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Fundamental and Clinical Evidence for Basal Ganglia Influences on Cognition

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1. INTRODUCTION AND OVERVIEW OF THE BASAL GANGLIA

1.1. Structures and Subdivisions

Over the past century, the term "basal ganglia" has at one time or another been used to indicate a wide variety of brain structures. In its present and most restrictive use, however, the term is generally reserved for three groups of brain structures called the "striatum," "pallidum," and "substantia nigra," and an additional structure termed the "subthalamic nucleus" (STN). Table 1 outlines the basic subdivisions of the basal ganglia. The striatum can be separated into two general components, the dorsal striatum, which consists of the caudate and putamen, and the ventral striatum, which consists of the nucleus accumbens, septum, and olfactory tubercle. The nucleus accumbens, in turn, is subdivided into a lateral core region and medial shell region. In a similar manner, the pallidum can also be divided into multiple divisions, including a lateral or external segment of the globus pallidus (GPe), a medial or internal segment of the globus pallidus (GPi), and a portion that lies ventral and anterior to the anterior commissure, designated the ventral pallidum (VP). The GPi is further divided anatomically by a distinct fiber bundle into a lateral outer portion and a medial inner portion. Finally, the substantia nigra is also composed of more than one component, a cell group rich in neuromelanin called the pars compacta (SNpc), which is responsible for the black appearance of the nucleus in gross specimens, and an unpigmented cell group known as the pars reticulata (SNpr). Further subdivision of the SNpr is also possible, due to the presence of a distinct subpopulation of cells located dorsolaterally in the SNpr, and is referred to as the pars lateralis.

1.2. Connections Between Basal Ganglia Subdivisions

The basic connections between the different components of the basal ganglia are now well described *(1–4)*. According to the simplest classification scheme, the nuclei within the basal ganglia can be subdivided into sets of "input," "output," and "intermediate" structures. Input structures include the caudate, putamen, and nucleus accumbens. Collectively, these input structures receive direct projections from nearly the entire cerebral cortex. These input structures then project to intermediate structures as well as output structures.

Intermediate structures within the basal ganglia include the STN, GPe, and SNpc. An additional structure, the pedunculopontine nucleus (PPN), is also occasionally viewed as an intermediate component of the basal ganglia due to its dense interconnectivity with other basal ganglia structures. In general, intermediate structures project most heavily to other basal ganglia nuclei, including the output structures as well as other intermediate structures.

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Table 1
Basal Ganglia Subdivisions

Basal ganglia structure	Primary subdivision	Secondary subdivision	Tertiary subdivision
Striatum	Dorsal striatum	Caudate	
		Putamen	
	Ventral striatum	Nucleus accumbens	Core
			Shell
		Septum	
		Olfactory tubercle	
Globus pallidus	External segment		
	Internal segment	Outer portion	
		Inner portion	
	Ventral pallidum		
Substantia nigra	Pars compacta		
	Pars reticulata	Pars lateralis	
Subthalamic nucleus			

The three principal output structures of the basal ganglia include the GPi, SNpr, and VP. For the most part, these output structures send their efferent projections to different subdivisions of the ventroanterior–ventrolateral (VA/VL), mediodorsal (MD), and intralaminar (IL) groups of thalamic nuclei (particularly the centrum medianum and parafasicularis intralaminar nuclei [CM/PF]) *(1–5)*. The VA/VL and MD nuclei of the thalamus, in turn, project largely back upon the cerebral cortex. Thus, one of the major features of basal ganglia anatomy is their participation in what has become known as cortical-basal ganglia-thalamocortical circuits (hereafter referred to as simply cortical-basal ganglia circuits). Notably, however, some of the neurons in VA/VL and MD, and many of the neurons in CM/PF, send projections to the striatum, and thus form a recurrent thalamic feedback loop with the basal ganglia. Although most early depictions of basal ganglia circuitry have emphasized the unidirectional flow of signals within these loops, as Fig. 1 illustrates, there is an increasing awareness of the importance that recurrent projections from the thalamus, as well as most intermediate and output structures, can play in modulating basal ganglia function.

1.3. Cellular Organization

Superimposed on the macro-organization of cortical-basal ganglia circuits are well-characterized relationships between the various cell types that comprise these circuits. Some of the early and most comprehensive studies of the cellular anatomy of the basal ganglia were made using purely morphological criteria and did not attempt to impose functional distinctions on the cell types. Recent investigations have used a more heuristic approach to describing the cellular components of the basal ganglia, which classifies them initially as either interneurons or projection neurons and differentiates them further within these classes based on morphological, neurochemical, physiological, and hodological features (Table 2) *(2–4,6)*.

1.4. The Basic Cortical-Basal Ganglia Circuit in Action

Many features of the cellular, neurochemical, and physiological organization of the basal ganglia are particularly important in understanding how the basal ganglia process information. Most of the cortical input to the basal ganglia is derived from layer V pyramidal cells that use glutamate (GLU) as a neurotransmitter. These cortical projection neurons can innervate one or more of several types of basal ganglia circuits. Most of the inputs from motor and higher association areas of cortex synapse on medium spiny cells in the striatum that are part of either the direct path or indirect path (see below)

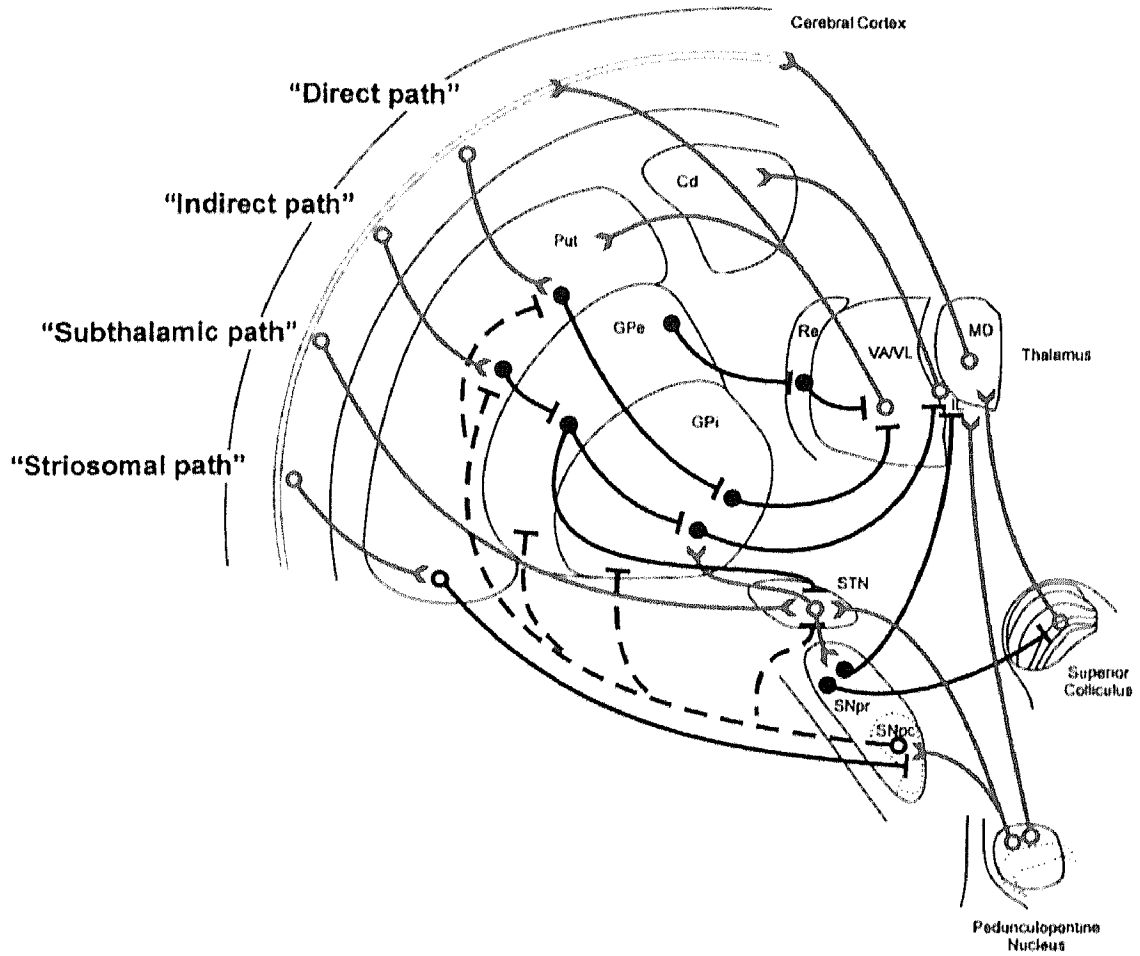

Fig. 1. Basic cortical-basal ganglia circuitry. The organization of connections between different components of the basal ganglia and the cerebral cortex, thalamus, superior colliculus, and pedunculopontine nucleus are shown. Much of the cortical influences on the circuitry of the basal ganglia can be grouped into one or more pathways (direct, indirect, subthalamic, or striosomal). Excitatory connections are shown in gray, and inhibitory connections are shown in black. Note that the influence of dopamine inputs from the SNpc to neurons in the striatum (broken line) can be both excitatory and inhibitory and is fundamentally different in nature from the signals processed in the other components of basal ganglia circuitry. Also note that nearly every component of these circuits has both a principal projection, which follows the direction of information flow within the circuit, as well as a recurrent projection to other basal ganglia components. Abbreviations as in text.

(Fig. 1). Many of these same cortical areas also contain cells that project directly to the STN and, thus, constitute a subthalamic path *(1–4,7)*. Notably, while the striatal inputs from motor and higher association areas in the cerebral cortex target neurons in the striatal matrix, which contain high levels of acetylcholinesterase, the inputs from many orbitofrontal and temporal limbic regions of the cortex target regions of the striatum called patches, or striosomes, which express low levels of acetylcholinesterase *(7,8)*. Neurons in the striosomes do not participate in the same types of circuitry as neurons in the striatal matrix. While medium spiny neurons in the matrix project largely to the γ-amino butyric acid (GABA)-ergic cells of the pallidum and nigra (GPe, GPi, or SNpr), the medium spiny cells in the striosomes project largely to dopamine synthesizing cells in the SNpc *(2–4)*. Thus, at least at the

Table 2
Major Cell Types and Chemical Properties of Basal Ganglia Neurons

Class	Name	Location	Main inputs	Main outputs	Transmitter	Representative markers
Projection	Striatal medium spiny neuron	Striosome	Limbic cortex, SNpc	SNpc	GABA	D1, substance P, GAD NMDA receptor (NR) 1/2B/2A, cannabinoids
		Matrix	Cortex, striatal interneurons, SNpc	GPe	GABA	D2, G(o), G(i), enkephalin, dynorphin, neurotensin, GAD, adenosine A2A receptors, NR1/2B/2A
			Cortex, striatal interneurons, SNpc	GPi, SNpr	GABA	D1, G(s), substance P, GAD, NR1/2B/2A, cannabinoids
	Spindle neurons	GPe	Striatum	Thalamic reticular N, GPi, STN	GABA	GABA subunits (α_{1-4}, β, γ_2, δ), GAD
		GPi	Striatum, GPe, STN	VA/VL	GABA	Cannabinoid receptor, 5HT2C receptor, GABA subunits (α_{1-4}, β, γ_2, δ), GAD
		SNpr	Striatum, Gpi	VA/VL, MD SC, reticular formation	GABA	Cannabinoid receptor, 5HT2C receptor, GABA subunits (α_{1-3}, β_{2-3}, γ_2, δ), GAD, CCK
	Excitatory	STN	Cortex, GPe	GPi, SNpr, PPN	GLU	GABA subunits (α_{1-3}, β_{2-3}, γ_2, δ), Glu receptor types
	Pigmented	SNpc	Striatum, SNpr	Striatum, GPi, SNpr, STN	DA	Neuromelanin, Nurr1, Reelin, D1, D2
						GABA subunits (α_{3-4}, β_{1-3}, γ_2, δ), torsin A, neurokinin
Interneuron	Large cholinergic	Striatum	Mostly thalamic and striatal projection neurons	Mostly striatal matrix	ACh	Acetylcholinesterase, D1/2, GluR1/4, m1/2/4, GAP-43, NR2C/D
	Medium	Striatum PV positive	Cortex	Adjacent striatal regions	GABA	PV, GAT-1, GAD-67, GluR1/2/3/4
		Striatum CR positive	Other CR positive cells, probably other striatal cells	Other CR positive cells	GABA	CR, GABA, GAD-67
		Striatum SS-NPY-NOS, positive	Cortex	Mostly striatal matrix	NPY, NO	SS, NPY, GAD-67, NOS, acetylcholinesterase, D1, m1/4, NR1/2B/2D, neurokinin, CB

Abbreviations: ACh, acetylcholine; CCK, cholecystokinin; CR, calretinin; CB, calbindin; D1/D2, dopamine receptor subtypes; DA, dopamine; GABA, γ aminobutyric acid; GAD, glutamate decarboxylase; GAP, growth associated protein; GAT-1, GABA transporter; G(i)/G(o)/G(s), G protein subtype; GLU, glutamate; GluR, glutamate receptor subtype; m, muscarinic receptor subtype; NO, nitric oxide; NOS, nitric oxide synthase; NPY, neuropeptide Y; NR, *N*-methyl-D-aspartate (NMDA) receptor subtype; PPN, pedunculopontine nucleus; PV, parvalbumin; SC, superior colliculus; SS, somatostatin, STN, subthalamic nucleus.

input stage of processing, a fourth type of circuit, the corticostriosomal path can be envisioned. The functional properties of these different paths are presented in a later section.

SNpc cells project densely back to widespread regions of the striatum (as well as the STN and pallidum) where they maintain high levels of extracellular and synaptic dopamine pools. The net effect of the dopamine on striatal cells depends largely on the types of receptors present on the target cells. For example, striatal cells in the direct path (that project to the GPi or SNpr) express high levels of D1 receptors, as well as substance P and dynorphin *(2–4)*. Activation of D1 receptors on these cells results in increased cellular activity and responsiveness through G(s)-mediated second messenger systems. In contrast, striatal cells in the indirect path (that project to the GPe) express high levels of D2 receptors as well as enkephalin (ENK) *(2–4)*. Activation of D2 receptors on these cells results in decreased cellular responsiveness and activity through G(i)- and G(o)-mediated second messenger mechanisms.

Despite the differences in the effects of dopamine on the direct and indirect pathways, the medium spiny cells in both of these circuits utilize GABA to inhibit their targets. Because the GPe cells that receive D2-mediated input project largely to the GPi, then the net effect of activation of the direct and indirect pathways in the presence of normal levels of dopamine is the same in terms of information flow; that is, cortical excitation of the basal ganglia input structures leads to less inhibition of the thalamus and increased activity of these circuits *(9–11)*. Importantly, however, cells in the GPe also send inhibitory inputs to the STN, which in turn exert a powerful excitatory influence on the GPi and SNpr. Thus, D2-mediated inhibition of the GPe can promote activity of the STN and allow the basal ganglia to increase inhibition of the thalamus. This effect would be further promoted by the action of direct cortical excitatory inputs to cells in the STN. In summary, the major projection systems within the basal ganglia contain at least two different pathways that lead to increased thalamocortical activation (the direct and indirect paths) and one that can lead to decreased thalamocortical activation (the subthalamic path).

Aside from the projection systems just outlined, however, several of the interneuronal populations of the basal ganglia also exert powerful influences on basal ganglia circuitry *(2,6)*. In the striatum, one important class of interneuron is the large or giant cholinergic interneuron (Table 2). These neurons receive most of their input from thalamic cells in CM/PF and other striatal cell types and a small input from the cortex. In turn, giant cholinergic cells have widespread projections to other striatal cells, largely within the matrix *(6)*. Giant cholinergic cells also express high levels of acetylcholinesterase activity, as well as D1, D2, and selected muscarinic and glutamatergic receptors *(6)*. Within sensorimotor regions of the striatum, these cells are thought to change their basic physiologic properties (tonic irregular firing) as an association is built between a sensory stimulus and an appropriate response *(12)*. Thus, by virtue of their connections with both input level and output level signals, the presence of multiple neurotransmitter phenotypes (including those associated with both direct and indirect pathways), and their widespread axonal collaterals in the striatum, the giant cholinergic cells may represent one of the most important interfaces between basal ganglia circuits that operate in different behavioral modalities.

Although the roles of the other interneuronal cell types in the basal ganglia have been less characterized, most of them appear to exert more local influences on other neurons within the structure they are found. Interneurons in the pallidum and STN, for example, appear to be more similar to the classical concept of a local circuit neuron, which connects adjacent or nearby cells *(2)*. In the striatum, however, at least two other classes of interneurons receive some cortical input (Table 2) *(6)*. It is also interesting to note the recent findings that most interneurons in the striatum and cerebral cortex are derived from a common set of precursor cells in the medial ganglionic eminences during brain development *(13)*. Thus, although basal ganglia interneurons are often overshadowed by projection neurons in terms of their influence on cortical-basal ganglia circuitry, such observations open the possibility that the wiring of basal ganglia circuits with the cerebral cortex could depend in part on cues left behind by these migrating interneurons during development, long before the circuits even become active. In fact, this migration may help define which circuits exist between the cerebral cortex and the basal ganglia altogether.

Table 3
Evolution of Theories of Basal Ganglia Function

Period	Theories	Main influences
Renaissance era—20th century	Basal ganglia influence all aspects of behavior and sensation.	Gross anatomists.
Early 20th century	Basal ganglia primarily influence the control of movement.	Early neuroanatomists and neuropathologists.
Middle 20th century	Basal ganglia solely involved in the control of movement.	Early neurophysiologists.
Late 20th century	Basal ganglia influence motor and nonmotor behavior, including many types of cognitive processing. Basal ganglia involved in goal-directed behavior and simple S-R associations.	Later neurphysiologists and neuroanatomists, neuroimagers, neuropsychologists, neurosurgeons.
Early 21st century	Major influences of basal ganglia on all forms of cognition may be driven by goals and rewards.	Neurophysiologists and neuroimagers.

1.5. *Basal Ganglia Circuits with the Cerebral Cortex: How Many, Open, or Closed?*

There is general agreement about the properties of the basal ganglia that have been discussed thus far. However, the basic theories regarding the function of the basal ganglia have evolved slowly over the past few centuries and continue to do so today (Table 3). One of the more recent controversies concerned the issue of how many cortical areas participated in basal ganglia circuits, and how the information from different cortical areas was processed within these circuits. Historically, at the input level of processing, the projections from the cerebral cortex to the basal ganglia were recognized as a highly organized and topographic projection system *(1,14,15)*. For example, anterior cortical areas were seen to project to anterior striatal regions, and posterior cortical areas were observed projecting to posterior striatal regions. Likewise, ventromedial regions of cortex projected to ventromedial striatal regions, whereas dorsolateral areas of cortex projected to dorsolateral striatal regions. However, beyond these features, most theories of basal ganglia function held that there was a great deal of convergence both within the striatum and in the projections from the striatum to the intermediate and output levels of processing. In other words, the basal ganglia were thought to have the ability to integrate sensory, limbic, and cognitive information with the commands for movement. In its extreme form, this theoretical concept was even used to argue that the basal ganglia were ultimately only concerned with the control of movement *(14)*.

There were two main reasons for the widespread acceptance of this viewpoint. The first reason was that the symptoms of basal ganglia dysfunction most often include characteristic motor abnormalities. Any cognitive or emotional disturbances also seen in patients with basal ganglia disease were often attributed to other causes and ruled secondary. The second major reason that the basal ganglia were viewed solely as a motor-related structure was the lack of substantive evidence for basal ganglia projections back to nonmotor regions of the cerebral cortex.

In 1986, Alexander, DeLong, and Strick *(1)* reviewed the results of numerous anatomical studies and suggested that rather than serving as a funnel for information from widespread cortical areas, the basal ganglia actually participated in multiple parallel segregated circuits with different regions of the frontal lobe. These regions included cortical areas concerned with skeletomotor and oculomotor control and three regions of the prefrontal cortex involved in cognitive and limbic functions. Recent

experimental evidence has supported and expanded on this proposal. In a recent review *(16)*, it was suggested that the original five circuit scheme, proposed by Alexander and colleagues *(1)*, should be broadened to include seven general categories of circuits: skeletomotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, medial orbitofrontal, cingulate, and inferotemporal–posterior parietal. Within each of these categories, anatomical evidence supports the existence of multiple (between two and seven) parallel cortical-basal ganglia circuits. This amount of finely tuned parallel anatomical circuitry may not be surprising to neuroanatomists. However, the diversity of functions that these circuits have the potential to influence is impressive. By virtue of their reciprocal connections with posterior cortical areas involved in visual and spatial perception, the basal ganglia would have the potential ability to influence an even broader range of behaviors than those proposed in the model by Alexander and colleagues *(1)*. In that model, the basal ganglia inputs from posterior cortical areas were integrated in basal ganglia circuits and ultimately influenced only regions of the frontal lobe.

Finally, although there is considerable evidence that much of the basal ganglia circuitry comprising the direct, indirect, and subthalamic pathways (Fig. 1) is topographically organized at multiple levels, there is much less evidence to suggest that the striosomal path (see Fig. 1) is similarly organized. Indeed, the recurrent projections from the SNpc to widespread regions of the striatum may represent the means for the basal ganglia to integrate information about primary reward and behavioral state received from limbic and sensory cortical areas with the modality-specific information being processed in the cortical-basal ganglia circuits. As such, these connections clearly represent an open-loop component of basal ganglia circuitry. The implications of this arrangement in terms of basal ganglia influences on cognition are reviewed in a later section.

2. BASAL GANGLIA INFLUENCES ON COGNITION

2.1. What Cognitive Functions Are Likely to be Influenced by the Basal Ganglia?

The anatomical substrate exists for the basal ganglia to process large amounts of information related to skeletomotor, oculomotor, cognitive, limbic, and sensory functions. Evidence suggests that at least some component of this processing takes place within multiple parallel circuits with different functionally defined cortical areas. However, these types of anatomical data do not establish the nature of the basal ganglia influence on cognitive function and whether this influence is independent of basal ganglia influences on limbic and motor function. Such issues can only be resolved by examining the behavioral relevance of these circuits. As a first step, it is helpful to define the specific types of cognitive operations that could be processed by such circuits by briefly reviewing the properties of three cortical areas within the prefrontal cortex that are known to participate in both cognitive function as well as basal ganglia circuits.

Areas 9, 46, and 12 are now known to participate in basal ganglia circuits. Areas 9 and 46 project to adjacent regions of the dorsal and lateral caudate, which in turn innervate adjacent regions of the rostral and dorsal GPi and SNpr. These regions of the GPi and SNpr are now known to project back upon areas 9 and 46 via neurons in VA/VL and MD *(16)*, thus completing the parallel circuit with these cortical areas. Area 12, in contrast, projects more ventrally in the caudate and appears to receive its input largely from the SNpr, but not GPi *(16)*. Nonetheless, it is clear that the physiological properties of each of these three prefrontal areas have the potential to drive basal ganglia circuits and, in turn, to be strongly influenced by the output of basal ganglia processing.

2.1.1. Physiological Studies

The physiological properties of the dorsal and lateral prefrontal cortex have been the subject of several in-depth analyses *(17–21)*. These studies have revealed that areas 9, 46, and 12 each appear to be involved in at least four different types of cognitive functions. First, many neurons in these areas display changes in activity related to the performance of delayed-response tasks. These tasks require sensory cues to be stored for a brief period of time and then used to generate a specific response. During

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such tasks, selective changes in neuronal activity can be seen during the presentation of cues (cue-related activity), the delay period following cue presentation (delay-related activity), and the response preparation and execution periods (response-related activity) *(17–30)*. Depending on the area of the prefrontal cortex in which one records or studies, there are additional task parameters that will determine the relative proportion of neurons involved in the performance of these delayed response tasks. For example, within areas 9 and 46, many neurons have cue- and delay-related activity that is tuned to the spatial position of stimuli (spatially-tuned activity) or the order in which the stimuli are present (sequentially-tuned activity). In contrast, within area 12, neurons appear to be much less involved in spatial and sequential information and more involved in remembering the identity of particular objects (object-tuned activity). Throughout areas 9, 46, and 12, there are also many neurons that appear to be more involved in the learning and remembering of specific rules or associations used in the performance of conditional response (forced choice) tasks (rule-related activity). An example of this type of task is the classic go/no-go task, in which one cue instructs the animal to make a response, while a different cue instructs the animal to withhold that response *(27–31)*. Finally, a relatively small but consistent proportion of neurons in areas 9, 46, and 12 also display changes in activity that coincide with the expectation or anticipation of primary reinforcement or food rewards (reward-related activity) (e.g., ref. *30*).

2.1.2. *Lesion Studies*

Lesion studies support some of the physiological observations regarding areas 9, 46, and 12. Bilateral damage to area 9 in monkeys produces severe and long-lasting impairments in the performance of tasks that require animals to monitor the order and identity of different objects (but not their spatial position), particularly when the sequence of cues to be remembered is self-ordered *(32)*. These deficits are similar to those found in human patients with dorsal prefrontal lesions *(33)*. In addition, patients with prefrontal lesions have been shown to be deficient in tasks that require the categorization and sorting of different stimuli, including card sorting tasks *(34)*, or the planning and monitoring of script events or sequential actions *(35–37)*. These types of tasks are thought to impose significant demands on planning and short-term (or working) memory for objects or sequential actions. Experimental lesions of area 46 result in an inability of animals to perform spatial delayed-response tasks, spatial delayed-alternation tasks, and go/no-go tasks *(17–21,38)*. These deficits are similar to the problems in attention, planning, working memory, and response inhibition reported in humans with lateral prefrontal lesions *(21,35,37,39,40)*. Finally, lesions of area 12 in monkeys have been shown to produce what has been referred to as an inability of animals to make switches in behavioral set. This deficit leads to perseverative responses on delayed-response tasks, in which the identity of different objects or colors must be remembered (object matching, object reversal, or object alternation tasks), or inappropriate responses in auditory-cued go/no-go tasks *(41–45)*. In addition, there is also evidence that large lesions of area 12 produce deficits in the learning and performance of visual discrimination tasks that do not involve delayed-responses *(46)*.

2.1.3. *Functional Imaging Studies*

Functional imaging studies in humans support many of the physiological and behavioral findings. Tasks that require difficult planning, the monitoring of sequences of hand movements, or the learning of new movement sequences *(47–55)* produce sites of peak activations in lateral portions of area 9, as do tasks that employ verbal working memory (including word generation tasks) *(56–62)*. Medial portions of area 9 have been shown to be activated by the processing of script events that requires monitoring the categories of events, which took place *(63)*. Kawashima and colleagues *(64)* also reported several foci of activation in area 9 when human subjects performed a go/no-go task, when compared with a simple response selection condition. Similar to area 9, area 46 is particularly active during spatial working memory tasks, difficult planning tasks, go/no-go tasks, some nonspatial object and ver-

bal working memory tasks, and verb generation tasks *(51,65–77)*. Area 46 has also been shown to be active during the generation and monitoring of multiple movement sequences involving the hand or fingers *(47,48,50,53,54,64)*. Many of these studies have concluded that the prefrontal activations in areas 9 and 46 are related to the elaboration or learning of novel sequences, since these activations are most apparent when comparing task performance during the learning phase with that seen after the task is well learned *(53,54,78)*. In contrast to areas 9 and 46, the human equivalent of area 12 (area 47) has been shown to be active during tasks that employ verbal working memory, including word generation tasks *(56,57,71,79,80)*, but not during spatial working memory tasks.

In summary, based on all the evidence presented thus far, one might predict that the influence of the dorsal and lateral prefrontal-basal ganglia circuits on behavior would be strongest for those functions related to spatial and object working memory, rule-based learning, and the monitoring of sequential or serial information used to guide future actions (i.e., planning), while information related to reward may also be present within these circuits, though to a lesser degree.

2.2. *What Is the Evidence for Basal Ganglia Influences on Cognition?*

Having defined a set of functions that are subserved by cognitive regions of the prefrontal cortex, we can now examine the evidence for basal ganglia influences on the same type of cognitive processes. We begin by discussing the results from selected physiological recording studies in awake primates and humans.

2.2.1. Physiological Studies

2.2.1.1. Input Stages of Basal Ganglia Processing

There have been hundreds of studies on the physiological properties of striatal cells. Only a small fraction of these, however, have examined the properties of striatal cells that could relate to cognitive processing. With few exceptions, these studies have focused on locating cells with activity related to a type of task and determining under what conditions such task-related activity is enhanced or suppressed.

In a study that examined the effect of task difficulty on caudate nucleus properties in humans, Abdullaev and colleagues *(81)* recorded from human subjects during reading, naming, recognition memory, categorization, and lexical decision making tasks. They found that, during visual processing of words, caudate cells exhibited excitatory responses related to both semantic and phonological-articulatory encoding and that the delay-related firing of cells was increased whenever semantic processing was required. Comparing the properties of striatal cells with those seen in the prefrontal (Broca's) area and in the temporal and parietal lobe areas, the authors found that the caudate cells had properties that were "strikingly similar" to those in Broca's area. Since portions of the prefrontal cortex are often activated during the same types of verbal tasks that activate Broca's area (reviewed in subheading 2.1.3.), it is possible that basal ganglia inputs from these areas also contributed to the findings of this study.

Striatal cell activity during sequential task performance has also been examined. Kermadi and Joseph *(82)* examined the properties of striatal cells during a task that required monkeys to engage in a sequential working memory task. They found that many of the cells with task-related activity had visual-related responses that varied according to the order of a given target, and moreover, that many of the caudate cells seemed to anticipate the fixation of specific targets. Such findings are similar to some of those reported in studies of areas 9 and 46 reviewed above.

Striatal cell activity has also been recorded during conditional task performance. Schultz and Romo *(83)* found many neurons with cue, delay, and response preparatory activity in the caudate and putamen of monkeys trained to perform a go/no-go task. They interpreted their results to indicate that most of these task-related neurons in the striatum were involved in response preparation. A slightly different conclusion was reached by Shuvaev and Shefer *(84)* in another conditional response task in monkeys. They found that the task-related striatal cells they recorded could be separated into two distinct groups.

While one group of cells was clearly tuned to response execution, another group of cells appeared to be more involved in the instructional decision-making process.

In contrast to these experiments that focused solely on formal cognitive operations, Nishino and colleagues *(85)* found that a small proportion of neurons in the head of the caudate nucleus of monkeys responded specifically to the sight of food or food rewards. Furthermore, the results from several recent studies strongly suggest that such reward-related properties can directly affect the cognitive properties of striatal cells. Using a memory-guided saccade task, Kawagoe and colleagues *(86)* demonstrated that the visual and memory responses of caudate cells were so affected by the expectation of reward, that their spatial tuning characteristics often changed specifically toward the rewarded direction, with subsequent responses in this direction becoming earlier and faster. These authors concluded that the caudate contributes to the determination of oculomotor outputs by connecting information about reward with visual signals. In a similar finding, Hassani and colleagues *(87)* observed that during a spatial-delayed response task, in which different picture cues were associated with specific rewards, many neurons in the anterior caudate, putamen, and ventral striatum of monkeys displayed different levels of task-related activity depending on the type of reward being offered and whether it was a preferred or nonpreferred reward of that animal. These authors concluded that their data support the concept that the striatum might help maintain a mental image of the outcome of an action, while the proper behavioral action is performed.

These studies provide clear evidence that striatal cells are involved in many of the same elements of cognitive processing as cells in the prefrontal cortex (including cue, delay, conditional responses, and reward periods of task performance). However, unlike some of the studies that have recorded from the output nuclei of the basal ganglia (see subheading 2.2.1.2.), most studies of striatal physiology have not been conducted with the goal of precisely defining the location or circuit relationship of the neurons involved in specific components of task performance. Thus, it is simply not possible to ascertain whether this involvement reflects the properties of particular basal ganglia circuits.

2.2.1.2. Output Stages of Basal Ganglia Processing

There have also now been numerous single unit recording studies carried out on the output nuclei of the basal ganglia of the human and primate. Results from these studies clearly show that only specific regions of the GPi and SNpr contain neurons whose activity is related to skeletomotor or oculomotor commands *(88–95)*. These regions of the GPi and SNpr largely coincide with the regions that have been shown to project to skeletomotor or oculomotor regions of cortex (reviewed in ref. *96*). In contrast, large portions of the GPi and SNpr contain neurons whose activity is not modulated by simple skeletomotor or oculomotor tasks. Many of these regions fall within the regions that innervate areas of prefrontal cortex involved in cognitive processing *(96)*. Evidence to support the involvement of some of these neurons in cognitive processing is also available. Hikosaka and Wurtz *(89)* and Hikosaka and colleagues *(97)* recorded the activity of neurons in the SNpr of monkeys trained to perform an oculomotor spatial-delayed response task. A considerable number of SNpr neurons were found whose activity was modulated during the delay period of the task. Many of these delay-related cells appeared to be separate from SNpr cells, which were purely saccade-related, but not delay-related, and a number of them were spatially tuned. As reviewed earlier, neuronal properties similar to these have been found in studies of area 46. Thus, nigral outputs to prefrontal cortex could be directly involved in tasks that involve spatial working memory and the planning of eye movements.

Similar conclusions about the presence of delay-related neurons, as well as the existence of sequence-related neurons, were reached by Mushiake and Strick *(98)*, who recorded from the GPi in monkeys trained to remember the spatial sequence (order and position) of three light flashes in a manual delayed-response task. They found that a small but consistent proportion of task-related neurons in the GPi had changes in activity during the instruction period in which the flashes occurred or during the delay period immediately following the instruction. Some of these neurons displayed activity that was specific for the particular sequence of cues the animal had to remember. Moreover, the location of these

instruction-related neurons tended to be within dorsomedial portions of the pallidum, a region that both receives input from and projects back upon areas 9 and 46 (via the striatum and thalamus, respectively) *(96,99)*. Thus, spatial and sequential aspects of delayed task performance were found within basal ganglia circuits that subserve prefrontal areas known to be involved in the same type of tasks.

Additional information about the involvement of the basal ganglia output nuclei in conditional response performance and reward processing is also available. In one of the earliest studies of pallidal physiology in awake trained primates, Travis and Sparks *(100)* recorded from the globus pallidus of squirrel monkeys trained to perform a go/no-go task. Surprisingly, only 3 of 89 pallidal neurons in their sample displayed activity related to gross motor movements, suggesting that they were not sampling the skeletomotor circuitry within GPi and may instead have been recording from regions with outputs to prefrontal cortex. Indeed, more than 40% of their task-related cells displayed changes in activity during the instruction period preceding the movement in the go tasks or during the period after the movement prior to the delivery of the reward. DeLong *(101)* pointed out that some of the cells that Travis and Sparks were recording were probably not true pallidal cells, but rather cells that lay in the border region between GPe and GPi. Nevertheless, Travis and Sparks concluded that many pallidal neurons displayed "attention, set, or anticipation activity," as well as activity "related to voluntary sequences of behavior leading to primary reinforcement." Such conclusions are quite similar to those reached decades later by other investigators recording from pallidal neurons. Gdowski and colleagues *(102)* recorded GPi activity during a manual delayed-response task in which monkeys received a reward for correctly executed movements, whereas movements during the return phase of the arm were not rewarded. The authors found that many GPi neurons discharged in a context-dependent manner, being specifically modulated during the cued rewarded movements, but not during the similar self-paced unrewarded movements.

In summary, the physiological properties of many neurons in the striatum and pallidum of humans and nonhuman primates appears to be similar in many respects to those reported in studies of the physiology of the prefrontal cortex. In addition, compared with the prefrontal cortex, there appears to be an increase in the relative proportion of neurons in the basal ganglia whose activity is significantly influenced by the expectation of reward. Thus, although the concept that parallel basal ganglia circuits can subserve different types of tasks appears valid, there clearly appears to be another system operating across circuit boundaries that integrates information about the rewarding value of a behavioral act. Shultz *(103)* proposed that the neural substrate for this reward system is the phasic activity of dopamine synthesizing cells in the SNpc, which conveys information about primary reinforcement and behavioral state to cells in the striatum. Because such influences exist throughout the striatum, it is quite likely that many, if not all, basal ganglia circuits utilize reward-related information to modify the properties of cells within them in order to carry out meaningful behavioral acts.

2.2.2. *Functional Imaging Studies*

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been used to examine the activity of the basal ganglia and prefrontal cortex during the performance of tasks involving specific cognitive functions. To date, these studies have not been done on the SNpr. In one of these studies, Jueptner and colleagues *(53,54)* listed significant activations in areas 9 and 46, dorsolateral portions of the caudate, rostrodorsal portions of the globus pallidus, and thalamic sites in VA and paralaminar MD in subjects during the learning of new sequences of eight key presses, compared with activations seen during previously learned sequences. Thus, nearly all of the brain regions that are thought to participate in basal ganglia circuits with the dorsolateral prefrontal cortex were activated during a sequence-learning task in humans.

In another PET study, Owen and colleagues *(104,105)* compared the activity of normal subjects and Parkinson's disease patients during the performance of a difficult planning task (the Tower of London task), a spatial working memory task, and a simple visually guided movement task. Previous studies from this group had strongly implicated areas 9 and 46 in the performance of both the planning and

spatial working memory tasks *(51,52)*. These investigators found that Parkinson's disease patients had very little GPi activation during the cognitive tasks, while normal subjects had greatly increased GPi activation during the same tasks. Furthermore, the amount of this differential activation was directly correlated with task difficulty, i.e., the greatest differences occurred in the tasks with the most cognitive demands, whereas there were no differences in GPi activation between normal and parkinsonian subjects in the simple motor task. Because patients with Parkinson's disease had previously been shown to be impaired in the performance of the same cognitive tasks *(106,107)*, the authors concluded that the GPi outputs to the dorsolateral prefrontal cortex (areas 9 and 46) played an important role in these tasks.

Finally, a number of recent studies have examined the functional activation of the basal ganglia and prefrontal cortex during cognitive tasks (mainly card gambling games) that have an artificial reward component *(108,109)*. In one of these studies *(108)*, the investigators obtained strong evidence for the involvement of the striatum, bilateral pallidum, and ventral anterior thalamus in context-dependent responses to increasing levels of rewards. Interestingly, in another study comparing normal and schizophrenic subjects during the performance of a similar task, abnormalities in the activation patterns were found in schizophrenic subjects specifically within the left dorsolateral prefrontal cortex, basal ganglia, and thalamus *(110)*. Moreover, such abnormalities were associated with poorer task performance in the schizophrenic subjects.

Collectively, these studies highlight the convergence of evidence from functional imaging and physiological recording studies on the basal ganglia of humans and nonhuman primates. Such evidence strongly supports a specific role of prefrontal-basal ganglia circuits in maintaining a working knowledge about the location and order of stimuli presented in a task, the rules or arbitrary associations involved in this task, and the planning of sequences of actions that lead to primary reinforcement in these tasks. Moreover, at least some components of the basal ganglia (e.g., neurons within the striatum and pallidum) appear to capable of performing all of these functions concurrently and, thus, may form part of the neuronal substrate for directing goal-oriented behavior.

2.2.3. *Basal Ganglia Pathology*

The results of animal lesion studies and human clinicopathological studies clearly established over a century ago that damage to the basal ganglia results in the production of characteristic motor symptoms and deficits *(111–113)*. The majority of these deficits are now thought to be due to interruption of basal ganglia outputs with motor areas of cortex, although other deficits are clearly due to more direct influences on descending pathways. It is surprising to note, however, that for nearly the same amount of time, basal ganglia lesions were also associated with higher order cognitive and behavioral symptoms (see refs. *1,111,114–116*).

The physiological and functional imaging studies discussed thus far lead to the prediction that a lesion of basal ganglia circuitry involving areas 9 and 46 would lead to disruption of spatial working memory, planning and sequential working memory, and rule-based behavior. It is also possible that such deficits would be particularly manifest in tasks that required reward information to be integrated with a behavioral act. In actual fact, however, it is not likely that lesions of single basal ganglia circuits exist. Most of the clinical and pathological reports of patients with basal ganglia damage indicate that these patients display a number of different symptoms, including both motor and nonmotor ones, and it is quite likely that these symptoms are due to involvement of several subcortical projection systems. Despite these limitations, it is possible to reach some conclusions about the relative involvement of the basal ganglia in cognitive function based on the analysis of fairly localized pathology of the input and output levels of processing.

2.2.3.1. Input Level Pathology

Reversible lesion studies in monkeys have shown that the anterior striatum is particularly important for the learning of new movement sequences, while middle regions of the striatum appear to be

spatial working memory tasks *(51,52)*. These investigators found that Parkinson's disease patients had very little GPi activation during the cognitive tasks, while normal subjects had greatly increased GPi activation during the same tasks. Furthermore, the amount of this differential activation was directly correlated with task difficulty, i.e., the greatest differences occurred in the tasks with the most cognitive demands, whereas there were no differences in GPi activation between normal and parkinsonian subjects in the simple motor task. Because patients with Parkinson's disease had previously been shown to be impaired in the performance of the same cognitive tasks *(106,107)*, the authors concluded that the GPi outputs to the dorsolateral prefrontal cortex (areas 9 and 46) played an important role in these tasks.

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more involved in the performance of previously learned movement sequences *(117)*. These findings are consistent with some of the previously discussed observations that portions of the striatum appear to be activated during the learning and the monitoring of sequences of motor acts that must be performed to complete some tasks. Interestingly, some patients with Parkinson's disease and Huntington's disease are also impaired on various tests of sequence learning and sequential task performance *(118–120)*. In view of the evidence, already reviewed, that dorsolateral prefrontal areas may be involved in aspects of sequential task performance, such as the learning and monitoring of sequences or behavioral actions, it is possible that damage to basal ganglia circuits with these areas could disrupt performance of these types of cognitive tasks.

The performance of spatial and nonspatial working memory and rule-based tasks is also affected by striatal pathology. In monkeys, experimental lesions of the dorsal caudate nucleus produce deficits in spatial delayed-response tasks that resemble the deficits seen after lesions of area 46 *(121)*. In contrast, lesions of the ventral caudate produce deficits in nonspatial delayed-response tasks that resemble those seen after area 12 lesions *(121)*. In humans, damage of some of these same striatal regions occurs in Huntington's disease and Parkinson's disease *(122,123)*. Detailed examinations of patients with these disorders have revealed striking deficits in spatial working memory and other cognitive tasks that precede the development of prominent motor symptoms *(124–132)*. Interestingly, recent studies using two of the animal models of Parkinson's disease and Huntington's disease also support these findings. Examination of primates early in the course of chronic low-dose 3-nitropropionic acid (3-NP) or 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) treatment has revealed the presence of profound cognitive deficits that precede the development of gross motor impairments *(133–136)*. Thus, one conclusion from these studies is that the initial striatal pathology selectively alters prefrontal-basal ganglia circuits to produce these cognitive deficits, while sparing (in most cases) motor circuits.

2.2.3.2. Output Level Pathology

An "isolated" bilateral lesion of the SNpr was reported in one elderly patient diagnosed with peduncular hallucinosis *(114)*. This individual demonstrated deficits in working memory and other cognitive functions, visual hallucinations, and mild neurological symptoms. It is possible that this lesion affected nigral outputs to the prefrontal as well as inferotemporal areas of cortex to produce the complex cognitive and perceptual symptoms that he displayed, while alterations of the outputs to motor areas may have led to his motor difficulties *(137)*.

Parallel findings have been reported in patients with "localized" lesions of the globus pallidus. In addition to varying degrees of motor deficits, the majority of these patients suffered from cognitive deficits such as working memory and card sorting difficulties, compulsive behaviors, and "psychic akinesia," or a lack of a desire to move *(138,139)*. Perhaps the best evidence for the involvement of the globus pallidus in cognitive function, however, has come from the careful evaluation of subjects who have undergone surgical pallidotomy for the treatment of Parkinson's disease. As one recent analysis has shown *(140)*, these subjects often display prominent cognitive impairments on tasks that would normally engage prefrontal-subcortical networks. Moreover, the degree of these impairments is directly related to the anatomical location of the pallidal lesion. Lesions confined to more rostral and dorsomedial regions of GPi produce the greatest cognitive deficits in the patients, consistent with the fact that these GPi regions contain neurons that project to prefrontal areas 9 and 46. In contrast, surgical lesions in more posterior and ventrolateral regions of GPi (which project to skeletomotor areas of cortex) have the greatest effect on motor symptoms. The authors of that study concluded that their results provide further evidence for the segregation of motor and cognitive circuitry within the basal ganglia.

Finally, there is some evidence that abnormalities in basal ganglia circuits may underlie some of the hallmark cognitive deficits seen in certain neuropsychiatric disorders, including schizophrenia, depression, obsessive–compulsive disorder, Tourette's syndrome, autism, and attention deficit disorder. In schizophrenia in particular, there is growing evidence that patients early in the course of the

illness have profound deficits in formal tests of planning, working memory, and rule formation *(141–143)* In fact, it appears that these deficits are very often present years before the onset of florid psychosis and may represent one of the best predictors of the course of the illness *(144)*. Obviously, for any serious mental illness, there is always the potential confound of medication on findings, and such concerns should be of paramount importance in the interpretation of findings regarding the basal ganglia. However, Early and colleagues *(145)* demonstrated conclusively that in 10 never-medicated subjects with schizophrenia, there was a consistent abnormality in blood flow within the globus pallidus that was not present in any of 20 control subjects. When this evidence is viewed along with the strong evidence for prefrontal, striatal, and thalamic abnormalities in schizophrenia *(146)*, it is tempting to think that there is a prefrontal-basal ganglia circuit dysfunction in this illness. Although there are now numerous theories describing how this dysfunction could contribute to the pathophysiology of schizophrenia, it is likely that Mettler *(147)* was the first to suggest that schizophrenia was a perceptual disorder caused by primary striatal and pallidal dysfunction, which resulted in secondary cortical dysfunction. Whether such a causal relationship exists remains to be seen.

2.2.4. *Molecular Clues to Basal Ganglia Influences on Cognition*

With the advent of modern molecular biological approaches to the study of complex disease states, it is now possible to rapidly screen the expression of thousands of genes at a time in different neurological and psychiatric disorders, as well as map the normal expression patterns of these genes through the brain. It is only a matter of time before the anatomical maps of gene expression in the brain rival the resolution of the anatomical maps of human brain activation produced by functional imaging studies. The incorporation and analysis of this vast amount of new information will require a thorough understanding of how all the pieces of the basal ganglia puzzle fit together. Space does not permit a complete or even partial review of the literature that is available on the effects of different agents on cognitive function that could be due to direct influences on prefrontal-basal ganglia circuits. Nonetheless, a few of the molecules, with rather striking patterns of expression in the basal ganglia, do appear to have the potential to be involved in cognitive processing and are briefly mentioned here.

2.2.4.1. Enkephalin

As previously noted, cells in all parts of the striatum that project to the external segment of the globus pallidus (and form part of the indirect pathway) express high levels of enkephalin. In early Huntington's disease, there appears to be a preferential loss of the enkephalin-containing cells in the caudate compared to substance P-containing cells that project to GPi *(148,149)* and, thus, a qualitatively different effect on the indirect versus the direct pathway. Recent reports of monkeys early in the course of MPTP treatment indicates that there is overexpression of preproenkephalin in dorsolateral regions of caudate and putamen, as well as the caudal body of the caudate, which occurs without any motor symptoms *(150)*. Thus, in early Huntington's disease and experimentally induced Parkinson's disease, some of the same neuronal populations could be affected in the same portions of the striatum; namely, those regions that receive input from cognitive areas and visual association areas of the cerebral cortex. This fact is all the more interesting in light of the evidence already presented that patients, early in the course of these disorders, as well as primates being treated with neurotoxins to mimic these disorders, all develop well-described impairments in cognitive and visual functions, often in the absence of gross motor impairments *(129–136)*.

Although it may not immediately be apparent how the preferential dysfunction of enkephalin-containing neurons in nonmotor regions of the striatum could arise, one remote possibility is that such findings may be related to the regional differences in dopamine receptor subtype expression within the striatum. For example, enkephalin-containing cells are known to be D2 positive, and D2 positive cells are most concentrated in the striatal matrix and increase in relative number from rostral to caudal. In contrast, D1 receptor subtypes are expressed most highly in striosomes and increase from caudal to rostral striatal regions. Thus, disruptions of enkephalin-containing cells in early Huntington's and

Parkinson's disease, as well as the animal models of these disorders, may produce more of an affect on cognitive function, because the rostral regions of the striatum would have less reserves of enkephalin and D2 positive cells to draw on to restore normal circuit function. Some indirect support for this possibility was provided in a study of enkephalin knock-out mice by Konig and colleagues *(151)*. Mice homozygous for the mutant gene were viable and fertile and cared for their offspring, but displayed a pattern of distinctive behavioral abnormalities that included hiding under the bedding, "frantic" running or jumping, and prolonged freezing in response to moderate noise. The authors also reported that the mice appeared more anxious and that the males were more aggressive, but none of the mice had gross motor impairments. Such symptoms are consistent with a preferential effect on rostral striatal regions.

2.2.4.2. Cannabinoids

In addition to enkephalin, there is a large body of evidence that cognitive alterations or enhancements can be produced by the selective action of certain receptor subtypes that have localized patterns of expression in the basal ganglia. Some of these include cannabinoids, which

have very well-described effects on motor and cognitive function. Cannabinoid receptors are extremely abundant in the output nuclei of the basal ganglia, in addition to prefrontal regions of the cerebral cortex *(152)*. In fact, cannabinoid binding intensity may be the highest in the SNpr compared to all other brain regions *(152)*. Recent studies that have analyzed formal cognitive processing in cannabis users compared to controls found a significant effect of cannabis abuse on tests of memory, learning, word fluency, speed of processing, and manual dexterity *(153)*. In Huntington's disease, there is an apparent preferential loss of cannabinoid receptors on striatal nerve terminals in the GPe versus GPi in all stages of this illness *(154)*. These observations provide further support for the preferential involvement of the indirect pathway in Huntington's disease, and also suggest that the cognitive effects of cannabinoid use may be strongly mediated through their action on prefrontal-basal ganglia circuits.

2.2.4.3. Adenosine

In contrast to cannabinoids, which impair cognitive processing, caffeine has a clear cognitive enhancing effect, when taken in moderate doses. It is thought that adenosine receptor antagonism by caffeine is the basis for this effect. A recent behavioral study with mice found that selective antagonists of the adenosine A2A receptor produce improvements in learning, but not selective A1 antagonists *(155)*. In the striatum, adenosine A2A receptors are highly expressed in medium spiny neurons in the striatal matrix *(156)*. Interestingly, a recent report found that selective A2A antagonist administration to Parkinson's disease patients had a protective effect, resulting in a slower progression of symptoms *(157)*. The precise mechanism for this effect is not clear, although it is possible that the A2A antagonist administration helped reduce abnormal activity in basal ganglia circuits brought on by loss of dopamine inputs to the striatum because it is known that adenosine and D2 receptors have strong interactions on G(i/o)-mediated second messenger systems in striatal cells.

2.2.4.4. Other Molecules and Directions

Some cholecystokinin receptor subtypes are also highly abundant in regions of the striatum and SNpr that participate in cognitive and limbic processing *(158)*. There is evidence that selective actions of some cholecystokinin receptors can greatly affect cognitive and limbic functions, including recall, anxiety, and satiety in addition to reward-seeking behavior *(158,159)*. Aside from these systems, it is also clear that manipulation of serotonin systems, neuropeptide systems, noradrenergic systems, and cholinergic systems, to name but a few, can produce cognitive impairments or enhancements that may be mediated, in part, by prefrontal-basal ganglia circuits. Such observations should not be viewed as necessarily surprising, but rather simply a reflection of the diverse anatomical and molecular relationships that exist between the prefrontal cortex and basal ganglia. In the near future, it may be possible to exploit new molecular biological technologies to identify circuit-specific genes and proteins and to develop agents that can selectively and therapeutically alter the expression of these molecules to correct a behavioral deficit or restore normal function.

3. SUMMARY AND CONCLUSION

The prefrontal cortex and basal ganglia participate in multiple anatomical circuits. These circuits appear to maintain many of the physiological and behavioral properties of the cortical areas that they subserve. In addition, there appears to be a considerable increase in the relative influence of reward on neurons within prefrontal-basal ganglia circuits compared to neurons in the cortical areas they innervate. Such influences cannot be completely separated from the role that basal ganglia circuits play in cognition, since the ultimate goal of most cognitive acts is the achievement of some predetermined goal or reward. In contrast, the effects of basal ganglia pathology on cognitive processing are clearly distinguishable from effects on motor behavior. However, whether the cognitive deficits that arise from basal ganglia dysfunction are solely a reflection of abnormal cognitive processing or also reflect dissolution of the influence that reward-related signals play on this processing is not clear. Indeed, much additional research is needed to help sort out the precise contributions of the basal ganglia to cognitive behavior.

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