38

The Basal Ganglia

Highlights

The traditional view that the basal ganglia play a role in movement arises primarily because diseases of the basal ganglia, such as Parkinson and Huntington disease, are associated with prominent disturbances of movement, and from the belief that basal ganglia neurons send their output exclusively to the motor cortex by way of the thalamus. However, we now know that the basal ganglia also project to wide areas of the brain stem and via the thalamus to nonmotor areas of the cerebral cortex and limbic system, thereby providing a mechanism whereby they contribute to a wide variety of cognitive, motivational, and affective operations. This understanding also explains why diseases of the basal ganglia are frequently associated with complex cognitive, motivational, and affective dysfunction in addition to the better-known motor disturbances.

This chapter provides a perspective on the fundamental contributions of the basal ganglia (Figure 38–1) to overall brain function. Recent advances in the fields of artificial neural networks and robotics emphasize that behavioral function is an emergent property of signal processing in physically connected networks (Chapter 5). Thus, how components of networks are connected and how their input signals are transformed into output signals impose important constraints on final behavioral outputs. We first describe the principal anatomical and physiological features of the basal ganglia network and consider the constraints these might impose on their function. We consider the extent to which the basal ganglia have been conserved during vertebrate brain evolution and, based on these insights, review evidence suggesting that the basal ganglia's normal functions are to select between incompatible behaviors and to mediate reinforcement learning. We conclude by examining important insights into how the system can malfunction in some of the major diseases involving the basal ganglia.

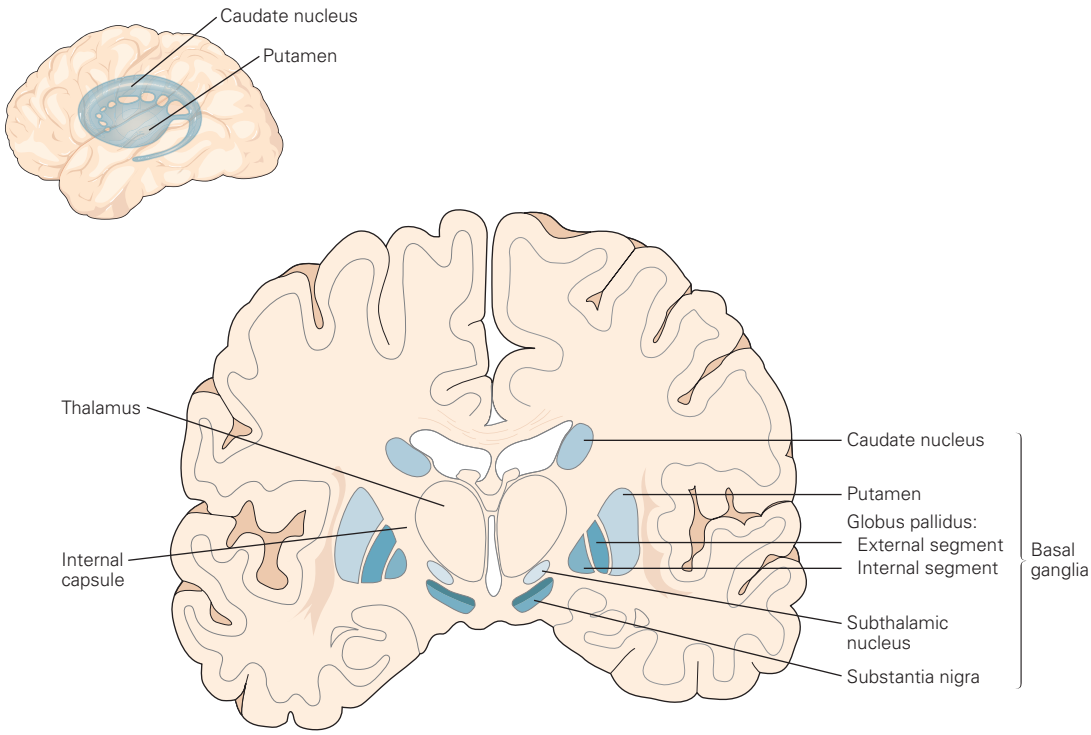

Figure 38–1 The basal ganglia and surrounding structures. The nuclei of the basal ganglia are identified on the right in this coronal section of a human brain. (Adapted from Nieuwenhuys, Voogd, and van Huijzen 1981.)

The Basal Ganglia Network Consists of Three Principal Input Nuclei, Two Main Output Nuclei, and One Intrinsic Nucleus

The striatum (a collective term for the caudate nucleus and putamen; see Figure 38–1), subthalamic nucleus, and substantia nigra pars compacta/ventral tegmental area are the three major input nuclei of the basal ganglia, receiving signals directly and indirectly from structures distributed throughout the neuraxis (Figure 38–2).

The Striatum, Subthalamic Nucleus, and Substantia Nigra Pars Compacta/Ventral Tegmental Area Are the Three Principal Input Nuclei of the Basal Ganglia

The striatum is the largest nucleus of the basal ganglia. It receives direct input from most regions of the cerebral cortex and limbic structures, including the amygdala and hippocampus. Important input from sensorimotor and motivational regions of the brain stem is relayed indirectly via the thalamus. In rodents, the number of contacts received in the striatum from the cerebral cortex and thalamus are approximately equivalent. Finally, important modulatory input to the striatum comes from the substantia nigra pars compacta (dopamine), midbrain raphe (serotonin), and pedunculopontine nucleus (acetylcholine).

The striatum is subdivided functionally on the basis of the organization of input connections, principally the topographically organized afferents from the cerebral cortex. Limbic, associative, and sensorimotor territories are generally recognized along a ventromedial-dorsolateral continuum. This diversity of input shows that the basal ganglia receive signals from brain regions involved in different motivational, emotional, cognitive, and sensorimotor processes, implying that whatever the basal ganglia are doing, they are doing it for a wide range of brain processes.

An additional architectural feature of the striatum suggests that the basal ganglia are performing more or less the same operations on their inputs from functionally diverse afferent structures. Specifically, within each of the striatum's functional territories, the cellular architecture is remarkably similar. In all regions, inhibitory γ-aminobutyric acid (GABA)-ergic medium spiny neurons are the principal cell type (>90% of all neurons). In addition, in all functionally defined regions, the medium spiny neurons are separated into two populations according to the relative expression of neuroactive peptides (substance P and dynorphin versus enkephalin) or the expression of D_1 and D_2 dopamine receptors, which are thought to positively and negatively modulate cyclic adenosine monophosphate signaling in these neurons. These populations contribute differentially to different efferent projections of the striatum. In addition to these long-range inhibitory connections to other basal ganglia nuclei, medium spiny neurons also send local collaterals to adjacent cells. Colocalized GABAergic and peptidergic neurotransmission provides local mutually inhibitory and excitatory influences. The remaining 5% to 10% of neurons in the striatum are purely GABAergic and cholinergic interneurons, which can be distinguished according to neurochemical, electrophysiological, and in some cases morphological characteristics. The fact that this local cellular architecture is present in all functional regions suggests that neurons in the striatum are applying the same or similar computations on functionally diverse afferent pathways.

The subthalamic nucleus has traditionally been considered an important internal relay in the "indirect output pathway" from the striatum to the basal ganglia output nuclei (see below). It is now also recognized as a second important input nucleus of the basal

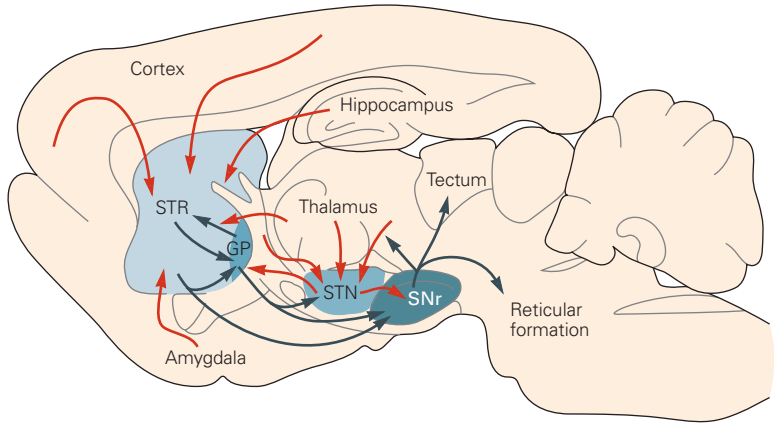

Figure 38–2 The principal input, intrinsic, and output connections of the mammalian basal ganglia. The main input nuclei are the striatum (**STR**), subthalamic nucleus (**STN**), and substantia nigra pars compacta (not shown). They receive input directly from the thalamus, cerebral cortex, and limbic structures (amygdala and hippocampus). The main output nuclei are the substantia nigra pars reticulata (**SNr**) and internal globus pallidus/entopeduncular nucleus (not shown). The external globus pallidus (**GP**) is classified as an intrinsic nucleus as most of its connections are with other basal ganglia nuclei. Structures are shown on a sagittal schematic of the rodent brain. **Red** and **dark gray arrows** denote excitatory and inhibitory connections, respectively.

ganglia. Topographically organized inputs derive not only from large parts of frontal cortex, but also from various thalamic and brain stem structures. The subthalamic nucleus is the only component of the basal ganglia that has excitatory (glutamatergic) output connections. These project to both output nuclei and to the intrinsic external globus pallidus.

The substantia nigra pars compacta/ventral tegmental area contain an important population of dopaminergic neurons. These neurons represent the third major input station of the basal ganglia and give rise to the nigrostriatal and mesolimbic/mesocortical dopamine projections. They receive significant afferent connections from other basal ganglia nuclei (the striatum, globus pallidus, and subthalamus), but also from many structures in the brain stem (eg, superior colliculus, rostromedial tegmental region, raphe nuclei, pedunculopontine nucleus, and parabrachial area). Other afferent connections are from the frontal cortex and the amygdala. This pattern of connectivity is important because it suggests the most important direct influence over the dopaminergic neurons arises from evolutionarily ancient parts of the brain (see below).

Individual dopaminergic neurons have highly branching axons that project into extensive regions of not only the other basal ganglia nuclei but also external structures (eg, frontal cortex, septal area, amygdala, habenula). This suggests that their important modulatory signals are widely broadcast throughout targeted structures. The highest concentration of dopaminergic terminals is found in the striatum, where synaptic and nonsynaptic contacts are formed with both medium spiny cells and interneurons. The existence of nonsynaptic contacts gives rise to what has been called *volume transmission*. This occurs when neurotransmitters diffuse through the brain's extracellular fluid from release points that may be remote from targeted cells. Consequently, volume transmission typically has a longer time course than synaptic neurotransmission. Deployment of volume transmission in targeted structures is further evidence for the idea that the effects of dopamine in targeted structures are widely broadcast and spatially imprecise. Variable proportions of GABAergic neurons (substantia nigra and the ventral tegmental area) and glutamatergic neurons (ventral tegmental area) contribute to local processing in these structures.

The Substantia Nigra Pars Reticulata and the Internal Globus Pallidus Are the Two Principal Output Nuclei of the Basal Ganglia

The internal globus pallidus/entopeduncular nucleus is one of the two principal output nuclei. It receives inputs from other basal ganglia nuclei and projects to external targets in the thalamus and brain stem. GABAergic input from the striatum and external globus pallidus are inhibitory, while input from the subthalamic nucleus is glutamatergic and excitatory. Neurons of the internal globus pallidus are themselves GABAergic and have high levels of tonic activity. Under normal circumstances, this imposes powerful inhibitory effects on targets in the thalamus, lateral habenula, and brain stem.

The substantia nigra pars reticulata is the second principal output nucleus. It also receives afferents from other basal ganglia nuclei and provides efferent connections to the thalamus and brain stem. Inhibitory (GABAergic) inputs come from the striatum and globus pallidus (external) and excitatory input from the subthalamus. Pars reticulata neurons are also GABAergic and impose strong inhibitory control over parts of the thalamus and brain stem, including the superior colliculus, pedunculopontine nucleus, and parts of the midbrain and medullary reticular formation.

The External Globus Pallidus Is Mostly an Intrinsic Structure of the Basal Ganglia

Most connections of the globus pallidus are with other basal ganglia nuclei, including inhibitory (GABAergic) input from the striatum and excitatory (glutamatergic) input from the subthalamus, and the globus pallidus provides inhibitory efferent connections to all the basal ganglia's input and output nuclei. This pattern of connections suggests that that the external globus pallidus is an essential regulator of internal basal ganglia activity.

Having described the core components of the basal ganglia, we will now consider in more detail how they are connected, first with each other and then with external structures in the brain.

The Internal Circuitry of the Basal Ganglia Regulates How the Components Interact

The Traditional Model of the Basal Ganglia Emphasizes Direct and Indirect Pathways

An influential interpretation of the intrinsic circuitry of the basal ganglia was proposed in the late 1980s by Roger Albin and colleagues (Figure 38–3A). In their scheme, signals originating in the cerebral cortex are distributed to two populations of medium spiny output neurons in the striatum.

Neurons containing substance P and a preponderance of D_1 dopamine receptors make direct inhibitory

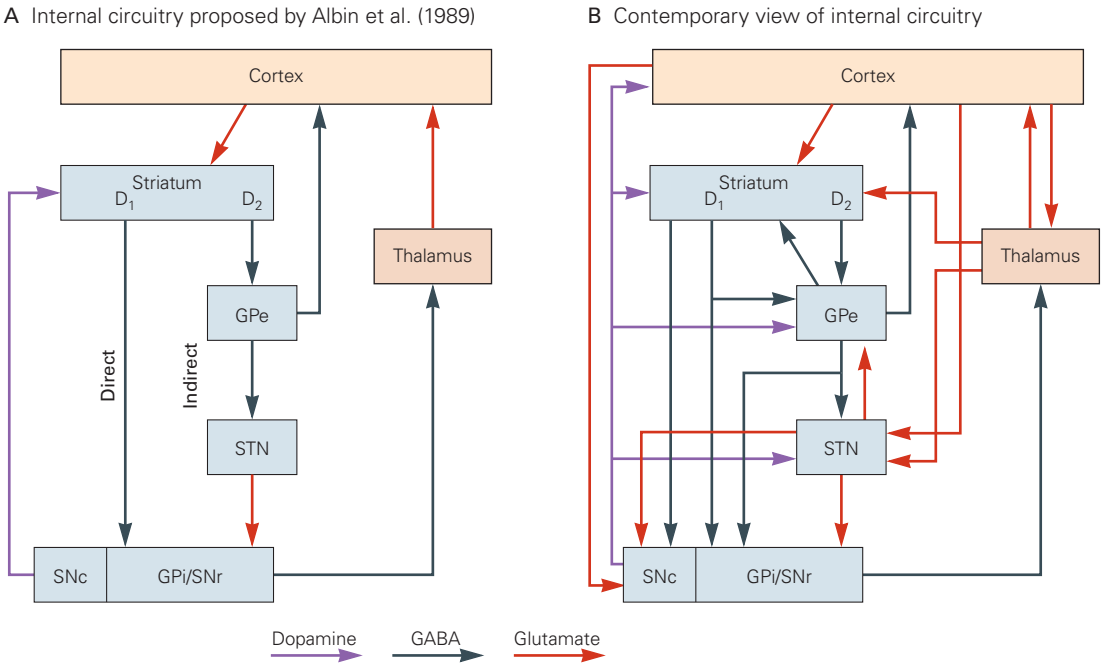

Figure 38–3 Intrinsic connections within the basal ganglia.

A. The influential proposal by Roger Albin and colleagues (1989) is presented, where output of the basal ganglia is determined by the balance between a *direct pathway* from the striatum to the output nuclei (internal globus pallidus [**Gpi**] and substantial nigra pars reticulata [**SNr**]), which promotes behavior, and an *indirect pathway* from the striatum to the output nuclei via relays in the external globus pallidus (**GPe**) and subthalamic nucleus (**STN**), which suppresses behavior. The balance between the direct and indirect projections was thought to be regulated by afferent dopaminergic signals from substantia nigra pars compacta (**SNc**) acting on differentially distributed D_1 and D_2 dopamine receptors.

B. More recent anatomical investigations have revealed a rather more complex organization where the transformations of basal ganglia inputs that generate outputs are less easy to predict.

contact with the basal ganglia output nuclei—the direct pathway. In contrast, striatal neurons containing enkephalin and expressing mainly D_2 dopamine receptors make excitatory contact with the output nuclei via relays in the globus pallidus and subthalamus—the indirect pathway. Basal ganglia output was thought to reflect a cortically determined balance between these inhibitory and excitatory projections terminating on the two output structures (the internal globus pallidus and substantia nigra pars reticulata). In this model, a behavior would be promoted when the direct pathway was dominant and inhibited when the indirect pathway was dominant.

Detailed Anatomical Analyses Reveal a More Complex Organization

Recent anatomical observations show that the internal circuitry of the basal ganglia is more complex than originally envisaged (Figure 38–3B). The main findings have been that: (1) medium spiny neurons of the direct pathway also provide collateral input to the globus pallidus; (2) globus pallidus neurons also make direct contact with the output nuclei in addition to the traditional indirect connections to the subthalamus—often with branching collaterals to all three structures; (3) the globus pallidus also projects back to the striatum and to structures outside the basal ganglia; (4) the subthalamic nucleus also projects back to the external globus pallidus, in addition to the feedforward connections to the two basal ganglia output nuclei; and (5) major inputs to the subthalamic nucleus originate from both cortical and subcortical structures external to the basal ganglia. Consequently, the subthalamus is now considered a major input structure of the basal ganglia (see above), rather than a simple relay in the intrinsic indirect projection. A modern appreciation of this complex organization within the basal ganglia suggests it is no longer possible to intuit how a particular input might be transformed by the basal ganglia to generate a specific output. For this reason, computational modeling of the internal circuitry of the basal ganglia has become increasingly important.

Although the overall pattern of intrinsic circuitry is complex (Figure 38–3B), connections between components of the basal ganglia are topographically ordered

throughout. Some of these projections are comparatively focused (eg, the striatonigral projection), while others are more diffuse (eg, the subthalamonigral projection). Significant reductions in the comparative numbers of neurons in afferent structures, the striatum, and the output nuclei suggest a dramatic compression of information as it is processed within the basal ganglia.

Basal Ganglia Connections With External Structures Are Characterized by Reentrant Loops

Inputs Define Functional Territories in the Basal Ganglia

The functional status of inputs to the striatum from the cerebral cortex, limbic structures, and thalamus provides the rationale for classifying functional territories within the basal ganglia nuclei (limbic, associative, and sensorimotor). However, the manner in which the afferent projections make contact with neurons of the basal ganglia nuclei suggests important functional differences. For example, axons arriving in the striatum from the cerebral cortex and central lateral thalamic nucleus appear to make few contacts with many striatal neurons. In contrast, inputs from other regions, principally the parafascicular thalamic nucleus, have axons that make many contacts with fewer individual striatal neurons. Afferent connections to the subthalamic nucleus, at least from cerebral cortex, are also topographically organized according to the limbic, associative, and sensorimotor classification. However, there is no evidence of the same kind of precise topographical input from external structures to SNc and VTA dopamine neurons in the ventral midbrain.

Output Neurons Project to the External Structures That Provide Input

Basal ganglia output neurons project to regions of the thalamus (the intralaminar and ventromedial nuclei) that project back to basal ganglia input nuclei as well as to those regions of cortex that provided the original inputs to the striatum. Similarly, outputs from the basal ganglia to the brain stem tend to target those regions that provide input to the striatum via the thalamic midline and intralaminar nuclei. Importantly, projections from the basal ganglia output nuclei to the thalamus and brain stem are also topographically ordered.

Finally, many output projections of the basal ganglia are extensively collateralized, thereby simultaneously contacting targets in the thalamus, midbrain, and hindbrain. An example of the functional consequences of this organization is that a subset of neurons in the substantia nigra pars reticulata associated with oral behavior can simultaneously influence the activity in the specific regions of the thalamus/cortex, midbrain, and hindbrain that interact during the production of oral behavior.

Reentrant Loops Are a Cardinal Principle of Basal Ganglia Circuitry

Spatial topographies associated with input projections, intrinsic connections, and outputs of the basal ganglia provided the basis for the influential organizational principle suggested by Garrett Alexander and colleagues in 1989. Connections between the cerebral cortex and basal ganglia can be viewed as a series of reentrant parallel projecting, partly segregated, cortico-striato-nigro-thalamo-cortical loops or channels (Figure 38–4). Thus, an important component of the projections from different functional areas of cerebral cortex (eg, limbic, associative, sensorimotor) makes exclusive contact with specific regions of the basal ganglia input nuclei. This regional separation is maintained in forward projections throughout the internal circuitry. Focused output signals from functional territories represented in the basal ganglia output nuclei are returned, via appropriate thalamic relays, to the cortical regions providing the original input signals.

The concept of parallel projecting reentrant loops through the basal ganglia has been extended to their connections with sensorimotor and motivational structures in the brain stem, including the superior colliculus, periaqueductal gray, pedunculopontine, and parabrachial nuclei. This implies that the reentrant loop architecture through the basal ganglia must have predated the evolutionary expansion of the cerebral cortex. An important difference is that for the cortical loops the thalamic relay is on the output side of the loop, whereas for the subcortical loops, the thalamic relay is on the input side (Figure 38–5). Further work will be required to test whether projections from different brain stem structures, as they pass through the thalamic and basal ganglia relays, are functionally distinct channels.

In summary, the partially segregated reentrant loop organization is one of the dominant features characterizing the connections between the basal ganglia and external structures. This pattern of connections provides important clues as to the role played by the basal ganglia nuclei in overall brain function. However, at

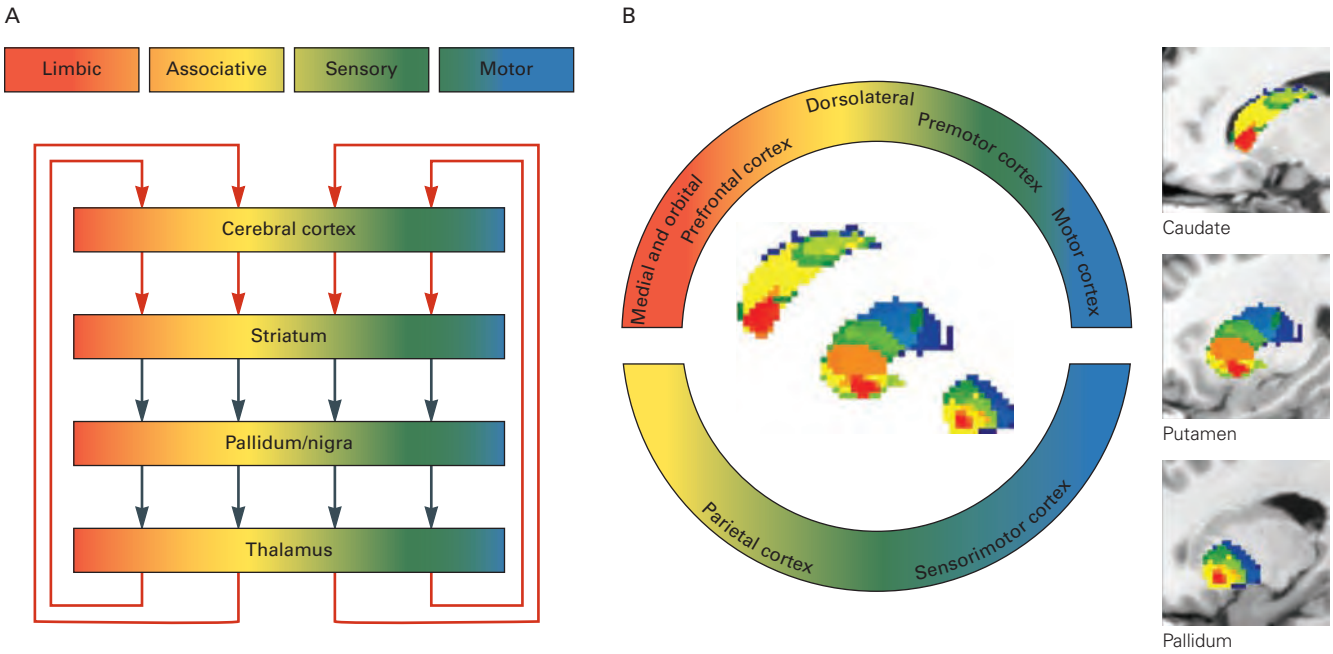

Figure 38–4 Connections between the basal ganglia and cerebral cortex.

A. The connections between the cerebral cortex and basal ganglia can be viewed as a series of parallel projecting, largely segregated loops or channels. Functional territories represented at the level of cerebral cortex are maintained throughout the basal ganglia nuclei and thalamic relays. However, for each loop, the relay points in the cortex, basal ganglia, and thalamus offer opportunities for activity inside the loop to be modified by signals from outside the loop. **Red** and **dark gray arrows** represent excitatory and inhibitory connections, respectively.

B. Spatially segregated rostral-caudal gradient of human frontal cortical connectivity in caudate, putamen, and pallidum. The color-coded ring denotes regions of cerebral cortex in the sagittal plane. (Reproduced, with permission, from Draganski et al. 2008. Copyright © 2008 Society for Neuroscience.)

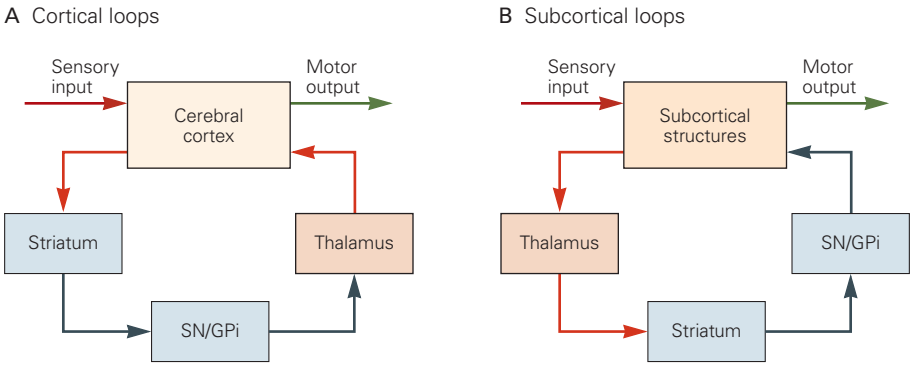

Figure 38–5 Cortical and subcortical sensorimotor loops through the basal ganglia.

A. For cortical loops, the position of the thalamic relay is on the return arm of the loop.

B. In the case of all subcortical loops, the position of the thalamic relay is on the input side of the loop. **Red** indicates predominantly excitatory regions and connections, while **dark gray** indicates inhibitory regions and connections. (Abbreviations: **SN/GPi**, substantia nigra/globus pallidus; **Thal**, thalamus.)

this point, it is important not to think of the reentrant loop architecture as comprising a series of independent and isolated functional channels. At each node or relay point in the loop (eg, in the cortex, the input nuclei, the output nuclei, and the thalamus), there is the opportunity for information flow within the loop to be modified by information from outside the loop (see the section on reinforcement learning below).

At the beginning of this chapter, we stated that behavior is an emergent property of signal processing within a neural network. Having specified the systems-level network of the basal ganglia, we now consider the signals that are being processed within this system.

Physiological Signals Provide Further Clues to Function in the Basal Ganglia

The Striatum and Subthalamic Nucleus Receive Signals Mainly from the Cerebral Cortex, Thalamus, and Ventral Midbrain

Signals received by the striatum from the cerebral cortex and thalamus are conveyed by excitatory glutamatergic neurotransmission. These fast, phasically active excitatory inputs are mediated predominantly by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors when the medium spiny neurons are near resting potential; *N*-methyl-D-aspartate (NMDA) receptors play a greater role when the neurons are depolarized. Glutamatergic inputs from both cerebral cortex and thalamus also impinge on striatal interneurons.

It is important to appreciate that these signals come from external structures that are simultaneously generating a wide range of behavioral options. Since these options could not all be expressed at the same time, these inputs to the basal ganglia are thought to be in competition with each other. Another important signal to the striatum is an efference copy of the output activity from the external structures that generate behavioral responses. For example, the sensorimotor territories of the dorsolateral striatum receive collateral fibers from motor cortex axons that send signals to the spinal cord.

The effects of dopaminergic inputs from the ventral midbrain on striatal neuronal activity are complicated, with many conflicting results. In part, this is due to the problem of evoking normal patterns of input activity in slice and anaesthetized preparations. However, recent developments in optogenetic technology in alert, active animals have enabled investigators both to record and manipulate dopamine signals to the striatum in a temporally controlled manner. Consequently, current evidence suggests dopamine can increase signal-to-noise ratios in the striatum, enhancing the effects of strong external inputs while suppressing weak ones. There is further evidence that dopamine can increase the excitability of medium spiny neurons in the direct pathways while at the same time decreasing the excitability of those in the indirect pathway.

Finally, dopamine input is necessary for both long-term potentiation and long-term depression of glutamatergic inputs to striatal medium spiny neurons from both cortex and thalamus. This latter point is of great significance for the role played by the basal ganglia in reinforcement learning (see below). Dopamine can also influence the activity of GABAergic and cholinergic interneurons. Although anatomically significant, much less is known about the role(s) of serotoninergic inputs to the basal ganglia.

The main external sources of input to the striatum also provide parallel inputs to the subthalamic nucleus. The subthalamus therefore receives phasic excitatory (glutamatergic) signals from the cerebral cortex, thalamus, and brain stem. Following cortical activation, short-latency excitatory effects in the subthalamus are thought to be mediated via these "hyperdirect" connections, whereas longer-latency suppressive effects are more likely to come from indirect inhibitory inputs from other basal ganglia nuclei, principally the external globus pallidus. The subthalamus receives short-latency excitatory sensory input from the brain stem (eg, the superior colliculus); it is also influenced by dopaminergic, serotonergic, and cholinergic modulatory inputs.

Ventral Midbrain Dopamine Neurons Receive Input From External Structures and Other Basal Ganglia Nuclei

Afferent signals to the dopaminergic neurons in the ventral midbrain come from a wide variety of autonomic, sensory, and motor areas and operate over a range of time scales. For example, laterally located neurons in the substantia nigra receive short-latency excitatory inputs from cortical and subcortical sensorimotor regions, while more medially positioned neurons receive both short-latency sensory signals and autonomic-related inputs from the hypothalamus over longer time scales.

Important inhibitory control over dopaminergic neurons is exercised by GABAergic neurons, both local and distant from areas like the rostromedial tegmentum. However, the densest inputs to the dopaminergic neurons are inhibitory inputs from the striatum and

globus pallidus and excitatory signals from the subthalamic nucleus. The midbrain raphe nuclei provide important modulatory serotonergic input, while both the pedunculopontine nucleus and lateral dorsal tegmental nucleus provide cholinergic and glutamatergic inputs. An important functional question concerning the wide range of afferent signals to dopaminergic neurons is whether dopamine performs a highly integrative role or performs an essential function that is accessed by numerous different systems at different times.

Disinhibition Is the Final Expression of Basal Ganglia Output

The basal ganglia exercise influence over external structures by the fundamental processes of inhibition and disinhibition (Figure 38–6). GABAergic neurons in the basal ganglia output nuclei typically have high tonic firing rates (40–80 Hz). This activity ensures that target regions of the thalamus and brain stem are maintained under a tight and constant inhibitory control.

Focused excitatory inputs from external structures to the striatum can impose focused suppression (mediated via direct pathway GABAergic inhibitory connections) on subpopulations of output nuclei neurons. This focused reduction of inhibitory output effectively releases or disinhibits targeted regions in the thalamus (eg, ventromedial nucleus) and brain stem (eg, superior colliculus) from normal inhibitory control. This sudden release from tonic inhibition allows activity in the targeted region to influence behavioral output, which in the case of the midbrain superior colliculus is to elicit saccadic eye movements.

The patterns of signaling within the basal ganglia architecture provide important insights into what the overall functional properties of these networks might be (see below). Further constraints on the likely core functions of the basal ganglia also become apparent when considering the evolutionary history of the vertebrate brain.

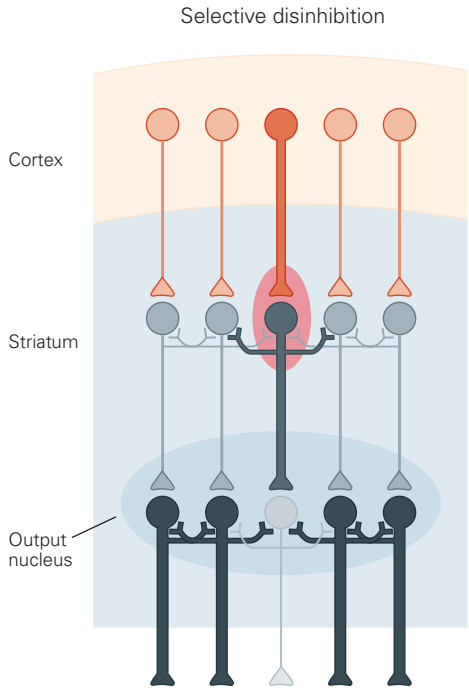

Figure 38–6 The diagram illustrates the principle of selection operating at the level of the basal ganglia output nuclei. Throughout the figure, the relative levels of activity within the competing channels are represented by the thickness of projections, and for clarity, the indirect pathway and the return connections of the loops via the thalamus have been omitted. One of the competing inputs to the striatum (the middle one) is more active than its competitors. Relative activities in the direct inhibitory pathways (shown here) differentially suppress activity in the different channels within the output nuclei. Because output nuclei neurons are also inhibitory and tonically active, the selected channel will be the one with the strongest inhibitory input from the striatum. Tonic inhibitory output is maintained on the nonselected channels. This selective disinhibitory mechanism operating at the level of the output nuclei means that selection will be an emergent property of the entire reentrant network. Disinhibition of selected external targets will allow them to direct movement, while nonselected targets remain inhibited and unable to influence behavior. **Red**, excitatory; **gray**, inhibitory.

Throughout Vertebrate Evolution, the Basal Ganglia Have Been Highly Conserved

Detailed comparisons between the mammalian basal ganglia and those found in phylogenetically ancient vertebrates (eg, the lamprey) have found striking similarities in their individual components, internal organization, inputs from external structures (the cortex/pallium and thalamus), and the efferent projections of their output nuclei. For example, both direct and indirect pathways from striatal medium spiny neurons have been observed in the lamprey. Similarly, tonically active GABAergic output neurons are present in the lamprey internal globus pallidus and substantia nigra pars reticulata. The neurotransmitters and membrane properties of basal ganglia neurons are also remarkably similar in evolutionarily ancient and modern species.

This high degree of morphological and neurochemical conservation implies that the architecture and operation of basal ganglia circuits have been retained for more than 500 million years. The basal ganglia are therefore an essential component of brain architecture