

## Primer

# The basal ganglia

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The basal ganglia, said Kinnear-Wilson in the 1920s, have all the clarity of a dark basement. And so it has remained for the better part of a century. There are now major new ideas about what these deep-lying structures in the forebrain may be doing. Lesions of the basal ganglia lead to devastating motor disorders, including Parkinson's disease and Huntington's disease. In addition, the basal ganglia have been implicated in a range of neuropsychiatric disorders, and basal ganglia function is disrupted in addictive states. The basal ganglia are also thought to have a major role in learning and memory. How can these structures have so many functions? Or is it possible that there is some common theme to these apparently disparate functions?

The position of the basal ganglia in the circuitry of the brain gives a clue to their function (Figure 1). They are the largest subcortical structures in the human forebrain. The basal ganglia receive inputs from the neocortex and, by way of their output nuclei, the basal ganglia nuclei project massively to thalamic

nuclei, which in turn project to the frontal cortex. This anatomy means the basal ganglia are in a prime position to influence the executive functions of the forebrain, such as planning for movement and even cognitive behaviors. In addition to this tight linkage with the frontal cortex, the basal ganglia send outputs to brainstem nuclei involved in motor control, including the superior colliculus, which controls axial orientation and saccadic eye movements.

The basal ganglia consist of several different nuclei (Figure 1), and each of these is profoundly important clinically. The striatum (made up of the caudate nucleus and the putamen) receives most of the cortical input to the basal ganglia. Degeneration of neurons in the striatum leads to Huntington's disease and related hyperkinetic disorders. The pallidum (consisting of external and internal segments) receives most of the output of the striatum. The pallidum is the site of therapeutic lesion (pallidotomy) and deep-brain stimulation procedures used to relieve Parkinson's disease. The subthalamic nucleus is a key structure controlling pallidal function, and is an increasingly favored site for deep-brain stimulation in the treatment of Parkinson's disease. The substantia nigra (with a dopamine-containing region, the pars compacta, and a

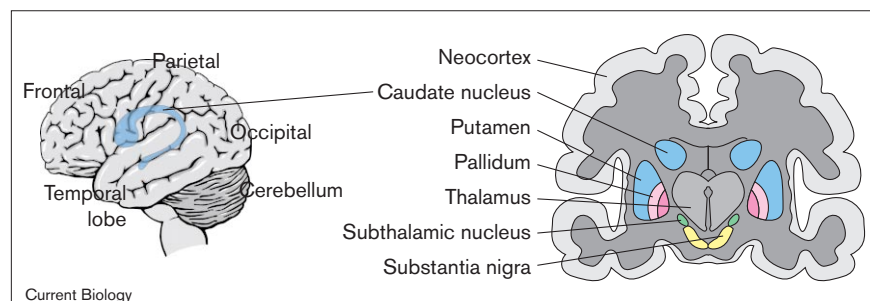
second region, the pars reticulata) is critical to basal ganglia function. Dopamine-synthesizing neurons in the substantia nigra pars compacta degenerate in Parkinson's disease and related parkinsonian disorders. The pedunculopontine nucleus of the brainstem is also associated with the basal ganglia and affects function in several nuclei of basal ganglia circuits, most notably the substantia nigra pars compacta.

### Motor system disorders

The leading model for motor disorders such as Parkinson's and Huntington's diseases is that the basal ganglia have distinct pathways that compete with each other functionally to release movement (the direct pathway) or to inhibit movement (the indirect pathway) (Figure 2). The competing pathways act like the brake and accelerator in a car. The brake–accelerator model suggests that release (disinhibition) of the thalamus by the direct pathway is opposed by the indirect pathway, which inhibits the thalamus via the additional, excitatory, subthalamic projection to the internal pallidum.

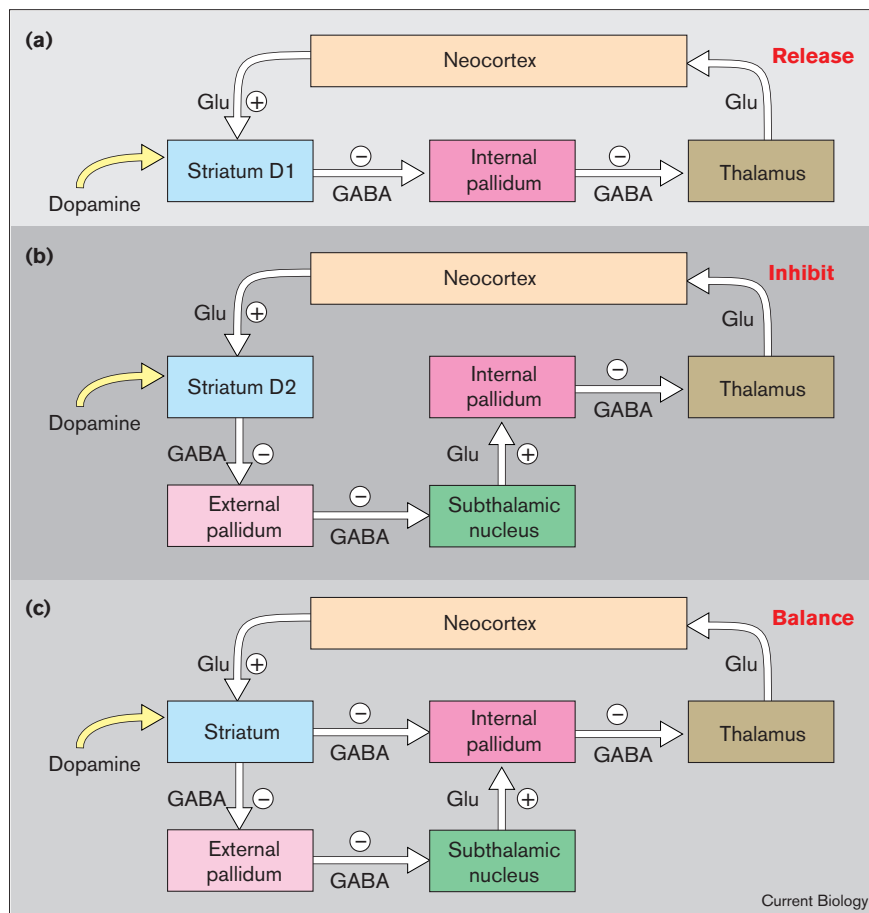
In the simplest view, the poverty of movement in Parkinson's disease results from over-activity of the indirect pathway, whereas excess movement in disorders such as Huntington's disease represent over-activity of the direct pathway. There are problems with this model, and there is also controversy about how the dopamine-containing inputs from the substantia nigra affect this system. One view is that D1-class dopamine receptors are mainly expressed on direct pathway striatal neurons and excite this pathway, whereas D2-class dopamine receptors are expressed on indirect pathway striatal neurons and inhibit this pathway. Coexpression of these receptors has also been claimed, however. It has been proposed that antagonism between the direct and indirect pathways helps select intended movements by suppressing

Figure 1



The basic anatomy of the brain showing the major regions within the basal ganglia: the striatum (blue), which is made up of the caudate nucleus and the putamen; the

pallidum (pink), which is made up of outer and inner segments; the subthalamic nucleus (green); and the substantia nigra (yellow).

**Figure 2**

The brake–accelerator model for basal ganglia motor disorders. **(a)** The direct pathway (leading to release of movement) consists of two successive GABAergic connections, from the striatum to the internal pallidum and from the internal pallidum to the thalamus. This flow diagram suggests that excitatory (glutamate; Glu) inputs from the neocortex to the striatum would disinhibit thalamic neurons. Dopamine

modulates the system mainly in the striatum, where it activates D1-class and D2-class dopamine receptors. **(b)** In the indirect pathway (leading to inhibition of movement), there is an extra step after the external pallidum, so that the subthalamic nucleus excites the internal pallidum. **(c)** Balance is achieved when these antagonistic systems are combined under normal circumstances.

unintended ones and promoting desired movements — a sculpting process for movement control.

An interesting recent development is the discovery that the torsion dystonia (*DYT1*) gene — a mutant form of the gene encoding torsin A, a chaperone protein associated with early onset dystonia — is strongly expressed in dopamine-containing neurons of the substantia nigra pars compacta. Defects in the dopamine system occurring at different ages may lead to dystonia or to Parkinson's disease.

Mutations in several genes have now been associated with hereditary forms of parkinsonism. These new findings should significantly help in understanding the cellular events underlying the neuropathology of these disorders.

#### Neuropsychiatric disorders

Neuropsychiatric symptoms in Parkinson's and Huntington's diseases have, until recently, mostly been interpreted as co-existing or secondary symptoms, but increasing evidence suggests that they may be

primary symptoms. Functional imaging methods have opened up a more direct way of detecting basal ganglia dysfunction in neuropsychiatric disorders, as these methods allow detection of metabolic brain abnormalities even where there is no evident large-scale degeneration (as is true for most neuropsychiatric disorders).

Metabolic abnormalities in the basal ganglia have been observed with PET (positron emission tomography) and fMRI (functional magnetic resonance imaging) brain imaging in patients suffering obsessive–compulsive disorder (OCD) and Tourette syndrome. In OCD, such studies have demonstrated abnormal activity in the caudate nucleus, in the orbitofrontal cortex and in the anterior cingulate cortex. These structures, together with their thalamic connections, are thought to form cortico–basal ganglia loops that are overactive or underactive when symptoms are evident. In some patients, drug treatment and behavioral therapy can help attenuate the abnormal activity. Neuroimaging studies of Tourette syndrome patients also show abnormal activity in the striatum, especially in the putamen, which includes the striatal regions receiving input from the sensory–motor cortex. Striking instances of compulsive behaviors have also been found in patients with focal lesions in the striatum or pallidum.

Brain mapping performed during deep-brain stimulation procedures suggests that the basal ganglia may directly contribute to neuropsychiatric syndromes. Sudden and severe depressive episodes have been induced by stimulation in the substantia nigra, followed by a euphoric rebound when the stimulation stops. This supports evidence from imaging experiments suggesting abnormal metabolic activity in the caudate nucleus during depression.

A large series of studies has implicated the ventral striatum

(including the nucleus accumbens), the ventral pallidum and the corresponding medial parts of the dopamine-containing cell groups of the midbrain (the ventral tegmental area) in the pathogenesis of schizophrenia. Whether dorsal striatal regions (caudate nucleus and putamen) are also involved is not clear. The fact that the prefrontal cortex is implicated in this disorder, and that the basal ganglia pathways linked to the caudate nucleus direct their outputs to prefrontal areas, raises the possibility that basal ganglia malfunction occurs in schizophrenia.

### Cortico-basal ganglia loops

The anatomy of basal ganglia connections suggests that, at least in part, these structures operate as part of recurrent circuits (loops) with the cerebral cortex. Broad subdivisions exist within these cortico-basal ganglia loops, suggesting that different loops operate in relation to different types of cortical function (for example, oculomotor versus working memory circuits). Not all cortical connections of the basal ganglia form these loops, however, and patterns of convergence and divergence within individual circuits may be crucial to their function. For example, this within-loop sorting may be a way to select particular outputs, and in turn to select particular behavioral actions.

### Habit learning

The striatum is part of the learning and memory machinery of the brain. Experimental evidence suggests that the striatum is involved in the type of procedural or implicit learning resulting in automatized responses, roughly equivalent to habits. This function is contrasted with hippocampus-based learning, which builds memories that are dependent on particular cues in the environment. This idea has been reinforced by studies of patients with Parkinson's and Huntington's diseases. In addition, my co-workers and I have found large-scale changes

in the ensemble activity of neurons in the sensorimotor striatum as rats learn a procedural task. If lesions are made in this striatal region after the period of learning, the animals have difficulty remembering how to do the task. These results suggest that the learning-related changes in striatal activity (probably accompanied by, or even resulting from, changes elsewhere in cortico-basal ganglia circuits) are necessary for the maintenance of new habits. The homologues of the basal ganglia in birds have been implicated in the highly stereotyped behavioral patterns developed in song learning. This suggests that the learning and memory functions of the basal ganglia may be highly conserved.

One important signaling mechanism for learning based in the basal ganglia occurs in the dopamine-containing neurons of the midbrain and their projections into the striatum (and into the neocortex). Inputs to the striatum from the dopamine-containing neurons have been suggested to deliver reward-predictive signals to the striatum. Interestingly, when rats are treated with cocaine or amphetamine, there is heightened activation of striosomes, one of the two tissue compartments of the striatum, and a proportionate increase in stereotyped behavior that occurs when the drugs are given repeatedly. The ventral striatum is implicated in the addictive changes that occur with drug use. Both striosomes and the ventral striatum project back to the dopamine-containing nuclei of the brainstem, and may influence these drug-related behavioral changes. This suggests that loops interconnecting the cortex, the striatum and the dopamine-containing cell groups in the midbrain are critical for reward-based learning and memory.

### A common theme?

The learning and memory functions of the basal ganglia may be related to

their importance in extrapyramidal motor disorders and neuropsychiatric disorders. In a forward model of the basal ganglia, the striatum and other basal ganglia nuclei would receive incoming signals about the current status of events (in action or mental space), as well as signals predicting future events. The cortico-basal ganglia loops running through the striatum and basal ganglia circuits would sort and combine such signals, and then influence cortical and subcortical networks responsible for the production of motor or cognitive activity. Under conditions of circuit dysfunction, at one extreme excessive and repetitive actions or thoughts could result, and at the other extreme poverty of movement or thought could be the result.

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