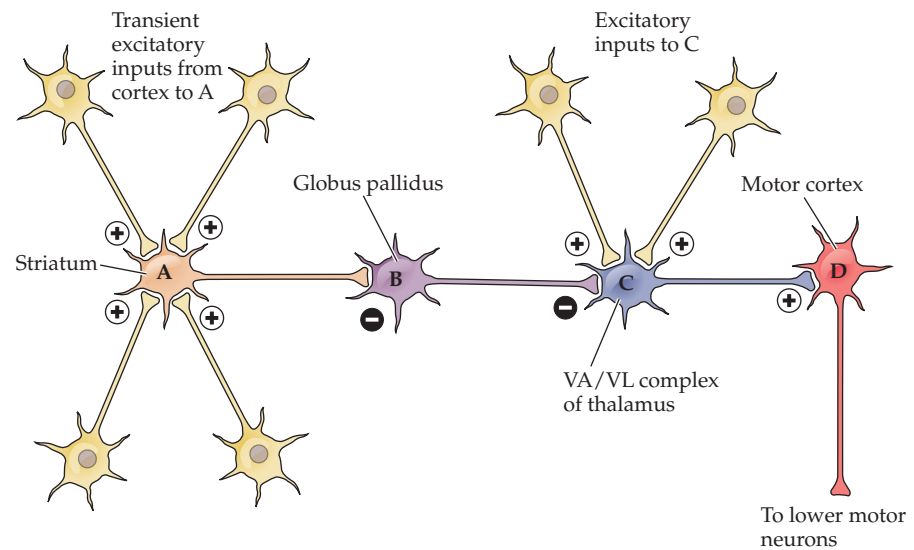
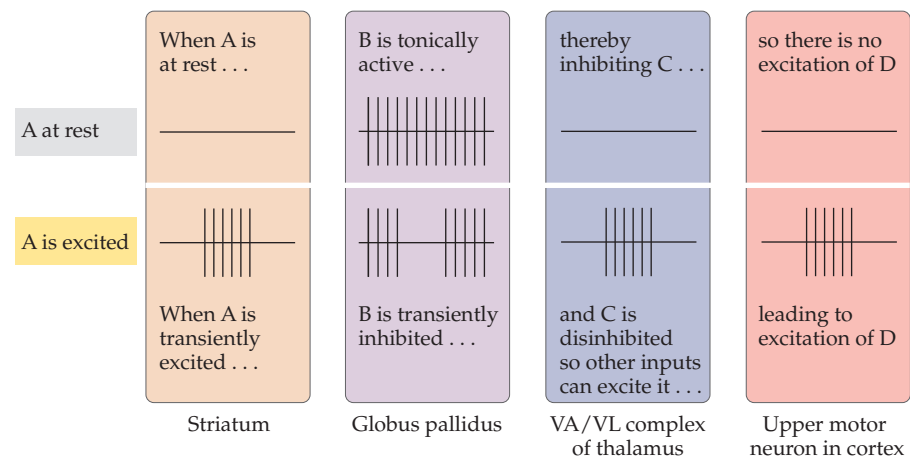


FIGURE 18.5 A chain of nerve cells arranged in a disinhibitory circuit. At the top is a diagram of the connections between neurons A and B and an excitatory neuron, C, which activates D, an upper motor neuron in the cortex. The colored boxes below diagram the pattern of action potential activity in A, B, C, and D both when neuron A is at rest and when neuron A fires transiently as a result of excitatory input. Such circuits are central to the gating operations of the basal ganglia.



the substantia nigra pars reticulata is part of the output circuitry of the basal ganglia. Instead of projecting to the ventral anterior and ventral lateral nuclei of the thalamus, however, it sends axons mainly to the deep layers of the superior colliculus. The upper motor neurons in these layers command the rapid, orienting movements of the eyes called *saccades* (see Chapter 20). When the eyes are fixating a visual target, these upper motor neurons are tonically inhibited by the spontaneously active reticulata cells, thus preventing unwanted saccades. Shortly before the onset of a saccade, the tonic discharge rate of the reticulata neurons is sharply reduced by input from the GABAergic medium spiny neurons of the caudate, which have been activated by signals from the cortex. The subsequent reduction in the tonic discharge from reticulata neurons disinhibits the upper motor neurons of the superior colliculus, allowing them to generate the bursts of action potentials that command the saccade. Thus, the projections from the substantia nigra pars reticulata to the upper motor neurons act as a physiological “gate” that must be “opened” to allow either sensory or other higher order signals from cognitive centers to activate the upper motor neurons and initiate a saccade.

This brief account of the genesis of saccadic eye movements provides an important illustration of the principal functions of the basal ganglia in motor control: The basal ganglia facilitate the *initiation* of motor programs that express movement and the *suppression* of competing or non-synergistic motor programs that would otherwise interfere with the expression of sensory-driven or goal-directed behavior (see Box 18A). Chapter 20 provides a more complete account of sensorimotor integration and the origins of eye movements; the remaining sections of this chapter will explain how the intrinsic and accessory circuits of the basal ganglia accomplish these principal



functions in motor control and why disease that afflicts elements of these circuits can lead to devastating movement disorders.

Circuits within the Basal Ganglia System

The projections from the medium spiny neurons of the caudate and putamen to the internal segment of the globus pallidus and, as illustrated in Figure 18.4, serve to release from tonic inhibition the thalamic neurons that drive cortical circuits of upper motor neurons. Thus, this direct pathway provides a means for the basal ganglia to facilitate the initiation of volitional movement. Figure 18.7A summarizes the functional organization of the direct pathway.

Additional circuits of the basal ganglia constitute a so-called *indirect pathway* linking the caudate and putamen to the internal segment of the globus pallidus (Figure 18.7B). This second pathway increases the level of tonic inhibition mediated by the projection neurons of the internal segment (and the substantia nigra pars reticulata). In the indirect pathway, a distinct population of medium spiny neurons

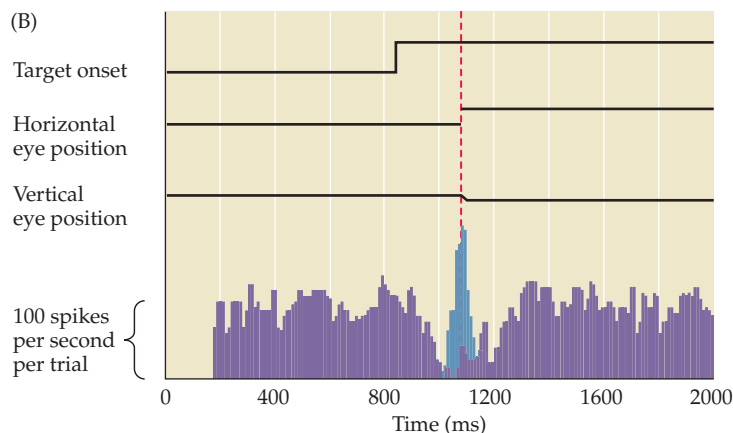
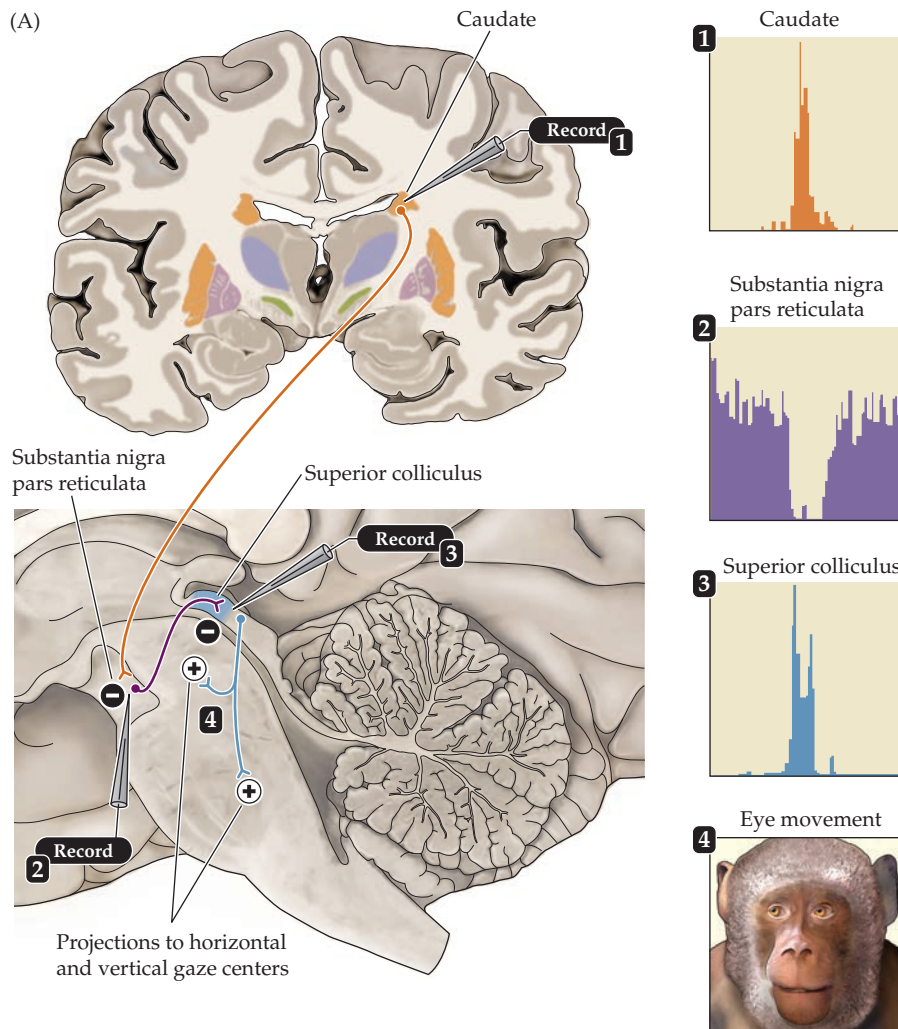


FIGURE 18.6 The role of basal ganglia disinhibition in the generation of saccadic eye movements. (A) Medium spiny cells in the caudate respond with a transient burst of action potentials to an excitatory input from the cerebral cortex (1). Spiny cells inhibit tonically active GABAergic cells in the substantia nigra pars reticulata (2). As a result, the upper motor neurons in the deep layers of the superior colliculus are no longer tonically inhibited and can generate the bursts of action potentials that command a saccade (3, 4). (B) The graph shows the temporal relationship between inhibition in the substantia nigra pars reticulata (purple) and disinhibition in the superior colliculus (light blue) preceding a saccade to a visual target. (A1 after Hikosaka and Wurtz, 1986; A2–3, B after Hikosaka and Wurtz, 1983.)

projects to the lateral division of the globus pallidus, called the **external segment**. The external segment of the globus pallidus sends projections to both the adjacent internal segment and the **subthalamic nucleus** of the ventral thalamus (see Figure 18.1). The subthalamic nucleus also receives excitatory projections from the cerebral cortex (sometimes referred to as the *hyperdirect pathway*) that work synergistically with the disinhibitory effect mediated by the projections from the external segment of the globus pallidus. In turn, the subthalamic nucleus projects diffusely back to the internal segment of the globus pallidus and to the substantia nigra pars reticulata. Thus, the indirect pathway feeds back onto the output nuclei that provide the means by which the basal ganglia gain access to upper motor neurons. But as will become clear in the following discussion, the *indirect pathway antagonizes the activity of the direct pathway*; together, they function to open or shut the physiological gates that initiate and terminate movements.

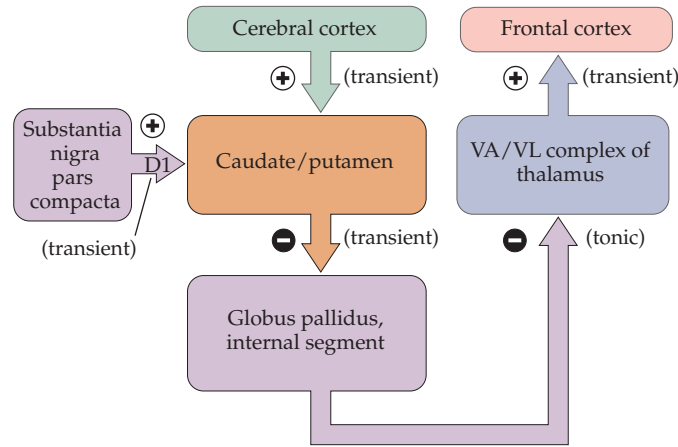
The indirect pathway through the basal ganglia modulates the disinhibitory actions of the direct pathway. The subthalamic nucleus neurons that project to the internal segment of the globus pallidus and substantia nigra pars reticulata use glutamate as their neurotransmitter and are excitatory. When signals from the cortex activate the indirect pathway, the striatal medium spiny neurons discharge and inhibit the tonically active GABAergic neurons of the external globus pallidus. As a result of the removal of this tonic inhibition and the simultaneous arrival of excitatory inputs from the cerebral cortex, the subthalamic cells become more active, and by virtue of their excitatory synapses with the GABAergic cells of the internal segment of the globus pallidus and substantia nigra pars reticulata, they increase the inhibitory outflow of the basal ganglia. In contrast to the direct pathway, which, when activated, releases thalamocortical and collicular circuits from tonic inhibition, the indirect pathway has the net effect of increasing the inhibitory influences of the basal ganglia. The balance of activity mediated by the

FIGURE 18.7 Disinhibition in the direct and indirect pathways through the basal ganglia. (A) In the direct pathway, transiently inhibitory neurons in the caudate and putamen project to tonically active inhibitory neurons in the *internal* segment of the globus pallidus, which project in turn to the VA/VL complex of the thalamus. Transiently excitatory inputs to the caudate and putamen from the cortex and substantia nigra are also shown, as is the transiently excitatory input from the thalamus back to the cortex. (B) In the indirect pathway (shaded), transiently active inhibitory neurons from the caudate and putamen project to tonically active inhibitory neurons of the *external* segment of the globus pallidus. Note that the influence of nigral dopaminergic input to neurons in the indirect pathway is inhibitory. The globus pallidus (external segment) neurons project to the subthalamic nucleus, which also receives a strong excitatory input from the cortex. The subthalamic nucleus in turn projects to the globus pallidus (internal segment), where its transiently excitatory drive acts to oppose the disinhibitory action of the direct pathway. In this way, the indirect pathway modulates the effects of the direct pathway.

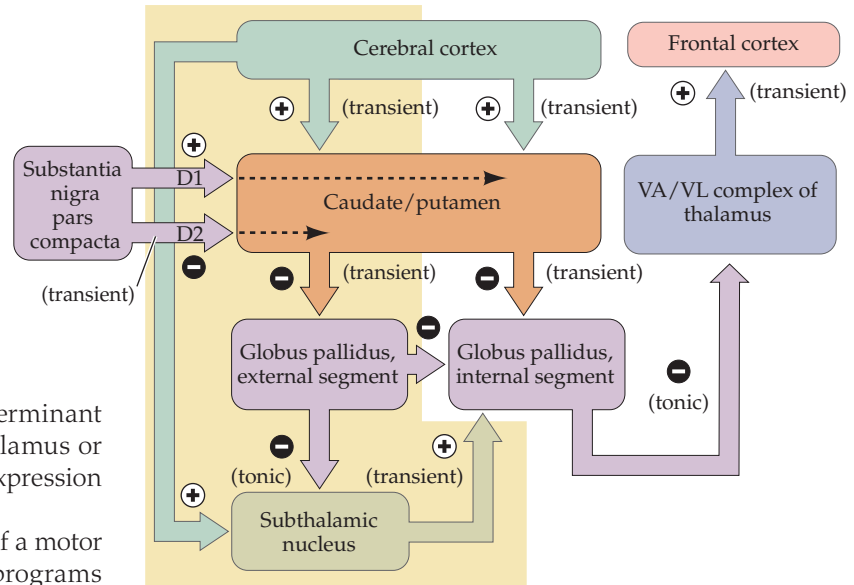
direct and indirect pathways is the principal determinant of whether output from the pallidum to the thalamus or superior colliculus will select and facilitate the expression of the intended motor program.

These circuits not only facilitate the selection of a motor program; they also suppress competing motor programs that could interfere with the expression of sensory-driven or goal-oriented behavior. A concept called *focused selection* has increased understanding of this antagonistic interaction. According to this concept, the direct and indirect pathways are functionally organized in a center-surround fashion within the output nuclei of the basal ganglia (Figure 18.8). The influence of the direct pathway is tightly focused on particular functional units in the internal segment of the globus pallidus (and the substantia nigra pars reticulata), whereas the influence of the indirect pathway is much more diffuse, covering a broader range of functional units. Recall that individual axons from the striatum to the internal segment of the globus pallidus tend to synapse densely on single pallidal neurons (despite making sparse contacts on numerous pallidal cells); this provides a means for the direct pathway to focus its input on a “central” functional unit at the output stage of the basal ganglia. In contrast, afferents from the subthalamic nucleus are distributed much more evenly throughout the internal segment, providing a means for the indirect pathway to suppress the activity of a broader “surrounding” set of functional units. Accordingly, when basal ganglia systems receive and process cortical signals, the suppression of competing or recently activated motor

(A) Direct pathway



(B) Indirect and direct pathways



programs is reinforced, and simultaneously, the activation of the particular thalamocortical (or collicular) circuits that underlie the intended movement is facilitated. Recent studies in rodent models using optogenetic methods to selectively activate or inhibit the striatal neurons giving rise to the direct and indirect pathways indicate that co-activation of both sets of striatal neurons is important for the smooth initiation and execution of new motor actions.

Precisely how these complex circuits of the basal ganglia interact to assist upper motor neuron systems in the execution of volitional behavior remains poorly understood, and this simplified description will undoubtedly be subject to revision as further anatomical and physiological details become available. Nevertheless, this account serves as a useful model for understanding the architecture and function of neural systems that achieve fine control of their output by an interplay between neural excitation and inhibition (recall, for example, the center-surround antagonism of ganglion cell receptive fields in the retina; see Chapter 11). Furthermore, this model provides an instructive framework for understanding disorders of movement that result

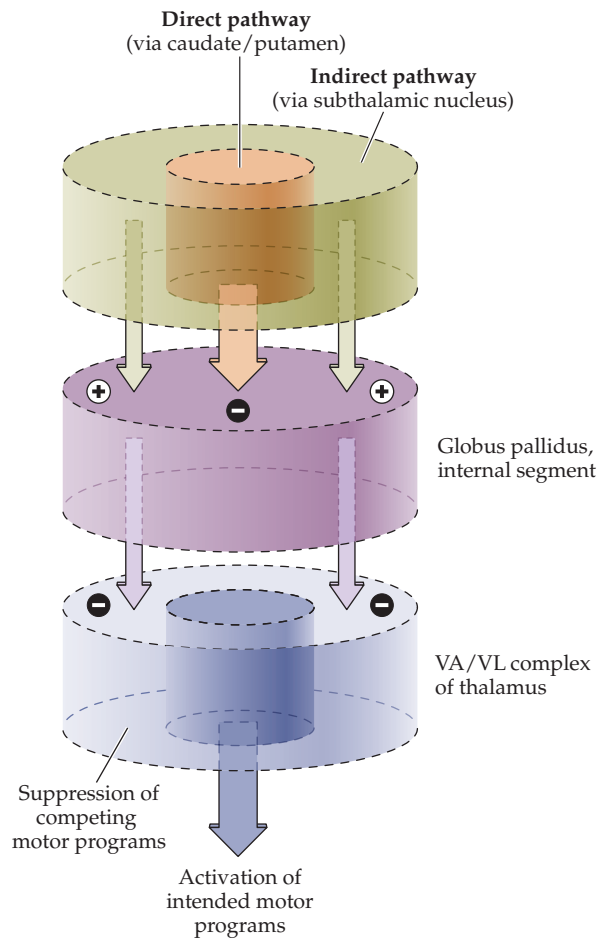


FIGURE 18.8 Center-surround functional organization of the direct and indirect pathways. Integration of cortical input by the striatum leads to the activation of the direct and indirect pathways. With activation of the indirect pathway, neurons in a “surround” region of the internal segment of the globus pallidus are driven by excitatory inputs from the subthalamic nucleus; this reinforces the suppression of a broad set of competing motor programs. Simultaneously, activation of the direct pathway leads to the focal inhibition of a more restricted “center” cluster of neurons in the internal segment; this in turn results in the disinhibition (bottom arrow) of the VA/VL complex and the expression of the intended motor program.

from injury or disease that afflicts one or more components of the basal ganglia system (see below).

Dopamine Modulates Basal Ganglia Circuits

As described earlier in this chapter, an important circuit within the basal ganglia system involves the dopaminergic cells in the pars compacta subdivision of the substantia nigra. Although this circuit derives from a relatively small pool of dopaminergic neurons, it exerts a profound influence over the integration of cortical input in the striatum. The medium spiny neurons of the striatum (especially from striosome compartments) project directly to the substantia nigra pars compacta, which in turn sends widespread dopaminergic projections back to the medium spiny neurons. The effects of dopamine on the spiny neurons are complex;

they illustrate the principle that the action of a neurotransmitter is determined by the types of receptors expressed in postsynaptic neurons and by the downstream signaling pathways to which the receptors are linked (see Chapter 6). In this case, the same nigral neurons can provide excitatory inputs to the spiny cells that project to the internal globus pallidus (the direct pathway) and inhibitory inputs to the spiny cells that project to the external globus pallidus (the indirect pathway). This duality is achieved by the differential expression of two types of dopamine receptors—types D1 and D2—by the medium spiny neurons.

Both D1 and D2 dopamine receptors are members of the 7-transmembrane G-protein-coupled family of cell surface receptors. The major functional difference between them is that the D1 receptors mediate the activation of G-proteins that *increase* cAMP, while D2 receptors act through different G-proteins that *decrease* cAMP. For both types of receptors, the dopaminergic synapses on medium spiny neurons tend to be located on the shafts of the spines that receive synaptic input from the cerebral cortex. This arrangement suggests that dopamine exerts its effects on the spiny neurons by modulating their responses to cortical input, with D1 receptors positioned to enhance the excitatory input from cortex and D2 receptors positioned to suppress this excitation. Since the actions of the direct and indirect pathways on the output of the basal ganglia are antagonistic, these different influences of dopamine on medium spiny neurons have the same effects—a decrease in the inhibitory outflow of the basal ganglia, and the consequent release of projections from the thalamus to the frontal cortex or projections from the superior colliculus to circuits of lower motor neurons in the brainstem.

This dopaminergic input to the striatum may contribute to reward-related modulation of behavior. For example, in monkeys the latencies of saccades toward a target are shorter when the goal of the movement is associated with a larger reward. This effect is eliminated by caudate injections of the dopamine D1 receptor antagonist and enhanced by injections in the same site of the D2 receptor antagonist. These results suggest that the influence of motivation on motor performance may be modulated by circuits in the basal ganglia that recruit dopaminergic input from the midbrain. The role of dopamine in motivated behavior and the deleterious impact of addictive substances on dopaminergic modulation of basal ganglia function will be discussed in more detail in Chapter 31.

Hypokinetic Movement Disorders

The modulatory influences of this dopaminergic circuit may also help explain many of the manifestations of basal ganglia disorders, especially those characterized by decreased voluntary movement (*hypokinesia*). For example, **Parkinson's disease** is the second most common degenerative disease of the nervous system (Alzheimer's disease

being the leader). Described by James Parkinson in 1817, this disorder is characterized by tremor at rest, slowness of movement (*bradykinesia*), rigidity of the extremities and neck, and minimal facial expressions. Walking entails short steps, stooped posture, and a paucity of associated movements such as arm swinging. In some individuals, these abnormalities of motor function are associated with dementia. Following a gradual onset, typically between the ages of 50 and 70, the disease progresses slowly and culminates in death some 10 to 20 years later.

Unlike in other neurodegenerative diseases (such as Alzheimer's disease and amyotrophic lateral sclerosis), in Parkinson's disease the spatial distribution of the degenerating neurons is largely restricted to the substantia nigra pars compacta. Thus, idiopathic Parkinson's disease is caused by the loss of the nigrostriatal dopaminergic neurons (Figure 18.9A). Although the cause of the progressive deterioration of these dopaminergic neurons is not known, genetic investigations provide clues to the etiology and pathogenesis. Whereas the majority of cases of Parkinson's disease are sporadic, there may be specific forms of susceptibility genes that confer increased risk of acquiring the disease, just as the e4 allele of the *ApoE* gene increases the risk of Alzheimer's disease (see Chapter 30). Familial forms of Parkinson's caused

by single gene mutations account for fewer than 10% of all cases; identification of these rare genes, however, is likely to provide insight into molecular pathways that may underlie the disease. Mutations of three distinct genes— α -synuclein, *Parkin*, and *DJ-1*—have been implicated in rare forms of Parkinson's disease. Their identification provides an opportunity to generate transgenic mice carrying the mutant form of the human gene, potentially providing an animal model in which the pathogenesis can usefully be elucidated and therapies can be tested.

As described above, activation of the nigrostriatal projection leads to opposite but synergistic effects on the direct and indirect pathways: The release of dopamine in the striatum increases the responsiveness of the direct pathway to corticostriatal input (a D1 effect) while decreasing the responsiveness of the indirect pathway (a D2 effect). Typically, both of these dopaminergic effects serve to decrease the inhibitory outflow of the basal ganglia and thus to increase the excitability of upper motor neurons. In contrast, when the dopaminergic cells of the pars compacta are destroyed, as occurs in Parkinson's disease, the inhibitory outflow of the basal ganglia is abnormally high, and timely thalamic activation of upper motor neurons in the motor cortex is therefore less likely (Figure 18.9B).

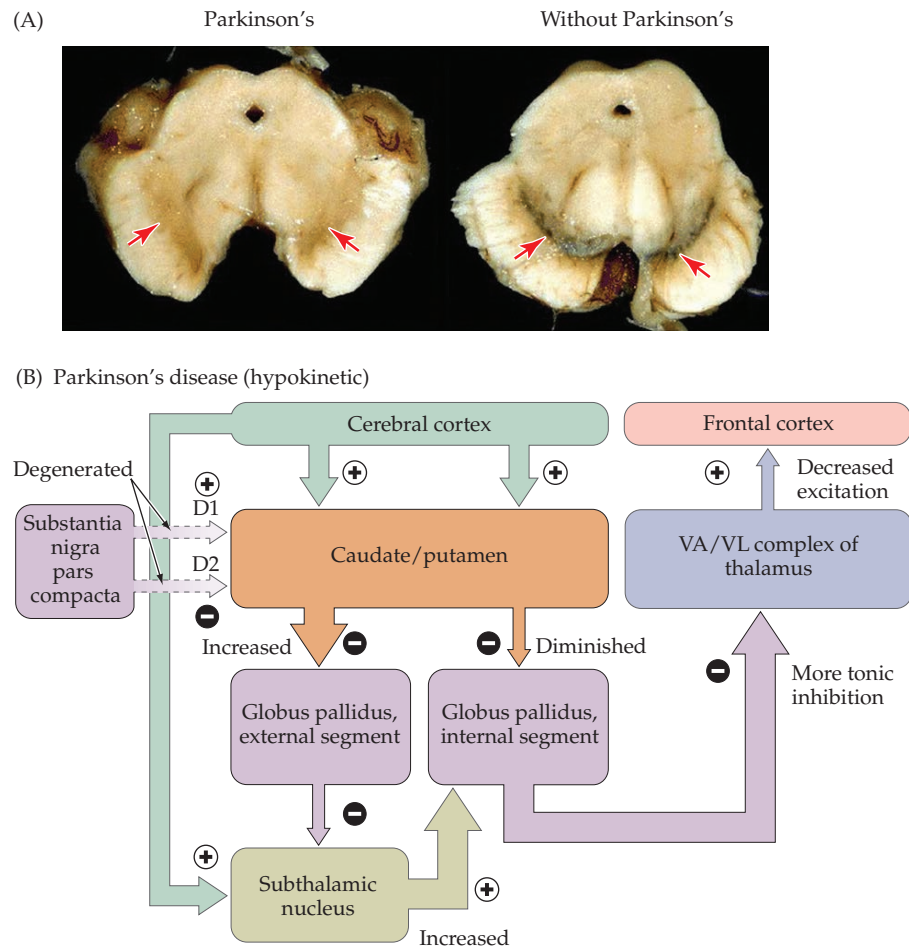


FIGURE 18.9 Degeneration of dopaminergic neurons reduces voluntary movement in Parkinson's disease.

(A) In the midbrain of an individual with Parkinson's disease, the substantia nigra (pigmented area) is largely absent in the region above the cerebral peduncles. The midbrain from an individual without Parkinson's disease shows intact substantia nigra (cf. regions indicated with red arrows). (B) In Parkinson's disease, the dopaminergic inputs provided by the substantia nigra pars compacta are diminished (dashed arrows), making it more difficult to generate the transient inhibition from the caudate and putamen. The result of this change in the direct pathway is to sustain or increase the tonic inhibition from the internal segment of the globus pallidus to the thalamus (thicker arrow than corresponding arrow in Figure 18.7B), making thalamic excitation of the motor cortex less likely (thinner arrow from thalamus to frontal cortex). (© 2010, European Association for Predictive, Preventive and Personalised Medicine; B after DeLong, 1990.)

In fact, many of the symptoms seen in Parkinson's disease and other hypokinetic movement disorders reflect a failure of the disinhibition normally mediated by the basal ganglia. Thus, individuals with Parkinson's tend to have diminished facial expressions and reduced amplitude of movement, such as diminished arm swinging during walking. Indeed, any movement is difficult to initiate and, once initiated, is often difficult to terminate. Disruption of the same circuits also increases the discharge rate of the inhibitory cells in the substantia nigra pars reticulata. The resulting increase in tonic inhibition reduces the excitability of upper motor neurons in the superior colliculus, thus reducing the frequency and amplitude of saccades.

Support for this explanation of hypokinetic movement disorders such as Parkinson's disease comes from studies of

monkeys in which degeneration of the dopaminergic cells of the substantia nigra pars compacta has been induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Monkeys (or humans) exposed to MPTP develop symptoms that are very similar to those of individuals with Parkinson's disease. Furthermore, a second lesion placed in the subthalamic nucleus results in significant improvement in the ability of these animals to initiate movement, as would be expected based on the circuitry of the indirect pathway (see Figure 18.9B). In humans, rather than creating lesions, neurologists and neurosurgeons are now increasingly using deep brain stimulation to normalize permissive patterns of neural activity in basal ganglia circuits, with the subthalamic nucleus emerging as a strategic target for neuromodulation (Clinical Applications).

CLINICAL APPLICATIONS

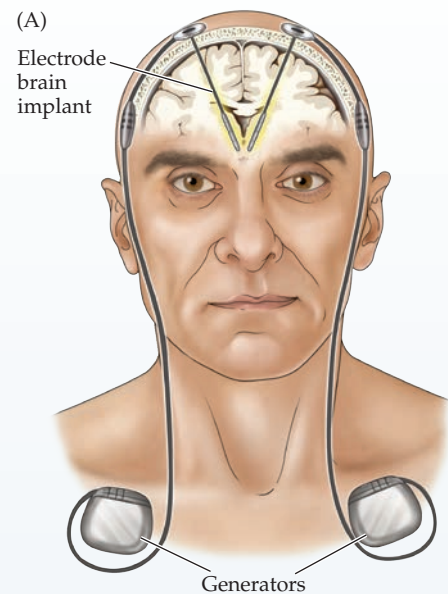
Deep Brain Stimulation

Since the seminal demonstration by G. Fritsch and E. Hitzig in the nineteenth century that bodily movements could be induced when electrical currents were applied to cerebral tissue (in this case, motor cortex), clinicians have considered the possibility that certain neurological disorders affecting volitional movement could be treated with the application of acute or chronic electrical stimulation to key motor centers in the brain. However, it was not until well after the internally implanted cardiac pacemaker was introduced in the 1960s that technological advances made possible the implantation of a comparable device for the focal stimulation of brain structures. Such devices were introduced in the 1990s for the treatment of movement disorders, with their targets being components of the basal ganglia and thalamus located deep in the forebrain; hence the common term for this intervention, *deep brain stimulation*.

Prior to the 1990s, the treatment options for individuals with movement disorders were limited to pharmacological intervention, physical therapy, and in the most intractable cases, neurosurgical ablation of sites in the basal ganglia and thalamus that gate the initiation of movement. For intractable cases, the introduction of deep brain stimulation provided an obviously welcome alternative to the permanent destruction of brain structure. Currently, a combination of deep brain stimulation and pharmacological intervention improves the health status of a significant number of individ-

uals (more than would the use of just one approach).

Deep brain stimulation entails the implantation of battery-powered generator units, usually near the clavicles. These units produce electrical discharges that are passed through subcutaneous wires to electrodes implanted bilaterally into the brain (Figure A). (Recall that, with the exception of medial divisions of the premotor cortex, all of the cortical and subcortical neural circuitry in the forebrain that governs the activity of upper motor neurons is organized unilaterally; therefore, bilateral deep brain stimulation is necessary to achieve symmetrical results.) The placement of the electrodes requires careful stereotaxic surgery combined with radiological imaging of the patient's brain and electrophysiological recordings of spontaneous and movement-related neuronal activity. The neuronal recordings are essential so that the neurosurgical team can recognize by sight and sound the characteristic discharge patterns of neurons in different nuclei of the basal ganglia and thalamus. This is done by displaying action potential waveforms on oscilloscopes and audio and computer monitors (see Figure 18.5). Once the target structures are localized, stimulation is tested to determine whether the desired clinical effect can be observed. After the patient has recovered from the implantation procedure, the generator units are activated and the parameters of stimulation are fine-tuned as various combinations of pulse widths, current amplitudes, and



(A) Illustration of a patient following implantation of a device for deep brain stimulation.

temporal patterns of pulse trains are employed and modified as needed.

A careful consideration of Figures 18.9B and 18.10B suggests several possible target sites of deep brain stimulation for individuals with hypokinetic or hyperkinetic movement disorders. In both diagnostic categories, neural activity in motor nuclei of the thalamus is abnormal; accordingly, the VA/VL complex of

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(B)

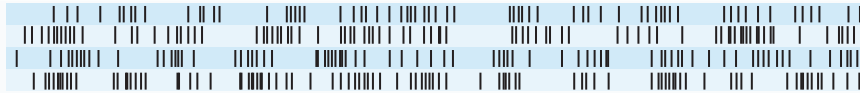
Prestimulation



During stimulation



Poststimulation



(B) Raster plots of action potentials recorded from a neuron in the internal segment of the globus pallidus in an awake rhesus monkey rendered Parkinsonian by the systemic administration of MPTP; each row lasts 1 s. The endogenous pattern of discharge is marked by irregular clusters of burst activity (top panel). Within seconds of the onset of subthalamic nucleus stimulation, the Parkinsonian symptoms abated, and the discharge of the pallidal neuron became much more regular (middle panel). (From Hashimoto et al., 2003.)

the thalamus is an appropriate target. However, abnormal activity in the thalamus is often the consequence of disturbances within the basal ganglia itself, and it is arguably more desirable to manipulate the influence of the basal ganglia on thalamocortical circuits rather than directly altering activity in upper motor neuronal circuits by exogenous electrical stimulation. Thus, the two most common sites for deep brain stimulation in individuals with movement disorders are the internal segment of the globus pallidus and the subthalamic nucleus. Regardless of whether the neurological disorder to be rectified is hypokinetic (manifested as difficulty in expression of movement) or hyperkinetic (manifested as expression of unwanted movement), deep brain stimulation can be used to override intrinsic, pathological discharge patterns with stable and highly structured patterns of neural activity that

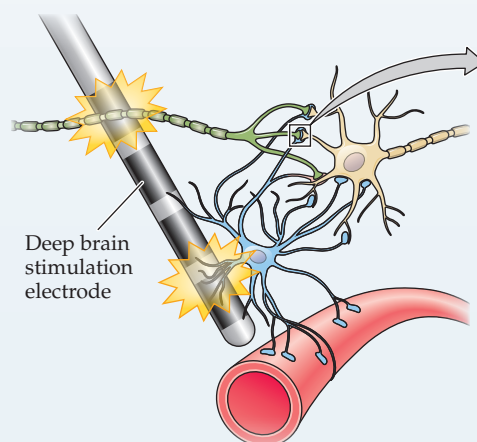
better facilitate the initiation and termination of volitional movement (Figure B).

Given the complexity of even a small volume of neural tissue (such as might be present near the tip of a stimulating electrode in the globus pallidus or subthalamic nucleus), it is not surprising that the exogenous induction of electrical currents can lead to complex patterns of activity and inactivity in the affected neural elements, as well as effects on non-neural elements (Figure C). Different intensities of deep brain stimulation may lead to the local release of neurotransmitters and neuromodulators. They may also lead to the generation of action potentials in afferent axons, neuronal cell bodies, efferent axons, and *fibers of passage* that originate elsewhere. However, the effects of electrical stimulation on certain intrinsic membrane properties, including voltage-dependent ionic conductances, may block the generation

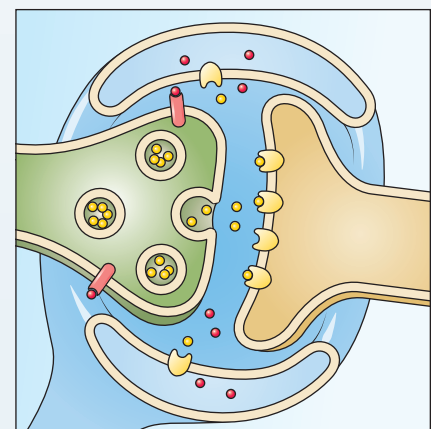
of action potentials, thus silencing the affected neurons. Ideally, the net effect of these diverse changes is the amelioration of abnormal network activity that hinders the normal operation of upper motor neurons.

Despite ongoing uncertainties regarding its mechanisms of action, deep brain stimulation has offered hope to thousands of individuals who suffer neurological dysfunction ranging from the movement disorders discussed here to related disorders of non-motor basal ganglia loops, such as Tourette syndrome, depression, and obsessive-compulsive disorder (see Box 18B). The fact that stimulation protocols are adjustable provides clinicians with an unprecedented ability to manipulate the activities and functions of basal ganglia circuits whose operations are crucial to the typical expression of thought, emotion, and motor behavior.

(C)



(C) Deep brain stimulation induces myriad effects in brain tissue, including the direct modulation of action potential generation (green axon) and synaptic transmission (inset), the direct modulation of the release of local substances from glial cells (blue cell) that modify synaptic plasticity (inset), and the indirect modulation (mediated by astrocytic end feet; see Appendix) of arteriole tone affecting local blood flow. (After McIntyre and Anderson, 2016.)



Other novel and promising therapeutic approaches include gene therapy and stem cell grafts. Gene therapy involves correcting a disease phenotype by introducing new genetic information into the affected organism. Although still in its infancy, this approach has the potential to revolutionize treatment of human disease. One such therapy proposed for Parkinson's disease would enhance release of dopamine in the caudate and putamen. In principle, this could be accomplished by implanting cells that have been genetically modified to express tyrosine hydroxylase, the enzyme that converts tyrosine to L-DOPA, which in turn is converted by a nearly ubiquitous decarboxylase into the neurotransmitter dopamine (see Figure 6.14). An alternative strategy involves "neural grafts" using stem cells. Stem cells are self-renewing, multipotent progenitors with broad developmental potential (see Chapters 22 and 26). This approach entails identifying and isolating stem cells, and identifying the growth factors needed to promote differentiation into the desired phenotype (i.e., dopaminergic neurons). The identification and isolation of multipotent mammalian stem cells has already been accomplished, and several factors likely to be important in differentiation of midbrain precursors into dopamine neurons have now been identified. Establishing the efficacy of this approach for individuals with Parkinson's disease would increase the possibility of its application to other neurodegenerative diseases.

Hyperkinetic Movement Disorders

Given the preceding discussion of how an overactive pallidum can suppress voluntary movement, it should not be surprising to learn that insufficient tonic output from the pallidum permits the expression of unwanted movement. Thus, knowledge of the architecture and neurophysiology of basal ganglia circuits also helps explain the motor abnormalities seen in *hyperkinetic* movement disorders, such as **Huntington's disease**.

In 1872, a physician named George Huntington described a group of patients seen by his father and grandfather in their practice in East Hampton, Long Island. The disease he defined, which became known as Huntington's disease (HD), is characterized by the gradual onset of defects in behavior, cognition, and movement beginning in the fourth and fifth decades of life. The disorder is inexorably progressive, resulting in death within 10 to 20 years. HD is inherited in an autosomal dominant pattern, a feature that has led to a much better understanding of its cause in molecular terms.

One of the more common inherited neurodegenerative diseases, HD usually presents as an alteration in mood (especially depression) or a change in personality that often takes the form of increased irritability, suspiciousness, and impulsive or eccentric behavior. Defects of memory and attention may also occur. The hallmark of

the disease, however, is a movement disorder consisting of rapid, jerky motions, with no clear purpose. These *choreiform* ("dancelike") movements may be confined to a finger or may involve a whole extremity, the facial musculature, or even the vocal apparatus. The movements themselves are involuntary, but the patient often incorporates them into apparently deliberate actions, presumably in an effort to obscure the problem. There is no weakness, ataxia, or deficit of sensory function.

A distinctive neuropathology is associated with these clinical manifestations: a profound but selective atrophy of the caudate and putamen, with some associated degeneration of the frontal and temporal cortices (Figure 18.10A). However, not all striatal neurons are equally susceptible, especially early in the course of disease. In patients with HD, medium spiny neurons that project to the external segment of the globus pallidus degenerate. In the absence of their normal inhibitory input from the spiny neurons, the external globus pallidus cells become abnormally active; this activity reduces in turn the excitatory output of the subthalamic nucleus to the internal segment of the globus pallidus, and the inhibitory outflow of the basal ganglia is reduced (Figure 18.10B). Without the restraining influence of the basal ganglia, upper motor neurons can be activated by inappropriate signals, resulting in the undesired ballistic (flailing or jerking) and choreiform movements that characterize the disease.

The availability of extensive HD pedigrees has allowed geneticists to decipher the molecular cause of this disease. HD was one of the first human diseases in which DNA polymorphisms were used to localize the mutant gene, which in 1983 was mapped to the short arm of chromosome 4. This discovery led to an intensive effort to identify the HD gene within this region by positional cloning. Ten years later, these efforts culminated in identification of the gene (named *Huntingtin*) responsible for the disease. The *Huntingtin* mutation is an unstable triplet repeat present within the coding region of the gene consisting of a DNA segment (CAG) that codes for the amino acid glutamine. In typical individuals, *Huntingtin* contains between 15 and 34 repeats, whereas in HD patients the gene contains from 42 to more than 66 repeats. The mechanism by which the increased number of polyglutamine repeats injures neurons is not clear. The leading hypothesis is that the increased numbers of glutamines alter protein folding, which somehow triggers a cascade of molecular events culminating in dysfunction and neuronal death.

Just as in Huntington's disease, imbalances in the fine control mechanism represented by the convergence of the direct and indirect pathways in the pallidum are apparent in other hyperkinetic movement disorders caused by diseases that affect primarily the subthalamic nucleus. The pathophysiology renders dysfunctional a source of excitatory input to the internal segment of the globus pallidus