of the experience, and (5) memory of one's deductions that were left in the person's mind.
2. *Skill memory* is frequently associated with motor activities of the person's body, such as all the skills developed for hitting a tennis ball, including automatic memories to (1) sight the ball, (2) calculate the relationship and speed of the ball to the racquet, and (3) deduce rapidly the motions of the body, the arms, and the racquet required to hit the ball as desired—all of these activated instantly based on previous learning of the game of tennis—then moving on to the next stroke of the game while forgetting the details of the previous stroke.

Short-Term Memory

Short-term memory is typified by one's memory of 7 to 10 numerals in a telephone number (or 7 to 10 other discrete facts) for a few seconds to a few minutes at a time but lasting only as long as the person continues to think about the numbers or facts.

Many physiologists have suggested that this short-term memory is caused by continual neural activity resulting from nerve signals that travel around and around a temporary memory trace in a *circuit of reverberating neurons.* It has not yet been possible to prove this theory. Another possible explanation of short-term memory is *presynaptic facilitation or inhibition*. This occurs at synapses that lie on terminal nerve fibrils immediately before these fibrils synapse with a subsequent neuron. The neurotransmitter chemicals secreted at such terminals frequently cause facilitation or inhibition lasting for seconds up to several minutes. Circuits of this type could lead to short-term memory.

Intermediate Long-Term Memory

Intermediate long-term memories may last for many minutes or even weeks. They will eventually be lost unless the memory traces are activated enough to become more permanent; then they are classified as long-term memories. Experiments in primitive animals have demonstrated that memories of the intermediate long-term type can result from temporary chemical or physical changes, or both, in either the synapse presynaptic terminals or the synapse postsynaptic membrane, changes that can persist for a few minutes up to several weeks. These mechanisms are so important that they deserve special description.

Memory Based on Chemical Changes in the Presynaptic Terminal or Postsynaptic Neuronal Membrane

Figure 57-9 shows a mechanism of memory studied especially by Kandel and his colleagues that can cause memories lasting from a few minutes up to 3 weeks in the large snail *Aplysia.* In this figure, there are two synaptic terminals. One terminal is from a sensory input neuron and terminates directly on the surface of the neuron that is to be stimulated; this is called the *sensory terminal.* The other terminal is a *presynaptic ending* that lies on the surface of the sensory terminal, and it is called the *facilitator terminal.* When the sensory terminal is stimulated repeatedly but without stimulation of the facilitator terminal, signal transmission at first is great, but it becomes less and less intense with repeated stimulation until transmission almost ceases. This phenomenon is *habituation,* as was explained previously. It is a type of *negative* memory that causes the neuronal circuit to lose its response to repeated events that are insignificant.

Conversely, if a noxious stimulus excites the facilitator terminal at the same time that the sensory terminal is stimulated, then instead of the transmitted signal into

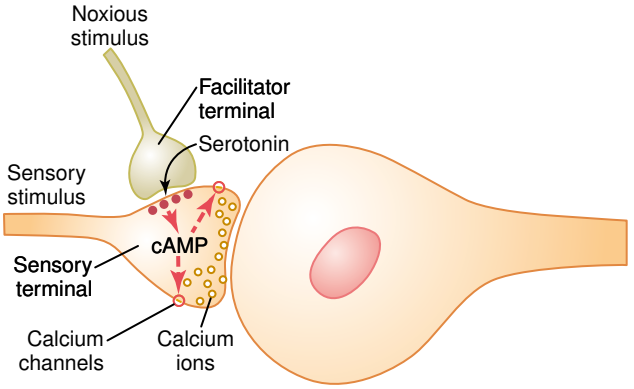


Figure 57-9 Memory system that has been discovered in the snail *Aplysia*.

the postsynaptic neuron becoming progressively weaker, the ease of transmission becomes stronger and stronger; and it will remain strong for minutes, hours, days, or, with more intense training, up to about 3 weeks even without further stimulation of the facilitator terminal. Thus, the noxious stimulus causes the memory pathway through the sensory terminal to become *facilitated* for days or weeks thereafter. It is especially interesting that even after habituation has occurred, this pathway can be converted back to a facilitated pathway with only a few noxious stimuli.

Molecular Mechanism of Intermediate Memory

Mechanism for Habituation. At the molecular level, the habituation effect in the sensory terminal results from progressive closure of calcium channels through the terminal membrane, though the cause of this calcium channel closure is not fully known. Nevertheless, much smaller than normal amounts of calcium ions can diffuse into the habituated terminal, and much less sensory terminal transmitter is therefore released because calcium entry is the principal stimulus for transmitter release (as was discussed in Chapter 45).

Mechanism for Facilitation. In the case of facilitation, at least part of the molecular mechanism is believed to be the following:

1. Stimulation of the facilitator presynaptic terminal at the same time that the sensory terminal is stimulated causes *serotonin* release at the facilitator synapse on the surface of the sensory terminal.
2. The serotonin acts on *serotonin receptors* in the sensory terminal membrane, and these receptors activate the enzyme *adenyl cyclase* inside the membrane. The adenyl cyclase then causes formation of *cyclic adenosine monophosphate (cAMP)* also inside the sensory presynaptic terminal.
3. The cyclic AMP activates a *protein kinase* that causes phosphorylation of a protein that itself is part of the potassium channels in the sensory synaptic terminal membrane; this in turn blocks the channels for potassium conductance. The blockage can last for minutes up to several weeks.
4. Lack of potassium conductance causes a greatly prolonged action potential in the synaptic terminal because flow of potassium ions out of the terminal is necessary for rapid recovery from the action potential.
5. The prolonged action potential causes prolonged activation of the calcium channels, allowing tremendous quantities of calcium ions to enter the sensory synaptic terminal. These calcium ions cause greatly increased transmitter release by the synapse, thereby markedly facilitating synaptic transmission to the subsequent neuron.

Thus, in a very indirect way, the associative effect of stimulating the facilitator terminal at the same time that the sensory terminal is stimulated causes prolonged increase in excitatory sensitivity of the sensory terminal, and this establishes the memory trace. Studies by Byrne and colleagues, also in the snail *Aplysia,* have suggested still another mechanism of synaptic memory. Their studies have shown that stimuli from separate sources acting on a single neuron, under appropriate conditions, can cause long-term changes in *membrane properties of the postsynaptic neuron* instead of in the presynaptic neuronal membrane, but leading to essentially the same memory effects.

Long-Term Memory

There is no obvious demarcation between the more prolonged types of intermediate long-term memory and true long-term memory. The distinction is one of degree. However, long-term memory is generally believed to result from actual *structural changes,* instead of only chemical changes, at the synapses, and these enhance or suppress signal conduction. Again, let us recall experiments in primitive animals (where the nervous systems are much easier to study) that have aided immensely in understanding possible mechanisms of long-term memory.

Structural Changes Occur in Synapses During the Development of Long-Term Memory

Electron microscopic pictures taken from invertebrate animals have demonstrated multiple physical structural changes in many synapses during development of long-term memory traces. The structural changes will not occur if a drug is given that blocks DNA stimulation of protein replication in the presynaptic neuron; nor will the permanent memory trace develop. Therefore, it appears that development of true long-term memory depends on physically restructuring the synapses themselves in a way that changes their sensitivity for transmitting nervous signals.

The most important of the physical structural changes that occur are the following:

1. Increase in vesicle release sites for secretion of transmitter substance

2. Increase in number of transmitter vesicles released
3. Increase in number of presynaptic terminals
4. Changes in structures of the dendritic spines that permit transmission of stronger signals

Thus, in several different ways, the structural capability of synapses to transmit signals appears to increase during establishment of true long-term memory traces.

Number of Neurons and Their Connectivities Often Change Significantly During Learning

During the first few weeks, months, and perhaps even year or so of life, many parts of the brain produce a great excess of neurons and the neurons send out numerous axon branches to make connections with other neurons. If the new axons fail to connect with appropriate neurons, muscle cells, or gland cells, the new axons themselves will dissolute within a few weeks. Thus, the number of neuronal connections is determined by specific *nerve growth factors* released retrogradely from the stimulated cells. Furthermore, when insufficient connectivity occurs, the entire neuron that is sending out the axon branches might eventually disappear.

Therefore, soon after birth, there is a principle of "use it or lose it" that governs the final number of neurons and their connectivities in respective parts of the human nervous system. This is a type of learning. For example, if one eye of a newborn animal is covered for many weeks after birth, neurons in alternate stripes of the cerebral visual cortex—neurons normally connected to the covered eye—will degenerate, and the covered eye will remain either partially or totally blind for the remainder of life. Until recently, it was believed that very little"learning" is achieved in adult human beings and animals by modification of numbers of neurons in the memory circuits; however, recent research suggests that even adults use this mechanism to at least some extent.

Consolidation of Memory

For short-term memory to be converted into long-term memory that can be recalled weeks or years later, it must become "consolidated." That is, the short-term memory if activated repeatedly will initiate chemical, physical, and anatomical changes in the synapses that are responsible for the long-term type of memory. This process requires 5 to 10 minutes for minimal consolidation and 1 hour or more for strong consolidation. For instance, if a strong sensory impression is made on the brain but is then followed within a minute or so by an electrically induced brain convulsion, the sensory experience will not be remembered. Likewise, brain concussion, sudden application of deep general anesthesia, or any other effect that temporarily blocks the dynamic function of the brain can prevent consolidation.

Consolidation and the time required for it to occur can probably be explained by the phenomenon of rehearsal of the short-term memory as follows.

Rehearsal Enhances the Transference of Short-Term Memory into Long-Term Memory. Studies have shown that rehearsal of the same information again and again in the mind accelerates and potentiates the degree of transfer of short-term memory into long-term memory and therefore accelerates and enhances consolidation. The brain has a natural tendency to rehearse newfound information, especially newfound information that catches the mind's attention. Therefore, over a period of time, the important features of sensory experiences become progressively more and more fixed in the memory stores. This explains why a person can remember small amounts of information studied in depth far better than large amounts of information studied only superficially. It also explains why a person who is wide awake can consolidate memories far better than a person who is in a state of mental fatigue.

New Memories Are Codified During Consolidation. One of the most important features of consolidation is that new memories are *codified* into different classes of information. During this process, similar types of information are pulled from the memory storage bins and used to help process the new information. The new and old are compared for similarities and differences, and part of the storage process is to store the information about these similarities and differences, rather than to store the new information unprocessed. Thus, during consolidation, the new memories are not stored randomly in the brain but are stored in direct association with other memories of the same type. This is necessary if one is to be able to "search" the memory store at a later date to find the required information.

Role of Specific Parts of the Brain in the Memory Process

Hippocampus Promotes Storage of Memories—Anterograde Amnesia After Hippocampal Lesions. The hippocampus is the most medial portion of the temporal lobe cortex, where it folds first medially underneath the brain and then upward into the lower, inside surface of the lateral ventricle. The two hippocampi have been removed for the treatment of epilepsy in a few patients. This procedure does not seriously affect the person's memory for information stored in the brain before removal of the hippocampi. However, after removal, these people have virtually no capability thereafter for storing *verbal and symbolic types* of memories (declarative types of memory) in long-term memory, or even in intermediate memory lasting longer than a few minutes. Therefore, these people are unable to establish new long-term memories of those types of information that are the basis of intelligence. This is called *anterograde amnesia*.

But why are the hippocampi so important in helping the brain to store new memories? The probable answer is that the hippocampi are among the most important output pathways from the "reward" and "punishment" areas

of the limbic system, as explained in Chapter 58. Sensory stimuli or thoughts that cause pain or aversion excite the limbic *punishment centers,* and stimuli that cause pleasure, happiness, or sense of reward excite the limbic *reward centers.* All these together provide the background mood and motivations of the person. Among these motivations is the drive in the brain to remember those experiences and thoughts that are either pleasant or unpleasant. The hippocampi especially and to a lesser degree the dorsal medial nuclei of the thalamus, another limbic structure, have proved especially important in making the decision about which of our thoughts are important enough on a basis of reward or punishment to be worthy of memory.

Retrograde Amnesia—Inability to Recall Memories from the Past. When retrograde amnesia occurs, the degree of amnesia for recent events is likely to be much greater than for events of the distant past. The reason for this difference is probably that the distant memories have been rehearsed so many times that the memory traces are deeply ingrained, and elements of these memories are stored in widespread areas of the brain.

In some people who have hippocampal lesions, some degree of retrograde amnesia occurs along with anterograde amnesia, which suggests that these two types of amnesia are at least partially related and that hippocampal lesions can cause both. However, damage in some thalamic areas may lead specifically to retrograde amnesia without causing significant anterograde amnesia. A possible explanation of this is that the thalamus may play a role in helping the person "search" the memory storehouses and thus "read out" the memories. That is, the memory process not only requires the storing of memories but also an ability to search and find the memory at a later date. The possible function of the thalamus in this process is discussed further in Chapter 58.

Hippocampi Are Not Important in Reflexive Learning. People with hippocampal lesions usually do not have difficulty in learning physical skills that do not involve verbalization or symbolic types of intelligence. For instance, these people can still learn the rapid hand and physical skills required in many types of sports. This type of learning is called *skill learning* or *reflexive learning;* it depends on physically repeating the required tasks over and over again, rather than on symbolical rehearsing in the mind.

Bibliography

Bailey CH, Kandel ER: Synaptic remodeling, synaptic growth and the storage of long-term memory in Aplysia, *Prog Brain Res* 169:179, 2008.

Glickstein M: Paradoxical inter-hemispheric transfer after section of the cerebral commissures, *Exp Brain Res* 192:425, 2009.

Haggard P: Human volition: towards a neuroscience of will, *Nat Rev Neurosci* 9:934, 2008.

Hickok G, Poeppel D: The cortical organization of speech processing, *Nat Rev Neurosci* 8:393, 2007.

Kandel ER: The molecular biology of memory storage: a dialogue between genes and synapses, *Science* 294:1030, 2001.

Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, ed 4, New York, 2000, McGraw-Hill.

LaBar KS, Cabeza R: Cognitive neuroscience of emotional memory, *Nat Rev Neurosci* 7:54, 2006.

Lee YS, Silva AJ: The molecular and cellular biology of enhanced cognition, *Nat Rev Neurosci* 10:126, 2009.

Lynch MA: Long-term potentiation and memory, *Physiol Rev* 84:87, 2004.

Mansouri FA, Tanaka K, Buckley MJ: Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex, *Nat Rev Neurosci* 10:141, 2009.

Nader K, Hardt O: A single standard for memory: the case for reconsolidation, *Nat Rev Neurosci* 10:224, 2009.

Osada T, Adachi Y, Kimura HM, et al: Towards understanding of the cortical network underlying associative memory, *Philos Trans R Soc Lond B Biol Sci* 363:2187, 2008.

Roth TL, Sweatt JD: Rhythms of memory, *Nat Neurosci* 11:993, 2008.

Shirvalkar PR: Hippocampal neural assemblies and conscious remembering, *J Neurophysiol* 101:2197, 2009.

Tanji J, Hoshi E: Role of the lateral prefrontal cortex in executive behavioral control, *Physiol Rev* 88:37, 2008.

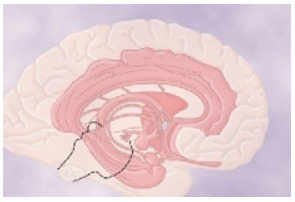
Tronson NC, Taylor JR: Molecular mechanisms of memory reconsolidation, *Nat Rev Neurosci* 8:262, 2007.

van Strien NM, Cappaert NL, Witter MP: The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network, *Nat Rev Neurosci* 10:272, 2009.

Wilson DA, Linster C: Neurobiology of a simple memory, *J Neurophysiol* 100:2, 2008.

Zamarian L, Ischebeck A, Delazer M: Neuroscience of learning arithmetic—evidence from brain imaging studies, *Neurosci Biobehav Rev* 33:909, 2009.

Behavioral and Motivational Mechanisms of the Brain—The Limbic System and the Hypothalamus



Control of behavior is a function of the entire nervous system. Even the wakefulness and sleep cycle discussed in Chapter 59 is one of our most important behavioral patterns.

In this chapter, we deal first with those mechanisms that control levels of activity in the different parts of the brain. Then we discuss the causes of motivational drives, especially motivational control of the learning process and feelings of pleasure and punishment. These functions of the nervous system are performed mainly by the basal regions of the brain, which together are loosely called the *limbic system,* meaning the "border" system.

Activating—Driving Systems of the Brain

Without continuous transmission of nerve signals from the lower brain into the cerebrum, the cerebrum becomes useless. In fact, severe compression of the brain stem at the juncture between the mesencephalon and cerebrum, as sometimes results from a pineal tumor, often causes the person to go into unremitting coma lasting for the remainder of his or her life.

Nerve signals in the brain stem activate the cerebral part of the brain in two ways: (1) by directly stimulating a background level of neuronal activity in wide areas of the brain and (2) by activating neurohormonal systems that release specific facilitory or inhibitory hormone-like neurotransmitter substances into selected areas of the brain.

Control of Cerebral Activity by Continuous Excitatory Signals from the Brain Stem

Reticular Excitatory Area of the Brain Stem

Figure 58-1 shows a general system for controlling the level of activity of the brain. The central driving component of this system is an excitatory area located in the *reticular substance of the pons and mesencephalon*. This area is also known by the name *bulboreticular facilitory area*. We also discuss this area in Chapter 55 because it is the same brain stem reticular area that transmits facilitory signals *downward to the spinal cord* to maintain tone in the antigravity muscles and to control levels of activity of the spinal cord reflexes. In addition to these downward signals, this area also sends a profusion of signals in the upward direction. Most of these go first to the thalamus, where they excite a different set of neurons that transmit nerve signals to all regions of the cerebral cortex, as well as to multiple subcortical areas.

The signals passing through the thalamus are of two types. One type is rapidly transmitted action potentials that excite the cerebrum for only a few milliseconds. These originate from large neuronal cell bodies that lie throughout the brain stem reticular area. Their nerve endings release the neurotransmitter substance *acetylcholine,* which serves as an excitatory agent, lasting for only a few milliseconds before it is destroyed.

The second type of excitatory signal originates from large numbers of small neurons spread throughout the brain stem reticular excitatory area. Again, most of these pass to the thalamus, but this time through small, slowly conducting fibers that synapse mainly in the intralaminar nuclei of the thalamus and in the reticular nuclei over the surface of the thalamus. From here, additional small fibers are distributed everywhere in the cerebral cortex. The excitatory effect caused by this system of fibers can build up progressively for many seconds to a minute or more, which suggests that its signals are especially important for controlling longer-term background excitability level of the brain.

Excitation of the Excitatory Area by Peripheral Sensory Signals. The level of activity of the excitatory area in the brain stem, and therefore the level of activity of the entire brain, is determined to a great extent by the number and type of sensory signals that enter the brain from the periphery. Pain signals in particular increase activity in this excitatory area and therefore strongly excite the brain to attention.

The importance of sensory signals in activating the excitatory area is demonstrated by the effect of cutting the brain stem above the point where the fifth cerebral nerves enter the pons. These nerves are the highest nerves entering the brain that transmit significant numbers of somatosensory signals into the brain. When all these

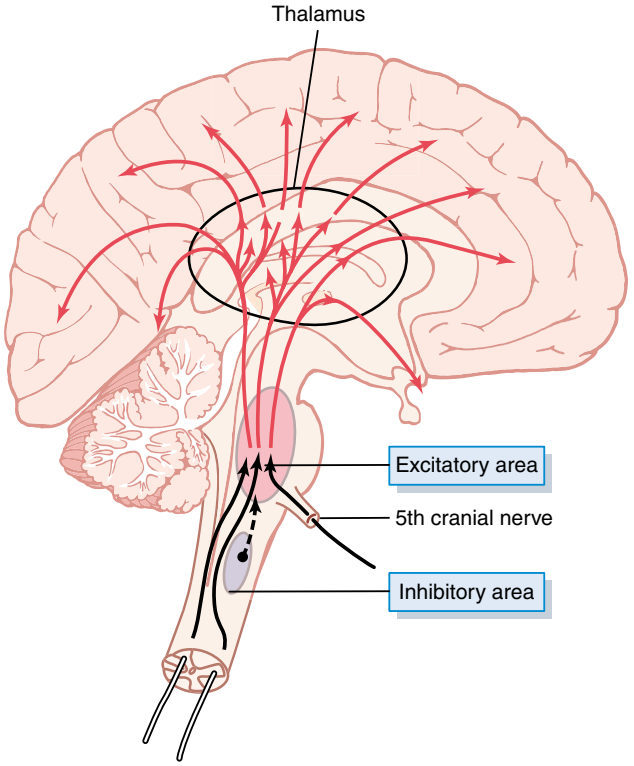


Figure 58-1 *Excitatory-activating system* of the brain. Also shown is an *inhibitory area* in the medulla that can inhibit or depress the activating system.

input sensory signals are gone, the level of activity in the brain excitatory area diminishes abruptly, and the brain proceeds instantly to a state of greatly reduced activity, approaching a permanent state of coma. But when the brain stem is transected *below* the fifth nerves, which leaves much input of sensory signals from the facial and oral regions, the coma is averted.

Increased Activity of the Excitatory Area Caused by Feedback Signals Returning from the Cerebral Cortex. Not only do excitatory signals pass to the cerebral cortex from the bulboreticular excitatory area of the brain stem, but feedback signals also return from the cerebral cortex back to this same area. Therefore, any time the cerebral cortex becomes activated by either brain thought processes or motor processes, signals are sent from the cortex to the brain stem excitatory area, which in turn sends still more excitatory signals to the cortex. This helps to maintain the level of excitation of the cerebral cortex or even to enhance it. This is a general mechanism of *positive feedback* that allows any beginning activity in the cerebral cortex to support still more activity, thus leading to an "awake" mind.

Thalamus Is a Distribution Center That Controls Activity in Specific Regions of the Cortex. As pointed out in Chapter 57 and shown in Figure 57-2, almost every area of the cerebral cortex connects with its own highly specific area in the thalamus. Therefore, electrical stimulation of a specific point in the thalamus generally activates its own specific small region of the cortex. Furthermore, signals regularly reverberate back and forth between the thalamus and the cerebral cortex, the thalamus exciting the cortex and the cortex then re-exciting the thalamus by way of return fibers. It has been suggested that the thinking process establishes long-term memories by activating such back-and-forth reverberation of signals.

Can the thalamus also function to call forth specific memories from the cortex or to activate specific thought processes? Proof of this is still lacking, but the thalamus does have appropriate neuronal circuitry for these purposes.

A Reticular Inhibitory Area Is Located in the Lower Brain Stem

Figure 58-1 shows still another area that is important in controlling brain activity. This is the reticular *inhibitory area,* located medially and ventrally in the medulla. In Chapter 55, we learned that this area can inhibit the reticular facilitory area of the upper brain stem and thereby decrease activity in the superior portions of the brain as well. One of the mechanisms for this is to excite *serotonergic neurons;* these in turn secrete the inhibitory neurohormone *serotonin* at crucial points in the brain; we discuss this in more detail later.

Neurohormonal Control of Brain Activity

Aside from direct control of brain activity by specific transmission of nerve signals from the lower brain areas to the cortical regions of the brain, still another physiologic mechanism is very often used to control brain activity. This is to secrete *excitatory* or *inhibitory neurotransmitter hormonal agents* into the substance of the brain. These neurohormones often persist for minutes or hours and thereby provide long periods of control, rather than just instantaneous activation or inhibition.

Figure 58-2 shows three neurohormonal systems that have been studied in detail in the rat brain: (1) a *norepinephrine system,* (2) a *dopamine system,* and (3) a *serotonin system.* Norepinephrine usually functions as an excitatory hormone, whereas serotonin is usually inhibitory and dopamine is excitatory in some areas but inhibitory in others. As would be expected, these three systems have different effects on levels of excitability in different parts of the brain. The norepinephrine system spreads to virtually every area of the brain, whereas the serotonin and dopamine systems are directed much more to specific brain regions—the dopamine system mainly into the basal ganglial regions and the serotonin system more into the midline structures.

Neurohormonal Systems in the Human Brain. Figure 58-3 shows the brain stem areas in the human brain for activating four neurohormonal systems, the same three discussed for the rat and one other, the *acetylcholine system*. Some of the specific functions of these are as follows:

1. *The locus ceruleus and the norepinephrine system.* The locus ceruleus is a small area located bilaterally and posteriorly at the juncture between the pons and mesencephalon. Nerve fibers from this area spread throughout the brain, the same as shown for the rat in the top frame of Figure 58-2, and they secrete

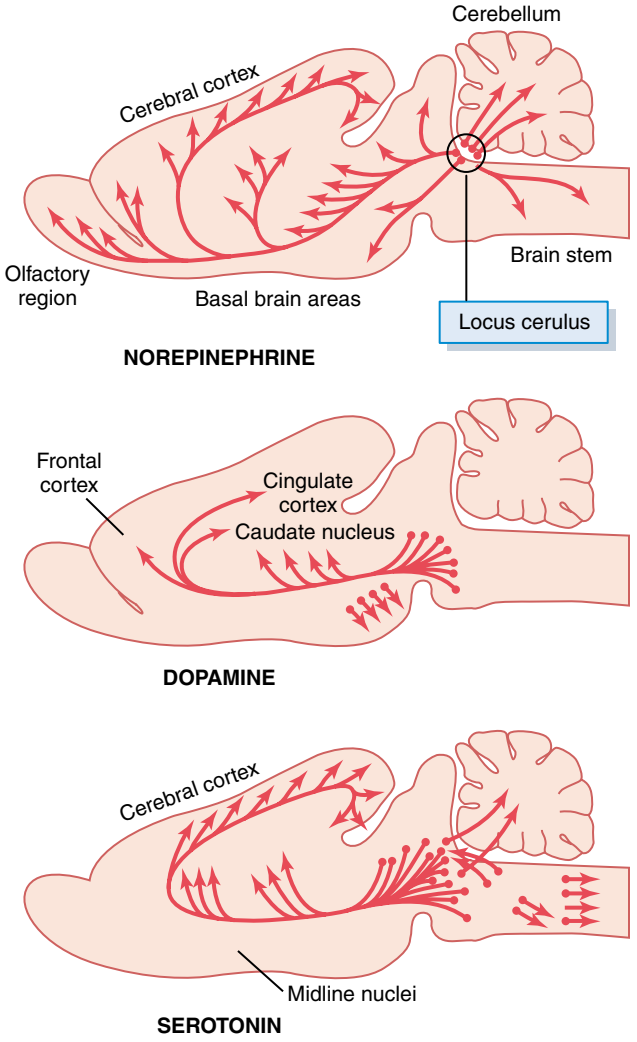


Figure 58-2 Three neurohormonal systems that have been mapped in the rat brain: a *norepinephrine system,* a *dopamine system,* and a *serotonin system.* (Adapted from Kelly, after Cooper, Bloom, and Roth: In: Kandel ER, Schwartz JH (eds): Principles of Neural Science, 2nd ed. New York: Elsevier, 1985.)

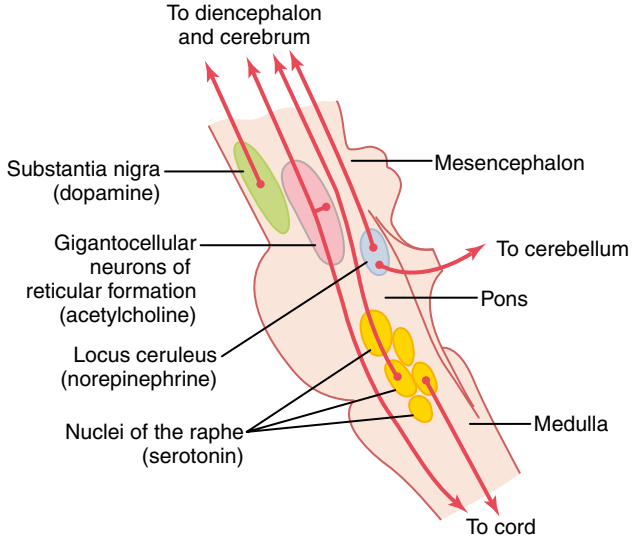


Figure 58-3 Multiple centers in the brain stem, the neurons of which secrete different transmitter substances (specified in parentheses). These neurons send control signals upward into the diencephalon and cerebrum and downward into the spinal cord.

norepinephrine. The norepinephrine generally excites the brain to increased activity. However, it has inhibitory effects in a few brain areas because of inhibitory receptors at certain neuronal synapses. Chapter 59 covers how this system probably plays an important role in causing dreaming, thus leading to a type of sleep called rapid eye movement sleep *(REM sleep).*

2. *The substantia nigra and the dopamine system.* The substantia nigra is discussed in Chapter 56 in relation to the basal ganglia. It lies anteriorly in the superior mesencephalon, and its neurons send nerve endings mainly to the caudate nucleus and putamen of the cerebrum, where they secrete *dopamine.* Other neurons located in adjacent regions also secrete dopamine, but they send their endings into more ventral areas of the brain, especially to the hypothalamus and the limbic system. The dopamine is believed to act as an inhibitory transmitter in the basal ganglia, but in some other areas of the brain it is possibly excitatory. Also, remember from Chapter 56 that destruction of the dopaminergic neurons in the substantia nigra is the basic cause of Parkinson's disease.
3. *The raphe nuclei and the serotonin system.* In the midline of the pons and medulla are several thin nuclei called the raphe nuclei. Many of the neurons in these nuclei secrete *serotonin.* They send fibers into the diencephalon and a few fibers to the cerebral cortex; still other fibers descend to the spinal cord. The serotonin secreted at the cord fiber endings has the ability to suppress pain, which was discussed in Chapter 48. The serotonin released in the diencephalon and cerebrum almost certainly plays an essential inhibitory role to help cause normal sleep, as we discuss in Chapter 59.
4. *The gigantocellular neurons of the reticular excitatory area and the acetylcholine system.* Earlier we discussed the gigantocellular neurons *(giant cells)* in the reticular excitatory area of the pons and mesencephalon. The fibers from these large cells divide immediately into two branches, one passing upward to the higher levels of the brain and the other passing downward through the reticulospinal tracts into the spinal cord. The neurohormone secreted at their terminals is *acetylcholine.* In most places, the acetylcholine functions as an excitatory neurotransmitter. Activation of these acetylcholine neurons leads to an acutely awake and excited nervous system.

Other Neurotransmitters and Neurohormonal Substances Secreted in the Brain. Without describing their function, the following is a partial list of still other neurohormonal substances that function either at specific synapses or by release into the fluids of the brain: enkephalins, gamma-aminobutyric acid, glutamate, vasopressin, adrenocorticotropic hormone, α-melanocyte stimulating hormone (α-MSH), neuropeptide-Y (NPY), epinephrine, histamine, endorphins, angiotensin II, and neurotensin. Thus, there are multiple neurohormonal systems in the brain, the activation of each of which plays its own role in controlling a different quality of brain function.

Limbic System

The word "limbic" means "border." Originally, the term "limbic" was used to describe the border structures around the basal regions of the cerebrum, but as we have learned more about the functions of the limbic system, the term *limbic system* has been expanded to mean the entire neuronal circuitry that controls emotional behavior and motivational drives.

A major part of the limbic system is the *hypothalamus,* with its related structures. In addition to their roles in behavioral control, these areas control many internal conditions of the body, such as body temperature, osmolality of the body fluids, and the drives to eat and drink and to control body weight. These internal functions are collectively called *vegetative functions* of the brain, and their control is closely related to behavior.

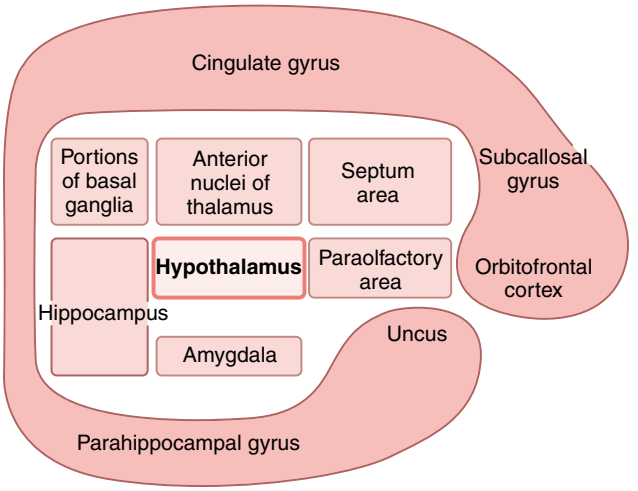


Figure 58-5 Limbic system, showing the key position of the hypothalamus.

Functional Anatomy of the Limbic System; Key Position of the Hypothalamus

Figure 58-4 shows the anatomical structures of the limbic system, demonstrating that they are an interconnected complex of basal brain elements. Located in the middle of all these is the extremely small *hypothalamus,* which from a physiologic point of view is one of the central elements of the limbic system. Figure 58-5 illustrates schematically this key position of the hypothalamus in the limbic system and shows surrounding it other subcortical structures of the limbic system, including the *septum, paraolfactory area, anterior nucleus of the thalamus, portions of the basal ganglia, hippocampus,* and *amygdala.*

And surrounding the subcortical limbic areas is the *limbic cortex,* composed of a ring of cerebral cortex in each side of the brain (1) beginning in the *orbitofrontal area* on the ventral surface of the frontal lobes, (2) extending upward into the *subcallosal gyrus,* (3) then over the

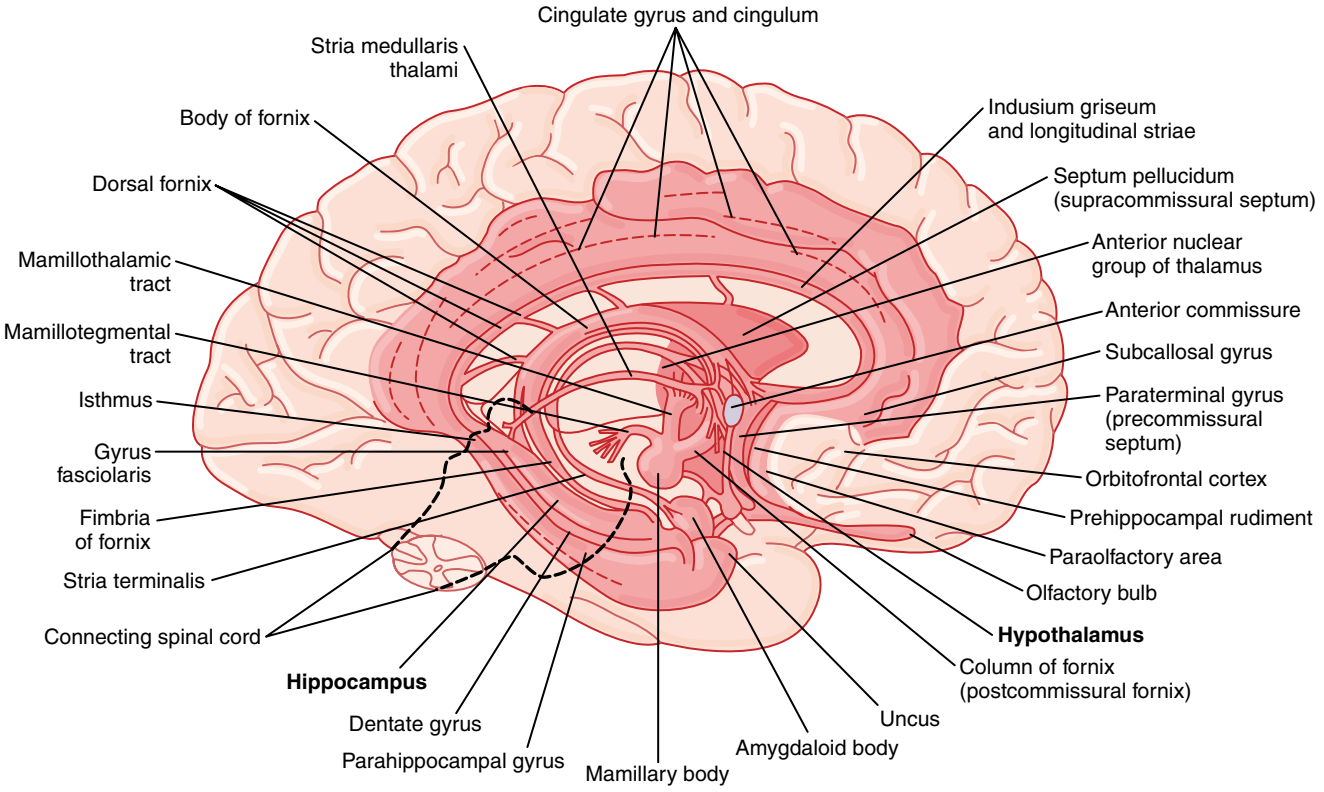


Figure 58-4 Anatomy of the limbic system, shown in the dark pink area. (Redrawn from Warwick R, Williams PL: Gray's Anatomy, 35th Br. ed. London: Longman Group Ltd, 1973.)

top of the corpus callosum onto the medial aspect of the cerebral hemisphere in the *cingulate gyrus,* and finally (4) passing behind the corpus callosum and downward onto the ventromedial surface of the temporal lobe to the *parahippocampal gyrus* and *uncus.*

Thus, on the medial and ventral surfaces of each cerebral hemisphere is a ring of mostly *paleocortex* that surrounds a group of deep structures intimately associated with overall behavior and emotions. In turn, this ring of limbic cortex functions as a two-way communication and association linkage between the *neocortex* and the lower limbic structures.

Many of the behavioral functions elicited from the hypothalamus and other limbic structures are also mediated through the reticular nuclei in the brain stem and their associated nuclei. It was pointed out in Chapter 55, as well as earlier in this chapter, that stimulation of the excitatory portion of this reticular formation can cause high degrees of cerebral excitability while also increasing the excitability of much of the spinal cord synapses. In Chapter 60, we see that most of the hypothalamic signals for controlling the autonomic nervous system are also transmitted through synaptic nuclei located in the brain stem.

An important route of communication between the limbic system and the brain stem is the *medial forebrain bundle,* which extends from the septal and orbitofrontal regions of the cerebral cortex downward through the middle of the hypothalamus to the brain stem reticular formation. This bundle carries fibers in both directions, forming a trunk line communication system. A second route of communication is through short pathways among the reticular formation of the brain stem, thalamus, hypothalamus, and most other contiguous areas of the basal brain.

Hypothalamus, a Major Control Headquarters for the Limbic System

The hypothalamus, despite its small size of only a few cubic centimeters, has two-way communicating pathways with all levels of the limbic system. In turn, the hypothalamus and its closely allied structures send output signals in three directions: (1) backward and downward to the brain stem, mainly into the reticular areas of the mesencephalon, pons, and medulla and from these areas into the peripheral nerves of the autonomic nervous system; (2) upward toward many higher areas of the diencephalon and cerebrum, especially to the anterior thalamus and limbic portions of the cerebral cortex; and (3) into the hypothalamic infundibulum to control or partially control most of the secretory functions of both the posterior and the anterior pituitary glands.

Thus, the hypothalamus, which represents less than 1 percent of the brain mass, is one of the most important of the control pathways of the limbic system. It controls most of the vegetative and endocrine functions of the body and many aspects of emotional behavior. Let us discuss first the vegetative and endocrine control functions and then return to the behavioral functions of the hypothalamus to see how these operate together.

Vegetative and Endocrine Control Functions of the Hypothalamus

The different hypothalamic mechanisms for controlling multiple functions of the body are so important that they are discussed in multiple chapters throughout this text. For instance, the role of the hypothalamus to help regulate arterial pressure is discussed in Chapter 18, thirst and water conservation in Chapter 29, appetite and energy expenditure in Chapter 71, temperature regulation in Chapter 73, and endocrine control in Chapter 75. To illustrate the organization of the hypothalamus as a functional unit, let us summarize the more important of its vegetative and endocrine functions here as well.

Figures 58-6 and 58-7 show enlarged sagittal and coronal views of the hypothalamus, which represents only a small area in Figure 58-4. Take a few minutes to study these diagrams, especially to see in Figure 58-6 the multiple activities that are excited or inhibited when respective hypothalamic nuclei are stimulated. In addition to the centers shown in Figure 58-6, a large *lateral hypothalamic* area (shown in Figure 58-7) is present on each side of the hypothalamus. The lateral areas are especially important in controlling thirst, hunger, and many of the emotional drives.

A word of caution must be issued for studying these diagrams because the areas that cause specific activities are not nearly as accurately localized as suggested in the figures. Also, it is not known whether the effects noted in the figures result from stimulation of specific control nuclei or whether they result merely from activation of fiber tracts leading from or to control nuclei located elsewhere. With this caution in mind, we can give the following general description of the vegetative and control functions of the hypothalamus.

Cardiovascular Regulation. Stimulation of different areas throughout the hypothalamus can cause many neurogenic effects on the cardiovascular system, including increased arterial pressure, decreased arterial pressure, increased heart rate, and decreased heart rate. In general, stimulation in the *posterior* and *lateral hypothalamus* increases the arterial pressure and heart rate, whereas stimulation in the *preoptic area* often has opposite effects, causing a decrease in both heart rate and arterial pressure. These effects are transmitted mainly through specific cardiovascular control centers in the reticular regions of the pons and medulla.

Regulation of Body Temperature. The anterior portion of the hypothalamus, especially the *preoptic area,* is concerned with regulation of body temperature. An increase in the temperature of the blood flowing through this area increases the activity of temperature-sensitive neurons, whereas a decrease in temperature decreases their activity. In turn, these neurons control mechanisms for increasing or decreasing body temperature, as discussed in Chapter 73.

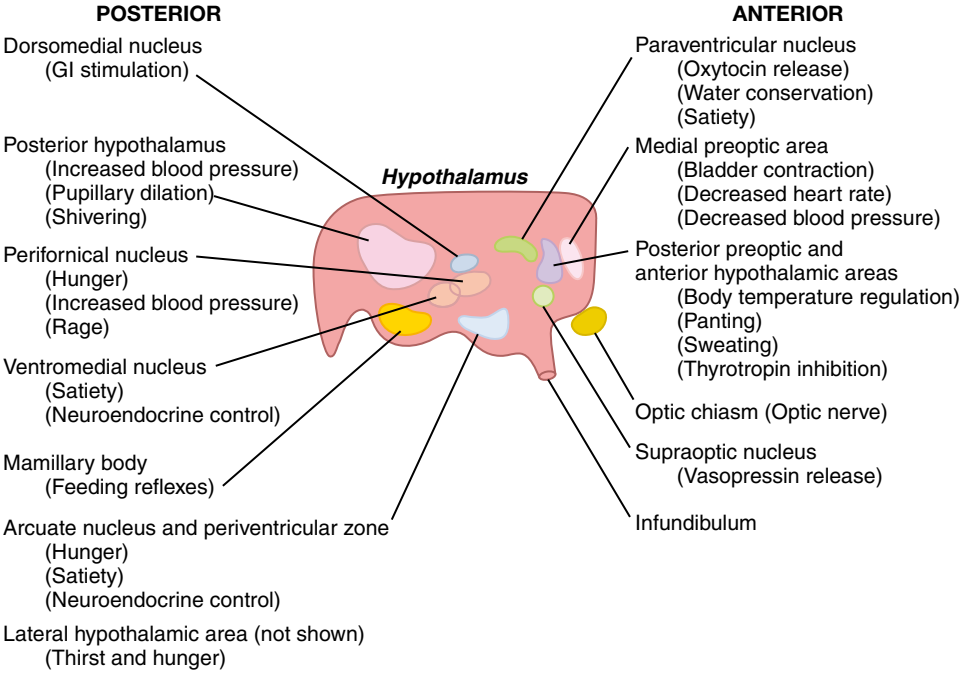


Figure 58-6 Control centers of the hypothalamus (sagittal view).

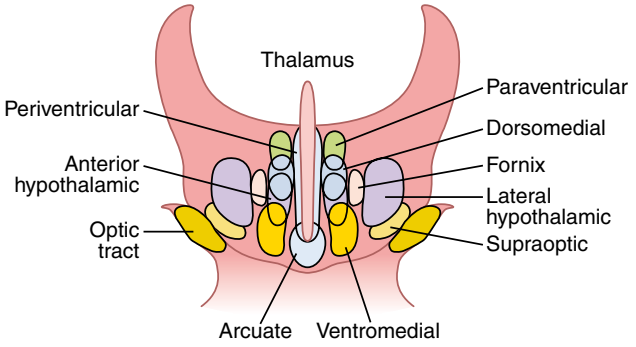


Figure 58-7 Coronal view of the hypothalamus, showing the mediolateral positions of the respective hypothalamic nuclei.

Regulation of Body Water. The hypothalamus regulates body water in two ways: (1) by creating the sensation of thirst, which drives the animal or person to drink water, and (2) by controlling the excretion of water into the urine. An area called the *thirst center* is located in the lateral hypothalamus. When the fluid electrolytes in either this center or closely allied areas become too concentrated, the animal develops an intense desire to drink water; it will search out the nearest source of water and drink enough to return the electrolyte concentration of the thirst center to normal.

Control of renal excretion of water is vested mainly in the *supraoptic* nuclei. When the body fluids become too concentrated, the neurons of these areas become stimulated. Nerve fibers from these neurons project downward through the infundibulum of the hypothalamus into the posterior pituitary gland, where the nerve endings secrete the hormone *antidiuretic hormone* (also called *vasopressin*). This hormone is then absorbed into the blood and transported to the kidneys, where it acts on the collecting ducts of the kidneys to cause increased reabsorption of water. This decreases loss of water into the urine but allows continuing excretion of electrolytes, thus decreasing the concentration of the body fluids back toward normal. These functions are presented in Chapter 28.

Regulation of Uterine Contractility and of Milk Ejection from the Breasts. Stimulation of the *paraventricular nuclei* causes their neuronal cells to secrete the hormone *oxytocin.* This in turn causes increased contractility of the uterus, as well as contraction of the myoepithelial cells surrounding the alveoli of the breasts, which then causes the alveoli to empty their milk through the nipples.

At the end of pregnancy, especially large quantities of oxytocin are secreted and this secretion helps to promote labor contractions that expel the baby. Then, whenever the baby suckles the mother's breast, a reflex signal from the nipple to the posterior hypothalamus also causes oxytocin release and the oxytocin now performs the necessary function of contracting the ductules of the breast, thereby expelling milk through the nipples so that the baby can nourish itself. These functions are discussed in Chapter 82.

Gastrointestinal and Feeding Regulation. Stimulation of several areas of the hypothalamus causes an animal to experience extreme hunger, a voracious appetite, and an intense desire to search for food. One area associated with hunger is the *lateral hypothalamic area.* Conversely, damage to this area on both sides of the hypothalamus causes the animal to lose desire for food, sometimes causing lethal starvation as discussed in Chapter 71.

A center that opposes the desire for food, called the *satiety center,* is located in the *ventromedial nuclei.* When this center is stimulated electrically, an animal that is eating food suddenly stops eating and shows complete indifference to food. However, if this area is destroyed bilaterally, the animal cannot be satiated; instead, its hypothalamic hunger centers become overactive, so it has a voracious appetite, resulting eventually in tremendous obesity. Another area of the hypothalamus that enters into overall control of gastrointestinal activity is the *mamillary bodies;* these control at least partially the patterns of many feeding reflexes, such as licking the lips and swallowing.

Hypothalamic Control of Endocrine Hormone Secretion by the Anterior Pituitary Gland. Stimulation of certain areas of the hypothalamus also causes the *anterior* pituitary gland

to secrete its endocrine hormones. This subject is discussed in detail in Chapter 74 in relation to neural control of the endocrine glands. Briefly, the basic mechanisms are the following.

The anterior pituitary gland receives its blood supply mainly from blood that flows first through the lower part of the hypothalamus and then through the anterior pituitary vascular sinuses. As the blood courses through the hypothalamus before reaching the anterior pituitary, specific *releasing* and *inhibitory hormones* are secreted into the blood by various hypothalamic nuclei. These hormones are then transported via the blood to the anterior pituitary gland, where they act on the glandular cells to control release of specific anterior pituitary hormones.

Summary. Several areas of the hypothalamus control specific vegetative and endocrine functions. These areas are still poorly delimited, so the specification given earlier of different areas for different hypothalamic functions is still partially tentative.

Behavioral Functions of the Hypothalamus and Associated Limbic Structures

Effects Caused by Stimulation of the Hypothalamus. In addition to the vegetative and endocrine functions of the hypothalamus, stimulation of or lesions in the hypothalamus often have profound effects on emotional behavior of animals and human beings.

Some of the behavioral effects of stimulation are the following:

1. Stimulation in the *lateral hypothalamus* not only causes thirst and eating, as discussed earlier, but also increases the general level of activity of the animal, sometimes leading to overt rage and fighting, as discussed subsequently.
2. Stimulation in the *ventromedial nucleus* and surrounding areas mainly causes effects opposite to those caused by lateral hypothalamic stimulation—that is, a sense of *satiety, decreased eating,* and *tranquility.*
3. Stimulation of a *thin zone of periventricular nuclei,* located immediately adjacent to the third ventricle (or also stimulation of the central gray area of the mesencephalon that is continuous with this portion of the hypothalamus), usually leads to *fear* and *punishment reactions.*
4. *Sexual drive* can be stimulated from several areas of the hypothalamus, especially the most anterior and most posterior portions of the hypothalamus.

Effects Caused by Hypothalamic Lesions. Lesions in the hypothalamus, in general, cause effects opposite to those caused by stimulation. For instance:

1. Bilateral lesions in the lateral hypothalamus will decrease drinking and eating almost to zero, often leading to lethal starvation. These lesions cause extreme *passivity* of the animal as well, with loss of most of its overt drives.
2. Bilateral lesions of the ventromedial areas of the hypothalamus cause effects that are mainly opposite to those caused by lesions of the lateral hypothalamus: excessive drinking and eating, as well as hyperactivity and often continuous savagery along with frequent bouts of extreme rage on the slightest provocation.

Stimulation or lesions in other regions of the limbic system, especially in the amygdala, the septal area, and areas in the mesencephalon, often cause effects similar to those elicited from the hypothalamus. We discuss some of these in more detail later.

"Reward" and "Punishment" Function of the Limbic System

From the discussion thus far, it is already clear that several limbic structures are particularly concerned with the *affective* nature of sensory sensations—that is, whether the sensations are *pleasant* or *unpleasant.* These affective qualities are also called *reward* or *punishment,* or *satisfaction* or *aversion*. Electrical stimulation of certain limbic areas pleases or satisfies the animal, whereas electrical stimulation of other regions causes terror, pain, fear, defense, escape reactions, and all the other elements of punishment. The degrees of stimulation of these two oppositely responding systems greatly affect the behavior of the animal.

Reward Centers

Experimental studies in monkeys have used electrical stimulators to map out the reward and punishment centers of the brain. The technique that has been used is to implant electrodes in different areas of the brain so that the animal can stimulate the area by pressing a lever that makes electrical contact with a stimulator. If stimulating the particular area gives the animal a sense of reward, then it will press the lever again and again, sometimes as much as hundreds or even thousands of times per hour. Furthermore, when offered the choice of eating some delectable food as opposed to the opportunity to stimulate the reward center, the animal often chooses the electrical stimulation.

By using this procedure, the major reward centers have been found to be located *along the course of the medial forebrain bundle,* especially in the *lateral* and *ventromedial nuclei of the hypothalamus.* It is strange that the lateral nucleus should be included among the reward areas—indeed, it is one of the most potent of all—because even stronger stimuli in this area can cause rage. But this is true in many areas, with weaker stimuli giving a sense of reward and stronger ones a sense of punishment. Less potent reward centers, which are perhaps secondary to the major ones in the hypothalamus, are found in the septum, the amygdala, certain areas of the thalamus and basal ganglia, and extending downward into the basal tegmentum of the mesencephalon.

Punishment Centers

The stimulator apparatus discussed earlier can also be connected so that the stimulus to the brain continues all the time *except* when the lever is pressed. In this case, the

animal will not press the lever to turn the stimulus off when the electrode is in one of the reward areas; but when it is in certain other areas, the animal immediately learns to turn it off. Stimulation in these areas causes the animal to show all the signs of displeasure, fear, terror, pain, punishment, and even sickness.

By means of this technique, the most potent areas for punishment and escape tendencies have been found in the central gray area surrounding the aqueduct of Sylvius in the mesencephalon and extending upward into the periventricular zones of the hypothalamus and thalamus. Less potent punishment areas are found in some locations in the amygdala and hippocampus. It is particularly interesting that stimulation in the punishment centers can frequently inhibit the reward and pleasure centers completely, demonstrating that *punishment and fear can take precedence over pleasure and reward*.

Rage—Its Association with Punishment Centers

An emotional pattern that involves the punishment centers of the hypothalamus and other limbic structures, and has also been well characterized, is the *rage pattern,* described as follows.

Strong stimulation of the punishment centers of the brain, especially in the *periventricular zone of the hypothalamus* and in the *lateral hypothalamus,* causes the animal to (1) develop a defense posture, (2) extend its claws, (3) lift its tail, (4) hiss, (5) spit, (6) growl, and (7) develop piloerection, wide-open eyes, and dilated pupils. Furthermore, even the slightest provocation causes an immediate savage attack. This is approximately the behavior that one would expect from an animal being severely punished, and it is a pattern of behavior that is called *rage.*

Fortunately, in the normal animal, the rage phenomenon is held in check mainly by inhibitory signals from the ventromedial nuclei of the hypothalamus. In addition, portions of the hippocampi and anterior limbic cortex, especially in the anterior cingulate gyri and subcallosal gyri, help suppress the rage phenomenon.

Placidity and Tameness. Exactly the opposite emotional behavior patterns occur when the reward centers are stimulated: placidity and tameness.

Importance of Reward or Punishment on Behavior

Almost everything that we do is related in some way to reward and punishment. If we are doing something that is rewarding, we continue to do it; if it is punishing, we cease to do it. Therefore, the reward and punishment centers undoubtedly constitute one of the most important of all the controllers of our bodily activities, our drives, our aversions, our motivations.

Effect of Tranquilizers on the Reward or Punishment Centers. Administration of a tranquilizer, such as chlorpromazine, usually inhibits both the reward and the punishment centers, thereby decreasing the affective reactivity of the animal. Therefore, it is presumed that tranquilizers function in psychotic states by suppressing many of the important behavioral areas of the hypothalamus and its associated regions of the limbic brain.

Importance of Reward or Punishment in Learning and Memory—Habituation Versus Reinforcement

Animal experiments have shown that a sensory experience that causes neither reward nor punishment is hardly remembered at all. Electrical recordings from the brain show that a newly experienced sensory stimulus almost always excites multiple areas in the cerebral cortex. But if the sensory experience does not elicit a sense of either reward or punishment, repetition of the stimulus over and over leads to almost complete extinction of the cerebral cortical response. That is, the animal becomes *habituated* to that specific sensory stimulus and thereafter ignores it.

If the stimulus *does* cause either reward or punishment rather than indifference, the cerebral cortical response becomes progressively more and more intense during repeated stimulation instead of fading away, and the response is said to be *reinforced.* An animal builds up strong memory traces for sensations that are either rewarding or punishing but, conversely, develops complete habituation to indifferent sensory stimuli.

It is evident that the reward and punishment centers of the limbic system have much to do with selecting the information that we learn, usually throwing away more than 99 percent of it and selecting less than 1 percent for retention.

Specific Functions of Other Parts of the Limbic System

Functions of the Hippocampus

The hippocampus is the elongated portion of the cerebral cortex that folds inward to form the ventral surface of much of the inside of the lateral ventricle. One end of the hippocampus abuts the amygdaloid nuclei, and along its lateral border it fuses with the parahippocampal gyrus, which is the cerebral cortex on the ventromedial outside surface of the temporal lobe.

The hippocampus (and its adjacent temporal and parietal lobe structures, all together called the *hippocampal formation*) has numerous but mainly indirect connections with many portions of the cerebral cortex, as well as with the basal structures of the limbic system—the amygdala, hypothalamus, septum, and mamillary bodies. Almost any type of sensory experience causes activation of at least some part of the hippocampus, and the hippocampus in turn distributes many outgoing signals to the anterior thalamus, hypothalamus, and other parts of the limbic system, especially through the *fornix*, a major communicating pathway. Thus, the hippocampus is an additional channel through which incoming sensory

signals can initiate behavioral reactions for different purposes. As in other limbic structures, stimulation of different areas in the hippocampus can cause almost any of the different behavioral patterns such as pleasure, rage, passivity, or excess sex drive.

Another feature of the hippocampus is that it can become hyperexcitable. For instance, weak electrical stimuli can cause focal epileptic seizures in small areas of the hippocampi. These often persist for many seconds after the stimulation is over, suggesting that the hippocampi can perhaps give off prolonged output signals even under normal functioning conditions. During hippocampal seizures, the person experiences various psychomotor effects, including olfactory, visual, auditory, tactile, and other types of hallucinations that cannot be suppressed as long as the seizure persists even though the person has not lost consciousness and knows these hallucinations to be unreal. Probably one of the reasons for this hyperexcitability of the hippocampi is that they have a different type of cortex from that elsewhere in the cerebrum, with only three nerve cell layers in some of its areas instead of the six layers found elsewhere.

Role of the Hippocampus in Learning

Effect of Bilateral Removal of the Hippocampi—Inability to Learn. Portions of the hippocampi have been surgically removed bilaterally in a few human beings for treatment of epilepsy. These people can recall most previously learned memories satisfactorily. However, they often can learn essentially no new information that is based on verbal symbolism. In fact, they often cannot even learn the names of people with whom they come in contact every day. Yet they can remember for a moment or so what transpires during the course of their activities. Thus, they are capable of short-term memory for seconds up to a minute or two, although their ability to establish memories lasting longer than a few minutes is either completely or almost completely abolished. This is the phenomenon called *anterograde amnesia* that was discussed in Chapter 57.

Theoretical Function of the Hippocampus in Learning. The hippocampus originated as part of the olfactory cortex. In many lower animals, this cortex plays essential roles in determining whether the animal will eat a particular food, whether the smell of a particular object suggests danger, or whether the odor is sexually inviting, thus making decisions that are of life-or-death importance. Very early in evolutionary development of the brain, the hippocampus presumably became a critical decision-making neuronal mechanism, determining the importance of the incoming sensory signals. Once this critical decision-making capability had been established, presumably the remainder of the brain also began to call on the hippocampus for decision making. Therefore, if the hippocampus signals that a neuronal input is important, the information is likely to be committed to memory.

Thus, a person rapidly becomes habituated to indifferent stimuli but learns assiduously any sensory experience that causes either pleasure or pain. But what is the mechanism by which this occurs? It has been suggested that the hippocampus provides the drive that causes translation of short-term memory into long-term memory—that is, the hippocampus transmits some signal or signals that seem to make the mind *rehearse over and over* the new information until permanent storage takes place. Whatever the mechanism, without the hippocampi, *consolidation* of long-term memories of the verbal or symbolic thinking type is poor or does not take place.

Functions of the Amygdala

The amygdala is a complex of multiple small nuclei located immediately beneath the cerebral cortex of the medial anterior pole of each temporal lobe. It has abundant bidirectional connections with the hypothalamus, as well as with other areas of the limbic system.

In lower animals, the amygdala is concerned to a great extent with olfactory stimuli and their interrelations with the limbic brain. Indeed, it is pointed out in Chapter 53 that one of the major divisions of the olfactory tract terminates in a portion of the amygdala called the *corticomedial nuclei,* which lies immediately beneath the cerebral cortex in the olfactory pyriform area of the temporal lobe. In the human being, another portion of the amygdala, the *basolateral nuclei,* has become much more highly developed than the olfactory portion and plays important roles in many behavioral activities not generally associated with olfactory stimuli.

The amygdala receives neuronal signals from all portions of the limbic cortex, as well as from the neocortex of the temporal, parietal, and occipital lobes—especially from the auditory and visual association areas. Because of these multiple connections, the amygdala has been called the "window" through which the limbic system sees the place of the person in the world. In turn, the amygdala transmits signals (1) back into these same cortical areas, (2) into the hippocampus, (3) into the septum, (4) into the thalamus, and (5) especially into the hypothalamus.

Effects of Stimulating the Amygdala. In general, stimulation in the amygdala can cause almost all the same effects as those elicited by direct stimulation of the hypothalamus, plus other effects. Effects initiated from the amygdala and then sent through the hypothalamus include (1) increases or decreases in arterial pressure; (2) increases or decreases in heart rate; (3) increases or decreases in gastrointestinal motility and secretion; (4) defecation or micturition; (5) pupillary dilation or, rarely, constriction; (6) piloerection; and (7) secretion of various anterior pituitary hormones, especially the gonadotropins and adrenocorticotropic hormone.

Aside from these effects mediated through the hypothalamus, amygdala stimulation can also cause several types of involuntary movement. These include (1) tonic movements, such as raising the head or bending the body; (2) circling movements; (3) occasionally clonic, rhythmical movements; and (4) different types of movements associated with olfaction and eating, such as licking, chewing, and swallowing.

In addition, stimulation of certain amygdaloid nuclei can cause a pattern of rage, escape, punishment, severe pain, and fear similar to the rage pattern elicited from the hypothalamus, as described earlier. Stimulation of other amygdaloid nuclei can give reactions of reward and pleasure.

Finally, excitation of still other portions of the amygdala can cause sexual activities that include erection, copulatory movements, ejaculation, ovulation, uterine activity, and premature labor.

Effects of Bilateral Ablation of the Amygdala—the Klüver-Bucy Syndrome. When the anterior parts of both temporal lobes are destroyed in a monkey, this removes not only portions of temporal cortex but also of the amygdalas that lie inside these parts of the temporal lobes. This causes changes in behavior called the *Klüver-Bucy syndrome,* which is demonstrated by an animal that (1) is not afraid of anything, (2) has extreme curiosity about everything, (3) forgets rapidly, (4) has a tendency to place everything in its mouth and sometimes even tries to eat solid objects, and (5) often has a sex drive so strong that it attempts to copulate with immature animals, animals of the wrong sex, or even animals of a different species. Although similar lesions in human beings are rare, afflicted people respond in a manner not too different from that of the monkey.

Overall Function of the Amygdalas. The amygdalas seem to be behavioral awareness areas that operate at a semiconscious level. They also seem to project into the limbic system one's current status in relation to both surroundings and thoughts. On the basis of this information, the amygdala is believed to make the person's behavioral response appropriate for each occasion.

Function of the Limbic Cortex

The most poorly understood portion of the limbic system is the ring of cerebral cortex called the *limbic cortex* that surrounds the subcortical limbic structures. This cortex functions as a transitional zone through which signals are transmitted from the remainder of the brain cortex into the limbic system and also in the opposite direction. Therefore, the limbic cortex in effect functions as a cerebral *association area for control of behavior.*

Stimulation of the different regions of the limbic cortex has failed to give any real idea of their functions. However, as is true of so many other portions of the limbic system, essentially all behavioral patterns can be elicited by stimulation of specific portions of the limbic cortex. Likewise, ablation of some limbic cortical areas can cause persistent changes in an animal's behavior, as follows.

Ablation of the Anterior Temporal Cortex. When the anterior temporal cortex is ablated bilaterally, the amygdalas are almost invariably damaged as well. This was discussed earlier in this chapter; it was pointed out that the Klüver-Bucy syndrome occurs. The animal especially develops consummatory behavior: it investigates any and all objects, has intense sex drives toward inappropriate animals or even inanimate objects, and loses all fear—and thus develops tameness as well.

Ablation of the Posterior Orbital Frontal Cortex. Bilateral removal of the posterior portion of the orbital frontal cortex often causes an animal to develop insomnia associated with intense motor restlessness, becoming unable to sit still and moving about continuously.

Ablation of the Anterior Cingulate Gyri and Subcallosal Gyri. The anterior cingulate gyri and the subcallosal gyri are the portions of the limbic cortex that communicate between the prefrontal cerebral cortex and the subcortical limbic structures. Destruction of these gyri bilaterally releases the rage centers of the septum and hypothalamus from prefrontal inhibitory influence. Therefore, the animal can become vicious and much more subject to fits of rage than normally.

Summary. Until further information is available, it is perhaps best to state that the cortical regions of the limbic system occupy intermediate associative positions between the functions of the specific areas of the cerebral cortex and functions of the subcortical limbic structures for control of behavioral patterns. Thus, in the anterior temporal cortex, one especially finds gustatory and olfactory behavioral associations. In the parahippocampal gyri, there is a tendency for complex auditory associations and complex thought associations derived from Wernicke area of the posterior temporal lobe. In the middle and posterior cingulate cortex, there is reason to believe that sensorimotor behavioral associations occur.

Bibliography

Adell A, Celada P, Abellan MT, et al: Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei, *Brain Res Brain Res Rev* 39:154, 2002.

Bechara A, Damasio H, Damasio AR: Role of the amygdala in decision-making, *Ann N Y Acad Sci* 985:356, 2003.

Bird CM, Burgess N: The hippocampus and memory: insights from spatial processing, *Nat Rev Neurosci* 9:182, 2008.

Ehrlich I, Humeau Y, Grenier F, et al: Amygdala inhibitory circuits and the control of fear memory, *Neuron* 62:757, 2009.

Guillery RW: Branching thalamic afferents link action and perception, *J Neurophysiol* 90:539, 2003.

Heinricher MM, Tavares I, Leith JL, et al: Descending control of nociception: Specificity, recruitment and plasticity, *Brain Res Rev* 60:214, 2009.

Holland PC, Gallagher M: Amygdala—frontal interactions and reward expectancy, *Curr Opin Neurobiol* 14:148, 2004.

Joels M, Verkuyl JM, Van Riel E: Hippocampal and hypothalamic function after chronic stress, *Ann N Y Acad Sci* 1007:367, 2003.

Jones EG: Synchrony in the interconnected circuitry of the thalamus and cerebral cortex, *Ann N Y Acad Sci* 1157:10, 2009.

Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, ed 4, New York, 2000, McGraw-Hill.

LeDoux JE: Emotion circuits in the brain, *Annu Rev Neurosci* 23:155, 2000.

Lumb BM: Hypothalamic and midbrain circuitry that distinguishes between escapable and inescapable pain, *News Physiol Sci* 19:22, 2004.

Neves G, Cooke SF, Bliss TV: Synaptic plasticity, memory and the hippocampus: a neural network approach to causality, *Nat Rev Neurosci* 9:65, 2008.

Pessoa L: On the relationship between emotion and cognition, *Nat Rev Neurosci* 9:148, 2008.

Phelps EA, LeDoux JE: Contributions of the amygdala to emotion processing: from animal models to human behavior, *Neuron* 48:175, 2005.

Roozendaal B, McEwen BS, Chattarji S: Stress, memory and the amygdala, *Nat Rev Neurosci* 10:423, 2009.

Sah P, Faber ES, Lopez De Armentia M, et al: The amygdaloid complex: anatomy and physiology, *Physiol Rev* 83:803, 2003.

Sara SJ: The locus coeruleus and noradrenergic modulation of cognition, *Nat Rev Neurosci* 10:211, 2009.

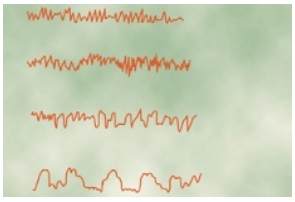
Ulrich-Lai YM, Herman JP: Neural regulation of endocrine and autonomic stress responses, *Nat Rev Neurosci* 10:397, 2009.

Vann SD, Aggleton JP: The mammillary bodies: two memory systems in one? *Nat Rev Neurosci* 5:35, 2004.

Woods SC, D'Alessio DA: Central control of body weight and appetite, *J Clin Endocrinol Metab* 93(11 Suppl 1):S37, 2008.

CHAPTER 59

States of Brain Activity—Sleep, Brain Waves, Epilepsy, Psychoses



All of us are aware of the many different states of brain activity, including sleep, wakefulness, extreme excitement, and even different levels of mood such as exhilaration, depression, and fear. All these states result from different activating or inhibiting forces generated usually within the brain itself. In Chapter 58, we began a partial discussion of this subject when we described different systems that are capable of activating large portions of the brain. In this chapter, we present brief surveys of specific states of brain activity, beginning with sleep.

Sleep

Sleep is defined as unconsciousness from which the person can be aroused by sensory or other stimuli. It is to be distinguished from *coma,* which is unconsciousness from which the person cannot be aroused. There are multiple stages of sleep, from very light sleep to very deep sleep; sleep researchers also divide sleep into two entirely different types of sleep that have different qualities, as follows.

Two Types of Sleep—Slow-Wave Sleep and Rapid Eye Movement (REM) Sleep. During each night, a person goes through stages of two types of sleep that alternate with each other. They are called (1) *slow-wave sleep*, in which the brain waves are strong and of low frequency, as we discuss later, and (2) *rapid eye movement sleep* (REM sleep), in which the eyes undergo rapid movements despite the fact that the person is still asleep.

Most sleep during each night is of the slow-wave variety; this is the deep, restful sleep that the person experiences during the first hour of sleep after having been awake for many hours. REM sleep, on the other hand, occurs in episodes that occupy about 25 percent of the sleep time in young adults; each episode normally recurs about every 90 minutes. This type of sleep is not so restful, and it is usually associated with vivid dreaming.

Slow-Wave Sleep

Most of us can understand the characteristics of deep slow-wave sleep by remembering the last time we were kept awake for more than 24 hours and then the deep sleep that occurred during the first hour after going to sleep. This sleep is exceedingly restful and is associated with decreases in both peripheral vascular tone and many other vegetative functions of the body. For instance, there are 10 to 30 percent decreases in blood pressure, respiratory rate, and basal metabolic rate.

Although slow-wave sleep is frequently called "dreamless sleep," dreams and sometimes even nightmares do occur during slow-wave sleep. The difference between the dreams that occur in slow-wave sleep and those that occur in REM sleep is that those of REM sleep are associated with more bodily muscle activity. Also, the dreams of slow-wave sleep are usually not remembered because consolidation of the dreams in memory does not occur.

REM Sleep (Paradoxical Sleep, Desynchronized Sleep)

In a normal night of sleep, bouts of REM sleep lasting 5 to 30 minutes usually appear on the average every 90 minutes. When the person is extremely sleepy, each bout of REM sleep is short and may even be absent. Conversely, as the person becomes more rested through the night, the durations of the REM bouts increase.

REM sleep has several important characteristics:

1. It is an active form of sleep usually associated with dreaming and active bodily muscle movements.
2. The person is even more difficult to arouse by sensory stimuli than during deep slow-wave sleep, and yet people usually awaken spontaneously in the morning during an episode of REM sleep.
3. Muscle tone throughout the body is exceedingly depressed, indicating strong inhibition of the spinal muscle control areas.
4. Heart rate and respiratory rate usually become irregular, which is characteristic of the dream state.

5. Despite the extreme inhibition of the peripheral muscles, irregular muscle movements do occur. These are in addition to the rapid movements of the eyes.
6. The brain is highly active in REM sleep, and overall brain metabolism may be increased as much as 20 percent. The electroencephalogram (EEG) shows a pattern of brain waves similar to those that occur during wakefulness. This type of sleep is also called *paradoxical sleep* because it is a paradox that a person can still be asleep despite marked activity in the brain.

In summary, REM sleep is a type of sleep in which the brain is quite active. However, the brain activity is not channeled in the proper direction for the person to be fully aware of his or her surroundings, and therefore the person is truly asleep.

Basic Theories of Sleep

Sleep Is Believed to Be Caused by an Active Inhibitory Process. An earlier theory of sleep was that the excitatory areas of the upper brain stem, the *reticular activating system,* simply fatigued during the waking day and became inactive as a result. This was called the *passive theory of sleep.* An important experiment changed this view to the current belief that *sleep is caused by an active inhibitory process:* it was discovered that transecting the brain stem at the level of the midpons creates a brain whose cortex never goes to sleep. In other words, a center located below the midpontile level of the brain stem appears to be required to cause sleep by inhibiting other parts of the brain.

Neuronal Centers, Neurohumoral Substances, and Mechanisms That Can Cause Sleep—A Possible Specific Role for Serotonin

Stimulation of several specific areas of the brain can produce sleep with characteristics near those of natural sleep. Some of these areas are the following:

1. The most conspicuous stimulation area for causing almost natural sleep is the *raphe nuclei in the lower half of the pons and in the medulla.* These nuclei comprise a thin sheet of special neurons located in the midline. Nerve fibers from these nuclei spread locally in the brain stem reticular formation and also upward into the thalamus, hypothalamus, most areas of the limbic system, and even the neocortex of the cerebrum. In addition, fibers extend downward into the spinal cord, terminating in the posterior horns, where they can inhibit incoming sensory signals, including pain, as discussed in Chapter 48. Many nerve endings of fibers from these raphe neurons secrete *serotonin.* When a drug that blocks the formation of serotonin is administered to an animal, the animal often cannot sleep for the next several days. Therefore, it has been assumed that serotonin is a transmitter substance associated with production of sleep.
2. Stimulation of some areas in the *nucleus of the tractus solitarius* can also cause sleep. This nucleus is the termination in the medulla and pons for visceral sensory signals entering by way of the vagus and glossopharyngeal nerves.
3. Sleep can be promoted by stimulation of several regions in the diencephalon, including (1) the rostral part of the hypothalamus, mainly in the suprachiasmal area, and (2) an occasional area in the diffuse nuclei of the thalamus.

Lesions in Sleep-Promoting Centers Can Cause Intense Wakefulness. Discrete lesions in the *raphe nuclei* lead to a high state of wakefulness. This is also true of bilateral lesions in the *medial rostral suprachiasmal area in the anterior hypothalamus.* In both instances, the excitatory reticular nuclei of the mesencephalon and upper pons seem to become released from inhibition, thus causing the intense wakefulness. Indeed, sometimes lesions of the anterior hypothalamus can cause such intense wakefulness that the animal actually dies of exhaustion.

Other Possible Transmitter Substances Related to Sleep. Experiments have shown that the cerebrospinal fluid and the blood or urine of animals that have been kept awake for several days contain a substance or substances that will cause sleep when injected into the brain ventricular system of another animal. One likely substance has been identified as *muramyl peptide,* a low-molecular-weight substance that accumulates in the cerebrospinal fluid and urine in animals kept awake for several days. When only micrograms of this sleep-producing substance are injected into the third ventricle, almost natural sleep occurs within a few minutes and the animal may stay asleep for several hours. Another substance that has similar effects in causing sleep is a nonapeptide isolated from the blood of sleeping animals. And still a third sleep factor, not yet identified molecularly, has been isolated from the neuronal tissues of the brain stem of animals kept awake for days. It is possible that prolonged wakefulness causes progressive accumulation of a sleep factor or factors in the brain stem or cerebrospinal fluid that lead to sleep.

Possible Cause of REM Sleep. Why slow-wave sleep is broken periodically by REM sleep is not understood. However, drugs that mimic the action of acetylcholine increase the occurrence of REM sleep. Therefore, it has been postulated that the large acetylcholine-secreting neurons in the upper brain stem reticular formation might, through their extensive efferent fibers, activate many portions of the brain. This theoretically could cause the excess activity that occurs in certain brain regions in REM sleep, even though the signals are not channeled appropriately in the brain to cause normal conscious awareness that is characteristic of wakefulness.

Cycle Between Sleep and Wakefulness

The preceding discussions have merely identified neuronal areas, transmitters, and mechanisms that are related to sleep. They have not explained the cyclical, reciprocal

operation of the sleep-wakefulness cycle. There is as yet no definitive explanation. Therefore, we might suggest the following possible mechanism for causing the sleep-wakefulness cycle.

When the sleep centers are *not* activated, the mesencephalic and upper pontile reticular activating nuclei are released from inhibition, which allows the reticular activating nuclei to become spontaneously active. This in turn excites both the cerebral cortex and the peripheral nervous system, both of which send numerous *positive feedback* signals back to the same reticular activating nuclei to activate them still further. Therefore, once wakefulness begins, it has a natural tendency to sustain itself because of all this positive feedback activity.

Then, after the brain remains activated for many hours, even the neurons themselves in the activating system presumably become fatigued. Consequently, the positive feedback cycle between the mesencephalic reticular nuclei and the cerebral cortex fades and the sleep-promoting effects of the sleep centers take over, leading to rapid transition from wakefulness back to sleep.

This overall theory could explain the rapid transitions from sleep to wakefulness and from wakefulness to sleep. It could also explain arousal, the insomnia that occurs when a person's mind becomes preoccupied with a thought, and the wakefulness that is produced by bodily physical activity.

Physiologic Functions of Sleep Are Not Yet Known

There is little doubt that sleep has important functions. It exists in all mammals and after total deprivation there is usually a period of "catch-up" or "rebound" sleep; after selective deprivation of REM or slow-wave sleep, there is also a selective rebound of these specific stages of sleep. Even mild sleep restriction over a few days may degrade cognitive and physical performance, overall productivity, and health of a person. The essential role of sleep in homeostasis is perhaps most vividly demonstrated by the fact that rats deprived of sleep for 2 to 3 weeks may actually die. Despite the obvious importance of sleep, our understanding of why sleep is an essential part of life is still limited.

Sleep causes two major types of physiologic effects: first, effects on the nervous system itself, and second, effects on other functional systems of the body. The nervous system effects seem to be by far the more important because any person who has a transected spinal cord in the neck (and therefore has no sleep-wakefulness cycle below the transection) shows no harmful effects in the body beneath the level of transection that can be attributed directly to a sleep-wakefulness cycle.

Lack of sleep certainly does, however, affect the functions of the central nervous system. Prolonged wakefulness is often associated with progressive malfunction of the thought processes and sometimes even causes abnormal behavioral activities. We are all familiar with the increased sluggishness of thought that occurs toward the end of a prolonged wakeful period, but in addition, a person can become irritable or even psychotic after forced wakefulness. Therefore, we can assume that sleep in multiple ways restores both normal levels of brain activity and normal "balance" among the different functions of the central nervous system. This might be likened to the "rezeroing" of electronic analog computers after prolonged use because computers of this type gradually lose their "baseline" of operation; it is reasonable to assume that the same effect occurs in the central nervous system because overuse of some brain areas during wakefulness could easily throw these areas out of balance with the remainder of the nervous system.

Sleep has been postulated to serve many functions including (1) neural maturation, (2) facilitation of learning or memory, (3) cognition, and (4) conservation of metabolic energy. There is some evidence for each of these functions, as well as physiologic purposes of sleep, but evidence supporting each of these ideas has been challenged. We might postulate that *the principal value of sleep is to restore natural balances among the neuronal centers.* The specific physiologic functions of sleep, however, remain a mystery, and they are the subject of much research.

Brain Waves

Electrical recordings from the surface of the brain or even from the outer surface of the head demonstrate that there is continuous electrical activity in the brain. Both the intensity and the patterns of this electrical activity are determined by the level of excitation of different parts of the brain resulting from *sleep, wakefulness,* or brain diseases such as *epilepsy* or even *psychoses.* The undulations in the recorded electrical potentials, shown in Figure 59-1, are called *brain waves,* and the entire record is called an EEG (electroencephalogram).

The intensities of brain waves recorded from the surface of the scalp range from 0 to 200 microvolts, and their frequencies range from once every few seconds to 50 or more per second. The character of the waves is dependent on the degree of activity in respective parts of the cerebral cortex, and the waves change markedly between the states of wakefulness and sleep and coma.

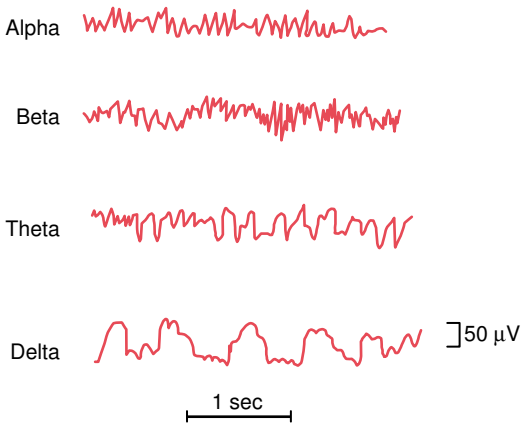


Figure 59-1 Different types of *brain waves* in the normal electroencephalogram.

Much of the time, the brain waves are irregular and no specific pattern can be discerned in the EEG. At other times, distinct patterns do appear, some of which are characteristic of specific abnormalities of the brain such as epilepsy, which is discussed later.

In healthy people, most waves in the EEG can be classified as *alpha, beta, theta,* and *delta waves,* which are shown in Figure 59-1.

Alpha waves are rhythmical waves that occur at frequencies between 8 and 13 cycles per second and are found in the EEGs of almost all normal adults when they are awake and in a quiet, resting state of cerebration. These waves occur most intensely in the occipital region but can also be recorded from the parietal and frontal regions of the scalp. Their voltage is usually about 50 microvolts. During deep sleep, the alpha waves disappear.

When the awake person's attention is directed to some specific type of mental activity, the alpha waves are replaced by asynchronous, higher-frequency but lower-voltage *beta waves.* Figure 59-2 shows the effect on the alpha waves of simply opening the eyes in bright light and then closing the eyes. Note that the visual sensations cause immediate cessation of the alpha waves and that these are replaced by low-voltage, asynchronous beta waves.

Beta waves occur at frequencies greater than 14 cycles per second and as high as 80 cycles per second. They are recorded mainly from the parietal and frontal regions during specific activation of these parts of the brain.

Theta waves have frequencies between four and seven cycles per second. They occur normally in the parietal and temporal regions in children, but they also occur during emotional stress in some adults, particularly during disappointment and frustration. Theta waves also occur in many brain disorders, often in degenerative brain states.

Delta waves include all the waves of the EEG with frequencies less than 3.5 cycles per second, and they often have voltages two to four times greater than most other types of brain waves. They occur in very deep sleep, in infancy, and in serious organic brain disease. They also occur in the cortex of animals that have had subcortical transections separating the cerebral cortex from the thalamus. Therefore, delta waves can occur strictly in the cortex independent of activities in lower regions of the brain.

Origin of Brain Waves

The discharge of a single neuron or single nerve fiber in the brain can never be recorded from the surface of the head. Instead, many thousands or even millions of neurons or fibers *must fire synchronously;* only then will the potentials from the individual neurons or fibers summate enough to be recorded all the way through the skull. Thus, the intensity of the brain waves from the scalp is determined mainly by the numbers of neurons and fibers that

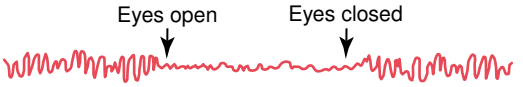


Figure 59-2 Replacement of the *alpha* rhythm by an asynchronous, low-voltage *beta* rhythm when the eyes are opened.

fire *in synchrony* with one another, not by the total level of electrical activity in the brain. In fact, strong *nonsynchronous* nerve signals often nullify one another in the recorded brain waves because of opposing polarities. This is demonstrated in Figure 59-2, which shows, when the eyes were closed, synchronous discharge of many neurons in the cerebral cortex at a frequency of about 12 per second, thus causing *alpha waves.* Then, when the eyes were opened, the activity of the brain increased greatly, but synchronization of the signals became so little that the brain waves mainly nullified one another. The resultant effect was low voltage waves of generally high but irregular frequency, the *beta waves.*

Origin of Alpha Waves. Alpha waves will *not* occur in the cerebral cortex without cortical connections with the thalamus. Conversely, stimulation in the nonspecific layer of *reticular nuclei* that surround the thalamus or in "diffuse" nuclei deep inside the thalamus often sets up electrical waves in the thalamocortical system at a frequency between 8 and 13 per second, which is the natural frequency of the alpha waves. Therefore, it is believed that the alpha waves result from spontaneous feedback oscillation in this diffuse thalamocortical system, possibly including the reticular activating system in the brain stem as well. This oscillation presumably causes both the periodicity of the alpha waves and the synchronous activation of literally millions of cortical neurons during each wave.

Origin of Delta Waves. Transection of the fiber tracts from the thalamus to the cerebral cortex, which blocks thalamic activation of the cortex and thereby eliminates the alpha waves, nevertheless does not block delta waves in the cortex. This indicates that some synchronizing mechanism can occur in the cortical neuronal system by itself—mainly independent of lower structures in the brain—to cause the delta waves.

Delta waves also occur during deep slow-wave sleep; this suggests that the cortex then is mainly released from the activating influences of the thalamus and other lower centers.

Effect of Varying Levels of Cerebral Activity on the Frequency of the EEG

There is a general correlation between level of cerebral activity and average frequency of the EEG rhythm, the average frequency increasing progressively with higher degrees of activity. This is demonstrated in Figure 59-3, which shows

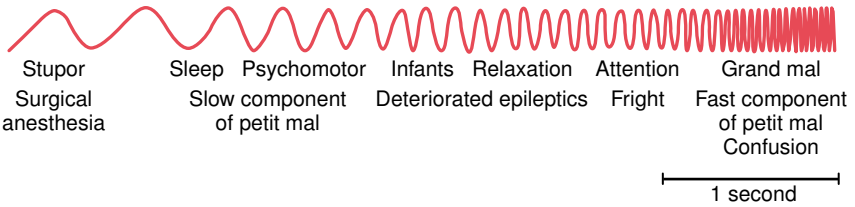


Figure 59-3 Effect of varying degrees of cerebral activity on the basic rhythm of the electroencephalogram. (Redrawn from Gibbs FA, Gibbs EL: Atlas of Electroencephalography, 2nd ed, vol I: Methodology and Controls.® 1974. Reprinted by permission of Prentice-Hall, Inc., Upper Saddle River, NJ.)

the existence of delta waves in stupor, surgical anesthesia, and deep sleep; theta waves in psychomotor states and in infants; alpha waves during relaxed states; and beta waves during periods of intense mental activity. *During periods of mental activity, the waves usually become asynchronous rather than synchronous, so the voltage falls considerably despite markedly increased cortical activity,* as shown in Figure 59-2.

Changes in the EEG at Different Stages of Wakefulness and Sleep

Figure 59-4 shows EEG patterns from a typical person in different stages of wakefulness and sleep. Alert wakefulness is characterized by high-frequency *beta waves,* whereas quiet wakefulness is usually associated with *alpha waves,* as demonstrated by the first two EEGs of the figure.

Slow-wave sleep is divided into four stages. In the first stage, a stage of light sleep, the voltage of the EEG waves becomes low. This is broken by "*sleep spindles*" (i.e,, short spindle-shaped bursts of alpha waves that occur periodically). In stages 2, 3, and 4 of slow-wave sleep, the frequency of the EEG becomes progressively slower until it reaches a frequency of only one to three waves per second in stage 4; these are *delta waves.*

Finally, the bottom record in Figure 59-4 shows the EEG during REM sleep. It is often difficult to tell the difference between this brain wave pattern and that of an awake, active person. The waves are irregular and of high frequency, which are normally suggestive of desynchronized nervous activity as found in the awake state. Therefore, REM sleep is frequently called *desynchronized sleep* because there is lack of synchrony in the firing of the neurons despite significant brain activity.

Epilepsy

Epilepsy (also called "seizures") is characterized by *uncontrolled* excessive activity of either part or all of the central nervous system. A person who is predisposed to epilepsy has attacks when the basal level of excitability of the nervous system (or of the part that is susceptible to the epileptic state) rises above a certain critical threshold. As long as the degree of excitability is held below this threshold, no attack occurs.

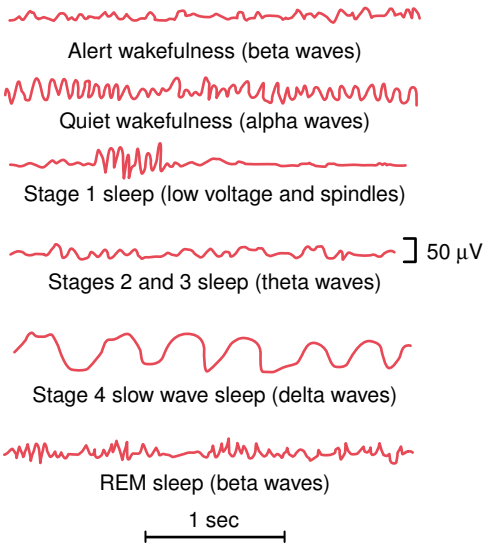


Figure 59-4 Progressive change in the characteristics of the brain waves during different stages of wakefulness and sleep.

Epilepsy can be classified into three major types: *grand mal epilepsy, petit mal epilepsy,* and *focal epilepsy.*

Grand Mal Epilepsy

Grand mal epilepsy is characterized by extreme neuronal discharges in all areas of the brain—in the cerebral cortex, in the deeper parts of the cerebrum, and even in the brain stem. Also, discharges transmitted all the way into the spinal cord sometimes cause generalized *tonic seizures* of the entire body, followed toward the end of the attack by alternating tonic and spasmodic muscle contractions called *tonic-clonic seizures.* Often the person bites or "swallows" his or her tongue and may have difficulty breathing, sometimes to the extent that cyanosis occurs. Also, signals transmitted from the brain to the viscera frequently cause urination and defecation.

The usual grand mal seizure lasts from a few seconds to 3 to 4 minutes. It is also characterized by *postseizure depression* of the entire nervous system; the person remains in stupor for 1 to many minutes after the seizure attack is over and then often remains severely fatigued and asleep for hours thereafter.

The top recording of Figure 59-5 shows a typical EEG from almost any region of the cortex during the tonic phase of a grand mal attack. This demonstrates that high-voltage, high-frequency discharges occur over the entire cortex. Furthermore, the same type of discharge occurs on both sides of the brain at the same time, demonstrating that the abnormal neuronal circuitry responsible for the attack strongly involves the basal regions of the brain that drive the two halves of the cerebrum simultaneously.

In laboratory animals and even in human beings, grand mal attacks can be initiated by administering a neuronal stimulant such as the drug pentylenetetrazol. They can also be caused by insulin hypoglycemia or passage of alternating electrical current directly through the brain. Electrical recordings from the thalamus, as well as from the reticular formation of the brain stem during the grand mal attack, show typical high-voltage activity in both of these areas similar to that recorded from the cerebral cortex. Therefore, a grand mal attack presumably involves not only abnormal activation of the thalamus and cerebral cortex but also abnormal activation in the subthalamic brain stem portions of the brain-activating system itself.

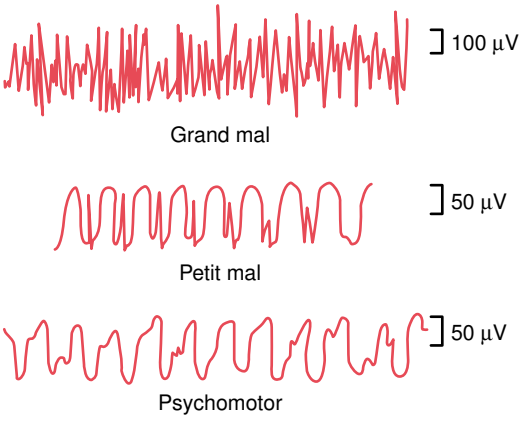


Figure 59-5 Electroencephalograms in different types of epilepsy.

What Initiates a Grand Mal Attack? Most people who have grand mal attacks have a hereditary predisposition to epilepsy, a predisposition that occurs in about 1 of every 50 to 100 persons. In such people, factors that can increase the excitability of the abnormal "epileptogenic" circuitry enough to precipitate attacks include (1) strong emotional stimuli, (2) alkalosis caused by overbreathing, (3) drugs, (4) fever, and (5) loud noises or flashing lights.

Even in people who are not genetically predisposed, certain types of traumatic lesions in almost any part of the brain can cause excess excitability of local brain areas, as we discuss shortly; these, too, sometimes transmit signals into the activating systems of the brain to elicit grand mal seizures.

What Stops the Grand Mal Attack? The cause of the extreme neuronal overactivity during a grand mal attack is presumed to be massive simultaneous activation of many reverberating neuronal pathways throughout the brain. Presumably, the major factor that stops the attack after a few minutes is *neuronal fatigue.* A second factor is probably *active inhibition* by inhibitory neurons that have been activated by the attack.

Petit Mal Epilepsy

Petit mal epilepsy almost certainly involves the thalamocortical brain activating system. It is usually characterized by 3 to 30 seconds of unconsciousness (or diminished consciousness) during which time the person has twitchlike contractions of muscles usually in the head region, especially blinking of the eyes; this is followed by return of consciousness and resumption of previous activities. This total sequence is called the *absence syndrome* or absence epilepsy. The patient may have one such attack in many months or, in rare instances, may have a rapid series of attacks, one after the other. The usual course is for the petit mal attacks to appear first during late childhood and then to disappear by the age of 30. On occasion, a petit mal epileptic attack will initiate a grand mal attack.

The brain wave pattern in petit mal epilepsy is demonstrated by the middle recording of Figure 59-5, which is typified by a *spike and dome pattern.* The spike and dome can be recorded over most or all of the cerebral cortex, showing that the seizure involves much or most of the thalamocortical activating system of the brain. In fact, animal studies suggest that it results from oscillation of (1) inhibitory thalamic reticular neurons (which are *inhibitory* gamma-aminobutyric acid [GABA]-producing neurons) and (2) *excitatory* thalamocortical and corticothalamic neurons.

Focal Epilepsy

Focal epilepsy can involve almost any local part of the brain, either localized regions of the cerebral cortex or deeper structures of both the cerebrum and brain stem. Most often, focal epilepsy results from some localized organic lesion or functional abnormality, such as (1) scar tissue in the brain that pulls on the adjacent neuronal tissue, (2) a tumor that compresses an area of the brain, (3) a destroyed area of brain tissue, or (4) congenitally deranged local circuitry.

Lesions such as these can promote extremely rapid discharges in the local neurons; when the discharge rate rises above several hundred per second, synchronous waves begin to spread over adjacent cortical regions. These waves presumably result from *localized reverberating circuits* that gradually recruit adjacent areas of the cortex into the epileptic discharge zone. The process spreads to adjacent areas at a rate as slow as a few millimeters a minute to as fast as several centimeters per second. When such a wave of excitation spreads over the motor cortex, it causes progressive "march" of muscle contractions throughout the opposite side of the body, beginning most characteristically in the mouth region and marching progressively downward to the legs but at other times marching in the opposite direction. This is called *jacksonian epilepsy.*

A focal epileptic attack may remain confined to a single area of the brain, but in many instances, the strong signals from the convulsing cortex excite the mesencephalic portion of the brain-activating system so greatly that a grand mal epileptic attack ensues as well.

Another type of focal epilepsy is the so-called *psychomotor seizure,* which may cause (1) a short period of amnesia; (2) an attack of abnormal rage; (3) sudden anxiety, discomfort, or fear; and/or (4) a moment of incoherent speech or mumbling of some trite phrase. Sometimes the person cannot remember his or her activities during the attack, but at other times he or she is conscious of everything that he or she is doing but unable to control it. Attacks of this type frequently involve part of the limbic portion of the brain, such as the hippocampus, the amygdala, the septum, and/or portions of the temporal cortex.

The lowest tracing of Figure 59-5 demonstrates a typical EEG during a psychomotor seizure, showing a low-frequency rectangular wave with a frequency between 2 and 4 per second and with occasional superimposed 14-per-second waves.

Surgical Excision of Epileptic Foci Can Often Prevent Seizures. The EEG can be used to localize abnormal spiking waves originating in areas of organic brain disease that predispose to focal epileptic attacks. Once such a focal point is found, surgical excision of the focus frequently prevents future attacks.

Psychotic Behavior and Dementia—Roles of Specific Neurotransmitter Systems

Clinical studies of patients with different psychoses or different types of dementia have suggested that many of these conditions result from diminished function of neurons that secrete a specific neurotransmitter. Use of appropriate drugs to counteract loss of the respective neurotransmitter has been successful in treating some patients.

In Chapter 56, we discussed the cause of Parkinson's disease. This disease results from loss of neurons in the substantia nigra whose nerve endings secrete *dopamine* in the caudate nucleus and putamen. Also in Chapter 56, we pointed out that in Huntington's disease, loss of GABA-secreting neurons and acetylcholine-secreting neurons is associated with *specific abnormal motor patterns* plus *dementia* occurring in the same patient.

Depression and Manic-Depressive Psychoses—Decreased Activity of the Norepinephrine and Serotonin Neurotransmitter Systems

Much evidence has accumulated suggesting that *mental depression psychosis,* which occurs in about 8 million people

in the United States, might be caused by *diminished formation in the brain of norepinephrine or serotonin, or both.* (New evidence has implicated still other neurotransmitters.) Depressed patients experience symptoms of grief, unhappiness, despair, and misery. In addition, they often lose their appetite and sex drive and have severe insomnia. Often associated with these is a state of psychomotor agitation despite the depression.

Moderate numbers of *norepinephrine-secreting neurons* are located in the brain stem, especially in the *locus ceruleus.* These neurons send fibers upward to most parts of the brain limbic system, thalamus, and cerebral cortex. Also, many *serotonin-producing neurons* located in the *midline raphe nuclei* of the lower pons and medulla send fibers to many areas of the limbic system and to some other areas of the brain.

A principal reason for believing that depression might be caused by diminished activity of norepinephrine- and serotonin-secreting neurons is that drugs that block secretion of norepinephrine and serotonin, such as reserpine, frequently cause depression. Conversely, about 70 percent of depressive patients can be treated effectively with drugs that increase the excitatory effects of norepinephrine and serotonin at the nerve endings—for instance, (1) *monoamine oxidase inhibitors,* which block destruction of norepinephrine and serotonin once they are formed, and (2) *tricyclic antidepressants,* such as *imipramine* and *amitriptyline,* which block reuptake of norepinephrine and serotonin by nerve endings so that these transmitters remain active for longer periods after secretion.

Mental depression can be treated by electroconvulsive therapy—commonly called "shock therapy." In this therapy, electrical current is passed through the brain to cause a generalized seizure similar to that of an epileptic attack. This has been shown to enhance norepinephrine activity.

Some patients with mental depression alternate between depression and mania, which is called either *bipolar disorder* or *manic-depressive psychosis,* and fewer patients exhibit only mania without the depressive episodes. Drugs that diminish the formation or action of norepinephrine and serotonin, such as lithium compounds, can be effective in treating the manic phase of the condition.

It is presumed that the norepinephrine and serotonin systems normally provide drive to the limbic areas of the brain to increase a person's sense of well-being, to create happiness, contentment, good appetite, appropriate sex drive, and psychomotor balance—although too much of a good thing can cause mania. In support of this concept is the fact that pleasure and reward centers of the hypothalamus and surrounding areas receive large numbers of nerve endings from the norepinephrine and serotonin systems.

Schizophrenia—Possible Exaggerated Function of Part of the Dopamine System

Schizophrenia comes in many varieties. One of the most common types is seen in the person who hears voices and has delusions of grandeur, intense fear, or other types of feelings that are unreal. Many schizophrenics are highly paranoid, with a sense of persecution from outside sources. They may develop incoherent speech, dissociation of ideas, and abnormal sequences of thought, and they are often withdrawn, sometimes with abnormal posture and even rigidity.

There are reasons to believe that schizophrenia results from one or more of three possibilities: (1) multiple areas in the cerebral cortex *prefrontal lobes* in which neural signals have become blocked or where processing of the signals becomes dysfunctional because many synapses normally excited by the neurotransmitter *glutamate* lose their responsiveness to this transmitter; (2) excessive excitement of a group of neurons that secrete *dopamine* in the behavioral centers of the brain, including in the frontal lobes; and/or (3) abnormal function of a crucial part of the brain's *limbic behavioral control system centered around the hippocampus.*

The reason for believing that the prefrontal lobes are involved in schizophrenia is that a schizophrenic-like pattern of mental activity can be induced in monkeys by making multiple minute lesions in widespread areas of the prefrontal lobes.

Dopamine has been implicated as a possible cause of schizophrenia because many patients with Parkinson's disease develop schizophrenic-like symptoms when they are treated with the drug called L-dopa. This drug releases dopamine in the brain, which is advantageous for treating Parkinson's disease, but at the same time it depresses various portions of the prefrontal lobes and other related areas.

It has been suggested that in schizophrenia excess dopamine is secreted by a group of dopamine-secreting neurons whose cell bodies lie in the ventral tegmentum of the mesencephalon, medial and superior to the substantia nigra. These neurons give rise to the so-called *mesolimbic dopaminergic system* that projects nerve fibers and dopamine secretion into the medial and anterior portions of the limbic system, especially into the hippocampus, amygdala, anterior caudate nucleus, and portions of the prefrontal lobes. All of these are powerful behavioral control centers.

An even more compelling reason for believing that schizophrenia might be caused by excess production of dopamine is that many drugs that are effective in treating schizophrenia—such as chlorpromazine, haloperidol, and thiothixene—all either decrease secretion of dopamine at dopaminergic nerve endings or decrease the effect of dopamine on subsequent neurons.

Finally, possible involvement of the hippocampus in schizophrenia was discovered recently when it was learned that *in schizophrenia, the hippocampus is often reduced in size,* especially in the dominant hemisphere.

Alzheimer's Disease—Amyloid Plaques and Depressed Memory

Alzheimer's disease is defined as premature aging of the brain, usually beginning in midadult life and progressing rapidly to extreme loss of mental powers—similar to that seen in very, very old age. The clinical features of Alzheimer's disease include (1) an amnesic type of memory impairment, (2) deterioration of language, and (3) visuospatial deficits. Motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the late phases of the disease. One consistent finding in Alzheimer's disease is loss of neurons in that part of the limbic pathway that drives the memory process. Loss of this memory function is devastating.

Alzheimer's disease is a progressive and fatal neurodegenerative disorder that results in impairment of the person's ability to perform activities of daily living, as well as a variety of neuropsychiatric symptoms and behavioral disturbances in the later stages of the disease. Patients with Alzheimer's disease usually require continuous care within a few years after the disease begins.

Alzheimer's disease is the most common form of dementia in the elderly, and more than 5 million people in the United States are estimated to be afflicted by this disorder. The percentage of persons with Alzheimer's disease approximately doubles with every 5 years of age, with about 1 percent of 60-year-olds and about 30 percent of 85-year-olds having the disease.

Alzheimer's Disease Is Associated with Accumulation of Brain Beta-Amyloid Peptide. Pathologically, one finds increased amounts of beta-amyloid peptide in the brains of patients with Alzheimer's disease. The peptide accumulates in amyloid plaques, which range in diameter from 10 micrometers to several hundred micrometers and are found in widespread areas of the brain, including in the cerebral cortex, hippocampus, basal ganglia, thalamus, and even the cerebellum. Thus, Alzheimer's disease appears to be a metabolic degenerative disease.

A key role for excess accumulation of beta-amyloid peptide in the pathogenesis of Alzheimer's disease is suggested by the following observations: (1) all currently known mutations associated with Alzheimer's disease increase the production of beta-amyloid peptide; (2) patients with trisomy 21 (Down syndrome) have three copies of the gene for amyloid precursor protein and develop neurological characteristics of Alzheimer's disease by midlife; (3) patients who have abnormality of a gene that controls apolipoprotein E, a blood protein that transports cholesterol to the tissues, have accelerated deposition of amyloid and greatly increased risk for Alzheimer's disease; (4) transgenic mice that overproduce the human amyloid precursor protein have learning and memory deficits in association with the accumulation of amyloid plaques; and (5) generation of anti-amyloid antibodies in humans with Alzheimer's disease appears to attenuate the disease process.

Vascular Disorders May Contribute to Progression of Alzheimer's Disease. There is also accumulating evidence that cerebrovascular disease caused by *hypertension* and *atherosclerosis* may play a role in Alzheimer's disease. Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia and likely contributes to cognitive decline in Alzheimer's disease. In fact, many of the common risk factors for cerebrovascular disease, such as hypertension, diabetes, and hyperlipidemia, are also recognized to greatly increase the risk for developing Alzheimer's disease.

Bibliography

Beenhakker MP, Huguenard JR: Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? *Neuron* 62:612, 2009.

Brayne C: The elephant in the room—healthy brains in later life, epidemiology and public health, *Nat Rev Neurosci* 8:233, 2007.

Canli T, Lesch KP: Long story short: the serotonin transporter in emotion regulation and social cognition, *Nat Neurosci* 10:1103, 2007.

Casserly I, Topol E: Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins, *Lancet* 363:1139, 2004.

Cirelli C: The genetic and molecular regulation of sleep: from fruit flies to humans, *Nat Rev Neurosci* 10:549, 2009.

Cummings JL: Alzheimer's disease, *N Engl J Med* 351:56, 2004.

de la Torre JC: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics, *Lancet Neurol* 3:184, 2004.

Golde TE: Alzheimer disease therapy: can the amyloid cascade be halted?, *J Clin Invest* 111:11, 2003.

Iadecola C, Park L, Capone C: Threats to the mind: aging, amyloid, and hypertension, *Stroke* 40(3 Suppl):S40, 2009.

Iadecola C: Neurovascular regulation in the normal brain and in Alzheimer's disease, *Nat Rev Neurosci* 5:347–360, 2004.

Jacob TC, Moss SJ, Jurd R: GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition, *Nat Rev Neurosci* 9:331, 2008.

Kilduff TS, Lein ES, de la Iglesia H, et al: New developments in sleep research: molecular genetics, gene expression, and systems neurobiology, *J Neurosci* 28:11814, 2008.

Krueger JM, Rector DM, Roy S, et al: Sleep as a fundamental property of neuronal assemblies, *Nat Rev Neurosci* 9:910, 2008.

McCormick DA, Contreras D: On the cellular and network bases of epileptic seizures, *Annu Rev Physiol* 63:815, 2001.

Ressler KJ, Mayberg HS: Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic, *Nat Neurosci* 10:1116, 2007.

Seeman P: Glutamate and dopamine components in schizophrenia, *J Psychiatry Neurosci* 34:143, 2009.

Selkoe DJ: Alzheimer disease: mechanistic understanding predicts novel therapies, *Ann Intern Med* 140:627, 2004.

Smith EE, Greenberg SM: *Beta-amyloid, blood vessels, and brain function* 40:2601, 2009.

Steinlein OK: Genetic mechanisms that underlie epilepsy, *Nat Rev Neurosci* 5:400–408, 2004.

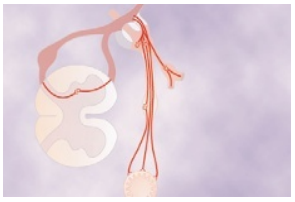
Tononi G, Cirelli C: Staying awake puts pressure on brain arousal systems, *J Clin Invest* 117:3648, 2007.

Viswanathan A, Rocca WA, Tzourio C: Vascular risk factors and dementia: how to move forward? *Neurology* 72:368, 2009.

Zacchigna S, Lambrechts D, Carmeliet P: Neurovascular signalling defects in neurodegeneration, *Nat Rev Neurosci* 9:169, 2008.

CHAPTER 60

The Autonomic Nervous System and the Adrenal Medulla



The *autonomic nervous system* is the portion of the nervous system that controls most visceral functions of the body. This system helps to control arterial pressure, gastrointestinal motility, gastrointestinal secretion, urinary bladder emptying, sweating, body temperature, and many other activities, some of which are controlled almost entirely and some only partially by the autonomic nervous system.

One of the most striking characteristics of the autonomic nervous system is the rapidity and intensity with which it can change visceral functions. For instance, within 3 to 5 seconds it can increase the heart rate to twice normal, and within 10 to 15 seconds the arterial pressure can be doubled; or, at the other extreme, the arterial pressure can be decreased low enough within 10 to 15 seconds to cause fainting. Sweating can begin within seconds, and the urinary bladder may empty involuntarily, also within seconds.

General Organization of the Autonomic Nervous System

The autonomic nervous system is activated mainly by centers located in the *spinal cord, brain stem,* and *hypothalamus.* Also, portions of the cerebral cortex, especially of the limbic cortex, can transmit signals to the lower centers and in this way influence autonomic control.

The autonomic nervous system also often operates through *visceral reflexes.* That is, subconscious sensory signals from a visceral organ can enter the autonomic ganglia, the brain stem, or the hypothalamus and then return *subconscious reflex responses* directly back to the visceral organ to control its activities.

The efferent autonomic signals are transmitted to the various organs of the body through two major subdivisions called the *sympathetic nervous system* and the *parasympathetic nervous system,* the characteristics and functions of which follow.

Physiologic Anatomy of the Sympathetic Nervous System

Figure 60-1 shows the general organization of the peripheral portions of the sympathetic nervous system. Shown specifically in the figure are (1) one of the two *paravertebral sympathetic chains of ganglia* that are interconnected with the spinal nerves on the side of the vertebral column, (2) two *prevertebral ganglia* (the *celiac* and *hypogastric*), and (3) nerves extending from the ganglia to the different internal organs.

The sympathetic nerve fibers originate in the spinal cord along with spinal nerves between cord segments T-1 and L-2 and pass first into the *sympathetic chain* and then to the tissues and organs that are stimulated by the sympathetic nerves.

Preganglionic and Postganglionic Sympathetic Neurons

The sympathetic nerves are different from skeletal motor nerves in the following way: Each sympathetic pathway from the cord to the stimulated tissue is composed of two neurons, a *preganglionic neuron* and a *postganglionic neuron,* in contrast to only a single neuron in the skeletal motor pathway. The cell body of each preganglionic neuron lies in the *intermediolateral horn* of the spinal cord; its fiber passes, as shown in Figure 60-2, through an *anterior root* of the cord into the corresponding *spinal nerve.*

Immediately after the spinal nerve leaves the spinal canal, the preganglionic sympathetic fibers leave the spinal nerve and pass through a *white ramus* into one of the *ganglia* of the *sympathetic chain.* Then the course of the fibers can be one of the following three: (1) It can synapse with postganglionic sympathetic neurons in the ganglion that it enters; (2) it can pass upward or downward in the chain and synapse in one of the other ganglia of the chain; or (3) it can pass for variable distances through the chain and then through one of the *sympathetic nerves* radiating outward from the chain, finally synapsing in a *peripheral sympathetic ganglion.*

The postganglionic sympathetic neuron thus originates either in one of the sympathetic chain ganglia or in one of the peripheral sympathetic ganglia. From either of these two sources, the postganglionic fibers then travel to their destinations in the various organs.

Sympathetic Nerve Fibers in the Skeletal Nerves. Some of the postganglionic fibers pass back from the sympathetic chain into the spinal nerves through *gray rami* at all levels of the cord, as shown in Figure 60-2. These sympathetic fibers are all very small type C fibers, and they extend to all parts

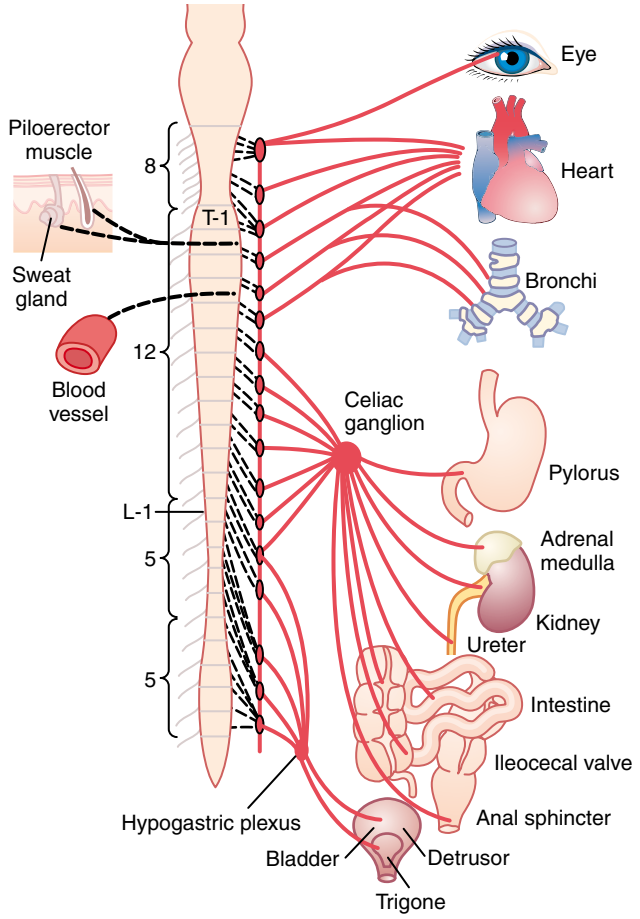


Figure 60-1 Sympathetic nervous system. The *black dashed lines* represent postganglionic fibers in the gray rami leading from the sympathetic chains into spinal nerves for distribution to blood vessels, sweat glands, and piloerector muscles.

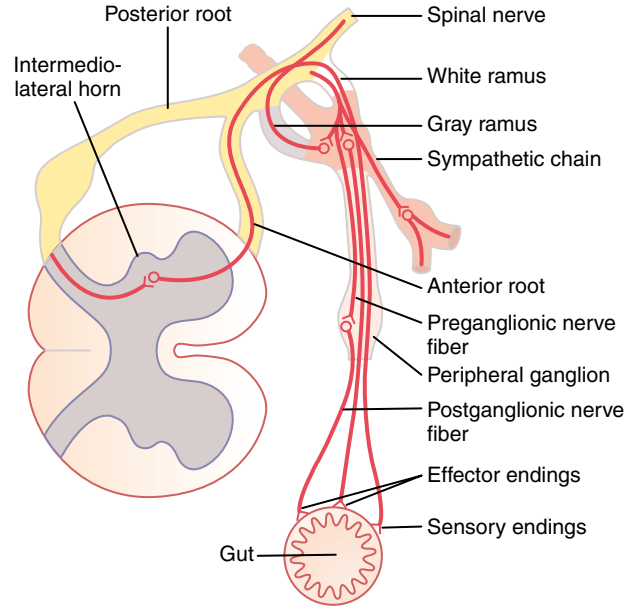


Figure 60-2 Nerve connections among the spinal cord, spinal nerves, sympathetic chain, and peripheral sympathetic nerves.

of the body by way of the skeletal nerves. They control the blood vessels, sweat glands, and piloerector muscles of the hairs. About 8 percent of the fibers in the average skeletal nerve are sympathetic fibers, a fact that indicates their great importance.

Segmental Distribution of the Sympathetic Nerve Fibers. The sympathetic pathways that originate in the different segments of the spinal cord are not necessarily distributed to the same part of the body as the somatic spinal nerve fibers from the same segments. Instead, the *sympathetic fibers from cord segment T-1 generally pass up the sympathetic chain to terminate in the head; from T-2 to terminate in the neck; from T-3, T-4, T-5, and T-6 into the thorax; from T-7, T-8, T-9, T-10, and T-11 into the abdomen; and from T-12, L-1, and L-2 into the legs.* This distribution is only approximate and overlaps greatly.

The distribution of sympathetic nerves to each organ is determined partly by the locus in the embryo from which the organ originated. For instance, the heart receives many sympathetic nerve fibers from the neck portion of the sympathetic chain because the heart originated in the neck of the embryo before translocating into the thorax. Likewise, the abdominal organs receive most of their sympathetic innervation from the lower thoracic spinal cord segments because most of the primitive gut originated in this area.

Special Nature of the Sympathetic Nerve Endings in the Adrenal Medullae. Preganglionic sympathetic nerve fibers pass, *without synapsing,* all the way from the intermediolateral horn cells of the spinal cord, through the sympathetic chains, then through the splanchnic nerves, and finally into the two adrenal medullae. There they end directly on modified neuronal cells that secrete *epinephrine* and *norepinephrine* into the blood stream. These secretory cells embryologically are derived from nervous tissue and are actually themselves postganglionic neurons; indeed, they even have rudimentary nerve fibers, and it is the endings of these fibers that secrete the adrenal hormones *epinephrine* and *norepinephrine.*

Physiologic Anatomy of the Parasympathetic Nervous System

The *parasympathetic nervous system* is shown in Figure 60-3, demonstrating that parasympathetic fibers leave the central nervous system through cranial nerves III, VII, IX, and X; additional parasympathetic fibers leave the lowermost part of the spinal cord through the second and third sacral spinal nerves and occasionally the first and fourth sacral nerves. About 75 percent of all parasympathetic nerve fibers are in the *vagus nerves* (cranial nerve X), passing to the entire thoracic and abdominal regions of the body. Therefore, a physiologist speaking of the parasympathetic nervous system often thinks mainly of the two vagus nerves. The vagus nerves supply parasympathetic nerves to the heart, lungs, esophagus, stomach, entire small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys, and upper portions of the ureters.

Parasympathetic fibers in the *third cranial nerve* go to the pupillary sphincter and ciliary muscle of the eye. Fibers from the *seventh cranial nerve* pass to the lacrimal, nasal, and

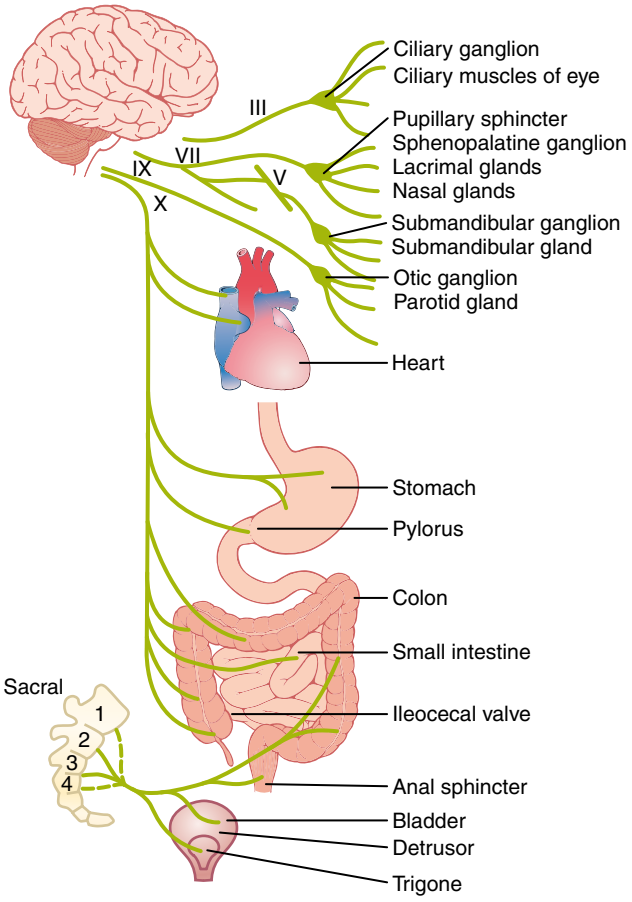


Figure 60-3 Parasympathetic nervous system.

submandibular glands. And fibers from the *ninth cranial nerve* go to the parotid gland.

The sacral parasympathetic fibers are in the *pelvic nerves,* which pass through the spinal nerve sacral plexus on each side of the cord at the S-2 and S-3 levels. These fibers then distribute to the descending colon, rectum, urinary bladder, and lower portions of the ureters. Also, this sacral group of parasympathetics supplies nerve signals to the external genitalia to cause erection.

Preganglionic and Postganglionic Parasympathetic Neurons. The parasympathetic system, like the sympathetic, has both preganglionic and postganglionic neurons. However, except in the case of a few cranial parasympathetic nerves, the *preganglionic fibers* pass uninterrupted all the way to the organ that is to be controlled. In the wall of the organ are located the *postganglionic neurons.* The preganglionic fibers synapse with these, and extremely short postganglionic fibers, a fraction of a millimeter to several centimeters in length, leave the neurons to innervate the tissues of the organ. This location of the parasympathetic postganglionic neurons in the visceral organ itself is quite different from the arrangement of the sympathetic ganglia because the cell bodies of the sympathetic postganglionic neurons are almost always located in the ganglia of the sympathetic chain or in various other discrete ganglia in the abdomen, rather than in the excited organ itself.

Basic Characteristics of Sympathetic and Parasympathetic Function

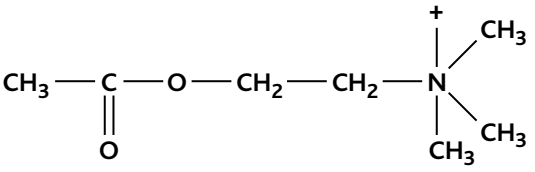
Cholinergic and Adrenergic Fibers—Secretion of Acetylcholine or Norepinephrine

The sympathetic and parasympathetic nerve fibers secrete mainly one or the other of two synaptic transmitter substances, *acetylcholine* or *norepinephrine.* Those fibers that secrete acetylcholine are said to be *cholinergic.* Those that secrete norepinephrine are said to be *adrenergic,* a term derived from *adrenalin,* which is an alternate name for epinephrine.

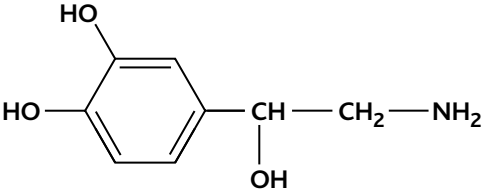
All *preganglionic neurons* are *cholinergic* in both the sympathetic and the parasympathetic nervous systems. Acetylcholine or acetylcholine-like substances, when applied to the ganglia, will excite both sympathetic and parasympathetic postganglionic neurons. Either *all or almost all of the postganglionic neurons of the parasympathetic system are also cholinergic.* Conversely, *most of the postganglionic sympathetic neurons are adrenergic.* However, the postganglionic sympathetic nerve fibers to the sweat glands, to the piloerector muscles of the hairs, and to a very few blood vessels are cholinergic.

Thus, the terminal nerve endings of the parasympathetic system *all or virtually all* secrete *acetylcholine.* Almost all of the sympathetic nerve endings secrete *norepinephrine,* but a few secrete acetylcholine. These neurotransmitters in turn act on the different organs to cause respective parasympathetic or sympathetic effects. Therefore, acetylcholine is called a *parasympathetic transmitter* and norepinephrine is called a *sympathetic transmitter.*

The molecular structures of acetylcholine and norepinephrine are the following:



Acetylcholine



Norepinephrine

Mechanisms of Transmitter Secretion and Subsequent Removal of the Transmitter at the Postganglionic Endings

Secretion of Acetylcholine and Norepinephrine by Postganglionic Nerve Endings. A few of the postganglionic autonomic nerve endings, especially those of the parasympathetic nerves, are similar to but much smaller than those of the skeletal neuromuscular junction. However, many of the parasympathetic nerve fibers and almost all the sympathetic fibers merely touch the effector cells of the organs that they innervate as they pass by; or in some instances, they terminate in connective tissue located adjacent to the cells that are to be stimulated. Where these filaments touch or pass over or near the cells to be stimulated, they usually have bulbous enlargements called *varicosities;* it is in these varicosities that the transmitter vesicles of acetylcholine or norepinephrine are synthesized and stored. Also in the varicosities are large numbers of mitochondria that supply adenosine triphosphate, which is required to energize acetylcholine or norepinephrine synthesis.

When an action potential spreads over the terminal fibers, the depolarization process increases the permeability of the fiber membrane to calcium ions, allowing these ions to diffuse into the nerve terminals or nerve varicosities. The calcium ions in turn cause the terminals or varicosities to empty their contents to the exterior. Thus, the transmitter substance is secreted.

Synthesis of Acetylcholine, Its Destruction After Secretion, and Its Duration of Action. Acetylcholine is synthesized in the terminal endings and varicosities of the cholinergic nerve fibers where it is stored in vesicles in highly concentrated form until it is released. The basic chemical reaction of this synthesis is the following:

$$\text{Acetyl-CoA + Choline} \xrightarrow{\text{Choline acetyltransferase}} \text{Acetylcholine}$$

Once acetylcholine is secreted into a tissue by a cholinergic nerve ending, it persists in the tissue for a few seconds while it performs its nerve signal transmitter function. Then it is split into an *acetate ion* and *choline,* catalyzed by the enzyme *acetylcholinesterase* that is bound with collagen and glycosaminoglycans in the local connective tissue. This is the same mechanism for acetylcholine signal transmission and subsequent acetylcholine destruction that occurs at the neuromuscular junctions of skeletal nerve fibers. The choline that is formed is then transported back into the terminal nerve ending, where it is used again and again for synthesis of new acetylcholine.

Synthesis of Norepinephrine, Its Removal, and Its Duration of Action. Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed inside the secretory vesicles. The basic steps are the following:

1. $\text{Tyrosine} \xrightarrow{\text{Hydroxylation}} \text{Dopa}$
2. $\text{Dopa} \xrightarrow{\text{Decarboxylation}} \text{Dopamine}$
3. Transport of dopamine into the vesicles
4. $\text{Dopamine} \xrightarrow{\text{Hydroxylation}} \text{Norepinephrine}$

In the adrenal medulla, this reaction goes still one step further to transform about 80 per cent of the norepinephrine into epinephrine, as follows:

5. $\text{Norepinephrine} \xrightarrow{\text{Methylation}} \text{Epinephrine}$

After secretion of norepinephrine by the terminal nerve endings, it is removed from the secretory site in three ways: (1) reuptake into the adrenergic nerve endings by an active transport process—accounting for removal of 50 to 80 percent of the secreted norepinephrine; (2) diffusion away from the nerve endings into the surrounding body fluids and then into the blood—accounting for removal of most of the remaining norepinephrine; and (3) destruction of small amounts by tissue enzymes (one of these enzymes is *monoamine oxidase,* which is found in the nerve endings, and another is *catechol-O-methyl transferase,* which is present diffusely in all tissues).

Ordinarily, the norepinephrine secreted directly into a tissue remains active for only a few seconds, demonstrating that its reuptake and diffusion away from the tissue are rapid. However, the norepinephrine and epinephrine secreted into the blood by the adrenal medullae remain active until they diffuse into some tissue, where they can be destroyed by catechol-O-methyl transferase; this occurs mainly in the liver. Therefore, when secreted into the blood, both norepinephrine and epinephrine remain active for 10 to 30 seconds; but their activity declines to extinction over 1 to several minutes.

Receptors on the Effector Organs

Before acetylcholine, norepinephrine, or epinephrine secreted at an autonomic nerve ending can stimulate an effector organ, it must first bind with specific *receptors* on the effector cells. The receptor is on the outside of the cell membrane, bound as a prosthetic group to a protein molecule that penetrates all the way through the cell membrane. When the transmitter substance binds with the receptor, this causes a conformational change in the structure of the protein molecule. In turn, the altered protein molecule excites or inhibits the cell, most often by (1) causing a change in cell membrane permeability to one or more ions or (2) activating or inactivating an enzyme attached to the other end of the receptor protein, where it protrudes into the interior of the cell.

Excitation or Inhibition of the Effector Cell by Changing Its Membrane Permeability. Because the receptor protein is an integral part of the cell membrane, a conformational change in structure of the receptor protein often *opens or closes an ion channel* through the interstices of the protein molecule, thus altering the permeability of the cell membrane to various ions. For instance, sodium and/or calcium ion channels frequently become opened

and allow rapid influx of the respective ions into the cell, usually depolarizing the cell membrane and *exciting* the cell. At other times, potassium channels are opened, allowing potassium ions to diffuse out of the cell, and this usually *inhibits* the cell because loss of electropositive potassium ions creates hypernegativity inside the cell. In some cells, the changed intracellular ion environment will cause an internal cell action, such as a direct effect of calcium ions to promote smooth muscle contraction.

Receptor Action by Altering Intracellular "Second Messenger" Enzymes. Another way a receptor often functions is to activate or inactivate an enzyme (or other intracellular chemical) inside the cell. The enzyme often is attached to the receptor protein where the receptor protrudes into the interior of the cell. For instance, binding of norepinephrine with its receptor on the outside of many cells increases the activity of the enzyme *adenylyl cyclase* on the inside of the cell, and this causes formation of *cyclic adenosine monophosphate* (cAMP). The cAMP in turn can initiate any one of many different intracellular actions, the exact effect depending on the chemical machinery of the effector cell.

It is easy to understand how an autonomic transmitter substance can cause inhibition in some organs or excitation in others. This is usually determined by the nature of the receptor protein in the cell membrane and the effect of receptor binding on its conformational state. In each organ, the resulting effects are likely to be different from those in other organs.

Two Principal Types of Acetylcholine Receptors—Muscarinic and Nicotinic Receptors

Acetylcholine activates mainly two types of *receptors.* They are called *muscarinic* and *nicotinic* receptors. The reason for these names is that muscarine, a poison from toadstools, activates only muscarinic receptors and will not activate nicotinic receptors, whereas nicotine activates only nicotinic receptors; acetylcholine activates both of them.

Muscarinic receptors are found on all effector cells that are stimulated by the postganglionic cholinergic neurons of either the parasympathetic nervous system or the sympathetic system.

Nicotinic receptors are found in the autonomic ganglia at the synapses between the preganglionic and postganglionic neurons of both the sympathetic and parasympathetic systems. (Nicotinic receptors are also present at many nonautonomic nerve endings—for instance, at the neuromuscular junctions in skeletal muscle [discussed in Chapter 7].)

An understanding of the two types of receptors is especially important because specific drugs are frequently used as medicine to stimulate or block one or the other of the two types of receptors.

Adrenergic Receptors—Alpha and Beta Receptors

There are also two major types of adrenergic receptors, *alpha receptors* and *beta receptors.* The beta receptors in turn are divided into *beta*$_1$, *beta*$_2$ and *beta*$_3$ receptors because certain chemicals affect only certain beta receptors. Also, there is a division of alpha receptors into alpha$_1$ and alpha$_2$ receptors.

Norepinephrine and epinephrine, both of which are secreted into the blood by the adrenal medulla, have slightly different effects in exciting the alpha and beta receptors. Norepinephrine excites mainly alpha receptors but excites the beta receptors to a lesser extent as well. Conversely, epinephrine excites both types of receptors approximately equally. Therefore, the relative effects of norepinephrine and epinephrine on different effector organs are determined by the types of receptors in the organs. If they are all beta receptors, epinephrine will be the more effective excitant.

Table 60-1 gives the distribution of alpha and beta receptors in some of the organs and systems controlled by the sympathetics. Note that certain alpha functions are excitatory, whereas others are inhibitory. Likewise, certain beta functions are excitatory and others are inhibitory. Therefore, alpha and beta receptors are not necessarily associated with excitation or inhibition but simply with the affinity of the hormone for the receptors in the given effector organ.

A synthetic hormone chemically similar to epinephrine and norepinephrine, *isopropyl norepinephrine,* has an extremely strong action on beta receptors but essentially no action on alpha receptors.

Excitatory and Inhibitory Actions of Sympathetic and Parasympathetic Stimulation

Table 60-2 lists the effects on different visceral functions of the body caused by stimulating either the parasympathetic nerves or the sympathetic nerves. From this table, it can be seen again that *sympathetic stimulation causes excitatory effects in some organs but inhibitory effects in others. Likewise, parasympathetic stimulation causes excitation in some but inhibition in others.* Also, when sympathetic stimulation excites a particular organ, parasympathetic stimulation sometimes inhibits it, demonstrating that the

Table 60-1 Adrenergic Receptors and Function

Alpha Receptor	Beta Receptor
Vasoconstriction	Vasodilation (β_2)
Iris dilation	Cardioacceleration (β_1)
Intestinal relaxation	Increased myocardial strength (β_1)
Intestinal sphincter contraction	Intestinal relaxation (β_2) Uterus relaxation (β_2)
Pilomotor contraction	Bronchodilation (β_2)
Bladder sphincter contraction	Calorigenesis (β_2)
Inhibits neurotransmitter release (α_2)	Glycogenolysis (β_2) Lipolysis (β_1) Bladder wall relaxation (β_2) Thermogenesis (β_3)

Table 60-2 Autonomic Effects on Various Organs of the Body

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands Nasal Lacrimal Parotid Submandibular Gastric Pancreatic	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated
Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted
Kidney	Decreased urine output and increased renin secretion	None
Bladder		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed
Penis	Ejaculation	Erection
Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

two systems occasionally act reciprocally to each other. But most organs are dominantly controlled by one or the other of the two systems.

There is no generalization one can use to explain whether sympathetic or parasympathetic stimulation will cause excitation or inhibition of a particular organ. Therefore, to understand sympathetic and parasympathetic function, one must learn all the separate functions of these two nervous systems on each organ, as listed in Table 60-2. Some of these functions need to be clarified in still greater detail, as follows.

Effects of Sympathetic and Parasympathetic Stimulation on Specific Organs

Eyes. Two functions of the eyes are controlled by the autonomic nervous system. They are (1) the pupillary opening and (2) the focus of the lens.

Sympathetic stimulation *contracts the meridional fibers of the iris that dilate* the pupil, whereas parasympathetic stimulation contracts the *circular muscle of the iris to constrict* the pupil.

The parasympathetics that control the pupil are reflexly stimulated when excess light enters the eyes, which is explained in Chapter 51; this reflex reduces the pupillary opening and decreases the amount of light that strikes the retina. Conversely, the sympathetics become stimulated during periods of excitement and increase pupillary opening at these times.

Focusing of the lens is controlled almost entirely by the parasympathetic nervous system. The lens is normally held in a flattened state by intrinsic elastic tension of its radial ligaments. Parasympathetic excitation contracts the *ciliary muscle,* which is a ringlike body of smooth muscle fibers that encircles the outside ends of the lens radial ligaments. This contraction releases the tension on the ligaments and allows the lens to become more convex, causing the eye to focus on objects near at hand. The detailed focusing mechanism is discussed in Chapters 49 and 51 in relation to function of the eyes.

Glands of the Body. The *nasal, lacrimal, salivary,* and many *gastrointestinal glands* are strongly stimulated by the parasympathetic nervous system, usually resulting in copious quantities of watery secretion. The glands of the alimentary tract most strongly stimulated by the parasympathetics are those of the upper tract, especially those of the mouth and stomach. On the other hand, the glands of the small and large intestines are controlled principally by local factors in the intestinal tract itself and by the *intestinal enteric nervous system* and much less by the autonomic nerves.

Sympathetic stimulation has a direct effect on most alimentary gland cells to cause formation of a concentrated secretion that contains high percentages of enzymes and mucus. But it also causes vasoconstriction of the blood vessels that supply the glands and in this way sometimes reduces their rates of secretion.

The *sweat glands* secrete large quantities of sweat when the sympathetic nerves are stimulated, but no effect is caused by stimulating the parasympathetic nerves. However, the sympathetic fibers to most sweat glands are *cholinergic* (except for a few adrenergic fibers to the palms and soles), in contrast to almost all other sympathetic fibers, which are adrenergic. Furthermore, the sweat glands are stimulated primarily by centers in the hypothalamus that are usually considered to be parasympathetic centers. Therefore, sweating could be called a parasympathetic function, even though it is controlled by nerve fibers that anatomically are distributed through the sympathetic nervous system.

The *apocrine glands* in the axillae secrete a thick, odoriferous secretion as a result of sympathetic stimulation, but they do not respond to parasympathetic stimulation. This secretion actually functions as a lubricant to allow easy sliding motion of the inside surfaces under the shoulder joint. The apocrine glands, despite their close embryological relation to sweat glands, are activated by adrenergic fibers rather than by cholinergic fibers and are also controlled by the sympathetic centers of the central nervous system rather than by the parasympathetic centers.

Intramural Nerve Plexus of the Gastrointestinal System. The gastrointestinal system has its own intrinsic set of nerves known as the *intramural plexus* or the *intestinal enteric nervous system,* located in the walls of the gut. Also, both parasympathetic and sympathetic stimulation originating in the brain can affect gastrointestinal activity mainly by increasing or decreasing specific actions in the gastrointestinal intramural plexus. Parasympathetic stimulation, in general, increases overall degree of activity of the gastrointestinal tract by promoting peristalsis and relaxing the sphincters, thus allowing rapid propulsion of contents along the tract. This propulsive effect is associated with simultaneous increases in rates of secretion by many of the gastrointestinal glands, described earlier.

Normal function of the gastrointestinal tract is not very dependent on sympathetic stimulation. However, strong sympathetic stimulation inhibits peristalsis and increases the tone of the sphincters. The net result is greatly slowed propulsion of food through the tract and sometimes decreased secretion as well—even to the extent of sometimes causing constipation.

Heart. In general, sympathetic stimulation increases the overall activity of the heart. This is accomplished by increasing both the rate and force of heart contraction.

Parasympathetic stimulation causes mainly opposite effects—decreased heart rate and strength of contraction. To express these effects in another way, sympathetic stimulation increases the effectiveness of the heart as a pump, as required during heavy exercise, whereas parasympathetic stimulation decreases heart pumping, allowing the heart to rest between bouts of strenuous activity.

Systemic Blood Vessels. Most systemic blood vessels, especially those of the abdominal viscera and skin of the limbs, are constricted by sympathetic stimulation. Parasympathetic stimulation has almost no effects on most blood vessels except to dilate vessels in certain restricted areas, such as in the blush area of the face. Under some conditions, the beta function of the sympathetics causes vascular dilation instead of the usual sympathetic vascular constriction, but this occurs rarely except after drugs have paralyzed the sympathetic alpha vasoconstrictor effects, which, in most blood vessels, are usually far dominant over the beta effects.

Effect of Sympathetic and Parasympathetic Stimulation on Arterial Pressure. The arterial pressure is determined by two factors: propulsion of blood by the heart and resistance to flow of blood through the peripheral blood vessels. Sympathetic stimulation increases both propulsion by the heart and resistance to flow, which usually causes a marked *acute* increase in arterial pressure but often very little change

in long-term pressure unless the sympathetics stimulate the kidneys to retain salt and water at the same time.

Conversely, moderate parasympathetic stimulation via the vagal nerves decreases pumping by the heart but has virtually no effect on vascular peripheral resistance. Therefore, the usual effect is a slight decrease in arterial pressure. But *very strong vagal parasympathetic* stimulation can almost stop or occasionally actually stop the heart entirely for a few seconds and cause temporary loss of all or most arterial pressure.

Effects of Sympathetic and Parasympathetic Stimulation on Other Functions of the Body. Because of the great importance of the sympathetic and parasympathetic control systems, they are discussed many times in this text in relation to multiple body functions. In general, most of the entodermal structures, such as the ducts of the liver, gallbladder, ureter, urinary bladder, and bronchi, are inhibited by sympathetic stimulation but excited by parasympathetic stimulation. Sympathetic stimulation also has multiple metabolic effects such as release of glucose from the liver, increase in blood glucose concentration, increase in glycogenolysis in both liver and muscle, increase in skeletal muscle strength, increase in basal metabolic rate, and increase in mental activity. Finally, the sympathetics and parasympathetics are involved in execution of the male and female sexual acts, as explained in Chapters 80 and 81.

Function of the Adrenal Medullae

Stimulation of the sympathetic nerves to the adrenal medullae causes large quantities of epinephrine and norepinephrine to be released into the circulating blood, and these two hormones in turn are carried in the blood to all tissues of the body. On average, about 80 percent of the secretion is epinephrine and 20 percent is norepinephrine, although the relative proportions can change considerably under different physiologic conditions.

The circulating epinephrine and norepinephrine have almost the same effects on the different organs as the effects caused by direct sympathetic stimulation, except that *the effects last 5 to 10 times as long* because both of these hormones are removed from the blood slowly over a period of 2 to 4 minutes.

The circulating norepinephrine causes constriction of most of the blood vessels of the body; it also causes increased activity of the heart, inhibition of the gastrointestinal tract, dilation of the pupils of the eyes, and so forth.

Epinephrine causes almost the same effects as those caused by norepinephrine, but the effects differ in the following respects: First, epinephrine, because of its greater effect in stimulating the beta receptors, has a greater effect on cardiac stimulation than does norepinephrine. Second, epinephrine causes only weak constriction of the blood vessels in the muscles, in comparison with much stronger constriction caused by norepinephrine. Because the muscle vessels represent a major segment of the vessels of the body, this difference is of special importance because norepinephrine greatly increases the total peripheral resistance and elevates arterial pressure, whereas epinephrine raises the arterial pressure to a lesser extent but increases the cardiac output more.

A third difference between the actions of epinephrine and norepinephrine relates to their effects on tissue metabolism. Epinephrine has 5 to 10 times as great a metabolic effect as norepinephrine. Indeed, the epinephrine secreted by the adrenal medullae can increase the metabolic rate of the whole body often to as much as 100 percent above normal, in this way increasing the activity and excitability of the body. It also increases the rates of other metabolic activities, such as glycogenolysis in the liver and muscle, and glucose release into the blood.

In summary, stimulation of the adrenal medullae causes release of the hormones epinephrine and norepinephrine, which together have almost the same effects throughout the body as direct sympathetic stimulation, except that the effects are greatly prolonged, lasting 2 to 4 minutes after the stimulation is over.

Value of the Adrenal Medullae to the Function of the Sympathetic Nervous System. Epinephrine and norepinephrine are almost always released by the adrenal medullae at the same time that the different organs are stimulated directly by generalized sympathetic activation. Therefore, the organs are actually stimulated in two ways: directly by the sympathetic nerves and indirectly by the adrenal medullary hormones. The two means of stimulation support each other, and either can, in most instances, substitute for the other. For instance, destruction of the direct sympathetic pathways to the different body organs does not abrogate sympathetic excitation of the organs because norepinephrine and epinephrine are still released into the circulating blood and indirectly cause stimulation. Likewise, loss of the two adrenal medullae usually has little effect on the operation of the sympathetic nervous system because the direct pathways can still perform almost all the necessary duties. Thus, the dual mechanism of sympathetic stimulation provides a safety factor, one mechanism substituting for the other if it is missing.

Another important value of the adrenal medullae is the capability of epinephrine and norepinephrine to stimulate structures of the body that are not innervated by direct sympathetic fibers. For instance, the metabolic rate of every cell of the body is increased by these hormones, especially by epinephrine, even though only a small proportion of all the cells in the body are innervated directly by sympathetic fibers.

Relation of Stimulus Rate to Degree of Sympathetic and Parasympathetic Effect

A special difference between the autonomic nervous system and the skeletal nervous system is that only a low frequency of stimulation is required for full activation of autonomic effectors. In general, only one nerve impulse every few seconds suffices to maintain normal sympathetic or parasympathetic effect, and full activation occurs when the nerve fibers discharge 10 to 20 times per second. This compares with full activation in the skeletal nervous system at 50 to 500 or more impulses per second.

Sympathetic and Parasympathetic "Tone"

Normally, the sympathetic and parasympathetic systems are continually active, and the basal rates of activity are known, respectively, as *sympathetic tone* and *parasympathetic tone.*

The value of tone is that *it allows a single nervous system both to increase and decrease the activity of a stimulated organ.* For instance, sympathetic tone normally keeps almost all the systemic arterioles constricted to about one-half their maximum diameter. By increasing the degree of sympathetic stimulation above normal, these vessels can be constricted even more; conversely, by decreasing the stimulation below normal, the arterioles can be dilated. If it were not for the continual background sympathetic tone, the sympathetic system could cause only vasoconstriction, never vasodilation.

Another interesting example of tone is the background "tone" of the parasympathetics in the gastrointestinal tract. Surgical removal of the parasympathetic supply to most of the gut by cutting the vagus nerves can cause serious and prolonged gastric and intestinal "atony" with resulting blockage of much of the normal gastrointestinal propulsion and consequent serious constipation, thus demonstrating that parasympathetic tone to the gut is normally very much required. This tone can be decreased by the brain, thereby inhibiting gastrointestinal motility, or it can be increased, thereby promoting increased gastrointestinal activity.

Tone Caused by Basal Secretion of Epinephrine and Norepinephrine by the Adrenal Medullae. The normal resting rate of secretion by the adrenal medullae is about 0.2 μg/kg/min of epinephrine and about 0.05 μg/kg/min of norepinephrine. These quantities are considerable—indeed, enough to maintain the blood pressure almost up to normal even if all direct sympathetic pathways to the cardiovascular system are removed. Therefore, it is obvious that much of the overall tone of the sympathetic nervous system results from basal secretion of epinephrine and norepinephrine in addition to the tone resulting from direct sympathetic stimulation.

Effect of Loss of Sympathetic or Parasympathetic Tone After Denervation. Immediately after a sympathetic or parasympathetic nerve is cut, the innervated organ loses its sympathetic or parasympathetic tone. In the case of the blood vessels, for instance, cutting the sympathetic nerves results within 5 to 30 seconds in almost maximal vasodilation. However, over minutes, hours, days, or weeks, *intrinsic tone* in the smooth muscle of the vessels increases—that is, increased tone caused by increased smooth muscle contractile force that is *not* the result of sympathetic stimulation but of chemical adaptations in the smooth muscle fibers themselves. This intrinsic tone eventually restores almost normal vasoconstriction.

Essentially the same effects occur in most other effector organs whenever sympathetic or parasympathetic tone is lost. That is, intrinsic compensation soon develops to return the function of the organ almost to its normal basal level. However, in the parasympathetic system, the compensation sometimes requires many months. For instance, loss of parasympathetic tone to the heart after cardiac vagotomy increases the heart rate to 160 beats per minute in a dog, and this will still be partially elevated 6 months later.

Denervation Supersensitivity of Sympathetic and Parasympathetic Organs After Denervation

During the first week or so after a sympathetic or parasympathetic nerve is destroyed, the innervated organ becomes more sensitive to injected norepinephrine or acetylcholine, respectively. This effect is demonstrated in Figure 60-4, showing blood flow in the forearm before removal of the sympathetics to be about 200 ml/min; a test dose of norepinephrine causes only a slight depression in flow lasting a minute or so. Then the stellate ganglion is removed, and normal sympathetic tone is lost. At first, the blood flow rises markedly because of the lost vascular tone, but over a period of days to weeks the blood flow returns much of the way back toward normal because of progressive increase in intrinsic tone of the vascular musculature itself, thus partially compensating for the loss of sympathetic tone. Then another test dose of norepinephrine is administered, and the blood flow decreases much more than before, demonstrating that the blood vessels have become about two to four times as responsive to norepinephrine as previously. This phenomenon is called *denervation supersensitivity.* It occurs in both sympathetic and parasympathetic organs but to far greater extent in some organs than in others, occasionally increasing the response more than 10-fold.

Mechanism of Denervation Supersensitivity. The cause of denervation supersensitivity is only partially known. Part of the answer is that the number of receptors in the postsynaptic membranes of the effector cells increases—sometimes manyfold—when norepinephrine or acetylcholine is no longer released at the synapses, a process called "up-regulation" of the receptors. Therefore, when a dose of the hormone is now injected into the circulating blood, the effector reaction is vastly enhanced.

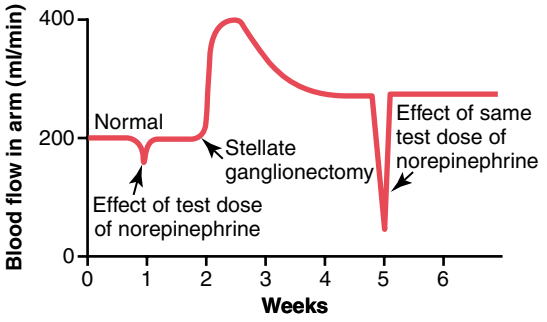


Figure 60-4 Effect of sympathectomy on blood flow in the arm, and effect of a test dose of norepinephrine before and after sympathectomy, showing ***supersensitization*** of the vasculature to norepinephrine.

Autonomic Reflexes

Many visceral functions of the body are regulated by *autonomic reflexes.* Throughout this text, the functions of these reflexes are discussed in relation to individual organ systems; to illustrate their importance, a few are presented here briefly.

Cardiovascular Autonomic Reflexes. Several reflexes in the cardiovascular system help to control the arterial blood pressure and the heart rate. One of these is the *baroreceptor reflex,* which is described in Chapter 18 along with other cardiovascular reflexes. Briefly, stretch receptors called *baroreceptors* are located in the walls of several major arteries, including especially the internal carotid arteries and the arch of the aorta. When these become stretched by high pressure, signals are transmitted to the brain stem, where they inhibit the sympathetic impulses to the heart and blood vessels and excite the parasympathetics; this allows the arterial pressure to fall back toward normal.

Gastrointestinal Autonomic Reflexes. The uppermost part of the gastrointestinal tract and the rectum are controlled principally by autonomic reflexes. For instance, the smell of appetizing food or the presence of food in the mouth initiates signals from the nose and mouth to the vagal, glossopharyngeal, and salivatory nuclei of the brain stem. These in turn transmit signals through the parasympathetic nerves to the secretory glands of the mouth and stomach, causing secretion of digestive juices sometimes even before food enters the mouth.

When fecal matter fills the rectum at the other end of the alimentary canal, sensory impulses initiated by stretching the rectum are sent to the sacral portion of the spinal cord, and a reflex signal is transmitted back through the sacral parasympathetics to the distal parts of the colon; these result in strong peristaltic contractions that cause defecation.

Other Autonomic Reflexes. Emptying of the urinary bladder is controlled in the same way as emptying the rectum; stretching of the bladder sends impulses to the sacral cord, and this in turn causes reflex contraction of the bladder and relaxation of the urinary sphincters, thereby promoting micturition.

Also important are the sexual reflexes, which are initiated both by psychic stimuli from the brain and by stimuli from the sexual organs. Impulses from these sources converge on the sacral cord and, in the male, result first in *erection*, *mainly a parasympathetic function*, and then *ejaculation*, *partially a sympathetic function*.

Other autonomic control functions include reflex contributions to the regulation of pancreatic secretion, gallbladder emptying, kidney excretion of urine, sweating, blood glucose concentration, and many other visceral functions, all of which are discussed in detail at other points in this text.

Stimulation of Discrete Organs in Some Instances and Mass Stimulation in Other Instances by the Sympathetic and Parasympathetic Systems

Sympathetic System Sometimes Responds by Mass Discharge. In some instances, almost all portions of the sympathetic nervous system discharge simultaneously as a complete unit, a phenomenon called *mass discharge.* This frequently occurs when the hypothalamus is activated by fright or fear or severe pain. The result is a widespread reaction throughout the body called the *alarm* or *stress response,* which is discussed shortly.

At other times, activation occurs in isolated portions of the sympathetic nervous system. Important examples are the following: (1) During the process of heat regulation, the sympathetics control sweating and blood flow in the skin without affecting other organs innervated by the sympathetics. (2) Many "local reflexes" involving sensory afferent fibers travel centrally in the peripheral nerves to the sympathetic ganglia and spinal cord and cause highly localized reflex responses. For instance, heating a skin area causes local vasodilation and enhanced local sweating, whereas cooling causes opposite effects. (3) Many of the sympathetic reflexes that control gastrointestinal functions operate by way of nerve pathways that do not even enter the spinal cord, merely passing from the gut mainly to the paravertebral ganglia, and then back to the gut through sympathetic nerves to control motor or secretory activity.

Parasympathetic System Usually Causes Specific Localized Responses. Control functions by the parasympathetic system are often highly specific. For instance, parasympathetic cardiovascular reflexes usually act only on the heart to increase or decrease its rate of beating. Likewise, other parasympathetic reflexes cause secretion mainly by the mouth glands and in other instances secretion is mainly by the stomach glands. Finally, the rectal emptying reflex does not affect other parts of the bowel to a major extent.

Yet there is often association between closely allied parasympathetic functions. For instance, although salivary secretion can occur independently of gastric secretion, these two also often occur together, and pancreatic secretion frequently occurs at the same time. Also, the rectal emptying reflex often initiates a urinary bladder emptying reflex, resulting in simultaneous emptying of both the bladder and the rectum. Conversely, the bladder emptying reflex can help initiate rectal emptying.

"Alarm" or "Stress" Response of the Sympathetic Nervous System

When large portions of the sympathetic nervous system discharge at the same time—that is, a *mass discharge*—this increases in many ways the ability of the body to perform vigorous muscle activity. Let us summarize these ways:

1. Increased arterial pressure
2. Increased blood flow to active muscles concurrent with decreased blood flow to organs such as the gastrointestinal tract and the kidneys that are not needed for rapid motor activity
3. Increased rates of cellular metabolism throughout the body
4. Increased blood glucose concentration

5. Increased glycolysis in the liver and in muscle
6. Increased muscle strength
7. Increased mental activity
8. Increased rate of blood coagulation

The sum of these effects permits a person to perform far more strenuous physical activity than would otherwise be possible. Because either *mental* or *physical stress* can excite the sympathetic system, it is frequently said that the purpose of the sympathetic system is to provide extra activation of the body in states of stress: this is called the sympathetic *stress response.*

The sympathetic system is especially strongly activated in many emotional states. For instance, in the state of *rage,* which is elicited to a great extent by stimulating the hypothalamus, signals are transmitted downward through the reticular formation of the brain stem and into the spinal cord to cause massive sympathetic discharge; most aforementioned sympathetic events ensue immediately. This is called the sympathetic *alarm reaction.* It is also called the *fight or flight reaction* because an animal in this state decides almost instantly whether to stand and fight or to run. In either event, the sympathetic alarm reaction makes the animal's subsequent activities vigorous.

Medullary, Pontine, and Mesencephalic Control of the Autonomic Nervous System

Many neuronal areas in the brain stem reticular substance and along the course of the tractus solitarius of the medulla, pons, and mesencephalon, as well as in many special nuclei (Figure 60-5), control different autonomic functions such as arterial pressure, heart rate, glandular secretion in the gastrointestinal tract, gastrointestinal peristalsis, and degree of contraction of the urinary bladder. Control of each of these is discussed at appropriate points in this text. Some of the *most important factors controlled in the brain stem are arterial pressure, heart rate, and respiratory rate.* Indeed, transection of the brain stem above the midpontine level allows basal control of arterial pressure to continue as before but prevents its modulation by higher nervous centers such as the hypothalamus. Conversely, transection immediately below the medulla causes the arterial pressure to fall to less than one-half normal.

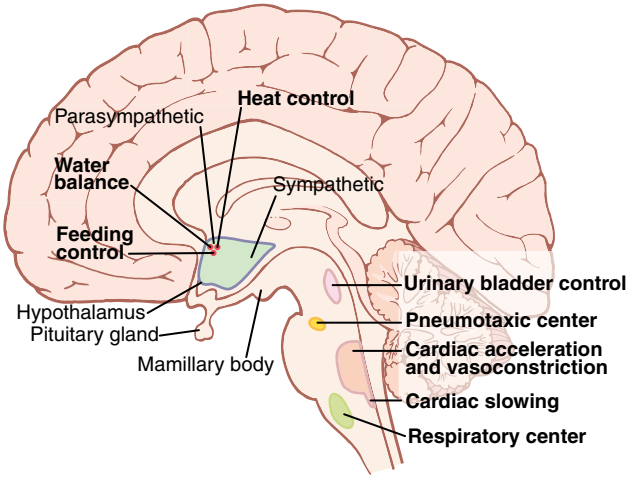


Figure 60-5 Autonomic control areas in the brain stem and hypothalamus.

Closely associated with the cardiovascular regulatory centers in the brain stem are the medullary and pontine centers for regulation of respiration, which are discussed in Chapter 41. Although this is not considered to be an autonomic function, it is one of the *involuntary* functions of the body.

Control of Brain Stem Autonomic Centers by Higher Areas. Signals from the hypothalamus and even from the cerebrum can affect the activities of almost all the brain stem autonomic control centers. For instance, stimulation in appropriate areas mainly of the posterior hypothalamus can activate the medullary cardiovascular control centers strongly enough to increase arterial pressure to more than twice normal. Likewise, other hypothalamic centers control body temperature, increase or decrease salivation and gastrointestinal activity, and cause bladder emptying. To some extent, therefore, the autonomic centers in the brain stem act as relay stations for control activities initiated at higher levels of the brain, especially in the hypothalamus.

In Chapters 58 and 59, it is pointed out also that many of our behavioral responses are mediated through (1) the hypothalamus, (2) the reticular areas of the brain stem, and (3) the autonomic nervous system. Indeed, some higher areas of the brain can alter function of the whole autonomic nervous system or of portions of it strongly enough to cause severe autonomic-induced disease such as peptic ulcer of the stomach or duodenum, constipation, heart palpitation, or even heart attack.

Pharmacology of the Autonomic Nervous System

Drugs That Act on Adrenergic Effector Organs—Sympathomimetic Drugs

From the foregoing discussion, it is obvious that intravenous injection of norepinephrine causes essentially the same effects throughout the body as sympathetic stimulation. Therefore, norepinephrine is called a *sympathomimetic* or *adrenergic drug. Epinephrine* and *methoxamine* are also sympathomimetic drugs, and there are many others. They differ from one another in the degree to which they stimulate different sympathetic effector organs and in their duration of action. Norepinephrine and epinephrine have actions as short as 1 to 2 minutes, whereas the actions of some other commonly used sympathomimetic drugs last for 30 minutes to 2 hours.

Important drugs that stimulate specific adrenergic receptors are *phenylephrine* (alpha receptors), *isoproterenol* (beta receptors), and *albuterol* (only $beta_2$ receptors).

Drugs That Cause Release of Norepinephrine from Nerve Endings. Certain drugs have an indirect sympathomimetic action instead of directly exciting adrenergic effector organs. These drugs include *ephedrine, tyramine,* and *amphetamine.* Their effect is to cause release of norepinephrine from its storage vesicles in the sympathetic nerve endings. The released norepinephrine in turn causes the sympathetic effects.

Drugs That Block Adrenergic Activity. Adrenergic activity can be blocked at several points in the stimulatory process, as follows:

1. The synthesis and storage of norepinephrine in the sympathetic nerve endings can be prevented. The best known drug that causes this effect is *reserpine.*
2. Release of norepinephrine from the sympathetic endings can be blocked. This can be caused by *guanethidine.*
3. The sympathetic *alpha* receptors can be blocked. Two drugs that cause this effect are *phenoxybenzamine* and *phentolamine.*
4. The sympathetic *beta* receptors can be blocked. A drug that blocks $beta_1$ and $beta_2$ receptors is *propranolol.* One that blocks mainly $beta_1$ receptors is *metoprolol.*
5. Sympathetic activity can be blocked by drugs that block transmission of nerve impulses through the autonomic ganglia. They are discussed in a later section, but an important drug for blockade of both sympathetic and parasympathetic transmission through the ganglia is *hexamethonium.*

Drugs That Act on Cholinergic Effector Organs

Parasympathomimetic Drugs (Cholinergic Drugs). Acetylcholine injected intravenously usually does not cause exactly the same effects throughout the body as parasympathetic stimulation because most of the acetylcholine is destroyed by cholinesterase in the blood and body fluids before it can reach all the effector organs. Yet a number of other drugs that are not so rapidly destroyed can produce typical widespread parasympathetic effects, and they are called *parasympathomimetic drugs.*

Two commonly used parasympathomimetic drugs are *pilocarpine* and *methacholine.* They act directly on the muscarinic type of cholinergic receptors.

Drugs That Have a Parasympathetic Potentiating Effect—Anticholinesterase Drugs. Some drugs do not have a direct effect on parasympathetic effector organs but do potentiate the effects of the naturally secreted acetylcholine at the parasympathetic endings. They are the same drugs as those discussed in Chapter 7 that potentiate the effect of acetylcholine at the neuromuscular junction. They include *neostigmine, pyridostigmine,* and *ambenonium.* These drugs inhibit acetylcholinesterase, thus *preventing rapid destruction of the acetylcholine* liberated at parasympathetic nerve endings. As a consequence, the quantity of acetylcholine increases with successive stimuli and the degree of action also increases.

Drugs That Block Cholinergic Activity at Effector Organs—Antimuscarinic Drugs. *Atropine* and similar drugs, such as *homatropine* and *scopolamine, block the action of acetylcholine on the muscarinic type of cholinergic effector organs.* These drugs *do not* affect the nicotinic action of acetylcholine on the postganglionic neurons or on skeletal muscle.

Drugs That Stimulate or Block Sympathetic and Parasympathetic Postganglionic Neurons

Drugs That Stimulate Autonomic Postganglionic Neurons. The preganglionic neurons of both the parasympathetic and the sympathetic nervous systems secrete acetylcholine at their endings, and this acetylcholine in turn stimulates the postganglionic neurons. Furthermore, injected acetylcholine can also stimulate the postganglionic neurons of both systems, thereby causing at the same time both sympathetic and parasympathetic effects throughout the body.

Nicotine is another drug that can stimulate postganglionic neurons in the same manner as acetylcholine because the membranes of these neurons all contain the *nicotinic type of acetylcholine receptor.* Therefore, drugs that cause autonomic effects by stimulating postganglionic neurons are called *nicotinic drugs.* Some other drugs, such as *methacholine*, have both nicotinic and muscarinic actions, whereas *pilocarpine* has only muscarinic actions.

Nicotine excites both the sympathetic and parasympathetic postganglionic neurons at the same time, resulting in strong sympathetic vasoconstriction in the abdominal organs and limbs but at the same time resulting in parasympathetic effects such as increased gastrointestinal activity and, sometimes, slowing of the heart.

Ganglionic Blocking Drugs. Many important drugs block impulse transmission from the autonomic preganglionic neurons to the postganglionic neurons, including *tetraethyl ammonium ion, hexamethonium ion,* and *pentolinium.* These drugs block acetylcholine stimulation of the postganglionic neurons in both the sympathetic and the parasympathetic systems simultaneously. They are often used for blocking sympathetic activity but seldom for blocking parasympathetic activity because their effects of sympathetic blockade usually far overshadow the effects of parasympathetic blockade. The ganglionic blocking drugs especially can reduce the arterial pressure in many patients with hypertension, but these drugs are not useful clinically because their effects are difficult to control.

Bibliography

Cannon WB: Organization for physiological homeostasis, ***Physiol Rev*** 9:399, 1929.

Dajas-Bailador F, Wonnacott S: Nicotinic acetylcholine receptors and the regulation of neuronal signalling, ***Trends Pharmacol Sci*** 25:317, 2004.

Dampney RA, Horiuchi J, McDowall LM: Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour, ***Auton Neurosci*** 142:3, 2008.

DiBona GF: Physiology in perspective: The Wisdom of the Body. Neural control of the kidney, ***Am J Physiol Regul Integr Comp Physiol*** 2005.

Eisenhofer G, Kopin IJ, Goldstein DS: Catecholamine metabolism: a contemporary view with implications for physiology and medicine, ***Pharmacol Rev*** 56:331, 2004.

Goldstein DS, Sharabi Y: Neurogenic orthostatic hypotension: a pathophysiological approach, ***Circulation*** 119:139, 2009.

Goldstein DS, Robertson D, Esler M, et al: Dysautonomias: clinical disorders of the autonomic nervous system, ***Ann Intern Med*** 137:753, 2002.

Guyenet PG: The 2008 Carl Ludwig Lecture: retrotrapezoid nucleus, CO2 homeostasis, and breathing automaticity, ***J Appl Physiol*** 105:404, 2008.

Guyenet PG: The sympathetic control of blood pressure, ***Nat Rev Neurosci*** 7:335, 2006.

Hall JE, Hildebrandt DA, Kuo J: Obesity hypertension: role of leptin and sympathetic nervous system, ***Am J Hypertens*** 14:103S, 2001.

Kvetnansky R, Sabban EL, Palkovits M: Catecholaminergic systems in stress: structural and molecular genetic approaches, ***Physiol Rev*** 89:535, 2009.

Lohmeier TE: The sympathetic nervous system and long-term blood pressure regulation, ***Am J Hypertens*** 14:147S, 2001.

Lohmeier TE, Hildebrandt DA, Warren S, et al: Recent insights into the interactions between the baroreflex and the kidneys in hypertension, ***Am J Physiol Regul Integr Comp Physiol*** 288:R828, 2005.

Olshansky B, Sabbah HN, Hauptman PJ, et al: Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy, ***Circulation*** 118:863, 2008.

Saper CB: The central autonomic nervous system: conscious visceral perception and autonomic pattern generation, ***Annu Rev Neurosci*** 25:433, 2002.

Taylor EW, Jordan D, Coote JH: Central control of the cardiovascular and respiratory systems and their interactions in vertebrates, ***Physiol Rev*** 79:855, 1999.

Ulrich-Lai YM, Herman JP: Neural regulation of endocrine and autonomic stress responses, ***Nat Rev Neurosci*** 10:397, 2009.

Wess J: Novel insights into muscarinic acetylcholine receptor function using gene targeting technology, ***Trends Pharmacol Sci*** 24:414, 2003.