CHAPTER

34

Basal Ganglia

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Two large subcortical motor systems send output via the thalamus to the cerebral cortex. These systems are the basal ganglia and the cerebellum. Although they appear to influence the same cortical areas, they project to the cortex via separate areas of the thalamus. Furthermore, the output of basal ganglia is inhibitory and that of the cerebellum is excitatory. We consider the basal ganglia in this chapter and the cerebellum in Chapter 35.

The basal ganglia are large subcortical structures comprising several interconnected nuclei in the forebrain, midbrain, and diencephalon (Fig. 34.1). It is generally agreed (see Box 34.1)[1-3] that the basal ganglia participate in the control of movement, for three reasons. First, most basal ganglia inputs and outputs are connected with motor areas. Second, the discharge of many basal ganglia neurons correlates with movement. Third, basal ganglia lesions can cause severe movement abnormalities. The connections and lesion effects of the basal ganglia suggest that these brain nuclei may also participate in some cognitive and emotional aspects of behavior. In this chapter, we concentrate on the motor functions of the basal ganglia (see Box 34.2). We begin with anatomy (structure) because it is anatomy that provides the infrastructure for physiology (function). Next we consider the activity of individual components of the basal ganglia during movement, and we describe the effect of placing a selective lesion in one component. Finally, we discuss some of the current hypotheses of basal ganglia motor function.

ANATOMY OF THE BASAL GANGLIA

The basal ganglia receive a broad spectrum of cortical inputs. The information conveyed to the basal ganglia is processed to produce a focused output to areas of the frontal lobes and brainstem that are involved in the planning and production of movement. As stated in the introduction, the basal ganglia output is inhibitory, which means that an increase in the basal ganglia output leads to a reduction in the activity of its targets. The fact that the basal ganglia output is inhibitory to other motor mechanisms is important to understanding its normal function.

The basal ganglia include the **striatum** (**caudate** and **putamen**), the **subthalamic nucleus,** the **globus pallidus** (internal and external segments) and the **substantia nigra** (**pars compacta** and **pars reticulata,** Fig. 34.2). At first glance, this anatomy may seem confusing. There are several component nuclei at different levels in the brain, and two of the nuclei (the substantia nigra and globus pallidus) are divided into functionally different components. Furthermore, the names of some structures are not the same in all mammals, and the names have changed over the years, so that an individual structure may have more than one name. However, with consistent use of modern terminology and a functional context in which to place the anatomy, it is easy to understand the organization of the basal ganglia.

Most inputs to the basal ganglia originate in the cerebral cortex and terminate in the striatum and subthalamic nucleus. There are no direct inputs from peripheral sensory or motor systems. The bulk of the output from the basal ganglia arises from the internal segment of the globus pallidus and the substantia nigra pars reticulata and projects to the thalamus and to an area in the brainstem. There are no direct outputs from the basal ganglia to spinal motor circuits.

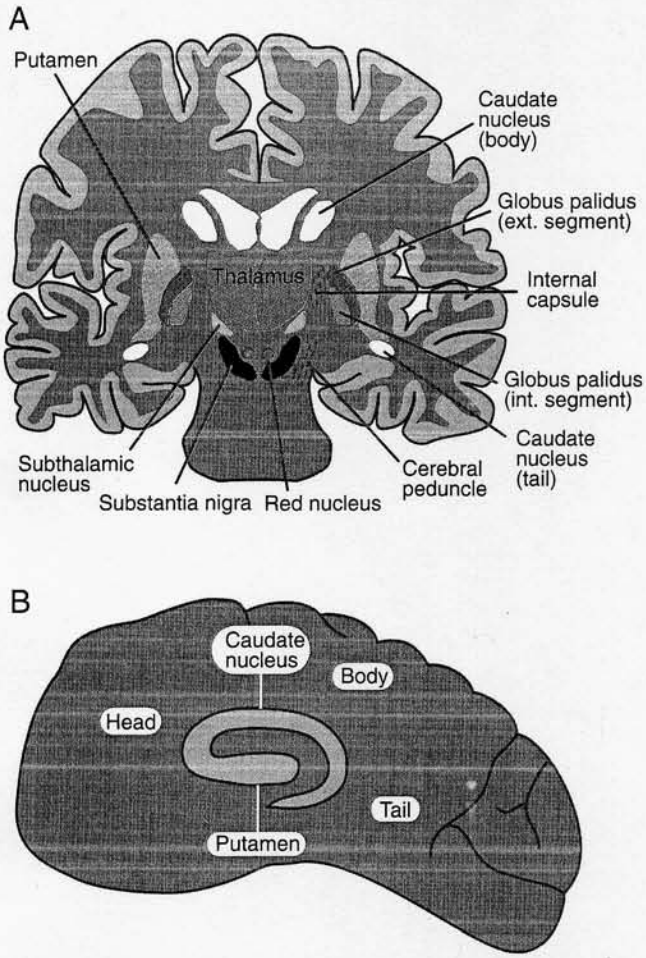

FIGURE 34.1 The location of the basal ganglia in the human brain. (A) Coronal section. (B) Sagittal section.

The Striatum Receives Most of the Inputs to the Basal Ganglia

The striatum is located in the forebrain and is composed of the caudate nucleus and putamen (the dorsal striatum or neostriatum).[4] Embryologically, the striatum develops from a basal region of the lateral telencephalic vesicle (see Chapter 2).[5] Its name is based on its striped appearance (Latin *stria*, furrow), which is due to the myelinated axons that pass through it. In rodents, the caudate and putamen are a single structure through which axons of the internal capsule course, but in carnivores and primates the caudate and putamen are separated by the internal capsule. The caudate and putamen receive input from the neocortex, and the size of these nuclei parallels the size of the neocortex throughout phylogeny.

Golgi staining and horseradish peroxidase labeling have revealed three major morphological types of neurons in the striatum,[6] which differ in the size of their somata and in the presence or absence of dendritic spines. By far the most numerous type is the medium spiny neuron[7] (Fig. 34.3).[8] These constitute 95% of striatal neurons and carry the output of the striatum to the globus pallidus (GP) and substantia nigra (SN). Medium spiny neurons have large dendritic trees that span 200–500 μm, and their extensive local axon collaterals may inhibit neighboring striatal neurons.[8] Although medium spiny neurons are morphologically homogeneous and use γ-aminobutyric acid (GABA) as one of their transmitters, they show considerable heterogeneity, as we shall see. The second type of striatal neuron, the large aspiny neuron, makes up 1–2% of the striatal population. These striatal interneurons are thought to use acetylcholine (ACh) as a neurotransmitter[9] and have extensive axon collaterals in the striatum that terminate on medium spiny neurons. The third type of neuron is the medium aspiny cell, which is thought to use somatostatin as a neurotransmitter.[10] (Neurotransmitters are discussed in detail in Chapter 8.)

The striatum receives excitatory input from all of the cerebral cortex with the exception of the primary auditory and visual cortex.[11] Cortical inputs use glutamate as a neurotransmitter and terminate largely on the heads of the dendritic spines of medium spiny neurons[12,13] (Fig. 34.4). The projection from the cerebral cortex to the striatum has a roughly topographical organization.[4] For example, the somatosensory and motor cortices project to the putamen, and the prefrontal cortex projects to the caudate.[14,15] Somatotopy is preserved within the somatosensory and motor projections,[16] which may provide a basis for the segregation of functionally different circuits in the basal ganglia[17] (Fig. 34.5).

Although somatotopy implies a certain degree of parallel organization in the corticostriatal projection, convergence and divergence also take place in this projection. The large dendritic fields of medium spiny neurons allow them to receive input from adjacent projections arising from different areas of the cortex.[18] Within the somatosensory and motor projections, inputs from more than one cortical area overlap,[19] and a single cortical area diverges to several striatal zones (Fig. 34.6).[18,19] Convergence and divergence provide an anatomical framework for the integration and transformation of information from several areas of the cerebral cortex.[20]

In addition to cortical inputs, medium spiny striatal neurons receive a number of other inputs, including excitatory and presumed glutamatergic inputs from the centromedian and parafascicular nuclei of the thalamus[21,22]; cholinergic inputs from large aspiny neurons[23]; inputs from adjacent medium spiny striatal neurons using GABA, substance P, and enkephalin[24]; and

BOX 34.1

THE CONCEPT OF THE EXTRAPYRAMIDAL MOTOR SYSTEM

Participation of the basal ganglia in normal motor control is an idea that dates back to the early part of the century. The British neurologist S. A. Kinnier Wilson described a disease whose symptoms included muscular rigidity, tremor, and weakness and was associated with pathological changes in the liver and the putamen (hepatolenticular degeneration).[1] Wilson noted that several symptoms of damage to the corticospinal tracts were not present in this disease, which led him to postulate that the motor abnormalities were due to disease of another motor system that functions independently of the pyramidal (corticospinal) motor system. He further postulated that the basal ganglia (striatum and globus pallidus) were the major constituents of this other motor system. In later writing, Wilson developed a view of the two motor systems, the phylogenetically old "extrapyramidal" system and the phylogenetically new pyramidal system.[2] He thought that the extrapyramidal system has an automatic, postural, and static function that is minimally modifiable, while the pyramidal system has a voluntary, phasic function that can be modified.

Wilson and others thought that the output of the basal ganglia went directly to the spinal cord. In the 1960s, however, more modern anatomical techniques showed that the bulk of the basal ganglia output projects via the thalamus to motor cortical areas.[3] In this sense, the basal ganglia output is prepyramidal, not extrapyramidal. With the developing model of initiation of movement by the basal ganglia, the prepyramidal function was emphasized as the most important aspect of basal ganglia output. More recently, the injection of fluorescent dyes has shown that the vast majority of neurons in the GPi branch and project to both the thalamus and the brainstem.[43] Hence, the basal ganglia can be considered both prepyramidal and extrapyramidal. Although we now know that the basal ganglia can act through the pyramidal system and that there are many extrapyramidal motor systems that project to the spinal cord independently of the pyramidal tract, the phase "extrapyramidal motor system" is still used to refer to the basal ganglia and to disorders that result from basal ganglia damage.

BOX 34.2

THE VENTRAL SYSTEM OF THE BASAL GANGLIA

Some nuclei in the brain historically have not been included in the basal ganglia but are analogous to the traditional components. These nuclei lie ventral to the neostriatum and globus pallidus and are called the ventral striatum (nucleus accumbens and olfactory tubercle) and the ventral pallidum. The ventral striatum receives input from the limbic and olfactory areas of the cortex, including the amygdala and hippocampus. Like the neostriatum, the ventral striatum receives a dopaminergic input, but it is from the ventral tegmental area (VTA), which lies medial to the substantia nigra. The ventral striatum sends a projection back to the VTA and to the adjacent SNpr. The ventral pallidum is analogous to both the GPe and GPi. It receives input from the ventral striatum and possibly from the STN, but unlike the globus pallidus, it also receives direct input from the amygdala. The output of the ventral pallidum projects to the dorsomedial nucleus of the thalamus (DM), and from there to the limbic area of the cortex. By virtue of its inputs and outputs, the ventral system is closely linked to the limbic system. This linkage suggests that the ventral system may be involved to some degree in motivation and emotion. The exact nature of this role is unclear, but it may be analogous to the motor role of the basal ganglia, with the inhibitory output of the ventral pallidum acting to suppress or select potentially competing limbic mechanisms.

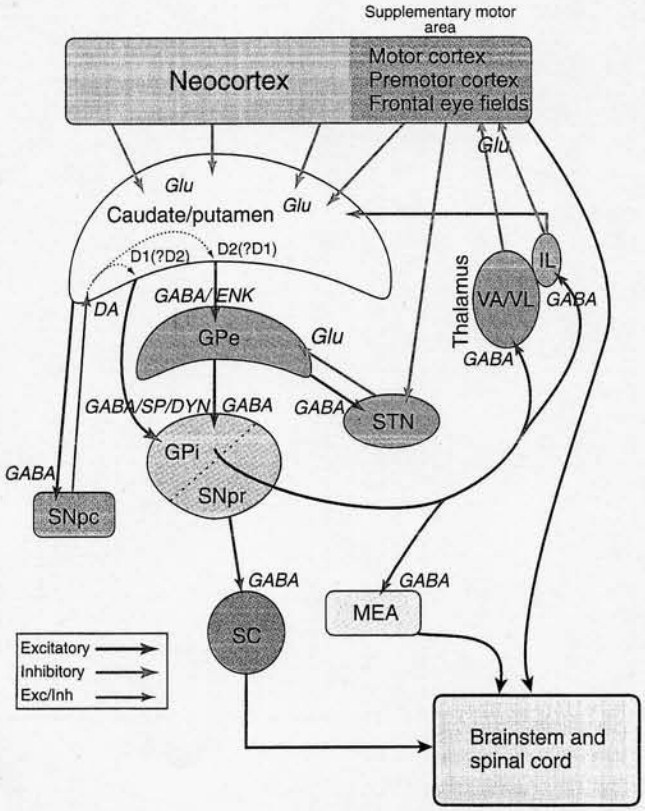

FIGURE 34.2 Schematic drawing of the basal ganglia circuitry. Excitatory connections are indicated with red arrows and inhibitory connections with green arrows. The dopamine-containing connection from the substantia nigra pars compacta (SNpc) is both excitatory and inhibitory, depending on the postsynaptic receptor. Structural abbreviations: GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; IL, intralaminar thalamic nuclei; MEA, midbrain extrapyramidal area; SC, superior colliculus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus. Neurotransmitter abbreviations: DA, dopamine; D1 and D2, dopamine receptor types 1 and 2; DYN, dynorphin; ENK, enkephalin; GABA, γ-aminobutyric acid; Glu, glutamate; SP, substance P; VA/VL, ventral anterior and ventral lateral nuclei of the thalamus.

dopaminergic inputs from the substantia nigra pars compacta (SNpc).[4]

The dopaminergic input to medium spiny neurons is of particular interest because of its role in Parkinson disease, which we discuss later in the chapter. These inputs terminate largely on the shafts of dendritic spines (see Fig. 34.4),[13] putting them in a position to modulate transmission from the cerebral cortex to the striatum. The action of dopamine on striatal neurons depends on which of the five types of G-protein-coupled dopamine receptors are involved. D1 and D5 receptors stimulate adenylate cyclase activity and may potentiate the effect of cortical input to striatal neurons. D2, D3, and D4 receptors inhibit adenylate cyclase activity and may have the opposite effect on cortical input.[25]

Medium spiny neurons contain the inhibitory neurotransmitter GABA as well as various peptide neurotransmitters.[24,26] On the basis of the particular peptide neurotransmitters they contain and the type of dopamine receptor they express, medium spiny neurons can be divided into two populations. One population contains dynorphin and substance P and primarily expresses D1 receptors. These neurons send axons directly to the internal segment of the globus pallidus (GPi) and to the substantia nigra pars reticulata

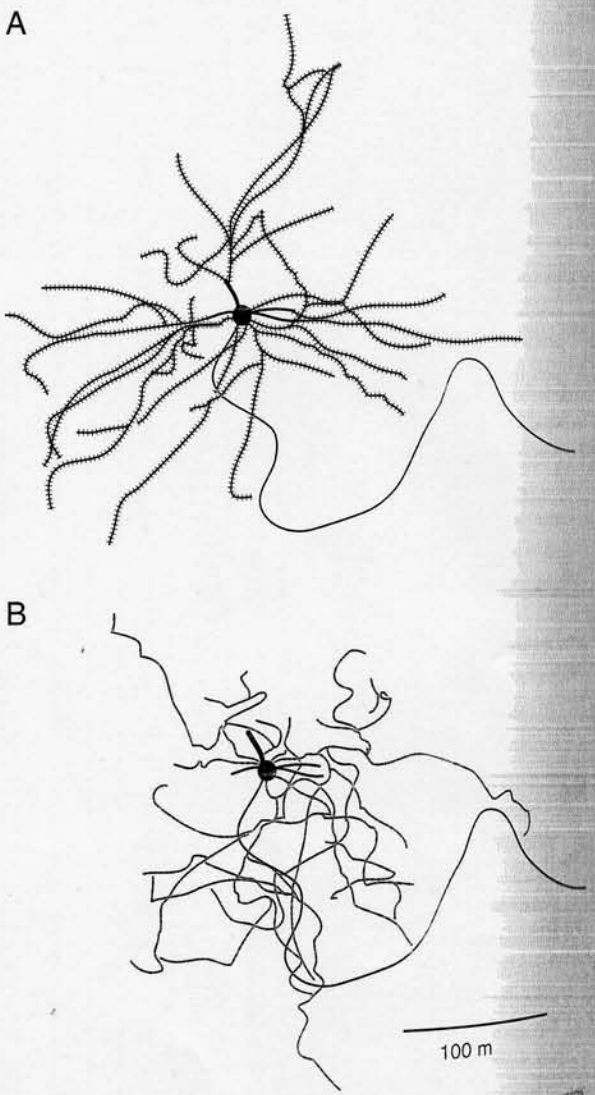

FIGURE 34.3 Two representations of a striatal medium spiny neuron that has been filled with HRP. (A) The soma and dendritic tree, with numerous dendritic spines. The thin process is the axon, which has been drawn without its collaterals. (B) The same neuron drawn to show the axonal collaterals, which branch extensively within the same field as the dendritic tree. From Wilson and Groves

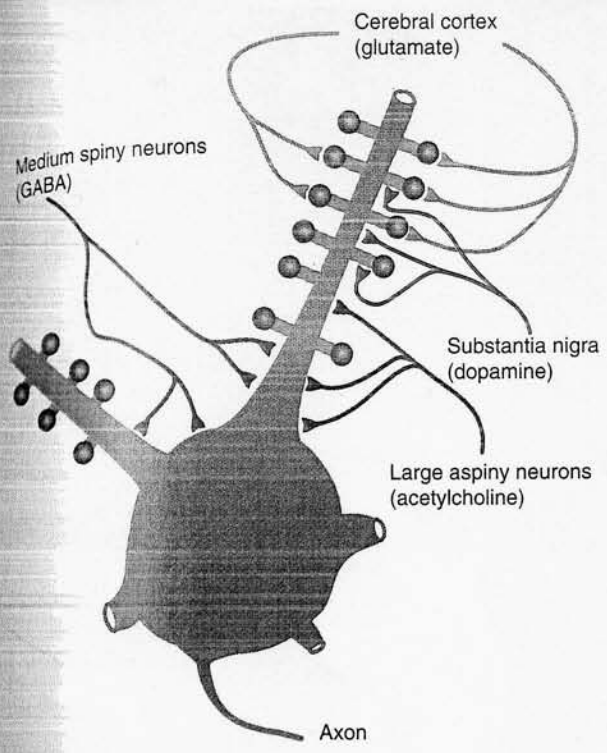

FIGURE 34.4 Pattern of termination of afferents on a medium spiny neuron. Shown here are the soma and the proximal section of two dendrites with their spines. Modified from Smith and Bolam, 1990.

(SNpr).[27-29] Although substance P is generally thought to be an excitatory neurotransmitter, the predominant effect of these neurons is inhibition of their targets. The second population contains enkephalin and primarily expresses D2 receptors. These neurons project to the external segment of the globus pallidus (GPe) and are inhibitory,[27-29] and thus their influence on GPi and SNpr is only expressed *indirectly*. The two populations of medium spiny neurons are morphologically indistinguishable and are not topographically segregated within the striatum[28] (Fig. 34.7). This commingling of neurons suggests that they receive similar inputs and thus may convey similar information to their respective targets. However, the different targets and transmitter types of the two populations may represent one level of functional segregation within the striatum.

Although no regional differences in the striatum are apparent from cell morphology, staining for calbindin or for acetylcholinesterase (AChE) activity reveals a patchy distribution of lightly stained regions, called **striosomes,** surrounded by more heavily stained regions, termed the **extrastriosomal matrix.**[30] The matrix forms the bulk of the striatal volume and receives input from most areas of the cerebral cortex. Within the matrix are clusters of neurons with similar inputs; these clusters are called **matrisomes.**[20] The bulk of the output from cells in the matrix is to both segments of the GP and to the SNpr. The striosomes receive input from the prefrontal cortex and send their output to the SNpc.[31] Immunohistochemical techniques have demonstrated that substance P, dynorphin, enkephalin, and other substances have a patchy distribution that may be partly or wholly in register with the striosomes.[32] The striosome matrix organization suggests another level of functional segregation within the striatum.

The Subthalamic Nucleus Receives Inputs from Motor Areas of Cerebral Cortex

The subthalamic nucleus (STN) is located at the junction of the diencephalon and midbrain, ventral to the thalamus and rostral and lateral to the red nucleus. Embryologically, it develops from the lateral hypothalamic cell column.[4,5] Phylogenetically, it increases in size in proportion to the neocortex. The STN receives an excitatory, glutamatergic input from motor areas of the cortex, including the primary motor cortex (area 4), premotor and supplementary motor cortices (area 6), and frontal eye fields (area 8).[33-35] The STN also receives an inhibitory GABAergic input from the GPe.[36] The output from the STN is excitatory and glutamatergic[37,38] and projects to the GPi, SNpr, and GPe.[39]

Although the STN is similar to the striatum in terms of its inputs and projection patterns, it differs from the striatum in that its cortical input is exclusively from motor areas and its output is excitatory. Of the two routes from the cortex to the GPi, GPe, and SNpr, the excitatory route through the STN is the faster.[40]

Globus Pallidus Internal Segment Is the Basal Ganglia Output for Limb Movements

The globus pallidus lies medial to the putamen and rostral to the hypothalamus. Embryologically, it arises from the lateral hypothalamic cell column.[4,5] In primates, the globus pallidus is separated into a medial or internal segment and a lateral or external segment by a fiber tract called the **internal medullary lamina.** In rodents and carnivores, the GPi lies within the internal capsule and is called the entopeduncular nucleus. The GPe is not a principal source of output from the basal ganglia, and we consider it in a later section.

The GPi is composed primarily of large neurons that project outside the basal ganglia.[41,42] The dendritic tree of a GPi neuron radiates from the soma in a disk-like distribution and is oriented so that the face of the disk is perpendicular to incoming striatal axons. The disk of an individual GPi neuron can be up to 1 mm

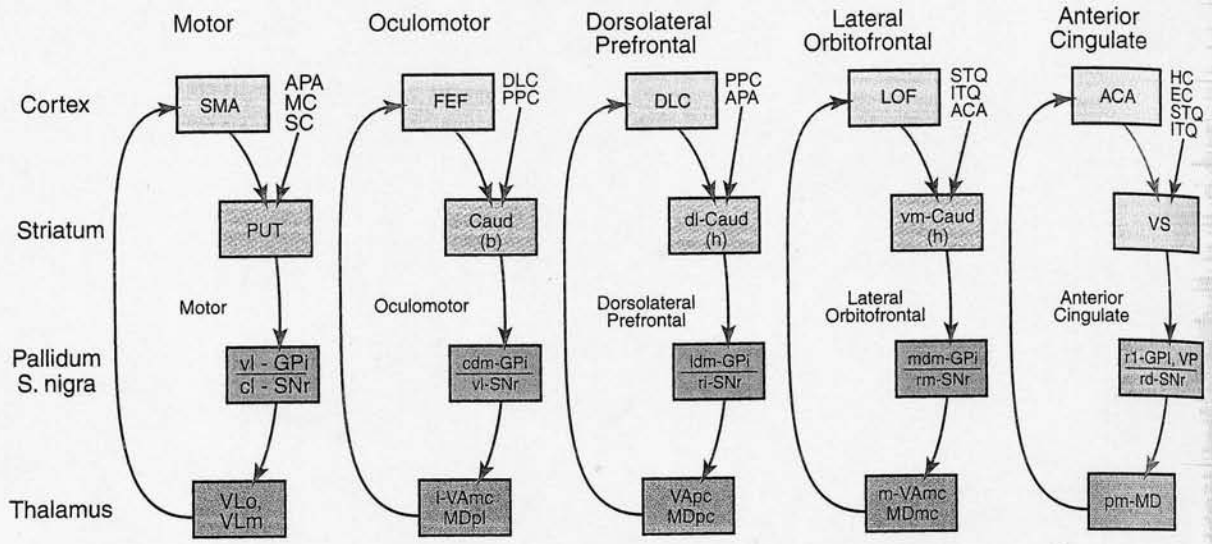

FIGURE 34.5 Hypothetical parallel segregated circuits connecting the basal ganglia, thalamus, and cerebral cortex. The five circuits are named according to the primary cortical target of the output from the basal ganglia: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate.[17] Abbreviations: ACA, anterior cingulate area; APA, arcuate premotor area; CAUD, caudate; (b) body; (h) head; DLC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FEF, frontal eye fields; GPi, internal segment of globus pallidus; HC, hippocampal cortex; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; MC, motor cortex; MDpl, mediulis dorsalis pars paralamellaris; MDme, medialis dorsalis pars magnocellularis; MDpc, medialis dorsalis pars parvocellularis; PPC, posterior parietal cortex; PUT, putamen; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; STG, superior temporal gyrus; VAmc, ventralis anterior pars magnocellularis; Vapc, ventralis anterior pars parvocellularis; VLm, ventralis lateralis pars medialis; VLo, ventralis lateralis pars oralis; VP, ventral pallidum; VS, ventral striatum; cl, caudolateral; cdm, caudal dorsomedial; dl, dorsolateral; l, lateral; ldm, lateral dorsomedial; m, medial; mdm, medial dorsomedial; pm, posteromedial; rd, rostrodorsal; rl, rostrolateral; rm, rostromedial; vm, ventromedial; vl, ventrolateral.

in diameter, giving these neurons the potential to receive a large number of converging inputs.[43]

The principal inputs to the GPi are from the striatum and the STN.[39] As we noted above, the striatal inputs contain GABA, substance P, and dynorphin and are inhibitory. Each striatal axon enters the GPi and sparsely contacts several neurons in passing before surrounding a single neuron with a dense termination.[44] The excitatory, glutamatergic projection from the STN to the GPi is highly divergent: each STN axon synapses on many GPi neurons[44] (Fig. 34.8). Recall that the striatal projection to the GPi is relatively slower than the STN projection. Thus, the GPi receives fast, widespread, divergent excitation from the STN and slower, focused, convergent inhibition from the striatum.

The output from the GPi is inhibitory and involves GABA as a neurotransmitter.[45] The majority of the output is sent via collaterals to both the thalamus and the brainstem.[46] In the thalamus, axons from the GPi terminate in the oral part of the ventrolateral nucleus (VLo) and in the principal part of the ventral anterior nucleus (VApc).[47] In turn, these thalamic nuclei project to the motor, premotor, supplementary motor, and possibly the prefrontal cortices.[48,49] Evidence indicates that an individual GPi neuron sends output via the thalamus to only one area of the cortex.[48] This means that GPi neurons that project to the motor cortex, for example, are adjacent to those that project to the premotor cortex. Thus, just as there appear to be parallel inputs from the cortex to the striatum, there also may be functionally parallel outputs from the GPi.

Collaterals of the axons that project from the GPi to the thalamus terminate in the midbrain extrapyramidal area, a region at the junction of the midbrain and pons near the pedunculopontine area.[50] The midbrain extrapyramidal area projects in turn to the reticulospinal motor system. Other GPi neurons (20%) project to the centromedian–parafascicular complex of the thalamus or to the lateral habenula.[46] The role of these projections is unknown.

Substantia Nigra Pars Reticulata Is the Basal Ganglia Output for Eye Movements

Like the globus pallidus, the substantia nigra is divided into two segments: the densely cellular

SNpc and the more sparsely cellular SNpr.[4] The SNpc contains dopamine cells and is not a principal output nucleus of the basal ganglia. We consider it later.

The SNpr is similar to the GPi in many ways, including the size of its neurons, their histochemistry, and their connectional anatomy. The SNpr contains large neurons that project outside the basal ganglia. The dendritic trees of these neurons are less discoidal than those of GPi neurons, but like those of GPi neurons they extend up to 1 mm and thus receive a wide field of inputs.[81] Like the GPi, the SNpr receives inhibitory inputs from the striatum, mediated by GABA, SP, and dynorphin, and excitatory glutamatergic inputs from the STN. The output of the SNpr is GABAergic and inhibitory to the medial part of ventrolateral thalamus

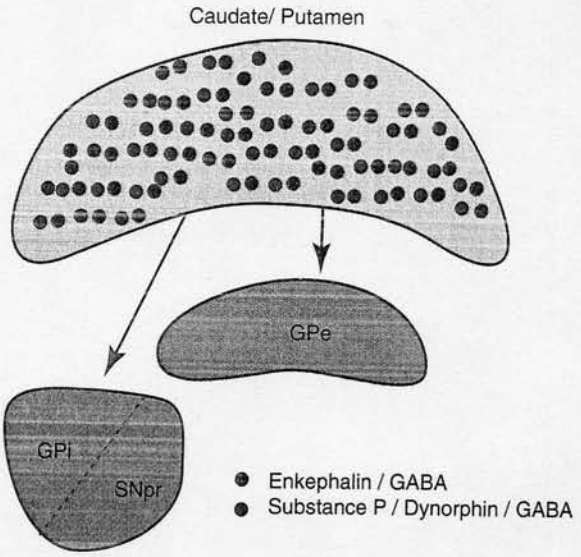

FIGURE 34.7 The two chemically defined populations of medium spiny neurons are intermixed in the striatum. One population (blue) projects to the globus pallidus pars externa (GPe) and contains GABA and enkephalin. The other population (red) projects to the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNpr) and contains GABA, dynorphin, and substance P.

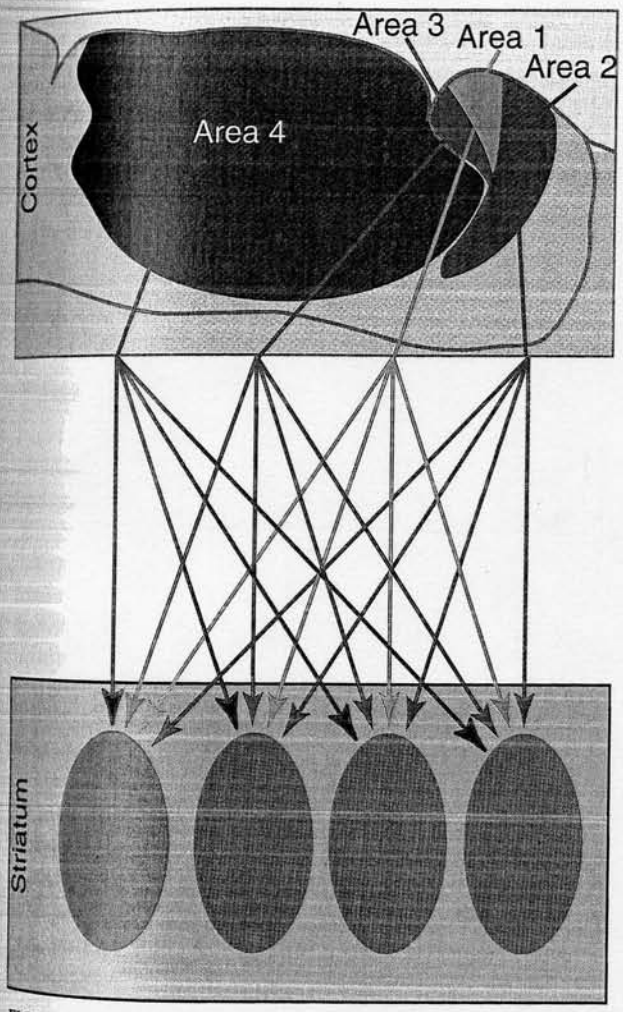

FIGURE 34.6 Schematic representation of projections to the striatum from arm areas in the somatosensory cortex (areas 1, 2, and 3) and motor cortex (area 4). Notice that each cortical area projects to several striatal zones and that several functionally related cortical areas project to a single striatal zone. After Flaherty and Graybiel.[19]

(VLm) and to the magnocellular part of ventral anterior thalamus (VAmc).[52–54] These thalamic areas in turn project to the premotor and prefrontal cortices.[55] Like the GPi, the SNpr sends collaterals to the midbrain extrapyramidal area and the centromedian–parafascicular complex of the thalamus.[56,57] The primary difference in the connectivity patterns of the GPi and SNpr is that the lateral portion of the SNpr sends an inhibitory projection to the superior colliculus and to the paralaminar part of the dorsal medial thalamus (DMpl).[52,58,59] The DMpl projects in turn to the frontal eye fields. Thus, the lateral portion of the SNpr is connected with cortical and brainstem areas that control eye movements.

Globus Pallidus External Segment Projects Primarily to the Subthalamic Nucleus

The GPe is one of two nuclei that may be viewed as intrinsic nuclei of the basal ganglia. The other is the SNpc, which we consider in the next section. Both the GPe and the SNpc receive the bulk of their input from and send the bulk of their output to other basal ganglia nuclei. The GPe is similar in some ways to the GPi. Its inputs are an inhibitory projection from the striatum and an excitatory projection from the STN. The patterns of termination of the striatal and STN afferents are similar, in that the striatal input is focused and convergent and the STN input is diver-

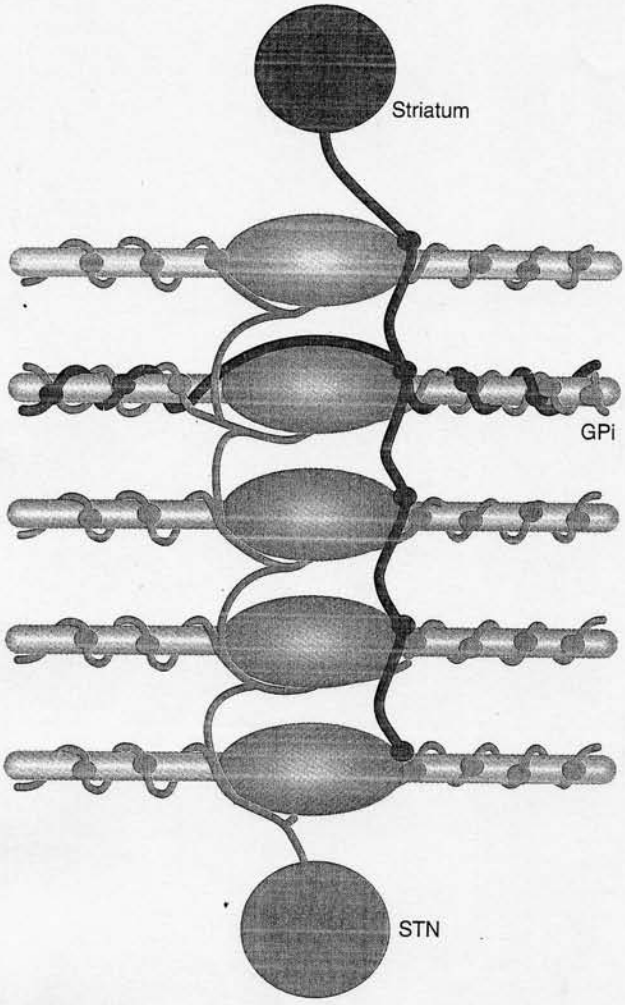

FIGURE 34.8 The two primary inputs to the globus pallidus pars interna (GPi) have different patterns of termination. Axons from the subthalamic nucleus (green) are excitatory and terminate extensively on multiple GPi neurons. Axons from the striatum (red) contact several GPi neurons weakly in passing and terminate densely on single neuron. Modified from Parent and Hazrati.[44]

gent.[44] Unlike the GPi, however, the GPe receives input from the striatum mediated by GABA and enkephalin but not substance P.[28,29] Furthermore, the output of the GPe is GABAergic and inhibitory and projects primarily back to the STN.[60] There is also a GABAergic inhibitory output from the GPe directly to the GPi and the SNpr.[61] As we noted above, the GPe and GPi receive input from neighboring striatal neurons and therefore are likely to receive similar information. The fact that the GPe inhibits the GPi directly or via the STN (the GPe inhibits the STN, and the STN inhibits the GPi, so the net effect is inhibition) suggests that the GPe may act to oppose, limit, or focus the effect of the striatal projection to the GPi.

Substantia Nigra Pars Compacta Provides Dopamine Input to Striatum

The SNpc is perhaps the most thoroughly studied structure in the basal ganglia. Its large dopamine-containing cells are the neurons that degenerate in Parkinson disease, which is characterized by abnormal movement. These neurons also contain neuromelanin, a dark pigment that makes the SNpc appear black and is the basis for the name substantia nigra (Latin, black substance). The SNpc receives GABAergic inhibitory input from the striatum, specifically from the striosomes.[62] Other inputs to the SNpc have been difficult to assess, because the dendrites of SNpc and SNpr neurons overlap. Thus, whether axons ending in the substantia nigra terminate on SNpc neurons, SNpr neurons, or both is not always clear. SNpc neurons project to all of the caudate and putamen in a topographic manner.[63] The action of the dopamine released by these neurons appears to be primarily a modulation of the excitatory corticostriatal input, with the nature of that modulation depending on the receptors expressed by the postsynaptic neurons, as we discusssed earlier.

Summary

Now that we have described the anatomy of the individual components of the basal ganglia, let us step back and summarize their connections with each other and with the rest of the brain.

1. The striatum receives input from nearly all of the cerebral cortex. Several functionally related cortical areas project to overlapping striatal zones, and an individual cortical area projects to several striatal zones. Cortical areas that are not functionally related project to separate zones of the striatum, although there may be some common projections to adjacent zones.
2. The striatum sends a focused and convergent inhibitory projection to the basal ganglia output nuclei, the GPi and SNpr.
3. The subthalamic nucleus receives input from the motor, premotor, and supplementary motor cortices and from the frontal eye fields. It sends a fast, divergent, excitatory projection to the GPi and SNpr.
4. Reciprocal and looplike connections among the basal ganglia nuclei may play a negative or positive feedback role or may result in focusing of signals.
5. The output from the GPi and SNpr is inhibitory and projects to motor areas in the brainstem and thalamus.

6. There are no direct connections between the basal ganglia and spinal sensory or motor circuits.

Researchers disagree whether the overall anatomic organization of the basal ganglia should be viewed as a convergence (or funneling) of information that produces a focused output or as a system of multiple, parallel, segregated loops, each with a separate output. Several observations support the convergence view: (1) there is a very marked reduction in the number of neurons at each level from the cortex to the striatum to the GPi and SNpr; (2) a large number of synapses are made on each striatal neuron; and (3) striatal, GPi, and SNpr neurons have large dendritic trees. Other observations support the idea of parallel segregated loops: (1) somatopy is preserved in the cortex, striatum, and GPi/SNpr, with separate representations of the face, arm, and leg; (2) topography is relatively well preserved through the basal ganglia, for example, from the prefrontal cortex to the caudate to the SNpr to the VA thalamus and back to the prefrontal cortex; and (3) separate groups of GPi neurons project via the thalamus to separate motor areas of the cortex. Clearly, there is convergence on a local scale and parallelism on a global scale, but what we still do not know is whether the parallel pathways are completely functionally segregated or interact with each other at their interfaces.

SIGNALING IN THE BASAL GANGLIA

Although the anatomic organization of the basal ganglia may provide some clues about their function, inference of function from anatomy is highly speculative. A direct way to study the function of an area of the central nervous system is to record the electrical activity of individual neurons with an extracellular electrode in awake, behaving animals. By sampling the activity of a part of the brain during behavior, we can gain some insight into what role that part might play in behavior. If an animal is trained to perform a task consistently, the activity of single neurons can be correlated with individual aspects of the task performance. Furthermore, the timing of neural activity in one part can be compared with the timing of activity in other parts and with the timing of the movement. This approach has shown that neurons within the different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement. In this section, we describe some of the signals in the basal ganglia that are correlated with movement or the preparation for movement.

The Striatum Has Low Spontaneous Activity That Increases during Movement

Most striatal neurons have low baseline discharge rates of 0.1–1 s^{-1} (Fig. 34.9).[64] These neurons project outside the striatum and therefore are probably medium spiny neurons.[65] In general, the activity of these neurons reflects the activity of the areas of cerebral cortex from which they receive inputs, with less modality specificity.[17,66] For example, neurons in areas of the putamen that receive input from the somatosensory and motor cortices have activity correlated with active and passive movement, but not with specific tactile modalities such as light touch, vibration, or joint position.

Neurons related to movement are somatotopically distributed in the striatum: neurons whose activity correlates with facial movements or leg movements are located in ventromedial or dorsolateral areas of the striatum, respectively[64]; neurons whose activity correlates with arm movements are located between the "face" and "leg" regions. Neurons with similar discharge characteristics tend to occur in clusters that may correspond to the matrisomes mentioned earlier. Movement is associated with an increase in the firing rate of these neurons above their very low baseline rates.[67] Movement-related striatal neurons fire an average of 20 ms prior to movement (Fig. 34.10), and half fire in relation to the direction of movement. Firing is correlated with the start of movement in some neurons and with the cessation of movement in others.[68] Neurons in the putamen may fire in relation to self-initiated movements, stimulus-triggered movements, or both.[69] Some neurons in the anterior part of the putamen and

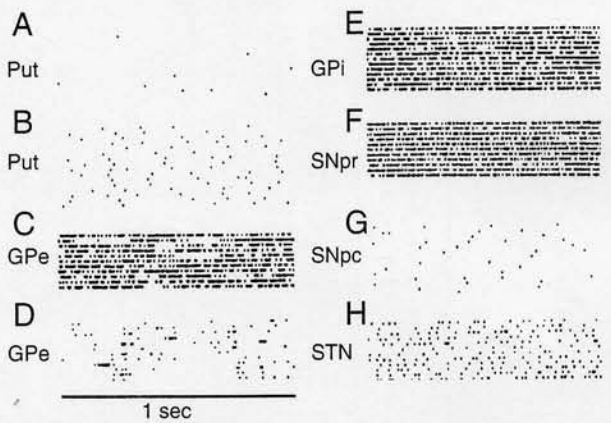

FIGURE 34.9 Representative neural discharge patterns from the various basal ganglia nuclei. In these raster displays, each dot indicates the occurrence of an action potential. Each horizontal raster line represents a one-second period of discharge. Several such periods are arranged vertically for each nucleus. From Crutcher and DeLong.[112]

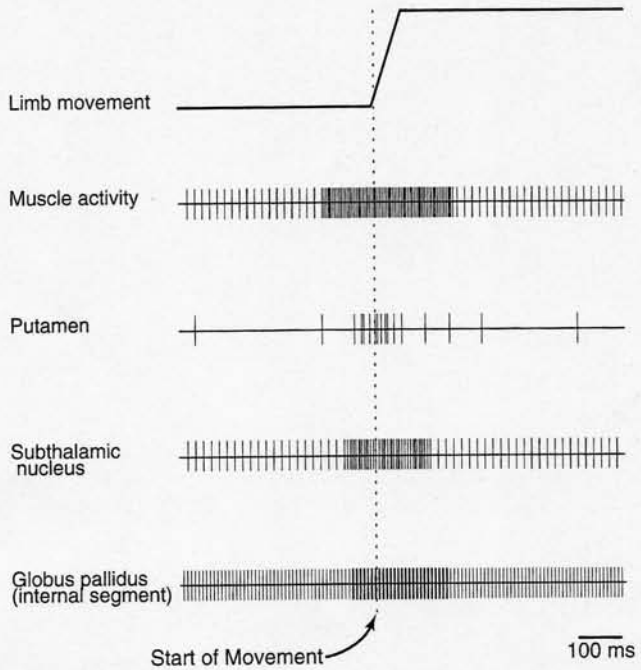

FIGURE 34.10 Schematic representation of the timing of neuronal activity in three nuclei of the basal ganglia in relation to limb movement and the muscle activity used to make the movement.

in the caudate nucleus that receive input from the premotor or prefrontal cortex are active during the preparation for movement.[70,71] Their activity is time-locked to instructional cues but not to the movement itself. In some neurons, firing is correlated with the instruction of whether or not to move ("set"); in others, it is correlated with the signal to move ("go"). Although particular neurons may have activity patterns that differently relate to specific tasks or task parameters, as a whole the striatum is not exclusively active in relation to any of these tasks or parameters.[69,70]

Some striatal neurons fire tonically at rates of 2–10 s^{-1}.[65] These neurons are distributed throughout the striatum. Although their discharge bears no specific relation to movement, it is related to certain sensory stimuli that are associated with reward. For example, a tonically active neuron may fire if a clicking sound precedes a fruit juice reward but not if the click or reward occurs alone.[72] For this reason, it has been suggested that these neurons signal aspects of tasks that are related to learning and reinforcement. The tonically active neurons are not activated by electrical stimulation of the globus pallidus; they may correspond to the cholinergic large aspiny neurons.[65] If so, that would place them in a position to modify the sensitivity of the medium spiny neurons to cortical input in relation to specific behavioral contexts.

Subthalamic Nucleus Has Moderate Spontaneous Activity That Increases during Movement

Neurons in the subthalamic nucleus are tonically active, with average baseline discharge rates of about 20 s^{-1} (Fig. 34.9).[73] They are organized somatotopically and change their activity in relation to eye or limb movement.[73–75] For 90% of the neurons, the change is an increase in firing rate that occurs an average of 50 ms prior to the movement (Fig. 34.10).[76] The activity of approximately half of all movement-related STN neurons is correlated with movement direction.

Globus Pallidus Internal Segment and Substantia Nigra Pars Reticulata Have High Spontaneous Activity That Increases or Decreases after Movement Initiation

As described above, the GPi and SNpr generate the output of the basal ganglia. Just as they are anatomically similar, they are physiologically similar. Neurons in these nuclei are tonically active, with average firing rates of 60–80 s^{-1} (Fig. 34.9).[77] They are organized somatotopically, with the leg and arm represented in the GPi and the face and eyes in the SNpr.[75,76,78,79] Because of this somatotopy, studies of limb movements have focused on the GPi, and studies of eye movements have focused on the SNpr. Because limb and eye movements are controlled differently, we discuss these studies separately.

Seventy percent of arm movement-related GPi neurons increase their activity during movement.[80] During wrist movement, GPi neurons change their firing rate after the wrist muscles become active (Fig. 34.10),[81] suggesting that the output of the basal ganglia does not initiate movement. The activity of GPi neurons does not consistently correlate with the amplitude or velocity of movement or with muscle activity or length.[80] In some tasks, GPi activity correlates with the direction of movement, but the correlation is not consistent across different tasks. The weak and inconsistent parameter coding suggests that the GPi is involved in some aspect of movement other than parameter control.

Like limb-movement neurons in the GPi, SNpr neurons that are related to saccadic eye movements are tonically active.[78] During saccades, SNpr activity begins after activity in the superior colliculus, a structure that initiates saccades.[56] Thus, for eye movements as well as limb movements, the basal ganglia are unlikely to initiate movement. Unlike GPi limb-movement neurons, however, all SNpr neurons related to saccades decrease their activity during the saccade. Whether

this difference between GPi neurons and SNpr neurons indicates a fundamental distinction between eye and limb movement control or whether it reflects task differences is not known. Other differences between GPi limb-movement neurons and SNpr saccade neurons have been noted. While the former have weak sensory responses, some of the latter respond strongly to visual stimuli.[81] For the visually responsive SNpr neurons, the spatial location of the stimulus seems to be the most salient feature. The activity of some SNpr neurons is related most strongly to saccades that are made to remembered targets.[82] For example, when a visual target is presented and then removed and a monkey is trained to look to where the target had been, some SNpr cells will decrease their firing rate more than when a saccade is made to a visible target. Whether a similar phenomenon exists for GPi neurons is not known. However, few GPi neurons change their activity in a task where monkeys must remember the direction, velocity, and amplitude of a self-initiated wrist movement.[83]

Globus Pallidus External Segment Has Irregular Activity That Increases or Decreases after Movement Initiation

Two types of neurons in the GPe have been described on the basis of their baseline activity patterns.[77] Most neurons fire in high-frequency (70 s^{-1}) bursts interrupted by long pauses. A smaller number of neurons fire in lower frequency (10 s^{-1}) bursts that occur more often. Both types of neurons change their activities in relation to limb movement, and in most cases these changes are increases in activity.[77,80] As has been described for the GPi, the coding of movement amplitude and velocity and the coding of muscle length and force are weak in the GPe.[80] Like the other nuclei of the basal ganglia, the GPe is unlikely to initiate movement.[76,80]

Substantia Nigra Pars Compacta Has Low Spontaneous Activity That Does Not Change with Movement

The activity of single neurons in the SNpc of trained animals is different from that of neurons in the other basal ganglia nuclei. SNpc neurons fire at a baseline rate of about 2 s^{-1}, and their firing is not related to movement itself. There is no apparent somatotopy in the SNpc,[79] and the neurons in this nucleus carry little specific information regarding sensory modality or spatial properties. The activity of SNpc neurons does change in relation to behaviorally significant events such as reward or the presentation of instructional cues.[84] The only responses to stimuli are those that occur when a stimulus is presented in the context of a movement task.[85] Furthermore, SNpc neuronal activity changes with conditioning. For example, if a reward is preceded by a tone, an SNpc neuron that had fired in relation to the reward will, after several trials, begin to fire in relation to the tone that predicts the reward.

Thus, SNpc dopamine neurons apparently can predictively signal the occurrence of a behavioral event. In this way, SNpc neurons are similar to tonically active striatal neurons. Remember that SNpc neurons also synapse extensively on the shafts of the dendritic spines of medium spiny striatal neurons. It has been suggested that the dopamine input from the SNpc changes the sensitivity of striatal neurons to cortical inputs that terminate on the heads of the dendritic spines. The activity of SNpc neurons could modify the response of striatal neurons to cortical input that occurs in a specific behavioral context.

Summary

We can make several general statements about the discharge of movement-related neurons in the basal ganglia:

1. Movement-related neurons in the striatum, subthalamic nucleus, globus pallidus, and substantia nigra pars reticulata are arranged somatotopically.
2. Neurons in the striatum are quiet at rest and increase their firing rate during movement. Neurons in STN are tonically active and also increase their firing rate during movement. Thus, GPi neurons receive a widespread, tonically active excitatory input and a focused, intermittent inhibitory input.
3. Neurons in the GPe and GPi are tonically active. Most increase their activity during limb movement, but up to one-third decrease their activity.
4. Neurons in the SNpr are tonically active. Those that are related to saccadic eye movements decrease their activity during the movement.
5. Neurons in the SNpc discharge in relation to rewards and behaviorally relevant stimuli but not to movement.
6. Activity changes in the basal ganglia begin at the onset of movement but after the muscles are already active. Thus, the basal ganglia are unlikely to initiate movement.

THE EFFECT OF BASAL GANGLIA DAMAGE ON BEHAVIOR

Valuable clues to the function of the basal ganglia have come from recording the activity of single neu-

rons in the basal ganglia during behavior. However, correlation of neural activity with an aspect of behavior does not necessarily mean that neural activity causes that aspect of behavior. Studying behavior after a specific component had been selectively removed from an otherwise intact system would aid in determining the role of the basal ganglia in behavior. Selective removal occurs in certain human neurological diseases that cause degeneration of neurons in the basal ganglia. Historically, these diseases have fueled great interest and have provided some insight into basal ganglia function. The movement disorders that result from basal ganglia damage are often dramatic. Depending on the site of the pathology, they range from extreme slowness of movement and rigidity to uncontrollable involuntary movements.

Although human diseases are of great interest, they often affect more than one structure. This necessarily limits the power of functional models derived from the study of human basal ganglia diseases. More selective lesions can be made in experimental animals, but until recently, reproducing the movement disorders associated with human basal ganglia disease was difficult. Experimental lesions can be made in a number of ways. Electric current can be passed through an electrode to permanently destroy both neuronal somata and axons in the area surrounding the electrode. This method has the disadvantage of destroying axons that pass through the area but which are not necessarily part of the structure of interest. Alternatively, a small amount of a toxic chemical (e.g., the potent excitotoxic amino acids kainic acid and ibotenic acid) can be injected into a restricted area of the brain and can be used to kill neurons whose somata are in the area of the injection, sparing axons that pass through the area. 6-Hydroxydopamine or MPTP (see Box 34.3) can be used to destroy dopamine neurons selectively. Agonists and antagonists of GABA can also be injected into the brain to cause temporary focal inactivation or disinhibition of neurons; the effects of these chemicals last for several hours and are followed by a complete return to the normal state. In this section, we review the results of selective basal ganglia lesions produced by these techniques in animals, and we discuss human basal ganglia diseases in the context of these experiments.

Damage to the Striatum Causes Slow Voluntary Movements or Involuntary Postures and Movements

Lesions in the striatum produce varying results that depend on the location of the lesion, the lesion method, and the parameter that is measured. Many studies of unilateral striatal lesions have described only minimal

BOX 34.3

THE MPTP STORY

Until the early 1980s, the quest for an complete animal model of Parkinson disease was largely unsuccessful. Although some of the abnormalities of Parkinson disease could be caused by electrolytic lesion of the SNpc or by injecting the neurotoxin 6-hydroxydopamine into SNpc, neither of these methods produced the full syndrome of Parkinson disease. In 1982, an unfortunate but fortuitous accident happened. Four young drug users in northern California developed the symptoms of Parkinson disease. Because the disease is highly unusual in young adults, the neurologists caring for these patients began a search for the cause.[98] They discovered that each of the patients had recently used a new synthetic heroin that contained an analog of the narcotic meperidine, 1-methyl-4-phenyl-proprionoxypiperidine (MPPP), as well as a contaminant, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP). It turned out that MPTP was the agent responsible for the parkinsonian symptoms. MPTP is oxidized in the brain to MPP^+ by monoamine oxidase. When MPP^+ is taken up by dopamine neurons, it kills them by inhibiting oxidative metabolism in the mitochondria.[99]

MPTP also produces a syndrome that resembles Parkinson disease in several species of monkeys.[100] Monkeys given MPTP develop tremors as well as slowness of movement, paucity of movement, and rigidity. In these monkeys, there is a nearly complete degeneration of dopamine neurons in the SNpc and the ventral tegmental area and a variable degeneration in the locus coeruleus. Like humans with Parkinson disease, MPTP monkeys improve when given the dopamine precursor L-dopa, and they have side effects of chorea when they are given too much L-dopa. Thus, by behavioral, pharmacological, and pathological measures, the MPTP monkey is an excellent model of human Parkinson disease. It is currently used to study the pathophysiology and pharmacology of Parkinson disease and has led to new ideas about possible causes of the disease.

BOX 34.4

OBSESSIVE–COMPULSIVE DISORDER

Obsessive–compulsive disorder (OCD) is a chronic disorder characterized by recurrent intrusive thoughts and ritualistic behaviors that consume much or most of the afflicted individual's attentional and goal-directed processes.[1] Among the more agonizing illnesses in clinical medicine, OCD is classified as an anxiety disorder because of the marked tension and distress produced by resisting the obsessions and compulsions. The most common obsessions involve thoughts about harming oneself or others (e.g., a mother who repeatedly thinks about taking her infant's life, despite her complete lack of desire or intent to do so and her horror over having such thoughts) or of contamination. Compulsions may be a response to obsessive thoughts (e.g., repetitive hand-washing following skin contact with any object due to obsessive worries of having contacted germs) or may instead reflect cognitive–behavioral rituals performed according to stereotyped rules (e.g., counting one's footsteps to avoid ending on certain numbers). Even though individuals with OCD often recognize that such thoughts and behaviors are irrational, they describe feeling irresistibly compelled to engage in them.

The onset of OCD usually occurs between late childhood and early adulthood. Without treatment, OCD is frequently disabling. However, the amount of time engaged in obsessions and compulsions and the magnitude of the associated anxiety can often be reduced by chronic treatment with drugs that potently inhibit serotonin reuptake.[2] Behavioral therapy involving repeated *in vivo* exposure and response prevention (e.g., having patients touch a toilet seat and subsequently preventing them from hand-washing) may also facilitate extinction of the anxiety responses generated by resisting the obsessive thoughts and compulsive behaviors.[1]

Although the etiology and pathophysiology of OCD are unknown, the anatomical circuits involved in the production of obsessions and compulsions have been elucidated by converging evidence from functional neuroimaging studies of OCD, analysis of the lesions that result in obsessive–compulsive symptoms, and observations regarding the neurosurgical interventions that can ameliorate OCD.[1–7] Positron emission tomographic (PET) imaging studies of primary OCD have shown that "resting" cerebral blood flow and glucose metabolism are abnormally increased in the orbital cortex and the caudate nucleus bilaterally in primary OCD.[3] With further symptom provocation during exposure to relevant phobic stimuli (e.g., skin contact with "contaminated" objects for OCD subjects with germ phobias), blood flow increases further in the orbital cortex, the caudate, the putamen, the thalamus, and the anterior cingulate cortex.[4] During effective pharmacotherapy, orbital metabolism decreases toward normal, and both drug treatment and behavioral therapy are associated with a reduction of caudate metabolism.[3] The baseline areas of hypermetabolism in the orbital cortex and the caudate may thus reflect physiological concomitants of obsessive thoughts and/or chronic anxiety, and conversely, the reduction in caudate metabolism associated with effective (but not ineffective) treatment may reflect a physiological correlate of symptom resolution rather than a primary mechanism of treatment. Moreover, given the evidence from electrophysiological and lesion analysis studies indicating that the orbital cortex participates in the correction of behavioral responses that have become inappropriate as reinforcement contingencies change, some orbital areas may be specifically activated as an endogenous attempt to interrupt the reverberating patterns of nonreinforced thought and behavior in OCD.[8] Compatible with this hypothesis, the posterior orbital cortex BF increases during symptom provocation in OCD, but the magnitude of this BF increase correlates *inversely* with the corresponding rise in obsession ratings ($r = -0.83$).[4]

Evidence that dysfunction within these basal ganglia and ventral prefrontal cortical structures or the circuits they form with other structures may be related to the etiopathology of OCD is provided by analysis of the neurological conditions that are associated with the development of secondary obsessions and compulsions. Such conditions include lesions of the lentiform nuclei that include involvement of the globus pallidus, Sydenham chorea (a poststreptococcal autoimmune disorder associated with neuronal atrophy in the caudate and putamen), Tourette disorder (an idiopathic syndrome characterized by motoric and phonic tics that may have a genetic relationship with OCD), chronic motor tic disorder, and lesions of the ventromedial prefrontal cortex.[1,5–7] Several of these conditions are associated with complex motor tics (repetitive, coordinated, involuntary movements occurring in patterned sequences in a spontaneous, unpredictable, and transient manner). Complex tics and obsessive thoughts may reflect homologous, aberrant neural processes that are manifested within the motor and cognitive–behavioral domains, respectively, because of their origination in distinct portions of the cortical–striatal–pallidal–thalamic circuitry.[9] Nevertheless, it is noteworthy that

imaging studies of obsessive–compulsive syndromes arising in the setting of Tourette syndrome or basal ganglia lesions have not found elevated BF and metabolism in the caudate and, in some cases, have found reduced metabolism in the orbital cortex in such subjects relative to controls.[5]

The differences in the functional anatomical correlates of primary versus secondary OCD suggest a neural model in which dysfunction arising at various points within the ventral prefrontal cortical–striatal–pallidal–thalamic circuitry may result in pathological obsessions and compulsions. This circuitry in general appears to be involved in the organization of internally guided behavior toward a reward, switching of response strategies, habit formation, and stereotypic behavior.[9] These circuits have also been implicated in the pathophysiology of major depressive disorder (MDD), another illness in which intrusive, distressing thoughts recur to the extent that the ability to switch to goal-oriented, rewarding cognitive–behavioral sets appears impaired. Although MDD and OCD appear distinct in their course, prognosis, genetics, and neurochemical concomitants, substantial comorbidity exists across these syndromes. For example, major depressive episodes occur in about one-half of patients with OCD, pathological obsessions commonly arise in MDD, and the pharmacological interventions that ameliorate OCD can also effectively treat MDD.[1]

The clinical comorbidity across these two disorders may conceivably reflect involvement of an overlapping neural circuitry by otherwise distinct pathophysiological processes. Consistent with this hypothesis, neurosurgical procedures that are effective at reducing both obsessive–compulsive and depressive symptoms in intractable cases of OCD and MDD all interrupt the white matter tracts that carry neural projections between the frontal lobe, the basal ganglia, and the thalamus.[1] Although the therapeutic mechanisms of these treatments are unknown, the locations of the surgical lesions placed in such procedures provide further support for the hypothesis that dysfunction involving the connections between the ventral PFC and the basal ganglia may be involved in the pathophysiology of obsessive thoughts and compulsive behaviors.

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References

1. Jenike, M. A., Baer, L., and Minichiello, W. E. *Obsessive Compulsive Disorders: Theory and Management*. Year Book Medical Publishers, Inc., Chicago.
2. Zohar, J., Murphy, D. L., Zohar-Kadouch, R. C., Pato, M. A. T., Wozniak, K. M., and Insel, T. R. (1990). Serotonin in obsessive compulsive disorder. In: *Serotonin in Major Psychiatric Disorders* (E. F. Coccaro and D. L. Murphy, eds.), pp. 99–126. American Psychiatric Press, Washington DC.
3. Baxter, L. R. (1995). Neuroimaging studies of human anxiety disorders. In *Psychopharmacology: The Fourth Generation of Progress* (F. E. Bloom and D. J. Kupfer, eds.), pp. 921–932. Raven Press, New York.
4. Rauch, S. L., Jenike, M. A., Alpert, N. M., *et al.* (1994). Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch. Gen. Psychiat.* **51:** 62–70.
5. LaPlane, D., *et al.* (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. *Brain* **112:** 699–725.
6. Swedo, S. E., Rapoport, J. L., Cheslow, D. L., *et al.* (1989). High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am. J. Psychiat.* **146:** 246–249.
7. Eslinger, P. J., and Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology* **35:** 1731–1741.
8. Rolls, E. T. (1995). A theory of emotion and consciousness, and its application to understanding the neural basis of emotion. In *The Cognitive Neurosciences* (M. Gazzaniga, ed.), pp. 1091–1106. MIT Press, Cambridge, MA.
9. Nauta, W. J. H. (1989). Reciprocal links of the corpus striatum with the cerebral cortex and limbic system: a common substrate for movement and thought? In *Neurology and Psychiatry: A Meeting of Minds* (J. Mueller, ed.). Karger, New York.

deficits.[86] If the putamen is unilaterally inactivated with the GABA agonist muscimol, the result is slightly slowed movement of the contralateral limb associated with increased activity of antagonist muscles.[87] Reaction time is generally normal, however, indicating that movement initiation is intact. Bilateral electrolytic lesions have had little effect in some studies. In other studies, they have resulted in paucity of movement, severe slowness of movement bilaterally, and postural abnormalities.[86] The reason for this discrepancy is not clear, but it may be due to differences in lesion size.

Huntington disease (or Huntington chorea) is a genetically based, degenerative disease in humans that results in disabling involuntary movements. These movements are called **chorea** (Greek, dance). They are frequent, brief, sudden, random, twitchlike movements that involve all parts of the body and resemble fragments of normal voluntary movement. In contrast to these excessive involuntary movements, the voluntary movements of patients with Huntington disease are slower than normal.[88] As the disease progresses, muscular rigidity appears. The pathologic hallmark of Huntington disease is a marked loss of neurons in the striatum. Surprisingly, however, experimental destruc-

tion of striatal neurons in monkeys does not result in chorea,[86] perhaps because the destruction involves neurons that project to the GPe as well as those that project to the GPi. Blocking the striatal–GPe pathway with a GABA antagonist does produce chorea.[89] A possible mechanism for this effect is that disinhibition of the GPe causes inhibition of the STN and ultimately decreased activity in the GPi. This results in abnormal overactivity of motor cortical and brainstem circuits, producing chorea.[29]

Damage to Subthalamic Nucleus Causes Large-Scale Involuntary Movements

In monkeys and humans, electrolytic or pharmacological lesions in the subthalamic nucleus cause dramatic involuntary flinging movements of the contralateral arm and leg.[86,90] These movements resemble chorea in their brief, random, and sudden nature, but they tend to be much larger in amplitude. Because of the flinging quality of these movements, they are referred to as **hemiballismus.** After a lesion in the STN, hemiballismus lasts for days to weeks before gradually resolving. Humans and experimental animals with hemiballismus can still make quite normal voluntary movements.[90] It has been suggested that the mechanism underlying hemiballismus is a loss of excitatory input to GPi, resulting in decreased GPi activity and ultimately in disinhibition of cortical and brainstem motor mechanisms.[29] In fact, blocking excitatory transmission from the STN to the GPi with the glutamate antagonist kynurenate also causes involuntary movements.[91] However, when hemiballismus is produced by an STN lesion in monkeys, it is abolished by a second lesion placed in the GPi.[92] Furthermore, in monkeys with STN lesions, the level of GPi activity is reduced even after hemiballismus resolves.[93] This reduction in activity suggests that hemiballismus is not caused simply by a tonic reduction of GPi activity. It seems more likely that hemiballismus reflects a fluctuating or bursting output from the basal ganglia, but the validity of this idea remains to be demonstrated.

Damage to Globus Pallidus Causes Slow Voluntary Movements and Involuntary Postures and Does Not Delay Movement Initiation

Because of the close proximity of the GPi and the GPe, it is difficult to lesion one without including part of the other. Therefore, one must use caution when interpreting the results of GP lesions. In most cases, however, combined GPe and GPi lesions have an effect similar to the effects of lesions of the GPi alone.[94] Unilateral lesions of the GPe and GPi cause slowness of movement and abnormal cocontraction of agonist and antagonist muscles, but they do not affect the initiation of movement. Bilateral lesions of the GPe and GPi result in even more severely abnormal flexed postures, which affected individuals are apparently unable to move out of.[95] Electrolytic lesions that have produced this severe abnormality have been large, involving both the GPe and the GPi as well as part of the internal capsule. Similar abnormalities are seen with carbon monoxide or carbon disulfide poisoning, which causes neuronal death in the GPi and SNpr.[86]

Lesions restricted to the GPi result in slowness of movement of the contralateral limbs. Reaction time is normal, however, indicating that the mechanisms involved in the initiation of movement are intact. In some studies, the slowness of movement was accompanied by cocontraction of agonist and antagonist muscles, producing rigidity.[91] In most cases, there is relatively more activity in flexor muscles, which is reflected in a tendency for the limbs to assume an abnormally flexed posture. If particular muscles are already contracting, GPi lesions cause movements to be more impaired when these muscles are relaxed than when they are more fully contracted (Fig. 34.11). Thus, lesions that remove the inhibitory output of the basal ganglia appear to interfere with the ability to turn off unwanted muscle activity.[94]

Lesions of Substantia Nigra Pars Reticulata Cause Involuntary Eye Movements

It is difficult to produce electrolytic lesions exclusively in the SNpr because of its proximity to the SNpc. However, it is possible to inactivate neurons focally in the SNpr by using the GABA agonist muscimol.[96] Injection of muscimol into the lateral SNpr inactivates neurons that are normally involved in saccadic eye movements, abolishing the ability to maintain visual fixation because involuntary saccades cannot be suppressed (Fig. 34.12). This defect appears to result from disinhibition of the superior colliculus, because injection of the GABA antagonist bicuculline into the superior colliculus mimics the effects of muscimol injection into the SNpr.[97] Thus, just as GPi inactivation results in abnormal excess limb and trunk muscle activity, SNpr inactivation results in abnormal excess eye movements.

Lesions of Substantia Nigra Pars Compacta Cause Symptoms of Parkinson Disease

Lesions of the SNpc are of particular interest because the dopamine neurons in this nucleus die in **Parkinson**

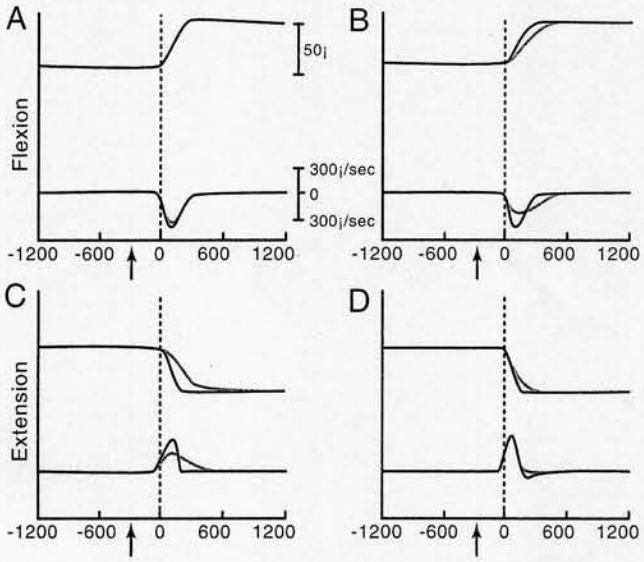

FIGURE 34.11 Wrist position and velocity in visually guided wrist movements before (black traces) and after (blue traces) a lesion of the globus pallidus pars interna. In each graph, the top traces represent wrist position and the lower traces represent wrist velocity. (A) Flexion with the flexor muscles loaded (movement made by further activating the loaded muscles). (B) Flexion with the extensor muscles loaded (movement made by turning off the loaded muscles). (C) Extension with the flexor muscles loaded (movement made by turning off the loaded muscles). (D) Extension with the extensor muscles loaded (movement made by further activating the loaded muscles). After the lesion, the peak velocity was lower for movements made by decreasing the activity of the loaded muscle than for those made by increasing the activity of the loaded muscle. From Mink and Thach.[94]

disease, a neurological disorder that affects older adults. The main symptoms of Parkinson disease are resting tremor that decreases during movement, slowness of movement (**bradykinesia**), paucity of movement (**akinesia**), muscular rigidity, and unstable posture. The primary pathology of the disease is a progressive degeneration of neurons in the SNpc. There is also some loss of dopamine neurons in the ventral tegmental area and of norepinephrine neurons in the locus coeruleus. Although Parkinson disease has been recognized since it was first described by James Parkinson in 1817, a reasonable animal model of the disease was not available until fairly recently. As we noted above, the interdigitation of the SNpc and SNpr has made selective electrolytic lesions of each area difficult to produce. In the 1970s, however, researchers discovered that injection of 6-hydroxydopamine (6-OHDA) bilaterally along the nigrastriatal projection causes selective degeneration of SNpc dopamine neurons. Lesions made in this way result in some of the abnormalities of Parkinson disease, namely, the slowness of movement and rigidity, but they do not produce tremor.[86] In the 1980s, a street drug contaminant called MPTP (see Box 34.3)[98–100] was found to produce all of the symptoms of Parkinson disease in humans and in certain species of monkeys.

Despite extensive investigation, the fundamental mechanism underlying the tremor in Parkinson disease is not known. Some evidence suggests that it results from abnormal bursting of neurons in the thalamus.[101] The slowness of movement in Parkinson disease has been associated with reduced magnitude and duration of muscle activity during movement.[86] In monkeys that have been given 6-OHDA or MPTP, the activity of motor cortex neurons during arm movements is also reduced compared with that in normal monkeys.[102] Some MPTP monkeys have abnormally increased neuronal activity in the STN and GPi and decreased activity in the GPe.[103] GPi neurons in the MPTP monkey have abnormal bursting activity and abnormally increased responses to somatosensory stimuli. It has been suggested that the increased activity of GPi neurons causes excessive inhibition of motor

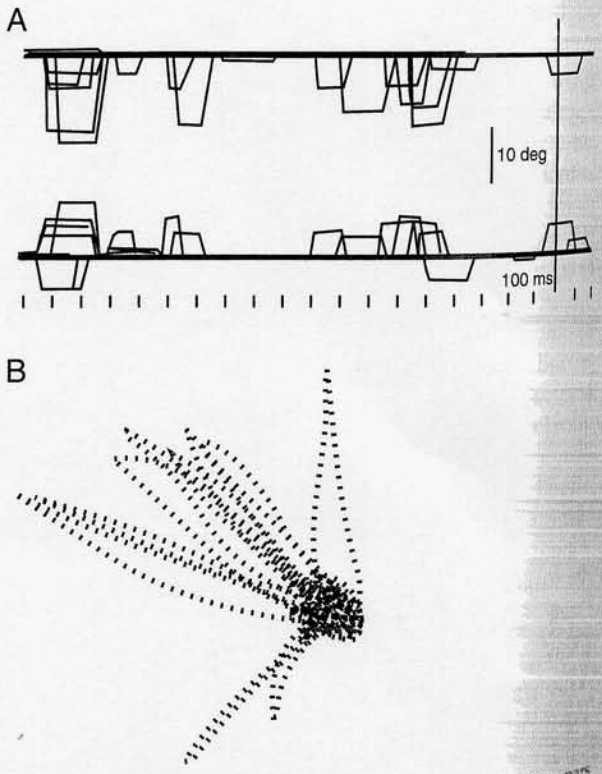

FIGURE 34.12 After inactivation of the substantia nigra pars reticulata, monkeys are unable to maintain fixation of gaze because of involuntary contraction of the eye muscles. (A) Vertical (top traces) and horizontal (bottom traces) eye position during attempted visual fixation. (B) The trajectory of involuntary eye movements in a monkey after injection of muscimol into the lateral SNpr. The monkey was instructed to maintain its gaze at the center dot. From Hikosaka and Wurtz.[96]

mechanisms in the cortex and brainstem, resulting in slower movements.[29,104]

The rigidity of Parkinson disease has been attributed in part to hyperactivity of the transcortical stretch reflex. Normally, this reflex acts to resist displacement from an actively held posture, but it is inhibited when subjects are instructed not to resist the displacement. People with Parkinson disease have abnormally active transcortical stretch reflexes and are unable to suppress them in response to instruction.[105] The inability to inhibit long-loop reflexes may also account for the postural instability of Parkinson disease. Parkinson patients have an inappropriate cocontraction of leg and back muscles in response to perturbation from an upright stance. When the same subjects are perturbed from a sitting position, they are unable to inhibit the postural reflexes that were active during stance.[106] This observation suggests that both rigidity and postural instability may involve an inability to suppress unwanted reflex activity.

Summary

1. Damage to any basal ganglia structures may cause slowness of voluntary movements, involuntary movements, involuntary postures, or a combination of these.
2. Damage to the striatum causes voluntary movements to be slow and may produce involuntary movements or postures depending on the mechanism of damage.
3. Damage to the subthalamic nucleus causes large-amplitude involuntary limb movements.
4. Damage to the globus pallidus causes slowness of movement, abnormal postures, and difficulty relaxing muscles, but does not delay movement initiation.
5. Damage to substantia nigra pars reticulata causes abnormal eye movements, but does not delay the initiation of eye movements.
6. Damage to substantia nigra pars compacta causes tremor at rest, slowness of movement, rigidity, and postural instability, which are the main features of Parkinson disease.

FUNDAMENTAL PRINCIPLES OF BASAL GANGLIA OPERATION

An old model of basal ganglia function proposed that the basal ganglia initiate movement. This model was based in large part on the manifestation of basal ganglia diseases. The paucity and slowness of movement in Parkinson disease were attributed to an inability to initiate movements, and the involuntary movements of chorea and hemiballismus were attributed to the release of normal motor systems from basal ganglia control. This model gained support from the fact that much of the output from the basal ganglia goes to parts of thalamus that project to the premotor and motor cortices. According to the model, motor programs are stored in the basal ganglia and are called up and sent to the motor cortex for execution. This model is no longer widely accepted, because it is now apparent that the basal ganglia are active relatively late in relation to movement and brain mechanisms that are known to be involved in the initiation of movement. Furthermore, lesions of the basal ganglia output nuclei do not delay the initiation of movement.

If the basal ganglia do not initiate movement, what do they do? We consider three current hypotheses. The first states that the basal ganglia contribute to the automatic execution of movement sequences. This hypothesis suggests that other mechanisms initiate the first component in a sequence, but the basal ganglia contain the programs for completing the sequence. The second hypothesis states that the basal ganglia circuitry is made up of opposing parallel pathways that adjust the magnitude of the inhibitory GPi output to increase or decrease movement. According to this hypothesis, increased GPi output slows movement and decreased GPi output increases movement. The third hypothesis states that the basal ganglia output is analogous to a brake. It proposes that a small part of the output decreases during voluntary movement to remove inhibition from the desired motor mechanism, while the majority of the output increases to prevent other motor mechanisms from competing with the desired mechanism.

Do the Basal Ganglia Automatically Generate Learned Movement Sequences?

The sequencing hypothesis states that the basal ganglia are responsible for the automatic execution of learned movement sequences.[107,108] Patients with Parkinson disease have difficulty moving several body parts simultaneously or sequentially, and this difficulty is more than one would expect from a simple addition of the deficits of each component of the movement. An example of difficulty with sequential movements in Parkinson disease is the phenomenon of **micrographia** (small writing). A patient begins to write a sentence with nearly normal-sized writing, but after several letters are written, the writing becomes progressively smaller so that by the end of the sentence, it may be illegible. In micrographia, the early components of the sequence are larger and faster than the

subsequent components. One experiment compared the performance of elbow flexion and hand grip individually and in sequence.[109] Patients with Parkinson disease performed each movement more slowly than did normal subjects. However, when each movement was part of a sequence, it was slowed to an even greater degree than when it was performed separately. In monkeys trained to perform two prompt wrist movements in sequence, some GPi neurons fired after the first component of the movement but before the second component.[108] Proponents of the sequencing hypothesis speculate that the loss of the GPi output signal in Parkinson disease is responsible for the relatively greater difficulty in producing sequential movements than in producing individual movements.

Do the Basal Ganglia Produce or Prevent Movement by Using Opposing Direct and Indirect Pathways?

The opponent parallel pathway hypothesis emphasizes two major paths of information flow from the striatum to the GPi and SNpr (Fig. 34.13).[29,104,110] One is an inhibitory "direct" pathway from the striatum to the GPi/SNpr. The other is a net excitatory "indirect" pathway from the striatum to the GPe (inhibitory), from the GPe to the STN (inhibitory), and from the STN to the GPi/SNpr (excitatory). This hypothesis maintains that the two pathways are in balance such that increased activity in the "direct" pathway causes decreased GPi/SNpr output, and increased activity in the "indirect" pathway causes increased GPi/SNpr output. By adjusting the balance, the cortical targets of the basal ganglia can be facilitated or inhibited. The hypothesis predicts that abnormally decreased output results in excessive movement (chorea) and abnormally increased output results in decreased movement (Parkinson disease). The primary evidence for this hypothesis is the finding that activity in the STN and GPi is increased in MPTP monkeys but decreased in monkeys with chorea.[93,103] How the physiology in these pathological states relates to the normal physiology of the basal ganglia output remains unclear.

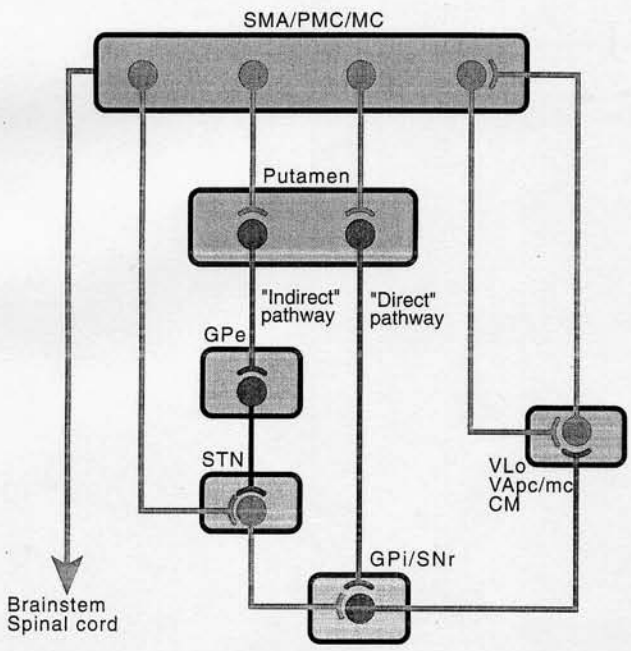

FIGURE 34.13 Schematic diagram of proposed "direct" and "indirect" pathways from the putamen to the GPi. See the text for a description. Red symbols represent inhibitory pathways, and green symbols represent excitatory pathways. From Alexander and Crutcher.[110]

Do the Basal Ganglia Act as a "Brake" to Prevent Unwanted Movement?

The output of the basal ganglia is inhibitory to posture and movement pattern generators in the cerebral cortex (via the thalamus) and in the brainstem. The inhibitory output neurons of the basal ganglia fire tonically at high frequencies. The brake hypothesis states that when a movement is initiated by a particular motor pattern generator, GPi neurons projecting to that generator decrease their firing frequency, thereby removing tonic inhibition and "releasing the brake" on that generator. GPi neurons projecting to other movement pattern generators increase their firing frequency, thereby increasing inhibition and "applying the brake" on those generators.[94,111] Thus, other postures and movements are prevented from interfering with the one selected.

Figure 34.14 illustrates how this mechanism might work. When one makes a voluntary movement, that movement is initiated by the prefrontal, premotor, and motor cortices and the cerebellum. The premotor and motor cortices send a corollary signal to the STN, exciting it. The STN projects to the GPi in a widespread pattern and excites it. In parallel, signals are sent from the cortex to the striatum, which inhibits the GPi focally via a direct pathway. The striatum can also disinhibit the GPi via two indirect pathways (striatum to GPe to GPi, and striatum to GPe to STN to SPi). The indirect pathways further focus the effects of the fast, excitatory, cortico-STN pathway and the slower, inhibitory, corticostriatal pathway to the GPi. The net result is to release the brake from the selected voluntary movement pattern generator and to apply the brake on potentially competing posture-holding pattern generators (transcortical, vestibular, tonic neck, and other postural reflexes).

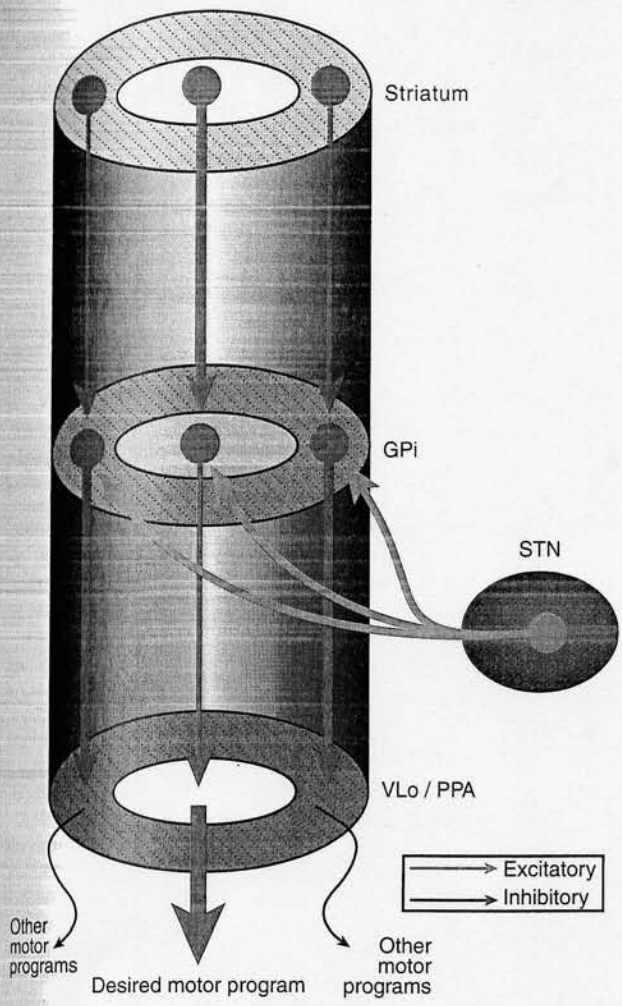

FIGURE 34.14 Relationship of proposed center-surround organization of the GPi to inputs from the striatum and subthalamic nucleus. During voluntary movement, excitatory STN neurons increase the activity of GPi neurons in the surround territory. At the same time, striatal neurons inhibit the functional center of the GPi in a focused manner. The GPi activity changes are conveyed to targets in the thalamus (VLo) and midbrain pedunculopontine area (PPA), causing disinhibition of neurons involved in the desired motor program and inhibition of surrounding neurons involved in competing motor programs. Excitatory projections are indicated by green arrows, and inhibitory projections are indicated by red arrows. The relative magnitude of activity is represented by line thickness.

Summary

The basal ganglia continue to be a target of active investigation. Their circuitry and chemistry are complicated and are still being defined. Diseases of the basal ganglia are relatively common, yet their causes are poorly understood at both a molecular and a systemic level. Although the prevailing hypotheses of basal ganglia differ substantially, they are not necessarily mutually exclusive. With further investigation, these hypotheses may be reconciled, consolidated, or superseded.

References

General

Adams, R. D., and Victor, M. (1993). *Principles of Neurology*, 5th ed. McGraw-Hill, New York.

Houk, J. C., Davis, J. L., and Beiser, D. G., eds. (1995). Models of information processing in the basal ganglia. In *Computational Neuroscience* (T. J. Sejnowski and T. A. Poggio, eds.). MIT Press, Cambridge, MA.

Mano, N., Hamada, I., and DeLong, M. R., eds. (1993). *Role of the Cerebellum and Basal Ganglia in Voluntary Movement*. Int. Congr. Ser. Elsevier, Amsterdam.

Parent, A. (1986). *Comparative Neurobiology of the Basal Ganglia*. Wiley, New York.

Penney, J. B., and Young, A. B. (1983). Speculations on the functional anatomy of basal ganglia disorders. *Annu. Rev. Neurosci.* **6:** 73–94.

Cited

1. Wilson, S. A. K. (1912). Progressive lenticular degeneration: A familial nervous system disease associated with cirrhosis of the liver. *Brain* **34:** 295–207.
2. Wilson, S. A. K. (1928). *Modern Problems in Neurology*. Arnold, London.
3. Nauta, W. J. H., and Mehler, W. H. (1966). Projections of the lentiform nucleus in the monkey. *Brain Res.* **1:** 3–42.
4. Carpenter, M. B. (1981). Anatomy of the corpus striatum and brain stem integrating systems. In *Handbook of Physiology* (V. B. Brooks, ed.), pp. 947–995, Sect. 1, Vol. II, Part 1. Am. Physiol. Soc. Bethesda, MD.
5. O'Rahilly, R., and Muller, F. (1994). *The Embryonic Human Brain*. Wiley-Liss, New York.
6. Gerfen, C. R. (1988). Synaptic organization of the striatum. *J. Electron. Microsc. Tech.* **10:** 265–281.
7. Kemp, J. M., and Powell, P. S. (1971). The structure of the caudate nucleus of the cat: Light and electron microscopy. *Philos. Trans. R. Soc. London, Ser. B* **262:** 383–401.
8. Wilson, C. J., and Groves, P. M. (1980). Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum: A study employing intracellular injection of horseradish peroxidase. *J. Comp. Neurol.* **194:** 599–614.
9. Phelps, P. E., Houser, C. R., and Vaughn, J. E. (1985). Immunocytochemical localization of choline acetyltransferase within the rat neostriatum: A correlated light and electron microscopic study of cholinergic neurons and synapses. *J. Comp. Neurol.* **238:** 286–307.
10. DiFiglia, M., and Aronin, N. (1982). Ultrastructural features of immunoreactive somatostatin neurons in the rat caudate nucleus. *J. Neurosci.* **2:** 1267–1274.
11. Kemp, J. M., and Powell, T. P. S. (1970). The corticostriate projection in the monkey. *Brain* **93:** 525–546.
12. Cherubini, E., Herrling, P. L., Lanfumey, L., and Stanzione, P. (1988). Excitatory amino acids in synaptic excitation of rat striatal neurones in vitro. *J. Physiol. (London)* **400:** 677–690.
13. Bouyer, J. J., Park, D. H., Joh, T. H., and Pickel, V. M. (1984). Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. *Brain Res.* **302:** 267–275.
14. Jones, E. G., Coulter, J. D., Burton, H., and Porter, R. (1977). Cells of origin and terminal distribution of corticostriatal fibers

arising in the sensory-motor cortex of monkeys. *J. Comp. Neurol.* **173:** 53–80.

15. Goldman, P. S., and Nauta, W. J. H. (1977). An intricately patterned prefronto-caudate projection in the rhesus monkey. *J. Comp. Neurol.* **171:** 369–386.
16. Kunzle, H. (1975). Bilateral projections from precentral motor cortex to putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis. Brain Res.* **88:** 195–209.
17. Alexander, G. E., DeLong, M. R., and Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* **9:** 357–381.
18. Selemon, L. D., and Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J. Neurosci.* **5:** 776–794.
19. Flaherty, A. W., and Graybiel, A. M. (1991). Corticostriatal transformations in the primate somatosensory system. Projections from physiologically mapped body-part representations. *J. Neurophysiol.* **66:** 1249–1263.
20. Graybiel, A. M., Aosaki, T., Flaherty, A. W., and Kimura, M. (1994). The basal ganglia and adaptive motor control. *Science* **265:** 1826–1831.
21. Lapper, S. R., and Bolam, J. P. (1992). Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. *Neuroscience* **51:** 533–545.
22. Sadikot, A. F., Parent, A., and Francois, C. (1992). Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: A PHA-L study of subcortical projections. *J. Comp. Neurol.* **315:** 137–159.
23. Izzo, P. N., and Bolam, J. P. (1988). Cholinergic synaptic input to different parts of spiny striatonigral neurons in the rat. *J. Comp. Neurol.* **269:** 219–234.
24. Penny, G. R., Afsharpour, S., and Kitai, S. T. (1986). The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: Evidence for partial population overlap. *Neuroscience* **17:** 1011–1045.
25. Surmeier, D. J., Reiner, A., Levine, M. S., and Ariano, M. A. (1993). Are neostriatal dopamine receptors co-localized? *Trends Neurosci.* **16:** 299–305.
26. Ribak, C. E., Vaughn, J. E., and Roberts, E. (1979). The GABA neurons and their axon terminals in rat corpus striatum as demonstrated by GAD immunocytochemistry. *J. Comp. Neurol.* **187:** 261–283.
27. Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J., and Sibley, D. R. (1990). D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* **250:** 1429–1432.
28. Gerfen, C. R., and Young, W. S., III (1988). Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: An in situ hybridization histochemistry and fluorescent retrograde tracing study. *Brain Res.* **460:** 161–167.
29. Albin, R. L., Young, A. B., and Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci.* **12:** 366–375.
30. Graybiel, A. M., and Ragsdale, C. W. (1978). Histochemically distinct compartments in the striatum of human, monkey and cat demonstrated by acetylcholinesterase staining. *Proc. Natl. Acad. Sci. U.S.A.* **75:** 5723–5726.
31. Gerfen, C. R. (1992). The neostriatal mosaic: Multiple levels of compartmental organization in the basal ganglia. *Annu. Rev. Neurosci.* **15:** 285–320.
32. Graybiel, A. M., Ragsdale, C. W., Yoneika, E. S., and Elde, R. P. (1981). An immunohistochemical study of enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with striosomal compartments visible with acetylcholinesterase staining. *Neuroscience* **6:** 377–397.
33. Rouzaire-Dubois, B., and Scarnati, E. (1987). Pharmacological study of the cortical-induced excitation of subthalamic nucleus neurons in the rat: Evidence for amino acids as putative neurotransmitters. *Neuroscience* **21:** 429–440.
34. Fujimoto, K., and Kita, H. (1993). Response characteristics of subthalamic neurons to the stimulation of the sensimotor cortex in the rat. *Brain Res.* **609:** 185–192.
35. Hartmann-von Monakow, K., Akert, K., and Kunzle, H. (1978). Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. *Exp. Brain Res.* **33:** 395–403.
36. Kita, H., Chang, H. T., and Kitai, S. T. (1983). Pallidal inputs to subthalamus: Intracellular analysis. *Brain Res.* **264:** 255–265.
37. Rinvik, E., and Ottersen, O. P. (1993). Terminals of subthalamonigral fibres are enriched with glutamate-like immunoreactivity: An electron microscopic, immunogold analysis in the cat. *J. Chem. Neuroanat.* **6:** 19–30.
38. Brotchie, J. M., and Crossman, A. R. (1991). D-[^{3}H]Aspartate and [^{14}C]GABA uptake in the basal ganglia of rats following lesions in the subthalamic region suggest a role for excitatory amino acid but not GABA-mediated transmission in subthalamic nucleus efferents. *Exp. Neurol.* **113:** 171–181.
39. Parent, A., Smith, Y., Filion, M., and Dumas, J. (1989). Distinct afferents to internal and external pallidal segments in the squirrel monkey. *Neurosci. Lett.* **96:** 140–144.
40. Kita, H. (1992). Responses of globus pallidus neurons to cortical stimulation: Intracellular study in the rat. *Brain Res.* **589:** 84–90.
41. DiFiglia, M., and Rafols, J. A. (1988). Synaptic organization of the globus pallidus. *J. Electron. Microsc. Tech.* **10:** 247–263.
42. Francois, C., Percheron, G., Yelnik, J., and Heyner, S. (1984). Golgi analysis of the primate globus pallidus. I. Inconstant processes of large neurons, other neuronal types, and afferent axons. *J. Comp. Neurol.* **227:** 182–199.
43. Percheron, G., Yelnik, J., and Francois, C. (1984). A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striato-pallidal complex. *J. Comp. Neurol.* **227:** 214–227.
44. Parent, A., and Hazrati, L.-N. (1993). Anatomical aspects of information processing in primate basal ganglia. *Trends Neurosci.* **16:** 111–116.
45. Penney, J. B., and Young, A. B. (1981). GABA as the pallidothalamic neurotransmitter: Implications for basal ganglia function. *Brain Res.* **207:** 195–199.
46. Parent, A., and De Bellefeuille, L. (1982). Organization of efferent projections from the internal segment of globus pallidus in primate as revealed by fluorescence retrograde labelling method. *Brain Res.* **245:** 201–213.
47. DeVito, J. L., and Anderson, M. E. (1982). An autoradiographic study of efferent connections of the globus pallidus in *Macaca mulatta. Exp. Brain Res.* **46:** 107–117.
48. Middleton, F. A., and Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* **266:** 458–461.
49. Hoover, J. E., and Strick, P. L. (1993). Multiple output channels in the basal ganglia. *Science* **259:** 819–821.
50. Rye, D. B., Lee, H. J., Saper, C. B., and Wainer, B. H. (1988). Medullary and spinal efferents of the pedunculopontine tegmental nucleus and adjacent mesopontine tegmentum in the rat. *J. Comp. Neurol.* **269:** 315–341.
51. Francois, C., Yelnik, J., and Percheron, G. (1987). Golgi study of the primate substantia nigra. II. Spatial organization of dendritic arborizations in relation to the cytoarchitectonic bound-

aries and to the striatonigral bundle. *J. Comp. Neurol.* **265:** 473–493.
52. Carpenter, M. B., Nakano, K., and Kim, R. (1976). Nigrothalamic projections in the monkey demonstrated by autoradiographic techniques. *J. Comp. Neurol.* **165:** 401–416.
53. Ueki, A. (1983). The mode of nigro-thalamic transmission investigated with intracellular recording in the cat. *Exp. Brain Res.* **49:** 116–124.
54. Oertel, W. H., and Mugnaini, E. (1984). Immunocytochemical studies of GABAergic neurons in rat basal ganglia and their relations to other neuronal systems. *Neurosci. Lett.* **47:** 233–238.
55. Kievit, J., and Kuypers, H. G. J. M. (1977). Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. *Exp. Brain Res.* **29:** 299–322.
56. von Krosigk, M., Smith, Y., Bolam, J. P., and Smith, A. D. (1992). Synaptic organization of GABAergic inputs from the striatum and the globus pallidus onto neurons in the substantia nigra and retrorubral field which project to the medullary reticular formation. *Neuroscience* **50:** 531–549.
57. Francois, C., Percheron, G., Yelnik, J., and Tande, D. (1988). A topographic study of the course of nigral axons and of the distribution of pallidal axonal endings in the centre median-parafascicular complex of macaques. *Brain Res.* **473:** 181–186.
58. Rinvik, E., Grofova, I., and Ottersen, O. P. (1976). Demonstration of nigrotectal and nigroreticular projections in the cat by axonal transport of proteins. *Brain Res.* **112:** 388–394.
59. Hikosaka, O., and Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. *J. Neurophysiol.* **49:** 1285–1301.
60. Rouzaire-Dubois, B., Hammond, C., Hamon, B., and Feger, J. (1980). Pharmacological blockade of the globus pallidus-induced inhibitory response of subthalamic cells in the rat. *Brain Res.* **200:** 321–329.
61. Bolam, J. P., and Smith, Y. (1992). The striatum and the globus pallidus send convergent synaptic inputs onto single cells in the entopeduncular nucleus of the rat: A double anterograde labelling study combined with postembedding immunocytochemistry for GABA. *J. Comp. Neurol.* **321:** 456–476.
62. Graybiel, A. M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci.* **13:** 244–254.
63. Hedreen, J. C., and DeLong, M. R. (1991). Organization of striatopallidal, striatonigral, and nigrostriatal projections in the macaque. *J. Comp. Neurol.* **304:** 569–595.
64. Crutcher, M. D., and DeLong, M. R. (1984). Single cell studies of the primate putamen. I. Functional organization. *Exp. Brain Res.* **53:** 233–243.
65. Kimura, M., Kato, M., and Shimazaki, H. (1990). Physiological properties of projection neurons in the monkey striatum to the globus pallidus. *Exp. Brain Res.* **82:** 672–676.
66. Alexander, G. E., and DeLong, M. R. (1985). Microstimulation of the primate striatum. II. Somatopic organization of striatal microexcitable zones and their relation to neuronal response properties. *J. Neurophysiol.* **53:** 1417–1430.
67. Crutcher, M. D., and DeLong, M. R. (1984). Single cell studies of the primate putamen. II. Relations to direction of movements and patterns of muscular activity. *Exp. Brain Res.* **53:** 244–258.
68. Montgomery, E. B., and Buchholz, S. R. (1991). The striatum and motor cortex in motor initiation and execution. *Brain Res.* **549:** 222–229.
69. Romo, R., Scarnati, E., and Schultz, W. (1992). Role of primate basal ganglia and frontal cortex in the internal generation of movements. II. Movement-related activity in the anterior striatum. *Exp. Brain Res.* **91:** 385–395.
70. Schultz, W., and Romo, R. (1992). Role of primate basal ganglia and frontal cortex in the internal generation of movements. I. Preparatory activity in the anterior striatum. *Exp. Brain Res.* **91:** 363–384.
71. Alexander, G. E. (1987). Selective neuronal discharge in monkey putamen reflects intended direction of planned limb movements. *Exp. Brain Res.* **67:** 623–634.
72. Aosaki, T., Tsubokawa, H., Ishida, A., Watanabe, K., Graybiel, A. M., and Kimura, M. (1994). Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *J. Neurosci.* **14:** 3969–3984.
73. Wichmann, T., Bergman, H., and DeLong, M. R. (1994). The primate subthalamic nucleus. I. Functional properties in intact animals. *J. Neurophysiol.* **72:** 494–506.
74. Hikosaka, O., Matsumura, M., Kojima, J., and Gardiner, T. W. (1993). Role of the basal ganglia in initiation and suppression of saccadic eye movements. In *Role of the Cerebellum and Basal Ganglia in Voluntary Movement*, (N. Mano, I. Hamada, and M. R. DeLong, eds.). Elsevier, Amsterdam.
75. DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. (1985). Primate globus pallidus and subthalamic nucleus: functional organization. *J. Neurophysiol.* **53:** 530–543.
76. Georgopoulos, A. P., DeLong, M. R., and Crutcher, M. D. (1983). Relation between parameters of step-tracking movements and single cell discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. *J. Neurosci.* **3:** 1586–1598.
77. DeLong, M. R. (1971). Activity of pallidal neurons during movement. *J. Neurophysiol.* **34:** 414–427.
78. Hikosaka, O., and Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. I. Relation of visual and auditory responses to saccades. *J. Neurophysiol.* **49:** 1230–1253.
79. DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. (1983). Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. *J. Neurosci.* **3:** 1599–1606.
80. Mink, J. W., and Thach, W. T. (1991). Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. *J. Neurophysiol.* **65:** 301–329.
81. Hikosaka, O., and Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. *J. Neurophysiol.* **49:** 1254–1267.
82. Hikosaka, O., and Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J. Neurophysiol.* **49:** 1268–1284.
83. Mink, J. W., and Thach, W. T. (1991). Basal ganglia motor control. I. Nonexclusive relation of pallidal discharge to five movement modes. *J. Neurophysiol.* **65:** 273–300.
84. Schultz, W., Apicella, P., and Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.* **13:** 900–913.
85. Schultz, W., and Romo, R. (1990). Dopamine neurons of the monkey midbrain: Contingencies of responses to stimuli eliciting immediate behavioral reactions. *J. Neurophysiol.* **63:** 607–624.
86. DeLong, M. R., and Georgopoulos, A. P. (1981). Motor functions of the basal ganglia. In *Handbook of Physiology* (V. B. Brooks, ed.), pp. 1017–1062, Sect. 1, Vol. II, Part 1. Am. Physiol. Soc., Bethesda, MD.

87. Kato, M., and Kimura, M. (1992). Effects of reversible blockade of basal ganglia on a voluntary arm movement. *J. Neurophysiol.* **68:** 1516–1534.
88. Thompson, P. D., Berardelli, A., Rothwell, J. C., Day, B. L., Dick, J. P. R., Benecke, R., and Marsden, C. D. (1988). The coexistence of bradykinesia and chorea in Huntington's disease and its implications for theories of basal ganglia control of movement. *Brain* **111:** 223–244.
89. Crossman, A. R. (1987). Primate models of dyskinesia: The experimental approach to the study of basal ganglia-related involuntary movement disorders. *Neuroscience* **21:** 1–40.
90. Hamada, I., and DeLong, M. R. (1992). Excitotoxic acid lesions of the primate subthalamic nucleus result in transient dyskinesias of the contralateral limbs. *J. Neurophysiol.* **68:** 1850–1858.
91. Robertson, R. G. Farmery, S. M., Sambrook, M. A., and Crossman, A. R. (1989). Dyskinesia in the primate following injection of an excitatory amino acid antagonist into the medial segment of the globus pallidus. *Brain Res.* **476:** 317–322.
92. Carpenter, M. B., Whittier, J. R., and Mettle, F. A. (1950). Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys. *J. Comp. Neurol.* **92:** 293–331.
93. Hamada, I., and DeLong, M. R. (1992). Excitotoxic acid lesions of the primate subthalamic nucleus result in reduced pallidal neuronal activity during active holding. *J. Neurophysiol.* **68:** 1859–1866.
94. Mink, J. W., and Thach, W. T. (1991). Basal ganglia motor control. III. Pallidal ablation: Normal reaction time, muscle cocontraction, and slow movement. *J. Neurophysiol.* **63:** 330–351.
95. Denny-Brown, D. (1962). *The Basal Ganglia.* Oxford University Press, London.
96. Hikosaka, O., and Wurtz, R. H. (1985). Modification of saccadic eye movements by GABA-related substances. II. Effects of muscimol in monkey substantia nigra pars reticulata. *J. Neurophysiol.* **53:** 292–308.
97. Hikosaka, O., and Wurtz, R. H. (1985). Modification of saccadic eye movements by GABA-related substances. I. Effect of muscimol and bicuculline in monkey superior colliculus. *J. Neurophysiol.* **53:** 266–291.
98. Langston, J. W., Ballard, P., Tetrud, J., and Irwin, I. (1983). Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* **219:** 979–980.
99. Tipton, K. F., and Singer, T. P. (1993). Advances in our understanding of the mechanisms of the neurotoxicity of MPTP and related compounds. *J. Neurochem.* **61:** 1191–1206.
100. Crossman, A. R., Clarke, C. E., Boyce, S., Robertson, R. G., and Sambrook, M. A. (1987). MPTP-induced Parkinsonism in the monkey: Neurochemical pathology, complications of treatment and pathophysiological mechanisms. *Can. J. Neurol. Sci.* **14:** 428–435.
101. Pare, D., Curro'Dossi, R., and Steriade, M. (1990). Neuronal basis of the parkinsonian resting tremor: A hypothesis and its implications for treatment. *Neuroscience* **35:** 217–226.
102. Watts, R. L., and Mandir, A. S. (1992). The role of motor cortex in the pathophysiology of voluntary movement deficits associated with Parkinsonism. *Neurol. Clin.* **10:** 451–469.
103. Wichmann, T., Bergman, H., and DeLong, M. R. (1994). The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of Parkinsonism. *J. Neurophysiol.* **72:** 521–530.
104. DeLong, M. R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13:** 281–285.
105. Tatton, W. G., and Lee, R. G. (1975). Evidence for abnormal long-loop reflexes in rigid Parkinsonian patients. *Brain Res.* **100:** 671–676.
106. Horak, F. B., Nutt, J. G., and Nashner, L. M. (1992). Postural inflexibility in Parkinsonian subjects. *J. Neurol. Sci.* **111:** 46–58.
107. Marsden, C. D. (1987). What do the basal ganglia tell premotor cortical areas? *Ciba Found. Symp.* **132:** 282–300.
108. Brotchie, P., Iansek, R., and Horne, M. K. (1991). Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. *Brain* **114:** 1685–1702.
109. Benecke, R., Rothwell, J. C., Dick, J. P. R., Day, B. L., and Marsden, C. D. (1986). Performance of simultaneous movements in patients with Parkinson's disease. *Brain* **109:** 739–757.
110. Alexander, G. E., and Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends Neurosci.* **13:** 266–271.
111. Mink, J. W., and Thach, W. T. (1993). Basal ganglia intrinsic circuits and their role in behavior. *Curr. Opin. Neurobiol.* **3:** 950–957.
112. DeLong, M. R., Georgopoulos, A. P., Crutcher, M. D., Mitchell, S. J., Richardson, R. T., and Alexander, G. E. (1984). Functions of the basal ganglia. *Ciba Found. Symp.* **107:** 64–82.