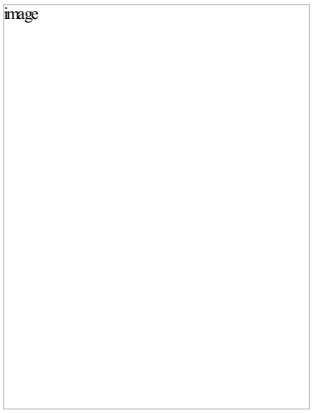

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Anatomy, Physiology, and Clinical Syndromes of the Basal Ganglia: A Brief Review

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Abstract:
Movement disorders typically arise from dysfunction of the basal ganglia, cerebellum, or both. The basal ganglia—a group of deep, subcortical structures—form complex circuits that shape motor control and motor learning, as well as limbic and associative functions. In this article, we summarize the anatomy and physiology of the basal ganglia and cerebellum, and briefly highlight the clinical syndromes that may arise in the context of their injury or dysfunction.

INTRODUCTION

The basal ganglia (BG) are subcortical structures primarily involved in motor control and motor learning. The clinical and pathological observations at the turn of 20th century shed light on the role of the BG in control of posture, tone, and movement. Furthermore, such observations led to the recognition of the "extrapyramidal motor system" whose lesions, contrary to those of the pyramidal system, do not paralyze the patient, but instead result in abnormal involuntary

movements. [1, 2] Mapping the connections of the BG and elucidating their functional role in the later parts of the 20th century resulted in functional theories explaining how the BG fulfills these many roles and how its malfunctions result in motor manifestations. Such research has also extended our understanding of the role of the BG beyond motor execution to encompass emotional processing, goal directed behavior, and conflict monitoring. The BG involvement in the latter might not be easily detected by a bedside exam, but can be demonstrated with more detailed neuropsychological evaluations. In this overview, we will first highlight the anatomy and physiology, respectively, of the individual structures comprising the BG, in addition to the circuitry connecting them. We will then briefly discuss the clinical correlates and phenomenology seen when these structures and circuits are disrupted.

OVERVIEW OF THE ANATOMY OF THE BASAL GANGLIA

The core components of the BG sit in the telencephalon and include the globus pallidus and the *striatum*, a term used to refer to the combination of the caudate and putamen, as shown in Figure 1. The associated nuclei of the BG reside in the diencephalon (subthalamic nucleus) and the mesencephalon (substantia nigra and pedunculopontine nucleus).[3]

The BG nuclei can be functionally categorized as *input*, *output,* and *intermediate nuclei*. The *input nuclei* include the striatum, nucleus accumbens, and olfactory tubercle. They receive afferents from the cerebral cortex, thalamus, and nigral nuclei. The *output nuclei* include the internal part of the globus pallidus (GPi), and the substantia nigra pars reticulata (SNr). These output nuclei exert control over the thalamus which in turn sends inputs to the cortex, closing the cortico-basal ganglia-thalamo-cortical loop. The *intermediate nuclei* include all remaining nuclei in between the input and output relays and include the globus pallidus externa (GPe), the subthalamic nucleus (STN), and the substantia nigra pars compacta (SNc).

Basal Ganglia Input: Striatum

The striatum contains two different types of neurons: *projection neurons*--also called medium-sized spiny neurons (MSNs)—and *interneurons.* MSNs comprise about 90% of striatal neurons and are GABAergic inhibitory neurons that receive excitatory cortical efferents. MSNs also receive modulatory dopaminergic input from the SNc through the nigrostriatal system. This dopaminergic input exerts different effects on the MSN depending on which type of dopaminergic receptors they possess. Striatal MSNs projecting directly to GPi and SNr contain dopamine receptor subtype 1 (D1 receptors), which activate adenylcyclase signaling and give rise to the *direct pathway* (striatum to GPi and SNr). The striatal MSNs innervating the GPe express the dopamine receptor subtype 2 (D2 receptors), which inhibit intracellular adenylcyclase through G-protein signaling, and give rise to the *indirect pathway* (striatum to GPe to STN to GPi and SNr).

Direct and indirect striatal MSNs also express additional neuropeptides. The indirect pathway MSNs (expressing D2 receptors) contain enkephalin, whereas the direct pathway MSNs (expressing D1 receptors) express substance P and dynorphin. These opiate peptides might be involved in modulating the dopaminergic input to the striatum.[4]

About 10% of the striatal neurons are interneurons.[5] Interneurons have smooth dendrites in contrast to MSNs, and the majority of these use acetylcholine as their neurotransmitter and are tonically active. The remainder of interneurons are GABAergic and are further divided into three subtypes based on their histochemical profiles: 1) GABAergic subtype that also contain the calcium-binding protein parvalbumin and show fast spiking, 2) those that contain the calcium binding protein calretinin, and 3) nitregic interneurons that use nitric oxide as their neurotransmitter. Both tonically active, cholinergic interneurons and fast-spiking GABAergic interneurons modulate the activity of MSNs and are themselves modulated by dopaminergic input from the SNc. Calretinin-positive and nitrergic interneurons innervate the other types of interneurons. This complex intrastriatal circuitry provides the basis of interaction between the direct and indirect pathways.

Basal Ganglia Input: Nucleus Accumbens and Olfactory Tubercle

The nucleus accumbens and the olfactory tubercle have morphological and anatomical similarities to striatum. They are considered ventral extensions of the striatum and receive their cortical input from the limbic cortices and their dopaminergic modulation from the mesolimbic dopaminergic system. The limbic basal ganglia is implicated in reward learning and addiction.[6, 7]

Striatal Compartments: Striosomes and Matrix

Immunohistochemical staining reveals two distinct anatomical subdivisions within the seemingly homogeneous striatum: *striosomes* and *matrix*. Briefly, striosomes are areas characterized by weak acetylcholinesterase (AChE) activity and strong immunoreactivity against enkephalin, substance P, GABA, and neurotensin.[8-10] The matrix compartment shows strong AChE activity and high immunoreactivity against parvalbumin and calbindin.[11, 12] MSN dendrites arborize widely but only within their own anatomical zone: the striosomal MSN dendrites never enter the matrix and vice versa.[13, 14] Moreover, striosomes and matrix have distinct input and output patterns, as described below.

Afferent and Efferent Connections of the Striatum

Sensory and motor cortical areas, their corresponding thalamic nuclei, and dopaminergic neurons from the dorsal SNc all target the matrix of the striatum. Limbic areas of the cortex, the basolateral amygdala, and ventral parts of the SNc mostly target striosomes.[15-17] These separate pathways hint at the functional segregation of motor and cognitive functions from limbic functions, however there may be functional interaction between these pathways in the stratum.[18] Corticostriatal inputs are topographically organized within the matrix.[19] The glutaminergic neurons in the corticostriatal inputs express glutamate transporter isoform 1 (vGlut1) whereas the glutaminergic neurons in the thalamocortical pathway mostly express vGlut2.[20, 21] There are some exceptions, however: the thalamic neurons in the ventral and associative nuclei of the thalamus co-express both vGlut1 and vGlut2 and only the intralaminar and midline thalamic nuclei solely express vGlut2.[22] The amygdala also projects glutaminergic input to the striosomes.[23] Even though the serotonergic input from the dorsal raphe nuclei to striatum have long been recognized, they have rather recently been implicated in levodopa-induced dyskinesia in Parkinson's disease.[24, 25]

The SNc provides the rich and vast nigrostriatal dopaminergic input to the striatal matrix and innervates both D1 and D2 receptor-expressing MSNs. As such, dopaminergic input is excitatory on the D1 MSNs (the origin of the direct pathway) and inhibitory on the D2 MSNs (the origin of the indirect pathway). This is the foundation of the classic model of the BG where dopaminergic input promotes the function of the direct pathway and inhibits the indirect pathways. As mentioned above, the ventral SNc participate in the mesostriatal and mesolimbic dopaminergic projections to the ventral striatum and project mainly to the striosomes. D1 receptor MSNs send their striatofugal output to GPi and SNr (direct pathway), and D2 receptor MSNs send their output to GPe (indirect pathway). There appears to be some degree of crosstalk between the two pathways, e.g. the MSN axons to GPi and SNr send collaterals to GPe.[5, 26, 27]

Basal Ganglia Output Nuclei: Globus Pallidus interna and Substantia Nigra pars reticulata

GPi and SNr are the output nuclei of the BG and share similar immunohistochemical structures. Both are mainly composed of tonically active GABAergic neurons that exert a constant inhibition on their output nuclei, namely thalamic and brainstem nuclei (including the pedunculopontine nucleus, or PPN, and superior colliculus). The pallidal output to the thalamus projects to different subdivisions of the ventral anterior nucleus of the thalamus (VA) than the projections from SNr to the thalamus.[28] GPi and SNr are also interconnected to the intralaminar nuclei of the thalamus (centromedian and parafascicular, or CmPf)[29], which are a hub in not only motor but also associative and limbic areas circuits, making the intralaminar nuclei a potential target for deep brain stimulation for Tourette's syndrome.[30] These pallidal efferents to the VA and intralaminar nuclei of the thalamus travel in two paths: the *ansa lenticularis* from the lateral GPi and the *lenticular fasciculus* from the medial GPi.

The primary inhibitory input to GPi and SNr as mentioned above is from GABAergic D1 receptor-expressing striatal MSNs as part of the direct pathway, which decreases the firing of the BG output pathways. The excitation to GPi and SNr comes from subthalamic glutaminergic neurons expressing vGlut-2[31] as part of the indirect as well as the hyperdirect pathway (see the section on circuitry and physiology of the BG below) and increases the inhibitory output of the BG.

Basal Ganglia Intermediate Nuclei: Subthalamic Nucleus, Globus Pallidus externa, and Substantia Nigra pars compacta

The GPe is the structure unique to the indirect pathway. It receives inhibitory GABAergic projections from D2 receptor-expressing striatal MSNs. These D2 striatal projections also express adenosine type 2A receptors[32] that have recently been the target of clinical drug developments[33]. GPe neurons are also reciprocally connected with STN neurons. They inhibit STN through GABAergic connections and in turn receive strong vGlut2 glutamatergic excitatory projections from the STN. GPe also receives a small glutaminergic connection from the intralaminar nuclei of the thalamus.

The STN is the subject of ample research, as it serves as the primary target of deep brain stimulation in Parkinson's patients.[34] It sits rostral to the substantia nigra and immediately ventral to the zona incerta under the thalamus. The traditional model of the BG[35, 36] considers STN as part of the indirect pathway and highlights the GABAergic connection from GPe to STN and glutaminergic connections from STN to all BG output nuclei.

However, a major source of input to STN are the glutaminergic connections directly from the motor, premotor, and frontal cerebral cortices, bypassing the basal ganglia input nuclei. This unique role of the STN has inspired a revision of the classic theory of the BG and the introduction of a new *hyperdirect pathway,* highlighting that STN can mediate a quick cortical excitation of the inhibitory BG output, effectively exerting a fast stop on an action or decision.[37, 38] Additional glutaminergic input to STN comes from ipsilateral and contralateral[39] thalamic intralaminar (CmPf) nuclei.[40] Subthalamic efferents have widespread and collateral reach into GPi and SNr, as well as GPe and thalamic nuclei.

The SNc is located in the midbrain and is the source of dopaminergic modulation to the BG. These neurons contain tyrosine hydroxylase and the dopamine precursor neuromelanin, the latter conferring its dark color on SNc. Different dopaminergic neurons in the midbrain target different brain structures: the dopaminergic neurons in the ventral tegmental area target the nucleus accumbens and are involved in reward processing, whereas those in the in the SNc and retrorubral field target the striatum and are involved in control of movement. Dopaminergic neuronal loss in the SNc related to α-synuclein accumulation leads to the motor manifestations of Parkinson's disease.

CIRCUITRY AND PHYSIOLOGY OF THE BASAL GANGLIA

The classic model of the BG has been challenged by recent findings however it is still popular among clinicians since it offers a simplified explanation of BG function. According to the classic model depicted in Figure 2,[35, 36] there are two major pathways in the basal ganglia that relay information from the cortex, through the basal ganglia into the thalamus, and back to the cortex: the *direct* and the *indirect* pathways. In order to appreciate the model, recall that the BG output nuclei exert tonic GABAergic inhibition upon the recipient thalamocortical loops, in effect stopping the movements planned by the cortex at baseline.

The direct pathway consists of the cortex exciting the D1 striatal MSNs, which in turn briefly inhibit the two output nuclei of GPi and SNr. The activation of the direct pathway thus leads to disinhibition of the thalamocortical loop, in effect releasing it from the usual BG inhibition. Dopaminergic modulation from SNc facilitates this same disinhibition through excitatory activation of D1 receptor-expressing striatal MSNs of the direct pathway.

In contrast in the indirect pathway, the neural information from the cortex to D2 striatal MSNs passes through the *intermediate inhibitory stage* of GPe/STN before converging on the output nuclei GPi and SNr. This results in a total sum of inhibition conveyed by the indirect pathway on thalamocortical loops, stopping the respective planned movements or decisions they serve.

Dopamine inhibits the striatal neurons of the indirect pathway through D2 type receptors, thus diminishing the total inhibitory effect of the indirect pathway on the actions.

According to this view, the BG acts as an arena in which different movement plans compete to gain control of the effectors. Each motor plan inhibits other competing plans through its indirect pathway. The winning motor plan, through its direct pathway, can facilitate its own thalamocortical loop, in effect opening the gate for its own execution. Dopamine facilitates a quick resolution of this competition between the direct and indirect pathways by tipping the balance towards the winning direct pathway. Dopaminergic depletion thus leads to hyperactivity of the indirect pathway, resulting in the overactivity of the STN and ultimately, increased inhibitory output of the BG. The phasic disinhibition of direct pathways representing different actions now have a harder time overcoming such pathologically strong inhibition, resulting in akinesia and bradykinesia. The opposite scenario happens in hyperactive movement disorders such as chorea, ballismus, and dopamine-induced dyskinesia, where an overactivity of the direct pathway results in reduced inhibition of thalamocortical loops, allowing conflicting movement plans to gain access to effectors.

Parallel circuits in the basal ganglia serve the functionality suggested by the classic model, as well as different cortical areas involved in eye movement control, executive function, and emotional regulation, thus it is not surprising that BG pathology yields more than just isolated movement disorders. The dorsal parts of the striatum—the BG loops—are mostly connected to motor and premotor cortices. The ventral parts of the striatum—including nucleus accumbens—are connected mostly to cingulate and orbitofrontal cortices and are involved in limbic loops of the BG. The medial parts of the striatum are connected to prefrontal and orbitofrontal cortices and are involved in the associative loops of BG. The dopaminergic innervation of the limbic and associative BG loops arise from the ventral tegmental area, which sends dopaminergic input not only to the ventral striatum, but also to prefrontal cortex.

The classic model has explained numerous experimental results in lab animals, primates, and humans. More recent optogenetic methods that allow selective *in vivo* activation or deactivation of MSNs have provided strong, confirmatory evidence for classical model. Specifically, activating the striatal D2-expressing MSNs results in arrest of movement, and activating D1-expressing MSNs results in movement activation[41]. However, despite its success, the classic model's predictions have also led to some famous paradoxes. One such paradox points out the fact that removal or ablation of the inhibitory output nuclei of BG should disinhibit or facilitate movement, but instead such lesions—most famously, pallidotomy for Parkinson's Disease—do not result in involuntary movement but rather, paradoxically, relieve the involuntary excessive movements known as dyskinesias[42]. Another such paradox points out that lesions of the STN, GPi, or motor thalamus do not worsen action in Parkinson patients, but rather, improve them. These observations are clearly problematic for the classical model.

The recognition of novel anatomical connections and the elucidation of their functional significance have forced the classical model of the BG to evolve. For example, as mentioned above, the recognition of direct cortical input to the STN that bypasses the striatum did not fit

into the classical model. This hyperdirect pathway provides the cortex with a direct and fast activation of the BG inhibitory output and the ability to quickly stop action planning. It is now suggested that under high conflict situations where a right action cannot be chosen easily, STN can slow down the selection in the BG arena and thus provide more time for a more rational action. Failure of STN thus leads to impulsive decisions, especially under high conflict. To highlight this functional significance, STN is now categorized as the main hub of this hyperdirect BG pathway, supplementing the function of the direct and indirect pathways.[37]

Another example of the evolving understanding of the classical model is the appreciation of several reciprocal reentry loops within different BG nuclei, emphasizing the fact that these nuclei are not just one-way relay stations, but might subserve more complex computations. It is suggested that inhibitory GPe connections to STN and reciprocal excitatory feedback from STN form a pacemaker that promotes the low frequency oscillations within the STN itself.[43] This rhythm gets pathologically robust in low dopamine states such as Parkinson's disease.[44] The connections of the BG to brainstem nuclei (e.g., superior and inferior colliculi, pedunculopontine nucleus, and reticular nuclei) subserve action planning and motor learning for these phylogenetically older structures in the same manner as the BG do for the higher-level cortex.[45] Finally, cerebellar connections with the basal ganglia have attracted some research[46] and it is suggested that the interaction of these two structures serve not only motor, but also associative and cognitive roles.[47]

The cortico-basal-thalamo-cortical circuitry should not be viewed in isolation from the other crucial structures involved in motor control, i.e. the cerebellum. Classically it was suggested that cortex, the BG, and the cerebellum serve three different kinds of motor and behavioral learning: unsupervised learning, reinforcement learning and supervised learning, respectively[48]. The BG and cerebellum functions were viewed largely as independent and complementary. A dedicated review of cerebellar anatomy and physiology is beyond the scope of this chapter and can be found in the outstanding review by Dr. Lynch within this volume. Here, we focus on the interaction between the BG and cerebellum. Briefly, the cerebellum was perceived as receiving a wide array of inputs from many different cortical areas and sending its ultimate output only to motor cortices. However, it is now recognized that cerebellar outputs target a myriad of thalamic nuclei and as a result, reach many different brain areas. This implicates the cerebellum in both motor and non-motor higher cortical functions. Both the cerebellum and the BG are part of multisynaptic loops that start and end in the cerebral cortex. However, the interaction between these two loops is not limited to the shared cerebral cortex node. Recent studies show that neurons from motor and non-motor domains of the cerebellar dentate nucleus are connected through thalamic nuclei to sensorimotor and associative regions in striatum [49]. These disynaptic connections provide a basis for fast coordination of BG and cerebellar activities during fine motor tasks. The cerebellar influence also affects learning in cortico-striatal loops, which might prove to underlie dystonia. This path also conveys the pathological cerebellar activity to the BG, as suggested, for example, in the classic Parkinsonian tremor.[50] Perhaps this explains why disrupting the thalamic relay of this cerebello-striatal connection can improve such a tremor, as occurs with deep brain stimulation. The subthalamic nucleus is connected through pontine

nuclei to motor and non-motor regions of the cerebellar cortex, providing a fast connection for BG output to directly modulate cerebellar activity.

CLINICAL SYNDROMES ASSOCIATED WITH BASAL GANGLIA PATHOLOGY

Hypokinetic movement disorders

For over 100 years, the role of BG has been recognized in akinetic and rigid movement disorders.[1] The hallmark of this group, Parkinson's disease, represents the opposite end of the spectrum from the hyperkinetic disorders of chorea, hemiballismus, dyskinesia, and dystonia. The classic model of the basal ganglia posits that normal motor (and cognitive) function depends on a balance between the excitation and inhibition in the direct and the indirect pathways. The overactivity of the indirect pathway partly due to dopaminergic neuronal loss in SNc, results in over-inhibition of the motor thalamocortical loops. This manifests as both slowing down and decrementing amplitude of voluntary and automated movements, referred to *bradykinesia* (slow, decrementing movements), and in its most severe form, *akinesia* (absence of movement). However, two of the other cardinal symptoms of Parkinson's disease—namely, tremor and rigidity—cannot be readily explained by the classic model, and their origin is debated to date.[51] Alterations of the cortico-ganglio-thalamo-cortical loops due to dopamine depletion and involvement of the cerebellum have been implicated in tremor generation. Similarly, even peripheral etiologies are suggested for rigidity.[52]

While PD is the prototypical hypokinetic syndrome and parkinsonism is rarely seen in children, the same principles can explain much of the symptomatology in pediatric syndromes with BG involvement, such as vascular and neoplastic lesions of the BG, inborn errors of metabolism, Wilson's disease, lysosomal storage diseases, etc. As reviewed above, dopamine is only one of the neurotransmitters that modulate the BG pathways. The cholinergic and serotonergic influences on the system may also be altered in various pathologic states that will be described in subsequent articles.

Hyperkinetic Movement Disorders

On the opposite end of the spectrum from Parkinson's disease, relative overactivity in the direct pathway results in the expression of unwanted movement sequences. This includes the phenomenological categories of chorea, dyskinesia, and dystonia. *Levodopa-induced dyskinesia* (LID) and *impulse control disorders* (ICDs) in Parkinson disease are additional examples of overactivity in the direct pathway in the motor and limbic loops, respectively. These disorders arise in patients with Parkinson's disease after a prolonged period of treatment with levodopa (in the case of LID) or dopamine agonists (in the case of ICDs), emphasizing that both neuronal loss due to the disease and dopamine receptor sensitization and hypersensitivity due to medication are involved to the pathophysiology of these conditions. Both phenomena are time- and dose-dependent. PD patients affected by LID exhibit involuntary choreiform movements when the blood level of levodopa peaks above a certain threshold. ICDs affect a large number of PD patients who are treated with dopamine agonists. ICDs include pathological gambling, hypersexuality, binge eating, excessive shopping, and a generalized inability to

control impulses. Imaging studies have shown dorsal striatal overstimulation in response to levodopa in LID and similarly, a disproportionately elevated release of dopamine in the ventral striatum in response to rewarding stimuli in ICD.[53]

Chorea

Chorea is defined as excessive, spontaneous, dance-like movements that are irregularly timed, non-repetitive, unpredictable, randomly distributed, and abrupt in character. Chorea is often thought of as a broader category of phenomenology, encompassing athetosis and ballism, as well. *Athetosis* is a slower form of chorea that usually involves the distal extremities. *Ballism* is a severe, large-amplitude, proximal, and usually unilateral form of chorea.

The prototypical choreic syndrome is Huntington's disease, resulting from a mutation in the huntingtin protein in the form of expanded CAG trinucleotide repeats. The pathologic huntingtin protein causes neuronal dysfunction and eventually degeneration mainly in the striatum, often appreciable on imaging as marked atrophy of the caudate with enlargement of the frontal horns. The neuronal loss disproportionately affects the indirect pathway MSNs, altering the homeostatic balance and yielding relative hyperactivity of the direct pathway.[54] Accordingly, medications that deplete dopamine--such as reserpine and tetrabenazine—or that block dopamine receptors—such as typical antipsychotics including haloperidol and thorazine—improve chorea. This pathology is not restricted to the motor loops of the BG and involves the cerebral cortex, cerebellum, limbic system, and memory systems, explaining why the clinical manifestations of the Huntington's disease extend far beyond chorea to include prominent cognitive and psychiatric symptoms. These symptoms include, but are not limited to, impairments in executive control, planning, and motor learning, as well as depression, mania, impulsivity, and suicide.

Ballism, or more commonly, its unilateral form *hemiballismus*, is traditionally localized to a unilateral lesion of the STN, contralateral to the involved limb.[55] However, hemiballismus has been reported after strokes in other brain regions such as cortex, caudate, putamen, thalamus, and brainstem. This again emphasizes that disruptions at various nodes of the BG network can share the same manifestation of loss of inhibitory gating on movements, resulting in hemiballismus.[56]

Dystonia

Dystonia is pathological, sustained co-activation of agonist and antagonist muscles resulting in twisting, repetitive movements and abnormal postures. The classic model of the BG suggests that decreased inhibitory BG output as measured by the firing rate of GPi neurons, results in the overactivity of thalamocortical motor loops, manifesting as dystonia. Some clinical observations are in line with this classic vision, and have shown reduced firing rates of GPi neurons during DBS surgery for dystonia,[57, 58], but there has been evidence to the contrary.[58]

As mentioned earlier, the classic model cannot readily explain why pallidotomy in Parkinson disease—which removes the inhibitory influence of the BG and thus should increase hyperkinetic movements—paradoxically *relieves* dystonia and dyskinesia. Abnormal plasticity

and associated aberrant somatosensory dysfunction have been implicated and debated[59] in the generation of some focal dystonias, such as musician's dystonia and writer's cramp.[60] Cerebellar circuits involved in this plasticity have been implicated in dystonia in addition to or in collaboration with the BG.[61] Moreover, the long delay between DBS surgery for dystonia and the onset of symptomatic improvement has been implicated as the evidence that abnormal plasticity plays a role in dystonia. The striatal striosomes (contrasted with matrix components) that are involved in the limbic BG and their nigral connections, and more specifically their cholinergic interneurons, have been implicated in this abnormal plasticity,[62] a finding that explains the usefulness of anticholinergic medications in dystonia management. In summary, the exact nature and circuitry of basal ganglia involvement in dystonia is still hotly debated.

Tics and Tourette's Syndrome

Tics are nonvoluntary movements of any part of the body that are rapid, sudden, repetitive but nonrhythmic, suppressible for at least a moment, and typically associated with an irresistible urge or premonitory sensation. Tics can include the vocal musculature, leading to various sounds including grunting, sniffing, and vocalizations of all types. Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by the onset of both motor and phonic tics before the age of 18. Very often, patients have comorbid obsessive-compulsive disorder and/or attention deficit hyperactivity disorder (ADHD), and all three conditions may run separately in one family.

The classic model of the BG readily explains how overactivity of the direct pathway in the motor and limbic loops leads to release of unwanted movements (motor tics) or of unwanted thoughts (obsessions). Dopaminergic input to the direct pathway of the BG increases in TS.[63] Considering that parallel cortico-basal-thalamo-cortical loops subserve the same general excitatory or inhibitory functions for different motor, limbic and associative functions, obsessive thoughts and related compulsive behaviors stemming from the limbic system could be thought of as a counterpart to dyskinesias or tics in the motor system. Similarly, ADHD may represent a failure of the associative and limbic loops.[64] Accordingly, dopamine blockers such as antipsychotics or dopamine depleting agents are effective in treatment of tics. The CmPf nuclei of the intralaminar thalamus are part of both motor and limbic loops of the BG, and have vast connections to frontal, prefrontal, and limbic cortices. They send efferents to ventral and motor striatum, and receive afferents from GPI and SNr.[65] CmPf nuclei as well as the GPi have thus been targets for DBS in refractory cases of TS.[66]

SUMMARY

The basal ganglia are closely involved in adaptive motor control and learning. The classic model from the late 1980s proposed how direct and indirect loops within the BG filter out competing motor plans and function as a gate to block unwanted movement plans. Though initially developed to explain movements, the model suggests that the same functional principles subserve the limbic and associative functions of the BG, too. It also explains how dopaminergic modulation of this system underlies many motor and non-motor disorders that arise from BG pathology. Even though shortcomings of the classic model are discovered as we learn more details about the macro- and micro-circuitry of the BG, the model still provides clinicians with an

intuitive insight to the pathophysiology of parkinsonism, dyskinesia, chorea, dystonia, tics, and their respective treatments.

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The authors would like to dedicate this article to the memory of our friend and colleague, Jessica A. Panzer, MD PhD, a brilliant pediatric movement disorders neurologist, researcher, mentor, and friend. The field of movement disorders and the care of our patients are immeasurably enriched by her contributions during a career cut far too short.

Abbreviations:

Table 1. Abbreviations used in this article	
BG	basal ganglia
CmPf	centromedian and parafascicular nuclei of thalamus
D1 receptor	dopamine receptor subtype 1
D2 receptor	dopamine receptor subtype 2
GABA	gamma-aminobutyric acid
GPe	globus pallidus externa
GPi	globus pallidus interna
ICD	impulse control disorders
LID	levodopa-induced dyskinesia
MSN	medium-sized spiny neurons
PPN	pedunculopontine nucleus
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
vGlut1 or 2	glutamate transporter isoform 1 or 2

Figure 1

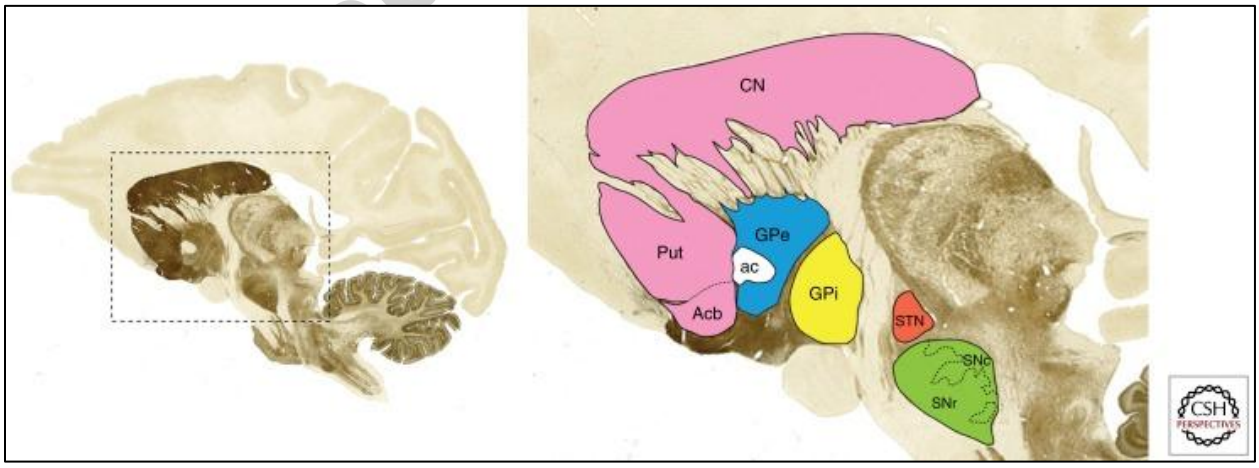

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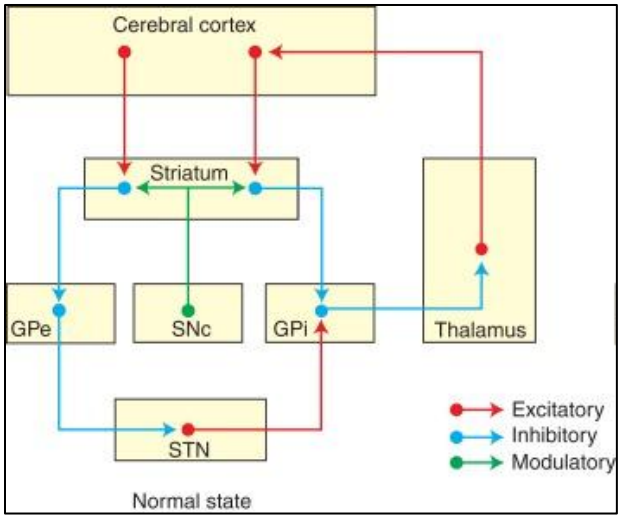
Figure 2



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(Cropped from their Figure 5)

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