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 dopamine signaling.
intended 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
and I have found large-scale changes on particular cues in the builds memories that are dependent roughly equivalent to habits. This resulting in automatized responses, of procedural or implicit learning. Experimental evidence suggests that and memory machinery of the brain. The striatum is part of the learning particular behavioral actions. outputs, and in turn to select may be a way to select particular example, this within-loop sorting may be crucial to their function. For divergence within individual circuits and patterns of convergence and ganglia form these loops, however, cortical connections 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.

Key references