Title
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ISBN
9783540237358

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Epstein, Marcelo
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Publication Date
2008

DOI
10.1007/978-3-540-29678-2_2

Peer reviewed

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Basal Ganglia Disorders

Definition

►Basal Ganglia

Basal Ganglia: Motor Functions of

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Definition

The basal ganglia consist of four prominent nuclei, which are interposed between the cerebral cortex and the lower centers of the brain stem and spinal cord. These nuclei include the:

1. Striatum (caudate, putamen, ventral striatum including nucleus accumbens)
2. Globus pallidus internal (GPi) and external (GPe) segments
3. Substantia nigra pars compacta (SNpc) and pars reticulata (SNpr)
4. Subthalamic nucleus (STN)

Most of the inputs and outputs of the basal ganglia arise from or go to the cortex either directly or indirectly through the thalamus. Thus, the basal ganglia form something of a side loop or detour in the relation of the brain to behavior. As a result, determining the function of the basal ganglia has been more difficult than for brain areas that more directly respond to impinging sensory stimuli (See ►Sensory Cortex) or elicit distinct motor outputs (See ►Motor Cortex).

While the basal ganglia mediate many nonmotor functions including cognition, emotion, and sensory processing, they have long been regarded as primarily involved with movement. Lesions of the basal ganglia cause motor deficits. The disorders most associated with the basal ganglia – such as Parkinson's disease (PD), dystonia, and Huntington's disease (HD) – are considered movement disorders, even though other functions can be disrupted in these patients (e.g. sleep in PD, mood in HD, cognition in both PD and HD).

Within the basal ganglia, the putamen is most directly associated with movement and receives abundant cortical input. From the putamen, impulses flow through the GPi/GPe, STN, and SNpr to the thalamus. The SNpc sends a large dopaminergic projection to the striatum (See ►Dopamine). The SNpc is the nucleus most degenerated in PD.

Characteristics

1. The basal ganglia is a source of motor disorders

   The close connection between the basal ganglia and movement goes back to classical clinical neurological findings showing basal ganglia damage in many patients with movement difficulties. Indeed, the whole field of *movement disorders* has focused primarily on conditions that involve the basal ganglia. More recent explorations using cellular recordings and neuroimaging (see below) have confirmed this finding by establishing abnormal activities within these nuclei in motor disorders [1].
2. Methods of elucidating the motor functions of the basal ganglia

   Several different techniques have contributed to our understanding of the organization and function of the basal ganglia. These techniques include neuroanatomical studies of animals and human autopsy tissue, cellular recordings from animals and humans undergoing invasive brain surgery, radiotracer and functional imaging studies (►functional neuroimaging methods), and behavioral studies of patients with motor disorders, particularly PD.

   a. Anatomical organization

   Earlier studies confirmed the general scheme of input and output relations of the basal ganglia. More recent studies have identified several more distinctive and specialized pathways. The following discussion is a simplified view of these results and omits much of the emerging complexity of the basal ganglia pathways.

   i. The direct and indirect pathways

These two pathways are thought to work as a push-pull system that can finely control the level of basal ganglia output. A correct balance is necessary for normal motor function. All basal ganglia output is thought to be inhibitory and to suppress thalamic activity, which in turn reduces stimulation of interconnecting cortical regions. The direct pathway runs from the striatum to the GPi and suppresses GPi output, thus releasing the thalamus to provide excitation to the cortex. The indirect pathway from the striatum to the GPe and STN, excites the GPi, thereby suppressing the thalamus and withdrawing excitation from the cortex. Selective activation of different elements of these pathways can create a "center-surround" input to the cortex that selects specific motor activities for expression while inhibiting others [2]. In PD, a hypokinetic disorder, relative hyperactivity of the indirect pathway leads to excessive inhibitory GPi output and poverty of movement; this may be due to thalamic inhibition, but it could also be due to a breakdown in the specificity and segregation of GPi output [3]. In dystonia, a hyperkinetic disorder, relative hyperactivity of the direct pathway leads to reduced GPi output and excessive, involuntary motor activity.

More recent studies indicate that a third, "hyperdirect" pathway exists, with cortical input going directly to the STN. This pathway would also tend to increase GPi inhibitory output and reduce cortical excitation.

ii. The nigrostriatal pathway

This dopamine projection is the most degenerated in PD and has abundant projections to the striatum, whereas other dopaminergic systems project widely from the cortex to the spinal cord. Its basic effect is to increase basal ganglia output by acting on ►D1 dopamine receptors in striatal neurons that stimulate the direct pathway and on ►D2 dopamine receptors that stimulate the indirect pathway. Much of SNpc activity tends to be tonic or sustained rather than phasic or transient, which has led to some difficulty in establishing the pathway's explicit contribution to motor control (►motor control Hierarchy).

iii. Basal ganglia loops

A major advance in understanding the circuitry of the basal ganglia was the recognition that its neurons were organized within a series of parallel loops. Each loop began in the cortex with excitation of the striatum followed by input to the GPi, which then variably inhibited the thalamus whose projections sent excitation back onto the original cortical source. Although this architecture continues to be studied, more than five separate loops and several divergent connections have been identified. The "motor loop" has been most studied and is best understood [1]. This form of organization is especially suited for feedback or feed-forward effects, while cross-talk between loops may be crucial for correlated activities in different cortical regions.

b. Single cell and local potential recording

Single cell recording was pioneered in animal models where implanted electrodes could be used to monitor cellular activity during a variety of behaviors. Such studies include normal primate models and disease models such as the MPTP monkey, which has been rendered Parkinsonian by the targeted administration of MPTP, a selective neurotoxin for dopaminergic cells. More recently, cellular studies have been extended to patients, especially those with PD, who have been recorded during ablative procedures or the installation of stimulators in the GPi, thalamus, or STN.

These studies have shown that like thalamic and cortical somatotopy, some degree of somatotopy exists throughout the nuclei of the basal ganglia, with activity in the skeletomotor loop segregated between arm, leg, and orofacial movements. While the general background activity of cells is one of frequent discharge, it can be modulated by the behavioral context both during preparatory periods prior to the onset of a goal-directed movement and during movement. Because most cells directly related to movement fire during, rather than before, a movement, basal ganglia activity does not appear to directly produce movement. Altogether, these observations are consistent with a role for the basal ganglia in planning movements and in motor learning [4]. The physiological changes in firing rate observed in normal animals have led to the suggestion that altered rate might underlie basal-ganglia dysfunction in PD. Indeed, GPi firing is excessive in PD, consistent with an overall inhibitory effect of this output on movement. However, this hypothesis is inconsistent with a similar increase of GPi firing in HD, a hyperkinetic disorder. Moreover, changes in firing frequency are modest. As a result, more attention has focused in recent years on the patterning of GPi output, especially the modulation of firing in an oscillatory manner within different frequency bands. It has been suggested that low frequency oscillatory activity – in the theta to beta range (4–30 Hz) – may be associated with inhibition of motor activity and bradykinesia, while higher frequency activity in the gamma range (>40 Hz) may facilitate movement. In both the MPTP monkey and humans with PD, slower oscillations are more prominent [5]. Treatment of PD with dopaminergic agents or deep brain stimulation (DBS) can enhance higher frequency oscillatory power.

c. Neuroimaging

►Radiotracer imaging, which measures nigrostriatal neuronal loss during a "resting state," has been

widely used in PD to study disease progression and the effects of pharmacotherapy. In contrast, functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), typically measure brain activity while a person actively performs a task to assess how neural systems function in different behavioral contexts. One standard method to study normal brain functioning is to compare brain activity at rest with activity during movement or motor learning in neurologically intact individuals. In general, basal ganglia and cortical activity are increased for self-generated movements. Similar to cellular recordings in animals, basal ganglia activity during task-activated fMRI is modulated by the behavioral context such that it increases with the complexity of movement in planning stages, but not during motor execution [6]. During motor learning, however, both increases and decreases in basal-ganglia and cortical activity have been reported, depending in large part on the degree of uncertainty about what movements are required and the amount of practice given [4]. Another approach has been to compare patients with normal individuals to identify abnormal patterns of brain activity in the patients. Some PET studies of resting-state brain activity have revealed a disease-related pattern of activity in PD characterized by elevated pallidal, thalamus, pontine and cerebellar activation and reduced premotor and parietal-occipital activity relative to normal individuals [7]. Even more interesting are PET and fMRI studies that have investigated brain functioning during movement and motor learning. In PD, dysfunction of the basal ganglia and interconnecting cortical regions can be studied by temporarily stopping pharmacotherapy so that dopamine levels are reduced to a practical "off state" or by turning off DBS devices. In areas specifically related to planning movements, such as the supplementary motor area, PD "off" patients typically show decreased activity. In other areas, such as the premotor, prefrontal and parietal cortices, PD patients can show hyperactivity together with a failure to show normal reductions in activation as motor behaviors become learned or "automatized" [8]. This abnormal functional pattern can be reduced by reinstatement of dopaminergic or DBS treatment.

3. Presumed functions of the basal ganglia

Progress has been made in understanding how the basal ganglia modulate different aspects of movements. In this section, we discuss the contribution of the basal ganglia to regulating intensive aspects of movement, motor planning, motor coordination, and motor learning. Although these facets of movement are not entirely independent, their relative importance can be emphasized by certain task conditions. Emerging research suggests that some treatments for PD can better remediate certain aspects of motor function, while having little or no effect on others, which lends support to their distinctiveness.

a. Intensive dimensions of movement

Peak force, velocity, and scaling are all aspects of movement that show a single major dimension of intensity. Clinically, PD patients are hypokinetic, so that they are slower, take longer to complete certain tasks, and generate less force. PD patients are also hypometric (e.g., ►micrographia) and tend to fall short of a target when reaching for it. With farther targets their output increases, but continues to be hypometric, even when it far exceeds the output needed to reach a closer target. Yet when permitted feedback of their position, PD patients can acquire targets as accurately as normal individuals. This may indicate a reliance on compensatory pathways that are relatively intact. Treatments of PD rather effectively remediate deficits in the intensity aspect of movements; with medication or surgical treatments, PD patients become faster and reach further. This suggests that the basal ganglia play a more trophic role with regard to movement intensity, which is mediated by the balance between direct and indirect pathways that inhibit undesired movements while facilitating chosen ones [2].

b. Feed-forward versus feedback control

In general, the basal ganglia are more important for self-generated movements that require feed-forward control than for sensory-guided movements under feedback control, suggesting that they play a key role in prediction or planning. This agrees with cellular and fMRI studies reporting that the basal ganglia exhibit dynamic modulation largely during response preparation [6]. These findings contrast with reports that PD patients can be faster than normal individuals in making saccadic eye movements to targets. This is likely due to relatively intact pathways involving the cerebellum, parietal cortex, and frontal eye fields, which process and modulate responses to external stimuli. Without adequate ability to prepare responses, feedback dominates predictive control.

c. Sensorimotor processing and integration

PD patients are also impaired in processing and utilizing proprioceptive information, a task analog of the postural deficit that is among the key clinical features of the disorder. As a general rule, PD patients have difficulty with integrating different forms of sensory input with sensorimotor (►sensorimotor integration) transforms that guide behavior, and with the integration of different

components of targeted movements (e.g. integration of reach and grasp components when moving to a target object) [9]. Such coordinative aspects of basal ganglia function are less readily normalized by pharmacologic or DBS treatment of PD. This suggests that current treatment approaches may restore more trophic or intensive functions of the basal ganglia, but may not restore the more precise, highly localized integrative functions related to specific brain regions or behaviors. Like most basal ganglia functions, we cannot indicate with great specificity how this occurs. One possible function is the ability of the BG to facilitate the binding of different cortical regions as they act in a coordinated fashion to shape motor behavior. Different sensory and motor coordinates resident in separate brain regions are required to effectively shape motor output, and the evidence from PD indicates that the basal ganglia are needed to facilitate their coordination.

Coordinative abilities are also important for sequencing motor behaviors and for dual task performance, both of which are impaired in PD. The basal ganglia may be most critically important in the preparation of motor sequences [6], which involves assembling a series of movements into a coordinated action. When preparation fails, actions may be decomposed into a series of movement segments rather than a smoothly structured sequence. Similarly, performance of even well-learned behavioral sequences may break down when a dual task is imposed [8].

d. Role in motor learning

The basal ganglia are important for learning new motor acts, which partially depend on preparative processes. A recent fMRI study reported that basal ganglia plasticity during both motor-sequence learning and when switching to new motor sequences correlated with reaction time, a measure of preparation [4]. No other structures, except the thalamus, showed this relationship, which agrees with its key role in preparation. This finding is consistent with slowed and incomplete visuomotor learning in PD, especially when there is a need to change from one behavioral context to another, a deficit in set shifting [10]. The distinction between preparation and learning may be one of degree; even well-learned behaviors need to be calibrated and prepared when called upon. Thus preparation and learning form a continuum in which overlapping abilities are needed to predict and model behavior.

Conclusions

New conceptualizations are emerging about corticostriatal circuitry, cellular properties of basal ganglia nuclei, and brain-behavior-treatment (e.g., pharmacotherapy, surgical) relationships, which have considerably advanced our knowledge about facets of motor function and their physiological underpinnings. One dominant theme is the central role of the basal ganglia in modulating intensive aspects of movement and feed-forward control, the latter of which may support to some extent other functions including integrative processing and learning. Especially fruitful have been studies demonstrating that these aspects of movement are differentially responsive to pharmacotherapy in PD. Exciting developments are also now taking place in neuroimaging studies of PD, which are beginning to delineate abnormal neural patterns associated with motor dysfunction, and assess their response to therapeutic interventions. Continued progress in these areas holds promise for further illuminating the workings of the basal ganglia nuclei and their modulation of motor, but also nonmotor functions represented more directly by the cerebral cortex.

Acknowledgments

This work was supported in part by NIH grant # NS36449 and NSF Center grant, The Temporal Dynamics of Learning Center, to UCSD.

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Basal Ganglia: Role in Eye Movements

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Definition

A major function of the basal ganglia is the control of body movements. This is illustrated by a variety of movement disorders caused by dysfunction of the basal ganglia, such as Parkinson's disease and Huntington's disease. Symptoms include the inability to initiate a movement and the inability to suppress involuntary movements. Eye movement is not an exception [1]. A fixed, vacant facial expression of patients with Parkinson's disease, which is often called the "Parkinson's mask," is due to the paucity of movements in the face, including the paucity of eye movements. Most affected among various kinds of eye movements are smooth pursuit and saccade, which require more voluntary control. Parkinsonian patients are often impaired in smoothly pursuing a moving object (deficit in smooth pursuit). They are also often impaired in shifting their gaze from one position in space to another (deficit in saccade).

Characteristics

Higher Level Processes

The impairment in ►saccadic eye movement in patients with basal ganglia disorders has been repeatedly demonstrated using more rigorous tests with accurate measurement of eye position [1]. Typically, the subjects are required to fixate their gaze on a spot of light (target) on the screen and, if the target steps, follow it by quickly shifting their gaze. This is called a "visually guided saccade task." Compared with age-matched control subjects, saccades (►Spontaneous Saccades) of parkinsonian patients tend to be small in amplitude (i.e., hypometric), slow, and delayed (i.e., long latency). Curiously, the deficit in saccade is often more severe if there is no visible object and the saccade must rely on memory. In a "memory-guided saccade task" a target appears briefly while the subject is fixating at the central spot and the subject has to make a saccade after a delay to the position where the target was presented. Parkinsonian patients are more impaired or selectively impaired in ►memory-guided saccades than in ►visually guided saccades. This phenomenon may illustrate the context-dependent movement deficits in Parkinson's disease, which are widely recognized among neurologists. Selective deficits in memory–guided saccades are observed in other basal ganglia disorders, including Huntington's disease. The similarity between Parkinson's and Huntington's diseases is noteworthy because they are caused by different mechanisms, the former by a loss of neurons in the substantia nigra (SN) and the latter by a loss of neurons in the caudate nucleus (CD). This suggests that the SN and the CD work together for the control of saccadic eye movement (see the sections ►caudate – role in eye movements and ►substantia nigra – role in eye movements).

How the basal ganglia might control eye movements has been studied by single unit studies using trained animals [1]. The animals were trained on the visually guided and ►saccade – memory-guided tasks. Electrical activity of single neurons was recorded with microelectrodes and was correlated with saccadic eye movements. Saccade-related activity has been found in various nuclei in the basal ganglia, including the substantia nigra, CD, ►subthalamic nucleus (STN), and ►globus pallidus (GP) [1]. Such saccade-related neurons are clustered in a sub-region of each nucleus: dorsolateral part of the pars reticulata of the substantia nigra (SNr), central-ventral part of the CD, ventral part of the STN, and dorsal part of the external segment of the globus pallidus (GPe). Anatomical studies have shown that these saccade-related parts are connected within the basal ganglia and with saccade-related regions outside the basal ganglia. For example, the saccade-related part of the CD receives inputs from the ►frontal eye field and the ►supplementary eye field in the frontal cerebral cortex [2], while the saccade-related part of the SNr projects their axons to the ►superior colliculus (SC) [3]. Note that neurons related to skeletal movements are found in different sub-regions in the basal ganglia, such as the putamen (equivalent to the CD) and the internal segment of the globus pallidus (GPi) (equivalent to the SNr). These facts are consistent with the idea that there are functional sub-divisions within the basal ganglia as well as in larger networks including the cerebral cortex and the cerebellum, each of which may form a closed-loop functional unit [4]. Recent studies, however, indicate that such functional segregation is not perfect.

Lower Level Processes

An interesting feature of the basal ganglia circuits is that they use inhibitory connections as a primary means