

The Basal Ganglia

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

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

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Detailed Anatomical Analyses Reveal a More Complex Organization

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Inputs Define Functional Territories in the Basal Ganglia

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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

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Attention Deficit Hyperactivity Disorder and Tourette Syndrome May Also Be Characterized by Intrusions of Nonselected Options

Obsessive-Compulsive Disorder Reflects the Presence of Pathologically Dominant Options

Addictions Are Associated With Disorders of Reinforcement Mechanisms and Habitual Goals

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 non-motor 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.

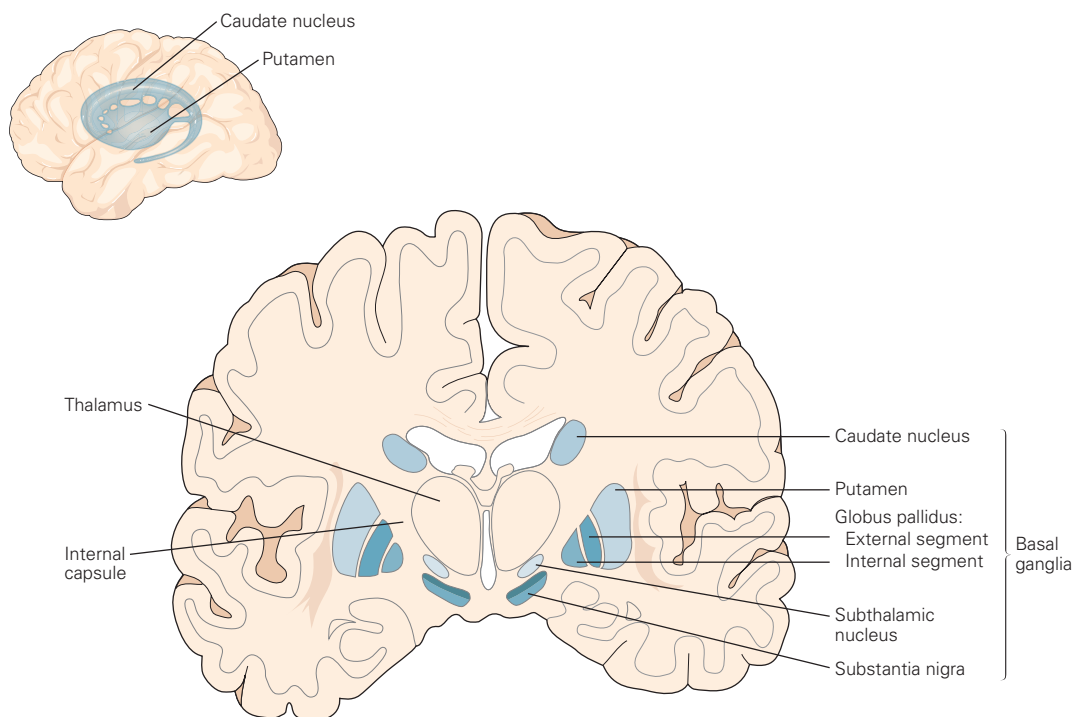


Figure 38–1 The basal ganglia and surrounding structures. The nuclei of the basal ganglia are identified on the right in this

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).

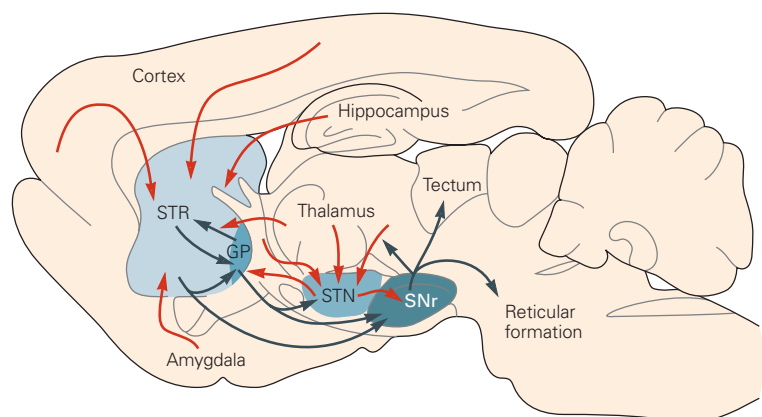
The striatum is subdivided functionally on the basis of the organization of input connections, principally the topographically organized afferents from the cerebral cortex. Limbic, associative, and sensorimotor territories are generally recognized along a ventromedial-dorsolateral continuum. This diversity 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 mid-brain 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 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 D₁ dopamine receptors make direct inhibitory

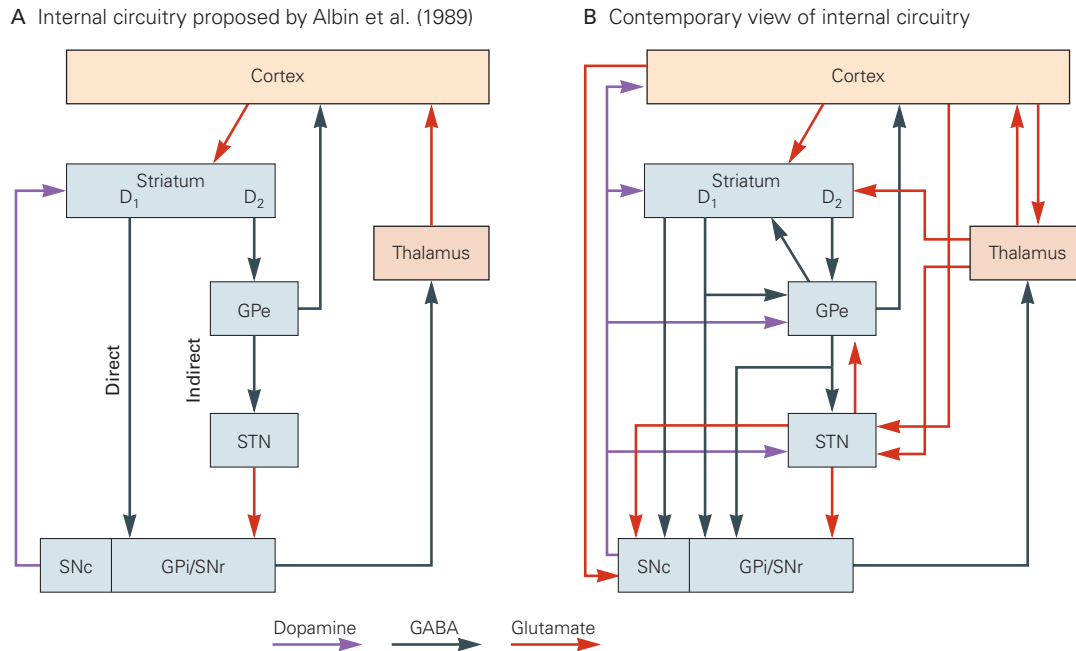


Figure 38-3 Intrinsic connections within the basal ganglia.

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 substantia 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, pedunculo-pontine, 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

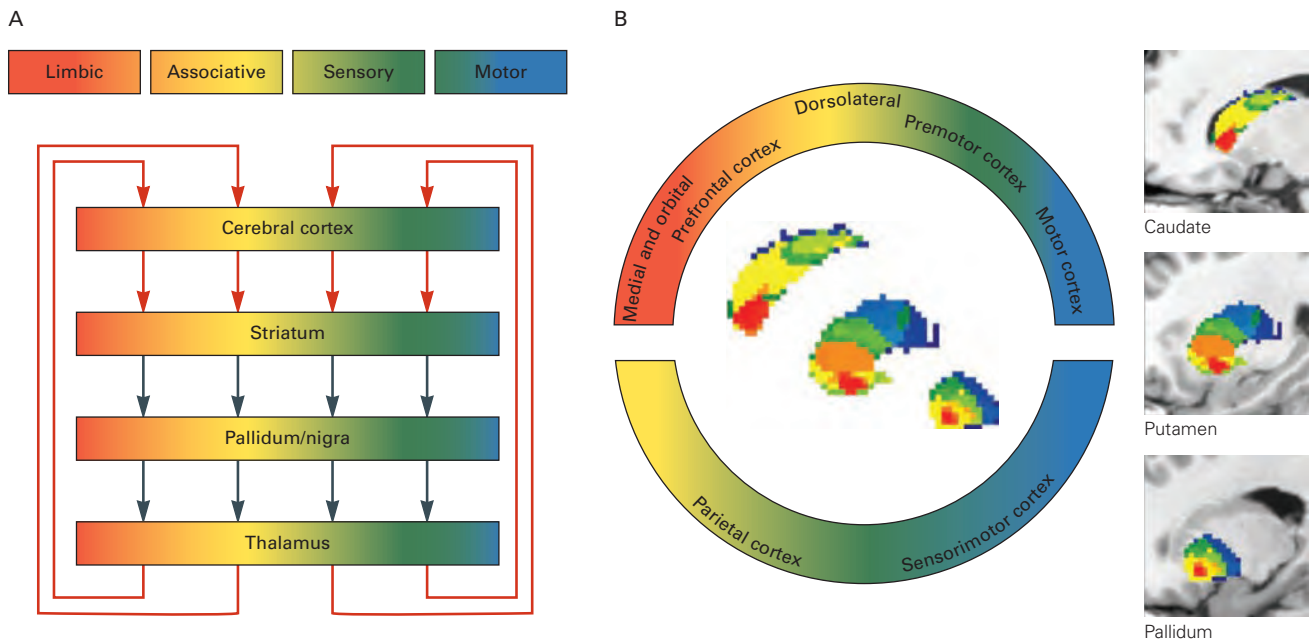


Figure 38-4 Connections between the basal ganglia and cerebral cortex.

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.)

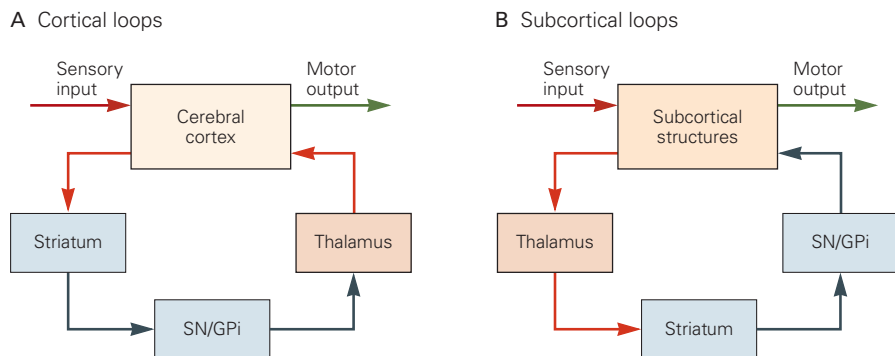


Figure 38-5 Cortical and subcortical sensorimotor loops through the basal ganglia.

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 serotonergic 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.

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

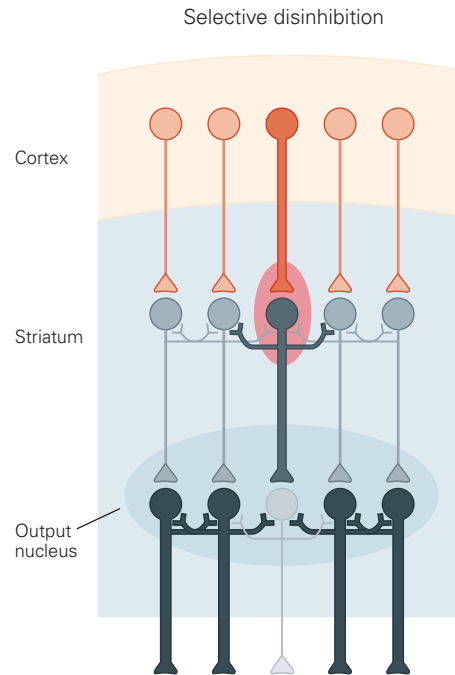


Figure 38–6 The diagram illustrates the principle of selection operating at the level of the basal ganglia output nuclei. Throughout the figure, the relative levels of activity within the competing channels are represented by the thickness of projections, and for clarity, the indirect pathway and the 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 disinhibition 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.

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

that is shared by all vertebrate species. Bearing in mind that a function emerges from specific patterns of signals being processed in specific neural networks, the conservation of basal ganglia architecture across vertebrate species places an additional important constraint on their overall function. Whatever computational problems the basal ganglia evolved to solve in evolutionarily ancient species, the same problems are likely to have remained unchanged and to confront all vertebrate species, including humans.

Thus far, we have identified features of basal ganglia morphology, connectional architecture, signal processing, and evolution that provide potential insights as to the role of the basal ganglia in overall brain function. Thus, proposed functions must be consistent with the predominant looped architecture that connects external structures with the basal ganglia and with an internal circuitry that is shared across the limbic, associative, and sensorimotor territories of the basal ganglia nuclei, and they must be shared by all vertebrate species. With these constraints in mind, we now consider functional properties that could be supported by the basal ganglia.

Action Selection Is a Recurring Theme in Basal Ganglia Research

Despite numerous suggestions that the basal ganglia are involved in a wide range of functions, including perception, learning, memory, attention, many aspects of motor function, and even analgesia and seizure suppression, evidence is accumulating that these nuclei have an underlying role in a variety of selection processes. Thus, throughout the prodigious literature on the basal ganglia there are recurring references to the involvement of these nuclei in the essential brain functions of action selection and reinforcement learning. In this and the next section we will evaluate the extent to which these core processes are consistent with the functional constraints identified above.

All Vertebrates Face the Challenge of Choosing One Behavior From Several Competing Options

Vertebrates are multifunctional organisms: They have to maintain energy and fluid balances, defend against harm, and engage in reproductive activities. Different areas of the brain operate in parallel to deliver these essential functions but must share limited motor resources. Sherrington's "final common motor path" means it is impossible to talk and drink at the same time. Thus, a fundamental selection problem,

continually faced by all vertebrates, is determining which functional system should be allowed to direct behavioral output at any point in time. This is a problem that has not changed materially over the course of 500 million years of evolutionary history. What has changed over this time are the behavioral options that have evolved in different species to implement the core functions of survival and reproduction. Consequently, there has to be a system in the vertebrate brain that can adjudicate between the motivational systems that simultaneously compete for behavioral expression.

A similar selection problem also arises within vertebrate multimodal sensory systems. The visual, auditory, olfactory, and tactile systems are continually faced with multiple external stimuli, each one of which could drive a movement incompatible with one specified by others (eg, orienting/approach, avoidance/escape). It is therefore imperative to select a stimulus that will become the focus of attention and direct movement. The problem is which stimulus should be given access to the motor systems at any one time. Selective attention provides an effective solution to this problem, making it an essential feature of vertebrate brain function.

In summary, despite great evolutionary changes in the range, power, and sophistication of the sensory, motivational, cognitive, and motor systems that compete for behavioral expression in different species, the fundamental computational problems of selection have remained unaltered. And, if the basal ganglia provide a generic solution to the problems of selection, a high degree of structural and functional conservation within vertebrate brain evolution would be expected.

Selection Is Required for Motivational, Affective, Cognitive, and Sensorimotor Processing

In his *Principles of Psychology* (1890), William James observed, "Selection is the very keel on which our mental ship is built." In this statement, he is telling us that the neural systems of motivation, emotion, cognition, perception, and motor performance, at some stage, need to consult a mechanism that can select between parallel processed but incompatible options (Figure 38–7). It is therefore significant that intrinsic circuits in the basal ganglia nuclei are similar across the limbic, associative, and sensorimotor territories.

Such repetition within the basal ganglia circuitry suggests that the same or similar computational processes are applied to inputs from very different functional origins. This duplicated circuitry would therefore be in a position to resolve competitions between high-level motivational goals in the limbic territories;

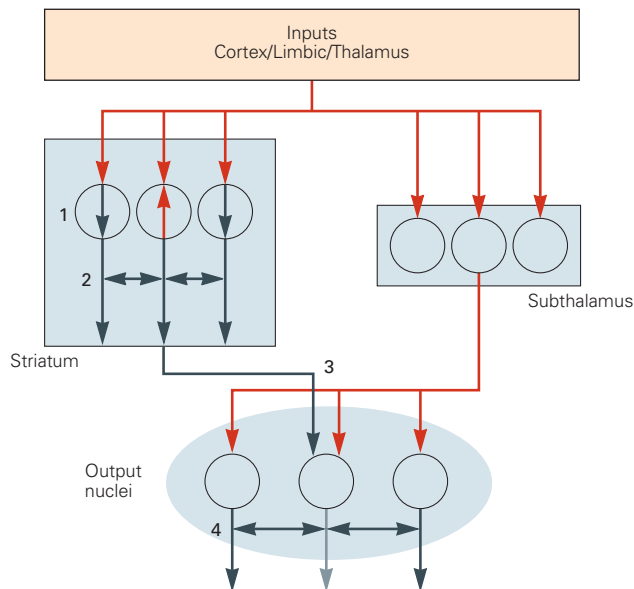


Figure 38-7 Cooperative mechanisms in the basal ganglia that would promote selection.

1. Because cortical and some thalamic inputs make comparatively few contacts with individual striatal neurons, a large population of sufficiently synchronized excitatory inputs is required to depolarize the membrane of a medium spiny neuron to an "up" state sufficient for it to fire action potentials. This mechanism can be seen as an input filter to exclude weak or less biologically significant competitors. The **internal arrows** in striatal neurons denote "up" (red) and "down" (gray) states.
2. Local GABAergic and peptidergic inhibitory collaterals between striatal spiny neurons and longer-range inhibitory effects of interneurons should cause highly activated striatal elements to suppress activity in adjacent more weakly activated channels.
3. The combination of focused inhibition from the striatum with the more diffuse excitation from the subthalamus would both decrease the activity in selected channels and increase activity in nonselected channels in the basal ganglia output nuclei. The output from just one of the striatal and subthalamic neurons has been illustrated to make this point.
4. Local inhibitory collaterals between output nuclei neurons should further sharpen the difference between inhibited and noninhibited channels.

competitions between incompatible cognitive representations in the central associative territories; and competitions between incompatible sensory and motor options resolved in the lateral sensorimotor regions.

The Neural Architecture of the Basal Ganglia Is Configured to Make Selections

At various times during the past 40 years, and more so recently, it has been argued that the principle function

of the basal ganglia is to select between competing and incompatible behavioral options. It has now been recognized that many aspects of the basal ganglia architecture are consistent with this view (Figure 38-6). The parallel loops originating from and returning to diverse cortical and subcortical functional systems can be viewed as the basic substrate for selection.

The phasic excitatory input signals from the cerebral cortex and thalamus to the different functional territories of the striatum can be seen to carry signals representing the behavioral options competing for expression. To ensure that all options could in principle be assessed against all others, there needs to be a "common currency." This term refers to the parameter according to which qualitatively different functional options can be compared for the purpose of selection. This parameter would be represented by the relative magnitudes of input signals to the striatum, thereby providing each competitor with a measure of relative biological importance or salience. In principle, it should be necessary only for the basal ganglia to appreciate which option is most salient in terms of the common currency.

Processing within the parallel projecting internal architecture (Figure 38-6) would ensure that channels associated with the most salient input activity would cause focused inhibition at the level of the output nuclei (the winning options), while at the same time maintaining or increasing the tonic inhibitory activity in output channels returning to regions specifying weaker (losing) options. Experiments that have recorded neural activity in basal ganglia output nuclei in active animals describe populations of task-sensitive neurons whose activity is reduced or paused prior to movement (the winning option). Conversely, there is a separate, often larger population whose high level of tonic activity is further increased or at least maintained (the losing options). The returning signals within the disinhibited channel(s) are necessary to permit the structures providing the strongest motivational, cognitive, or sensorimotor inputs to access the shared motor resources. Importantly, the maintained or increased levels of inhibitory efferent signals within nonselected channels would prevent the output of nonselected target structures from distorting the selected option's input to the motor system. Thus, this model of the basal ganglia works by keeping all potential behavioral options under tight inhibitory control and selectively removing the inhibition from the option proving the most salient input.

A central-selection control architecture, similar to the systems-level architecture of the basal ganglia just described, was used successfully to select actions for

an autonomous mobile robot. Subsequently, it was confirmed that a biologically constrained computer simulation of basal ganglia architecture could do likewise. This work with artificial agents is important because it confirms that selection is indeed an emergent property of systems-level basal ganglia circuitry. The next question is: If the overall architecture can select, are there mechanisms within the basal ganglia that would support or facilitate this function?

Intrinsic Mechanisms in the Basal Ganglia Promote Selection

At each of the major relay points within each of the reentrant loops passing through the basal ganglia (external structures, input nuclei, intrinsic nuclei, output nuclei, and the thalamus), signals flowing within the parallel channels can be subjected to influences originating outside the loop. The selection model outlined above requires features within the internal circuitry of the basal ganglia that permit different channels to interact competitively with each other. Several of these can be identified (Figure 38-7). Together, these mechanisms can be viewed as a cooperative sequence of processes, each of which would facilitate the overall goal of selection. In addition, there is substantial evidence that the relative activity of direct and indirect striatal projection pathways is critical for action selection. The traditional and widely accepted view is that the relative activity in the direct and indirect pathways determines whether or not an animal will perform a particular movement. For example, recent optogenetic stimulation of direct pathway neurons leads to more movement, while optogenetic stimulation of indirect pathway neurons leads to less movement. However, an alternative view for which there is increasing evidence is that simultaneous activity in both pathways is critical for the process of selecting what to do. Here, the idea is that the direct pathway conveys signals representing the most salient options, while the indirect pathway is important for inhibiting the competing weaker options. The latter idea is consistent with the now repeated observations that both projection pathways are concurrently active during movement initiation and that specific patterns of activity in each pathway are associated with different movements.

Selection Function of the Basal Ganglia Questioned

Despite the wide appeal of the selection hypothesis of basal ganglia function, it is by no means universally accepted. Indeed, arguments against it have been

voiced based on different studies, the results of which are considered incompatible with the selection model. For example, it has been reported that lesions or suppression of neural activity in motor territories of the internal globus pallidus failed to alter the reaction time between a sensory cue and the triggered movement.

These results could indicate that the basal ganglia are mainly involved in selecting and executing actions that are self-paced, or memory-driven, rather than cue-driven. However, a possibility not considered by these studies is that for well-practiced tasks it is likely that the sensory regions of the basal ganglia will be the most important. This is because such tasks can be performed under stimulus-response habitual control, where selection of the stimulus that triggers the response would be the critical selection. Thus, a failure to disrupt sensory cue selection in such tasks following experimental disruption of the relevant sensory region of basal ganglia would be far stronger evidence against the selection model.

Another recent study claims that in some tasks action choice is already clear in cortical activity even before it reaches the basal ganglia and that the basal ganglia activity is mainly related to reinforcing the commitment to perform the action. This study, and many others like it, base their claims on recordings from afferent structures showing that the neurons are coding the selected stimulus/action/motor program prior to relevant neural responses recorded from within the basal ganglia. An alternative interpretation of these data would be that recordings from all afferent structures that provide competing inputs to the basal ganglia will have shorter latencies than related signals recorded from within the basal ganglia. If in these experiments afferent recordings were from the structure proving the most salient of the competing inputs, then it will be coding for the ultimately selected option *before* it has been selected by basal ganglia.

Other findings are that recordings in the basal ganglia correlate with metrics of movement (eg, speed) and that dopamine signals in the striatum can affect the probability and also the vigor of movement. It is sometimes argued that these results are more indicative of the basal ganglia helping to commit to movement and determining the parameters of movement rather than simply selecting what to do. At least two alternative views could explain why recorded activity in the basal ganglia correlates with movement metrics. First, as mentioned above, one of the significant inputs to the striatum is an efference copy of signals relayed to the motor plant. It would be strange if these signals did not contain information about movement metrics. Second, at this point, it is probably wise to recognize

that actions are multidimensional and, as they are learned, require selections about not only *what* to do but also *where* to do it, *when* to do it, and *how* to do it.

The fact that correlates of these various properties of action can be recorded within the basal ganglia nuclei should not necessarily be surprising. Recent studies suggest that *what* and *where* options may arrive to the basal ganglia via glutamatergic input, for example, from the cortex, while *when* options may be modulated by dopaminergic inputs. One of the reasons we know that actions comprise these different dimensions is that each of them can be independently manipulated by reinforcement learning. It is to that topic, which is likely to be an inherent property of a selection architecture, that we now turn.

Reinforcement Learning Is an Inherent Property of a Selection Architecture

The basal ganglia have long been associated with fundamental processes of reinforcement learning. In his famous Law of Effect, first published in his book *Animal Intelligence* (1911), Edward Lee Thorndike proposed that “any act which in a given situation produces satisfaction becomes associated with that situation so that when the situation recurs the act is more likely than before to recur also.” Using contemporary language, Thorndike is stating that in a given context an action that has been associated with reward is more likely to be selected in the future when the same or similar contexts are encountered.

Stated in this way, reinforcement learning can be seen as a process for biasing action selection; consequently, it would be expected to operate by modulating activity in the mechanism(s) responsible for selection. How would a reinforcer (reward or punishment) bias selection in the basal ganglia architecture described above? Theoretically, competition between the options represented in the reentrant loops could be biased by sensitizing a reward-related loop at any of its relay points (cortex, input nuclei, globus pallidus, output nuclei, and thalamus). Here, we present just two examples where there is good evidence that reward operating at different nodes within the basal ganglia’s reentrant loop circuitry can bias selection (Figure 38–8).

Intrinsic Reinforcement Is Mediated by Phasic Dopamine Signaling Within the Basal Ganglia Nuclei

The popular view of reinforcement in the basal ganglia is that action selection is biased by a dopamine

teaching signal that adjusts the sensitivity of intrinsic circuitry so that responses to inputs associated with unpredicted rewards are enhanced (Figure 38–8A). In this model, therefore, the process of reinforcement learning is intrinsic to the basal ganglia nuclei. However, as we have seen above, dopaminergic neurons have highly divergent axons that terminate in wide areas of targeted nuclei. Add to this the problem of volume transmission and the fact that dopaminergic neurons often respond together as a population to relevant events and the problem of how to reinforce only those elements associated with reward or punishment immediately becomes apparent.

It is thought that this issue is addressed by invoking the concept of a decaying eligibility trace. That is, spiking activity in the population of neurons associated with an action that leads to reward is thought to alter the state specifically of those neurons, making them receptive to later widely broadcast reward-related reinforcement signals. There is evidence that this process operates within the basal ganglia. Thus, in most contemporary models, competing behavioral options are represented by specific neurons, the activity of which can be reinforced by phasic increases or decreases in afferent dopamine signals.

Because behavioral experiments have established that unpredicted reward rather than reward per se is critical for learning, the phasic response properties of dopaminergic neurons have captured the imagination of both the biological and computational neuroscience communities. The powerful combination of biological experimentation and computational analyses now indicates clearly that the phasic activity of midbrain dopaminergic neurons provides a teaching signal for reinforcement learning.

While recording from dopaminergic neurons in the ventral midbrain, most studies presented subjects (usually monkeys) either with rewards or neutral stimuli that predicted rewards. The results of these experiments showed that the phasic dopamine responses evoked by unexpected rewards, or the onset of stimuli that predict them, had short response latencies (~100 ms from stimulus onset) and short durations (again ~100 ms). The magnitude of these responses was shown to be influenced by a range of factors including the size, reliability, and extent the reward would be delayed. Importantly, when a neutral stimulus predicted reward (as in traditional Pavlovian conditioning), the phasic dopamine response transferred from the reward to the predicting stimulus. Alternatively, if a reward was predicted but not delivered, the dopaminergic neurons paused briefly at the time the reward would have been delivered. A particularly exciting

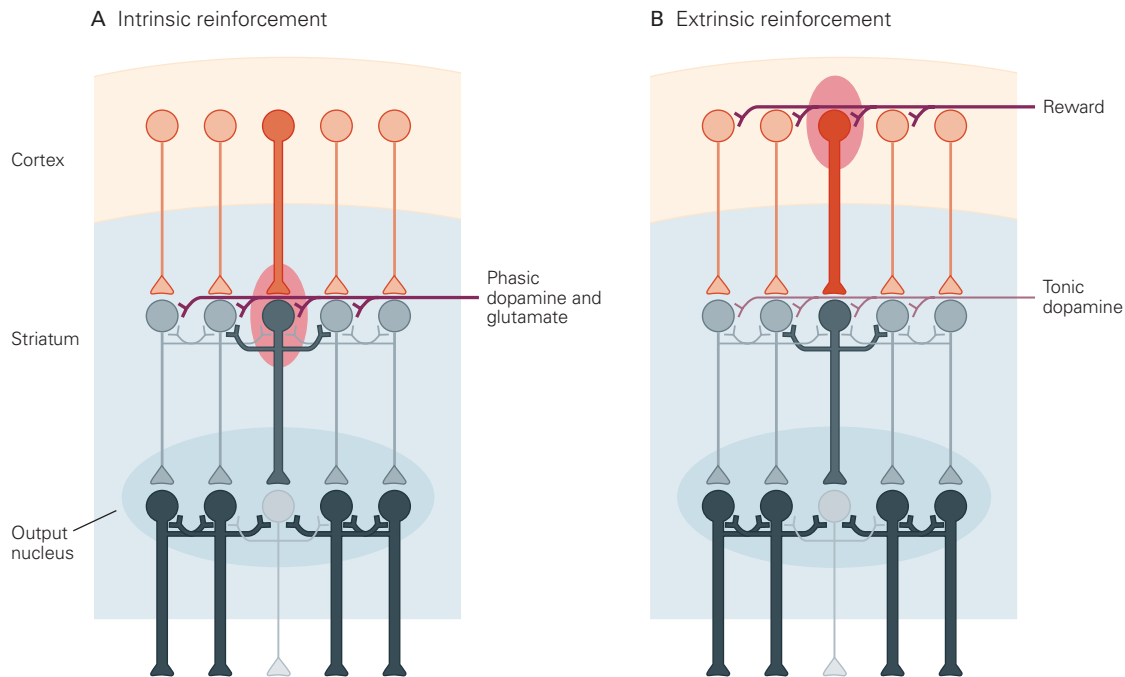


Figure 38–8 Two separate reinforcement mechanisms can bias selection within the reentrant parallel-loop architecture of the basal ganglia. (Return connections of the loops via the thalamus have been omitted for clarity.)

A. Intrinsic reinforcement (red oval) involves the selective sensitization of corticostriatal neurotransmission (indicated by the relative thickness of striatal projection neurons in different channels). Transmission in recently active (selected) channel(s) is reinforced by the combined phasic release of dopamine and glutamate evoked by an unpredicted biologically salient sensory event (eg, reward). Nonactive channels lack the eligibility trace required for dopamine reinforcement at the synapse.

The resulting selective plasticity would cause reinforced versions of recent behavioral output to be preferentially reselected, thereby establishing an association between action and outcome.

B. Recent investigations demonstrate that an association with reward (red oval) can potentiate processing in structures providing afferent signals to the striatum. Insofar as selection by the basal ganglia is determined in part by the relative strength of inputs to the striatum (the common currency), reward-related modulation of afferent signals would effectively bias selection to favor reward-related inputs. Again, the thickness of projections in the figure denotes relative levels of activation.

finding was that these responses resembled the reward prediction error term in a machine learning reinforcement algorithm. It was therefore widely concluded that phasic dopamine responses could be operating as the brain's teaching signal in reinforcement learning.

With the advent of optogenetic methodology, it has now been established beyond reasonable doubt that phasic dopamine responses can signal both positive and negative reward prediction errors and that these responses correspondingly increase and decrease the probability that prior behavior will be selected. It is thought that phasic dopamine acts by strengthening inputs onto direct pathway neurons in the striatum and weakening inputs onto indirect pathway neurons. Consequently, there is evidence that direct pathway activity can lead animals to do more of a certain action, while indirect pathway activity would lead animals not to do an action.

However, the roles of these pathways may be more complex than this simple dichotomy. In accordance with the different action dimensions outlined above (*what, where, when, and how*), activity in both the direct and indirect pathways can reinforce or discourage faster or slower movements, depending on which movements lead to reward in that context. Furthermore, the effects of optogenetic self-stimulation of these pathways on action reinforcement seem to be different between the associative (dorsomedial) and sensorimotor (dorsolateral) domains of the striatum. This could be consistent with different dopamine signals observed in the ventral tegmental area, which projects more medially in the striatum, compared to those in the substantia nigra pars compacta, which projects more laterally. The latter has a higher proportion of dopaminergic neurons that respond to stimulus salience and preferentially respond when the animal

initiates self-paced movements (eg, pressing a lever for food whenever it wants, rather than when a sensory cue is presented).

Nonetheless, a wealth of experimental data indicates that phasic dopamine-evoked neural plasticity in the basal ganglia can bias future behavioral selections according to the value of the predicted outcome. This conclusion is consistent with the view that the basal ganglia operate as a generic selection mechanism that can support reinforcement learning.

Extrinsic Reinforcement Could Bias Selection by Operating in Afferent Structures

A second, less widely acknowledged mechanism for biasing selection within the reentrant loop architecture is by modulation of the input salience of competing behavioral options that previously have been associated with a reinforcer—reward or punishment (Figure 38–8B). Since the relative magnitudes of input saliences in competing channels are the common currency by which competing options are judged, reinforcement-induced boosting of a particular channel's input to a selection mechanism would increase the probability of that option being selected in the future.

Evidence in the literature indicates that when a particular stimulus is associated with reward, its representation is enhanced in many of the afferent structures projecting to the basal ganglia. The origin of the reinforcement signals that modulate processing in the input structures is currently unknown. However, the pretuning of basal ganglia inputs by association with reward implies that options associated with high-value outcomes would have a correspondingly higher probability of being selected. Continual updating of input saliences by reward and punishment would bias selections in such a way that the acquisition of reward (or avoidance of punishment) would be maximized in the long term. Finally, it is probably the reward-related tuning of afferent input to the ventral midbrain that enables dopaminergic neurons to accurately report reward prediction errors.

In summary, it is likely that reinforcement learning will be an additional inherent property of a selection architecture. The synaptic relay points at various locations around the parallel reentrant loop architecture provide ample opportunity for the activity in specific loops to be modulated by reward and punishment. There is now good evidence that selection bias can be achieved by reward via a mechanism involving the widespread release of dopamine within the basal ganglia. Reinforcement selectivity is likely to be achieved via some form of eligibility mechanism. A second

possibility is that the relative salience of behavioral options can be modulated by reward and punishment acting directly within the structures that provide input to the basal ganglia.

Behavioral Selection in the Basal Ganglia Is Under Goal-Directed and Habitual Control

Over the past decades, it has become apparent that actions can be learned and then selected based on goal-directed or habitual control. Initially, as we learn to perform particular actions to obtain specific outcomes, these actions are goal-directed, and their performance is highly sensitive to changes in the expected value of the outcome or to changes in the contingency between the action and the outcome. With repetition and consolidation, actions can become not only more efficient but also more automatic, controlled by a stimulus–response type circuit.

In the case of habits, performance becomes less sensitive to changes in the outcome value or changes in contingency between action and the outcome, but rather is controlled by the salience of antecedent stimuli or contexts. Interestingly, shifts from goal-directed to habitual behaviors can be produced not only by extended training, but also by different schedules of reinforcement. Thus, the formation of habits is favored when rewards are delivered according to random time intervals, while goal-directed control is favored when rewards are delivered after a random number of actions.

Different cortical-basal ganglia loops seem to support the learning and performance of goal-directed actions versus habits. The acquisition of goal-directed actions appears to rely on the associative cortical-basal ganglia circuit involving the dorsomedial or associative striatum, the prefrontal cortex, the mediodorsal thalamus, the orbitofrontal cortex, and the amygdala. On the other hand, the formation of habits depends upon circuits coursing through the dorsolateral or sensorimotor striatum, infralimbic cortex, and the central amygdala.

It has been shown that since these two fundamental modes of behavioral control operate through different reentrant loops it has been possible to cause shifts between them through specific manipulations within the basal ganglia. Thus, damage to or inactivation of the associative territories effectively blocks goal-directed control while leaving automatic habitual control relatively unimpaired. Conversely, disruption of the sensorimotor basal ganglia causes habitual performance to switch back to goal-directed control.

Finally, efficient habits, where known stimuli or circumstances trigger a particular response, are very helpful in everyday life such as tying one's shoelaces or locking the front door. However, we also encounter circumstances that cause us to reevaluate our actions. Shifting between goal-directed actions and habits allows us to act flexibly in the environment, and inability to do so may underlie distorted behaviors observed in addiction and other behavioral and neurological disorders of the basal ganglia. It is to this topic that we now turn.

Diseases of the Basal Ganglia May Involve Disorders of Selection

The focus of this chapter has been how the functional architecture of the basal ganglia and their evolutionary history have determined their role in overall brain function. One of the motivations for this exercise that we all have is an intrinsic scientific interest in trying to understand something we currently do not. However, there is another important reason to better understand how the basal ganglia operate. In humans, basal ganglia dysfunction is associated with numerous debilitating conditions including Parkinson disease, Huntington disease, Tourette syndrome, schizophrenia, attention

deficit disorder, obsessive-compulsive disorder, and many addictions. Numerous studies have attempted to shed light on how basal ganglia dysfunction leads to the symptoms that characterize these disorders. This effort can only be helped if we have a better understanding of what a complicated system like the basal ganglia is trying to do when it is operating normally.

A Selection Mechanism Is Likely to Be Vulnerable to Several Potential Malfunctions

Thus far, we have considered the theoretical and empirical evidence supporting the idea that the looped circuitry of the basal ganglia acts as a generic selection mechanism within which reinforcement learning operates to maximize reward and minimize punishment. If action selection and reinforcement learning are the normal functions of the basal ganglia, it should be possible to interpret many of the human basal ganglia-related disorders in terms of selection or reinforcement malfunctions.

Normal selection requires that the selected option is disinhibited at the level of basal ganglia output, while inhibition of nonselected or losing options is maintained or increased (Figure 38–9A). An obvious failure in such a system would be if none of the options were able to achieve sufficient disinhibition to reach a

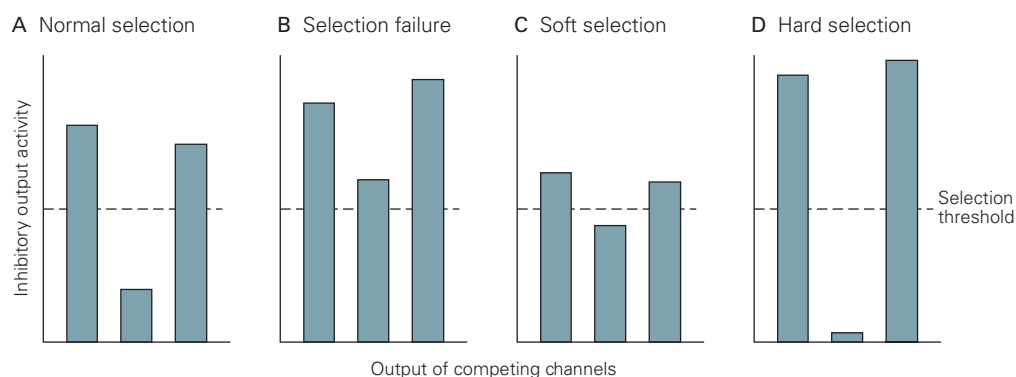


Figure 38–9 Potential disorders of behavior selection.

A. Normal selection within the basal ganglia is characterized by a reduction in inhibition of selected channels below a proposed selection threshold (central channel) while maintaining or increasing inhibition of nonselected channels (left and right channels). Consequently, the disinhibited target structure is able to initiate the action it controls, while the nonselected targets are maintained under inhibitory control.

B. Insufficient reduction in tonic inhibition of all channels means no target structure would be sufficiently disinhibited. This circumstance could explain the akinesia in Parkinson disease.

C. A failure to adequately disinhibit the selected channel or suppress disinhibitory activity in competing channels would cause current selections to be vulnerable to interruption. This disorder could account for the inability to maintain a train of thought and easy distraction by nonattended events in schizophrenia and attention deficit hyperactivity disorder.

D. One channel may become pathologically dominant either through abnormal disinhibition of the selected channel or excessive tonic inhibition of competing channels. This would make the relevant option easy to select and highly resistant to interruption. Hard selections may explain obsessive-compulsive disorder and addictive behaviors.

critical selection threshold (Figure 38–9B). However, a further important point when thinking about selection malfunctions is to appreciate that output inhibition and disinhibition are likely to be continuously variable rather than discrete on/off states. In that case, the difference between the disinhibited and inhibited channels would determine how “hard” or “soft” the selection is. When the difference is large (Figure 38–9D), competing options are likely to find the current selection is resistant to interruption—a larger than normal input salience would be required to cause the system to switch selections. Conversely, when the difference is small (Figure 38–9C), it would be comparatively easy for a competing option to initiate a selection switch.

Support for these ideas comes from behavioral observations showing that at the beginning of task learning there is frequently easy switching between strategies. However, as the task becomes well learned, the system becomes increasingly resistant to alternative strategies. Appreciation of the concepts of hard and soft selection could therefore play an important role when thinking about how a selection mechanism might become dysfunctional in the context of basal ganglia diseases.

Parkinson Disease Can Be Viewed in Part as a Failure to Select Sensorimotor Options

The cardinal symptoms of Parkinson disease are akinesia (difficulties in initiating movement), bradykinesia (initiated movements are slow), and rigidity (stiffness and resistance to passive movement). Tremor is often but not always present. The principal neurological deficit responsible for the motor symptoms of Parkinson disease is thought to be the progressive degeneration of dopaminergic neurotransmission in the basal ganglia.

A consequence of this loss of dopamine is increased tonic and oscillatory activity in the recordings from basal ganglia output nuclei. Since the output of the basal ganglia is GABAergic and inhibitory, in Parkinson disease, targeted structures are receiving high and uneven levels of inhibitory input. This condition impairs the normal selective (disinhibitory) function of the basal ganglia; movements are difficult to select and, when possible, are slow to execute.

Parkinson disease is, however, more nuanced than this. Over much of this progressive condition, the loss of dopaminergic transmission differentially affects the sensorimotor territories of the basal ganglia, leaving the limbic and associative territories comparatively unaffected. As discussed in the section on goal-directed and habitual control, the sensorimotor territories of the basal ganglia

play an essential role in selecting habitual actions. Perhaps, therefore, it is not surprising that many of the motor features of Parkinson disease can be interpreted in terms of a loss of automatic habits. While patients can do things, they are trapped in the slower, serial, and voluntary mode of goal-directed control. In the future, it will be interesting to see if subtle losses of habitual control can be detected before clinical symptoms appear, thereby acting as an early marker for the condition.

Huntington Disease May Reflect a Functional Imbalance Between the Direct and Indirect Pathways

Huntington disease is a genetically transmitted disorder, the initial symptoms of which are subtle changes in mood, personality, cognition, and physical skills. The abnormal movements are characterized by jerky, random, and uncontrollable movements called chorea. The disease is associated with neuronal degeneration. Damage in the early stage is most evident in the striatal medium spiny neurons, but later spreads to other regions of the nervous system.

Observations that neuronal degeneration is evident in limbic, associative, and sensorimotor territories of the striatum would explain why the disease is characterized by disturbances of affect, cognition, and sensorimotor function. Also noteworthy is that the most vulnerable neurons are those in the striatum that project to the external globus pallidus (the indirect pathway) rather than the neurons that project directly to the basal ganglia output nuclei. At the level of the output nuclei, this disturbance would tip the balance in favor of the striatal projection responsible for disinhibition. Consequently, the symptoms of Huntington disease could reflect interference with expression of the selected affective, cognitive, and sensorimotor behaviors by competitors not being sufficiently suppressed.

Schizophrenia May Be Associated With a General Failure to Suppress Nonselected Options

Schizophrenic psychosis is a condition in which there are also disturbances of affect, cognition, and sensorimotor function. Typical symptoms include delusions (false beliefs not based in reality), hallucinations (hearing or seeing things that do not exist), disorganized thinking (inferred from disorganized speech), and abnormal motor behavior (unpredictable agitation, stereotypy, and failure to concentrate on the matter in hand). The disease is progressive, and in later stages, negative symptoms characterized by flattened affect, social withdrawal, absence of thought, and reduced motor behavior become evident (Chapter 60).

Understanding the neurobiological basis of schizophrenia has been complicated by many inconsistent experimental procedures, high variability in symptoms, the side effects of medications, substance abuse, and variability in response to treatments. There is, however, a consistent link between schizophrenia and the basal ganglia insofar as a major class of antipsychotic drugs acts to suppress dopaminergic neurotransmission. In terms of simple regional density of axon terminals and postsynaptic dopamine receptors, dopaminergic transmission within the basal ganglia is likely to be influenced most profoundly by dopamine-related pharmacological therapies. Moreover, there is evidence that dopamine dysregulation in the basal ganglia is intrinsic to the pathology of schizophrenia rather than a medication side effect; predates the psychosis; and is a risk factor for the illness. The implication here is that schizophrenia is associated with a net excess of dopaminergic transmission in the basal ganglia.

So how might dysregulation of this form distort the normal functions of selection and reinforcement? First, the observation that schizophrenia is characterized by disturbances of affect, cognition, and sensorimotor behavior again suggests that the neurobiological substrate will be present in each of the basal ganglia's functional territories. Second, a recurrent theme is that with the positive symptoms there seems to be too much of everything—intense emotional intrusions, too many ideas out of control, spontaneous sensory experiences, too many distracting stimuli, and unpredictable motor agitation. One way of unifying this confusing array of symptoms is to assume that they represent a similar basic fault playing out in different functional territories of the basal ganglia. Here, the basic fault could be a failure on the part of the mechanism responsible for suppressing the impact of competing but nonselected options. Consequently, in all functional territories, the currently selected option would be pathologically vulnerable to interruption (Figure 38–9C).

Attention Deficit Hyperactivity Disorder and Tourette Syndrome May Also Be Characterized by Intrusions of Nonselected Options

Further examples of hyperactive conditions that have been linked to basal ganglia dysfunction may also be due to a faulty selection mechanism where the system in each case is vulnerable to intrusions. Attention deficit hyperactivity disorder (ADHD), like schizophrenia, could in part be the result of a failure in the mechanism responsible for suppressing nonselected sensory options, thereby making it difficult to maintain a focus of attention. Alternatively, the impulsive aspects of

the condition could reflect a malfunction in the neural systems that generate behavioral options based on the value of likely consequences. In this situation, options driven by immediately desired sensory events would take precedence over competing representations of disadvantageous longer-term consequences.

In the case of Tourette syndrome, converging evidence indicates that the involuntary behavioral intrusions (verbal and motor tics) are associated with aberrant activity in the cortical–basal ganglia–thalamic loops. In animal models, similar motor tics can be evoked by blocking inhibitory neurotransmission in local areas of the sensorimotor striatum. Were the disease state also to cause a similar failure of inhibition or inappropriate excitation in parts of the striatum not engaged by the current selection, disruptive motor intrusions might be expected. Furthermore, were the locus of the excessive excitation to remain constant and the motor characteristics of the intrusion to be repeated, it is likely that the mechanism for establishing automatic habits would be engaged, thereby further enhancing the automatic involuntary nature of the intrusion.

Obsessive-Compulsive Disorder Reflects the Presence of Pathologically Dominant Options

Persons with obsessive-compulsive disorder compulsively repeat specific actions (hand washing, counting things, checking things) or have particular thoughts repeatedly come to mind uninvited (obsessions). Studies using functional neuroimaging when the symptoms are present consistently report abnormal activation at various locations within the cortical–striatum–thalamus–cortical loops.

In terms of a selection mechanism dysfunction, the symptoms of obsessive-compulsive disorder would be expected when, for whatever reason, the input salience of relevant functional channels would be abnormally dominant, thereby making it difficult for competing options to interrupt or cause behavioral or attentional switching (hard selection). The fact that the obsessional and compulsive options are dominant behaviors that have been learned suggests that the fault responsible for obsessive-compulsive disorder may lie with the reinforcement mechanism capable of adjusting input salience. Of course, such a fault could be of genetic and/or environmental origin.

Addictions Are Associated With Disorders of Reinforcement Mechanisms and Habitual Goals

Addiction to drugs and other behaviors (eg, gambling, sex, eating) represents a dramatic dysregulation of

motivational selections. This is caused by an exaggerated salience of addiction-related stimuli, binge indulgence, and withdrawal anxiety. When addictions are being acquired, changes in dopaminergic and opioid peptide transmission in the basal ganglia have been reported.

Insofar as these transmission systems have been linked with fundamental mechanisms of reinforcement, it might be expected that the selective reinforcement of addiction-related stimuli would lead to observed increases in the ability of these stimuli to capture behavior. Alternatively, the increases in negative emotional states and stress-like responses experienced during withdrawal have been associated with reductions in dopamine function. In the limbic territories of the basal ganglia, such reductions are typically associated with negative reinforcement.

A final point to note is that if addiction-associated stimuli can automatically trigger the motivation/goal to indulge (ie, an automatic stimulus–goal association), a similar kind of mechanism may be operating in the limbic territories as is currently assigned to stimulus–response habits in the sensorimotor territories. Thus, if in the case of drug addiction the goal of drug acquisition may be correctly described as a stimulus-driven habit, the practicalities of obtaining the drug can be highly goal directed (eg, robbing a convenience store, phoning the dealer) and not at all habitual.

From the above sections, it can be seen that interpreting disorders of the basal ganglia in terms of dysregulations of selection and reinforcement does not require implausible intellectual contortions. Indeed, this could be regarded as further support for the view that the systems-level function of the basal ganglia is to operate as a generic selection mechanism. Moreover, having an overriding conceptual framework based on potential disorders of normal function has an important advantage for guiding future research. Instead of fishing in the brains of patients and animal models for clues of what might have gone wrong, one is hunting within a specified network for a malfunction that would be expected to produce the observed disorder.

Highlights

1. The basal ganglia are an interconnected group of nuclei located at the base of the forebrain and midbrain. There are three major input structures (the striatum, the subthalamic nucleus, and the dopamine cells of substantia nigra) and two major output structures (the internal globus pallidus and substantia nigra pars reticulata).
2. Input structures receive projections from most regions of the cerebral cortex, limbic system, and brain stem, many via relays in the thalamus. Inputs to the striatum and subthalamus are topographically organized.
3. The spatial topography is maintained throughout the intrinsic basal ganglia connections, as well as in projections back to the cortex, limbic system, and brain stem structures. Thus, an essential feature of systems-level basal ganglia architecture can be viewed as a series of reentrant loops.
4. The striatum was thought to be connected to the output nuclei via direct and indirect pathways. However, recent anatomical evidence suggests a more complex internal architecture.
5. Phasic excitatory input to the basal ganglia is mediated by the neurotransmitter glutamate. Tonic inhibitory output from the basal ganglia is mediated by the neurotransmitter GABA. The reentrant loops keep afferent structures under strong inhibitory control. For any task, the tonic inhibitory firing of some output neurons pauses, while for others, it is maintained or increased.
6. Basal ganglia architecture appeared at the outset of vertebrate evolution and has been highly conserved throughout. This suggests that the computational problems they solve are likely to be problems faced by all vertebrate species.
7. The internal microarchitecture of the intrinsic basal ganglia nuclei is largely the same throughout their motivational, affective, cognitive, and sensorimotor territories. This suggests that the same basal ganglia algorithm is applied to all general classes of brain function.
8. A recurring theme within the basal ganglia literature is their involvement in action selection and reinforcement learning.
9. The selection hypothesis is supported by the following: (1) Selection is a generic problem faced by all vertebrates. (2) A selection algorithm common to all basal ganglia territories could resolve competitions between incompatible motivational, affective, cognitive, and sensorimotor options. (3) Many intrinsic processes could support a selection function. (4) Selective removal of output inhibition within a multiple reentrant looped architecture is necessarily a selection process. (5) Computational models of basal ganglia architecture effectively select the actions of multifunctional robots.
10. Abundant evidence indicates that the basal ganglia are an essential substrate for reinforcement

learning where selections are biased by the valence/value of past outcomes.

11. The multidimensional aspects of action (what, where, when, and how to do something) can be independently modified by reinforcement learning. It will be important to determine whether these different aspects of action are learned within the same or different functional territories of the basal ganglia.
12. Recent optogenetic investigations have confirmed that phasic dopamine signaling can act as a training signal for reinforcement learning.
13. Within the reentrant looped architecture, future selections can be biased not only within the basal ganglia by dopamine but also at synapses in external afferent structures and the thalamic relays.
14. Reinforcement learning can bias selections on the basis of outcome value (goal-directed), or by operating on an acquired automatic stimulus–response association (habit). Goal-directed and habitual selections are made in different functional territories of the basal ganglia.
15. Insofar as diseases of the basal ganglia in humans can be interpreted as selection malfunctions, additional support is provided for the idea that the basal ganglia operate as a generic selection module.

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Suggested Reading

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