43
The Basal Ganglia

THE TRADITIONAL VIEW THAT THE BASAL ganglia play a role in movement stems largely from the fact that diseases of the basal ganglia, such as Parkinson and Huntington disease, are associated with prominent disturbances of movement and from the earlier belief that basal ganglia neurons send their output exclusively to the motor cortex by way of the thalamus. However, we now know that the basal ganglia also project to nonmotor areas of the cerebral cortex, providing a mechanism whereby they may participate in a wide variety of nonmotor functions, and that diseases of the basal ganglia are associated with complex behavioral and neuropsychiatric disturbances.

In this chapter we first describe the individual nuclei of the basal ganglia anatomically and then discuss their function in the context of the larger networks in which they participate. The delineation of brain circuits into which the basal ganglia are incorporated has enabled researchers to better understand the pathophysiology of some of the major diseases affecting basal ganglia functions. These disease states are described at the end of the chapter.

The Basal Ganglia Consist of Several Interconnected Nuclei

The basal ganglia comprise four principal structures: the striatum, globus pallidus, substantia nigra, and subthalamic nucleus (Figure 43–1).

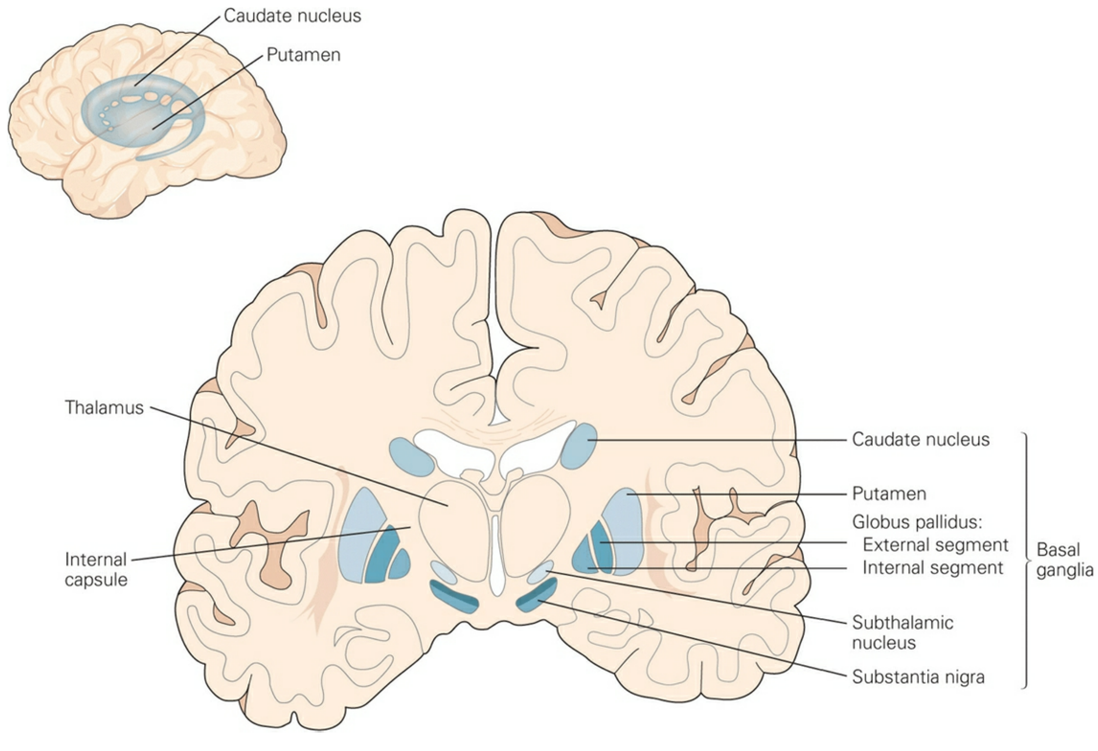

Figure 43-1 The basal ganglia and surrounding structures. The nuclei of the basal ganglia are identified on right in this coronal section. (Adapted, with permission, from Nieuwenhuys, Voogd, and van Huijzen 1981.)

The *striatum* is separated by the internal capsule into the caudate nucleus and the putamen. The striatum is the major input structure of the basal ganglia, receiving prominent projections from the cerebral cortex, brain stem, and thalamus. The *globus pallidus* consists of two separate nuclei, the external and internal segments, each with different connectivity and functions. The internal segment is one of the major output structures of the basal ganglia, whereas the external segment is part of their intrinsic circuitry.

The *substantia nigra* includes two separate nuclei, the pars compacta and pars reticulata. Along with portions of the ventral tegmental area and other midbrain areas, the pars compacta, or mediodorsal portion of the substantia nigra, contains dopaminergic cells that project heavily to the striatum and to the other nuclei of the basal ganglia. The pars reticulata, or ventrolateral portion of the substantia nigra, is the other major output nucleus of the basal ganglia. In fact, the pars reticulata of the substantia nigra and the internal segment of the globus pallidus can be viewed as a single output structure divided by the internal capsule.

The fourth principal structure of the basal ganglia, the *subthalamic nucleus*, is a small nucleus situated between the thalamus and the substantia nigra. This nucleus receives projections from the external segment of the globus pallidus, the cerebral cortex, thalamus, and brain stem, and sends output to both segments of the globus pallidus and to the substantia nigra pars reticulata. The cortical inputs to the subthalamic nucleus and the related subthalamopallidal projections are referred to as the *hyperdirect* pathway (Figure 43–2).

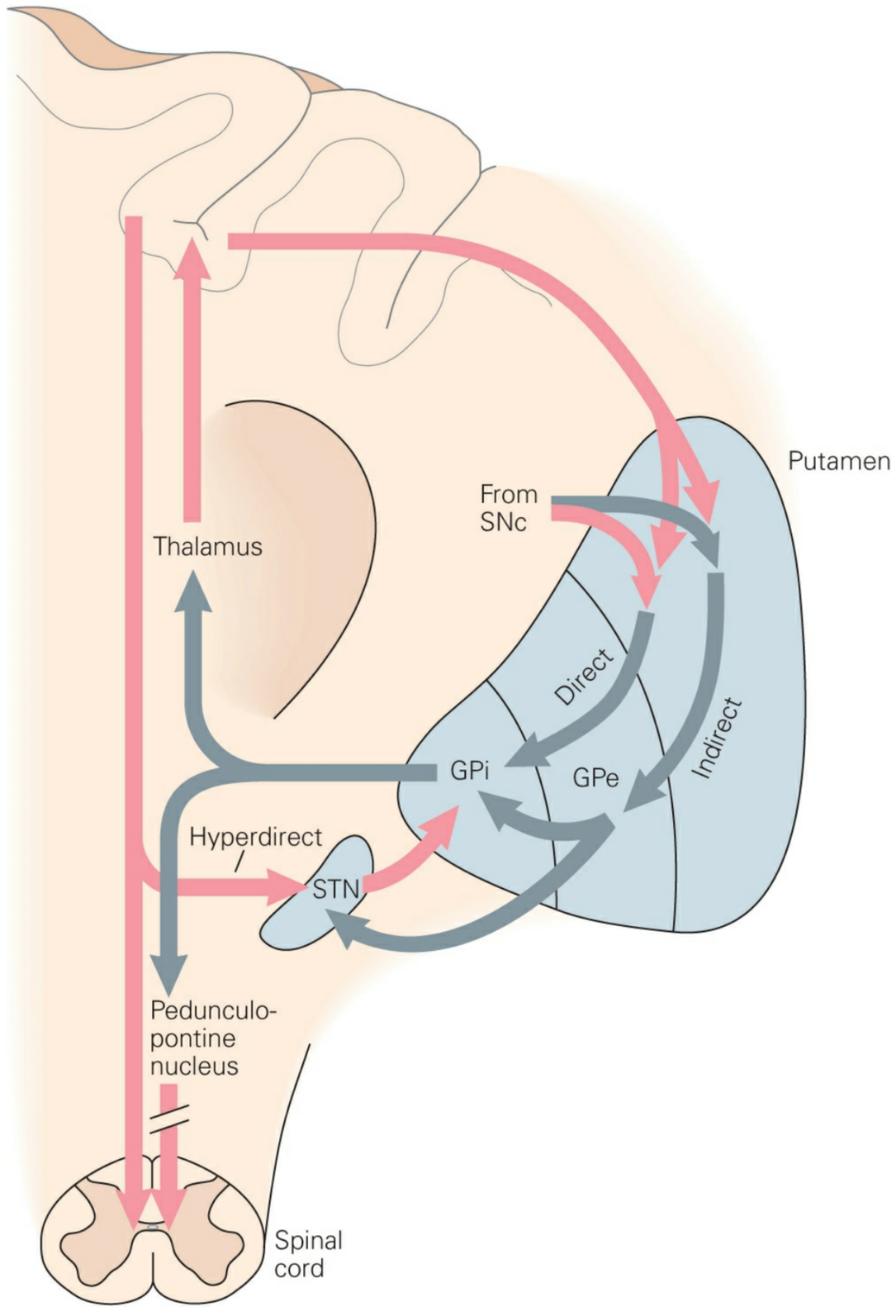

Figure 43-2 The basal ganglia–thalamocortical circuitry. The circuitry of the basal ganglia includes the striatum (here represented by one of its components, the putamen), the external and internal segments of the globus pallidus (GPe and GPi, respectively), the substantia nigra pars reticulata (not shown) and pars compacta (SNc), and the subthalamic nucleus (STN). Cortical input enters the striatum and subthalamic nucleus. Basal ganglia output is conveyed to several thalamic nuclei (the centromedian and parafascicular nuclei and the ventral anterior and ventral lateral nuclei) and the pedunculopontine nucleus. Excitatory connections are shown in red, inhibitory pathways in gray. The dopaminergic SNc projection to the striatum regulates corticostriatal transmission along direct and indirect pathways.

The striatum, the main input nucleus of the basal ganglia, projects to the two basal ganglia output nuclei, the internal pallidal segment and the substantia nigra pars reticulata. The axons from the striatum follow two different pathways: a *direct* monosynaptic connection, and an *indirect* polysynaptic pathway that passes first to the external pallidal segment and from there to both output nuclei, either directly or via the intercalated subthalamic nucleus.

The output nuclei project to specific thalamic and brain stem areas. Projections to the thalamus are directed to the ventral anterior, the ventrolateral, and the intralaminar nuclei. Thalamic projections to the frontal lobe then transmit the output of the basal ganglia to the same areas of frontal cortex that provide input to the basal ganglia. In addition, descending pallidal and nigral projections to the brain stem, such as those to the pedunculopontine nucleus and superior colliculus, provide pathways by which the basal ganglia may directly influence brain stem and spinal motor circuits, especially those related to gait and balance. The brain stem nuclei may integrate basal ganglia inputs with cerebellar inputs. The pedunculopontine nucleus is part of several feedback circuits through its projections back to the basal ganglia and thalamus. Output of the substantia nigra pars reticulata is also directed to the superior colliculus, which is involved in the control of head and eye movements.

In the striatum the most common neuronal cell type is the GABAergic (γ-aminobutyric acid) medium spiny neuron. These cells are so named because of the abundance of spines on their dendrites. They receive inputs from the cerebral cortex and thalamus as well as from several classes of local interneurons in the striatum, including large cholinergic interneurons and smaller GABAergic interneurons.

The activities of medium spiny neurons are modulated by other neurotransmitters, specifically inputs from dopaminergic neurons in the substantia nigra pars compacta and the ventral tegmental area. Some of the dopaminergic fibers terminate on the necks of dendritic spines of medium spiny neurons, where they are in a position to influence corticostriatal transmission (Figure 43–3). Dopamine released from terminals close to the dendritic spines may have similar effects through spillover and diffusion of the neurotransmitter.

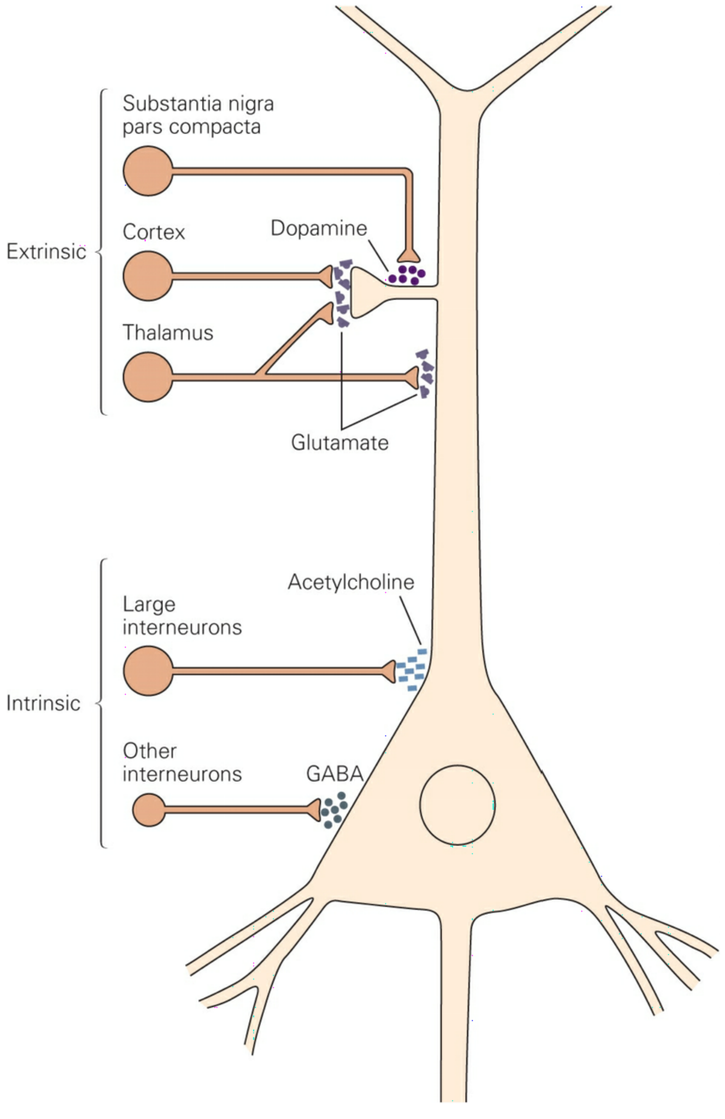

Figure 43-3 The medium spiny neurons in the striatum have extrinsic and intrinsic inputs. Glutamatergic inputs from the cerebral cortex and dopaminergic inputs from the substantia nigra pars compacta terminate on dendritic spines of medium spiny neurons. The reward-related dopaminergic inputs are thought to modulate the strength of cortical inputs and to play a role in synaptic changes and reinforcement learning in the striatum. Glutamatergic inputs from the thalamus end on the spines and shafts of dendrites of medium spiny neurons. Medium spiny neurons also receive cholinergic and GABAergic input from interneurons in the striatum.

The cytoarchitecture of the other basal ganglia nuclei is distinctly different from that of the striatum. Both segments of the globus pallidus consist of large GABAergic neurons that receive input from the striatum. The substantia nigra pars reticulata is histologically similar to the internal pallidal segment, containing GABAergic neurons that interdigitate with the more dorsal dopaminergic cells of the substantia nigra pars compacta. The subthalamic nucleus is a densely packed structure whose projection neurons, unlike those in the other basal ganglia nuclei, are glutamatergic.

A Family of Cortico–Basal Ganglia–Thalamocortical Circuits Subserves Skeletomotor, Oculomotor, Associative, and Limbic Functions

Areas of the cerebral cortex project in a highly topographic manner onto the striatum.

The topographic termination pattern establishes functional domains that are replicated throughout the basal ganglia–thalamocortical circuits by virtue of highly topographic projections at each synaptic relay. The different pathways that pass through the basal ganglia are named after the presumed functions of the regions of the frontal cortex from which they originate: the skeletomotor, oculomotor, pre-frontal (associative), and limbic circuits. The frontal lobe origins of these circuits in the cerebral cortex are shown in Figure 43–4 and the synaptic relays are depicted in Figure 43–5.

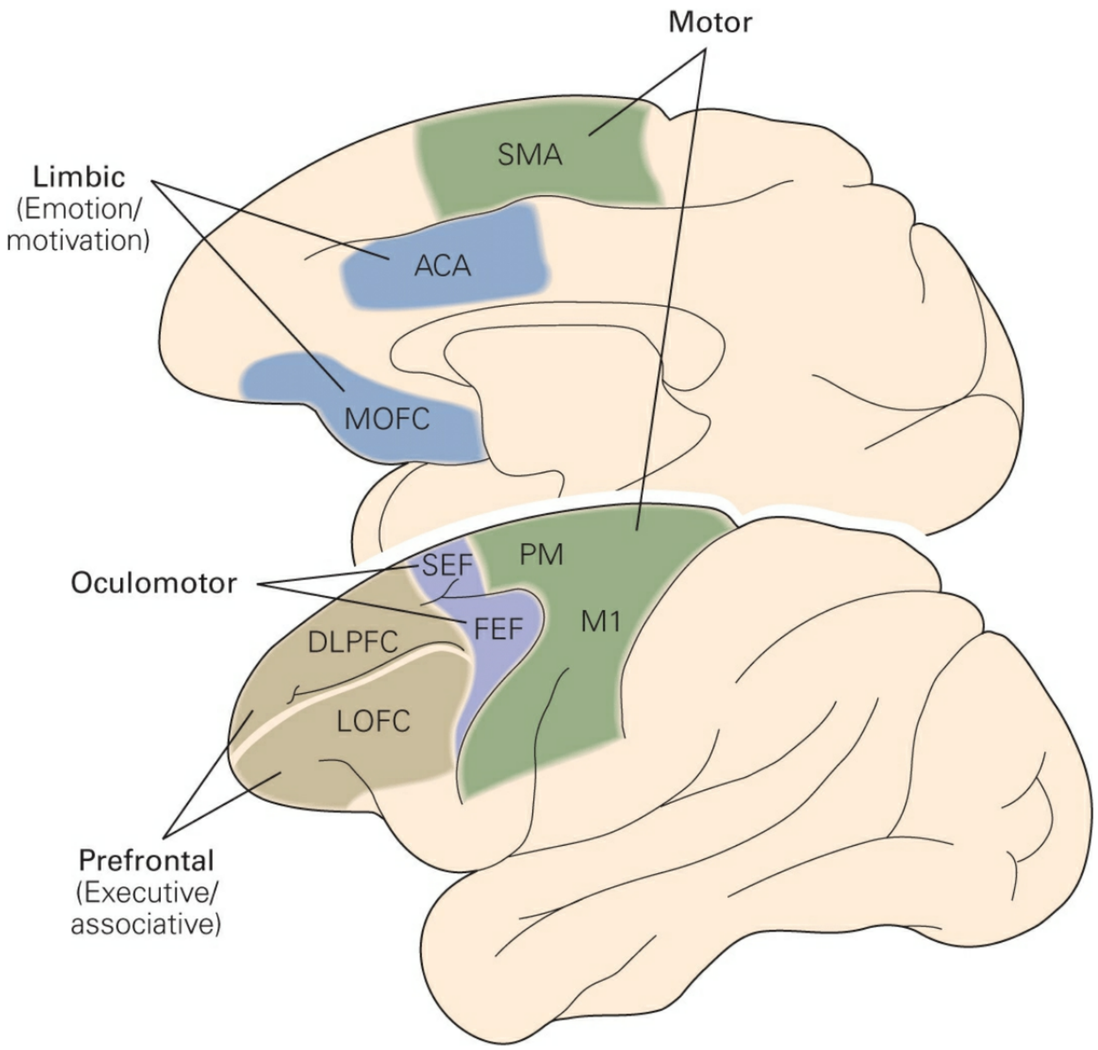

Figure 43-4 Four basal ganglia–thalamocortical circuits originate in four functionally distinct areas of frontal cortex. (ACA, anterior cingulate area; DLPFC, dorsolateral pre-frontal cortex; FEF, frontal eye field; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MOFC, medial orbitofrontal cortex; PM, premotor cortex; SEF, supplementary eye field; SMA, supplementary motor area.) (Adapted, with permission, from Alexander and Crutcher 1990.)

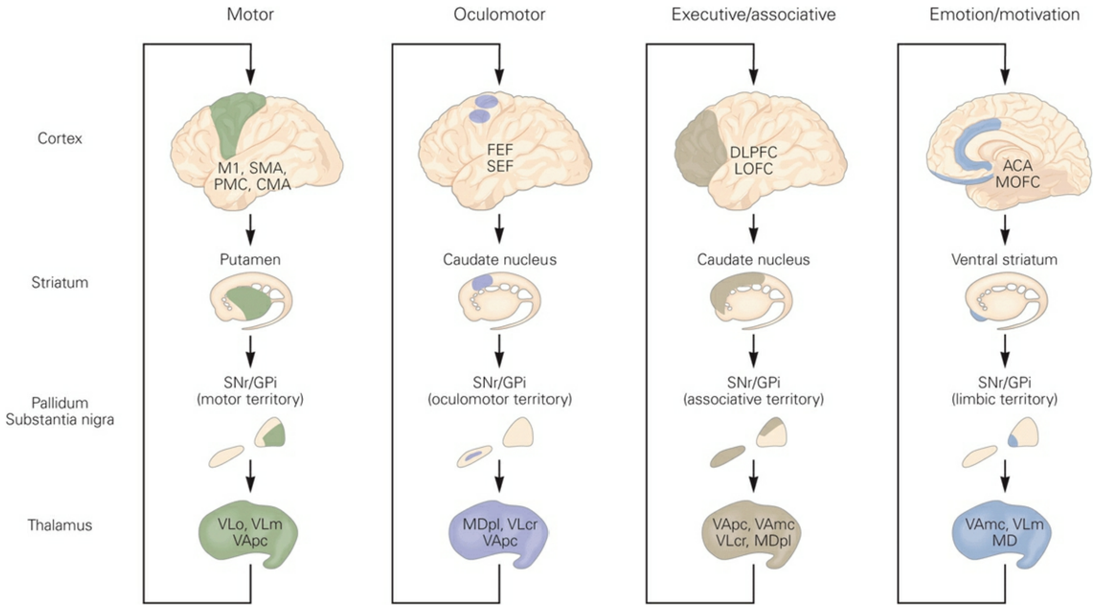

Figure 43-5 Global anatomy of cortico–basal ganglia–thalamocortical circuits. (ACA, anterior cingulate area; CMA, cingulate motor area; DLPFC, dorsolateral pre-frontal cortex; FEF, frontal eye field; GPi, internal segment of the globus pallidus; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MDpl, mediodorsal nucleus of thalamus, lateral part; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SEF, supplementary eye field; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; VAmc, ventral anterior nucleus of thalamus, magnocellular part; VApc, ventral anterior nucleus of thalamus, parvocellular part; VLcr, ventrolateral nucleus of thalamus, caudal part, rostral division; VLm, ventrolateral nucleus of thalamus, medial part; VLo, ventrolateral nucleus of thalamus, pars oralis.) (Adapted, with permission, from Wichmann and DeLong 2006.)

Additional projections from the parietal, temporal, and occipital lobes that are reciprocally interconnected with the frontal areas converge onto the same areas in the striatum. Importantly, however, although each circuit receives both pre- and postcentral cortical inputs, output of the different circuits terminates only in the frontal lobe areas of their respective origin.

Ascending output in each functional pathway is projected in a somatotopical manner to the thalamus and from there to the frontal cortical area from which the circuit originated, thus partially closing a system of cortico-subcortical loops. The subcortical segregation of the functionally distinct circuits may allow different aspects of behavior to be processed in parallel.

The Cortico–Basal Ganglia–Thalamocortical Motor Circuit Originates and Terminates in Cortical Areas Related to Movement

Most of our knowledge about the anatomy and physiological functions of the basal ganglia–thalamocortical circuits comes from studies of the motor circuit. This circuit has attracted the attention of researchers because pathology within its anatomical elements has been implicated in several major disorders of movement.

The motor circuit originates in the pre- and postcentral sensorimotor cortical fields, which project to the putamen in a somatotopical manner. This arrangement has been demonstrated not only with anatomical methods but also with electrophysiological recordings of neuronal activity while animals were subjected to passive movements or carried out active movements of individual body parts. These studies showed that neurons responding to leg movements are found in a dorsolateral zone of the putamen, neurons responding to orofacial movements are located ventromedially, and neurons responding to arm movement are found in a zone between the leg and orofacial areas.

Neurons in the putamen project to the caudoventral portions of both segments of the pallidum and to the lateral portions of the substantia nigra pars reticulata. In turn, the motor portions of the internal pallidal segment and the substantia nigra pars reticulata project to specific motor-related areas of the ventral lateral, ventral anterior, and centromedian nucleus of the thalamus. The motor circuit is then closed by projections from the ventral lateral and ventral anterior nuclei to the motor cortex, supplementary motor area, and premotor cortex. The centromedian nucleus, one of the intralaminar nuclei of the thalamus, projects largely to the putamen as part of a subcortical feedback loop.

The larger motor circuit consists of segregated subcircuits, each cen-

tered on an individual precentral motor field. These subcircuits are believed to be responsible for different aspects of motor processing, such as motor planning, coordination of sequences of movement, or movement execution. Evidence for the subcircuit organization comes from anatomical studies. Several stages of the basal ganglia circuitry in the same animal have been traced by Peter Strick and his colleagues using small intracerebral injections of herpes and rabies viruses. Taken up by neurons and transported transsynaptically, the virus particles can be stained in anatomical slices. Using this technique at different time points after the injection, one may visualize circuit elements that lie two or more synapses away from the injection site.

Separate injections of the primary motor cortex, supplementary motor area, and lateral premotor area produces retrograde labeling of separate populations of neurons in specific areas of the ventral lateral nucleus in the thalamus and separate populations of neurons in the internal pallidal segment, demonstrating that the separate cortical domains remain segregated throughout the basal ganglia networks. Segregated anterograde transsynaptic transport of input from cortical areas to the striatum and pallidum has likewise been shown, providing further support for the segregated circuit concept.

Because axons of cortical neurons terminate on a far smaller number of striatal neurons, there is considerable convergence of cortical information in the striatum. Similarly, the number of neurons in the pallidum and substantia nigra is smaller than that in the striatum, allowing further convergence along the direct and indirect pathways. However, given the somatotopic arrangement of striatopallidal and pallido-subthalamic projections, it appears that convergence occurs largely within rather than between the different basal ganglia–thalamocortical circuits and subcircuits.

The Motor Circuit Plays a Role in Multiple Aspects of Movement

The motor circuit has been examined in experimental studies in which portions of the basal ganglia were activated or inactivated, in studies using extracellular electrophysiological recordings of the activity of single neurons, as well as imaging and behavioral studies. Based on these investigations the motor circuit has been implicated in a wide range of motor behaviors including action selection, preparation for movement, movement execution, sequencing of movement, self-initiated or remembered movements, the control of movement parameters, and reinforcement learning.

The idea that the basal ganglia have a role in action selection and the initiation of movement was first suggested by early clinical observations in patients with movement disorders. The concept that the basal ganglia play a role in action selection, in the broadest sense, implies that they also participate in the acquisition of behaviors that lead to a reward or reinforcement and the avoidance of acts that lead to punishment or adverse outcomes. Reward may be simply the delivery of a pleasurable stimulus such as food, but may also involve the successful reaching of a goal or intended action. By modulating the strength of specific corticostriatal synapses, dopamine is widely implicated in this action selection function, as described below.

The general concept that the basal ganglia play a role in the acquisition and selection of beneficial behaviors later evolved into the idea that the basal ganglia act to focus specific movements through interactions between the direct (permissive) and indirect (inhibitory) pathways at the level of the internal pallidal segment, somewhat equivalent to the center-surround inhibition in a sensory system. This “focusing model” stems from the observation that the basal ganglia provide sustained inhibitory output to thalamocortical neurons. According to the model, cortical phasic activation of striatal neurons that contribute to the direct pathway transiently suppresses the high spontaneous discharge rate of movement-related neurons in the output nuclei of the basal ganglia. This in turn removes inhibition from specific thalamocortical neurons and allows cortical areas to become active, thus facilitating the selected movement. In contrast, phasic activation of striatal neurons that contribute to the indirect pathway, or of cortical neurons that project to the subthalamic nucleus, transiently increases inhibition of thalamocortical neurons and thereby inhibits movement. If the direct pathway is activated in anticipation of intended movements, and the indirect pathway is activated simultaneously to broadly inhibit pallidal inhibitory output, the combination facilitates intended movements and suppresses compet-

ing ones.

Although this focusing model is attractive, there are several strong arguments against it. For instance, the hypothesis would require that axons in the indirect and hyperdirect pathways diffusely target large areas of the pallidum in order to prevent unwanted movements, whereas the direct pathway would act on small areas of the internal pallidal segment to selectively facilitate the selected movement. Neither of these anatomical prerequisites is supported by anatomic studies, which indicate instead that inputs of the indirect pathway to the internal pallidal segment from the subthalamic nucleus are highly topographic. Furthermore, pallidal activation during movement initiation is generally considered to occur too late to play a significant role in the selection of movement.

Evidence that the motor circuit has a role in the preparation of movement comes from single-neuron recordings in monkeys performing delayed-response motor tasks. The animals were required to move an arm to a specified target after a delay period. In such studies the firing frequency of neurons in frontal and pre-frontal cortical areas changed after animals were presented with a visual cue that specified the desired direction of movement (see Chapter 38). Changes similar to those found in the cortex are also found in the motor portions of the putamen, the internal segment of the globus pallidus, and the substantia nigra pars reticulata. These changes in activity occur while the animal is preparing the movement but not during the execution of the movement itself. Such changes are interpreted as involvement in a preparatory stage of motor control referred to as *motor set*.

Other basal ganglia neurons change their firing frequency phasically in relation to the onset of a movement, suggesting that they may be concerned with movement execution. As mentioned above, these changes in neural activity in a variety of stimulus-triggered movement tasks occur well *after* movement-related activities in the cerebral cortex or cerebellum, indicating that the basal ganglia do not participate in the initiation of such movements. This conclusion is reinforced by the results of a study with primates trained on a simple reaction time task: Pallidal lesions involving the motor circuit did not alter the reaction time between a cue and the movement triggered by that cue.

Changes in the activity of movement-related neurons in the internal pallidal segment correlate with the amplitude and velocity of arm movement, suggesting a role in the scaling of movement. In monkeys the activity of 30% to 50% of all movement-related neurons in the supplementary motor area, motor cortex, putamen, and pallidum is correlated with the direction of limb movement, but not with the activity of individual muscles. This suggests a role in the higher-level aspects of movement. The finding that individual neurons in the basal ganglia tend to be concerned with either the preparation or the execution of motor action suggests that these functions are mediated by separate subcircuits in the motor circuit.

Positron emission tomography and functional magnetic resonance imaging of humans have demonstrated that during simple finger or arm movements the peak activation of the basal ganglia occurs in the post-commissural putamen, and that changes in fundamental kinematic parameters, such as movement velocity, correlates with activity in the posteroventral pallidum, an area that has been identified as part of the motor territory of the basal ganglia in nonhuman primates (Figure 43–6). By contrast, in cognitively demanding tasks—for example, tasks that require subjects to generate novel sequences of movement or to imagine hand movements—anterior portions of the striatum (caudate nucleus and putamen rostral to the anterior commissure) are activated, along with the pre-frontal cortex and the anterior cingulate area.

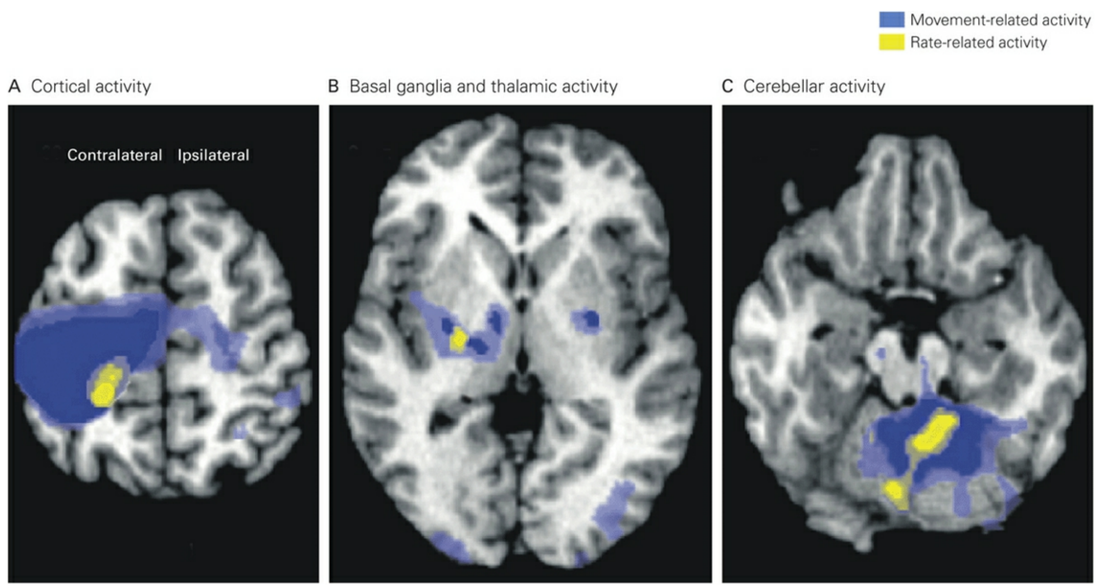

Figure 43-6 Areas of the brain with movement-related activity. PET im-

ages show significant levels of activity in human volunteers performing a sinusoidal arm movement. The images are shown superimposed on corresponding structural MRI images. The "ipsilateral" and "contralateral" hemispheres are in relation to the moving arm. (Adapted, with permission, from Turner et al. 1998.)

A. Movement-related activity in the cortex covers large portions of the primary sensorimotor, dorsolateral and mesial premotor, and dorsal parietal cortices, predominately contralateral to the moving extremity. Activity related to the rate of movement is restricted to a small band of cortex surrounding the contralateral central sulcus.

B. Movement-related activity in the basal ganglia and thalamus is seen in motor-related portions of the basal ganglia and thalamus primarily on the side contralateral to the moving arm. Rate-related activity is restricted to the posterior globus pallidus.

C. A large portion of the anterior cerebellum ipsilateral to the moving arm is active during movement. Movement-related activity is seen in a band covering the mesial portions of the cerebellum.

Dopamine has opposite actions in the direct and indirect pathways. Direct-pathway neurons are facilitated by dopamine through the activation of dopamine D_1 receptors, whereas indirect-pathway neurons are inhibited by dopamine, possibly by means of the activation of dopamine D_2 receptors. By virtue of the different polarities of connections between the basal ganglia nuclei, dopamine release in the striatum reduces activity in the output nuclei, thereby leading to disinhibition of thalamocortical neurons and perhaps facilitation of movement. These effects of dopamine have significant implications for our understanding of the pathophysiology of movement disorders.

Mechanistic models of motor circuit function are attractive because of their relative simplicity, because they provide researchers with testable hypotheses, and because they may help us understand how disorders of dopaminergic input in the striatum affect motor performance. However, these models are largely speculative; there is little direct experimental support for an important role of the basal ganglia in the online-control of movements. As noted, lesions of the motor circuit in the internal pallidal segment have little or no effect on reaction time or movement time.

Dopaminergic and Cholinergic Inputs to the Striatum Are Implicated in Reinforcement Motor Learning

Given the potential function of dopamine in regulating the balance between direct and indirect pathways, it is perhaps surprising that dopaminergic neurons in the substantia nigra pars compacta that project to the striatum are not activated in relation to specific aspects of movement. Instead, many of these neurons are activated in connection with behavioral reinforcement cues (Figure 43–7). This finding has resulted in the development of a highly specific hypothesis regarding the role of dopaminergic neurons in reinforcement learning.

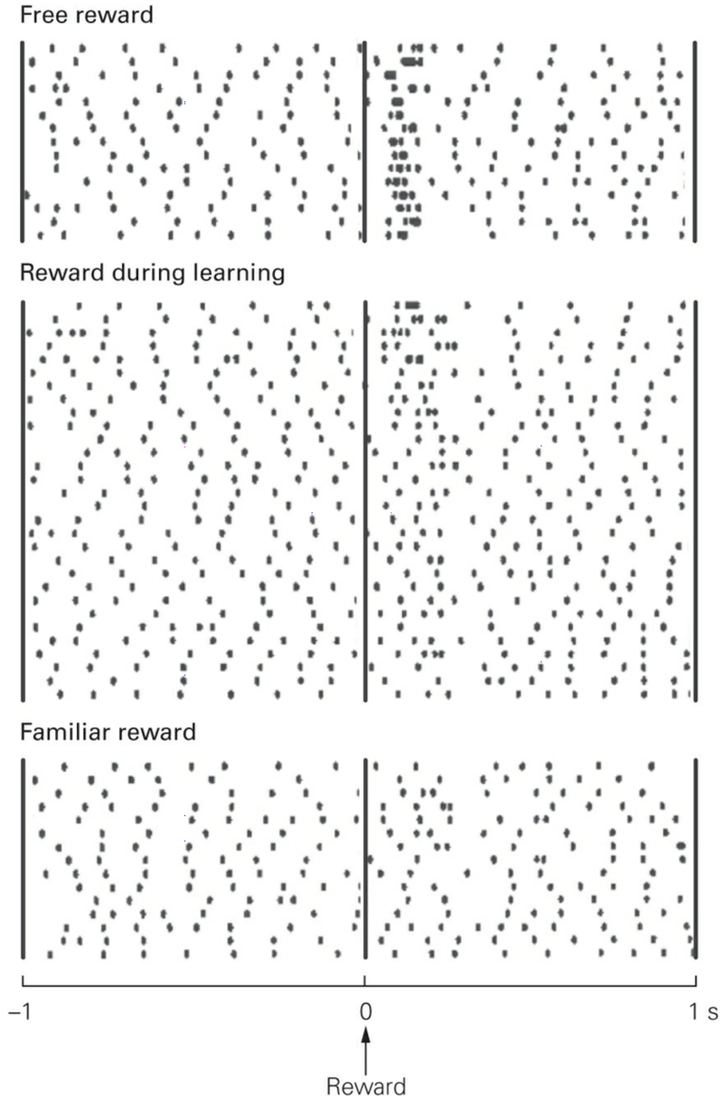

Figure 43-7 Dopaminergic neurons respond to behavioral rewards or reinforcements. Raster plots show the discharge of a dopaminergic neuron in a monkey. All trials are aligned to the time of presentation of a reward. The neuron responds each time a reward is given at random times (top). The responses to rewards decrease during learning of the association between a novel stimulus and a reward (middle). Once the reward has become familiar and predictable (lower), the neuron no longer responds to it. (Adapted, with permission, from Hollerman and Schultz 1998.)

The specific interpretation is that changes in the activity of the dopaminergic cells during behavioral tasks signal a discrepancy, the reward prediction error, between the expectation of a reward and its delivery. This signal triggers the release of dopamine that helps to shape the animal's behavior by strengthening synapses that are involved in generating the rewarded behavior. To effectively fulfill this role, dopaminergic neurons signal the presence of reinforcing or salient cues with very short latency. The sources of this information have not been identified, but they may include subcortical areas such as the superior colliculus, the pedunculopontine nucleus, the raphe nuclei, the lateral habenular nucleus, the amygdala, or limbic areas of cortex.

In addition to dopaminergic neurons in the substantia nigra pars compacta, cholinergic interneurons in the striatum are also activated in rewarded behavioral tasks. These cells are highly interconnected and tonically active. Their discharge is briefly reduced in response to rewards, reinforcements, noxious stimuli, and other behaviorally salient stimuli. Such responses are shaped in part by input to these neurons from the centromedian nucleus of the thalamus. Recent studies of the timing of cholinergic and dopaminergic inputs to the striatum suggest that the cholinergic interneurons may inform the medium spiny neurons in the striatum about the occurrence of salient stimuli (irrespective of their function as rewards), whereas the dopaminergic inputs may provide information about the behavioral value of the stimuli.

Chronic extracellular recordings have demonstrated that the striatal projection neurons alter their activity in the process of learning. Because the activity of striatal medium-sized spiny neurons is almost entirely driven by their excitatory cortical and thalamic inputs, such changes may reflect changes in these inputs to the striatum or in the strength of cortico- or thalamostriatal synapses through modification of the efficacy of synaptic transmission in the form of long-term potentiation (LTP), long-term depression (LTD), or spike-time dependent modulation of synaptic strength, brought about by the joint actions of the dopaminergic and cholinergic inputs. The striatum seems to be specifically involved with motor learning and the formation of habitual movement patterns (procedural memory). Storing such motor patterns in the form of larger behavioral units may be computationally advantageous to the brain—programmed sequences avoid the cost of repeatedly having to sequence individual movements.

The formation and execution of habitual movements appear to involve different areas of the striatum. During early stages of procedural learning the ventral striatum and caudate nucleus seem to be the primary sites of activity, whereas during later stages of learning and the execution of learned movements the dorsolateral striatum is more active. For example, experimental inactivation of the caudate nucleus in primates disrupts the acquisition of sequences of movement, whereas inactivation of the putamen interferes with the performance of previously learned sequences. As discussed earlier, however, lesions of the output from the motor circuit do not appear to have a significant effect on the execution of learned motor sequences.

Studies in songbirds also provide evidence that the basal ganglia are involved in motor learning. In some bird species lesions of the anterior forebrain pathway, the equivalent of the basal ganglia–forebrain circuitry in mammals, abolish the bird's ability to learn species-specific songs during its critical period for learning. Lesioning after the critical period does not interfere with song production but does prevent adaptive changes that may shape the bird's song in different acoustic environments, and the learned song may deteriorate over time.

Other Basal Ganglia Circuits Are Involved in the Regulation of Eye Movements, Mood, Reward, and Executive Functions

Because the patterns of connectivity of nonmotor circuits in the basal

ganglia resemble those for the motor circuit, the fundamental processing in these different circuits is believed to be similar. For example, the role of the basal ganglia in the control of eye movements mirrors their role within the skeletomotor system. The *oculomotor* circuit originates from the frontal eye field and supplementary eye field, and engages oculomotor regions in the posterior caudate nucleus and precommissural putamen, oculomotor neurons in the external segment of the globus pallidus, the subthalamic nucleus and substantia nigra pars reticulata, and the mediodorsal, ventral anterior, and ventrolateral nuclei of the thalamus. In addition to this reentrant pathway that links the basal ganglia with the cerebral cortex, the substantia nigra pars reticulata provides descending projections to the superior colliculus that may be involved in the initiation and facilitation of saccadic eye movements (see Chapter 39).

The function of the descending nigrotectal pathway has been studied in detail, starting with seminal studies by Okihide Hikosaka and Robert Wurtz in the early 1980s. The available evidence indicates that voluntary saccades are initiated within the frontal eye fields of the cerebral cortex. Cortical neuronal discharge activates the GABA-ergic medium spiny neurons in the oculomotor region of the caudate nucleus, which in turn inhibit the tonic activity of GABA-ergic neurons in the substantia nigra, via the direct pathway. The resulting pause in nigral activity results in a transient disinhibition of the neurons in the superior colliculus that drive the brain stem saccade-generating machinery, resulting in a saccade. The circuit may also have a role in cognitive events associated with movement, such as memory-guided saccades.

In a general sense the oculomotor circuit appears to function in a manner similar to that originally proposed for limb movements by the motor circuit. However, the effects of manipulation of the nigro-collicular pathway have no clear parallel in the motor circuit. Whereas inactivation of the substantia nigra results in a disruption of saccades and the emergence of irrepressible involuntary saccades, inactivation of the basal ganglia output site of the motor circuit does not result in excessive limb movements.

Two pre-frontal circuits involved in different aspects of cognitive and executive function have been identified. The larger *pre-frontal circuit* is divided into the dorsolateral pre-frontal and lateral orbitofrontal circuits. The *dorsolateral pre-frontal circuit* originates in Brodmann's areas 9 and 10 of the cerebral cortex and projects to the head of the caudate nucleus, which in turn projects directly and indirectly to the dorsomedial portion of the internal pallidal segment and the rostral substantia nigra pars reticulata. Projections from these regions terminate in the ventral anterior and mediodorsal nuclei of the thalamus and in the dorsolateral area of pre-frontal cortex. The dorsolateral pre-frontal circuit has been implicated in executive functions such as organizing behavioral responses to complex problems and using verbal skills in problem solving.

The *lateral orbitofrontal circuit* arises in the lateral pre-frontal cortex and projects to the ventromedial caudate nucleus. It engages portions of the basal ganglia output structures and thalamus and then returns to the orbitofrontal cortex. It appears to play a major role in the mediation of empathic and socially appropriate behavior.

The *limbic circuit* begins with projections from the anterior cingulate and medial orbitofrontal cortices to the ventral striatum, which also receives input from the hippocampus, amygdala, and entorhinal cortices. The ventral striatum projects to the ventral and rostromedial pallidum and rostrodorsal substantia nigra pars reticulata. From there the pathway continues to neurons in the paramedian portion of the mediodorsal nucleus of the thalamus, which projects back to the anterior cingulate cortex. The anterior cingulate circuit plays an important role in motivated behavior. Through inputs to the ventral tegmental areas and substantia nigra pars compacta, it may reinforce stimuli to diffuse areas of the basal ganglia and cerebral cortex.

Diseases of the Basal Ganglia Are Associated with Disturbances of Movement, Executive Function, Behavior, and Mood

Abnormalities in the Basal Ganglia Motor Circuit Result in a Wide Spectrum of Movement Disorders

Movement disorders arise from dysfunction of the basal ganglia–thalamocortical motor circuit, ranging from hypokinetic disorders, of which Parkinson disease is the best-known example, to hyperkinetic disorders,

exemplified by Huntington disease, dystonia, and hemiballism.

Pathological changes in specific regions of the basal ganglia strongly affect neuronal activity throughout the entire basal ganglia–thalamocortical network and the activity of descending projections to the brain stem. The most severe and disruptive movement disturbances result from dysfunction in the striatum and subthalamic nucleus. By contrast, interruption of the major output nucleus of the basal ganglia, the internal segment of the globus pallidus, has little or no effect on movement. The reasons for these different effects are not understood. It seems, however, that the clinical features of specific disorders depend on unique combinations of changes in discharge rates and patterns, synchronization of discharge, and varying degrees of involvement of individual motor subcircuits.

Hypokinetic disorders are characterized by impairments of movement initiation (*akinesia*), reduction in the amplitude and velocity of voluntary movements (*bradykinesia*), muscular rigidity (increased resistance to passive displacements), and a 4–6 Hz tremor at rest and flexed posture. Hyperkinetic disorders, in contrast, are characterized by involuntary movements, such as *chorea* (random fragmented movements of individual body parts), *ballism* (large-amplitude movements particularly of the proximal limbs), and *dystonia* (slower, twisting movements and sustained abnormal postures).

A Deficiency of Dopamine in the Basal Ganglia Leads to Parkinsonism

Parkinson disease, first described by James Parkinson in 1817, affects over one million people in North America alone. In addition to the cardinal features of this condition—akinesia, bradykinesia, muscular rigidity, and tremor—other prominent motor features include a shuffling gait, flexed posture, reduced facial expression, decreased blinking, and small handwriting. These motor features are summarily referred to as parkinsonism.

Another clinical aspect of Parkinson disease is a loss of the automaticity of movement and the need for increased voluntary control manifested as difficulty carrying out simultaneous movements. The disruption of automatic and well-learned movements is believed to reflect a loss of the basal ganglia's role in procedural learning.

The salient pathological feature of idiopathic Parkinson disease is degeneration of the dopaminergic cells in the substantia nigra pars compacta that project to the striatum and to a lesser extent to other basal ganglia nuclei. Dopamine loss in these areas is considered to cause most of the movement abnormalities in this disorder, since they respond to dopamine replacement therapies. Nonmotor features of the disease include depression and anxiety, cognitive impairment, sleep disturbances, and autonomic dysfunction. These nonmotor signs and symptoms respond poorly or not at all to dopamine replacement therapy.

According to recent studies these features may be caused by additional pathological changes that affect widespread areas of the brain, with a slowly progressive ascending involvement of the lower brain stem nuclei, including the dorsal motor nucleus of the vagus nerve, locus ceruleus, nucleus gigantocellularis, raphe nuclei, amygdala, and thalamus, as well as portions of the cerebral cortex. Because little is known about the specific physiologic changes produced by these nonmotor signs, we focus here on the better-known causes and effects of dopaminergic cell loss in Parkinson disease.

The etiology of Parkinson disease is uncertain in most patients, who are said to suffer from "sporadic" Parkinson disease. Nevertheless, the disorder is believed to result from a combination of environmental and genetic factors. Exposure to environmental toxins, such as pesticides, is thought to underlie the association of Parkinson disease with rural living and consumption of well water. Several such compounds are mitochondrial toxins that may damage dopaminergic cells by interfering with their energy metabolism. Other environmental factors, such as a history of smoking or caffeine consumption, are known to *lower* the risk of developing Parkinson disease.

singlegene mutations may also result in parkinsonism. For example, in several families with autosomal dominant parkinsonism the disorder is linked to a defect in the gene on chromosome 4 encoding α-synuclein or to duplication or triplication of the gene. This protein is one of the major components of eosinophilic inclusions (Lewy bodies) that are found in degenerating neurons in the substantia nigra pars compacta. In both sporadic and hereditary forms of Parkinson disease the accumulation of

α-synuclein appears to be a major factor accounting for neuronal dysfunction and cell death. More common than mutations in the α-synuclein gene are parkinsonism-causing defects in the *parkin* gene on chromosome 6, or the more recently identified LRRK2 gene mutation. The pathogenetic mechanisms triggered by these mutations are not clear. However, it appears that factors such as oxidative damage, dysfunction of cellular mechanisms involved in the removal of toxic metabolites, and abnormal cellular calcium handling may contribute to the loss of dopaminergic cells in parkinsonism.

Direct evidence for the reduction of dopaminergic inputs to the striatum comes from postmortem biochemical analyses and from PET studies in humans with Parkinson disease (Figure 43–8). With PET the dopaminergic system can be visualized in vivo. Such studies have demonstrated that the reduction of dopamine is most severe in the caudal putamen, the portion of the striatum containing the motor circuit. This result is consistent with the observation that the earliest and most prominent manifestations of the disease involve the development of motor signs and symptoms.

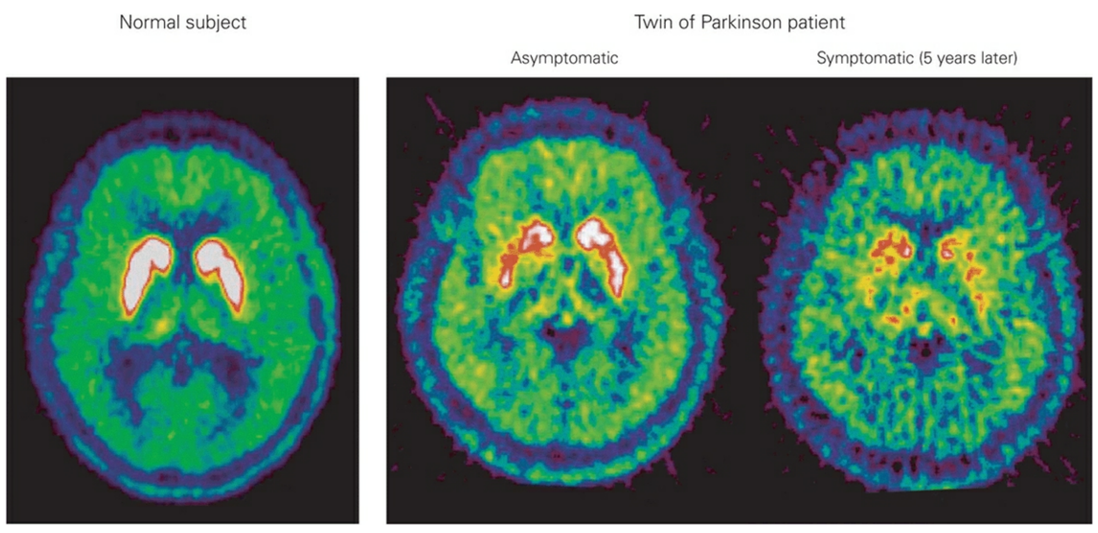

Figure 43-8 Loss of dopamine in the striatum in Parkinson disease. Positron emission tomography (PET) images of ^{18}F-DOPA uptake in the striatum in a normal subject and in a twin of a Parkinson patient show the extent of dopamine metabolism. In the twin, ^{18}F-DOPA uptake in the putamen was reduced when the subject was asymptomatic and more severely reduced five years later when symptomatic. (Adapted, with permission, from Brooks 2000.)

Postmortem studies that have compared the brains of parkinsonian and control patients, as well as studies in experimental animals, have shown that the first overt motor signs of the disease occur when 70% or more of striatal dopamine are lost, attesting to a significant capacity of the basal ganglia–thalamocortical network to compensate for changes in dopamine levels. The presymptomatic compensation for dopamine loss may occur within the dopaminergic system itself, through increased activity of healthy dopaminergic neurons, sprouting of remaining dopaminergic fibers, and changes in the synthesis, release, or metabolism or receptor sensitivity. Mechanisms independent of dopamine, such as synaptic changes in the thalamus or cortex, may also play a role.

Dopamine loss in other nuclei of the basal ganglia (specifically the subthalamic nucleus, the internal pallidal segment, and the substantia nigra pars reticulata) may also contribute to the manifestations of Parkinson disease. Whether dopamine loss in regions outside the basal ganglia, such as the thalamus and frontal cortex, is a factor in the development of parkinsonism has not been examined in detail.

In the early 1980s a group of drug addicts injected themselves with a synthetic opioid that was contaminated with the meperidine analog MPTP (1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine), a potent mitochondrial toxin. Soon after the exposure some of these individuals developed profound and irreversible parkinsonism. Investigations by William Langston and others revealed that MPTP is a potent neurotoxin able to destroy selectively the dopaminergic neurons in the midbrain. An important consequence of this discovery was that it allowed researchers to develop a pheno-typically and anatomically convincing animal model of dopamine depletion, the MPTP-treated primate. Anatomical and electrophysiological studies in these animals have contributed greatly to circuit models of the pathophysiology of Parkinson disease.

Early microelectrode recordings and neuro-imaging studies in MPTP-treated primates demonstrated that induction of parkinsonism is accompanied by a decrease in the discharge rates of neurons in the external pallidal segment and an increase in activity the subthalamic nucleus and internal pallidal segment. These changes, along with the motor signs of parkinsonism, can be reversed by systemic administration of dopamine

receptor agonists. These findings led to the development of a highly influential pathophysiologic model in which loss of dopaminergic input to the striatum led to increased activity in the indirect pathway and decreased activity in the direct pathway. Both of these changes are thought to lead to a net increase of the activity of neurons in the internal segment of the globus pallidus and the substantia nigra pars reticulata. This increase in basal ganglia output would result in increased inhibition of thalamocortical and midbrain tegmental neurons and account for the hypokinetic features of the disease.

This so-called "rate model" of Parkinson disease has now been largely supplanted by models that place greater emphasis on changes in neuronal firing pattern and synchrony. The rate model cannot account for the lack of akinesia following thalamic lesions and of involuntary movements following lesions of the internal pallidum, as demonstrated in both experimental animal models and surgically treated patients.

Electrophysiological recordings from the basal ganglia in parkinsonian animals and in humans undergoing neurosurgical procedures have shown obvious abnormalities of firing patterns (Figure 43–9). Abnormal burst discharges and synchronized oscillatory neuronal activity throughout the basal ganglia–thalamocortical circuitry are now thought to be at least as important for the development of parkinsonian akinesia and tremor as the changes in discharge rates. It is important to emphasize that the abnormalities that result in parkinsonism in the earlier rate model as well as in the newer models that emphasize pattern abnormalities are primarily found in the indirect pathway of the basal ganglia.

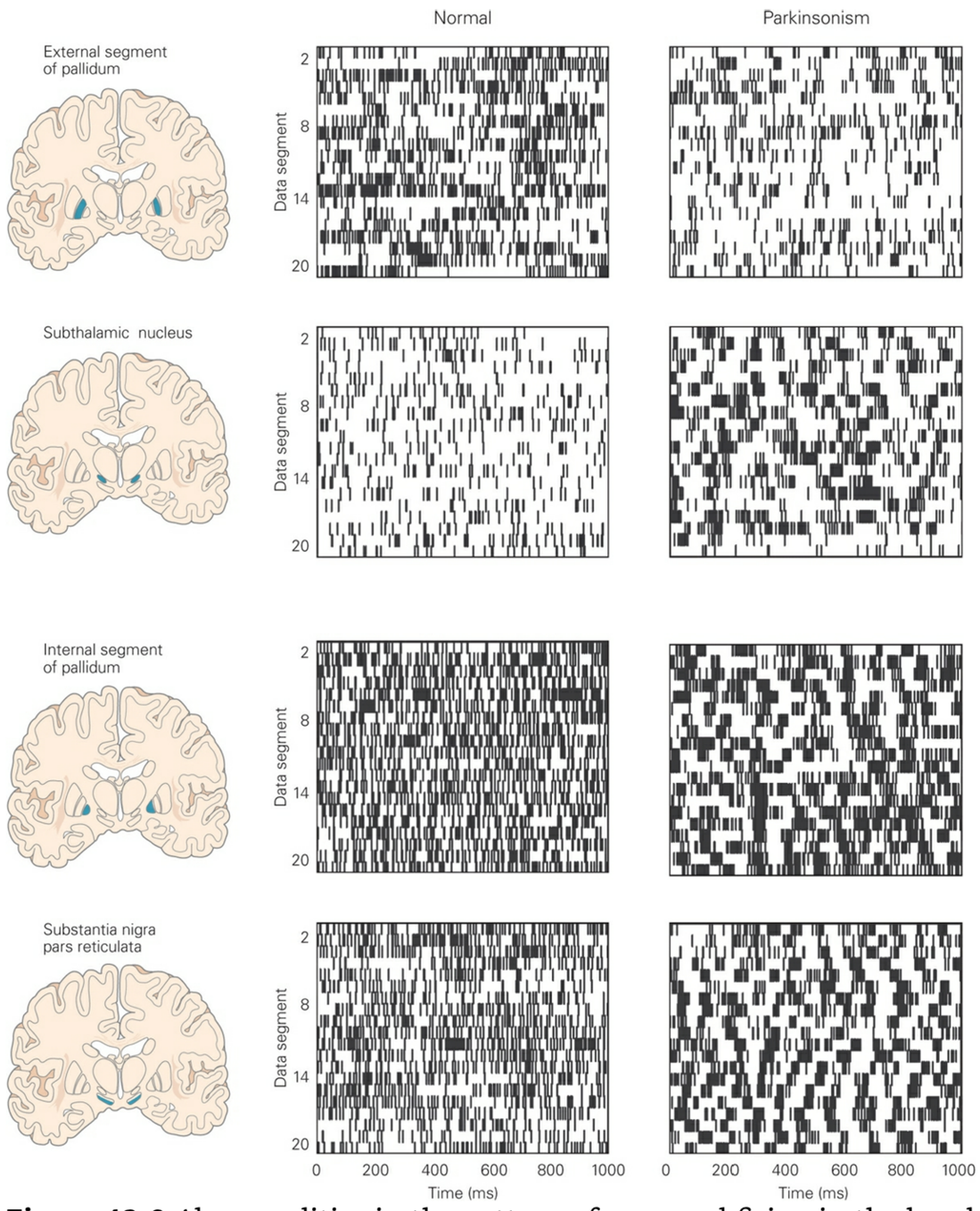

Figure 43-9 Abnormalities in the pattern of neuronal firing in the basal ganglia of parkinsonian monkeys. Raster plots show continuous data recordings from selected representative neurons situated in the structures portrayed at the left.

Recording of cells in vitro and related neural network modeling studies

have elucidated some of the mechanisms that may underlie these abnormal patterns of activity in the basal ganglia. Because most pathways in the basal ganglia are GABA-ergic, the role of *rebound bursting*, triggered by prolonged and pathological GABAergic inhibition of basal ganglia cells, has been extensively studied. One of the connections studied in detail is the interaction between the external segment of the globus pallidus and the subthalamic nucleus. Subthalamic nucleus neurons fire spontaneously as a result of the interplay between a persistent depolarizing Na^+ current and after hyperpolarization, both of which follow each action potential and are in part caused by a K^+ current that is activated by Ca^{2+} entry into the cell associated with the action potential. These normal oscillations are reset by single inhibitory postsynaptic potentials evoked by pallidal inputs. In the presence of stronger inhibition, as may occur when the synchronicity of pallidal activity is increased in parkinsonism, the hyperpolarization may be sufficient to trigger rebound depolarization, a phenomenon that appears to be central to the generation of bursts of action potentials in subthalamic nucleus neurons.

In recent years oscillatory activity in the basal ganglia has also been assessed by recording of local field potentials. Such recordings, reflecting the activity of larger ensembles of neurons and their synaptic inputs, can be made in parkinsonian patients implanted with macroelectrodes. It was found that parkinsonism is associated with high-amplitude oscillation in the high alpha and beta frequencies (10–30 Hz) in the subthalamic nucleus, internal pallidal segment, and cerebral cortex. Such oscillation may prevent the circuitry (specifically in the cortex) from engaging in oscillations at higher (gamma-band) frequencies. Gamma-band oscillatory activity in frontal cortex and related areas is seen as a prerequisite for normal movement, and lack of gamma-band oscillations may contribute to akinesia and bradykinesia.

Changes in the cortical activity of parkinsonian patients that may result from disordered subcortical inputs have also been evaluated by functional imaging. The time resolution of such imaging is too low to show directly any changes in firing patterns. However, PET scans of patients performing a movement show decreases in synaptic activity in the anterior cingulate, supplementary motor area, and dorsolateral prefrontal cortex. In addition, brain areas that are not normally activated are recruited when patients perform visuomotor tracking. These changes may be compensatory or they may be part of the motor problem, as normal function in the newly recruited areas may be disrupted.

Progress in understanding the pathophysiology of Parkinson disease, and the finding that lesioning of motor circuit structures in parkinsonian animals has strong antiparkinsonian effects, has contributed to the resurgence of neurosurgical procedures to treat patients with advanced Parkinson disease. Initially, surgical lesioning of basal ganglia and thalamic targets was used to interrupt abnormal activity in the motor circuit, but these (irreversible) procedures have now been largely replaced by chronic high-frequency deep brain stimulation. In this less invasive and reversible procedure a programmable pulse generator, similar to a cardiac pacemaker, is placed subcutaneously and connected to a stimulating electrode inserted into the subthalamic nucleus or internal segment of the globus pallidus. Although the mechanisms of action of deep brain stimulation remain controversial, it is likely that chronic high-frequency stimulation in patients with Parkinson disease acts primarily by replacing the irregular, abnormal basal ganglia output to the cortex with a more regular and better-tolerated pattern that may then allow the cerebral cortex to function more normally. Alternatively, chronic stimulation may disrupt the abnormal and disruptive beta-frequency oscillations.

Reduced and Abnormally Patterned Basal Ganglia Output Results in Hyperkinetic Disorders

Lesions of the basal ganglia or imbalances in their neurotransmitter systems may result in involuntary movements such as hemiballism, Huntington disease, dystonia, and drug-induced involuntary movements.

Hemiballism is a hyperkinetic disorder characterized by spontaneous involuntary movements of the contralateral proximal limbs. Hemiballism most often results from lesions restricted to the subthalamic nucleus, usually as the result of small strokes. Experimental lesioning of the subthalamic nucleus in monkeys shows that involuntary movements result only when the lesion is confined to the nucleus and 20% or more of the nucleus is damaged. Such experimental lesions significantly reduce the tonic discharge of neurons in the internal segment of the globus pallidus and decrease the phasic responses of these neurons to limb displacement.

The reduced inhibitory input from the internal segment may permit thalamocortical neurons to respond in an exaggerated or abnormal manner to cortical or other inputs. If the basal ganglia inhibit planned or ongoing movements under physiological conditions, loss of this function could conceivably result in excessive movements, particularly involuntary movements. However, the finding that lesions of the internal segment relieve rather than worsen ballism and other hyperkinetic disorders argues strongly that this view is too simplistic, and that not only global activity changes but also altered patterns and synchrony of neuronal discharge in the thalamus and cortex play a major role in the generation and manifestation of hyperkinetic disorders.

Huntington disease is a hereditary disorder that affects men and women equally at a frequency of 5 to 10 per 100,000 individuals. The onset of the disease occurs most often after the third decade of life. The disease is characterized by the gradual development of motor symptoms, including chorea and eye-movement abnormalities. Nonmotor disturbances such as depression, behavioral disturbances, and cognitive impairment are also very common. Death occurs as the result of medical complications of the underlying neurological disease, in most cases 15 to 20 years after onset.

Huntington disease results from a defect on chromosome 4, affecting the gene that codes for the protein huntingtin, and is inherited in an autosomal dominant fashion. The disease is a prime example of a disorder resulting from trinucleotide repeats in a small portion of a gene (see Chapter 44). Higher numbers of trinucleotide repeats are associated with an earlier onset of the disease (anticipation).

Because of the lack of suitable animal models of Huntington disease, the pathophysiologic changes that underlie the clinical signs and symptoms in this disease are not as well established as those in Parkinson disease. The available evidence suggests that neuronal degeneration early in the disease process occurs primarily in the striatum, affecting strongly those output neurons that give rise to the indirect pathway. This reduces inhibition of neurons in the external segment of the globus pallidus leading to excessive inhibition of subthalamic nucleus neurons and a subsequent reduction in basal ganglia output. The functional inactivation of the subthalamic nucleus could explain the appearance of involuntary movements, which are similar to those seen in cases of hemiballism.

In later stages of Huntington disease a rigid and akinetic phenotype develops in most cases, possibly as the result of additional loss of the striatal neurons that project to the internal segment of the globus pallidus and substantia nigra pars reticulata. The resulting removal of inhibition from neurons of the internal segment may convert the hyperkinetic movement disorder into a hypokinetic problem with increasing rigidity and akinesia.

The gradual loss of brain stem and cortical neurons may also contribute to some aspects of the movement disorder. The profound behavioral, psychiatric, and cognitive problems seen in Huntington disease reflect the fact that nonmotor areas of the cortex and basal ganglia are involved in the pathology.

Dystonia is distinguished clinically from chorea and hemiballism by the presence of slower, twisting movements, often resulting in abnormal postures. Dystonic movements are triggered by voluntary movements. Typically, patients show co-contraction of agonist-antagonist muscle groups and an inability to restrict movements to a single body part (overflow).

Most of the pathological conditions that result in dystonia affect the functioning of the basal ganglia–thalamocortical network. Dystonia may result from genetic defects, focal lesions of the basal ganglia or other structures, or disorders of dopamine metabolism. Whereas most cases of dystonia in adults are focal and nonfamilial, dystonia starting in childhood (or in young adults) is often generalized and genetic in origin. These genetic forms of dystonia do not feature prominent neuronal degeneration. A common autosomal dominant form of generalized dystonia originates from a trinucleotide deletion on chromosome 9, leading to the formation of a mutant variant of a normal protein (torsinA). Another interesting form of dystonia is dopamine-responsive dystonia, resulting from mutations in genes involved in the production of tetrahydrobiopterin, an essential cofactor in the biosynthesis of dopamine and other biogenic amines (see Chapter 13). Similar to Parkinson disease, this disorder can be treated with dopamine replacement.

The exact role of the basal ganglia in dystonia remains poorly defined, at least in part because existing animal models of the disease do not fully replicate the phenotype. Some of the evidence regarding the role of

the basal ganglia in dystonia comes from recordings in a small number of human patients undergoing neurosurgical procedures and from PET scans of dystonic patients. These studies have found that the average discharge rate in both segments of the globus pallidus is low. As in the other movement disorders, abnormally patterned or synchronized activity of the basal ganglia output neurons may play an important role in the pathophysiology of dystonia. In some cases dopaminergic dysfunction may also contribute to the development of dystonia. This view is supported by the findings that alterations in striatal dopamine transmission are seen in some forms of dystonia, that dystonia may occur in untreated Parkinson disease, and that dystonia can be seen in some patients receiving dopamine receptor-blocking drugs.

Dystonia has also been interpreted as a disorder of abnormal synaptic plasticity in the basal ganglia. A key finding supporting this view is that sensorimotor maps in the basal ganglia–thalamocortical circuits are less defined in patients with focal hand dystonia than in controls. Because focal hand dystonia is often seen in the hands of patients with writer's cramp or musician's dystonia, it is interpreted as the end product of pathological synaptic plasticity in subcortical or cortical regions. Evidence for disordered plasticity in the cortico–basal ganglia–thalamocortical circuits also comes from the finding that the beneficial effects of surgical treatments such as lesioning or chronic electrical stimulation of the globus pallidus require weeks or months to develop.

Abnormal Neuronal Activity in Nonmotor Circuits Is Associated with Several Neuropsychiatric Disorders

Disturbances of the nonmotor basal ganglia–thalamocortical circuits may contribute to the development of cognitive and behavioral problems accompanying movement disorders and to primary psychiatric disorders, such as obsessive-compulsive disorder, Tourette syndrome, and depression. Although processes outside the basal ganglia–thalamocortical loop systems may also contribute to the psychiatric disturbances, we concentrate here on the possible involvement of the basal ganglia circuitry.

The evidence for the functional relevance of the nonmotor areas comes mostly from clinical observations. In addition, animal studies employing microinjections of a GABA receptor antagonist, bicuculline, into motor, associative, and limbic portions of the external pallidal segment in primates have provided evidence for the notion that different neurobehavioral syndromes arise from dysfunction of different basal ganglia–thalamocortical circuits. Injections in the limbic part of the external segment of the globus pallidus induced stereotypic movements, whereas injections in the associative part induced hyperactivity. As predicted, abnormal movements were observed only when bicuculline was injected into the motor territory. These studies provide experimental support for the proposed behavioral domains in the basal ganglia and their role in abnormal motor and nonmotor behaviors.

Damage to the dorsolateral pre-frontal cortex or subcortical portions of the pre-frontal circuit results in a variety of abnormalities related to cognitive or executive functions, whereas damage to the lateral orbitofrontal circuit (for example, in stroke patients) is associated with lack of empathy, emotional lability, irritability, and failure to respond to social cues.

One of the best-studied psychiatric disorders arising from pathology in a nonmotor circuit is obsessive-compulsive disorder. The stereotypic behaviors (rigid behavioral patterns) and compulsions that are characteristic of this disorder have been interpreted as evidence for dysfunctional procedural learning. Functional imaging studies of patients with this disorder have demonstrated abnormalities in activity in the basal ganglia–thalamocortical limbic circuits that originate in portions of the orbitofrontal and anterior cingulate cortices. The most prominent changes are seen in the ventral striatum, specifically in the nucleus accumbens and ventromedial caudate nucleus, and in the midbrain. The beneficial outcome of neurosurgical treatments directed at the limbic circuitry, such as lesioning or stimulation of the anterior limb of the internal capsule and the ventral striatum, or lesions involving fibers emanating from orbitofrontal or anterior cingulate cortex, is evidence that the limbic circuit is involved in obsessive-compulsive disorder.

Tourette syndrome, in which obsessive-compulsive symptoms are associated with motor or vocal tics (brief involuntary movements or vocalizations), is also characterized by abnormalities in the limbic circuit. The fact that dopamine receptor-blocking drugs suppress tics implicates the basal ganglia in these disorders. Additional changes in brain activity occur in cortical areas associated with motor functions, particularly in

the sensorimotor cortex and supplementary motor area. Chronic stimulation of the limbic and motor circuit at the pallidal and thalamic levels is now being explored as a treatment of severe, refractory Tourette syndrome.

An Overall View

It is now clear that the basal ganglia, together with the thalamus and cerebral cortex, participate in a family of neuronal networks that are involved not only in motor functions, but also in the higher-order aspects of behavior, linking emotion, reward, executive function, and mood, and that they may have specific relevance for adaptive shaping of behavior and action selection.

Basal ganglia disturbances are a factor in many major movement, behavioral, and psychiatric disorders that appear to result from dysfunction in specific basal ganglia–thalamocortical circuits. The existing models of basal ganglia function and dysfunction have stimulated research on the role of the basal ganglia in health and disease and contributed to the development of successful new treatments for these disorders.

Nevertheless, the present models are not fully satisfactory because they are too strongly based on disease considerations and the outcome of inactivation and disruptive manipulations that have remote effects, that do not necessarily reflect the actual functions of the basal ganglia, and that do not fully incorporate the adaptive properties of the circuits involved. Accordingly, future versions of functional models will need to take into account many of the more recent findings, including the close interactions of the basal ganglia with the brain stem and other structures and the role of abnormal neuronal activity patterns and synchrony in the pathophysiology of movement, cognitive, behavioral, and psychiatric disorders.

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