Advanced Review

The basal ganglia

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Through its connections with widespread cortical areas and with dopaminergic midbrain areas, the basal ganglia are well situated to integrate patterns of cortical input with the dopaminergic reward signal originating in the midbrain. In this review, we consider the functions of the basal ganglia in relation to its gross and cellular anatomy, and discuss how these mechanisms subserve the thresholding and selection of motor and cognitive processes. We also discuss how the dopaminergic reward signal enables flexible task learning through modulation of striatal plasticity, and how reinforcement learning models have been used to account for various aspects of basal ganglia activity. Specifically, we will discuss the important role of the basal ganglia in instrumental learning, cognitive control, sequence learning, and categorization tasks. Finally, we will discuss the neurobiological and cognitive characteristics of Parkinson's disease, Huntington's disease and addiction to illustrate the relationship between the basal ganglia and cognitive function.

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INTRODUCTION

The basal ganglia (BG) are a group of subcortical nuclei that are anatomically and neurochemically similar across all vertebrate species,[1] suggesting that they may perform similar computations across species. Although they are well known for their important role in the gating and thresholding of motor actions, the BG also influence higher-level cognitive functions via similar computations. In rat, primate and human models, the BG have been implicated in motor learning,[2] addiction,[3] reward-mediated learning,[4] the acquisition of habits,[5,6] and categorization processes.[7]

As BG lesions have long been known to be associated with chorea and akinesia, many early researchers suspected that the BG were primarily involved in motor functions. This belief was supported by the finding that the BG receive afferent projections from all cortical areas, and send 'funneled' efferent projections, via the thalamus, to motor regions.[8] For many early researchers, this evidence suggested that BG might aid in the selection of motor movements via a serial process by which information was translated into information suitable for the motor system. We now know that the BG's connectivity allows it to facilitate and inhibit patterns of cortical activity in response to reward-associated feedback signals from mesencephalic dopaminergic inputs.

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BG ANATOMY

Gross Anatomy

As shown in Figure 1, the BG are a group of subcortical nuclei consisting primarily of the striatum (putamen, caudate, and ventral striatum) and the globus pallidus. The globus pallidus is further divided into two separate regions, the internal (GPi) and external (GPe) compartments. Two brainstem nuclei with significant functional interconnections with the BG, the subthalamic nucleus (STN), and the substantia nigra pars reticulata (SNr), are sometimes considered part of the BG as well. In the past, the amygdala was commonly classified as part of the BG, but given its significant functional differences, most researchers now believe that the amygdala should not be considered a part of the BG.

The striatum is commonly subdivided into ventral (VS) and dorsal (DS) components. Although there are no clear differences between the VS and DS in terms of cytoarchitecture or chemoarchitecture, the striatum is topographically organized, and its regions can be dissociated via differences in their

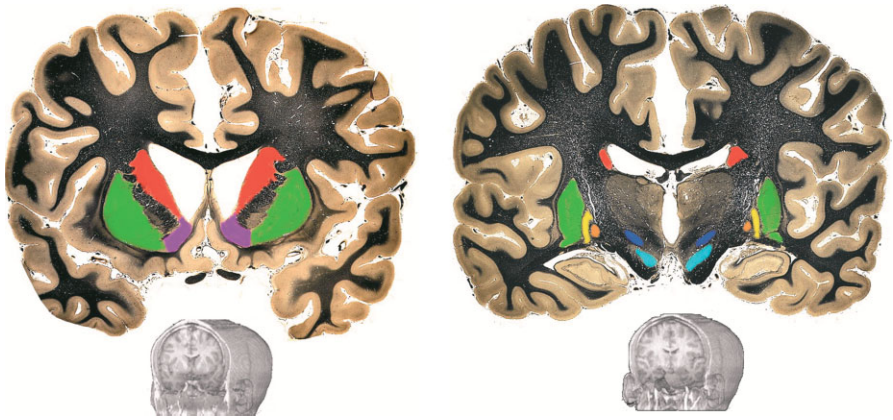

FIGURE 1 | The human basal ganglia and midbrain nuclei: red: caudate; green: putamen; purple: ventral striatum/nucleus accumbens; yellow: internal segment of the globus pallidus; orange: external segment of the globus pallidus; dark blue: subthalamic nucleus; light blue: substantia nigra.(Reprinted with permission from http://www.brains.rad.msu.edu, and http://brainmuseum.org, supported by the US National Science Foundation.)

connectivity.[9] The gross anatomy of the DS differs between primates and rodents. In primates it is separated into two nuclei, the caudate and putamen. In rodents, these regions are contiguous and are typically referred to as the dorsomedial and dorsolateral striatum, respectively.

The ventral striatum encompasses the ventral extent of the striatum in rodents, corresponding to the ventral putamen and ventral caudate in primates. A large portion of the ventral striatum forms the nucleus accumbens (NAcc). Although the NAcc is properly defined as the ventromedial portion of the rostral VS, many researchers unfamiliar with the BG mistakenly assume that the VS and the NAcc are distinct structures, perhaps due to the tendency of researchers using rodent models to use the term 'NAcc' and of researchers studying humans to use 'VS.' Difficulties in clearly delineating the nucleus accumbens via the neuroimaging methods used in the majority of human experiments, likely underlies this disparity.

The NAcc can be further subdivided into core and peripheral shell regions. The shell is associated with the performance of goal-directed behaviors, behavioral sensitization, and changes in affective states.[10] The principle source of inputs into the shell are medial regions of the prefrontal cortex, the midline regions of the thalamic nucleus, posterior regions of the basolateral amygdala, and CA1 region of the hippocampus.[11] The principle source of dopaminergic input to the shell is the VTA. Output from the shell projects principally to the ventral pallidum, the lateral hypothalamus, and dopaminergic cells in the SNc and dorsal ventral tegmental area (VTA).[11] As these dopaminergic cells in the VTA and SNc influence processing in other striatal regions, shell projections to these cell groups may represent a mechanism by which the shell can influence activity in other striatal regions.[12]

Lesions of the NAcc core are associated with increases in impulsivity[13] and attenuation of instrumental responding in response to pavlovian cues.[14] The principle source of inputs to the core are the ventromedial caudate and putamen, dorsolateral frontal cortex, cingulate, the intralaminar thalamic nuclei, rostral basolateral amygdala, and parahippocampal gyrus.[12,15] The core receives dopaminergic input from both the VTA and SNc.[16] Outputs from the core are similar to the those of the caudate and putamen: the ventral pallidum, medial entopeduncular nucleus (GPi), and the dorsomedial SNr.[12]

Cellular Anatomy of the Striatum

The predominant neuron type (>97%)[17] within the striatum is the striatal medium spiny neuron (MSN). These GABAergic neurons are also referred to as striatal projection neurons, or as phasically active neurons (PANs) due to a low level of baseline firing combined with phasic bursts of activity. The remaining 2% of striatal cells consist of interneurons, of which there are two primary types: GABAergic and cholinergic (often referred to as tonically active neurons, or TANs, due to their high and constant level of baseline activity). GABAergic interneurons can be further divided into at least two different types, fast spiking, and low threshold spiking (see Ref 17 for a comprehensive review).

Although they comprise less than 1% of all striatal neurons, TANs have extensive axonal fields that project to widespread striatal regions.[18] TANs have a tonic inhibitory effect on cortically induced MSN

activity,[19] can affect dopamine release, and pause in rewarding contexts.[20] Although its precise functional significance is somewhat unclear, TAN inhibition of striatal responding may reflect a mechanism that protects striatal learning from decay under conditions when no reward is available.[21] TANs may also serve to enhance the salience of the dopaminergic signal,[22] or may aid in the determination of reinforcement value.[23]

Neurons within the striatum are organized in a modular structure with two main compartments: patch ('striosome') and matrix ('matrisome').[24] These compartments contain two different types of MSN that can be distinguished via their connectivity. While MSNs in both the patch and matrix compartments project to the direct and indirect pathways, only patch MSNs project to the VTA and SNc.[25] Patch MSNs also project to the rat entopeduncular nucleus and GP.[25] In non-primates, the entopeduncular nucleus is homologs to the combined GPi and entopeduncular nucleus in primates. Matrix MSNs do not project to VTA and SNc, but instead project to regions of the GPe, GPi, and SNr associated with motor processing,[25,26] suggesting that matrix MSNs may influence motor activity. The patch striatonigral projections may therefore reflect an important pathway whereby the striatum influence reward signaling in the VTA and SNr.

Pathways through the BG

Figure 2 illustrates the three primary pathways through which the BG interacts with cerebral cortex. These pathways exert their effects though opposing influences on thalamic excitation. The first two pathways to be identified were the 'direct' and 'indirect' pathways.[27,28] The GABAergic MSNs in the 'direct' pathway (also sometimes referred to as the 'Go' pathway) inhibit activity in the internal segment of the globus pallidus (GPi), attenuating its tonic inhibitory influence on the thalamus, and ultimately lowering the threshold required for the thalamus to become excited in response to other inputs.[29] The MSNs in the indirect pathway (also sometimes referred to as the 'NoGo' pathway) inhibit activity in the external segment of the globus pallidus (GPe), thereby attenuating its tonic inhibitory effect on the GPi. The GPi's tonic inhibitory influence on the thalamus is thereby increased, raising the threshold required to elicit thalamic activity. The direct and indirect pathways influence the threshold required for thalamic activity, but thalamic excitation seems to be driven primarily via direct projections from other regions. The medial dorsal thalamic nucleus, for instance is primarily innervated by the PFC, and the ventral lateral nucleus is primarily innervated by premotor

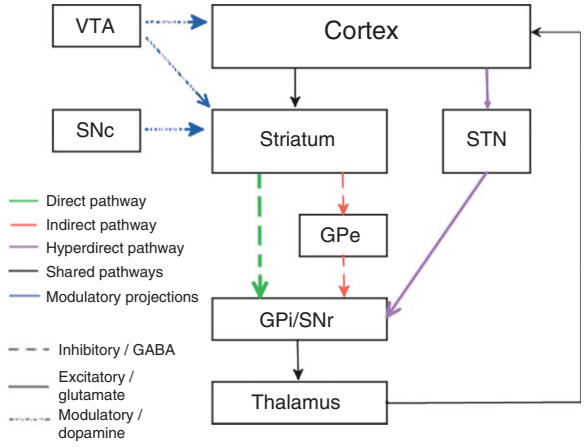

FIGURE 2 | Primary pathways through the basal ganglia. GPe, external portion of the globus pallidus; GPi, internal portion of the globus pallidus; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; VTA, ventral tegmental area.

regions.[30] Some thalamocortical cells, however, show post-inhibitory rebound bursting,[31] suggesting that the BG output nuclei may have at least some direct excitatory influence on thalamic cells.

A third pathway, the 'hyperdirect' pathway,[32] projects to the STN and then to the GPi, bypassing the striatum. This pathway is glutamatergic rather than GABAergic, and so cortically-driven excitation of the STN excites the GPi, ultimately inhibiting the thalamus. Projections from the STN to the thalamus are diffuse, and as a consequence, several models (e.g., Ref 33) posit that while the direct and indirect pathways are responsible for thresholding specific input/output associations, excitation of the hyperdirect pathway instead raises the global thalamic excitation threshold such that stronger cortical innervation is required to produce any thalamic output. This global inhibition would likely be useful in situations in which it is desirable to withhold fast responding in order to improve accuracy.

Corticostriatal Loops

Projections from the cortex to striatum are topographically organized so that different cortical regions project to different regions of the striatum. As a result, the corticostriatal network can be divided into partially overlapping, but largely segregated, corticostriatal loops.[7,34,35] There are a number of possible divisions of the corticostriatal network; one common approach is into four different loops, as illustrated in Figures 3 and 4. The executive loop involves the anterior region of the caudate (the 'head' of the caudate), which receives cortical afferents primarily from regions associated with executive functions: the

lateral prefrontal cortex (PFC) and the posterior parietal lobe. The visual loop involves the posterior regions of the caudate (the 'body' and the 'tail' of the caudate), which receive afferents primarily from regions associated with high-level visual processing: the extrastriate visual areas, the inferior temporal cortex and the frontal eye fields. The motor loop involves the putamen, which is primarily innervated by cortical motor regions such as the premotor cortex, the supplementary motor area (SMA), and somatosensory regions. The motivational loop involves the ventral striatum, which receives its primary innervation from cortical regions associated with motivational processes: the orbitofrontal cortex, the medial parahippocampal cortex, and the amygdala.

Corticostriatal loops must interact with each other to produce meaningful cognitive or behavioral output. The first mechanism that may facilitate this coordination is overlap of the axonal terminations from cortex within the striatal dendritic receptive fields,[36] such that projections from adjacent cortical regions may converge on the same MSNs. In addition to this limited overlap between adjacent cortical regions, a subset (approximately 15%) of corticostriatal projections project diffusely across the striatum, possibly providing a mechanism by which multiple loops have access to the same input.[36,37] Another mechanism is a series of recurrent 'spiral' connections between the striatum and the SNc and VTA.[38] Striatonigral neurons project to the VTA and medial SNc, which, in turn project to more dorsal regions of the striatum. The net result is that striatal regions influence one another via a ventro–antero–medial to dorso–postero–lateral gradient, wherein the motivational loop influences the visual and executive loops, and these loops in turn influence the motor loop.[38]Finally, the corticostriatal loops may also form 'open loops,' projecting to different cortical regions than those from which they originated.[39] Although this latter mechanism is potentially the most effective method of coordination between loops, it is also one of the least-well understood, due to difficulties tracing projections from the BG though thalamus and back to the cortex.

DOPAMINE, LEARNING, AND PLASTICITY WITHIN THE BG

Dopamine Projections and Reward Sensitivity

The BG are primary targets of dopaminergic projections from the midbrain nuclei, in particular the SNc and VTA. These dopamine neurons fire in response to rewards, and thus enable the BG to be sensitive to the motivational context of the environment. Olds and Milner[40] were the first to recognize that the VS (specifically the NAcc) plays an important role in reward processing, and in particular in reward-mediated learning. Via electrodes implanted in various subcortical regions of the rat, these researchers found that NAcc stimulation elicited increases in lever-pressing behavior similar to that observed in response to direct reward.

Reward mediated mesencephalic dopamine cell activity occurs in response not only to primary rewards (e.g., food, water, sexual activity), but to secondary rewards including money, praise, signals of social status, and stimulus novelty.[41] The reward signal has traditionally been considered a unitary signal; however, it may be more accurately modeled as multiple processes[42] associated with various levels of abstraction. Reward representations need not be direct indicators of reward but can be cognitively mediated. Examples include reward related activity in response to the achievement of unrewarded goals[43] and to imagined possible but not actually experienced rewards (sometimes termed fictive reward).[44] This wide variety of types of reward enable the BG to contribute to reward related learning across a broad range of situations.

The dorsal striatum is also sensitive to reward, but the sensitivity is greatest when reward is contingent upon the organism's behavior.[45] This differing pattern of activity has led to theories inspired by actor-critic reinforcement learning models[46] in which the ventral striatum is considered to play the role of the critic (evaluating the effectiveness of behavior in terms of the reward received) and the dorsal striatum the actor (using reward related knowledge to decide on the best course of action).

Because of the importance of dopamine in the BG, different alleles of genes affecting dopamine have strong effects on BG function.[47] Particularly important are genes that code for the dopamine transporter (e.g., DAT1, which regulates striatal dopamine levels through reuptake), the dopamine receptor (e.g., DRD2, which regulates receptor density in the striatum), and for factors that regulate the effects of dopamine on synaptic plasticity (e.g., DARPP-32). DARPP-32 appears to be particularly important for D1 receptor mediated 'Go' learning, but not for D2 receptor mediated 'No Go' learning. Conversely, DRD2 appears to be particularly important for D2 receptor mediated learning.[48]

Role of Dopamine in Long Term Potentiation and Depression

The corticostriatal synapse is the key site of BG plasticity. It has a tripartite structure in which glutamatergic

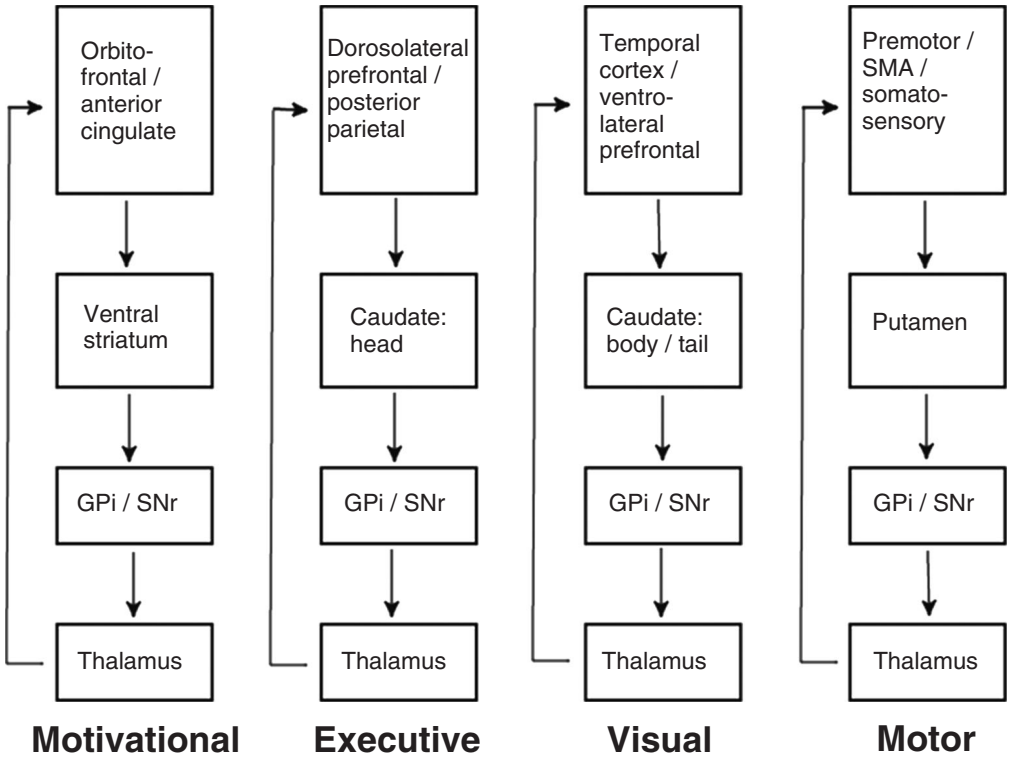

FIGURE 3 | A diagram of the four corticostriatal loops. Each loop projects from the cortex to the striatum to the output nuclei (second from bottom) and then to the thalamus. For simplicity, only primary cortical afferents are shown. SMA, supplementary motor area; GPi, internal segment of the globus pallidus; SNr, substantia nigra pars reticulata.

projections from the cortex synapse on MSN dendritic spines and dopaminergic projections from the SNc synapse primarily on the necks.[49,50] These SNc synapses are well-situated to allow dopamine to modulate the excitatory post-synaptic effects of cortical input. The mesencephalic dopaminergic reward signal[51] affects activity and plasticity in both the direct and indirect pathways through the BG, but has different effects based on the preponderance of D1 and D2 receptors in these pathways. Phasic bursts of dopaminergic input facilitate long-term potentiation (LTP) at the D1 synapses[52] of the direct pathway such that, according to several models (e.g., Refs 33 and 53), the input/output associations which gave rise to the reward signal are strengthened. In contrast, these models posit that these bursts facilitate long-term depression (LTD) at the D2 synapses of the indirect pathway, such that the tonic inhibitory effect of this pathway on the thalamus will be attenuated in response to similar patterns of future input. When an expected reward is not received, the firing of mesencephalic dopamine neurons is briefly suppressed,[54] and these models posit that LTD is elicited at D1-expressing synapses of the direct pathway, and LTP is elicited at D2-expressing synapses of the indirect pathway.

Reinforcement Learning

Broadly, reinforcement learning (RL) models posit that any decision involves four basic steps: identification of behavioral context ('state'), valuation of potential actions, action selection, and updating of action values based on subsequent feedback. RL models involve calculating for each stimulus, or state, an estimate of the potential reward that could be achieved by performing an appropriate action. This estimate is typically referred to as reward prediction or as value. RL models also involve calculation of another measure, reward prediction error (RPE), which is calculated as the difference between predicted and actual reward. In recent years RL models have been used to account for BG activity, inspired by the discovery that the dopaminergic reward signals projecting from the midbrain had activity patterns that were well fit by reinforcement learning measures of the RPE.[51] Along with research establishing the necessity of dopamine for corticostriatal LTP and LTD, this raised the possibility that RL could also account for BG functions.

Activity in the orbitofrontal cortex and VS is well characterized by the RPE.[55] This representation in the VS (and its associated motivational loop) may be propagated to the dorsal striatal loops via 'spiral'

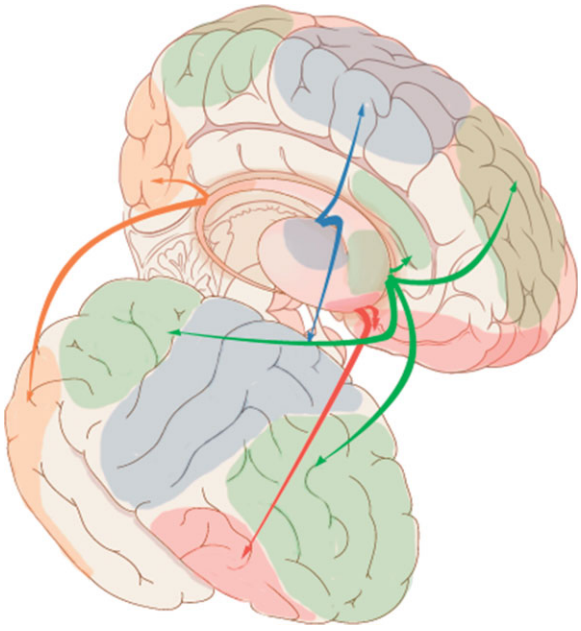

FIGURE 4 | Four corticostriatal loops. Red: the orbitofrontal cortex and the anterior cingulate project to the ventral striatum in the motivational loop. Green: prefrontal and parietal cortices project to the head of the caudate in executive loop. Blue: the ventrolateral prefrontal and temporal cortices project to the body and tail of the caudate in the visual loop. Orange: the premotor, supplementary motor and somatosensory cortices project to the putamen in the motor loop.

striatonigral connectivity.[56] Similarly, the striatum may be hierarchically organized to coordinate reward-mediated output at varying levels of abstraction,[57] such that the VS codes the value associated with a global abstract action (such as taking a rest), the dorsomedial striatum may encode values related to abstract specific actions (such as 'turning left') and the dorsolateral striatum may encode values related to specific actions (such as moving a specific limb).

Although it has been largely successful, RL is not the only theory describing the activity of midbrain dopaminergic neurons. As dopaminergic activity is observed very quickly after stimulus onset in response to unrewarding and unpredicted stimuli,[51] Redgrave et al.[58,59] have argued that midbrain dopamine neurons do not receive sufficient afferent sensory information concerning the reward value of unpredicted stimuli to fulfill the role posited by RL. Instead, they have suggested that phasic DA activity may serve to encourage animals to repeat the behaviors that preceded the unpredicted events. This could, they suggest, facilitate exploration of the actions associated with a novel biologically relevant stimulus. Berridge[60] has also suggested that phasic dopaminergic activity may not be directly associated with learning, or with the generation of reward predictions, but rather may allow an animal to attribute incentive salience to rewarded stimuli.

FUNCTIONS OF THE BG

Selection and Response Thresholding

Early modern theories focused on BG roles in motor control,[27] in particular through activity in the direct and indirect pathways described above. These theories focus on how the BG enable selection and initiation of appropriate motor responses. BG disorders are characterized by impairments in selection that can lead to hypokinesia, as in Parkinson's disease, or hyperkinesia, as in Huntington's disease, Tourette syndrome, and attention deficit hyperactivity disorder. A number of researchers have developed formal computational models of response selection.[61–63] Models of selection focus on the net effects of direct and indirect pathways on the BG output nuclei, in particular the globus pallidus,[64] and as such may complement RL models that focus on the striatum and dopamine input. One example of such a hybrid model was proposed by Lo and Wang.[65]

Recent research has focused on how the BG may contribute to selection in a contextually dependent way through setting an appropriate response threshold for a task, as in the speed-accuracy tradeoff. When speed is emphasized over accuracy, several researchers have noted increased activity in the striatum, and in cortical areas such as the pre-supplementary motor area. Forstmann et al.[66] for instance, found that across participants, activity in the pre-SMA and striatum was associated with adjustments to response threshold, such that individual variation in striatal activity was associated with variation in response thresholding. It is currently unknown whether decision thresholding is specific to a particular motor effector, or whether it functions at a more abstract level. The finding that learning itself can be tied to specific motor effectors[67] particularly in tasks that depend strongly on the BG[68,69] suggests a specific mechanism. However, global inhibition of motor output could be mediated via the hyperdirect pathway, and may allow the PFC to override a pre-potent response mediated by the striatum.[70]

Instrumental Learning and Interactions between Model-Based and Model-Free Learning

The BG are not only involved in response selection, but can learn what responses lead to the best outcomes, improving selection in the future. Learning to perform context dependent actions that lead

to rewarding outcomes is broadly the domain of instrumental learning; instrumental learning tasks are often analyzed in terms of stimulus, response, and reward or feedback. A variety of tasks share this basic stimulus–response–reward structure, including rule learning and arbitrary visuomotor learning in monkey, and simple categorization and decision making tasks in humans.[71] All of these tasks have been associated with the BG. Electrophysiological and neuroimaging work finds that the BG overall are active during stimulus, response, and feedback; however, there are some regional differences, with the putamen being particularly active during response, and the caudate and ventral striatum during stimulus presentation and feedback.[72–74]

Instrumental learning is often divided into two types, goal-directed (or model-based) and habitual (or model-free), which have been associated with the caudate (rodent dorsomedial striatum) and putamen (rodent dorsolateral striatum), respectively. In goal directed learning animals use knowledge about the contingencies between actions and outcomes to select appropriate behaviors.[5,75] Goal directed behaviors can be formalized using model-based reinforcement learning algorithms that potentially implement forward (or 'tree') searching[76] or mental-simulation,[77] to maximize rewards and minimize punishments. Functional neuroimaging studies have found caudate activity consistent with these model-based measures.[76,78]

Once animals have sufficient experience with action outcomes, behavior is thought to become habitual, or in reinforcement learning terms, dependent primarily upon a model-free reinforcement learning system.[73] Activity in the posterior putamen is well characterized by a model-free system, in which animals learn action values directly, through experience with action consequences.[79] In learning theory, habitual behavior is elicited based on stimuli in the environment without consideration of outcome or reward expectancy.[5,75] Outcome sensitivity is often assessed via reward devaluation: for example, lever pressing is considered habitual when a rat will continue to press the lever for food even after it has become satiated through consumption of as much food as desired. Lesion of the dorsolateral striatum in rat (homologous to the the human putamen) increases reward-devaluation sensitivity,[80] while lesion of the dorsomedial striatum in the rat (homologous to the caudate) can facilitate the expression of model-free behavior early in learning.[81] Reward devaluation, however, is only one of several ways that researchers have dissociated the influences of goal-directed and habitual systems on behavior. Other researchers (see Ref 82 for a review) have suggested that habitual behavior should be resistant to interference from a simultaneously performed dual task,[83] or require extensive training.[84]

Little is also known about how we might integrate model-free and model-based signals to aid in the selection of advantageous behavior. There are two important ways in which the systems may interact dynamically. One is through a direct influence of one system on another. Some studies have found that the model-based network modulates striatal activity in accordance with the rule or theory being entertained, and in contrast to the actual reward contingencies.[85] Another method is through periodic switching between primary control of decision making. In a real world environment it is sometimes useful to rely strictly on past experience or habit, and sometimes useful to follow a novel strategy; this is known as the exploration–exploitation tradeoff.[86] Sheth and colleagues[87] have found evidence that the globus pallidus may influence behavioral switches between exploration and exploitation. These researchers found that GPi neuron activity decreased during early stages of learning but returned to baseline rates with more practice. On a trial-to-trial basis, the firing rates of these neurons predicted exploratory behavior, such that lower rates were associated with exploration and higher rates were associated with exploitation. Interestingly, Daw et al.[88] have recently found evidence that the ventral striatum, which has been extensively studied in relation to the model-free RPE, also carries information concerning the model-based error signal. This finding suggests that these systems may be at least partially integrated.

Cognitive Control and Executive Functions

The distinction between habit and goal-directed instrumental learning described above leads to increased emphasis on how the BG can contribute to cognitive function more broadly. Disorders of executive function such as attention deficit hyperactivity disorder involve fronto-striatal dysregulation,[89] and the BG, in particular the caudate, are recruited across executive function domains in control subjects.[90] Recent research has identified specific contributions of the BG that are consistent with the computational functions of the BG discussed above: tonic inhibition of cortex, selection of appropriate representations, and switching between representations. The BG are important for selecting which specific items should enter working memory.[91,92] People with BG lesions are impaired in their ability to filter irrelevant information,[93] and effective models of

working memory often incorporate the BG.[94] The BG are also involved in switching across a number of domains, including attentional shifting to salient events.[95] switching from automatic behaviors to controlled behaviors,[72] and switching between languages in bilinguals.[96]

Sequence Learning and Chunking

Most real-world behavioral tasks require that several movements be linked together into sequences. Behavioral evidence suggests that sequence representations are represented hierarchically such that long sequences of actions are segmented into shorter chunks.[97] Sequence learning can therefore be represented by two processes: sequence concatenation, whereby individual actions become 'chained' to other actions, and segmentation, whereby these chains are differentiated from others. Concatenation appears to be associated with activity in the bilateral putamen while segmentation is associated with activity in the frontoparietal network.[98] During sequence tasks, the DS and SNr are active at the beginning and end of sequence chunks[73,99,100] and when MSN activity is disrupted, sequence learning is also impaired.[101]

Sequence learning across time exhibits a similar shift from executive to motor corticostriatal loop as is present in instrumental learning. While the caudate nucleus and anterior putamen (dorsomedial striatum) appear to be particularly involved in the early stages of motor learning, the posterior putamen (dorsolateral striatum) becomes more active when a sequence becomes well-practiced.[102,103] Blockade of anterior regions of the caudate and putamen causes impairment in learning, while blockade of the middle-posterior putamen has been associated with the execution of well-learned motor sequences.[104]

Categorization

The BG also play an important role in human categorization. As described above in the discussion of instrumental learning, categorization learning tasks typically involve trial and error learning, in which subjects view a stimulus, make a response indicating category membership, then receive feedback. The BG are active for all of these components of category learning; in particular, the head of the caudate is particularly sensitive to feedback processing and the posterior caudate and putamen to stimulus processing.[74,105] However, the BG can also be differentially recruited by different categorization tasks based on the specific demands of each task. One particularly influential distinction is between 'rule-based' and 'information-integration' category learning. Whereas rule-based categories can be characterized via a verbalizable rule, and can be learned via an explicit hypothesis generating and testing procedure, information-integration tasks can only be approximately described by complex rules. See Ashby[106] for review) Accordingly, information-integration tasks typically take longer to learn and, once learned, the strategy is often difficult to verbalize. Whereas rule-based category learning is thought to be subserved via a working memory-dependent hypothesis testing procedure, information-integration category learning is thought to be subserved by the procedural memory system whereby participants learn to associate regions of perceptual space with particular motor responses.[107] The head of the caudate, which is reciprocally connected with cortical regions associated with working memory within the executive corticostriatal loop, has been found to play an important role on rule-based categorization,[108] while posterior regions of the striatum (particularly the tail of the caudate and posterior putamen, which are reciprocally connected with high-level visual and motor areas) are thought to play an important role in information-integration category learning.[109]

DISORDERS OF THE BG

A wide variety of developmental, neurological and psychiatric disorders have been linked to disruption of corticostriatal networks, including Tourette syndrome,[110] stuttering[111] obsessive-compulsive disorder,[112] attention deficit hyperactivity disorder,[89] and schizophrenia.[113] In this section we focus on three of the most commonly studied disorders, Huntington's disease, Parkinson's disease, and addiction.

Huntington's Disease

Huntington's disease is a fatal neurodegenerative disease that is associated with emotional disturbances and symptoms of hyperkinesia.[114] Degeneration of indirect pathway, which is typically associated with the inhibition of motor responding, may underlie choreic motor behaviors.[115–117] It is also associated with cell death in the neocortex and in the striatum. Post-mortem studies have revealed that patients with mood disturbances tend to display reduced cell-density in the striosomal compartment[118] and in the anterior cingulate cortex[119] compared to participants who displayed primarily motor symptoms.

Parkinson's Disease

Parkinson's disease is characterized by difficulty initiating voluntary movements, muscle rigidity,

difficulty maintaining stable posture, and mild cognitive deficits similar to those seen in patients with frontal damage. Patients have difficulty gating cognitive representations and to be impaired on tasks that require participants to ignore distracting stimuli.[93] Additionally, they are specifically impaired in learning reward-related learning tasks.[120] Parkinson's disease is primarily associated with cell death in the SNc, but cells are also lost from the VTA. The resulting dopamine depletion is most severe, and occurs earliest in striatal motor regions (i.e., the putamen), but later extends to other regions of the striatum as well.[121] This spatiotemporal gradient appears to have functional correlates; as non-motor symptoms of Parkinson's disease seem to gain prominence as the disease progresses.

While treatment with L-DOPA, a dopamine precursor,[122] ameliorates many symptoms of Parkinson's disease, it exacerbate others. Cools et al.[123] found, for instance, that patients treated with L-DOPA tend to display improved task-switching performance (which is known to be mediated by the DS), but impaired probabilistic reversal learning (which is known to mediated by the VS). As cognitive function follows an inverted 'U' shaped curve, whereby both excessive and insufficient dopamine innervation are associated with non-optimal performance,[123] the differential effects of L-DOPA therapy on task-switching and reversal learning may be mediated by different baseline levels of dopamine in the DS and VS. Excessive DA stimulation of the striatum via L-DOPA therapy also causes dyskinesias in 40% of patients.[124] These dyskinesias are specifically associated with excessive stimulation of the D1 receptors in the direct pathway responsible for initiating motor movements,[125] and of cells in the patch compartment.[126] Interestingly, increased activation of cells in the patch compartment is also associated with over-stimulation of the DA system with drug-use, and can sometimes lead to similar dyskinesias.

Addiction and Drug Abuse

Drug abuse and addiction are also associated with abnormal function of the BG. Early exposure to drugs of abuse activates brain regions associated with motivational and emotional processes, such as the NAcc and amygdala, whereas repeated use tends to activate regions associated with executive processes, such as the DS and neocortex.[127] This transition appears to parallel the self reports from drug users indicating early hedonic motivation, and the finding that the DS striatum mediates habitual behaviors. Crittenden and Graybiel[126] have suggested that this transition from VS to DS regions may be subserved by the recurrent spiral connectivity between the striatum and the SNc/VTA. In support of this argument, lesion of these connections has been found to disrupt habitual drug-seeking behavior in the rat.[128]

CONCLUSION

The BG are anatomically well situated to integrate information about context, actions and outcomes to help animals optimize future behavior based on past experience. They are especially well-known for their important role in the gating and thresholding of motor processes, but influence cognitive processes through similar computations. Thresholding is contextually sensitive and can be global or specific to particular actions, but it is currently unknown whether thresholding is specific to particular motor effectors.

Reinforcement learning models have been effective at characterizing activity in BG regions. Activity in mesencephalic dopamine areas is well characterized by the reward prediction error, as is activity in the ventral striatum. Activity in the dorsal striatum, however, is more closely related to action-reward associations. Striatal plasticity is mediated by this reward signal, and via this mechanism, the BG play an important role in strengthening associations between rewarded patterns of input and output, and weakening unrewarded associations. Via recurrent circuits between the striatum and dopaminergic regions in the midbrain, the BG can modulate the reward signal itself, influencing both activity and plasticity in distal regions.

In addition to directly modulating thresholding and learning processes, the BG may also influence behavioral strategies used at various times in the learning process. The executive corticostriatal loop is involved in the goal-directed learning process that characterizes early learning, while activity in the motor loop is associated with the habitual behavior that characterizes later task performance. Shifts from the executive to motor loops have been noted in instrumental conditioning tasks.[73]

In order to facilitate advantageous future behavior, reward knowledge must generalize to novel contexts. The BG may contribute to this capacity through the well-known information convergence through the BG,[37,129] or through processing of abstract cortical representations.[7] More research, however, is needed to fully understand the mechanisms that underlie this fundamental capacity.

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