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.

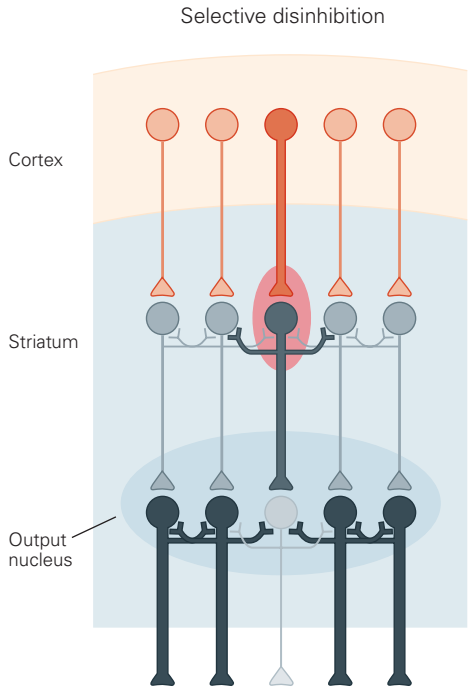

Figure 38–6 The diagram illustrates the principle of selection operating at the level of the basal ganglia output nuclei. Throughout the figure, the relative levels of activity within the competing channels are represented by the thickness of projections, and for clarity, the indirect pathway and the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

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;

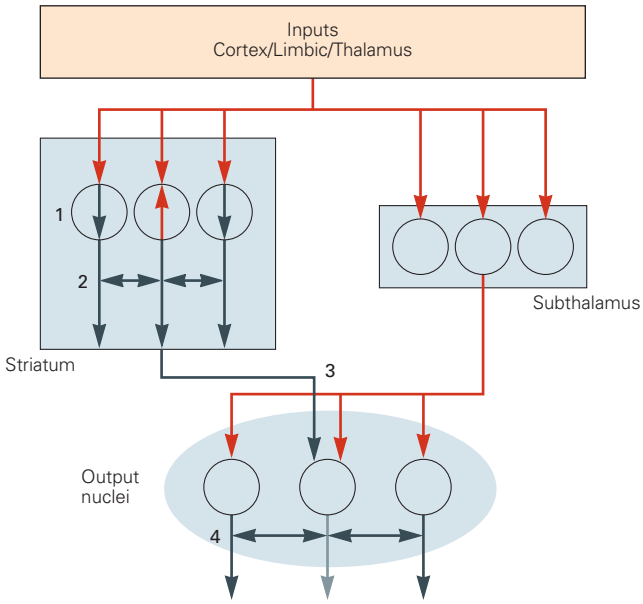

Figure 38–7 Cooperative mechanisms in the basal ganglia that would promote selection.

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 though 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

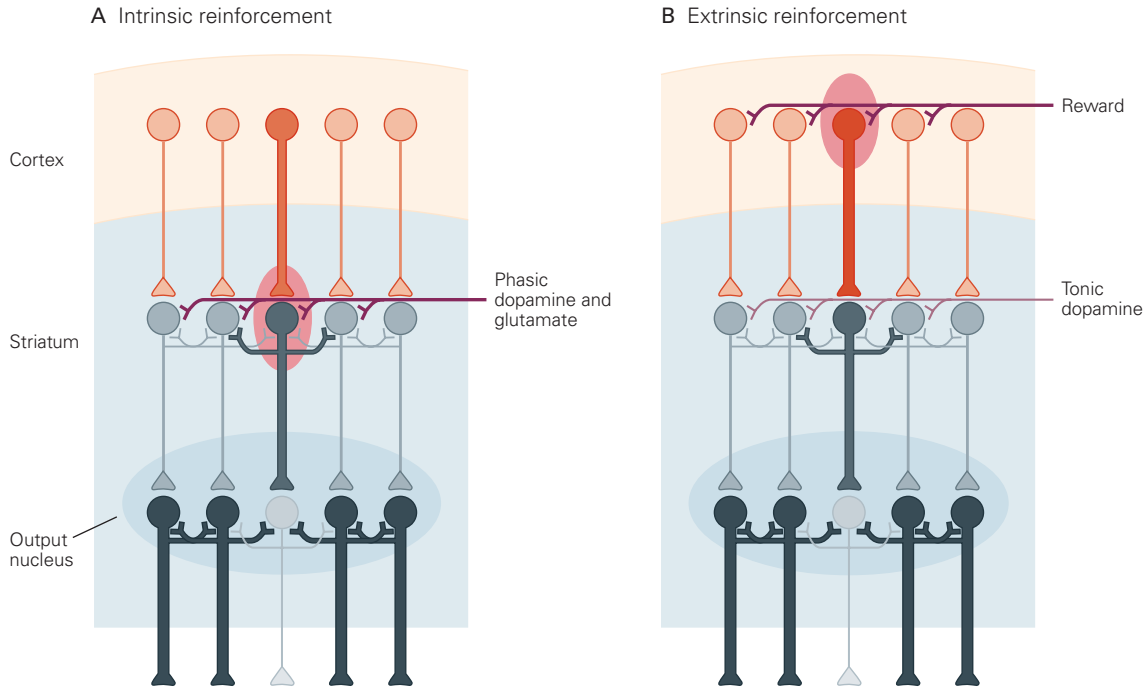

Figure 38–8 **Two separate reinforcement mechanisms can bias selection within the reentrant parallel-loop architecture of the basal ganglia.** (Return connections of the loops via the thalamus have been omitted for clarity.)

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 prelimbic 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

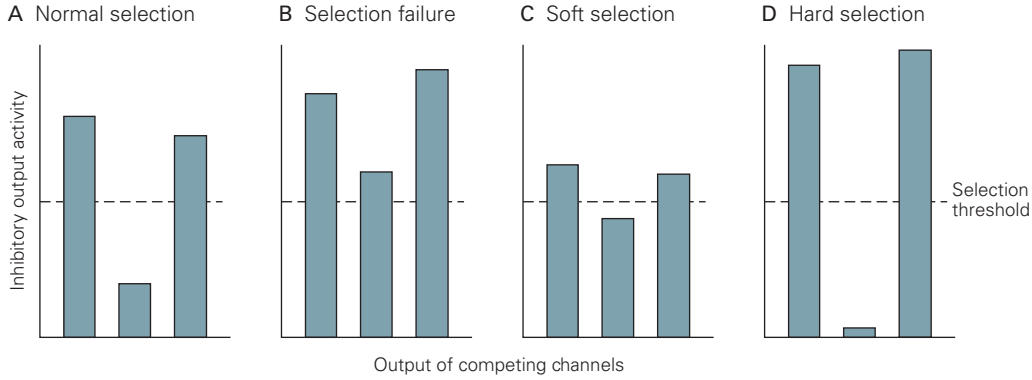

Figure 38–9 Potential disorders of behavior selection.

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).