Basal Ganglia: Basic Principles

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Abstract

The full range of basal ganglia functions is still uncertain, but they are principally concerned with the release and suppression of cortically generated movements. They are phylogenetically old, being present in all vertebrates including the reptiles, which have essentially no neocortex. It is likely therefore that their function was originally related to aspects of motivation and homeostasis, mediated by the allocortex (limbic cortex, amygdala, and hippocampus). More recently, they have become closely associated with the neocortex (frontal sensory and motor cortices) and therefore provide a link between cognitive processes and movement.

Keywords

Basal ganglia • Cogwheel rigidity • Guam's syndrome • Huntington's disease • Hyperkinesia • Hypokinesia • Internal globus pallidus • Matrisomes • Parkinson's disease • Staining techniques • Striosomes • Substantia nigra • Thalamic nuclei

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Abbreviations

CM	Centromedial nucleus of the thalamus
GABA	Gamma-aminobutyric acid
GPe	Globus pallidus external compartment
GPi	Globus pallidus internal compartment
l-DOPA	l-3,4-dihydroxyphenylalanine a metabolic precursor of dopamine
MD	Mediodorsal nucleus of the thalamus
MPTP	1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine
NMDA	*N*-methyl-d-aspartic acid or *N*-methyl-d-aspartate
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
VA	Ventroanterior nucleus of the thalamus
VL	Ventrolateral nucleus of the thalamus

Brief History

The full range of basal ganglia functions is still uncertain, but they are principally concerned with the release and suppression of cortically generated movements. They are phylogenetically old, being present in all vertebrates including the reptiles, which have essentially no neocortex. It is likely therefore that their function was originally related to aspects of motivation and homeostasis, mediated by the allocortex (limbic cortex, amygdala, and hippocampus). More recently, they have become closely associated with the neocortex (frontal sensory and motor cortices) and therefore provide a link between cognitive processes and movement.

Anatomy and Connections

Summary of Anatomy and Function

The basal ganglia are a group of large nuclei lying deep in the cerebral hemispheres: They comprise the striatum, globus pallidus, and the subthalamic nucleus (Fig. 1). The substantia nigra, which lies within the brainstem, is functionally included. In primates, the striatum consists of the caudate nucleus and putamen, separated by the internal capsule. The globus pallidus is separable into an internal (medial) and external (lateral) segment, and the substantia nigra into a dorsal and ventral region (the pars compacta and pars reticulata). Some textbooks also include the amygdala, but it is not functionally related.

The basal ganglia receive from almost the whole cortex, and their major output is to ventrolateral nuclei of the thalamus which project back to the cortex. However, they receive no direct sensory inputs and have no direct motor outputs.

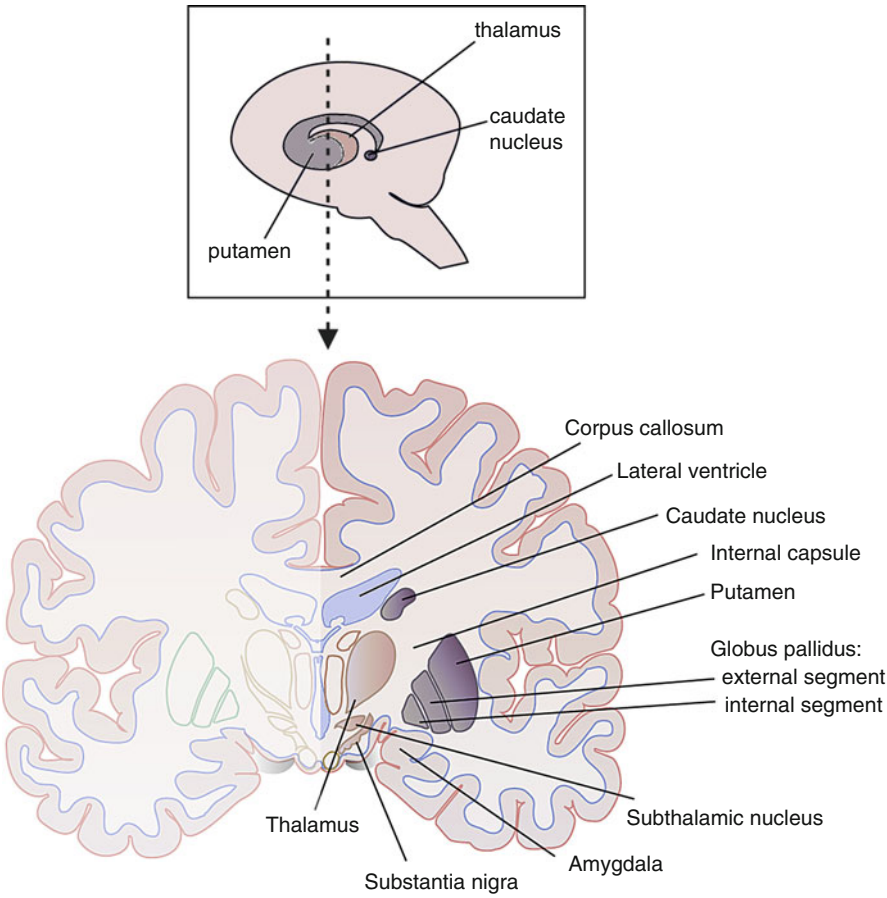

Fig. 1 The basal ganglia. The gross anatomy of the basal ganglia is shown in this transverse section through the brain (see the *inset diagram above*). In reality, the substantia nigra lies somewhat beneath and behind the subthalamic nucleus

Circuits Through the Basal Ganglia

Understanding the basal ganglia is difficult for three reasons. First, they are highly interconnected (Fig. 2). Information, rather than flowing simply through them, can flow in closed loops between the nuclei. Second, the majority of the neurons are inhibitory and act through inhibition and disinhibition. Third, the basal ganglia contain an extraordinary number of different neurotransmitters and neuromodulators, so an understanding of their pharmacology is probably at least as important as their neural connectivity. However, the circuits through the basal ganglia can be simplified as two routes: a "direct" pathway and a parallel "indirect" pathway. The balance between the two circuits is maintained by a third modulating circuit. The major diseases of the basal ganglia can then be explained by shifting the balance toward one or other pathway.

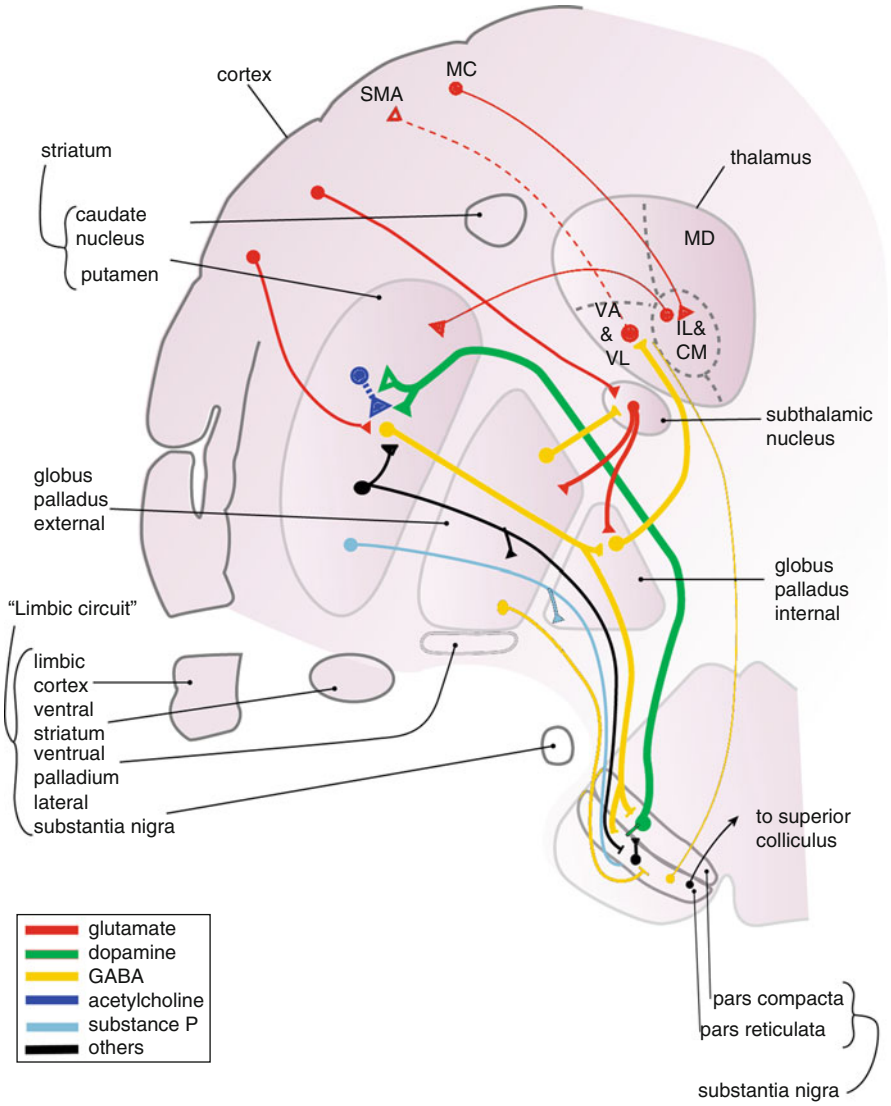

Fig. 2 Connections within the basal ganglia. The major pathways between the cortex, basal ganglia, and thalamus are indicated, color coded for the transmitter type. The *black arrow* indicates pathways with mixed or unidentified neurotransmitters

The Direct Circuit

This runs from cortex to striatum to the internal segment of the Globus Pallidus (GPi) and then to thalamus and back to cortex (Fig. 3a).

The striatum (or neostriatum): Like the striate visual cortex, this nucleus is named for its myelin stripes that can be seen under the light microscope. It is the major input

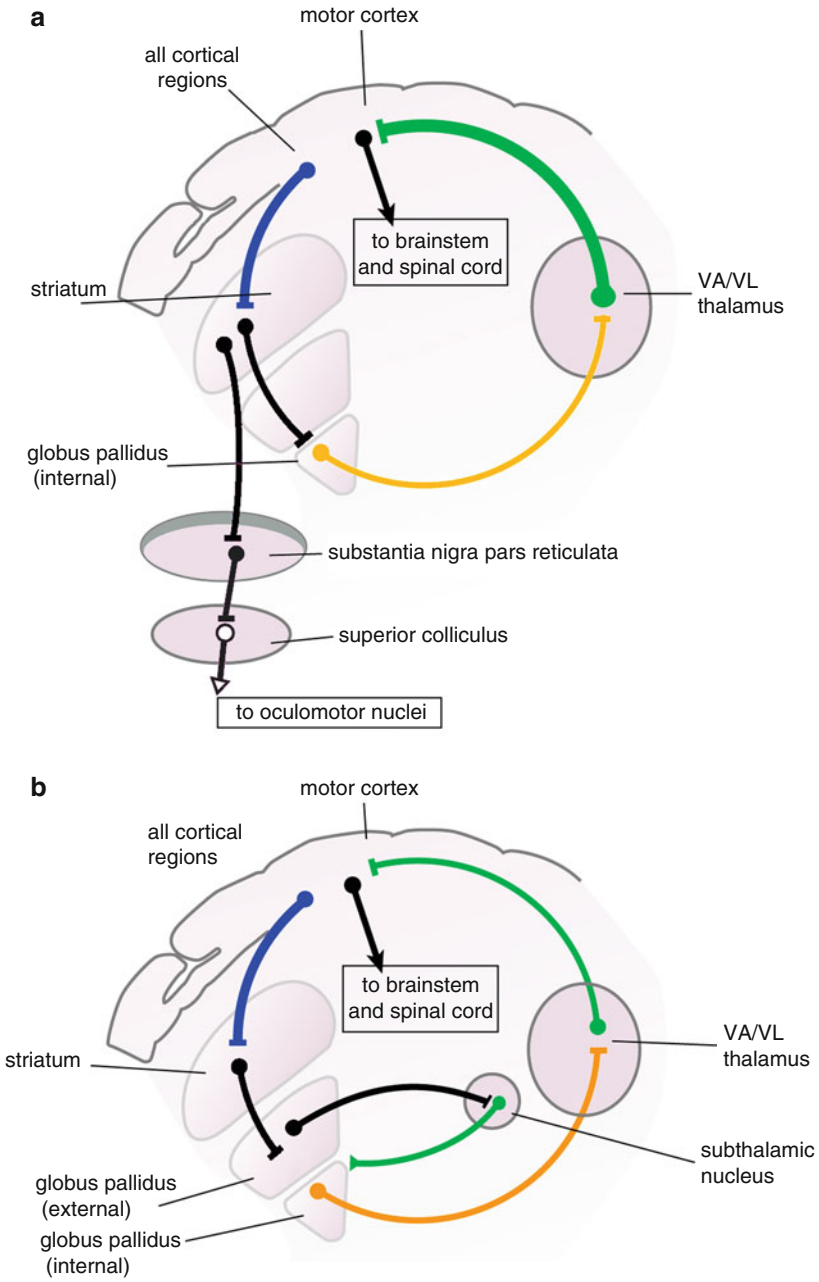

Fig. 3 This figure and Figs. 4 and 6 are simplifications based on the connectivity and anatomy shown in Fig. 2. The "direct" (**a**) and "indirect" circuits (**b**) link the cortex, striatum, pallidum, thalamus, and subthalamic nucleus. The indirect circuit has an additional connection via the subthalamic nucleus. Note that the colors used here do not correspond to those used in Fig. 2

region of the basal ganglia, receiving excitatory glutamate inputs from layer 5 pyramidal cells from almost all regions of the cerebral cortex, but especially from the frontal cortex, the motor areas, and the limbic cortex. Like all other regions of the basal ganglia, it is somatotopically arranged with separate regions of the striatum, pallidum, and thalamus activated by face, hand, and leg actions. This was somewhat unexpected, as the early ideas of basal ganglia circuits suggested that there might be a "funneling" of information through successive levels, so that less specificity was expected at sites further removed from the cortical input. Certainly, the volume of the nuclei supported the idea of a funnel, as the striatum is the largest, followed by the external and then internal segments of the globus pallidus. However, it seems that the basal ganglia circuits must be partly parallel and partly convergent.

The striatum contains largely medium sized GABAergic output cells which send an inhibitory projection to the globus pallidus; there are also excitatory cholinergic interneurons. The "direct circuit" projection to GPi contains both GABA and substance P; the indirect circuit projection to GPe contains both GABA and enkephalin.

The internal globus pallidus: GPi is structurally and functionally similar to the substantia nigra pars reticulata, and the two can be treated as equivalent. They provide the major output projection from the basal ganglia to the thalamus and brainstem nuclei; this output is also GABAergic, inhibiting the thalamic target cells.

The thalamus: The projections from the GPi and SNpr terminate in a number of ventrolateral thalamic nuclei: the ventral anterior, ventral lateral, centromedian, and mediodorsal nuclei (VA, VL, CM, and MD). Originally, it was thought that the ventral lateral thalamus provided a site through which wide areas of the cortex could converge onto the motor cortex, combining the outflow of both the basal ganglia and of the cerebellum. However, it is clear now that there is almost no overlap of cerebellar and basal ganglia outflow. Moreover, the thalamic nuclei project to different regions of the cerebral cortex, forming a set of distinct loops from cortex to basal ganglia and back to the cortex (Fig. 4). This is especially obvious in the "limbic loop" which has a somewhat separate circuit, from limbic cortex to the ventral striatum and then to ventral pallidum and the lateral substantia nigra (see Fig. 2). Hence, there are prefrontal and limbic loops projecting from the basal ganglia to frontal regions of the cortex (the prefrontal cortex and cingulate gyrus) via CM and MD and oculomotor and motor loops that project via VA and VL to the frontal eye fields and supplementary motor area (and to a lesser degree to the primary motor and premotor cortices). It is still not clear how distinct these loops are. Each loop may be further separable. For example, the prefrontal loop is actually made up of two distinct circuits. The motor loop has a clear somatotopic organization, with distinct regions in each nucleus representing arm versus leg versus face. Figure 2 shows that there are also reciprocal projections from the cortex to the CM thalamus and from the thalamus to the striatum.

Other outputs: The GPi and SNpr output cells also project to the superior colliculus, and this pathway is important for the control of eye movements. Other outputs terminate in the red nucleus, inferior olive, hypothalamus, and midbrain tegmentum.

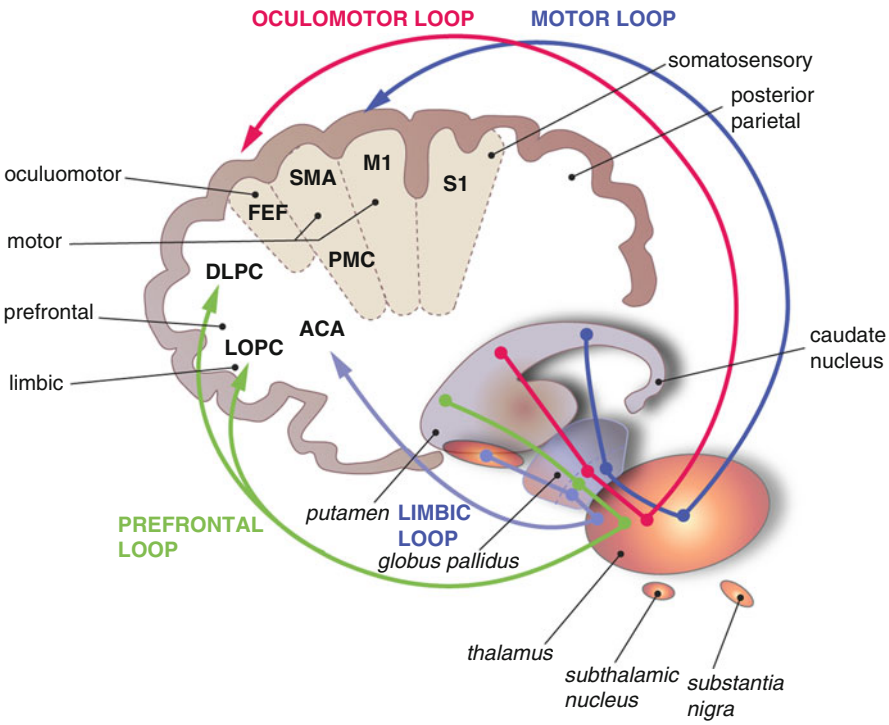

Fig. 4 Parallel loops through the basal ganglia. In this "exploded" view of the cortex and brainstem, five functionally distinct circuits are shown linking areas of the cortex with the basal ganglia, and return via the thalamus

There is an important projection to the peduncular-pontine nucleus (PPN), modulating locomotor activity (see ▶ Chap. 35, "Systems Descending from the Brainstem: Basic Principles: Other Descending Pathways and Motor Control").

The Indirect Circuit

This projects from striatum to the external segment of the Globus Pallidus (GPe) to the subthalamic nucleus and back to GPi (Fig. 3b). The striatal cells projecting to GPe contain GABA and enkephalin.

The external globus pallidus: The internal and external segments of the globus pallidus are histologically distinct. While both receive from the striatum, they have different output pathways. GPe is reciprocally connected with the subthalamic nucleus, sending an inhibitory GABAergic projection and receiving back an excitatory glutaminergic projection.

The subthalamic nucleus: This small nucleus lies beneath the thalamus, receiving from the external segment of the globus pallidus and projecting back to both segments of the pallidus and to the substantia nigra. It also receives a cortical input.

A Modulating Circuit

The direct and indirect pathways are modulated by a circuit reciprocally linking the substantia nigra and striatum.

The substantia nigra. This large nucleus has a distinct dorsal region, the pars compacta (SNpc), densely pigmented with melanin which gives it a dark appearance under the light microscope, and thus the name substantia nigra ("black substance"). The dendrites of the pars compacta cells descend into the pars reticulata, and it is thought that here they monitor activity levels. These dendrites release dopamine and also AChE, which may act as neuromodulators and thus influence their further inputs. The pars compacta cells send a crucial dopaminergic projection back to the striatum, and their terminals have the highest concentrations of dopamine in the brain. The dopamine input to the striatum is critical in maintaining the apparent balance between the direct and indirect circuits. Because there are two populations of interneurons with two different dopamine receptors within the striatum, this dopaminergic input is both excitatory (via D1 receptors, projecting to the substantia nigra pars reticulata) and inhibitory (via D2 receptors, projecting to the pallidum). This complex path can modulate striatal sensitivity to both glutaminergic and GABAergic signals from the cortex and within the striatum. ACh interneurons also influence the balance within the striatum.

The striatum has multiple transmitters and neuromodulators. The colocalization of certain neuropeptides with GABA in the striatum has revealed different populations (or "compartments") of interneurons. In fact, the striatum is far from a homogeneous structure. Staining techniques have revealed an extremely complex organization, with isolated islands or "striosomes" supported within a matrix (Fig. 5). The matrix may itself contain separate regions ("matrisomes"), and there is also evidence for gradients of transmitters across larger regions of the matrix. The dendrites of some striatal interneurons spread across different compartments; others are restricted to a single striosome or matrisome. It seems that the striosomes and matrix represent separate channels through the striatum. The motor and oculomotor circuits preferentially travel through the matrix, whereas the limbic and prefrontal circuits are preferentially localized to the striosomes, which then project to the substantia nigra pars compacta. The full significance of this organization is far from clear, but it is proposed to allow integration of modulation of sensorimotor information being processed by the cortico-striato-pallido-thalamic pathway through the basal ganglia with other information in limbic and prefrontal regions. This could be a critical mechanism to ensure motor responses are appropriate to the current state and motivations drives of the animal.

Neural Response Patterns in the Basal Ganglia

Striatal cells have low spontaneous firing rates, and a clear increase in firing rate can be seen coincident with movement. A significant proportion of cells respond to the direction of movement rather than the precise muscle activity pattern. Others are

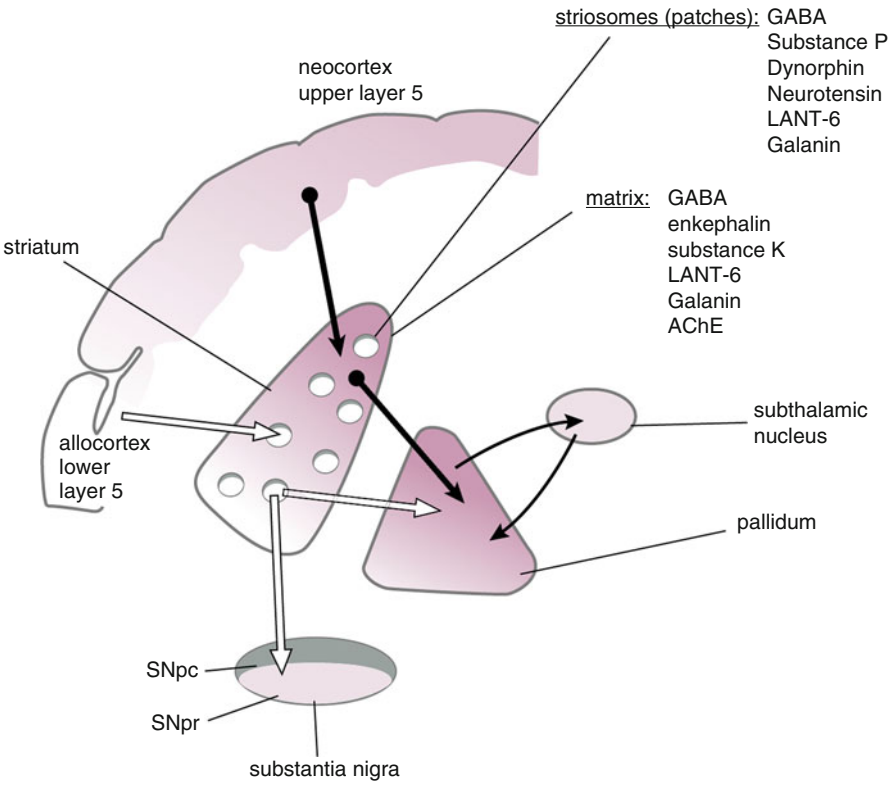

Fig. 5 The striosome/matrix organization of the striatum can be visualized by staining for acetylcholinesterase (*AChE*). Listed on the right are some of the many different transmitters, neuromodulators, and metabolic markers found in each compartment. The matrix itself may be modular with subdivisions of different neurotransmitters

muscle-related. A third group are context-dependent, firing in relationship to several stimulus modalities, and not clearly related to the actual movement made.

When rapid stimulus-triggered movements are made, the activity in the striatum starts, on average, a little earlier than muscle activation. However, the activity in the cerebral cortex and in all areas of the basal ganglia shows considerable overlap and frequently overlaps with or even follows movement onset. There is an unresolved paradox in these activation time studies: basal ganglia activity can follow that seen in the supplementary motor area (SMA), an area important in planning voluntary actions and active well before movement (see ▶ Chap. 41, "Cortical Motor Control"). However, the SMA is the cortical target of much of the outflow of the basal ganglia. Thus, the basal ganglia probably do not actually *initiate* movement themselves but may "filter" signals passing repeatedly through the closed corticobasal-cortical loop, thereby selecting out the appropriate action for the current circumstances.

The output cells of the basal ganglia, GPi and SNpr, have high spontaneous discharge rates and are briefly inhibited by the striate activity. In turn, they tonically inhibit the thalamus or brainstem targets so that they are disinhibited during movement.

Cells in the SNpr also show eye movement–related activity. Their output reaches a cortical region known as the frontal eye field and also project directly to the superior colliculus. The responses are often complex: context-dependent, stimulus-dependent, or related to saccades made to memorized targets.

The substantia nigra pars compacta cells show rather different properties. Their basic firing rate is low (<10 spikes per second), and their firing rate changes rather slowly only during the largest movements of the limbs. They seem not to relate to any specific aspects of movement, reinforcing the idea that they modulate the overall balance of the basal ganglia. Many dopaminergic neurons in the brainstem, including the substantia nigra, are modulated by reward-predicting stimuli. They have been proposed to signal a "reward error," in other words, the difference between the reward expected on performance of a particular action and the actual reward (more or less than expected). This is thought to contribute to reinforcement learning, leading to reinforcement of behaviors that are rewarded and a reduction of behaviors that are unrewarded or punished.

Cells of the subthalamic nucleus also show a slow but maintained firing rate, inhibited by the outflow of the globus pallidus.

Disorders of the Basal Ganglia

Disorders of the basal ganglia are characterized either by poverty of movement (hypokinesia) or by unwanted release of movement (hyperkinesia).

Hypokinetic Syndromes: Parkinson's Disease

The most common disease of the basal ganglia is Parkinson's disease, reaching an incidence of 1 % in the elderly. The symptoms are a great reduction in voluntary movement (hypokinesia or akinesia) and "lead pipe" rigidity of the limbs (hypertonia). Other symptoms are a reduction in movement speed (bradykinesia), masklike face (with few spontaneous facial expressions), postural instability with a pronounced stoop and shuffling gait, loss of righting reflexes and protective reflexes, and a slow 4–6 Hz tremor of the head and hands when at rest. The combination of rigidity and tremor is known as "cogwheel" rigidity.

These diverse symptoms can be summarized as difficulties in initiating voluntary movements and in modulating underlying postural reflexes, coupled with tremor. The basal ganglia are probably not involved in the guidance of movement once initiated because the movements are accurate, even if slow. The deficit in initiation can be largely alleviated by providing external stimuli. For example an otherwise immobile patient may be able to follow a chalk mark on the floor, or move out of the

way of an approaching car, but this dependence on external stimuli can also lead to "freezing" when passing through a doorway. There may also be difficulties in switching between different movement programs, for example, from running to walking.

The disease results from the loss of dopaminergic cells in the substantia nigra pars compacta, although what triggers this cell death is unclear. It seems that perhaps 80 % of the cells must degenerate before the symptoms are noticeable. In the early 1980s, a heroin analog known as MPTP (1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine) caused acute Parkinson's disease in a group of Californian drug addicts, suggesting that an unknown environmental agent may be responsible for some cases. It also provided a useful experimental model of the disease.

Figure 6a indicates how the balance of signals through the basal ganglia may be upset in Parkinson's disease. The degeneration of SNpc cells inhibits the direct striatum-GPi-thalamic circuit and disinhibits the indirect circuit. The result is profound inhibition of the thalamus and hence hypokinesia. The reasons why hypokinesia is coupled with rigidity and tremor are not clear. It may be that the basal ganglia normally have a role in inhibiting postural reflexes to allow voluntary movement.

Clinical Box: Treatment of Parkinson's Disease

The hypokinetic symptoms of the disease are greatly reduced by treatment with L-DOPA, a metabolic precursor that can enter the brain and be converted to dopamine. The success of this treatment is probably due to the fact that the SNpc cells normally contain the vast majority of all dopamine in the CNS; thus, any change in dopamine levels will preferentially affect their target cells.

The exogenous dopamine may either be taken up by those few nigrostriatal cells that remain or may swamp the enzymes that would inactivate intrinsically released dopamine. l-DOPA treatment is usually coupled with a monoamine oxidase B inhibitor; these cannot cross into the brain and therefore prevent l-DOPA converting to dopamine in the peripheral nervous system. Bromocriptine, a dopamine agonist, can also be used to directly activate the dopamine receptors. Treatment may be combined with anticholinergic agents which block the output of the acetylcholinergic interneurons within the striatum.

Unfortunately, although highly successful at reducing the akinetic symptoms, long-term L-DOPA treatment is difficult. The patient becomes increasingly sensitive to the drug and shows sudden swings from immobility to involuntary dyskinetic movements (chorea). Much more recently, fetal stem cells or dopaminergic cells have been implanted into the striatum, and seem to survive, providing an intrinsic source of dopamine. However, the effectiveness of this treatment was rather poor and it is not common. Tremor is not relieved by l-DOPA however. Small surgical lesions of the ventrolateral thalamus (thalamotomy) used to be made to reduce it, before the advent of l-DOPA treatments, and are increasingly being used to treat

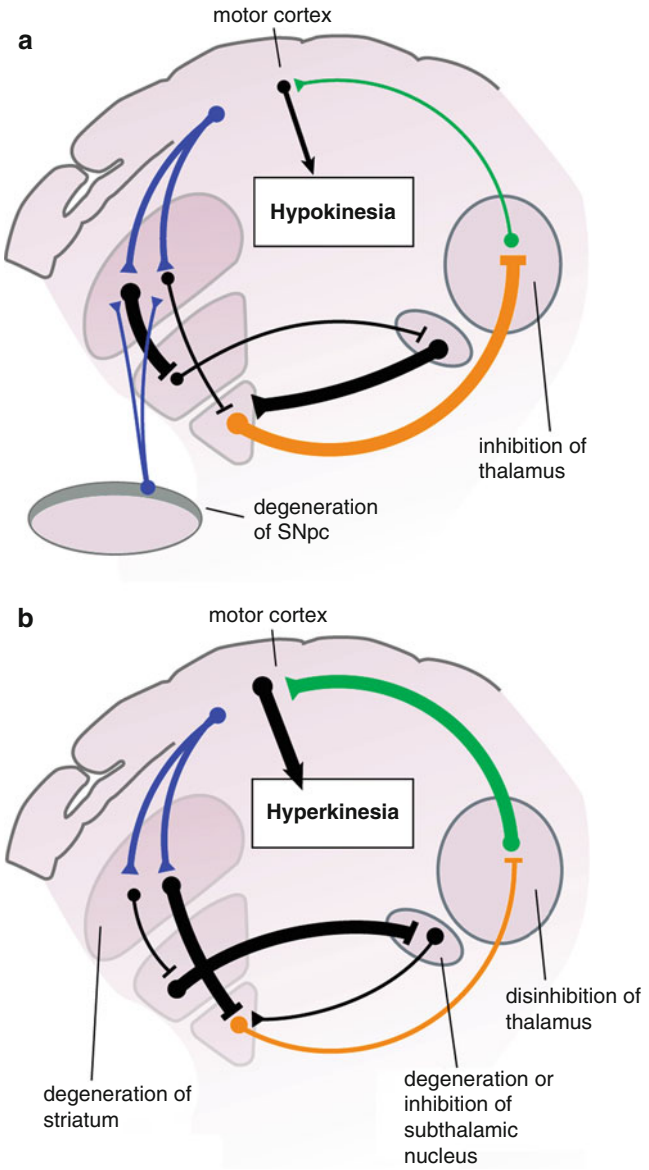

Fig. 6 Models of basal ganglia dysfunction. The pathways from Fig. 3a, b have been modified to reflect a shift in favor of the increased activity in the indirect (**a**) or direct (**b**) circuits. The thickness of the arrows indicates the amount of activity in each pathway. (**a**) Hypokinetic disorders such as Parkinson's disease which is caused by degeneration of the dopaminergic cells in SNpc which leads to disinhibition of the indirect circuit through the subthalamic nucleus and thus inhibition of the thalamus. (**b**) In hyperkinetic disorders, degeneration of the striatum (in Huntington's disease) or lesions of the subthalamic nucleus (in ballismus) lead to disinhibition of the thalamus and the unwanted release of movements

patients for whom drug treatments are no longer effective. Indwelling "deep brain stimulators" are used more often than permanent lesions nowadays.

Parkinson's disease is progressive, and in later stages may be combined with some cognitive deficits, because of secondary cortical damage, perhaps related to chronic dopamine deficiency throughout the CNS. There is often degeneration in other areas of the brainstem.

Hyperkinetic Syndromes: Huntington's Disease and Ballismus

Hyperkinetic disorders are much rarer and are characterized by the inappropriate release of movements. The motor symptoms of Huntington's disease are incessant abnormal movements. It is progressive, starting with mild clumsiness and eccentric behavior then irregular slow writhing movements of the face and limbs (chorea) and with gradually worsening dementia. Death usually follows within 10–15 years. Postmortem examination has shown a severe loss of small to medium GABAergic cells within the striatum and a reduction in GABA and its metabolic enzymes. Those cells projecting to GPe are greatest affected. There may also be a selective degeneration of acetylcholine interneurons within the striatum.

In ballism, or ballismus, the patient repeatedly flings out one or both arms, or occasionally also the legs. The movements are much more rapid than the chorea of Huntington's disease and have similarities with protective reflexes normally seen, for example, when falling over. The cause is usually a lesion of the subthalamic nucleus.

Figure 6b summarizes these changes; it is essentially reverse of the changes shown in Fig. 6a. The indirect pathway is impaired, either because of the STN lesion or because of degeneration in the striatum. Thus, the balance of the striatal activity shifts toward the direct circuit, disinhibiting the thalamus and resulting in the release of movements.

Clinical Box: Huntington's Disease

Huntington's disease is known to be caused by a dominant autosomal gene near the tip of the short arm of chromosome 4. It leads to a malfunction of NMDA glutamate receptors on striatal cells which then causes their death through excessive depolarization ("excitotoxicity"). There is also degeneration in other areas of the basal ganglia and in the cerebral cortex. There is no satisfactory treatment for the disease, although dopamine antagonists may alleviate the chorea. It seems that there may also be an NMDA-related excitotoxic response leading to Parkinsonism, which is associated with a staple diet of sago ("Guam's syndrome").

There are several well-documented genealogical studies that suggest that Huntington's disease originated from a rare mutation. For example, all cases of the disease in South Africa descended from an English immigrant from East Anglia; there is also evidence that all North American cases descended from perhaps two English immigrants. Unfortunately, the symptoms usually start in middle age, often after the patient has had children. Recent discovery of a genetic marker for the disease has raised an uncomfortable question – should someone at risk be told that they will develop an incurable, hereditary disease?

There are a number of other diseases on the basal ganglia, fortunately all quite rare, summarized in Table 1.

Table 1 Disorders of the basal ganglia

Disease	Incidence	Symptoms	Cause	Pathology	Treatment
Parkinson's disease	1:1,000 rising to 1:100 at 80 years	Slow tremor of head and hands at rest, cogwheel rigidity, akinesia, bradykinesia and postural deficits	Unknown, onset at 50–60 years; 15 % incidence of PD in close relatives	Degeneration of SNpc nigrostriatal dopamine cells, later degeneration of other brainstem nuclei	l-DOPA, anticholinergic agents. Lesions of subthalamic nucleus (successful in MPTP-treated monkeys)
		Progressive	MPTP poisoning in drug addicts		Fetal dopamine tissue implants
Huntington's disease	1:20,000	Chorea, reduced muscle tone and dementia	Autosomal dominant gene, onset at 40–50 years	Degeneration of intrastriatal and cortical cholinergic interneurons and GABAergic neurons	Dopamine antagonists may reduce chorea
		Progressive, death within 15 years			
Ballismus (hemiballism)	Rare	Wild, repeated movements of contralateral limbs, chorea	Often acute vascular accidents (stroke)	Lesions of subthalamic nucleus	Neuroleptics (antipsychotics) act by blocking dopamine receptors (and also cholinergic and adrenergic receptors)
		Gradual recovery over several weeks			Lesions of thalamus
Tardive dyskinesia	Rare	Involuntary movements of face and tongue, tics	Long-term neuroleptic drug treatment	Hypersensitivity of striate dopamine receptors	Discontinue drug treatment
		Usually temporary			
Torsion dystonia	Rare	Twisted posture of neck (torticollis), trunk, or limbs	Unknown	Sometimes lesions of globus pallidus	Neuroleptics block dopamine receptors
Wilson's disease	Rare	Dystonic posture, abnormal movements	Copper metabolism disorder	Damage to putamen	Copper chelation by penicillamine, if early, may halt progress

Outlook

The basal ganglia are a major subcortical system involved in the initiation of voluntary movements of the limbs and eyes and in the control of posture. There is a critical balance between dopamine and GABA within the striatum (among several other transmitters), and characteristic symptoms are shown if this balance is lost. Thus, dysfunction of the basal ganglia results in either excessive movement (hyperkinesia) or in movement poverty and postural disturbances (hypokinesia and dystonia). There may be important nonmotor (cognitive) functions of basal ganglia, as they have strong connections with prefrontal and limbic regions of the cortex. Key questions about the function of basal ganglia are raised by the enormous biochemical complexity of the striatal compartments, with multiple combinations of neurotransmitters in the striosome and matrix, and by the details of reward-sensitive signals in the dopaminergic pathway.

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