

The Basal Ganglia

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Some Movement Disorders Result From Imbalances in the Direct and Indirect Pathways in the Basal Ganglia

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The Gene for Huntington Disease Has Been Identified

Glutamate-Induced Neuronal Cell Death Contributes to Huntington Disease

The Basal Ganglia Also Have a Role in Cognition, Mood, and Nonmotor Behavior Function

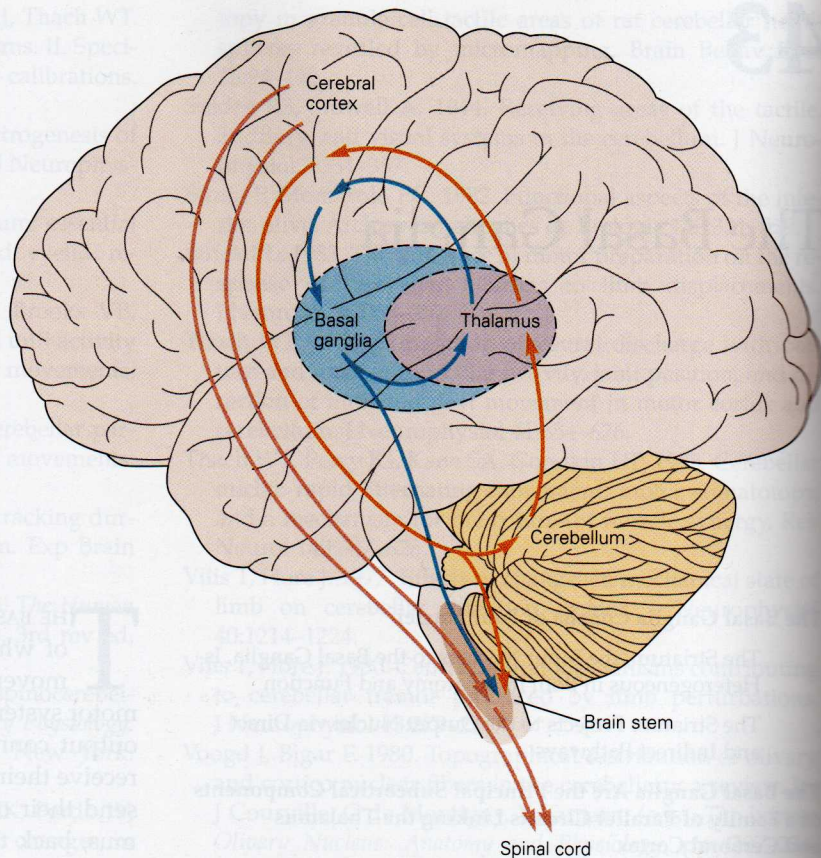
An Overall View

THE BASAL GANGLIA CONSIST of four nuclei, portions of which play a major role in normal voluntary movement. Unlike most other components of the motor system, however, they do not have direct input or output connections with the spinal cord. These nuclei receive their primary input from the cerebral cortex and send their output to the brain stem and, via the thalamus, back to the prefrontal, premotor, and motor cortices. The motor functions of the basal ganglia are therefore mediated, in large part, by motor areas of the frontal cortex.

Clinical observations first suggested that the basal ganglia are involved in the control of movement and the production of movement disorders. Postmortem examination of patients with Parkinson disease, Huntington disease, and hemiballismus revealed pathological changes in these subcortical nuclei. These diseases have three characteristic types of motor disturbances: (1) tremor and other involuntary movements; (2) changes in posture and muscle tone; and (3) poverty and slowness of movement without paralysis. Thus, disorders of the basal ganglia may result in either diminished movement (as in Parkinson disease) or excessive movement (as in Huntington disease). In addition to these disorders of movement, damage to the basal ganglia is associated with complex neuropsychiatric cognitive and behavioral disturbances, reflecting the wider role of these nuclei in the diverse functions of the frontal lobes.

Primarily because of the prominence of movement abnormalities associated with damage to the basal ganglia, they were believed to be major components of a motor system, independent of the pyramidal (or corticospinal) motor system, the "extrapyramidal" motor system. Thus, two different motor syndromes were

Figure 43-1 The relationships of the basal ganglia to the major components of the motor system. The basal ganglia and the cerebellum may be viewed as key elements in two parallel reentrant systems that receive input from and return their influences to the cerebral cortex through discrete and separate portions of the ventrolateral thalamus. They also influence the brain stem and, ultimately, spinal mechanisms.



distinguished: the *pyramidal tract syndrome*, characterized by spasticity and paralysis, and the *extrapyramidal syndrome*, characterized by involuntary movements, muscular rigidity, and immobility without paralysis.

There are several reasons why this simple classification is no longer satisfactory. First, we now know that, in addition to the basal ganglia and corticospinal systems, other parts of the brain participate in voluntary movement. Thus, disorders of the motor nuclei of the brain stem, red nucleus, and cerebellum also result in disturbances of movement. Second, the extrapyramidal and pyramidal systems are not truly independent but are extensively interconnected and cooperate in the control of movement. Indeed, the motor actions of the basal ganglia are mediated in large part through the supplementary, premotor, and motor cortices via the pyramidal system.

Because they are so common, disorders of the basal ganglia have always been important in clinical neurology. Parkinson disease was the first disease of the nervous system to be identified as a molecular disease caused by a specific defect in transmitter metabolism. Therefore, in addition to providing important informa-

tion about motor control, the study of diseased basal ganglia has provided a paradigm for studying the relationship of transmitters to disorders of mood, cognition, and nonmotor behavior, topics that will be considered in detail in Chapters 60 and 61. The use of a variety of anatomical, molecular, and neural imaging techniques as well as animal models of basal ganglia disorders has led to major advances in understanding the organization and function of the basal ganglia. These insights have, in turn, led to new pharmacologic and neurosurgical approaches to treatment of diseases of the basal ganglia.

The Basal Ganglia Consist of Four Nuclei

The basal ganglia consist of several interconnected subcortical nuclei with major projections to the cerebral cortex, thalamus, and certain brain stem nuclei. They receive major input from the cerebral cortex and thalamus and send their output back to the cortex (via the thalamus) and to the brain stem (Figure 43-1). Thus, the basal ganglia are major components of large cortical-

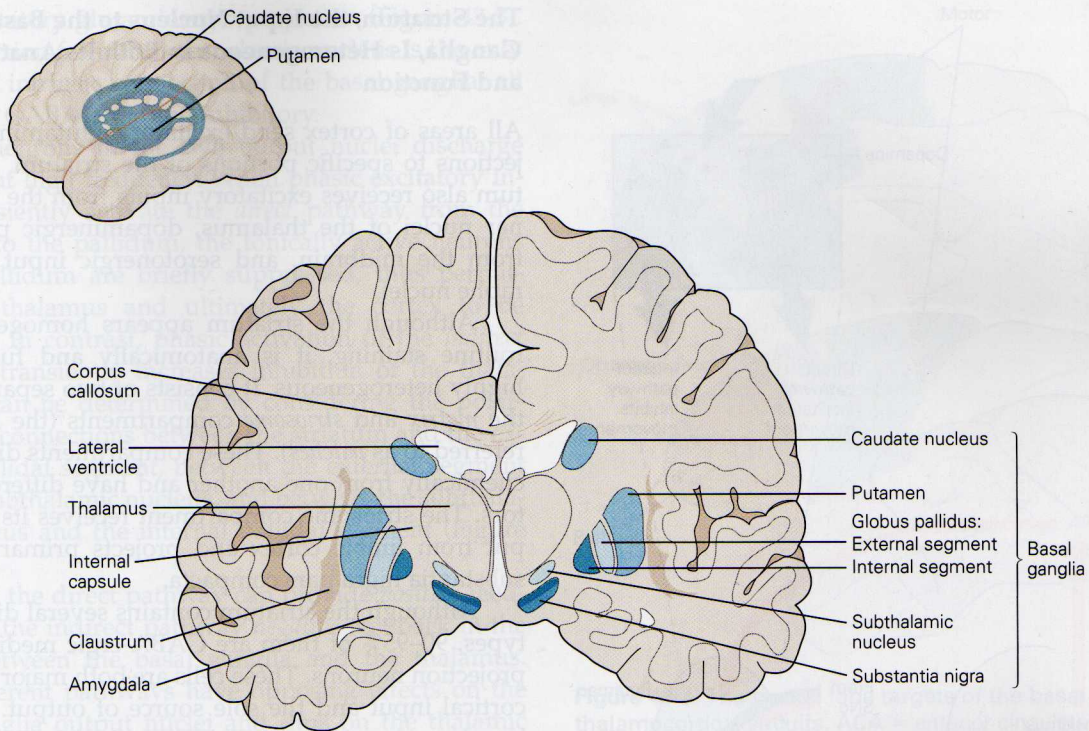


Figure 43-2 This coronal section shows the basal ganglia in relation to surrounding structures. (Adapted from Nieuwenhuys et al. 1981.)

subcortical reentrant circuits linking cortex and thalamus.

The four principal nuclei of the basal ganglia are (1) the striatum, (2) the globus pallidus (or pallidum), (3) the substantia nigra (consisting of the pars reticulata and pars compacta), and (4) the subthalamic nucleus (Figure 43-2). The striatum consists of three important subdivisions: the caudate nucleus, the putamen, and the ventral striatum (which includes the nucleus accumbens). Except at its most anterior pole, the striatum is divided into the caudate nucleus and putamen by the *internal capsule*, a major collection of fibers that run between the neocortex and thalamus in both directions. All three subdivisions of the striatum have a common embryological origin.

The striatum is the major recipient of inputs to the basal ganglia from the cerebral cortex, thalamus, and brain stem. Its neurons project to the globus pallidus and substantia nigra. Together these two nuclei, whose cell bodies are morphologically similar, give rise to the major output projections from the basal ganglia. The globus pallidus lies medial to the putamen, just lateral to the internal capsule, and is divided into external and internal segments. The internal pallidal segment is related functionally to the pars reticulata of the substantia

nigra, which lies in the midbrain on the medial side of the internal capsule. The cells of the internal pallidal segment and pars reticulata use γ -aminobutyric acid (GABA) as a neurotransmitter. Just as the caudate nucleus is separated from the putamen by the internal capsule, the internal pallidal segment is separated from the substantia nigra.

In addition to its reticular portion, the substantia nigra also has a compact zone (pars compacta). This zone is a distinct nucleus that lies dorsal to the pars reticulata although some of its neurons lie within the pars reticulata. The cells of the pars compacta are dopaminergic and also contain neuromelanin, a dark pigment derived from oxidized and polymerized dopamine. Neuromelanin, which accumulates with age in large lysosomal granules in cell bodies of dopaminergic neurons, accounts for the dark discoloration of this structure. Dopaminergic cells are also found in the ventral-tegmental area, a medial extension of the pars compacta.

The subthalamic nucleus is closely connected anatomically with both segments of the globus pallidus and the substantia nigra. It lies just below the thalamus and above the anterior portion of the substantia nigra. The glutaminergic cells of this nucleus are the only excitatory projections of the basal ganglia.

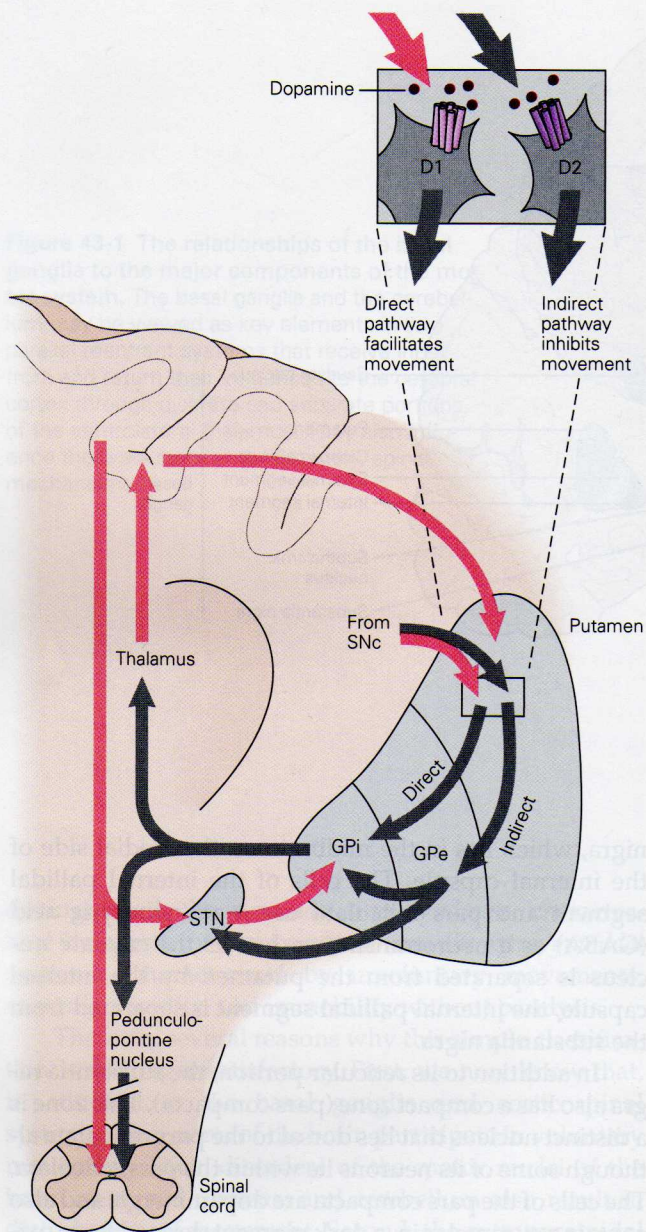


Figure 43-3 The anatomic connections of the basal ganglia-thalamocortical circuitry, indicating the parallel direct and indirect pathways from the striatum to the basal ganglia output nuclei. Two types of dopamine receptors (D1 and D2) are located on different sets of output neurons in the striatum that give rise to the direct and indirect pathways. Inhibitory pathways are shown as **gray arrows**; excitatory pathways, as **pink arrows**. GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; STN = subthalamic nucleus.

The Striatum, the Input Nucleus to the Basal Ganglia, Is Heterogeneous in Both Its Anatomy and Function

All areas of cortex send excitatory, glutaminergic projections to specific portions of the striatum. The striatum also receives excitatory inputs from the intralaminar nuclei of the thalamus, dopaminergic projections from the midbrain, and serotonergic input from the raphe nuclei.

Although the striatum appears homogeneous on routine staining, it is anatomically and functionally highly heterogeneous. It consists of two separate parts, the *matrix* and *striosome* compartments (the latter also referred to as *patches*). These compartments differ histochemically from one another and have different receptors. The striosome compartment receives its major input from limbic cortex and projects primarily to the substantia nigra pars compacta.

Although the striatum contains several distinct cell types, 90–95% of them are GABA-ergic medium-spiny projection neurons. These cells are both major targets of cortical input and the sole source of output. They are largely quiescent except during movement or in response to peripheral stimuli. In primates the medium-spiny neurons of the striatum can be subdivided into two groups. Those that project to the external pallidal segment express the neuropeptides enkephalin and neurotensin; those that project to the internal pallidal segment or substantia nigra pars reticulata express substance P and dynorphin.

The striatum also contains two types of local inhibitory interneurons: large cholinergic neurons and smaller cells that contain somatostatin, neuropeptide Y, or nitric oxide synthetase. Both classes of inhibitory interneurons have extensive axon collaterals that reduce the activity of the striatal output neurons. Although few in number, they are responsible for most of the tonic activity in the striatum.

The Striatum Projects to the Output Nuclei via Direct and Indirect Pathways

The two output nuclei of the basal ganglia, the internal pallidal segment and the substantia nigra pars reticulata, tonically inhibit their target nuclei in the thalamus and brain stem. This inhibitory output is thought to be modulated by two parallel pathways that run from the striatum to the two output nuclei: one direct and the other indirect. The indirect pathway passes first to the external pallidal segment and from there to the subthalamic nucleus in a purely GABA-ergic pathway, and finally from the subthalamic nucleus to the output nuclei

in an excitatory glutaminergic projection (Figure 43-3). The projection from the subthalamic nucleus is the only excitatory intrinsic connection of the basal ganglia; all others are GABA-ergic and inhibitory.

The neurons in the two output nuclei discharge tonically at high frequency. When phasic excitatory inputs transiently activate the *direct* pathway from the striatum to the pallidum, the tonically active neurons in the pallidum are briefly suppressed, thus permitting the thalamus and ultimately the cortex to be activated. In contrast, phasic activation of the *indirect* pathway transiently increases inhibition of the thalamus, as can be determined by considering the polarity of the connections between the striatum and the external pallidal segment, between the external segment and the subthalamic nucleus, and between the subthalamic nucleus and the internal pallidal segment (Figure 43-3).

Thus, the direct pathway can provide *positive* feedback and the indirect pathway *negative* feedback in the circuit between the basal ganglia and the thalamus. These efferent pathways have opposing effects on the basal ganglia output nuclei and thus on the thalamic targets of these nuclei. Activation of the direct pathway disinhibits the thalamus, thereby increasing thalamocortical activity, whereas activation of the indirect pathway further inhibits thalamocortical neurons. As a result, activation of the direct pathway facilitates movement, whereas activation of the indirect pathway inhibits movement.

The two striatal output pathways are affected differently by the dopaminergic projection from the substantia nigra pars compacta to the striatum. Striatal neurons that project directly to the two output nuclei have D1 dopamine receptors that facilitate transmission, while those that project in the indirect pathway have D2 receptors that reduce transmission.

Although their synaptic actions are different, the dopaminergic inputs to the two pathways lead to the same effect—reducing inhibition of the thalamocortical neurons and thus facilitating movements initiated in the cortex. We can now see how depletion of dopamine in the striatum, as occurs in Parkinson disease, may lead to impaired movement. Without the dopaminergic action in the striatum, activity in the output nuclei increases. This increased output in turn increases inhibition of the thalamocortical neurons that otherwise facilitate initiation of movement. Dopaminergic synapses are also found in the pallidum, the subthalamic nucleus, and the substantia nigra. Dopaminergic action at these sites, and in the cortex, could further modulate the actions of the direct and indirect pathways from the striatum.

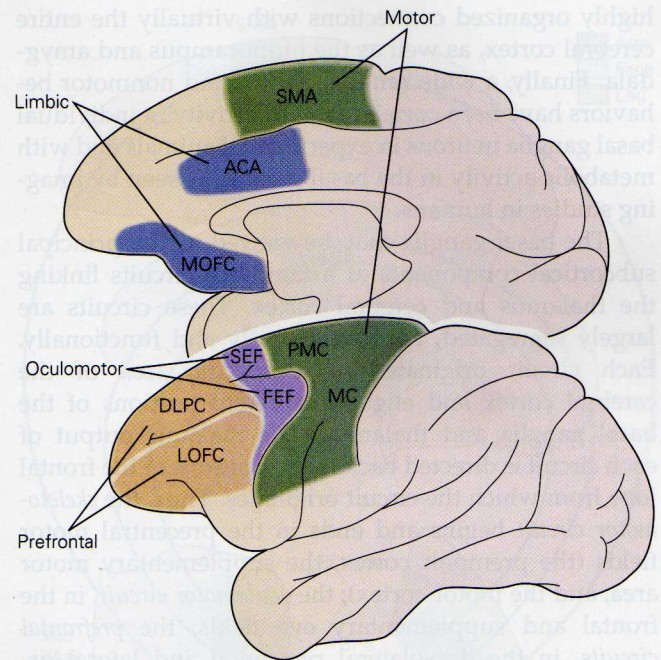


Figure 43-4 The frontal lobe targets of the basal ganglia-thalamocortical circuits. ACA = anterior cingulate area; DLPC = dorsolateral prefrontal cortex; FEF = frontal eye field; LOFC = lateral orbitofrontal cortex; MC = primary motor cortex; MOFC = medial orbitofrontal cortex; PMC = premotor cortex; SEF = supplementary eye field; SMA = supplementary motor area.

The Basal Ganglia Are the Principal Subcortical Components of a Family of Parallel Circuits Linking the Thalamus and Cerebral Cortex

The basal ganglia were traditionally thought to function only in voluntary movement. Indeed, for some time it was believed that the basal ganglia sent their entire output to the motor cortex via the thalamus and thus act as a funnel through which movement is initiated by different cortical areas. It is now widely accepted, however, that through their interaction with the cerebral cortex the basal ganglia also contribute to a variety of behaviors other than voluntary movement, including skeleto-motor, oculomotor, cognitive, and even emotional functions.

Several observations point to diversity of function. First, certain experimental and disease-related lesions of the basal ganglia produce adverse emotional and cognitive effects. This was first recognized in patients with Huntington disease. Patients with Parkinson disease also have disturbances of affect, behavior, and cognition. Second, the basal ganglia have extensive and

highly organized connections with virtually the entire cerebral cortex, as well as the hippocampus and amygdala. Finally, a wide range of motor and nonmotor behaviors have been correlated with activity in individual basal ganglia neurons in experimental animals and with metabolic activity in the basal ganglia as seen by imaging studies in humans.

The basal ganglia may be viewed as the principal subcortical components of a family of circuits linking the thalamus and cerebral cortex. These circuits are largely segregated, both structurally and functionally. Each circuit originates in a specific area of the cerebral cortex and engages different portions of the basal ganglia and thalamus. The thalamic output of each circuit is directed back to the portions of the frontal lobe from which the circuit originates. Thus, the *skeletomotor circuit* begins and ends in the precentral motor fields (the premotor cortex, the supplementary motor area, and the motor cortex); the *oculomotor circuit*, in the frontal and supplementary eye fields; the *prefrontal circuits*, in the dorsolateral prefrontal and lateral orbitofrontal cortices; and the *limbic circuit*, in the anterior cingulate area and medial orbitofrontal cortex (Figure 43-4). Each area of the neocortex projects to a discrete region of the striatum and does so in a highly topographic manner. Association areas project to the caudate and rostral putamen; sensorimotor areas project to most of the central and caudal putamen; and limbic areas project to the ventral striatum and olfactory tubercle.

The concept of segregated basal ganglia-thalamocortical circuits is a valuable anatomic and physiologic framework for understanding not only the diverse movement disorders associated with basal ganglia dysfunction but also the many-faceted neurologic and psychiatric disturbances resulting from basal ganglia disorders. Structural convergence and functional integration occur *within*, rather than between, the five identified basal ganglia-thalamocortical circuits. For example, the skeletomotor circuit has subcircuits centered on different precentral motor fields, with separate somatotopic pathways for control of leg, arm, and orofacial movements.

Within each of these subunits there may even be discrete pathways responsible for different aspects of motor processing. Injection of transsynaptically transported herpes simplex virus that is transmitted in the retrograde direction into the primary motor cortex, supplementary motor area, and lateral premotor area results in labeling of distinct populations of output neurons in the internal pallidal segment (see Figure 5-9 for technique). Virus transported in the anterograde direction was labeled in distinctly separate regions of the

putamen. Given the highly topographic connections between the striatum and the pallidum and between the pallidum and the subthalamic nucleus, it is unlikely that there is significant convergence between neighboring circuits. There is, however, some anatomical evidence that the circuits converge to some degree in the substantia nigra pars reticulata.

The Skeletomotor Circuit Engages Specific Portions of the Cerebral Cortex, Basal Ganglia, and Thalamus

Since movement disorders are prominent in diseases of the basal ganglia, it is appropriate here to focus on the skeletomotor circuit. In primates the skeletomotor circuit originates in the cerebral cortex in precentral motor fields and postcentral somatosensory areas and projects largely to the putamen. The putamen is thus an important site for integration of movement related and sensory feedback information related to movement. The putamen receives topographic projections from the primary motor cortex and premotor areas, including the arcuate premotor area and the supplementary motor area. Somatosensory areas 3a, 1, 2, and 5 project in an overlapping manner to the motor portions of the putamen. Topographically organized projections from each cortical area result in a somatotopic organization of movement-related neurons in the putamen. The leg is represented in a dorsolateral zone, the orofacial region in a ventromedial zone, and the arm in a zone between the two (Figure 43-5). Each of these representations extends along virtually the entire rostrocaudal axis of the putamen. Recent anatomical and physiological data indicate that the skeletomotor circuit is further subdivided into several independent subcircuits, each centered on a specific precentral motor field.

Output neurons in the putamen project topographically to the caudoventral portions of both segments of the pallidum and to the caudolateral portions of the substantia nigra pars reticulata. In turn, the motor portions of the internal pallidal segment and substantia nigra pars reticulata send topographic projections to specific thalamic nuclei, including three ventral nuclei—the ventral lateral nucleus (pars oralis) and the lateral ventral anterior nuclei (pars parvocellularis and pars magnocellularis)—and the centromedian nucleus (see Figure 18-4 for the organization of the thalamic nuclei). The skeletomotor circuit is then closed by projections from the ventral lateral and ventral anterior (pars magnocellularis) nuclei to the supplementary motor area, from the lateral ventral anterior (pars parvocellularis) and the ventral lateral nuclei to the premotor cortex, and from

the ventral lateral and centromedian nuclei to the precentral motor fields.

Single Cell Recording Studies Provide Direct Insight into the Role of the Motor Circuits

The contribution of the basal ganglia to movement can be assessed most directly by studying the activity of neurons within the skeletomotor circuit of behaving primates, especially activity in the internal segment of the pallidum, the principal output nucleus. The onset of rapid, stimulus-triggered limb movements is preceded first by changes in neuronal firing in the motor circuits of the cortex and only later in the basal ganglia. This sequential firing suggests that a *serial* processing occurs within the basal ganglia–thalamocortical circuits and that much of the activity within these circuits is initiated at the cortical level.

During the execution of a specific motor act, such as wrist flexion or extension, the normally high rate of spontaneous discharge in movement-related neurons in the internal pallidal segment becomes even higher in the majority of cells, but in some it decreases. Neurons that exhibit phasic decreases in discharge may play a crucial role in movement by disinhibiting the ventrolateral thalamus and thereby gating or facilitating cortically initiated movements (via excitatory thalamocortical connections). Populations of neurons that show phasic increases in discharge would have the opposite effect, further inhibiting thalamocortical neurons and thus suppressing antagonistic or competing movements.

Little is known about how movement-related signals from the direct and indirect pathways are integrated in the internal pallidal segment to control basal ganglia output. One possibility, of course, is that signals associated with a particular voluntary movement are directed over both pathways to the same population of pallidal neurons. With this arrangement, the inputs from the indirect pathway might assist in braking or possibly smoothing the movement, while those in the direct pathway simultaneously facilitate the movement. This reciprocal regulation would be consistent with the basal ganglia's apparent role in *scaling* the amplitude or velocity of movement. Alternatively, the direct and indirect inputs associated with a particular movement could be directed to separate sets of neurons in the output nuclei of the basal ganglia. In this configuration, the skeletomotor circuit might play a dual role in modulating voluntary movements by both reinforcing the selected pattern (via the direct pathway) and suppressing potentially conflicting patterns (via the indirect pathway). This dual role could result in *focusing* the neural activity

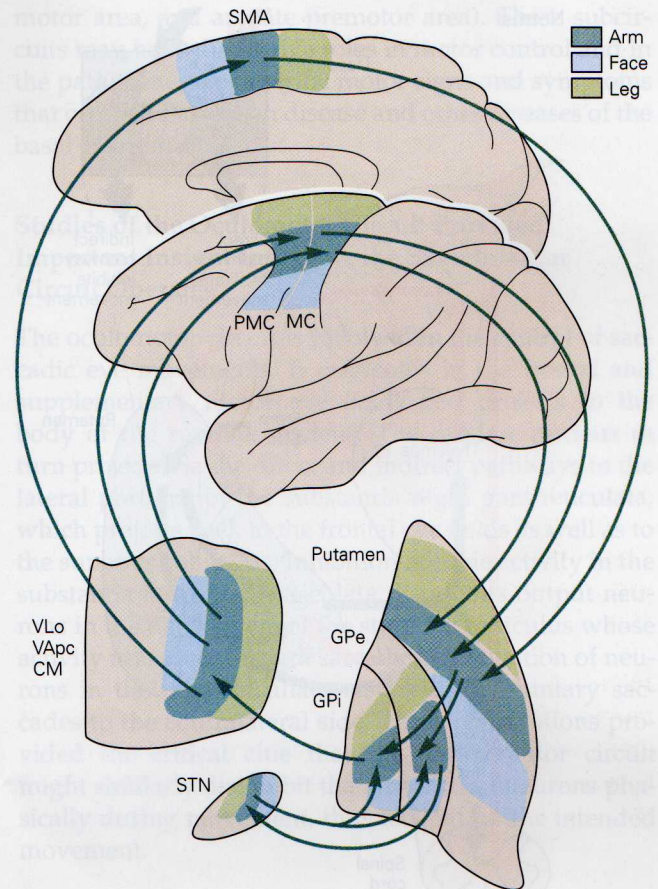
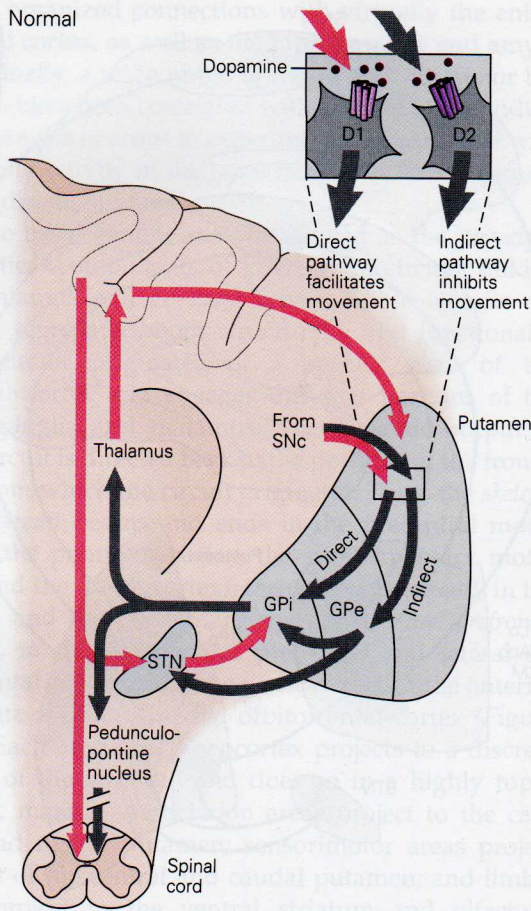


Figure 43-5 The somatotopic organization of the basal ganglia–thalamocortical motor circuit is illustrated in these mesial and lateral views of a monkey brain, as well as the basal ganglia and thalamus. The motor circuit is divided into a “face” representation (blue), “arm” representation (dark green), and “leg” representation (light green). Arrows show subcircuits within the portion of the motor circuit concerned with the arm. CM = centromedian nucleus of the thalamus; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; MC = primary motor cortex; PMC = prefrontal motor cortex; SMA = supplementary motor area; STN = subthalamic nucleus; VApc = parvocellular portion of the ventral anterior nucleus of the thalamus; VLo = pars oralis of the ventrolateral nucleus of the thalamus.

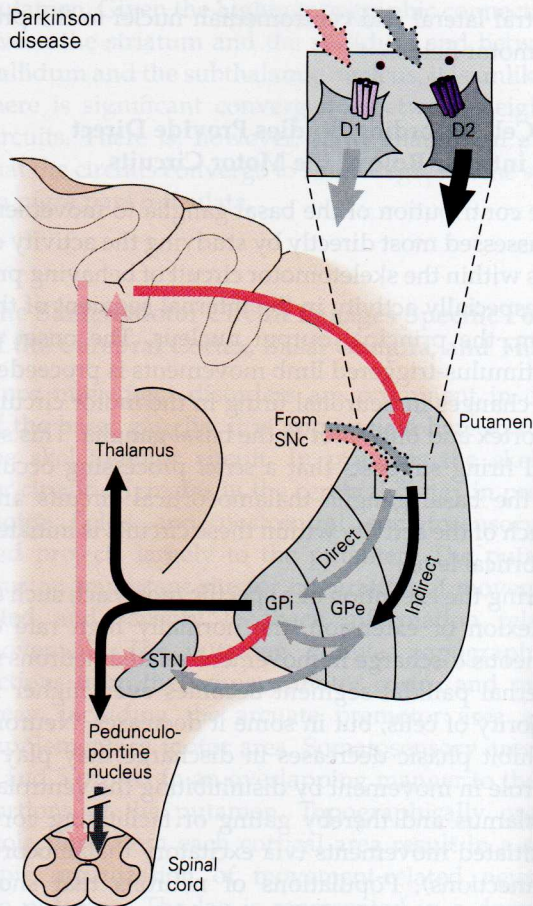
that mediates each voluntary movement in a way similar to the inhibitory surround described for various sensory systems.

Neuronal activity within the skeletomotor circuit has been examined in monkeys performing a variety of motor tasks. At all stages of the circuit (cortical, striatal, and pallidal) the activity of substantial proportions of movement-related neurons depends upon the direction of limb movement, independent of the pattern of mus-

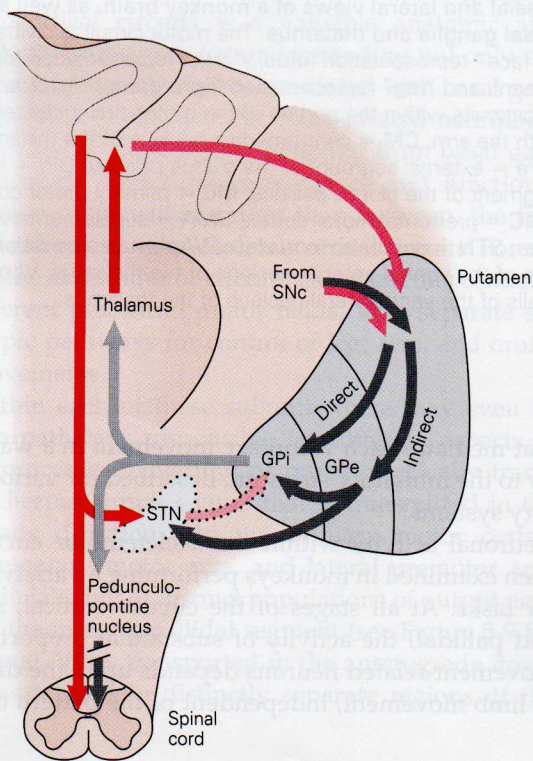
Normal



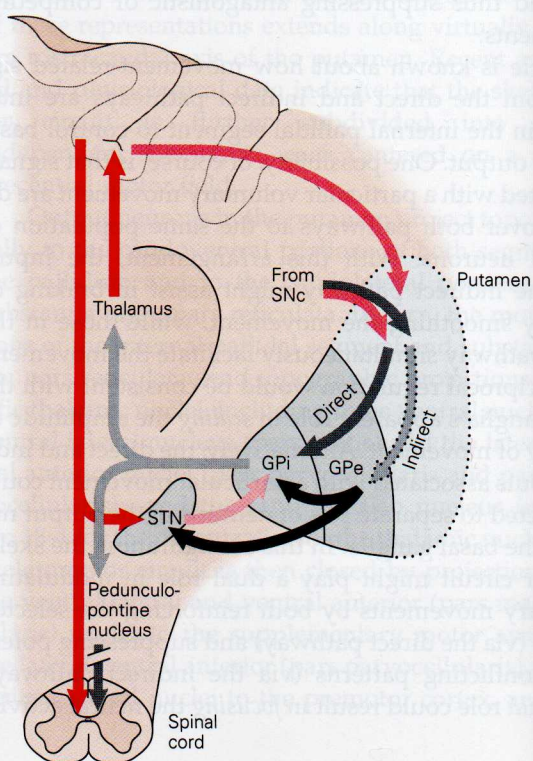
Parkinson disease



Hemiballism



Chorea



cle activity. These directional cells comprise 30–50% of the movement-related neurons in the supplementary motor area, motor cortex, putamen, and pallidum. All of these neurons are arranged somatotopically. In the motor cortical, but not in the basal ganglia many movement-related cells have been found whose firing does depend on the pattern of muscle activity. In trained primates, the activity in arm-related neurons of the internal pallidal segment also is clearly correlated with amplitude and velocity.

Studies combining behavioral training and single-cell recording indicate that the skeletomotor circuit is involved not only in the execution but also in the preparation for movement. In the precentral motor fields, including the premotor cortex, supplementary motor area, and motor cortex, striking changes in discharge rate occur in some neurons after the presentation of a cue that specifies the direction of limb movement to be executed later. These changes in activity persist until the movement-triggering stimulus is presented. They thus represent a neural correlate of one of the preparatory aspects of motor control referred to as “motor set” (Chapter 38).

Directionally selective activity before movement also occurs within the putamen and the internal segment of the pallidum. Individual neurons within these structures tend to exhibit *either* preparatory (set-related) or movement-related responses, suggesting that the preparation and execution of motor action are mediated by separate subchannels in the skeletomotor circuit. In the internal segment of the pallidum subpopulations of neurons that receive input from the supplementary motor area tend to exhibit set-like preparatory responses. However, neurons receiving inputs from the motor cortex tend to exhibit phasic, movement-related responses. These different response patterns further support the idea that the skeletomotor circuit is composed of distinct subcircuits that connect to different precentral motor fields (motor cortex, supplementary

motor area, and arcuate premotor area). These subcircuits may have distinctive roles in motor control and in the pathogenesis of specific motor signs and symptoms that occur in Parkinson disease and other diseases of the basal ganglia.

Studies of the Oculomotor Circuit Provided Important Insight Into How the Skeletomotor Circuit Operates

The oculomotor circuit is involved in the control of saccadic eye movements. It originates in the frontal and supplementary motor eye fields and projects to the body of the caudate nucleus. The caudate nucleus in turn projects via the direct and indirect pathways to the lateral portions of the substantia nigra pars reticulata, which projects back to the frontal eye fields as well as to the superior colliculus. Inhibition of tonic activity in the substantia nigra pars reticulata disinhibits output neurons in the deep layers of the superior colliculus whose activity is associated with saccades. Inactivation of neurons in the pars reticulata results in involuntary saccades to the contralateral side. These observations provided the critical clue that the skeletomotor circuit might similarly disinhibit thalamocortical neurons phasically during movement, thus facilitating the intended movement.

Some Movement Disorders Result From Imbalances in the Direct and Indirect Pathways in the Basal Ganglia

Considerable progress has been made in understanding the mechanisms underlying the major movement disorders of the basal ganglia. *Hypokinetic disorders* (of which Parkinson disease is the best-known example) are characterized by impaired initiation of movement (*akinesia*) and by a reduced amplitude and velocity of voluntary movement (*bradykinesia*). They are usually accompanied by muscular rigidity (increased resistance to passive displacement) and tremor.

Hyperkinetic disorders (exemplified by Huntington disease and hemiballismus) are characterized by excessive motor activity, the symptoms of which are involuntary movements (*dyskinesias*) and decreased muscle tone (*hypotonia*). The involuntary movements may take several forms—slow, writhing movements of the extremities (athetosis); jerky, random movements of the limbs and orofacial structures (chorea); violent, large-amplitude, proximal limb movements (ballism), and more sustained abnormal postures and slower movements with underlying cocontraction of agonist and

Figure 43-6 (Opposite) The basal ganglia–thalamocortical circuitry under normal conditions and in Parkinson disease, hemiballismus, and chorea. Inhibitory connections are shown as gray and black arrows; excitatory connections, as pink and red. Degeneration of the nigrostriatal dopamine pathway in Parkinson disease leads to differential changes in activity in the two striatopallidal projections, indicated by changes in the darkness of the connecting arrows (darker arrows indicate increased neuronal activity and lighter arrows, decreased activity). Basal ganglia output to the thalamus is increased in Parkinson disease and decreases in ballismus and chorea. GPe = external segment of the globus pallidus; Gpi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; STN = subthalamic nucleus.

antagonist muscles (dystonia). Various types of involuntary movements often occur in combination and some appear to have a common underlying cause. The best example is the similarity between chorea and ballism, which may simply be distal (chorea) or proximal (ballism) forms of the same underlying disorder.

In recent years the development of primate models of both hypo- and hyperkinetic disorders, induced by systemic or local administration of selective neurotoxins, has made it possible to study some of the pathophysiologic mechanisms underlying this diverse symptomatology. Both extremes of the movement disorder spectrum can now be explained as specific disturbances within the basal ganglia-thalamocortical motor circuit. Normal motor behaviors depend on a critical balance between the direct and indirect pathways from the striatum to the pallidum. In the simplest of terms, overactivity in the indirect pathway relative to the direct pathway results in hypokinetic disorders, such as Parkinson disease; underactivity in the indirect pathway results in chorea and ballism (Figure 43-6).

Overactivity in the Indirect Pathway Is a Major Factor in Parkinsonian Signs

Parkinson disease, first described by James Parkinson in 1817, is one of the most common movement disorders, affecting up to one million people in the United States alone. It is also one of the most studied and best understood. Parkinson's description still captures the characteristic posture and movements of the patients with this disease:

. . . involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and intellects being uninjured.

The cardinal symptoms of the disease include a paucity of spontaneous movement, akinesia, bradykinesia, increased muscle tone (rigidity), and a characteristic tremor (4–5 per second) at rest. A shuffling gait as well as flexed posture and impaired balance are also prominent. The appearance of the typical patient with Parkinson disease is instantly recognizable and unforgettable: tremor, mask-like facial expression, flexed posture, and paucity and slowness of movement.

Parkinson disease is the first example of a brain disorder resulting from a deficiency of a single neurotransmitter. In the mid 1950s Arvid Carlsson showed that 80% of the brain's dopamine is in the basal ganglia. Next, Oleh Hornykiewicz found that the brains of patients

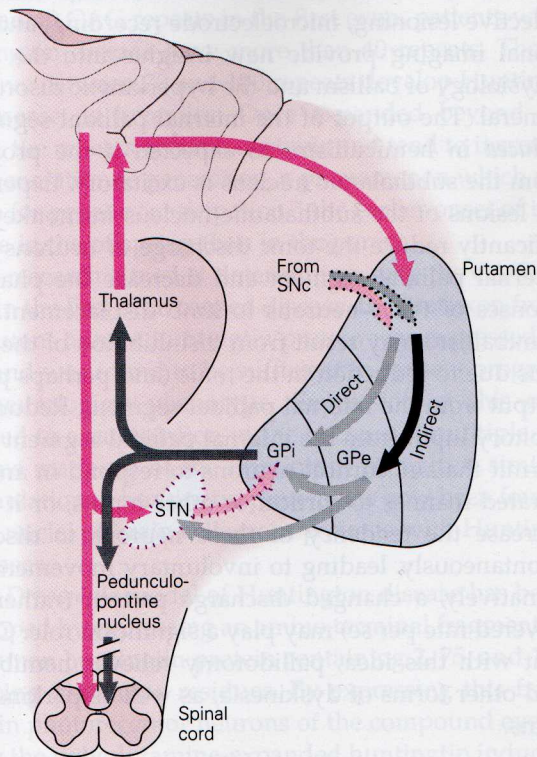
with Parkinson disease are deficient in dopamine, in the striatum, most severely in the putamen. In the early 1960s Parkinson disease was shown to result largely from the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Walter Birkmayer and Hornykiewicz found that intravenous administration of L-dihydroxyphenylalanine (L-DOPA), the precursor of dopamine, provided a dramatic, although brief, reversal of symptoms. The subsequent demonstration by George Cotzias that gradual increases in oral administration of L-DOPA could provide significant and continuous benefit began the modern era of pharmacologic therapy. Even with the development of newer and more effective antiparkinsonian drugs, the benefits of drug therapy usually begin to wane after about five years; and troublesome side effects develop in the form of motor response fluctuations and drug-related dyskinesias.

Research in Parkinson disease was recently revitalized by William Langston's discovery that drug addicts exposed to the meperidine derivative 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) develop a profound Parkinsonian state. This observation led to intense investigation of the role of exogenous toxins in the pathogenesis of Parkinson disease and to the development of a nonhuman primate animal model for experimental study. Primarily on the basis of studies in MPTP-treated primates, a working model of the pathophysiology of Parkinson disease has been developed. According to this model, loss of dopaminergic input from the substantia nigra pars compacta to the striatum leads to increased activity in the indirect pathway and decreased activity in the direct pathway (see Figure 43-6) because of the different actions of dopamine on the two pathways (via D1 and D2 receptors, respectively). Both of these changes lead to increased activity in the internal pallidal segment, which results in increased inhibition of thalamocortical and midbrain tegmental neurons and thus the hypokinetic features of the disease.

Experiments with MPTP-treated monkeys have shown significant changes in neuronal activity along the indirect pathway. For example, microelectrode recording studies have shown that tonic activity is decreased in the external pallidal segment but increased in the subthalamic nucleus and internal pallidal segment. The changes in tonic discharge in the pallidum (and the abnormal motor signs) are reversed by systemic administration of the dopamine receptor agonist apomorphine. The excessive activity in the indirect pathway at the subthalamic nucleus appears to be an important factor in the production of parkinsonian signs, since lesioning of the subthalamic nucleus, which reduces the excessive

Parkinson disease + surgical therapies

STN lesion



GPi lesion

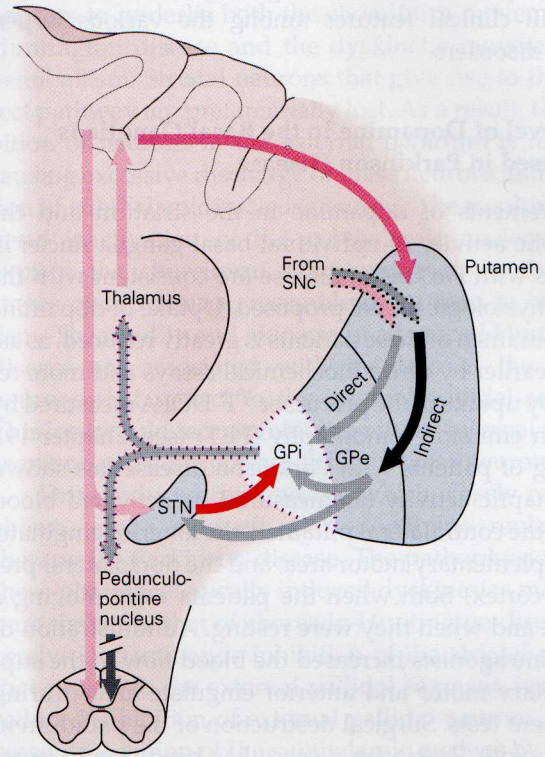


Figure 43-7 Sites of surgical intervention in Parkinson disease. Lesions of the subthalamic nucleus (left) or internal segment of the globus pallidus (right) effectively reduce parkinsonian signs and dyskinesias by respectively normalizing or

eliminating abnormal and excessive output from the internal pallidal segment. **GPe** = external segment of the globus pallidus; **GPi** = internal segment of the globus pallidus; **STN** = subthalamic nucleus; **SNc** = substantia nigra pars compacta.

excitatory drive on the internal pallidal segment, markedly ameliorates parkinsonian signs in MPTP-treated monkeys. Selective inactivation of the *sensorimotor* portion of either the subthalamic nucleus or the internal pallidal segment is sufficient to ameliorate the cardinal parkinsonian motor signs (akinesia, tremor, and rigidity) in MPTP-treated animals (Figure 43-7). Surgical lesions of the posterior (sensorimotor) portion of the internal pallidal segment (pallidotomy) in patients with advanced, medically intractable cases of Parkinson disease is also highly effective in reversing parkinsonian signs. Pallidotomy has undergone a revival in recent years as an effective treatment of patients with advanced disease whose symptoms are poorly controlled by medication alone and who experience drug-induced motor complications (as will be further discussed later).

Thus the hypokinetic features of Parkinson disease appear to result from increased (inhibitory) output from the internal pallidal segment as a result of increased (excitatory) drive from the subthalamic nucleus. Accordingly akinesia and bradykinesia are no longer viewed as negative signs that reflect loss of basal ganglia function, but rather as positive signs that, like rigidity and tremor, result from excessive and abnormal activity in intact structures. This abnormal motor activity can be reversed by reducing or abolishing the pathological output.

In addition to the increase in tonic output of the internal pallidal segment in MPTP-treated monkeys, phasic activity also changes. These changes in the *pattern* of discharge in basal ganglia output are likely to be equally as important as the changes in the rate of discharge. Indeed, recent data suggest that tremor may be due to

increased synchronization of oscillatory discharge within the basal ganglia nuclei. Differences in spatial temporal patterns and discharge may account for differences in clinical features among the various hyperkinetic disorders.

The Level of Dopamine in the Basal Ganglia Is Decreased in Parkinson Disease

Measurements of dopamine in the striatum and the metabolic activity of individual basal ganglia nuclei in patients with Parkinson disease are consistent with the pathophysiologic model proposed. Uptake of dopamine in the putamen of these patients is greatly reduced, as assessed earlier by direct biochemical assays and more recently by uptake of the precursor ^{18}F -DOPA measured by positron emission tomography (PET) (see Chapter 19). Imaging of patients with Parkinson disease has shown less synaptic activity (as measured by activated blood flow in the contralateral putamen, the anterior cingulate, the supplementary motor area, and the dorsolateral prefrontal cortex) both when the patients were moving a joystick and when they were resting. Administration of dopamine agonists increased the blood flow to the supplementary motor and anterior cingulate areas during movement tests. Surgical destruction of the pallidum in patients with Parkinson disease has been shown to restore activity in the supplementary motor and premotor areas during this same movement task. These neuroimaging studies lend strong additional support to the importance of the pallidothalamocortical portion of the motor circuit in normal movement and the production of akinesia and bradykinesia.

Underactivity in the Indirect Pathway Is a Major Factor in Hyperkinetic Disorders

Involuntary movements in patients with basal ganglia disorders may result either from clear-cut lesions of these nuclei or from imbalances in neurotransmitter systems. Apart from parkinsonism, the basal ganglia disorder for which the neuropathology is least in doubt is hemiballism. In humans, lesions (usually due to small strokes) restricted to the subthalamic nucleus may result in involuntary, often violent, movements of the contralateral limbs (called "ballism" because of the superficial resemblance of the movements to throwing). In addition to the involuntary movements of the proximal limbs, involuntary movements of more distal limbs may occur in an irregular (choreic) or more continuous writhing form.

Experimental lesions of the subthalamic nucleus in monkeys show that dyskinesias result only when le-

sions are made selectively in the nucleus, leaving intact the adjacent projections from the internal pallidal segment to the thalamus. More recent studies combining selective lesioning, microelectrode recording, and functional imaging provide new insights into the pathophysiology of ballism and the hyperkinetic disorders in general. The output of the internal pallidal segment is *reduced* in hemiballism, as expected if the projection from the subthalamic nucleus is excitatory. Experimental lesions of the subthalamic nucleus in monkeys significantly reduce the tonic discharge of neurons in the internal pallidal segment and decrease the phasic responses of these neurons to limb displacement. Thus hemiballism may result from disinhibition of the thalamus due to reduction in the tonic (and perhaps phasic) output from the internal pallidal segment. Reduced inhibitory input from the internal pallidal segment might permit thalamocortical neurons to respond in an exaggerated manner to cortical or other inputs, or it might increase the tendency of these neurons to discharge spontaneously, leading to involuntary movements. Alternatively, a changed discharge pattern (rather than lowered rate per se) may play a significant role. Consistent with this idea, pallidotomy relieves hemiballism and other forms of dyskinesia, as well as parkinsonian signs.

Huntington Disease Is a Heritable Hyperkinetic Disorder

The other hyperkinetic disorder most often associated with dysfunction of the basal ganglia is Huntington disease. This disease affects men and women with equal frequency, about 5–10 per 100,000. It is characterized by five features: heritability, chorea, behavioral or psychiatric disturbances, cognitive impairment (dementia), and death 15 or 20 years after onset. In most patients the onset of the disease occurs in the third to fifth decade of life. Many people have already had children by the time the disease is diagnosed.

The Gene for Huntington Disease Has Been Identified

Huntington disease is one of the first complex human disorders to be traced to a single gene, which was identified by mapping genetic polymorphisms (see Box 3-3). The disease is a highly penetrant, autosomal dominant disorder with a gene defect on chromosome 4. This gene encodes a large protein, huntingtin, the function of which has yet to be determined (Chapter 3). The protein normally is located in the cytoplasm. As we have seen

in Chapter 3, the first exon of the gene contained repeats of the trinucleotide sequence CAG, which encodes the amino acid glutamine. Whereas normal subjects have less than 40 CAG repeats in the first exon, patients with Huntington disease have more than 40 repeats. Those that have between 70 and 100 repeats develop Huntington disease as juveniles. Once expanded beyond 40 copies, the repeats become unstable and tend to increase from generation to generation, a phenomenon which accounts for genetic "anticipation," the earlier onset of the disease in the offspring than in the parent.

In research aimed at determining why the CAG repeats in the first exon caused disease, the first exon from the mutant human huntingtin protein was expressed in mice and was found to be sufficient to cause a progressive neurological phenotype. Expression of this one exon led to accumulation in the nucleus of multiple inclusions made up of the huntingtin protein. A similar accumulation of huntingtin protein has now been found in the nuclei of brain cells from patients with Huntington disease.

A *Drosophila* model of Huntington disease has been developed by expressing an amino terminal fragment of the human huntingtin protein containing 2, 75, and 120 repeating glutamine residues. By expressing this fragment in photoreceptor neurons of the compound eye of the fly the polyglutamine-expanded huntingtin induced neuronal degeneration much as it does in human neurons. The age on the onset and severity of the neuronal degeneration again correlated with the length of the repeat, and the nuclear localization of huntingtin again presaged neuronal degeneration.

Finally, a cellular model of Huntington disease has been created by transfecting the mutant Huntington's gene into cultured striatal neurons. Here the gene induced neurodegeneration by an apoptotic mechanism, consistent with the idea that the Huntington protein acts in the nucleus to induce apoptosis. Blocking nuclear localization of the mutant huntingtin suppresses its ability to form intranuclear inclusions and to induce apoptosis. However, this apoptotic death did not correlate with the formation of intranuclear inclusions. Full length huntingtin forms inclusions very rarely, raising the possibility that intranuclear inclusions may not play a causal role in mutant huntingtin's induced death. In fact, exposure of transfected striatal neurons to conditions that suppressed the formation of inclusions resulted in an increase in huntingtin-induced death. These findings suggests that mutant huntingtin may act within the nucleus to induce neurodegeneration, but that the intranuclear inclusions themselves may reflect a defense mechanism designed to protect against the death induced by huntingtin rather than reflecting a mechanism of cell death.

Although Huntington disease is characterized by widespread loss of neurons in the brain, the pathology is seen earliest in the striatum. A common mechanism appears to underlie both the choreiform movements of Huntington disease and the dyskinetic movements in hemiballism. Striatal neurons that give rise to the indirect pathway are preferentially lost. As a result, the inhibition of neurons in the external pallidum is reduced, causing excessive discharge of these neurons and inhibition of subthalamic nucleus neurons. The resulting *functional* inactivation of the subthalamic nucleus could explain the choreiform symptoms that, in the early stages of the disease, resemble those seen in hemiballism. The rigidity and akinesia in advanced Huntington disease are associated with the loss of the striatal neurons that project to the internal pallidal segment. This loss would reduce inhibition in the internal pallidal segment and thus increase firing in these neurons.

Drug-induced dyskinesias, which closely resemble chorea, are a side effect of dopamine replacement therapy for Parkinson disease. The pathophysiology of these pharmacologically induced dyskinesias may be in part similar to that of chorea in Huntington disease: excessive dopaminergic inhibition of the striatal neurons that project to the external pallidal segment, leading to reduced inhibition of external pallidal neurons and excessive inhibition of the subthalamic nucleus by overactive neurons in the external pallidal segment. The decrease in activity in the subthalamic nucleus would lower the output from the internal pallidal segment in a manner similar to that seen after direct inactivation of the subthalamic nucleus by surgical lesions. This decreased excitatory drive on the internal pallidal segment would be compounded by excessive dopaminergic stimulation of striatal neurons of the direct pathway and the resulting increased inhibitory input to the internal pallidum. Since administration of L-DOPA does not produce dyskinesias in normal individuals or in patients with Parkinson disease early in the course of therapy, the symptoms probably result from receptor upregulation, supersensitivity, and altered gene expression caused by prolonged administration of the drug. Intermittent dosing of L-DOPA appears to be a significant factor in the emergence of drug-induced dyskinesias.

Glutamate-Induced Neuronal Cell Death Contributes to Huntington Disease

Glutamate is the principal excitatory transmitter in the central nervous system. It excites virtually all central neurons and is present in nerve terminals at high concentration (10^{-3} M). In normal synaptic transmission the extracellular glutamate rises transiently, and this

rise is restricted to the synaptic cleft. In contrast, sustained and diffuse increases in extracellular glutamate kill neurons. This mechanism of cell death occurs primarily by the persistent action of glutamate on the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors and the resulting excessive influx of Ca^{2+} (Chapter 12). Excess Ca^{2+} has several damaging consequences that lead to cytotoxicity and death. First, it can activate calcium-dependent proteases (calpains). Second, Ca^{2+} activates phospholipase A_2 , which liberates arachidonic acid, leading to the production of eicosanoids, substances that produce inflammation and free radicals that cause tissue damage.

Toxic changes produced by glutamate, called *glutamate excitotoxicity*, are thought to cause cell damage and death after acute brain injury such as stroke or excessive convulsions. In addition, excitotoxicity may contribute to chronic degenerative diseases of the brain, such as Huntington disease. It has been shown that injection of NMDA agonists into the rat striatum reproduces the pattern of neuronal cell loss characteristic of Huntington disease. Thus, it is possible that the altered gene on chromosome 4 produces an abnormality that leads to excessive activation of NMDA receptors or release of glutamate.

The Basal Ganglia Have a Role in Cognition, Mood, and Nonmotor Behavior

Some circuits in the basal ganglia are involved in nonmotor aspects of behavior. These circuits originate in the prefrontal and limbic regions of the cortex and engage specific areas of the striatum, pallidum, and substantia nigra.

The *dorsolateral prefrontal circuit* originates in Brodmann's areas 9 and 10 and projects to the head of the caudate nucleus, which then 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 medial dorsal thalamic nuclei, which in turn project back upon the dorsolateral prefrontal area. The dorsolateral prefrontal circuit has been implicated broadly in so-called "executive functions" (Chapter 19). These include cognitive tasks such as organizing behavioral responses and using verbal skills in problem solving. Damage to the dorsolateral prefrontal cortex or subcortical portions of the circuit is associated with a variety of behavioral abnormalities related to these cognitive functions.

The *lateral orbitofrontal circuit* arises in the lateral prefrontal cortex and projects to the ventromedial cau-

date nucleus. The pathway from the caudate nucleus follows that of the dorsolateral circuit (through the internal pallidal segment and substantia nigra pars reticulata and thence to the thalamus) and returns to the orbitofrontal cortex. The lateral orbitofrontal cortex appears to play a major role in mediating empathetic and socially appropriate responses. Damage to this area is associated with irritability, emotional lability, failure to respond to social cues, and lack of empathy. A neuropsychiatric disorder thought to be associated with disturbances in the lateral orbitofrontal cortex and circuit is obsessive-compulsive disorder (Chapter 61).

The *anterior cingulate circuit* arises in the anterior cingulate gyrus and projects to the ventral striatum. The ventral striatum also receives "limbic" input from the hippocampus, amygdala, and entorhinal cortices. The projections of the ventral striatum are directed to the ventral and rostromedial pallidum and the rostromedial substantia nigra pars reticulata. From there the pathway continues to neurons in the paramedian portion of the medial dorsal nucleus of the thalamus, which in turn project back upon the anterior cingulate cortex. The anterior cingulate circuit appears to play an important role in motivated behavior, and it may convey reinforcing stimuli to diffuse areas of the basal ganglia and cortex via inputs through the ventral tegmental areas and the substantia nigra pars compacta. These inputs may play a major role in procedural learning (see Chapter 62). Damage to the anterior cingulate region bilaterally can cause akinetic mutism, a condition characterized by profound impairment of movement initiation.

In general, the disorders associated with dysfunction of the prefrontal cortex and corticobasal ganglia-thalamocortical circuits involve action rather than of perception or sensation. These disturbances are associated both with either intensified action (impulsivity) and flattened action (apathy). Obsessive-compulsive behavior can be viewed as a form of hyperactivity. The disturbances of mood associated with circuit dysfunction are believed to span the extremes of mania and depression. Both dopamine and serotonin, two biogenic amines that modulate neuronal activity within the circuits, are important to depression (Chapter 61).

These observations suggest that the neural mechanisms underlying complex behavioral disorders might be analogous to the dysfunctions of the motor circuits described in this chapter. Thus, schizophrenia might be viewed as a "Parkinson disease of thought." By this analogy, schizophrenic symptoms would arise from disordered modulation of prefrontal circuits. Other cognitive and emotional symptoms may similarly be equivalents of motor disturbances such as tremor, dyskinesia, and rigidity.

An Overall View

In 1949 Linus Pauling revolutionized medical thinking by coining the term "molecular disease." He and his collaborators observed the altered electrophoretic mobility of hemoglobin S and reasoned that sickle cell anemia, a disease known to be genetic, could be explained by a mutation of a gene for a specific protein. A decade later Vernon Ingram showed that this alteration in charge occurs in the amino acid sequence of hemoglobin S, where a glutamic acid residue is replaced by a valine. This change from a single negatively charged residue in normal hemoglobin to a neutral one explains the altered molecular properties of hemoglobin S, and these in turn account for the intermolecular differences and disordered cell stacking observed in sickled red cells. Thus, a single molecular change is fundamental to understanding the patient's pathology, symptoms, and prognosis.

While the explanation for other diseases may not be as simple, it is a fundamental principle of modern medicine that every disorder has a molecular basis. Research in Parkinson disease and myasthenia gravis first made the medical community realize that particular components of chemical synapses can be specific targets for disease. In myasthenia gravis the molecular target is the acetylcholine receptor. In the disorders of the basal ganglia some components of the synthesis, packaging, or turnover of dopamine and serotonin are altered. The causes of the pathological alterations of these loci, whether genetic, infectious, toxic, or degenerative, are not yet known. Although we have identified the mutant gene for Huntington disease, as yet we have no idea about the function of the protein that the wild-type gene encodes. It is clear that rational treatment for diseases of transmitter metabolism requires a good understanding of synaptic transmission in the affected pathways.

Mahlon R. DeLong

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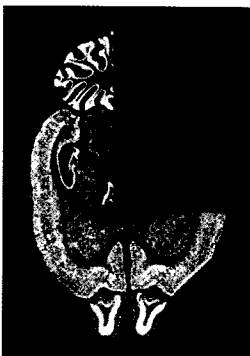
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Cover image: The autoradiograph illustrates the widespread localization of mRNA encoding the NMDA-R1 receptor subtype determined by in situ hybridization. Areas of high NMDA receptor expression are shown as light regions in this horizontal section of an adult rat brain.

From Moriyoshi K, Masu M, Ishi T, Shigemoto R, Mizuno N, Nakanishi S. 1991. Molecular cloning and characterization of the rat NMDA receptor. *Nature* 354:31-37.