Pathophysiology of the basal ganglia in Parkinson’s disease

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Insight into the organization of the basal ganglia in the normal, parkinsonian and L-dopa-induced dyskinesia states is critical for the development of newer and more effective therapies for Parkinson’s disease. We believe that the basal ganglia can no longer be thought of as a unidirectional linear system that transfers information based solely on a firing-rate code. Rather, we propose that the basal ganglia is a highly organized network, with operational characteristics that simulate a non-linear dynamic system.


Understanding the role and function of the basal ganglia in Parkinson’s disease (PD) and L-Dopa-induced dyskinesia is a long-standing challenge. In the late 1980s, a model was proposed to explain how the basal ganglia are organized and how dopamine deficiency leads to motor disturbances in PD (Refs 8–11). This was facilitated by the discovery that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces a selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and a parkinsonian syndrome. The model has served us well in providing new targets for the surgical treatment of PD (Ref. 12). However, the model does not account for a variety of anatomical, physiological, experimental and clinical findings. In this article, we review the original model of basal ganglia pathophysiology with respect to the normal, parkinsonian and dyskinetic states, discuss its strengths and weaknesses, and provide a hypothesis to explain some of the apparent paradoxes.

The classical model of basal ganglia function in PD

The basal ganglia form a complex network of parallel loops that integrate cerebral regions (associative, oculomotor, limbic and motor), basal ganglia nuclei and the thalamus. The ‘motor circuit’ is the circuit that is most directly related to the pathophysiology of movement disorders, and its organization is illustrated in Fig. 1a. Cortical motor areas project in a somatotopic fashion to the postero-lateral putamen where they establish excitatory, glutamatergic synaptic connections with medium spiny neurons containing GABA. These neurons give rise to two pathways that connect the striatum to the output nuclei of the basal ganglia, namely the globus pallidus pars interna (Gpi) and the substantia nigra pars reticulata (SNr). Neurons in the ‘direct pathway’ project directly from the putamen to Gpi/SNr. They bear dopamine D1 receptors, coexpress the peptides substance P and dynorphin, and provide a direct inhibitory effect on Gpi/SNr neurons. Striatal neurons in the ‘indirect pathway’ connect the putamen with the Gpi/SNr via synaptic connections in the globus pallidus pars externa (Gpe) and subthalamic nucleus (STN). They contain D2 receptors and the peptide enkephalin (Enk). Projections from putamen to GPe and from GPe to STN are GABAergic and inhibitory. Neurons originating in the STN use glutamate as a neurotransmitter and activate neurons in the Gpi/SNr. Stimulation of neurons in the indirect pathway leads to inhibition of the Gpe, disinhibition of the STN and excitation of the Gpi/SNr. Thus, the output activity of the basal ganglia is influenced by the opposing effects of inhibitory inputs from the direct pathway and excitatory inputs from the indirect pathway. This, in turn, provides an inhibitory effect on brainstem and thalamo–cortical neurons involved in motor activities. In support of this model, experiments in monkeys demonstrate that facilitation of movement is associated with pauses in neuronal activity of Gpi/SNr neurons, and that activation of neurons from the direct and indirect pathways facilitates and suppresses motor activity, respectively. Thus, the direct and indirect pathways have opposing effects on the output function of the basal ganglia. The model proposes that dopamine modulates glutamatergic effects on corticostriatal inputs by exerting a dual effect on striatal neurons: exciting D1-receptor-expressing neurons in the direct pathway and inhibiting D2-receptor-expressing neurons in the indirect pathway.

The parkinsonian state

According to this model, the essential pathophysiological characteristic of the parkinsonian state is increased neuronal activity in the Gpi/SNr output nuclei of the basal ganglia, which leads to excessive inhibition of thalamo–cortical and brainstem motor systems (Fig. 1b). The model predicts that reduced activation of dopamine receptors, caused by dopamine deficiency, results in reduced inhibition of neurons of the indirect pathway and decreased excitation of neurons of the direct pathway. Reduced inhibition from the indirect pathway leads to overinhibition of the Gpe, disinhibition of the STN and increased excitation of Gpi/SNr neurons, whereas decreased activation from the direct pathway causes a reduction in its inhibitory influence on the Gpi/SNr. The net result is an excessive activation of basal ganglia output neurons accompanied by excessive inhibition of motor systems, leading to parkinsonian motor features. Considerable evidence supports the use of this model in the parkinsonian state (Box 1). Following dopaminergic lesions, expression of D2 receptor and preproenkephalin mRNA increases in striatal neurons...
of the indirect pathway, whereas expression of mRNA encoding the D1 receptor, substance P and dynorphin decreases in neurons of the direct pathway. In MPTP-treated monkeys, an increase in STN and GPi/SNr activity has been demonstrated using 2-deoxyglucose uptake as a marker of synaptic afferent activity, in situ hybridization of cytochrome oxidase subunit I (CO-I) mRNA as a measure of mitochondrial activity, glutamic acid decarboxylase (GAD) mRNA as a measure of GABA activity, and neurophysiological studies measuring the mean neuronal firing rate in single-cell recordings (Box 1). Furthermore, lesions of the STN and GPi induce marked improvement in motor control in MPTP-treated monkeys, which is accompanied by reduced activity in GPi/SNr neurons. These experiments provide convincing evidence that neuronal activity is increased in the STN and GPi, as predicted by the model, and serve as the basis for surgical treatments in PD designed to reduce excess neuronal activity in these structures. Indeed, lesions or high frequency deep-brain stimulation (DBS) of these regions provide dramatic benefit to PD patients and restore thalamo-cortical activity.

**Levodopa-induced dyskinesia**

The model proposes that chorea-ballism results from reduced activity in the STN, GPi and GPi/SNr neurons, the opposite of the effects seen in parkinsonism. This could result from a putaminal lesion causing decreased inhibition of GPe and consequent over-inhibition of the STN (Ref. 35), or by a lesion of the STN itself. Levodopa-induced dyskinesia (LID) is thought to occur through a similar mechanism. The model predicts that l-dopa induces dyskinesia in dopamine-deficient animals and PD patients by excessive inhibition of neurons of the putamenal-GPe projection, thereby leading to disinhibition of the GPe, overinhibition of the STN, reduced STN excitatory drive and hypoactivity in GPi/SNr output neurons (Fig. 1c). Furthermore, it is proposed that decreased output from neurons of the basal ganglia reduces their inhibitory effects on thalamo-cortical neurons accompanied by excess drive of cortical motor areas and the appearance of dyskinesia. This series of events is supported by electrophysiological studies showing increased neuronal activity in the GPe and decreased neuronal firing in the GPi during apomorphine-induced dyskinesia in MPTP-treated monkeys and PD patients.

**Problems with the classical model of basal ganglia function**

Although present notions of the organization of the basal ganglia serve as a good starting point, there are numerous clinical and experimental findings that cannot be explained or are not addressed by this model. In the normal state, there is no question that the organization of the basal ganglia is far more elaborate than assumed in the current model. The notion that dopamine has a dichotomous effect on neurons comprising the direct and indirect striato-pallidal pathways is difficult to reconcile with growing evidence that D1 and D2 receptors colocalize on most striatal neurons and that dopamine acts primarily to modulate the interaction between glutamate and dopamine receptors, rather than to excite or inhibit striatal neurons directly. The model also excludes evidence of dopaminergic innervation of extrastriatal regions including the GPe, GPi, SNr and SNc, and red arrows represent excitatory projections. The thickness of the arrows indicates the degree of activation of each projection. Note that the striatum communicates with output neurons in the globus pallidus pars interna (GPI) and substantia nigra pars reticulata (SNr) through a direct pathway, and with synaptic connections in the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN) through an indirect pathway. Dopamine is thought to inhibit neuronal activity in the indirect pathway and to excite neurons in the direct pathway. (b) In the parkinsonian state, dopamine depletion leads to disinhibition of dopamine D2-receptor-bearing striatal neurons in the indirect pathway leading to increased inhibition of the GPe, and disinhibition of the STN. The resulting overactivity in STN neurons leads to excess excitation of neurons in the GPe/SNr and overinhibition of thalamo-cortical and brainstem motor centers resulting in parkinsonism. (c) Dyskinesia induced by l-dopa is characterized by reduced activity in the STN. The classical model proposes that this is due to dopamine-induced overinhibition of striato-GPe neurons, resulting in excess inhibition of the STN and reduced activation of GPe/SNr. The net result is reduced inhibition of thalamo-cortical neurons with excess drive of cortical motor areas resulting in dyskinesia. Abbreviations: DA, dopamine; PPN, pedunculopontine nuclei; SNc, substantia nigra pars compacta; VL, ventralis lateralis. Reproduced with permission from Ref. 7.
Box 1. Observations for and against the model of the origin of motor features and L-dopa-induced dyskinesias in Parkinson’s disease

Data indicating hyperactivity in the subthalamic and pallidal output to the thalamus

Uptake of 2-deoxyglucose (2-DG), which reflects the activity of synaptic afferents, is decreased in the subthalamic nucleus (STN) of monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This indicates reduced inhibition from the globus pallidum lateralis (GPe). In situ hybridization indicates increased levels of mRNA encoding cytochrome oxidase I (CO-I), an enzyme of the respiratory mitochondrial chain which is involved in cellular metabolism, in the STN, globus pallidus pars interna (GPI) and substantia nigra pars reticulata (SNr) of MPTP-treated monkeys. In situ hybridization reveals increased levels of the mRNA encoding the enzyme glutamic acid decarboxylase (GAD), involved in the synthesis of GABA, in the GPI and SNR of MPTP-treated monkeys.

In monkeys treated with MPTP, firing frequency is significantly higher in the STN and GPI and reduced in the GPe (Refs 1,2), in keeping with a state of reduced inhibition from the GPe to the STN, which leads to increased excitation of the GPI by the STN.

Administration of apomorphine or L-dopa to rats with 6-hydroxydopamine-induced lesions or to MPTP-treated monkeys improves motor function and reduces firing frequency in the STN (Ref. 3) and GPI and increases activity in the GPe (Ref. 4).

The improvement in parkinsonian features following administration of L-dopa to MPTP-treated monkeys is accompanied by a reduction in the GAD and CO-I mRNA levels in the GPI, SNR and STN (Refs 5-7).

Lesion of the STN in MPTP-treated monkeys improves parkinsonian features and reduces hyperactivity in the GPI/SNR (Refs 8,9).

Pallidotomy and deep-brain stimulation (DBS) of the STN or GPI in patients with PD can induce marked clinical improvement and reactivate cortical motor areas as shown by positron emission tomography and electrophysiological studies.

Problems with the model

In situ hybridization indicates that levels of GAD and CO-I mRNA are not reduced in the GPe in monkey and rat models of PD compared with control values.

In MPTP-treated monkeys with L-dopa-induced dyskinesias (LID), levels of GAD and CO-I mRNA in the GPe are not augmented compared with the parkinsonian state, as predicted by the model.

Although the expression of GAD and CO-I mRNA in the GPe and STN of MPTP-treated monkeys with LID is reduced compared with the parkinsonian state, it remains above normal levels. According to the model, however, it should be reduced below normal levels, in keeping with hypoactivity of the STN and GPI.

2-DG uptake in the GPe of parkinsonian monkeys with LID is not reduced compared with untreated MPTP-lesioned monkeys and, therefore, increased inhibitory afferent activity from the striatum cannot be confirmed. Pallidotomy eliminates LID in PD and in patients with hemiballismus.

Pallidotomy, thalamotomy or DBS of the pallidus, thalamus and STN do not impair motor function.

References

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on reducing the excess neuronal activity in STN and GPi. Indeed, such therapies provide marked improvement in parkinsonian motor features\(^{23}\). However, the model provides no insight into the pathophysiology of the specific motor abnormalities that are found in PD (see Ref. 52 for review). For example, dystonic and simple movements, such as arm swinging and blinking, automatic but complex muscle contractions, as those involved in walking, simultaneous and sequential movements, and selection of the appropriate degree of muscle activity in voluntary movements can all be impaired to different degrees in different individuals. External stimuli can have dual, and opposite, effects on motor function. On the one hand, ongoing motor actions can be interrupted by sensory stimulation; an example is freezing while walking in response to a visual stimulus. On the other hand, movement execution might improve when patients are given an external cue\(^{53,54}\). These observations illustrate the difficulty explaining the different aspects of akinnesia and bradykinesia that are seen in PD simply as the result of an augmentation in the inhibitory output from the basal ganglia. A similar analysis can be made with respect to rigidity, which typically accompanies akinnesia in PD (Ref. 55).

The situation with respect to tremor is even more complex. PD is characterized by a resting tremor, but this is not apparent in all PD patients and, in the early stages, the tremor can be predominantly postural. Lesions of the ventro-intermediolateral nucleus of the thalamus consistently ameliorate tremor, but do not improve other parkinsonian features. By contrast, dopaminergic agents frequently improve bradykinesia and rigidity, but not tremor. Tremor is associated with rhythmic synchronous neuronal discharges in the basal ganglia (GPe, GPi and STN) and thalamic nuclei\(^{56}\). These same neurons are activated during passive or active movement of the affected body part, perhaps explaining why PD tremor frequently stops during voluntary movement\(^{57,58}\). Blocking neuronal activity in any of these basal ganglia or thalamic structures halts tremor. Lesion of the voluntary cortico-spinal motor pathways also stops tremor, although this also impairs voluntary movement. The question is, how does dopamine deficiency lead to oscillatory activity in the basal ganglia? Slow (<2 Hz), rhythmic, self-perpetuating discharges are described in organotypic cultures linking neurons of the STN and GPe (Ref. 39). The membrane characteristics of STN neurons appear to make them especially prone to discharge in a repetitive, bursting mode\(^{59}\) and hyperpolarizing them with GABAergic drugs enhances this tendency\(^{60}\). It might be that dopamine deficiency, acting at different levels of the basal ganglia, increases the likelihood that synchronous firing will occur, with feedback loops resulting in the generation of self-maintained oscillatory activity. Whatever the mechanism, why tremor only occurs in some PD patients, and why medical and surgical therapies differentially affect tremor and other motor features, is not accounted for by the present model.

Despite these limitations, lesions or deep-brain stimulation of the STN and GPi can provide dramatic amelioration of parkinsonian motor features. Such an effect suggests that hyperactivity of STN-GPi projections leads to the development of parkinsonism in an all-or-nothing fashion. Here too, however, more detailed examination reveals that the situation is more complex than suggested by the model. Improvement in motor function following surgery is not homogeneous\(^{60,62,63}\). Tremor and bradykinesia tend to be substantially improved, but other features, such as repetitive tapping or the pegboard test, are not, and can even deteriorate. Clinical effects also depend upon the topography of the lesion\(^{64}\). Lesions in the rostral GPi have a profound antidysskinetic effect, caudal lesions are more effective against tremor and lesions in the middle of the GPi provide the best antiparkinson effects. It is likely, therefore, that the different motor manifestations in PD are mediated by more complex pathophysiological mechanisms than are envisaged in the classic model\(^{14,55}\).

Experimental findings. Metabolic and neuropathological studies also disagree with the present explanation for the origin of increased activity in the STN (Refs 64,65) leading to augmented excitatory activity in the GPe/SNR. The model suggests that overactivity of the STN is caused by hypoactivity of the GPe which, in turn, results from the loss of the inhibitory influence of dopamine on striatal neurons of the indirect pathway (Fig. 1b). However, the chain of events leading to STN and GPe hyperactivity in the parkinsonian state is not clearly established\(^{66-68}\). Studies in MPTP-treated monkeys and patients with PD indicate that these conditions reduce the rate of neuronal firing in the GPe, particularly compared with the GPe (Refs 26,39,69). However, metabolic measures of cell activity, such as the levels of CO-I mRNA, increase rather than decrease in the GPe of MPTP-treated monkeys\(^{24}\) and rodents lesioned using 6-hydroxydopamine (6-OHDA) (Ref. 67). Similarly, expression of GAD mRNA increases in the GP of rats with 6-OHDA lesions\(^{50}\) and is normal (not reduced) in the GPe of MPTP-treated monkeys\(^{55}\). In addition, increased firing of the STN in parkinsonian models occurs before depletion of striatal dopamine in 6-OHDA-lesioned rats\(^{67}\) and is not accompanied by a reduction in the discharge rate of the GPe in MPTP-treated monkeys\(^{48}\). These findings suggest that the origin of STN hyperactivity in the parkinsonian state is not as simple as suggested by the model, and might not depend solely on a reduction in inhibitory tone from GPe (see later).

In interpreting this data, one must consider that, because in situ hybridization studies do not identify the different subdivisions (motor, associative and limbic) within regions of the basal ganglia, regional changes might be missed. Also, single-cell recordings evaluate only a small number of neurons and might not accurately reflect activity of the majority of nerve cells. Nonetheless, one must consider that the discrepancies between the predictions of the model and metabolic markers of GPe activity are real. One explanation for these differences could relate to the reciprocal connections that exist between the GPe and STN. STN axons that project to the GPe form thin, highly branched collaterals arranged in a dense network around large numbers of dendrites and somata\(^{70}\). By contrast, striatal afferents to the GPe have fewer collaterals that establish close synaptic contact with the proximal segment of GPe axons. This arrangement suggests that the STN might exert a widespread, uniform excitatory effect on the GPe, whereas the striatum might have more powerful inhibitory actions on individual neurons\(^{71}\). The consequence of this in the parkinsonian state could be that increased excitatory drive from the STN enhances...
proposes that depletion of dopamine in the striatum renders striatal neurons in this pathway hypoactive, but this has not been confirmed by electrophysiological or metabolic measurements. Previous studies implicating D1-bearing striatal neurons in the pathophysiology of parkinsonism are based on observations that D1 receptor agonists elicit motor responses. These must now be reinterpreted with the knowledge that D1 and D2 receptors colocalize on neurons that project from the striatum and that anatomical connections between striatal neurons increase markedly in the dopamine-denervated state. Finally, a model for the organization of the basal ganglia in the parkinsonian state needs to take into account the observation that the STN and PPN provide excitatory inputs to the SNc, and that overactivity of these structures might contribute to the neurodegenerative process. In support of this concept, cell loss in the SNc is prevented by lesion of the STN in 6-OHDA-lesioned rodents and by PPN lesions in monkeys treated with MPTP (Ref 79).

**In l-dopa-induced dyskinesia**

We have recently reviewed the pathophysiology of LID and problems with the current model (see Box 1). The model predicts that dyskinesia results from reduced neuronal firing in GPi and SNr neurons following increased GPe activity and excess inhibition of the STN. There are data to support this model. Administration of l-dopa or apomorphine to MPTP-treated monkeys or patients with PD is associated with a significant increase in the firing frequency of GPe neurons and a reduction in GPi firing rate, which is further depressed as dyskinesias develop.

Analysis of the ratio of the GPe:GPi firing frequency in different motor states provides a clue as to the pathophysiology of LID (Fig. 2). Usually, the firing rates in the GPe and GPi are similar. In the parkinsonian state, however, the GPe:GPi ratio is lower than normal (<0.75) because of the large increase in GPi firing frequency. In chorea-hemiballismus, which occurs following an STN lesion, the ratio is further reduced (0.4–0.6) because the diminished excitatory drive to both structures causes them both, and especially the GPe, to fire at very low rates. However, in l-dopa-treated parkinsonian monkeys and PD patients who have developed dyskinesia, the ratio is >1.5. This is higher than normal, and the opposite of what occurs in dyskinesia induced by a lesion of the STN. An increase in the GPe:GPi ratio during LID is consistent with predictions based on the model. Measurement of metabolic activity by analysis of the ratio between expression levels of GAD and CO-I mRNA gives comparable results (Fig. 2). It appears, therefore, that LID might be associated with excessive activation of the GPe and that this could reduce neuronal activity in the GPi directly, through inhibitory projections between the GPe and GPi, and indirectly, by blocking the excitatory effect of the STN on the GPi.

Although these data indicate that reduction in the GPe-firing frequency is a factor in the development of LID, neurophysiological, metabolic and clinical studies suggest that LID cannot be attributed exclusively either to increased GPe activity or to a reduction in the activity level of GPi neurons. Expression of preproenkephalin mRNA, which is thought to reflect activity in neurons that project from the striatum to the GPe (Refs 19, 20), is increased further in LID, above the already augmented levels associated with dopamine lesions.

![Graph](image-url)
This suggests inhibition, not activation, of the GPe and initially, at least, seems inconsistent with the classic model. However, it has recently been proposed that ENK might reduce the release of GABA through a modulatory effect on action potentials arriving at the synapse\(^6\), so that increased preproenkephalin levels might represent a compensatory response to excessive stimulation of D2-receptor-bearing striatal neurons by dopamine. However, a recent study in PD patients finds no evidence for a reduction in GPI firing rates on LID, below that obtained in the ‘on’ state\(^6\). Furthermore, electrophysiological studies in dyskinetic monkeys indicate that changes in the neuronal firing rate in the GPe and GPI are heterogeneous, and that neighboring neurons in these structures either increase or decrease firing frequency\(^69\).

Perhaps the strongest argument against GPI hypoactivity as the primary mechanism for the development of LID is the finding that pallidotomy, which by definition reduces GPI neuronal output, consistently ameliorates, rather than induces, dyskinesia\(^85\)\(_8\). This has led to the concept that LID results from abnormal firing patterns in output neurons of the basal ganglia\(^7\)\(_1\),\(_3\)\(_7\),\(_8\). We envision that the firing pattern in GPI neurons is a signaling code that communicates information about the selection of correct motor programs from the basal ganglia to motor regions of the cortex. We believe that the neuronal firing pattern comprises a number of factors in addition to firing frequency. These include the degree and duration of bursting activity, the length of interpotential pauses, and the degree of temporal and spatial neuronal synchronization. GPI output to the cortex cannot simply be analyzed in terms of the firing rate of any given set of neurons, or by the overall rate of discharge. Rather, it is the pattern of GPI activity that is transmitted to the cortex that codes for the facilitation or inhibition of normal and abnormal movements\(^7\)\_.\(_8\). This hypothesis suggests that it is the disruption of an abnormal firing pattern in GPI output neurons, rather than a change in firing frequency per se, that accounts for the clinical benefits associated with pallidotomy.

**Revisiting the model of the basal ganglia in PD and LID**

The role of the basal ganglia in movement control has, until now, been thought of as a serial and hierarchical process. Accordingly, proper selection and execution of a desired movement is thought to follow a sequence of excitatory and inhibitory events\(^5\)\(_7\), within specific cortico–basal ganglia–cortical loops\(^6\)\(_9\)\(_1\)\(_4\)\(_7\). This assumes that the motor system uses an algorithmic approach to execute motor programs and that the basal ganglia aids in the selection and operation of these motor programs in an ‘automatic’ fashion\(^6\)\(_9\). This model has been reinforced by its success in predicting the effect of lesioning the STN and GPI in PD. However, several features are at odds with this concept. First, the anatomy of the motor circuitry of the basal ganglia is much more complex than envisaged by the original model. The ‘motor’ basal ganglia is not only arranged in separate parallel circuits\(^16\)\(_9\), but each cortical motor area, such as area 4, area 6, the supplementary motor area (SMA) and the dorsal prefrontal cortex (DLPFC), is organized in a somatotopic manner\(^5\)\(_9\)\(_4\)\(_7\). For example, of the GPI neurons that represent the arm, those that project to SMA are dorsolateral, those that project to the premotor cortex are ventrolateral, those that connect to area 4 are in between these two groups and those projecting to the DLPFC are dorsomedial\(^5\)\(_9\)\(_1\)\(_3\). A similar, distinct distribution is present with regard to the frontal eye fields\(^9\). This segregated anatomical organization has a physiological significance. For example, SMA-related neurons primarily fire tonically for about 1–2 seconds in preparation for movement, whereas area-4-related neurons fire phasically approximately 100 ms before the onset of movement\(^5\). This functional specificity can be quite selective. Thus, a large proportion of pallidal neurons discharge only in relation to a specific task and only some change activity during one of several different sequences of a motor paradigm\(^9\). By contrast, other neurons discharge with the execution of a given movement and are activated after movement onset, but before the next in sequence\(^9\). There also seems to be a relationship between the physiological function and the anatomical location of GPI neurons. More dorsally placed GPI neurons which project to the DLPFC, SMA and cingulate cortical areas are mainly involved in preparatory tasks and are activated before movement onset\(^5\)\(_9\)\(_4\)\(_7\), whereas neurons located more posterocentrally, which are mainly connected with premotor areas 6 and 4 (Ref. 90), tend to discharge at, or just after, movement onset\(^5\)\(_9\)\(_7\). It is tempting, therefore, to suggest that the variety of motor manifestations associated with deple- tion of dopamine in PD is mediated by specific alterations in the firing patterns of these different motor loops\(^6\)\(_4\)\(_7\).

It appears that the motor circuits of the basal ganglia should be considered as a complex network formed by discrete and finely arranged cortico–basal ganglia–cortical parallel motor loops, which provide positive feedforward signaling for motor preparation and execution, and ‘internal’ circuits, which mainly serve a feedback-stabilizing function (Fig. 3).

**Cortico–basal ganglia–cortical loops**

These include cortico–striatal and cortico–STN projections. Cortico–striatal glutamatergic projections activate medium spiny neurons in both the direct and indirect pathways and thereby induce inhibition or excitation of GPe/SNr output neurons with respective facilitation or inhibition of movement\(^9\)\(_6\)\(_9\). The prominent role of neurons of the direct pathway in the performance of complex oculomotor and manual movements has been demonstrated in monkeys\(^6\)\(_6\)\(_9\)\(_8\)\(_9\)\(_9\). The role of the indirect pathway is not so clearly established. Focal activation of the sensorimotor cortex induces expression of immediate–early genes (IEGs), encoding c-Fos and Jun-B, primarily in enkephalinergic striatal neurons. This suggests preferential involvement of neurons of the indirect pathway in these behaviors\(^10\)\(_1\)\(_0\)\(_2\). However, in these studies, animals were anesthetized and the sensorimotor cortex was activated by local infusion of picROTOXIN or electrical stimulation, not by physiological movement. Cortico–STN projections are fast-conducting monosynaptic neurons\(_7\)\(_9\), which are activated together with cortico–spinal projections during movement\(_5\)\(_6\)\(_9\)\(_7\). Thus, activation of cortical motor areas has rapid and powerful disynaptic effects on the GPI/SNr that are either inhibitory, through the direct pathway, or excitatory, through the STN (Fig. 3). This arrangement makes these two projections well suited for the control of repetitive movements and learned motor sequences. By contrast, the polysynaptic indirect pathway, which
also has an excitatory effect on output activity of the GPi/SNr, is more likely to be involved in complex tasks, perhaps during the motor-learning process.

**Internal circuits of the basal ganglia**

The internal circuits of the basal ganglia are closed loops seemingly arranged to modulate the excitability of the basal ganglia itself. Four such internal circuits have been identified: (1) the CM/Pf-striatum-GPi-CM/Pf circuit, which is probably a positive feedback loop; (2) the CM/Pf-STN-GPi-CM/Pf circuit, which is most probably a negative feedback loop; (3) the STN-GPe-STN excitatory-inhibitory circuit, which functions as an anti-stabilizing loop; and (4) the GPe-GPI circuit, which can be viewed as an ‘open-interconnected loop’, by which the STN induces dual effects. These include a direct monosynaptic excitatory effect and a polysynaptic inhibitory effect owing to excitation of GPe fibers which project to GPi. These circuits are illustrated in Fig. 3. An important feature of these ‘internal’ circuits is that the striatum, CM/Pf and STN receive direct projections from motor regions suggesting that they have other functions in addition to modulating output activity of the basal ganglia. In addition to the above, the PPN in the brainstem is likely to have an important role in motor function in both normal and pathological conditions. It receives excitatory and inhibitory inputs, from STN and GPi, respectively and, in turn, provides excitatory innervation to CM/Pf, STN and SNc (Ref. 49). The possible importance of the PPN in PD is illustrated by the fact that lesions induce parkinson-like disturbances in gait and posture suggesting that cell bursting under some circumstances, protecting against MPTP toxicity in monkeys. The nigrostriatal dopaminergic projection to the striatum becomes acquired and automated. In the early stages of learning, a complex task is executed by relying on the associative prefrontal cortex and the anterior basal ganglia, Parkinson’s disease and levodopa therapy. TINS supplement

**Conclusions and perspectives**

The basal ganglia can no longer be thought of as a simple, unidirectional system that transfers information based solely on a firing-rate code. Rather, it must now be considered a highly organized network, with operational characteristics that simulate a non-linear dynamic system. Different parts of the network might be activated, depending upon circumstances. For example, Hikosaka et al. provide evidence of the involvement of different motor loops as a sequential task becomes acquired and automated. In the early stages of learning, a complex task is executed by relying on the associative prefrontal cortex and the anterior basal ganglia, Parkinson’s disease and levodopa therapy. TINS supplement

**Fig. 3. A modern view of the motor circuitry of the basal ganglia.** Somatotopically-organized parallel projections form closed loops (black arrows) between the motor cortex, the basal ganglia and the motor cortex. Several horizontal loops provide ‘internal’ stabilization of basal ganglia activity. The centromedian-parafascicular complex (CM/Pf) forms a CM/Pf-striatum-GPi-CM/Pf positive feedback loop (blue arrows) and a CM/Pf-STN-GPi-CM/Pf negative feedback loop (red arrows). The STN controls the activity of the GPi through a direct STN-GPi monosynaptic excitatory connection and an STN-GPe-GPI excitatory-inhibitory loop (green arrows). The GPe exerts a reciprocal inhibitory effect on the STN. Dopaminergic modulation of the striatum, STN, GPe and SMA motor cortex is indicated by grey arrows. Brainstem loops are not represented for the sake of simplicity. Abbreviations: GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; SNc, substantia nigra pars compacta; SMA, supplementary motor area; STN, subthalamic nucleus; VL, ventrolateral.
ganglia. However, as the sequence becomes routine, premotor and primary motor areas and the posterior basal ganglia are predominantly engaged in the task. The nigrostriatal dopamine system plays an essential modulatory role during this learning process. These plastic changes are likely to reflect the macro-organization of the network, rather than changes in individual loops and synapses. Indeed, present evidence suggests that the basal ganglia is not only involved in movement control, but also in planning, ‘working memory’ and emotion, all of which may be abnormal in PD. We have concentrated on the motor system because of its obvious relevance to PD, but it is possible that the basal ganglia might have many other roles. Nevertheless, we believe that thought, motivation and emotion can be intimately linked to action, and it might be that integrating these different aspects of behavior is an essential characteristic of the basal ganglia network.

We hypothesize that the tonic dopaminergic system and the internal circuits of the basal ganglia are designed to maintain the stability of the motor control network. Dopamine depletion destabilizes this network and leads to large increases in neuronal synchronization and oscillatory activity in several basal ganglia loops. PD features become evident when the self-stabilizing loops of the basal ganglia fail in their compensatory role leading to a drastic shift in neuronal activity. Surgical lesions of the STN or GPi regain a certain level of equilibrium by eliminating major sources of instability in the network. Interruption of such circuits is not accompanied by overt motor deficits because of the widespread and non-serial organization of the basal ganglia–motor system, but could lead to motor defects under special circumstances where critical components of the network are required. Examples of such situations are the need to change a motor behavior when an unexpected event occurs, learning a novel task or undertaking fine and precise manual tasks. Indeed, pallidotomy and DBS of the STN or GPi in PD patients are reported to interfere with motor learning and the execution of some complex motor tasks.

In the dopamine-depleted state, intermittent i-dopa administration might act as a destabilizing stimulus by alternately exposing the basal ganglia to large concentrations of unregulated, mainly extrasynaptic i-dopa on the one hand and severe dopamine deficiency on the other. These oscillations between periods of extremely low and excessively high dopaminergic activity might force an already abnormal network to adapt to an even more stressful situation. How dopamine depletion and chronic pulsatile stimulation with i-dopa combine to induce plastic changes in the basal ganglia needs to be more precisely defined. We and others, have postulated that intermittent use of short-acting dopaminergic agents such as i-dopa results in abnormal pulsatile stimulation of striatal dopamine receptors. This leads to consequent dysregulation of genes and proteins in downstream neurons and alterations in neuronal-firing patterns and dyskinetic behavior. This concept is supported by an increasing body of information indicating that LID in MPTP-treated monkeys and PD patients can be prevented or reversed with long-acting dopaminergic agents that protect against pulsatile stimulation of dopamine receptors by agents that interfere with intracellular signals that promote abnormal phosphorylation of glutamate receptors, or by surgical lesions that eliminate the communication of altered firing patterns from the basal ganglia to cortical motor areas. This hypothesis...
implies that, from the perspective of PD, it is better to have no input from the basal ganglia than a deranged input with an abnormal signaling pattern. Although some of these mechanisms are now beginning to be deciphered, it is likely that they too will represent a complex process involving many different intracellular signal-transduction pathways.

For further discussion on this topic see Box 2.

**Selected references**


Box 2. Discussion (cont’d)

happens to the PPN following STN stimulation. It receives both inhibitory and excitatory inputs from GPI and STN respectively and has both cholinergic and glutamatergic output neurons. Clearly, more work on the role of this nucleus in PD and in DBS and other therapies is warranted. 

Schapira: Would you comment on the potential of STN overactivity to accelerate degeneration of SNC neurons? 

Olano: We have speculated that STN overactivity could lead to excitotoxic damage in its target structures, which include the SNC and PPN, as well as the GPI. In support of this hypothesis, increased intracellular nitrotyrosine in the SNC and activated microglia in the GPI and PPN. STN lesions protect against 6-OHDA-induced nigral cell loss. And, disease progression has recently been reported in MPTP intoxicated patients. All of these findings are in keeping with this hypothesis. Further, the complex I defect found in SNC neurons in PD may make these neurons particularly vulnerable to even slight increases in glutamate. 

Patient: In considering the role of the STN in PD we should take into account that, at least in the monkey, STN neurons project primarily to the substantia nigra pars reticulata, and not so much to the SNC. 

Obeso: I think it’s fascinating to see how one can modulate motor behavior in a Parkinsonian patient through actions on different basal ganglia nuclei. What we need to do now is to reveal the function of some of our transplanted patients. This suggests that transplanted cells can stabilize basal ganglia network circuitry. In addition, we had robust survival of implanted neurons at post-mortem. The striatum was re-innervated in an organotypic fashion with patch-matrix appearance, normal appearing host-graft and graft-host synaptic connections, and normal levels of cytochrome oxidase, tyrosine hydroxylase, and TH mRNA expression. Patients were not restored to normal function; and connections of nigral dopaminergic neurons to targets such as SNC and STN were not re-established, but we were impressed by just how much improvement we saw in these patients and the relatively normal appearance of the grafted regions. 

Hirsch: You mentioned that when you have dyskinesia, you have a change in the firing pattern of basal ganglia neurons, and that this may play a role in the development of dyskinesia. However, even when you have a dopaminergic lesion of the substantia nigra you have changes in the firing pattern. For instance, in the STN you go from a regular firing pattern to bursting activity. What changes in the firing pattern are specifically involved in the development of dyskinesia? 

Olanowitz: The precise answer to your question is not known. But, I think it is important to think of the firing pattern in basal ganglia neurons as a code for the transfer of information from the basal ganglia to the cerebral cortex circuits that are involved. We have to take into account, not only what is happening, but what is it affecting. This is why we feel it is so important to think of the organization of the basal ganglia as a network in which changes in one compartment have the capacity to influence others. 

Smith: I think the situation is even more complex than what we appreciate at the receptor level. EM studies demonstrate that even in normal conditions, most striatal neurons are extra-synaptic. Most G-protein-coupled receptors, including dopamine receptors, muscarinic receptors, and metabotrophic glutamate receptors are primarily found extra-synaptically along the membrane of neurons. Only a few of them are found right at the synapse, even in the normal state. Thus, it is likely that most neurotransmission is not utilizing the synapse. 

Graybiel: I want to emphasize what Yelena and Smith just said. It puts a real premium on understanding the whole presynaptic terminal where the receptors are actually doing their business and not just concentrating on the synapse. 

Obeso: Collectively, these findings all illustrate the complexity of the basal ganglia, and the importance of considering these interactions as a network and not merely in linear terms, even though this concept served us well in the past.

18 Cepeda, C. et al. (1993) Neuronal activity changes in dopamine in the expression. Patients were not restored to normal function; and connections of nigral dopaminergic neurons to targets such as SNC and STN were not re-established, but we were impressed by just how much improvement we saw in these patients and the relatively normal appearance of the grafted regions. 

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