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Parkinson's

SECOND EDITION

Parkinson's Disease and Movement Disorders

Under the Banner of
Parkinson's Disease and Movement Disorder Society

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CHAPTER 2

Basal Ganglia Anatomy and Functions

Aditya Ashok Murgai, Mandar Jog

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INTRODUCTION

Basal ganglia (BG) are a group of large subcortical nuclei important for motor learning, action selection, motor control, motivation, and reward. BG circuits are organized in a way to facilitate desired voluntary movement and inhibit competing movements. They form the extrapyramidal system which is involved in various movement disorders such as Parkinson's disease, Huntington's disease, and Tourette's syndrome. Over the years many anatomical, functional neuroimaging, and neurophysiology studies have tried to understand the functions of BG and its circuits. Another approach of understanding BG functions has been to study the deficits that occur in patients with BG disorders. In the following sections we would discuss in detail about BG microstructure, circuits, and their role in motor control, behavior, and cognition.

BASAL GANGLIA STRUCTURE

The principal components of the BG are the striatum, subthalamic nucleus (STN), pallidum, and substantia nigra. The striatum can be functionally and anatomically divided into a dorsal and ventral portion. The dorsal striatum is composed of the putamen and caudate nucleus (CN) and the ventral striatum includes the nucleus accumbens (NA). For such a large nucleus, the striatum is unique as it lacks glutamatergic neurons and most of the output cells are gamma-aminobutyric acid-ergic (GABAergic). The STN is a biconvex-shaped nucleus, approximately 9 × 7 × 4 mm (length, height, weight). Subthalamic nuclei lies just below the thalamus and can also be considered an input nucleus as it receives input from the cerebral cortex. It also receives input from the globus pallidus external (GPe) and gives excitatory output to globus pallidus interna (GPi) nucleus. The STN is divided into dorsolateral, ventromedial, and medial portions, which differ in their connectivity and functions. Dorsolateral STN, which is the sensorimotor region receiving direct projections from the primary motor cortex (M1) and supplementary motor area (SMA). The ventromedial STN contains the associative region, receiving projections from the premotor cortex (PMC), prefrontal cortex (PFC), SMA, frontal eye field (FEF), and supplementary eye field. Lastly, the medial portion which represents the limbic region and receives projections from the caudal cingulate motor cortex.[1] The GP is separated into two nuclei: The more laterally positioned nucleus is called the GPe, whereas the medial nucleus is called the GPi, both receiving GABAergic input from the striatal neurons.[2]

The putamen and caudate are the main input nuclei while the GPi along with substantia nigra pars reticulata (SNr) form the main output nuclei of BG. The BG provide output to the thalamus, the superior colliculus (SC), and the pedunculopontine nucleus (PPN). BG influence motor, sensory, and cognitive information processing through their innervation of the thalamus, eye movements through innervation of SC, and locomotion and postural control through innervation of the PPN.[2]

Striatum receives dopaminergic input from the ventral midbrain, which consists of three main groups of neurons. Ventral tegmental area (A10) projects to NA and ventral pallidum and is involved in addiction and motivation, substantia nigra compacta (SNc) (A9) and retro-rubral field (A8), both project to the striatum.[3] Substantia nigra can be separated into two regions, SNc and SNr. SNr cells are involved in saccadic eye movements and there is some evidence showing their role in cognitive processing.[4] In the following sections we will discuss the microanatomy of the striatum, STN, and GP in greater.

Striatal Compartments: Striosomes and Matrix

Striatum comprising of putamen and caudate is composed of two distinct compartments, the striosomes (patches) and matrix.[5] Acetylcholine esterase (AChE) staining of striatum shows weak AChE activity in striosomes in a background of more intense AChE staining of matrix. Also, striosomes shows strong immunoreactivity for enkephalin, substance P, GABA, and neurotensin, whereas the matrix compartment shows immunoreactivity for parvalbumin.[3] Both the compartments have medium spiny neurons (MSNs) and the dendrites of MSNs in striosomes and matrix remain restricted to their respective compartment with minimal interaction.

Each cortical area projects to both the patches and the matrix of the striatum. Deep layer V and layer VI corticostriate neurons project principally to the patches, whereas, superficial layer V and layer II and III corticostriatal neurons project mainly to the matrix. However, allocortical areas provide a greater input to the patches and neocortical areas to the matrix.[5]

Striatal Neurons: Projection Neurons and Interneurons

There are two populations of neurons in the striatum, projection neurons (striatofugal) and interneurons. Striatofugal neurons are MSNs (medium as they are about 20 µm in diameter and spiny as their dendrites have numerous spines) which constitute about 90% of striatal neurons and interneurons constitute the remaining 10%. The soma of MSN gives rise to 5–10 smooth primary dendrites that become densely invested with spines about 20 µm from the soma.[6] These dendrites branch moderately to about 30–35 dendritic tips and form a roughly spherical arbor unless distorted by the presence of a boundary between the striosome and matrix compartments which they do not cross (**Fig. 1**).[7]

Medium spiny neuronal membrane potential fluctuates between a relatively hyperpolarized "Down" state (–80 mV) and a relatively depolarized "Up" state (–50 mV). These neurons usually fire while in the Up state exhibiting a phasic burst pattern with a low firing rate. The occurrence of Up and Down states in striatal neurons requires phasic changes in the cortical and thalamic inputs to striatal neurons.[8] Excitatory cortical inputs on MSN end on the head of spines and dopaminergic terminals from the SNc terminate in close association with the corticostriate inputs on the spine necks or dendritic shafts (**Fig. 1**).[9]

The sources of the striatofugal direct and indirect pathways are also GABAergic neurons that can be segregated into two populations based on their peptide content, and by the preferential expression of dopamine receptors. Direct pathway neurons contain substance P/dynorphin and preferentially express D1-receptors whereas, indirect pathway neurons contain enkephalin and preferentially express D2-receptors. Striatal MSNs synapse with GPi/SNr, which gives output to the thalamus and then to cortex forming the direct pathway. Indirect pathway involves striatal MSNs, GPe, STN, GPi/SNr, thalamus, and cortex (**Fig. 2**). The input into GPi/SNr from the striatum and STN is such that the striatum provides a focused, context-dependent inhibition, while the STN provides a less specific and divergent excitation. Because the output from the GPi/SNr is inhibitory, this results

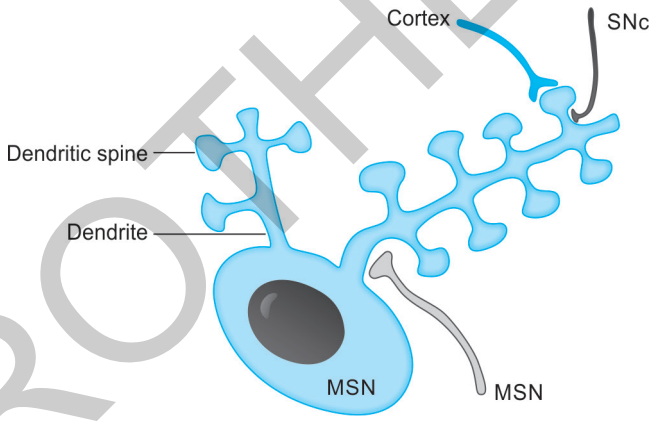
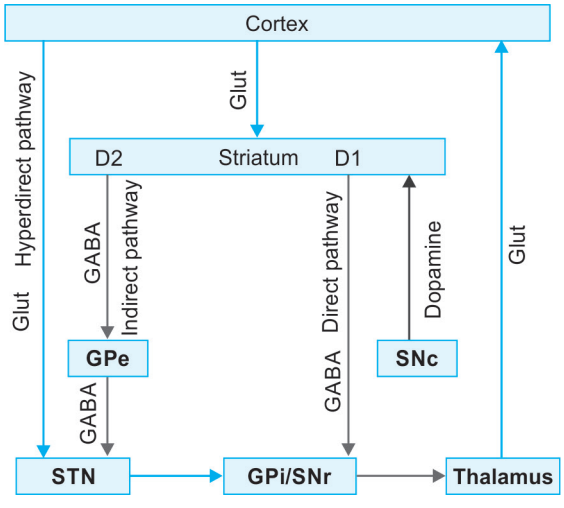


FIG. 1: Schematic image of a medium spiny neuron (MSN) structure. The glutaminergic input from cortex goes to the head of the dendritic spine, whereas the modulatory dopaminergic input from substantia nigra pars compacta (SNc) goes to the shaft of the dendritic spine.



(GABA: gamma-aminobutyric acid; GPe: globus pallidus external; GPi: globus pallidus interna; SNc: substantia nigra compacta; SNr: substantia nigra reticulata; STN: subthalamic nucleus)

FIG. 2: Direct, indirect, and hyperdirect pathways in basal ganglia. The excitatory output is shown in blue and inhibitory output in gray color.

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in a focused facilitation associated with a surround inhibition of motor phenomenon. This organization results in selective facilitation of desired movements and inhibition of competing movements.[10] Dopamine acts on D1 receptors increasing the production of cyclic adenosine monophosphate (cAMP) resulting in facilitation of the pathway through long-term potentiation whereas dopamine acting on D2 receptors causes reduction of cAMP resulting in long-term depression in the indirect pathway. Hence, dopamine has a facilitatory effect on the motor output from BG.

Striatal interneurons are inhibitory and use GABA as a neurotransmitter. These neurons are classified into four groups. The most abundant group of interneurons consist of large aspiny cholinergic neurons, comprising 0.3–2% of the neurons in the rodent striatum. They show a continuous and constant firing pattern and hence are also known as tonically active neurons (TANs). Aspiny cholinergic neurons can fire spontaneously unlike MSNs and have synaptic connections with MSNs and other interneurons. These neurons exhibit a relatively depolarized resting membrane potential between –55 and –60 mV and do not display the discrete "Up" and "Down" states like MSNs. The remaining interneurons are GABAergic, distinguishable on electrophysiological, morphological, and neurochemical bases. Parvalbumin (calcium binding protein) positive GABAergic interneuron, also known as fast-spiking interneurons (FSI) can fire at a high frequency of up to 300 Hz. The second type of GABAergic interneurons are medium size, calretinin (calcium binding protein) positive interneurons. The third type of GABAergic interneurons use nitric oxide as the neurotransmitter. TAN and FSI interneurons modulate the activity of striatofugal neurons and are under dopaminergic control whereas, calretinin and nitrergic GABAergic interneurons innervate TAN and FSI interneurons.[3]

ULTRASTRUCTURE OF GLOBUS PALLIDUS AND SUBTHALAMIC NUCLEUS

The STN is a lens-shaped densely populated structure. It is predominantly made up of glutamatergic projection neurons with 7.5% of GABAergic interneuron cells.[11] The STN consisted of tightly packed neurons distributed within a neuropil filled with large numbers of blood vessels and thinly myelinated fibers. STN neurons, dendrites, and initial axon segments are tightly apposed without any intervening glial membranes.[12]

The GP is divided by a thin lamina into an inner and outer segment. The entopeduncular nucleus in rodent is considered homologous to the GPi in primates. Unlike STN and striatum, the neurons are sparsely distributed across GP. Most of the cell bodies in GP are large (35–70 μ) in size.[13,14] These large pallidal neurons are characterized by sparsely branched dendritic arborizations with thick, smooth, and long dendrites.[15] Ultrastructural of GP shows highly prevalent synaptic interaction between glutamic acid decarboxylase (GAD) immune-reactive axon terminals and GAD positive pallidal neurons.[16]

BASAL GANGLIA CIRCUITS

Basal ganglia receive cortical input from multiple cortical areas including primary motor cortex, somatosensory cortex, PMC, supplementary motor cortex, dorsolateral PFC, orbitofrontal cortex, and anterior cingulate cortex. Alexander, DeLong, and Strick in 1986 proposed five cortico-BG circuits involved in motor, oculomotor, cognition, emotion, and motivation.[17] They proposed that each circuit receives multiple, partially overlapping corticostriate inputs, which are progressively integrated and projected to a restricted cortical area. The thalamocortical projections of the motor circuit terminate largely within the SMA while the corticostriate inputs to this circuit include projections from the SMA, motor, premotor, and sensory cortex. Oculomotor circuit consists of fibers from FEFs (Brodmann's area 8) along with projections from dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (area 7), projecting to the body of the CN. The caudate projects to the GPi/SNr, which then projects to the ventro-anterior (VA)/dorso-medial (DM) nuclei of thalamus and back to FEF. Oculomotor circuit is involved in generation of saccadic eye movement. SNr neurons show pause in activity just before the onset of saccadic eye movement and this is associated with a burst activity in SC neurons producing a saccade. DLPFC also known as association circuit consists of projections from DLPFC to the CN to GPi/SNr, which then projects to VA nucleus of thalamus and back to DLFPC. The cortical connections to caudate suggest a role of this circuit in forward planning of complex motor tasks. It is believed that when a motor task becomes automatic, the motor circuit takes over that task from the dorsolateral prefrontal circuit. There is some evidence to suggest that this circuit also participates in processes subserving spatial memory. Lateral orbitofrontal circuit consists of fibers projecting from orbitofrontal cortex to CN to GPi/SNr, which then projects to VA/DM thalamic nuclei and back to orbitofrontal cortex. Bilateral lesions of this circuit have shown to interfere with appropriate switches in behavioral set. Anterior cingulate or limbic circuit consists of fibers from the anterior cingulate cortex, hippocampus, and entorhinal cortex projecting to ventral striatum (NA) to ventral pallidum, which projects to DM nucleus of thalamus and then back to anterior cingulate cortex. This circuit is believed to be involved in motivation.[17]

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Basal Ganglia and Cerebellum

The cerebellar circuits and BG circuits were believed to be anatomically and functionally distinct and interact at the level of cortex. Recent animal studies have shown bidirectional disynaptic connection between cerebellar cortex and striatum through the dentate nucleus. Also, anatomical connection has been found between cerebellar cortex and STN through the pontine nuclei. These connections suggest that BG and cerebellum exchange information in real time to provide appropriate input to the frontal cortex.[18] A recent model proposes that cerebellar, BG, and motor cortex are interlinked and their abnormal interactions results in abnormal movements in Parkinsonism and levodopa-induced dyskinesias.[19]

Basal Ganglia and Motor Control

Over last few decades various functions of BG have been proposed including selection of action and suppression of potentially competing actions, regulation of speed and size of the movement, online correction of motor error, motor learning, and production of overlearned motor skills.[20] There are two basic theories for the motor control, learning, and action selection by striatum. The oldest and the most long-standing theory is of lateral inhibition by MSNs which works on the principle of winner takes it all. Lateral inhibition is important in the selection of competing motor programs. It is based on the fact that each MSN has numerous inhibitor GABAergic connections with the neighboring MSNs, which causes their inhibition in order to increase the signal to noise ratio of the striatal output. Another theory is based upon feed-forward model of inhibition by the FSI in the striatum, which are GABAergic. These neurons get their input directly from the cortex and not from within the striatum and hence the name feed forward. Computational modeling of BG has shown the importance of both the models in proper BG functioning. Lateral inhibition is required for motor learning, action initiation and control, and the impairment may result in chorea and bradykinesia. Feedforward inhibition is expected to be involved in selection of appropriate actions and its impairment has been observed in Tourette's disease and obsessive-compulsive disorder.[21]

A study by Crutcher et al. published in 1990 showed that SMA neurons discharge significantly earlier than those in motor cortex, which in turn were earlier than those in putamen.[22] Late onset of movement-related activity argues against a role of the putamen in the initiation of movement but some putamen neurons do have activity several hundred milliseconds in advance of movement. This early putamen neuronal activity is thought to be related to instruction cue, which conveys information regarding the correct direction of movement, how far to move, or whether to move at all. This is followed by the "go" signal which provides information on when to move. Thus, BG are responsible for the quality and correctness of a movement and may not play an important role in initiation of movement.[23]

Medium spiny neurons are difficult to excite and need strong convergent input from cortex to become active. Corticostriatal system fibers from different functionally related cortical areas converge on the same neuron or groups of MSNs (ensemble). These neurons are activated only when a sufficient number of their excitatory corticostriatal afferents are active.[9] Dopamine release has a focusing or attentional effect facilitating the output of a particular ensemble of striatal neurons at the expense of others thus having a gating role. Dopamine effect on MSNs also leads to synaptic plasticity, building and shaping striatal output modules, and a role in the process of reward-based motor and behavioral learning.[9,24] Hence BG are involved in forming reward-based associations, which over the course of practice train show Hebbian learning in thalamocortical circuits.[20] It is believed that BG circuits are necessary for new skill learning, but become less important in retention and recall of well-learned motor skills. Another hypothesis to explain BG function is of movement gain. It is based on a simple concept that BG regulate the speed and size of movement (movement gain). Gain hypothesis is supported by the neurophysiological findings showing that movement-related activity in the pallidum is correlated with the amplitude or velocity of the limb movements.[20]

Basal Ganglia Role in Reward and Language Processing

Ventral striatum (NA) projections to the ventral pallidum translates limbic motivation signals into motor output and this accounts for the limbic-motor integration. Lesional studies have shown the ventral pallidum may be crucial for learning or performing learned responses related to rewards. Growing evidence suggests role of ventral pallidum in food reward, sex, social affiliation, drug abuse, winning money, and other rewards. Hence, ventral pallidum might be viewed as a convergent point for hedonic and motivational signaling pathways in the brain and hence a final pathway for reward.[25] Striatum also plays an important role in language processing including lexical processing (e.g., word retrieval) and grammatical rule application (syntax). A positron emission tomography (PET) study in Huntington disease patients showed that the left striatum encompasses linguistic (lexical processing and rule application) and arithmetic circuits. Ventrally located regions in striatum are dedicated to rule computations and dorsal regions to lexical processing.[26]

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CONCLUSION

Basal ganglia network is a complex structure consisting of multiple subcortical nuclei and parallel circuits. The most important function of the BG is in motor control including selection of action, suppression of competing actions, regulation of speed and size of the movement, and motor learning. BG also play a crucial role in behavior, reward, and language processing.

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Parkinson's Disease and Movement Disorders

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- There is a separate chapter on "biomarkers".
- Chapters on future advances in therapy of Parkinson's disease and other disorders.
- A dedicated chapter to the six grand masters of movement disorders.
- An approach to many difficult clinical syndromes.
- An approach to radiological and nuclear imaging in movement disorders.
- A separate section on nonmotor symptoms in Parkinson's disease.
- Dedicated chapters on botulinum toxin injections and deep brain stimulation.

This book will help the students in neurology and also consultants in the field of neurology as a quick reference when seeing patients.

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