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Seven problems on the basal ganglia

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Our knowledge on the functions of the basal ganglia has increased enormously during the last two decades. However, we still do not completely understand the primary function of the basal ganglia. In this article, I review fundamental problems on the basal ganglia that have emerged from recent findings, and propose their solutions in the following seven topics: first, organization of the cortico–basal ganglia loop, second, limitations of the '*direct* and *indirect* pathways model', third, feedforward inhibition in the striatum, fourth, contribution of the basal ganglia to cortical activity through the thalamus, fifth, focused selection of movements and learning, sixth, firing rate model versus firing pattern model for the pathophysiology of movement disorders, and lastly mechanisms of stereotaxic surgery.

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Introduction

Since 1990, our understanding on the basal ganglia has changed substantially. The basal ganglia circuitry was simplified as represented by the *direct* and *indirect* pathways, and the pathophysiology of movement disorders was explained by firing rate changes through these two pathways. During the last two decades since then, our knowledge on the functions of the basal ganglia has increased tremendously. However, we still do not have a straight answer to the simple question, 'What is the primary function of the basal ganglia?'. This article will discuss the current problems on the basal ganglia that have emerged from recent findings. Trying to solve these problems will lead us to better understanding of their functions and better treatment for movement disorders.

Problem 1: how is the cortico–basal ganglia loop organized?

The basal ganglia receive inputs from wide areas of the cerebral cortex. The information processed in the basal ganglia returns primarily to the cerebral cortex, in particular the frontal lobe, via the thalamus, to form a cortico–basal ganglia loop [1,2]. Additional output from the basal ganglia descends to the brain stem. The cortico–basal ganglia loops are composed of several parallel, segregated, and functionally distinct, but homologous loops (Figure 1) [1,3]. The motor loop, which controls voluntary limb movements, originates from the motor cortices, such as the primary motor cortex (MI), supplementary motor area (SMA), and premotor cortex (PM), and projects to the somatomotor territories of the basal ganglia. The motor loop outputs from the basal ganglia terminate in the oral part of the ventral lateral nucleus (VLo) and the parvicellular part of the ventral anterior nucleus (VApc) of the thalamus, which then project to the MI, SMA, and PM. This loop has been confirmed by transneuronal transport of viruses [3–6]. In addition to the motor loop, the oculomotor, prefrontal, and limbic loops connect the cerebral cortical areas (the frontal/supplementary eye fields, prefrontal cortex, and limbic cortex, respectively) with the corresponding parts of the basal ganglia and thalamic nuclei. Through these multiple loops, the basal ganglia control eye movements, higher brain functions and emotions, as well as limb movements.

Despite their parallel organization, the cortico–basal ganglia loops should be viewed more as a continuum rather than subdivisions with strict boundaries. The projections from the MI, SMA, and PM partially overlap in the striatum [7–9], and a substantial number (around one-fourth) of striatal neurons receive convergent inputs from the MI and SMA. The functions of this convergence remain unknown. On the other hand, MI-receiving, SMA-receiving, and MI + SMA-receiving striatal neurons project to the segregated parts of the external (GPe) and internal (GPi) segments of the globus pallidus [10]. Thus, further convergence does not occur in the striato–GPe/GPi projections.

Another issue is the relationship between the basal ganglia and cerebellum, both of which control cortical activity through the thalamus. Anatomical and physiological studies have repeatedly shown that projections from the GPi, substantia nigra pars reticulata (SNr), and deep cerebellar nuclei (CN) terminate in different regions of the thalamus. The CN project to the oral part of the ventral posterolateral nucleus (VPLo), the caudal part of the ventral lateral nucleus (VLc), and area X of the thalamus, which then project to the MI, SMA, and PM [3,4,6,11]. The information from the basal ganglia and cerebellum reaches the motor cortices independently without interactions in the thalamus. However, local

interactions between the two inputs via thalamic interneurons and the thalamic reticular nucleus cannot be excluded. Interactions between the basal ganglia and cerebellum via the CN–thalamo–striatal pathway have also been suggested [12].

Problem 2: is the '*direct* and *indirect* pathways model' still reasonable?

The basal ganglia circuitry is considered to be composed of two major projection systems: the '*direct*' and '*indirect*' pathways (Figure 1) [2]. The *direct* pathway arises from GABAergic striatal neurons containing substance P and dynorphin, and projects monosynaptically to the GPi/SNr. The *indirect* pathway arises from GABAergic striatal neurons containing enkephalin, and projects polysynaptically to the GPi/SNr by way of sequential connections with the GPe and subthalamic nucleus (STN). In addition, dopaminergic projections from the substantia nigra pars compacta (SNc) differentially modulate the activity of striatal projection neurons in the *direct* and *indirect* pathways. Dopamine excites striatal neurons in the *direct* pathway through dopamine D1 receptors (D1Rs), while it inhibits striatal neurons in the *indirect* pathway through dopamine D2 receptors (D2Rs) [2,13•]. This '*direct* and *indirect* pathways model' has been widely accepted. However, it may be oversimplified, and has been questioned as a result of the following observations:

(1) The STN receives direct cortical inputs, and is therefore considered another input station of the basal ganglia, in addition to the striatum. The cortico–STN–GPi/SNr '*hyperdirect*' pathway conveys strong excitatory signals from the cortex to the GPi/SNr with faster conduction velocity than the *direct* and *indirect* pathways (Figures 1 and 2) [14,15]. Thus, GPi activity is influenced by signals through the *hyperdirect*, *direct*, and *indirect* pathways. The detailed information that each pathway conveys and its contribution to movement remain to be elucidated. The *hyperdirect* pathway seems to be important for inhibiting irrelevant motor programs and/or changing motor plans [15,16••,17••].

(2) This model assumes a clear distinction between the *direct* and *indirect* pathways. A recent study has shown that neurons in these two pathways exhibit different properties, such as a higher release probability for the excitatory synapses and larger *N*-methyl-D-aspartate (NMDA) receptor currents in striatal neurons in the *indirect* pathway than in the *direct* pathway [18•]. However, tracing studies have shown that some single neurons project to the both GPe and GPi [19]. Some striatal projection neurons express both D1Rs and D2Rs [20].

(3) An important issue is whether striatal neurons in the *direct* and *indirect* pathways receive similar inputs from the cortex. Neurons in the *direct* pathway receive inputs from nonpyramidal tract neurons that have intratelencephalic projections with *en passant* terminals, whereas neurons in the *indirect* pathway receive collateral inputs from pyramidal tract neurons [21]. Thus, striatal neurons in the *direct* and *indirect* pathways may receive different inputs, with the former receiving associative signals, and the latter receiving corollary discharges of descending motor commands. However, a recent study suggests that intratelencephalic neurons project to neurons in both pathways [22•]. According to electrophysiological experiments using monkeys, corticostriatal neurons originate from a population of neurons that is distinct from neurons projecting to the spinal cord and/or brain stem, and the activity of these corticostriatal neurons during behavior differs from that of other MI neurons [23]. Corticostriatal neurons are selective for specific movements, stimuli or context, whereas pyramidal tract and corticopontine neurons show muscle-like movement-related activity. Both corticostriatal neurons and pyramidal tract/corticopontine neurons change their activity well before the onset of movements, while corticostriatal neurons show later onset. To understand these distinctions, it is necessary to compare striatal neuronal activity in the *direct* and *indirect* pathways during behavior. The collaterals of pyramidal tract neurons project to the STN, and therefore, the *hyperdirect* pathway may transmit corollary discharges.

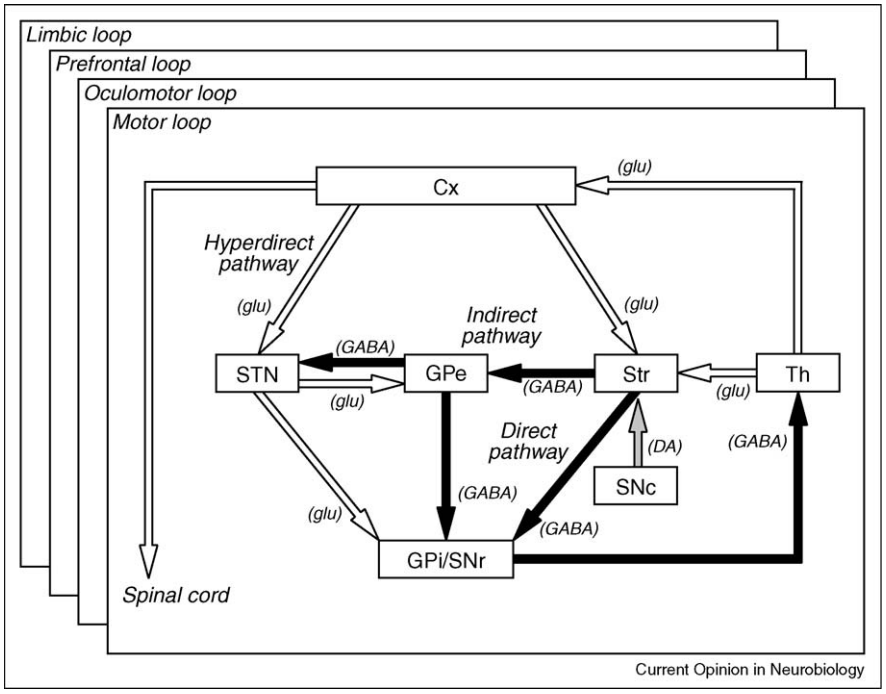
(4) Thalamic neurons send dense projections to the striatum, suggesting a short striato–GPi–thalamo–striatal circuit loop (Figure 1) [24]. The difference between the information conveyed by the thalamo-striatal projections and that by the corticostriatal projections remains to be clarified.

(5) The GPe sends GABAergic projections not only to the GPi/SNr, but also to the striatum and GPe itself through local axon collaterals [25]. Thus, the GPe may be viewed as a central nucleus projecting to multiple sites within the basal ganglia. On the other hand, GPe and GPi neurons show similar activity during behavior and in response to cortical stimulation [26,27••]. Thus, the GPe–GPi projections might be weak.

(6) The STN projects to the GPe, as well as to the GPi through axon collaterals. The STN and GPe have intimate interconnections via the STN–GPe excitatory and GPe–STN inhibitory projections, and the interconnected groups of neurons in the GPe and STN innervate the same population of neurons in the GPi [28,29]. Thus, the STN and GPe are coupled to each other and may work together.

(7) Dopaminergic projections from the SNc terminate not only in the striatum, but also in the GPe, GPi, and STN. The basal ganglia also receive serotonergic projections from the dorsal raphe nucleus [30] that encode expected and received rewards [31].

Figure 1



Basic circuitry of the basal ganglia, including the Cx–STN–GPi/SNr *hyperdirect*, Cx–Str–GPi/SNr *direct*, and Cx–Str–GPe–STN–GPi/SNr *indirect* pathways. Open and filled arrows represent excitatory glutamatergic (glu) and inhibitory GABAergic (GABA) projections, respectively. The gray arrow represents dopaminergic (DA) projections. Cx, cerebral cortex; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus (modified from Ref. [14]).

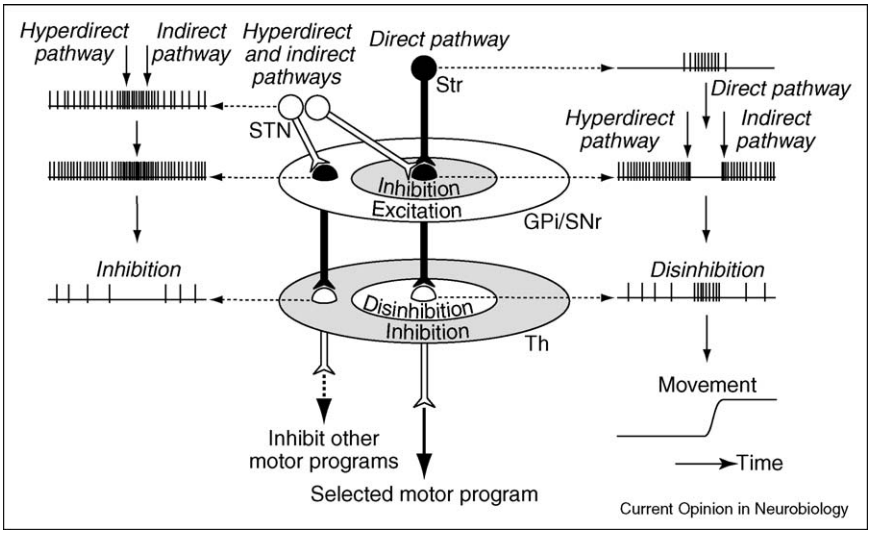
(8) In addition to fast ionotropic receptors, slow metabotropic receptors, such as $GABA_B$ and metabotropic glutamate receptors (mGluRs) transmit signals through the basal ganglia circuitry [32,33]. The functions of metabotropic receptors have yet to be determined and quantitated.

Problem 3: what kind of computation does the striatum perform?

The striatum, one of the input nuclei of the basal ganglia, is composed primarily of projection neurons (80–95%) as well as a small population of interneurons [34]. The projection neurons are GABAergic medium spiny neurons that receive glutamatergic excitatory inputs from the cortex and thalamus, and dopaminergic inputs from the SNc. They send their axons to the GPe, GPi, and SNr. In addition, they have extensive local axon collaterals that form synapses with other neighboring projection neurons. They are usually silent and fire only when they receive inputs, and are therefore described as phasically active neurons (PANs) in behaving monkeys. They fire in a somatotopically organized manner. For example, PANs in the forelimb region fire in relation to forelimb movements. The interneurons, on the other hand, lack spines and are classified into at least four groups: first, cholinergic large aspiny neurons, second, parvalbumin (PV)-containing GABAergic aspiny neurons, third, somatostatin/nitric oxide synthase-containing GABAergic aspiny neurons, and fourth, calretinin-containing GABAergic aspiny neurons. The cholinergic large aspiny neurons fire spontaneously at 2–10 Hz, are described as tonically active neurons (TANs) in behaving monkeys, and show reward-related activity. The PV-containing interneurons are electrophysiologically characterized as fast-spiking interneurons that exhibit very narrow action potentials and repetitive firing following cortical stimulation *in vivo* [35]. The activity patterns, especially during behavior, of the other interneurons *in vivo* remain to be elucidated.

Interneurons, as well as projection neurons, receive inputs from the cerebral cortex, thalamus and SNc, and synapse on projection neurons, controlling their activity. Electrophysiological studies *in vitro* and computational models suggest that the activity of projection neurons is controlled by feedforward inhibition through GABAergic interneurons and feedback inhibition through the axon collaterals of projection neurons [36•]. PV-containing GABAergic interneurons receive a powerful excitatory input from the cortex [35] and send their axons to the cell bodies and proximal dendrites of projection neurons. Through these close contacts, they produce large $GABA_A$-mediated inhibitory postsynaptic potentials

Figure 2



Spatial and temporal distribution of basal ganglia activity during voluntary movements. Signals through the *direct* pathway inhibit GPi/SNr neurons in the center area, activate thalamic neurons by disinhibition, and finally release the selected motor program. On the other hand, signals through the *hyperdirect* and *indirect* pathways have broad excitatory effects on GPi/SNr neurons in temporal and spatial domains, making clear initiation and termination of the selected motor program and inhibiting other irrelevant motor programs. Open and filled neurons represent excitatory glutamatergic and inhibitory GABAergic neurons, respectively (modified from Ref. [89]).

(IPSPs) in projection neurons, which are strong enough to delay or inhibit action potential firings in the target neurons [36•,37,38•]. Other GABAergic interneurons, including somatostatin-containing interneurons, also receive excitatory inputs from the cortex and potently inhibit projection neurons. On the other hand, projection neurons have extensive local axon collaterals that usually cover the dendritic arborization of the original neurons and other projection neurons. Most of the synapses are formed on the dendrites and spine necks, with a smaller portion on the somata. These connections are selectively distributed [39•]. D2R-containing neurons make synaptic connections both with other D2R-containing neurons and with D1R-containing neurons, whereas D1R-containing neurons form synaptic connections only with other D1R-containing neurons. However, electrophysiological studies have shown only weak functional synaptic connectivity through the collaterals of projection neurons [36•,38•], probably because of a small number of release sites and distally located synapses. These electrophysiological studies suggest that collateral inhibition between projection neurons controls local dendritic events [36•]. The functions of feedforward and feedback inhibition in the striatum of behaving animals should be investigated. Several methods could be considered, including, firstly, recording neuronal activity of striatal projection neurons and behavior in awake monkeys before and after injection of GABA receptor antagonists, and secondly, ablation of PV-containing interneurons in transgenic mice that are genetically engineered to express a target molecule for recombinant immunotoxins (immunotoxin cell targeting) [40].

Although the striatum looks histologically homogeneous, it can be divided anatomically into the μ opiate receptor-rich 'patch' compartment ('striosome') and the surrounding 'matrix' compartment. The patch and matrix have different input and output connections. Dendritic fields of projection neurons in the patch or matrix are confined within each compartment and never cross the patch/matrix border [41]. On the other hand, dendritic fields of interneurons do cross the border. Thus, information conveyed by projection neurons is processed within each patch/matrix compartment, while interneurons convey information between the patch and matrix. Projection neurons in the patch and those in the matrix are morphologically and electrophysiologically similar. The functional significance of the compartmentalization is not well understood.

Problem 4: how do the basal ganglia contribute to the cortical and thalamic activity?

The classical and widely accepted 'disinhibition theory' [42] states that inhibitory GABAergic neurons in the output nuclei of the basal ganglia fire spontaneously at high frequency, continuously inhibiting neurons in target structures, such as the thalamus (Figure 2). When striatal neurons are activated by cortical inputs, the striatal neurons inhibit GPi/SNr activity through the striato–GPi/SNr *direct* pathway. The continuous inhibition from the output nuclei to the target structures is temporarily removed (disinhibited), and neurons in the thalamus are activated. These mechanisms have been investigated in

saccadic eye movements. Indeed, SNr neurons decrease their activity in relation to saccadic eye movements, while many GPi neurons increase their activity in relation to forelimb movements. The increase-to-decrease ratio of GPi neurons, which is the number of neurons that increase their activity during movements divided by the number of neurons that decrease their activity, is larger than 1.0. The excitation of GPi neurons can be explained by the excitatory inputs from the STN, as described in the next section. The disinhibition theory predicts that a lesion of the GPi and thalamus induces involuntary movements and akinesia, respectively. However, such a lesion is not usually associated with severe motor deficits, except that hypometria [43,44] or reaction time changes are reported with a GPi inactivation. It has also been suggested that rebound excitation after IPSPs might be more important than inhibition [45].

The spontaneous activity of thalamic neurons in the area receiving input from the GPi is lower than that receiving input from the CN [46]. Continuous inhibition from the GPi on thalamic neurons might cause the lower activity. Microstimulation in the CN-receiving areas evokes movements, while no movements are evoked by stimulation in the GPi-receiving areas [47,48]. Both GPi-receiving and CN-receiving thalamic neurons show movement-related activity [49]. It is a reasonable possibility that these thalamic activity changes are caused by input from the GPi and CN. Blockade of the GPi increases the tonic discharge rate of thalamic neurons in the GPi-receiving areas, but has little effect on movement-related activity [43]. The thalamic activity may reflect not only pallidal inputs, but also other inputs, such as cortical activity via corticothalamic projections.

Thalamic activity finally reaches the cortex through the thalamocortical projections. Electrophysiological experiments have suggested two types of thalamocortical projections: the superficial thalamocortical projections that terminate in the superficial layers of the cerebral cortex (layers I and II) and the deep thalamocortical projections that terminate in the deeper layers (layers III–V) [50]. Recent anatomical studies also support two types of thalamocortical projections. Neurons in the thalamus can be classified into calbindin-positive 'matrix' cells and PV-positive 'core' cells [51]. Matrix cells project to the superficial layers of the cerebral cortex, while core cells project to the middle layers. Electrophysiological studies have shown that thalamic neurons with basal ganglia inputs terminate in the superficial layers of the cerebral cortex [52]. On the other hand, thalamic neurons with cerebellar inputs terminate in the deeper layers. Cerebellar outputs have strong excitatory effects on cortical neurons through deep thalamocortical projections and may initiate movement. In contrast, basal ganglia outputs have modulatory effects on cortical neurons and control the overall level of cortical activity through the superficial thalamocortical projections. The difference in the synaptic strength of basal ganglia and cerebellar outputs on the cortex may explain the difference in microexcitability between the GPi-receiving and CN-receiving thalamus. The contribution of basal ganglia output to cortical activity should be investigated by recording neuronal activity in the MI before and after blocking GPi activity.

The timing of basal ganglia activity in relation to movement is another important issue. Activity changes in the basal ganglia begin at movement onset, and are too late for movement initiation [53,54]. Therefore, the basal ganglia contribute to the control of on-going movements, not to the initiation of movements. However, other studies have suggested that the activity changes are much earlier [55]. The timing in activity changes of GPi-receiving and CN-receiving thalamic neurons is comparable [49]. These data should be reinvestigated using modern techniques.

Problem 5: what is the function of the basal ganglia?

Focused selection of movements

Disinhibition via the striato–GPi/SNr *direct* pathway releases a selected motor program. On the other hand, signals through the *hyperdirect* and *indirect* pathways have excitatory effects on the GPi/SNr, and therefore, have inhibitory effects on thalamic and cortical neurons (Figure 2) [15,16••,56]. Considering the onset timing and conduction velocity of cortical neurons (Figure 1), signals through the *hyperdirect* pathway first actively inhibit thalamic neurons, then those through the *direct* pathway disinhibit them, and finally those through the *indirect* pathway inhibit thalamic neurons again. Thus, signals through the *hyperdirect* and *indirect* pathways make clear initiation and termination of the selected motor program. In addition to a temporal aspect, the enhancement by differential inputs through the *hyperdirect*, *direct*, and *indirect* pathways may work spatially as well (Figure 2). Anatomical studies have shown that STN–GPi fibers arborize more widely and terminate on more proximal neuronal elements than striato–GPi fibers. Signals through the *hyperdirect* and *indirect* pathways activate GPi/SNr neurons extensively, thereby inhibiting large areas of the thalamus. Signals through the *direct* pathway, however, disinhibit thalamic neurons only in the center area. Thus, signals through the *hyperdirect* and *indirect* pathways inhibit thalamic neurons in the surrounding area, which are involved in other unnecessary competing motor programs. By way of temporal and spatial inputs to the target structure through the *hyperdirect*, *direct*, and *indirect* pathways, only the selected motor program is executed at the selected time, and other competing motor programs are cancelled. The oculomotor, prefrontal, and limbic loops seem to control the activity of corresponding cortical areas in a similar manner to the motor loop.

Learning, especially motor learning

Accumulating evidence suggests a function for the basal ganglia in motor learning, especially procedural or habit learning [57,58]. Dopaminergic neurons in the SNc and striatal neurons (projection neurons and cholinergic interneurons) show activity changes in the course of motor learning. The activity of dopaminergic neurons in the SNc may reflect a difference between a real reward and a predicted reward, supporting a 'reinforcement learning' system [59], in which animals adjust their behavior to the goal of maximizing the frequency, magnitude or both of the reinforcing events they encounter over time. Dopaminergic inputs may induce plastic changes in the corticostriatal synapses [13•,60•]. Origins of reward information to the SNc may include the striato–SNc projections from the patch compartment. Recently, the lateral habenular nucleus has been shown to transmit negative reward signals to the SNc [61•].

The above two major hypotheses may be complementary. Dopamine release from the SNc axon terminals changes the efficacy of corticostriatal synapses, that is, the synaptic weight of the *direct* and *indirect* pathways. Then, an appropriate movement is initiated by focused selection through the *hyperdirect*, *direct*, and *indirect* pathways [62••,63]. It will be important to determine whether dopamine released from the SNc terminals changes corticostriatal neurotransmission and striatal activity, especially reward-related activity, and finally results in the selection of appropriate movements.

Problem 6: what is the pathophysiology of movement disorders?

Firing rate model

Malfunctions of the basal ganglia cause movement disorders, such as Parkinson's disease, Huntington's disease, hemiballism, and dystonia, which are characterized by disturbances in the execution of voluntary movements (hyperkinetic–hypokinetic) and in muscle tone (hypertonic–hypotonic). DeLong [64] has proposed that activity imbalance between the *direct* and *indirect* pathways changes the mean firing rate of the output nuclei of the basal ganglia and induces hypokinetic or hyperkinetic disorders. For example, dopamine depletion reduces tonic excitation to striatal neurons in the *direct* pathway through D1Rs and tonic inhibition to striatal neurons in the *indirect* pathway through D2Rs [64,65••]. These changes in the *direct* and *indirect* pathways induce increased activity in GPi/SNr neurons and decreased activity in thalamic and cortical neurons, which result in akinesia. However, recent electrophysiological studies using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonian monkeys have failed to detect an expected increase in GPi activity [32,66,67,68•]. Morphological changes, including selective elimination of glutamatergic synapses on striatal neurons in the *indirect* pathway [69•] and a loss of recurrent collateral connections between striatal projection neurons [39•], were reported. However, their significance remains unclear. On the other hand, decreased GPi activity has been reported in hyperkinetic disorders, such as dystonia and hemiballism [14,70,71,72••], supporting the firing rate model.

By modifying the firing rate model, the dynamic changes in GPi activity may explain the pathophysiology of Parkinson's disease [73]. In Parkinson's disease, this model postulates that movement-related activity through the *direct* pathway decreases, and activity through the *indirect* pathway increases. These changes reduce movement-related inhibition and enhance surrounding excitation in the GPi, with little change in the mean firing rate, leading to reduced movement-related disinhibition in the thalamus and cortex, resulting in akinesia. The increase-to-decrease ratio of GPi neurons during movements is increased after MPTP-treatment [74•,75••]. Dynamic changes in the *hyperdirect*, *direct*, and *indirect* pathways are also suggested in the parkinsonian state [68•,76,77•]. On the other hand, in hyperkinetic disorders, excessive inhibition in the GPi through the *hyperdirect*, *direct*, and *indirect* pathways may induce uncontrollable disinhibition in the thalamus and cortex, leading to involuntary movements [14,72••]. To test this model, it is essential to record movement-related activity in the basal ganglia in animal models of Parkinson's disease and hyperkinetic disorders.

Firing pattern model

Oscillatory and/or synchronized activity is observed in the basal ganglia of patients with movement disorders and animal models, and disturbance of information processing in the basal ganglia is suggested [78]. Unit activity and local field potentials recorded from parkinsonian animals and patients have shown oscillatory and synchronized activity in the GPe, GPi, and STN [67,78–80,81••]. The frequency bands include the frequency of resting tremor (4–9 Hz) and the beta band (10–30 Hz). Beta band oscillation may contribute to akinesia, since treatment for akinesia with drugs or stereotaxic surgery suppresses the beta band oscillation. However, in the course of MPTP-treatment of monkeys, the appearance of parkinsonian motor symptoms precedes that of oscillatory activity [75••], which does not support the firing pattern model.

The above two models can explain the pathophysiology of akinesia, but not the mechanisms of muscle tone disorders, such as the rigidity seen in Parkinson's disease and the hypotonia seen in hemiballism. The mechanism of parkinsonian tremor is also unresolved. Tremor-related activity is frequently recorded in the basal ganglia and the thalamus, particularly the ventrointermediate nucleus (Vim). A small lesion in the Vim completely abolishes parkinsonian tremor. However, the Vim receives input from the CN, not from the GPi. These data suggest that tremor-related activity may originate in the basal ganglia

and be amplified by cerebro–cerebellar interactions to manifest tremor [82].

Problem 7: how does stereotaxic surgery work?

Recent developments in stereotaxic surgery have shown that lesions or high frequency stimulation, that is, deep brain stimulation (DBS), in the basal ganglia, ameliorates the motor disabilities of movement disorders. Nuclei that fire abnormally, such as with abnormally high or low frequency discharges or abnormal oscillatory firings, are the targets for surgery. Both small lesions and high frequency stimulation show similar clinical results. In Parkinson's disease, the GPi and STN exhibit increased firing rates, based on the firing rate model of movement disorders. Indeed, pallidotomy and subthalamotomy ameliorate parkinsonian symptoms. On the other hand, lesions in the anterior and posterior parts of the ventrooral nucleus (Voa/p) of the thalamus, which are GPi-receiving areas whose decreased activity is predicted by the model, ameliorate parkinsonian symptoms. Thus, the firing rate model by itself cannot explain the mechanism of stereotaxic surgery.

Mechanism of DBS: inhibition versus excitation

The mechanism of the effectiveness of DBS is still unclear: DBS may inhibit or excite local neuronal elements [83]. The inhibition theory is based on the observation that DBS shows similar effects as lesions. This mechanism could include: firstly, silencing neuronal activity by a depolarization block or activation of specific ion channels, and/or secondly, activation of inhibitory pathways, such as afferent inhibitory inputs and local inhibitory interneurons. GPi stimulation induces inhibitory responses in neighboring GPi neurons in human patients by the stimulation of GABAergic inhibitory afferent fibers from the striatum and/or the GPe [84]. The excitation theory is based on the fact that high frequency stimulation excites local neuronal elements as single stimulation does. This mechanism could include: firstly, 'jamming' of the conduction of abnormal activity or normalization of the neuronal activity pattern [76,85–87], and/or secondly, inhibition of output nuclei through the basal ganglia circuitry. Indeed, STN-DBS increases GPi activity through the excitatory STN–GPi projections, and GPi-DBS decreases thalamic activity through the inhibitory GPi–thalamic projections [85,86]. However, other reports show different results [88]. Repetitive stimulation of the STN produces inhibition in the GPi, while a single stimulation pulse produces excitation. Repetitive stimulation of the STN excites the GPe, which inhibits GPi activity through the GABAergic inhibitory GPe–GPi pathway, overcoming the excitatory STN–GPi pathway. Taken together, these data suggest that the mechanism of stereotaxic surgery may be an interruption in abnormal information flow through the basal ganglia circuitry in movement disorders, not a simple increase or decrease in firing rates.

Bilateral GPi-DBS has a dramatic effect on idiopathic torsion dystonia including DYT1. The GPi neurons in dystonia show low firing rates and burst and oscillatory firings. We do not know whether GPi-DBS excites or inhibits GPi activity, or whether the mechanism of DBS for dystonia is the same as that for Parkinson's disease. Benefits take weeks to months to occur. Thus, some plastic changes may occur, such as normalization of GPi activity. These questions will be answered by recording neuronal activity after using GPi-DBS in dystonia models.

Conclusions

This article has discussed current problems regarding the basal ganglia. To solve these problems, we should focus on the information flow through the basal ganglia rather than the information representation. The following experiments will be important.

(1) Neuronal activity should be recorded from behaving animals, especially from monkeys. In addition to well-established chronic experiments, we should combine electrical stimulation and/or local drug injection into the vicinity of recording neurons in order to identify the afferent inputs to recording neurons.
(2) Recording neuronal activity from animal models of movement disorders and using stereotaxic surgery in these models will be important. Many genetic mouse models of movement disorders that have been developed recently should be analyzed.
(3) Recording neuronal activity during stereotaxic surgery of human patients will also provide important clues in understanding the pathophysiology of the movement disorders.

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References and recommended reading

Papers of particular interest, published within two years, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Alexander GE, DeLong MR, Strick PL: **Parallel organization of functionally segregated circuits linking basal ganglia and cortex**. *Annu Rev Neurosci* 1986, **9**:357-381.

2. Alexander GE, Crutcher MD: **Functional architecture of basal ganglia circuits: neural substrates of parallel processing**. *Trends Neurosci* 1990, **13**:266-271.

3. Middleton FA, Strick PL: **Basal ganglia and cerebellar loops: motor and cognitive circuits**. *Brain Res Brain Res Rev* 2000, **31**:236-250.

4. Hoover JE, Strick PL: **The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1**. *J Neurosci* 1999, **19**:1446-1463.

5. Miyachi S, Lu X, Imanishi M, Sawada K, Nambu A, Takada M: **Somatotopically arranged inputs from putamen and subthalamic nucleus to primary motor cortex**. *Neurosci Res* 2006, **56**:300-308.

6. Akkal D, Dum RP, Strick PL: **Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output**. *J Neurosci* 2007, **27**:10659-10673.

7. Takada M, Tokuno H, Nambu A, Inase M: **Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex**. *Exp Brain Res* 1998, **120**:114-128.

8. Takada M, Tokuno H, Hamada I, Inase M, Ito Y, Imanishi M, Hasegawa N, Akazawa T, Hatanaka N, Nambu A: **Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey**. *Eur J Neurosci* 2001, **14**:1633-1650.

9. Nambu A, Kaneda K, Tokuno H, Takada M: **Organization of corticostriatal motor inputs in monkey putamen**. *J Neurophysiol* 2002, **88**:1830-1842.

10. Kaneda K, Nambu A, Tokuno H, Takada M: **Differential processing patterns of motor information via striatopallidal and striatonigral projections**. *J Neurophysiol* 2002, **88**:1420-1432.

11. Lu X, Miyachi S, Ito Y, Nambu A, Takada M: **Topographic distribution of output neurons in cerebellar nuclei and cortex to somatotopic map of primary motor cortex**. *Eur J Neurosci* 2007, **25**:2374-2382.

12. Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL: **The cerebellum communicates with the basal ganglia**. *Nat Neurosci* 2005, **8**:1491-1493.

13. • Surmeier DJ, Ding J, Day M, Wang Z, Shen W: **D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons**. *Trends Neurosci* 2007, **30**:228-235.
This review summarizes the effects of dopamine on striatal projection neurons through D1Rs and D2Rs.

14. Nambu A, Tokuno H, Hamada I, Kita H, Imanishi M, Akazawa T, Ikeuchi Y, Hasegawa N: **Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey**. *J Neurophysiol* 2000, **84**:289-300.

15. Nambu A, Tokuno H, Takada M: **Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway**. *Neurosci Res* 2002, **43**:111-117.

16. •• Leblois A, Boraud T, Meissner W, Bergman H, Hansel D: **Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia**. *J Neurosci* 2006, **26**:3567-3583.
This study suggests a model that selection of movements is achieved by the competition between the *hyperdirect* and *direct* pathways.

17. •• Isoda M, Hikosaka O: **Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement**. *J Neurosci* 2008, **28**:7209-7218.
This study shows that the *hyperdirect* pathway from the pre-SMA to the STN may contribute to situation-dependent switching of movements.

18. • Kreitzer AC, Malenka RC: **Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models**. *Nature* 2007, **445**:643-647.
The activity of striatal neurons in the *direct* and *indirect* pathways, which are labeled by transgenic methods, is compared in normal and parkinsonian conditions.

19. Levesque M, Parent A: **The striatofugal fiber system in primates: a reevaluation of its organization based on single-axon tracing studies**. *Proc Natl Acad Sci U S A* 2005, **102**:11888-11893.

20. Aizman O, Brismar H, Uhlen P, Zettergren E, Levey AI, Forssberg H, Greengard P, Aperia A: **Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons**. *Nat Neurosci* 2000, **3**:226-230.

21. Lei W, Jiao Y, Del Mar N, Reiner A: **Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats**. *J Neurosci* 2004, **24**:8289-8299.

22. • Ballion B, Mallet N, Bezard E, Lanciego JL, Gonon F: **Intratelencephalic corticostriatal neurons equally excite striatonigral and striatopallidal neurons and their discharge activity is selectively reduced in experimental parkinsonism**. *Eur J Neurosci* 2008, **27**:2313-2321.
The authors demonstrate that striatal neurons in the both *direct* and *indirect* pathways receive inputs from intratelencephalic corticostriatal neurons in the rat.

23. Turner RS, DeLong MR: **Corticostriatal activity in primary motor cortex of the macaque**. *J Neurosci* 2000, **20**:7096-7108.

24. McFarland NR, Haber SN: **Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate**. *J Neurosci* 2000, **20**:3798-3813.

25. Kita H: **Neostriatal and globus pallidus stimulation induced inhibitory postsynaptic potentials in entopeduncular neurons in rat brain slice preparations**. *Neuroscience* 2001, **105**:871-879.

26. Kita H, Nambu A, Kaneda K, Tachibana Y, Takada M: **Role of ionotropic glutamatergic and GABAergic inputs on the firing activity of neurons in the external pallidum in awake monkeys**. *J Neurophysiol* 2004, **92**:3069-3084.

27. •• Tachibana Y, Kita H, Chiken S, Takada M, Nambu A: **Motor cortical control of internal pallidal activity through glutamatergic and GABAergic inputs in awake monkeys**. *Eur J Neurosci* 2008, **27**:238-253.
This study shows that the activity of GPi neurons is controlled by phasic and tonic inputs through the *hyperdirect*, *direct*, and *indirect* pathways.

28. Shink E, Bevan MD, Bolam JP, Smith Y: **The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey**. *Neuroscience* 1996, **73**:335-357.

29. Smith Y, Bevan MD, Shink E, Bolam JP: **Microcircuitry of the direct and indirect pathways of the basal ganglia**. *Neuroscience* 1998, **86**:353-387.

30. Kita H, Chiken S, Tachibana Y, Nambu A: **Serotonin modulates pallidal neuronal activity in the awake monkey**. *J Neurosci* 2007, **27**:75-83.

31. Nakamura K, Matsumoto M, Hikosaka O: **Reward-dependent modulation of neuronal activity in the primate dorsal raphe nucleus**. *J Neurosci* 2008, **28**:5331-5343.

32. Kaneda K, Tachibana Y, Imanishi M, Kita H, Shigemoto R, Nambu A, Takada M: **Down-regulation of metabotropic glutamate receptor 1α in globus pallidus and substantia nigra of parkinsonian monkeys**. *Eur J Neurosci* 2005, **22**:3241-3254.

33. Kita H, Chiken S, Tachibana Y, Nambu A: **Origins of $GABA_A$ and $GABA_B$ receptor-mediated responses of globus pallidus induced after stimulation of the putamen in the monkey**. *J Neurosci* 2006, **26**:6554-6562.

34. Kawaguchi Y: **Neostriatal cell subtypes and their functional roles**. *Neurosci Res* 1997, **27**:1-8.

35. Mallet N, Le Moine C, Charpier S, Gonon F: **Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum in vivo**. *J Neurosci* 2005, **25**:3857-3869.

36. • Tepper JM, Wilson CJ, Koos T: **Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons**. *Brain Res Rev* 2008, **58**:272-281.
This review summarizes the current concepts of microcircuitry in the striatum.

37. Koos T, Tepper JM: **Inhibitory control of neostriatal projection neurons by GABAergic interneurons**. *Nat Neurosci* 1999, **2**:467-472.

38. Gustafson N, Gireesh-Dharmaraj E, Czubayko U, Blackwell KT, Plenz D: **A comparative voltage and current-clamp analysis of feedback and feedforward synaptic transmission in the striatal microcircuit in vitro**. *J Neurophysiol* 2006, **95**:737-752.
This study compares the strength between feedback and feedforward inhibitions in the striatum.

39. Taverna S, Ilijic E, Surmeier DJ: **Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson's disease**. *J Neurosci* 2008, **28**:5504-5512.
This study shows that recurrent connections between striatal neurons in the *direct* and *indirect* pathways are specific and not random.

40. Kobayashi K: **Controlled cell targeting system to study the brain neural circuitry**. *Neurosci Res* 2007, **58**:118-123.

41. Kawaguchi Y, Wilson CJ, Emson PC: **Intracellular recording of identified neostriatal patch and matrix spiny cells in a slice preparation preserving cortical inputs**. *J Neurophysiol* 1989, **62**:1052-1068.

42. Hikosaka O, Takikawa Y, Kawagoe R: **Role of the basal ganglia in the control of purposive saccadic eye movements**. *Physiol Rev* 2000, **80**:953-978.

43. Inase M, Buford JA, Anderson ME: **Changes in the control of arm position, movement, and thalamic discharge during local inactivation in the globus pallidus of the monkey**. *J Neurophysiol* 1996, **75**:1087-1104.

44. Desmurget M, Turner RS: **Testing basal ganglia motor functions through reversible inactivations in the posterior internal globus pallidus**. *J Neurophysiol* 2008, **99**:1057-1076.

45. Person AL, Perkel DJ: **Unitary IPSPs drive precise thalamic spiking in a circuit required for learning**. *Neuron* 2005, **46**:129-140.

46. Vitek JL, Ashe J, DeLong MR, Alexander GE: **Physiologic properties and somatotopic organization of the primate motor thalamus**. *J Neurophysiol* 1994, **71**:1498-1513.

47. Vitek JL, Ashe J, DeLong MR, Kaneoke Y: **Microstimulation of primate motor thalamus: somatotopic organization and differential distribution of evoked motor responses among subnuclei**. *J Neurophysiol* 1996, **75**:2486-2495.

48. Buford JA, Inase M, Anderson ME: **Contrasting locations of pallidal-receiving neurons and microexcitable zones in primate thalamus**. *J Neurophysiol* 1996, **75**:1105-1116.

49. Nambu A, Yoshida S, Jinnai K: **Movement-related activity of thalamic neurons with input from the globus pallidus and projection to the motor cortex in the monkey**. *Exp Brain Res* 1991, **84**:279-284.

50. Sasaki K: **Electrophysiological studies on thalamo-cortical projections**. *Int Anesthesiol Clin* 1975, **13**:1-35.

51. Jones EG: **The thalamic matrix and thalamocortical synchrony**. *Trends Neurosci* 2001, **24**:595-601.

52. Jinnai K, Nambu A, Yoshida S: **Thalamic afferents to layer I of anterior sigmoid cortex originating from the VA–VL neurons with entopeduncular input**. *Exp Brain Res* 1987, **69**:67-76.

53. Mink JW, Thach WT: **Basal ganglia motor control: II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters**. *J Neurophysiol* 1991, **65**:301-329.

54. Turner RS, Anderson ME: **Pallidal discharge related to the kinematics of reaching movements in two dimensions**. *J Neurophysiol* 1997, **77**:1051-1074.

55. Nambu A, Yoshida S, Jinnai K: **Discharge patterns of pallidal neurons with input from various cortical areas during movement in the monkey**. *Brain Res* 1990, **519**:183-191.

56. Mink JW: **The basal ganglia: focused selection and inhibition of competing motor programs**. *Prog Neurobiol* 1996, **50**:381-425.

57. Graybiel AM: **The basal ganglia: learning new tricks and loving it**. *Curr Opin Neurobiol* 2005, **15**:638-644.

58. Samejima K, Ueda Y, Doya K, Kimura M: **Representation of action-specific reward values in the striatum**. *Science* 2005, **310**:1337-1340.

59. Daw ND, Doya K: **The computational neurobiology of learning and reward**. *Curr Opin Neurobiol* 2006, **16**:199-204.

60. Shen W, Flajolet M, Greengard P, Surmeier DJ: **Dichotomous dopaminergic control of striatal synaptic plasticity**. *Science* 2008, **321**:848-851.
The authors show that dopamine plays a complementary role to synaptic plasticity, which is bidirectional and Hebian.

61. Matsumoto M, Hikosaka O: **Lateral habenula as a source of negative reward signals in dopamine neurons**. *Nature* 2007, **447**:1111-1115.
This study shows that the lateral habenular nucleus transmits negative reward signals to dopamine neurons in monkeys performing a reward-biased saccade task.

62. Nakamura K, Hikosaka O: **Role of dopamine in the primate caudate nucleus in reward modulation of saccades**. *J Neurosci* 2006, **26**:5360-5369.
This study observes the effects of dopamine receptor antagonist injection into the caudate nucleus while monkeys saccade to visual targets. Blocking D1Rs selectively slows reaction times to high-value targets, whereas blocking D2Rs slows reaction times to contralateral low-value targets.

63. Nakamura K, Hikosaka O: **Facilitation of saccadic eye movements by postsaccadic electrical stimulation in the primate caudate**. *J Neurosci* 2006, **26**:12885-12895.

64. DeLong MR: **Primate models of movement disorders of basal ganglia origin**. *Trends Neurosci* 1990, **13**:281-285.

65. Mallet N, Ballion B, Le Moine C, Gonon F: **Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats**. *J Neurosci* 2006, **26**:3875-3884.
Using electrophysiological methods, the authors show that striatal neurons in the *direct* pathway are inhibited, whereas those in the *indirect* pathways are activated in parkinsonian rats.

66. Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR: **Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates**. *Exp Brain Res* 1999, **125**:397-409.

67. Raz A, Vaadia E, Bergman H: **Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism**. *J Neurosci* 2000, **20**:8559-8571.

68. Rivlin-Etzion M, Marmor O, Saban G, Rosin B, Haber SN, Vaadia E, Prut Y, Bergman H: **Low-pass filter properties of basal ganglia cortical muscle loops in the normal and MPTP primate model of parkinsonism**. *J Neurosci* 2008, **28**:633-649.
The authors perform microstimulation in the MI or GPe/GPi in MPTP-treated parkinsonian monkeys and suggest that the functional connectivity between the MI and GPe/GPi is greatly enhanced after MPTP-treatment.

69. Day M, Wang Z, Ding J, An X, Ingham CA, Shering AF, Wokosin D, Ilijic E, Sun Z, Sampson AR *et al.*: **Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models**. *Nat Neurosci* 2006, **9**:251-259.
Using multiphoton imaging, the authors show that dopamine depletion leads to a rapid and profound loss of spines and glutamatergic synapses on striatal neurons in the *indirect* pathway, but not on striatal neurons in the *direct* pathway.

70. Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, Triche S, Mewes K, Hashimoto T, Bakay RA: **Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus**. *Ann Neurol* 1999, **46**:22-35.

71. Gernert M, Bennay M, Fedrowitz M, Rehders JH, Richter A: **Altered discharge pattern of basal ganglia output neurons in an animal model of idiopathic dystonia**. *J Neurosci* 2002, **22**:7244-7253.

72. Chiken S, Shashidharan P, Nambu A: **Cortically-evoked long inhibition of pallidal neurons in a transgenic mouse model of dystonia**. *J Neurosci* 2008, in press.

The authors observe neuronal activity in a transgenic mouse model of DYT1 dystonia. Cortically-evoked inhibition in the GPi is enhanced, and somatotopic arrangements in the GPi are disorganized.

73. Nambu A: **A new approach to understand the pathophysiology of Parkinson's disease**. *J Neurol* 2005, **252(Suppl 4)**:IV1-IV4.

74. • Leblois A, Meissner W, Bezard E, Bioulac B, Gross CE, Boraud T: **Temporal and spatial alterations in GPi neuronal encoding might contribute to slow down movement in parkinsonian monkeys**. *Eur J Neurosci* 2006, **24**:1201-1208.
The authors compare neuronal encoding of movements in normal and parkinsonian monkeys. After dopamine depletion, the number of neurons responding to movements is increased, and GPi neuronal responses to movements occur earlier and are prolonged.

75. •• Leblois A, Meissner W, Bioulac B, Gross CE, Hansel D, Boraud T: **Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism**. *Eur J Neurosci* 2007, **26**:1701-1713.
The authors observe spontaneous and movement-related activity in the GPi of monkeys during MPTP-treatment. Parkinsonian motor symptoms are better correlated to the disruption of movement-related activity than to the synchronous oscillations.

76. Degos B, Deniau JM, Thierry AM, Glowinski J, Pezard L, Maurice N: **Neuroleptic-induced catalepsy: electrophysiological mechanisms of functional recovery induced by high-frequency stimulation of the subthalamic nucleus**. *J Neurosci* 2005, **25**:7687-7696.

77. • Dejean C, Gross CE, Bioulac B, Boraud T: **Dynamic changes in the cortex–basal ganglia network after dopamine depletion in the rat**. *J Neurophysiol* 2008, **100**:385-396.
This result suggests that SNr neurons are driven by late inputs from the *indirect* pathway in normal conditions; however, they are activated by inputs from the *hyperdirect* pathway after dopamine depletion.

78. Bergman H, Feingold A, Nini A, Raz A, Slovin H, Abeles M, Vaadia E: **Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates**. *Trends Neurosci* 1998, **21**:32-38.

79. Levy R, Hutchison WD, Lozano AM, Dostrovsky JO: **High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor**. *J Neurosci* 2000, **20**:7766-7775.

80. Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V: **Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease**. *J Neurosci* 2001, **21**:1033-1038.

81. •• Brown P: **Abnormal oscillatory synchronisation in the motor system leads to impaired movement**. *Curr Opin Neurobiol* 2007, **17**:656-664.
This is an excellent review on oscillatory activity of the basal ganglia observed in parkinsonian patients and its suggested functions.

82. Rivlin-Etzion M, Marmor O, Heimer G, Raz A, Nini A, Bergman H: **Basal ganglia oscillations and pathophysiology of movement disorders**. *Curr Opin Neurobiol* 2006, **16**:629-637.

83. Lozano AM, Dostrovsky J, Chen R, Ashby P: **Deep brain stimulation for Parkinson's disease: disrupting the disruption**. *Lancet Neurol* 2002, **1**:225-231.

84. Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM: **Microstimulation-induced inhibition of neuronal firing in human globus pallidus**. *J Neurophysiol* 2000, **84**:570-574.

85. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL: **Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons**. *J Neurosci* 2003, **23**:1916-1923.

86. Anderson ME, Postupna N, Ruffo M: **Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey**. *J Neurophysiol* 2003, **89**:1150-1160.

87. Maurice N, Thierry AM, Glowinski J, Deniau JM: **Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus**. *J Neurosci* 2003, **23**:9929-9936.

88. Kita H, Tachibana Y, Nambu A, Chiken S: **Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey**. *J Neurosci* 2005, **25**:8611-8619.

89. Nambu A: **Globus pallidus internal segment**. *Prog Brain Res* 2007, **160**:135-150.