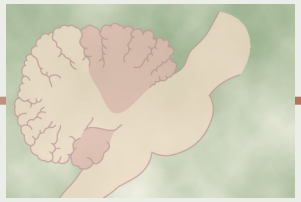

CHAPTER 57

UNIT XI

Cerebellum and Basal Ganglia Contributions to Overall Motor Control

In addition to areas in the cerebral cortex that stimulate muscle contraction, two other brain structures are essential for normal motor function—the *cerebellum* and the *basal ganglia*. Neither of these structures can control muscle function by itself. Instead, these structures always function in association with other systems of motor control.

The cerebellum plays major roles in timing of motor activities and in rapid, smooth progression from one muscle movement to the next. It also helps 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 plan and control complex patterns of muscle movement. They control relative intensities of the separate movements, directions of movements, and sequencing of multiple successive and parallel movements to achieve 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.

THE CEREBELLUM AND ITS MOTOR FUNCTIONS

The cerebellum, illustrated in **Figures 57-1** and **57-2**, 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 lack of coordination of these activities, even though its loss does not cause paralysis of any muscles.

How can the cerebellum be so important when it has no direct ability to cause muscle contraction? The answer is that it helps sequence and monitor motor activities and makes corrective adjustments while activities 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. If a movement does not occur exactly as intended, the cerebellar circuit learns to make a stronger or weaker movement the next time. To make this adjustment, changes occur in the excitability of appropriate cerebellar neurons, thus bringing subsequent muscle contractions into better correspondence with the intended movements.

Anatomical and Functional Areas of the Cerebellum

Anatomically, the cerebellum is divided into three lobes by two deep fissures, as shown in **Figures 57-1** and **57-2**: (1) the *anterior lobe,* (2) the *posterior lobe,* and (3) the *flocculonodular lobe.* The flocculonodular lobe is the oldest portion of the cerebellum; it developed along with (and functions with) the vestibular system in controlling body equilibrium, as discussed in Chapter 56.

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 the longitudinal axis, as demonstrated in **Figure 57-2**, 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

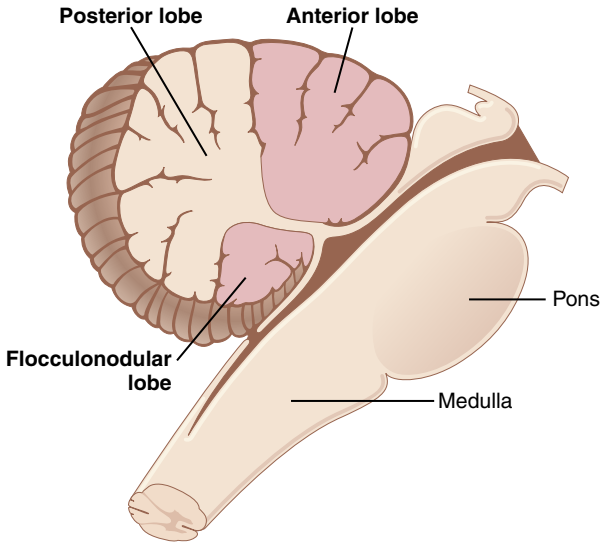

Figure 57-1 Anatomical lobes of the cerebellum as seen from the lateral side.

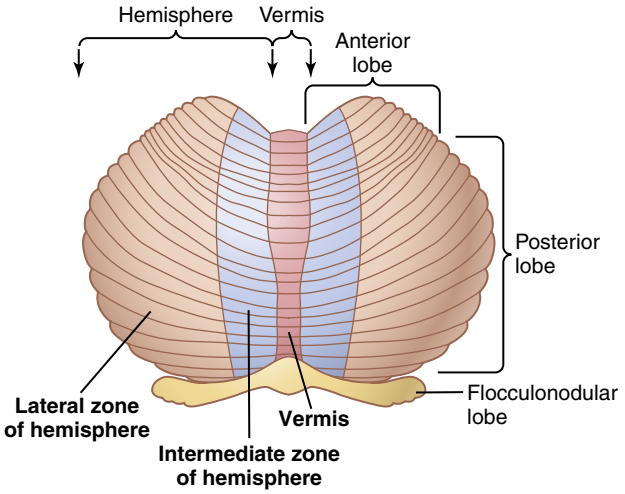

Figure 57-2 Functional parts of the cerebellum as seen from the posteroinferior view, with the inferiormost portion of the cerebellum rolled outward to flatten the surface.

the *vermis,* which is separated from the remainder of the cerebellum by shallow grooves. Most cerebellar control functions for muscle movements of the *axial body*, *neck*, *shoulders*, *and hips* are located in this area.

To each side of the vermis is a large, laterally protruding *cerebellar hemisphere;* 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, fingers, 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 uncoordinated, as we discuss more fully later in this chapter.

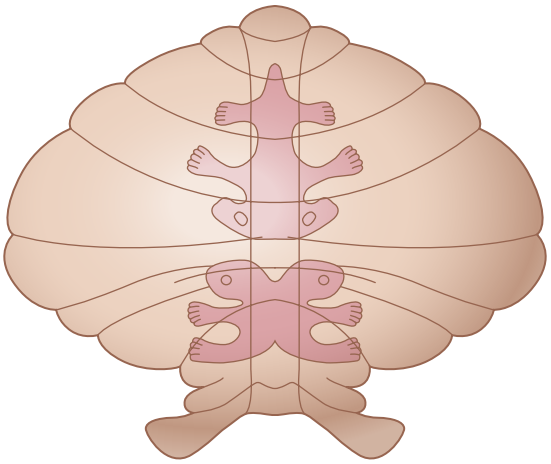

Figure 57-3 Somatosensory projection areas in the cerebellar cortex.

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 does the vermis and intermediate zones of the cerebellum. Figure 57-3 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 input signals almost exclusively from the cerebral cortex, especially the premotor areas of the frontal cortex, and from the somatosensory and other sensory association areas of the parietal cortex. 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 57-2 and 57-3. 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 57-4. An extensive and important afferent pathway is the corticopontocerebellar pathway, which originates in the

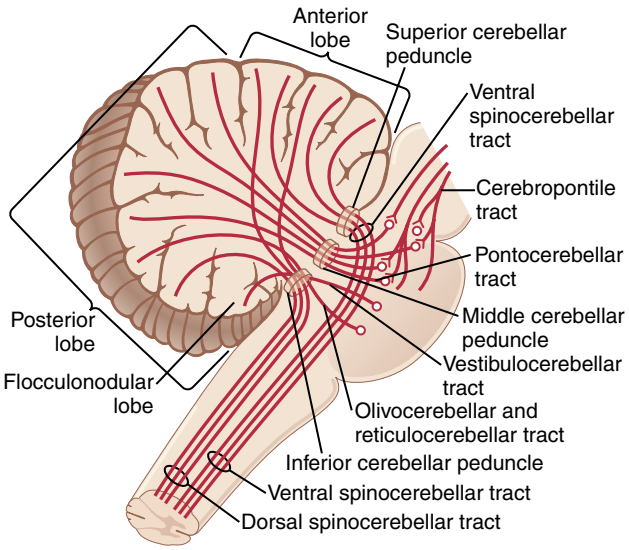

Figure 57-4 Principal *afferent* tracts to the cerebellum.

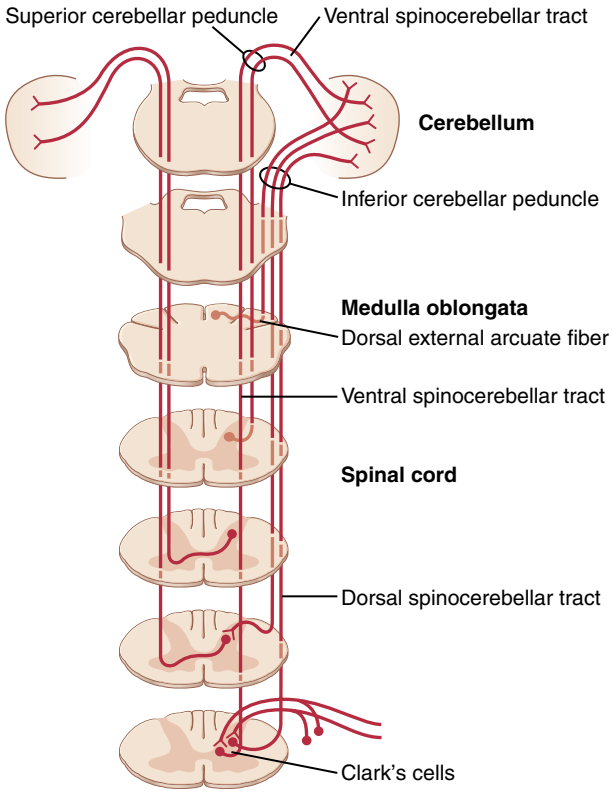

Figure 57-5 Spinocerebellar tracts.

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.

In addition, important afferent tracts originate in each side of the brain stem. These tracts include the following: (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, with almost all of these fibers terminating 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 57-5, 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.

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 speed 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 are 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. Signals are then 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.

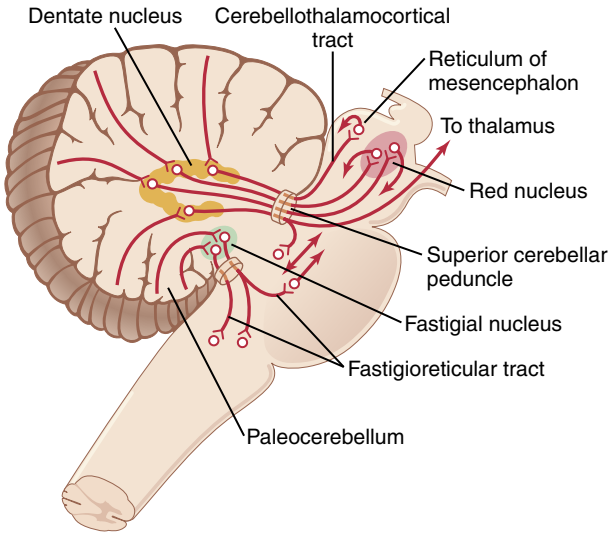

Figure 57-6 Principal *efferent* tracts from the cerebellum.

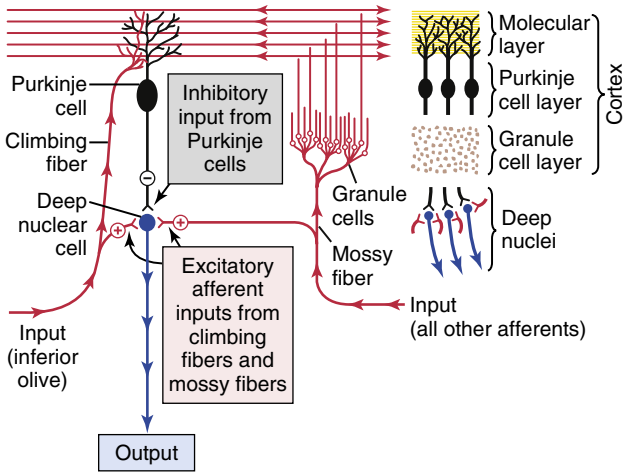

Figure 57-7 Deep nuclear cells receive excitatory and inhibitory inputs. The *left side* of this figure shows the basic neuronal circuit of the cerebellum, with excitatory neurons shown in *red* and the Purkinje cell (an inhibitory neuron) shown in *black*. To the *right* is shown the physical relationship of the deep cerebellar nuclei to the cerebellar cortex with its three layers.

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.

The general plan of the major efferent pathways leading out of the cerebellum is shown in **Figure 57-6** and consists of the following pathways:

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 56 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 mainly helps coordinate 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 AND DEEP NUCLEAR CELLS

The cerebellum has about 30 million nearly identical functional units, one of which is shown to the left in **Figure 57-7**. 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 57-7**, 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 57-7** 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—the higher brain, brain stem, and spinal cord. These fibers also send collaterals to excite the deep nuclear cells. They then proceed to the granule cell layer of the cortex, where they also 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. Many millions of these *parallel nerve fibers* exist 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 fire 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 57-7, 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, 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.

Basket Cells and Stellate Cells Cause Lateral Inhibition of Purkinje 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*, which 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 the turn-on signals to the antagonists. Although the exact details are not fully known, one can speculate from the basic cerebellar circuit of Figure 57-7 how this process 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, which 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 effect 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 to build up enough excitation in the dendrites of the Purkinje cell to excite it. However, once the Purkinje cell is excited, it sends a strong *inhibitory signal* to the same deep nuclear cell that had originally turned on the movement. Therefore, this signal helps *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 also cause a *precisely timed* turn-off of the same agonist contraction after a given period.

Now, let us speculate on the circuit for the antagonist muscles. Most important, remember that there are reciprocal agonist-antagonist circuits throughout the spinal cord 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 also remember that the cerebellum contains several other types of inhibitory cells besides Purkinje cells. The functions of some of these cells 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.

These mechanisms are still partly speculation. They are presented here to illustrate ways by which the cerebellum could cause exaggerated turn-on and turn-off signals, thus 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 of inhibition at the end of contraction, and the timing of these are almost always incorrect for precise movements. However, 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 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 1 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 alter the long-term sensitivity of the Purkinje cells in some way. Over a period, 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 state 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:

1. The *vestibulocerebellum.* This level 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 level 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 level 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. These movements are planned as much as tenths of a second in advance of the actual movements. This process is called development of "motor imagery" of movements to be performed.

The 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 56, 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.

In people with vestibulocerebellar dysfunction, equilibrium is far more disturbed *during performance of rapid motions* than during inactivity, especially when these movements involve *changes in direction* of movement and stimulate the semicircular ducts. This phenomenon 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.

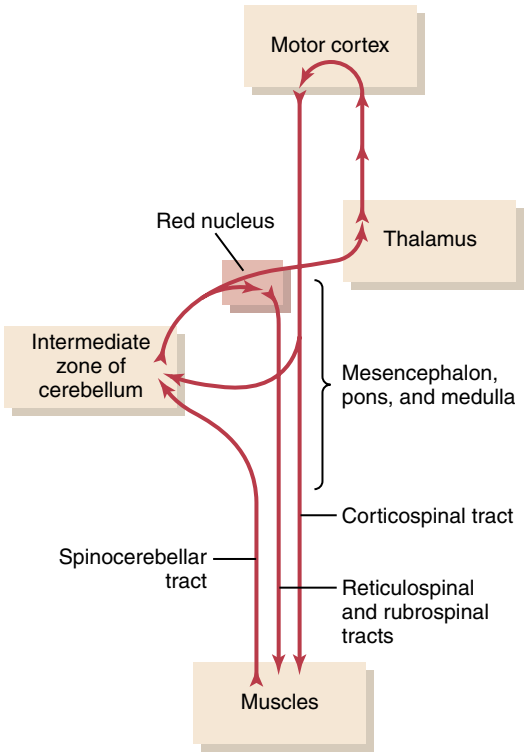

Figure 57-8 Cerebral and cerebellar control of voluntary movements, involving especially the intermediate zone of the cerebellum.

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 via the Intermediate Cerebellar Cortex and the Interposed Nucleus

As shown in **Figure 57-8,** 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 lateralmost 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, coordinated movements of the agonist and antagonist muscles of the distal limbs for performing 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 information 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 and to "Damp" Movements. Almost all movements of the body are "pendular." For example, 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 occurs in a person whose cerebellum has been destroyed, the conscious centers of the cerebrum eventually recognize this error and initiate a movement in the reverse direction to attempt to bring the arm to its intended position. However, 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.*

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 activity 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.

Three major changes occur in these ballistic movements when the cerebellum is removed: (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 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. Also, 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 humans the lateral zones of the two cerebellar hemispheres are highly developed and greatly enlarged. This characteristic 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. In addition, almost all communication between these lateral cerebellar areas and the cerebral cortex is not with the primary cerebral motor cortex 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 condition has been difficult to understand because there is no 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) planning of sequential movements and (2) "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 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 the cerebellum and the 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 for Sequential Movements. 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 (e.g., 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 example, 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 into the wall of a corridor because it is unable to predict when it will reach the wall.

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 to a great extent 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 movement 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 initiate this motor signal, 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 effect 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 condition 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 structures and the inability to adjust in advance either the intensity of sound or the duration of each successive sound causes jumbled vocalization, with some syllables loud, some weak, some held for long intervals, and some held for short intervals, with resultant speech that is often unintelligible. This condition is called *dysarthria.*

Cerebellar Nystagmus—Tremor of the Eyeballs. *Cerebellar nystagmus* is tremor of the eyeballs that usually occurs 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 the failure of damping by the cerebellum. It occurs especially when the flocculonodular lobes of the cerebellum are damaged; in this case, 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.

THE BASAL GANGLIA AND 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 and also return almost all their output signals back to the cortex.

Figure 57-9 shows the anatomical relationships 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. 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 57-10. 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 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 the basal ganglia sustain serious damage, the cortical system of motor control can no longer provide these patterns. Instead, one's writing becomes crude, as if one were learning how to write for the first time.

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.

Neural Pathways of the Putamen Circuit. Figure 57-11 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, and next to the ventroanterior and ventrolateral relay nuclei of the thalamus, and they 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 the*

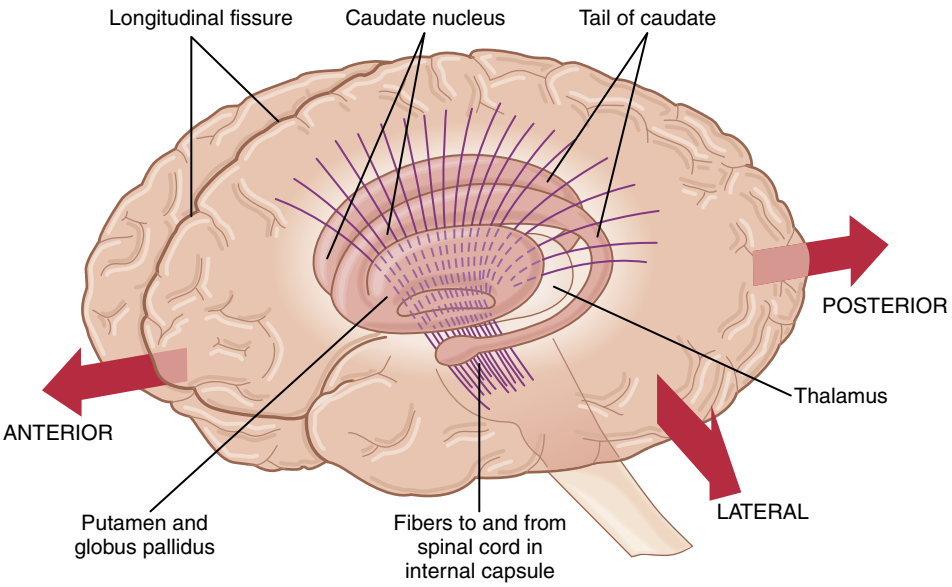

Figure 57-9 Anatomical relations of the basal ganglia to the cerebral cortex and thalamus, shown in three-dimensional view.

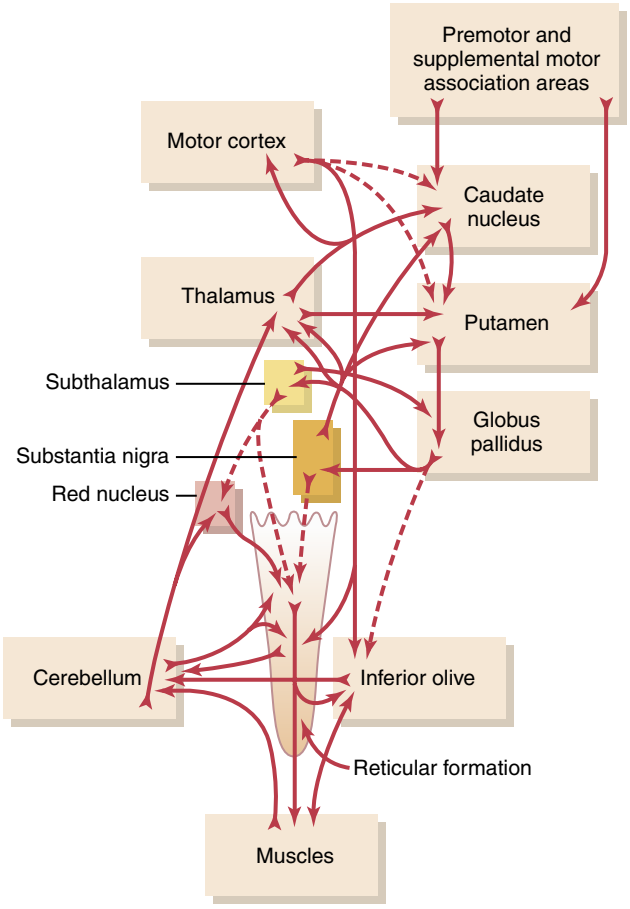

Figure 57-10 Relationship of the basal ganglial circuitry to the corticospinal-cerebellar system for movement control.

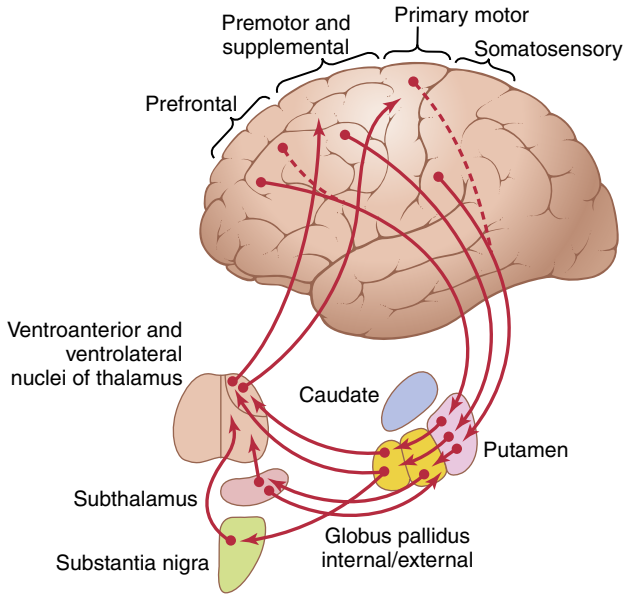

Figure 57-11 Putamen circuit through the basal ganglia for subconscious execution of learned patterns of movement.

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? Little is known about this function. However, when a portion of the circuit is damaged or blocked, certain patterns of movement become severely abnormal. For example, lesions in the *globus pallidus* frequently lead to spontaneous and often continuous *writhing movements* of a hand, an arm, the neck, or the face. These movements are called *athetosis.*

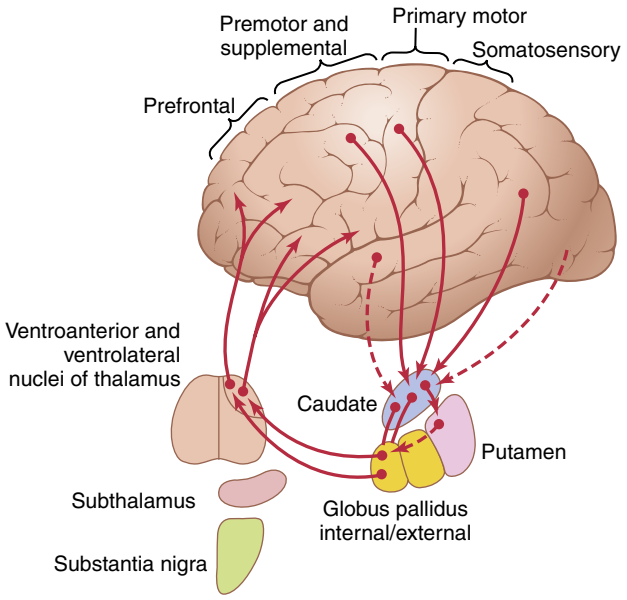

Figure 57-12 Caudate circuit through the basal ganglia for cognitive planning of sequential and parallel motor patterns to achieve specific conscious goals.

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 in this chapter.

ROLE OF THE BASAL GANGLIA FOR COGNITIVE CONTROL OF MOTOR PATTERN SEQUENCES—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 57-12**, are somewhat different from those of the putamen circuit. Part of the reason for this difference is that the caudate nucleus, as shown in **Figure 57-9**, 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 transmitted to the internal globus pallidus, then to the relay nuclei of the 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 the accessory motor regions in the premotor and supplementary motor areas that are concerned with building sequential patterns of movement lasting 5 seconds or more instead of exciting individual muscle movements.

A good example of this phenomenon 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 to (1) determine how rapidly the movement is to be performed and (2) control how large the movement will be. For example, 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; rather, 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 relationship 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 perceive objects accurately through normally functioning sensory mechanisms, a condition called *agnosia.* **Figure 57-13** shows how a person with a lesion in the right posterior parietal cortex might try to copy drawings.

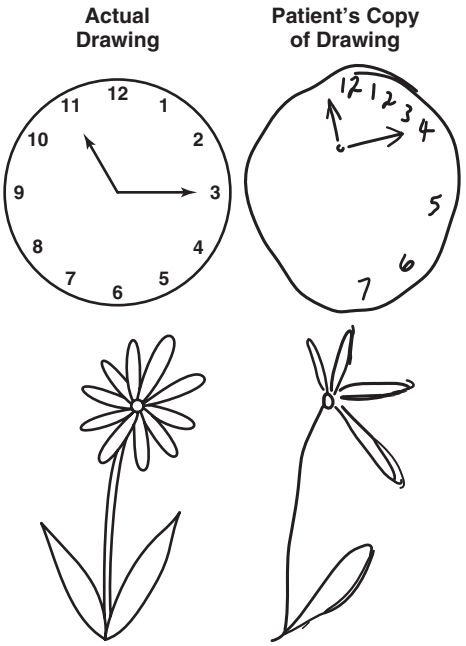

Figure 57-13 Illustration of drawings that might be made by a person who has *neglect syndrome* caused by severe damage in his or her right posterior parietal cortex compared with the actual drawing the patient was requested to copy. Note that the person's ability to copy the left side of the drawings is severely impaired.

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; the person may not even wash this side of the body *(personal neglect syndrome),* almost not knowing that these parts of the 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 the timing and scaling of movements are functions of this caudate cognitive motor control circuit. However, our understanding of basal ganglia function is still so imprecise that much of what is discussed in the last few sections is analytical deduction rather than proven fact.

FUNCTIONS OF SPECIFIC NEUROTRANSMITTER SUBSTANCES IN THE BASAL GANGLIAL SYSTEM

Figure 57-14 demonstrates the interplay of several specific neurotransmitters that are known to function in the basal ganglia, showing the following: (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

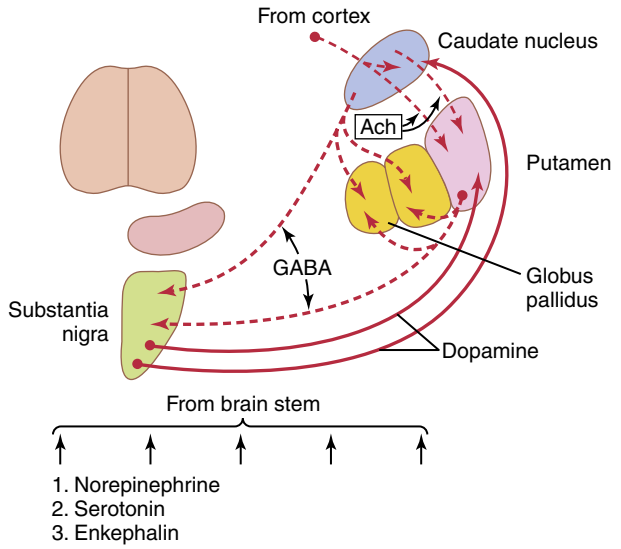

Figure 57-14 Neuronal pathways that secrete different types of neurotransmitter substances in the basal ganglia. Ach, Acetylcholine; GABA, gamma-aminobutyric acid.

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 GABA functions as an inhibitory neurotransmitter. 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 diseases are *Parkinson's disease* and *Huntington's disease.*

Parkinson's Disease

Parkinson's disease, which is also known as *paralysis agitans,* results from widespread degeneration of the 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 the following: (1) rigidity of much of the musculature of the body; (2)

involuntary tremor at a fixed rate of 3 to 6 cycles/sec of the involved areas, even when the person is resting; (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 not fully understood. However, the dopamine secreted in the caudate nucleus and putamen is an inhibitory transmitter; therefore, destruction of the dopaminergic neurons in the substantia nigra 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* in patients with Parkinson's disease.

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.

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 a person with severe Parkinson's disease must exert the highest degree of concentration to perform even the simplest movement. 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 decrease might reduce the psychic drive for motor activity so greatly that akinesia results.

Nonmotor features of Parkinson's disease include sleep disturbances, depression and anxiety, autonomic dysfunction, and cognitive impairment in advanced stages.

Treatment With L-Dopa. Administration of the drug *L-dopa* to patients with Parkinson's disease usually ameliorates many of the motor disturbances, especially the rigidity and akinesia, but has little beneficial effect on nonmotor symptoms. The reason for the amelioration of motor disorders 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 does not have the same effect because dopamine has a chemical structure that will not allow it to pass through the blood–brain barrier; the slightly different structure of L-dopa allows it to pass through this barrier.

Treatment With Monoamine Oxidase Inhibitors. Another treatment for Parkinson's disease includes drugs that inhibit 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 that are 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 monoamine oxidase inhibitor therapy usually provide much better treatment than use of one of these drugs alone.

Treatment With Transplanted Fetal Dopamine Cells. Transplantation of fetal dopamine-secreting brain cells into the caudate nuclei and putamen has been used with some short-term success to treat Parkinson's disease. If persistence could be achieved, perhaps this treatment would become the treatment of the future.

Huntington's Disease (Huntington's Chorea)

Huntington's disease is an autosomal dominant 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 the loss of most of the cell bodies of the GABA-secreting neurons in the caudate nucleus and putamen and the loss 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.

Dementia in persons with 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 codon (CAG) that repeats many times and codes for multiple extra *glutamine* amino acids in the molecular structure of an abnormal neuronal cell protein called *huntingtin* that causes the symptoms. How this protein causes the disease effects is now the question for major research efforts.

INTEGRATION OF THE MANY PARTS OF THE TOTAL MOTOR CONTROL SYSTEM

Finally, we will 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 example, 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 rhythmic 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, almost 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, with 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 rapid muscle movements are required. 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 puts 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 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. All of these 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 more detail in Chapter 59.

Bibliography

Beckinghausen J, Sillitoe RV: Insights into cerebellar development and connectivity. Neurosci Lett 688:2, 2019.

Bostan AC, Strick PL: The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci 19:338, 2018.

Bushart DD, Shakkottai VG: Ion channel dysfunction in cerebellar ataxia. Neurosci Lett 688:41, 2019.

Cerminara NL, Lang EJ, Sillitoe RV, Apps R: Redefining the cerebellar cortex as an assembly of non-uniform Purkinje cell microcircuits. Nat Rev Neurosci 16:79, 2015.

Chadderton P, Schaefer AT, Williams SR, Margrie TW: Sensory-evoked synaptic integration in cerebellar and cerebral cortical neurons. Nat Rev Neurosci 15:71, 2014.

De Zeeuw CI, Hoebeek FE, Bosman LW, et al: Spatiotemporal firing patterns in the cerebellum. Nat Rev Neurosci 12:327, 2011.

De Zeeuw CI, Ten Brinke MM: Motor learning and the cerebellum. Cold Spring Harb Perspect Biol 2015 Sep 1;7(9):a021683. doi: 10.1101/cshperspect.a021683

Eidelberg D, Surmeier DJ: Brain networks in Huntington disease. J Clin Invest 121:484, 2011.

Elkouzi A, Vedam-Mai V, Eisinger RS, Okun MS: Emerging therapies in Parkinson disease - repurposed drugs and new approaches. Nat Rev Neurol 15:204, 2019.

Gao Z, van Beugen BJ, De Zeeuw CI: Distributed synergistic plasticity and cerebellar learning. Nat Rev Neurosci 13:619, 2012.

Hallett PJ, Cooper O, Sadi D et al: Long-term health of dopaminergic neuron transplants in Parkinson's disease patients. Cell Rep 7:1755, 2014.

Hikosaka O, Kim HF, Amita H et al: Direct and indirect pathways for choosing objects and actions. Eur J Neurosci 49:637, 2019.

Okun MS: Deep-brain stimulation for Parkinson's disease. N Engl J Med 367:1529, 2012.

Sathyanesan A, Zhou J, Scafidi J, Heck DH, Sillitoe RV, Gallo V: Emerging connections between cerebellar development, behaviour and complex brain disorders. Nat Rev Neurosci 20:298, 2019.

Shepherd GM: Corticostriatal connectivity and its role in disease. Nat Rev Neurosci 14:278, 2013.

Ten Brinke MM, Boele HJ, De Zeeuw CI: Conditioned climbing fiber responses in cerebellar cortex and nuclei. Neurosci Lett 688:26, 2019.

Therrien AS, Bastian AJ: The cerebellum as a movement sensor. Neurosci Lett 688:37, 2019.

Ullsperger M, Danielmeier C, Jocham G: Neurophysiology of performance monitoring and adaptive behavior. Physiol Rev 94:35, 2014.

Zuccato C, Valenza M, Cattaneo E: Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev 90:905, 2010.