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.

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UNDERSTANDING the role and function of the basal ganglia in Parkinson's disease (PD) and L-dopa-induced dyskinesia is a long-standing challenge[1-7]. 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[7,13,14]. 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[15]. 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[16], and that activation of neurons from the direct and indirect pathways facilitate and suppress motor activity, respectively. Thus, the direct and indirect pathways have opposing effects on the output function of the basal ganglia[10,17]. 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[18,19].

The parkinsonian state

According to this model, the essential pathophysiologic 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)[9-11,13]. 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[7,8]. 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
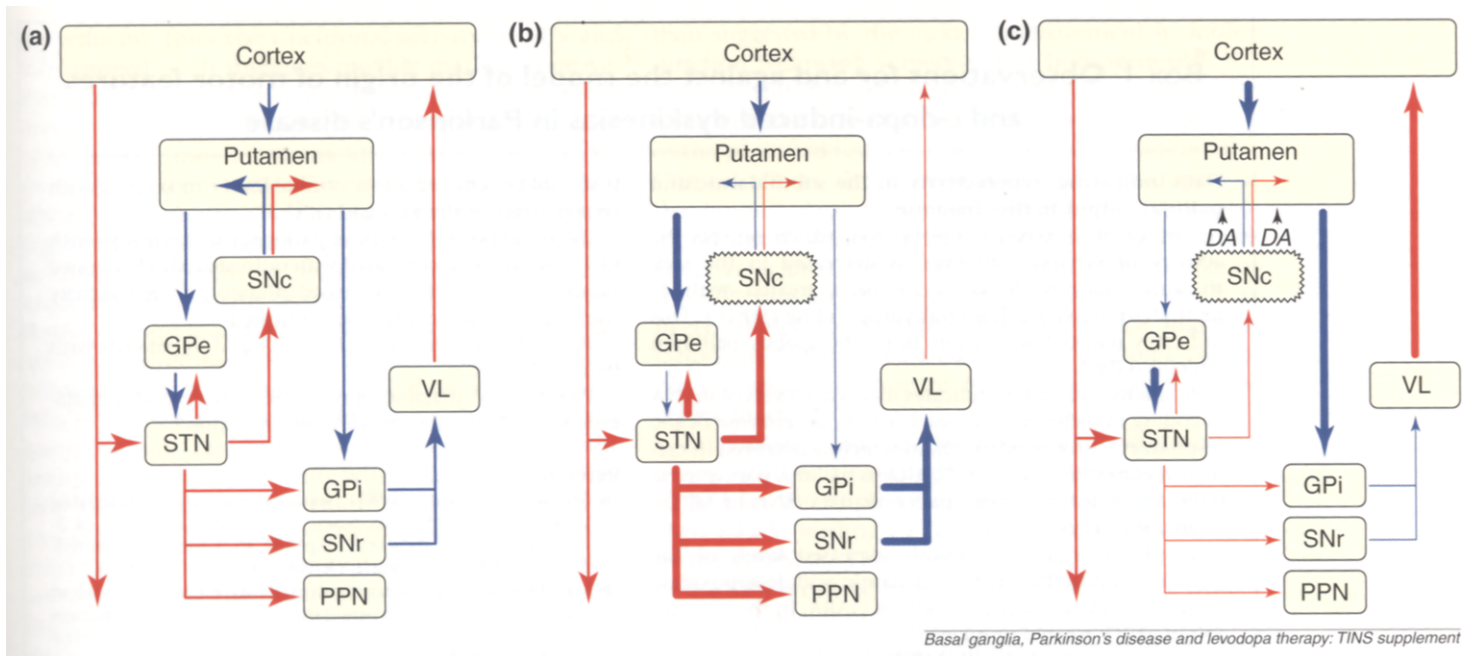
Fig. 1. *Schematic of the classic model of the basal ganglia. The* **(a)** *normal,* **(b)** *parkinsonian and* **(c)** *dyskinetic states are depicted. Blue arrows indicate inhibitory projections and red arrows represent excitatory projections. The thickness of the arrows indicates the degree of activation of each projection. Note that the striatum communicates with output neurons in the globus pallidus pars interna (GPi) and substantia nigra pars reticularis (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 GPi/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 GPi/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.

of the indirect pathway, whereas expression of mRNA encoding the D1 receptor, substance P and dynorphin decreases in neurons of the direct pathway[20–22]. 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[23], *in situ* hybridization of cytochrome oxidase subunit I (CO-I) mRNA as a measure of mitochondrial activity[24], glutamic acid decarboxylase (GAD) mRNA as a measure of GABA activity[25] and neurophysiological studies measuring the mean neuronal firing rate in single-cell recordings[26] (Box 1). Furthermore, lesions of the STN and GPi induce marked improvement in motor control in MPTP-treated monkeys[27–29] which is accompanied by reduced activity in GPi/SNr neurons[30,31]. 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[13,14]. Indeed, lesions or high frequency deep-brain stimulation (DBS) of these regions provide dramatic benefit to PD patients and restore thalamo–cortical activity[32,33].

Levodopa-induced dyskinesia

The model proposes that chorea-ballism results from reduced activity in the STN, GPi and GPi/SNr neurons[10,11,34], the opposite of the effects seen in parkinsonism. This could result from a putamenal lesion causing decreased inhibition of GPe and consequent overinhibition of the STN (Ref. 35), or by a lesion of the STN itself[36]. Levodopa-induced dyskinesia (LID) is thought to occur through a similar mechanism[37]. 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[38] and PD patients[39].

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[40] and that dopamine acts primarily to modulate the interaction between glutamate and dopamine receptors, rather than to excite or inhibit striatal neurons directly[41]. The model also excludes evidence of dopaminergic innervation of extrastriatal regions including the GPe, GPi, SNr and

Box I. 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 pallidus lateralis (GPe)[a].

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[b].

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[c,d].

In monkeys treated with MPTP, firing frequency is significantly higher in the STN and GPi and reduced in the GPe (Refs e,f), 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. g) and GPi and increases activity in the GPe (Ref. h).

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 b–d).

Lesion of the STN in MPTP-treated monkeys improves parkinsonian features and reduces hyperactivity in the GPi/SNr (Refs i,j).

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[k,l].

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[b,d].

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[b,d], as predicted by the model.

Although the expression of GAD and CO-I mRNA in the GPi and STN of MPTP-treated monkeys with LID is reduced compared with the parkinsonian state, it remains above normal levels[b,d]. 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[m].

Pallidotomy eliminates LID in PA and in patients with hemiballismus[n].

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

References

a Mitchell, I.J. *et al.* (1989) Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 32, 213–226

b Vila, M. *et al.* (1997) Consequences of nigrostriatal denervation on the functioning of the basal ganglia in human and nonhuman primates: an *in situ* hybridization study of cytochrome oxidase subunit I mRNA. *J. Neurosci.* 17, 765–773

c Vila, M. *et al.* (1996) Consequences of nigrostriatal denervation on the gamma-aminobutyric acidic neurons of substantia nigra pars reticulata and superior colliculus in parkinsonian syndromes. *Neurology* 46, 802–809

d Herrero, M.T. *et al.* (1996) Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum. *Neurology* 47, 219–224

e Bergman, H. *et al.* (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.* 72, 507–519

f Filion, M. *et al.* (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP induced parkinsonism. *Brain Res.* 547, 142–151

g Papa, S.M. *et al.* (2000) Neuronal activity correlates of levodopa-induced dyskinesias in the basal ganglia. *Neurology* (Suppl. 3), A456

h Boraud, T.H. *et al.* (1998) Effects of L-DOPA on neuronal activity of the globus pallidus externalis (GPe) and globus pallidus internalis (GPi) in the MPTP-treated monkey. *Brain Res.* 787, 157–160

i Wichmann, T. *et al.* (1994) The primate subthalamic nucleus III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *J. Neurophysiol.* 72, 521–529

j Guridi, J. *et al.* (1996) Subthalamotomy in parkinsonian monkeys: Behavioural and biochemical analysis. *Brain* 119, 1717–1727

k Limousine, P. *et al.* (1997) Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann. Neurol.* 42, 283–291

l Brown, R.G. *et al.* (1999) Impact of deep brain stimulation on upper limb akinesia in Parkinson's disease. *Ann. Neurol.* 45, 473–488

m Mitchell, I.J. *et al.* (1992) A 2-deoxyglucose study of the effects of dopamine agonists on parkinsonian primate brain. Implications for the neural mechanisms that mediate dopamine agonist-induced dyskinesia. *Brain* 115, 809–824

n Marsden, C.D. and Obeso, J.A. (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 117, 877–897

STN (Ref. 42; see also Y. Smith and J.Z. Kieval[43] in this supplement) and does not consider the issue of volume transmission, based on evidence that most striatal dopamine receptors are located extra-synaptically[44]. Furthermore, the model does not address the role of striatal cholinergic interneurons[45], the existence of striatal dopaminergic interneurons[46], anatomical and functional differences between neurons originating in the striosome and matrix components of the striatum[47] (see also A.M. Graybiel *et al.*[48] in this supplement) and the putative importance of other regions, such as the

pedunculopontine nuclei (PPN) and the centromedian parafascicular (CM/Pf) complex in the thalamus, which appear to be intimately connected with the basal ganglia and motor functions[49]. The vast axonal collateralization that interconnects circuits of the basal ganglia[50] (see also A. Parent *et al.* in this supplement[51]) is another example of the complexity of the basal ganglia system that is not addressed in the present model.

In Parkinson's disease

Clinical aspects. The model has served well in providing brain targets for surgical treatments of PD based

on reducing the excess neuronal activity in STN and GPi. Indeed, such therapies provide marked improvement in parkinsonian motor features[12]. 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, automatic and simple movements, such as arm swinging and blinking, automatic but complex muscle contractions, such 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 akinesia 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 bradykinesia 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 rhythmical synchronous neuronal discharges in various 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), rhythmical, self-perpetuating discharges are described in organotypic cultures linking neurons of the STN and GPe (Ref. 59). The membrane characteristics of STN neurons appear to make them especially prone to discharge in a repetitive, bursting mode[60], and hyperpolarizing them with GABAergic drugs enhances this tendency[61]. 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 homogenous[32,62,63]. 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[63]. Lesions in the rostral GPi have a profound antidyskinetic 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 neurophysiological 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 GPi/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 GPi 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 GPi (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[66] and is normal (not reduced) in the GPe of MPTP-treated monkeys[25]. 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[68]. 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 soma[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[70]. The consequence of this in the parkinsonian state could be that increased excitatory drive from the STN enhances
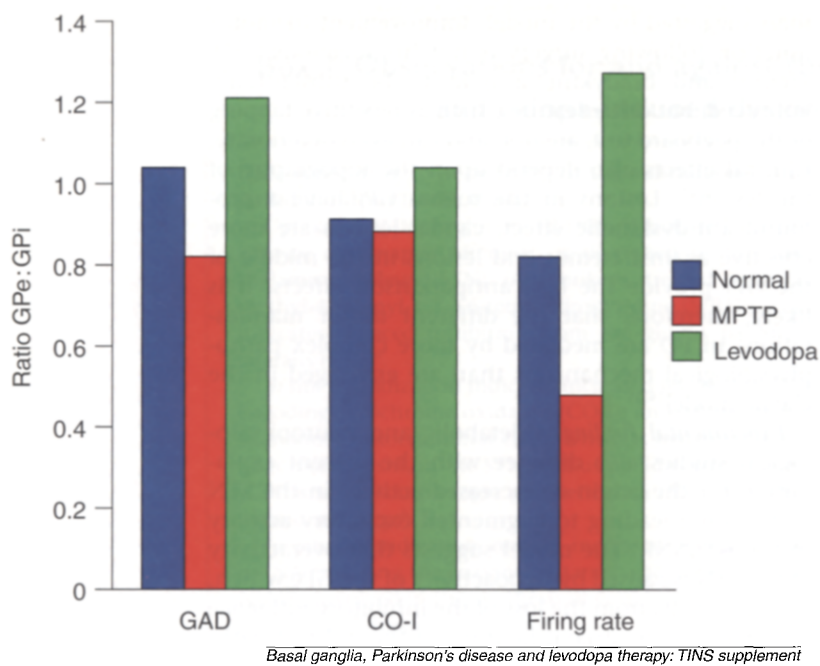
Fig. 2. *Activity in GPe and GPi neurons of parkinsonian monkeys in the normal, MPTP-treated, and L-dopa-induced dyskinesia states. Measurements include expression of cytochrome oxidase subunit-I (CO-I) and glutamic acid decarboxylase (GAD) mRNA, and neuronal discharge rate in the GPe and GPi neurons. The overall picture is consistent with a relative increment of GPe activity with respect to the GPi in L-dopa-induced dyskinesias. Abbreviations: GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.*

cellular metabolic activity within the GPe, but increased inhibition from the striatum has a more powerful effect on membrane excitability and causes reduced neuronal firing.

Interrelationships between the GPe and STN are likely to play an important role in the pathophysiology of PD. Firing in either nucleus is rapidly (within 1–2 msec) mirrored by reciprocal firing in the other[71], to form a highly stable excitatory–inhibitory loop. It seems, therefore, that normal activity in one area should maintain normal activity in the other. In the parkinsonian state it is possible that both the STN and GPe are affected, causing a loss of the normal equilibrium. The activity of the STN activity could also be affected by sources other than the GPe; the sensorimotor cortex, the CM/Pf complex of the thalamus and the PPN each provide excitatory inputs to the STN (Ref. 72). Increased activity in the parafascicular nucleus has been reported in 6-OHDA-lesioned rats[73] and cortical motor areas and the PPN are affected in PD. It is also conceivable that neuronal activity in the STN is influenced by the loss of a direct modulatory effect of dopamine. Dopamine-containing neurons project from the SNc to the STN, which expresses both D1 and D2 receptors[74]. Indeed, direct injection of dopamine agonists into the STN can modify its neuronal firing pattern[75]. We envisage that the characteristic parkinsonian motor features are consequences of events at multiple brain levels and that the parkinsonian syndrome results from failure of compensatory mechanisms to stabilize the basal ganglia network. It might be, therefore, that the reduction in GPe activity, and the accompanying inability to modulate STN hyperactivity, is a secondary effect of depletion of dopamine in the striatum, but that hyperactivity in the STN develops through other mechanisms[76].

The role of the direct pathway in the development of the parkinsonian state is less well studied. The model 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[40] and that anatomical connections between striatal neurons increase markedly in the dopamine denervated state[77]. 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[76]. In support of this concept, cell loss in the SNc is prevented by lesion of the STN in 6-OHDA-lesioned rodents[78] 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[7] (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[39,69], which is further depressed as dyskinesias develop[80].

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 (to 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-1 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 GPi-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[7]. 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[81].

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[82], 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[83]. 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[69,84].

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[85,86]. This has led to the concept that LID results from abnormal firing patterns in output neurons of the basal ganglia[7,13,87,88]. 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[7,88]. 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[8,9] within specific cortico–basal ganglia–cortical loops[10,14,17]. 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[4,89]. 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 more complex than envisaged by the original model. The 'motor' basal ganglia is not only arranged in separate parallel circuits[16,19], but each cortical motor area, such as area 4, area 6, the supplementary motor area (SMA) and the dorsolateral prefrontal cortex (DLPFC), is organized in a somatotopic manner[90-92]. 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[90,91,93]. A similar, distinct distribution is present with regard to the frontal eye fields[91]. 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[94]. This functional specificity can be quite selective. Thus, a large proportion of pallidal neurons discharge only in relation to a specific task and some only change activity during one of several different sequences of a motor paradigm[94]. By contrast, other neurons discharge with the execution of a given movement and are activated after movement onset, but before the next in sequence[95]. 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[91,93,96], whereas neurons located more posteroventrally, which are mainly connected with premotor areas 6 and 4 (Ref. 90), tend to discharge at, or just after, movement onset[96,97]. It is tempting, therefore, to suggest that the variety of motor manifestations associated with depletion of dopamine in PD is mediated by specific alterations in the firing patterns of these different motor loops[6,14,55].

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 movement 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 GPi/SNr output neurons with respective facilitation or inhibition of movement[8-10,98]. The prominent role of neurons of the direct pathway in the performance of complex oculomotor and manual movements has been demonstrated in monkeys[16,98-100]. 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[101,102]. 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[71,99], which are activated together with cortico–spinal projections during movement[96,97]. 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
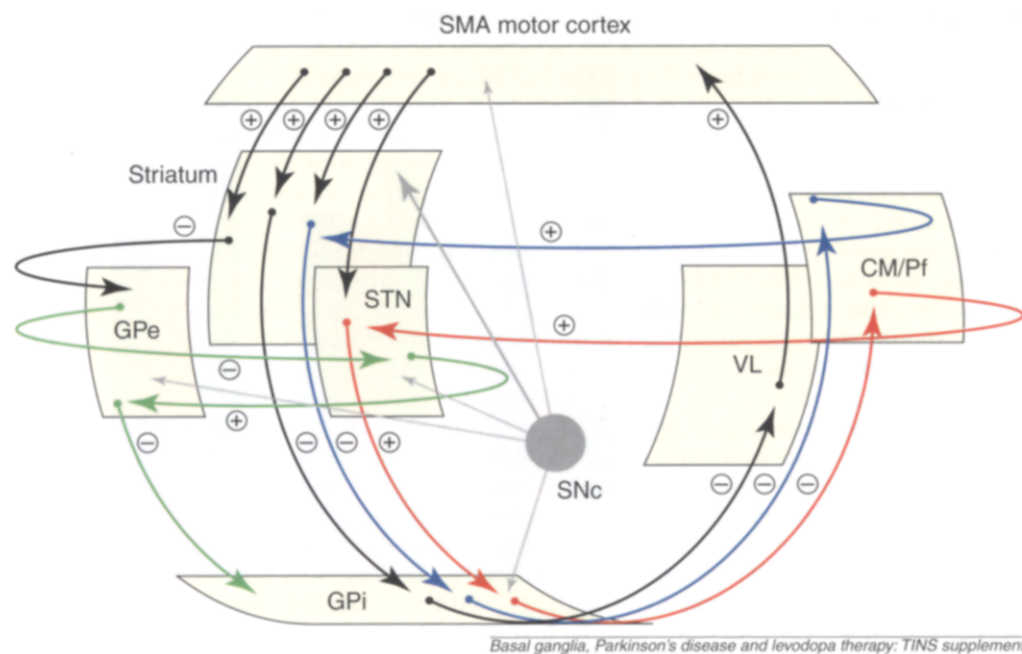
Fig. 3. A modern view of the motor circuitry of the basal ganglia. *Somatotopically-organized parallel projections form closed loops (black arrows) between the motor cortex, the basal ganglia and the motor cortex. Several horizontal loops provide 'internal' stabilization of basal ganglia activity. The 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, GPi, GPe and SMA motor cortex is indicated by gray 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, ventralis lateralis.*

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[103]; (2) the CM/Pf–STN–GPi–CM/Pf circuit, which is most probably a negative feedback loop[103,104]; (3) the STN–GPe–STN excitatory–inhibitory circuit, which functions as an auto-stabilizing loop[59,71]; and (4) the GPe–STN–GPi circuit, which can be viewed as an 'open-interconnected loop'[105], by which the STN induces dual effects on GPi (Ref. 106). 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 reports that lesions induce parkinson-like disturbances in gait and posture[107] and protect against MPTP toxicity in monkeys[79]. The nigrostriatal dopaminergic projection is also organized topographically. Additionally, rostral and caudal SNc neurons differ in their expression of

cholecystokinin[108] and calcium-binding proteins[109], suggesting that they might have different physiological functions. Finally, we now appreciate that the GPe, GPi, SNr and STN receive dopaminergic innervation[42]. Although these fibers are less profuse than the nigro-striatal projection, they could have an important regulatory influence on the internal circuits of the basal ganglia, and thereby modulate the output activity of the basal ganglia.

A modern view of the basal ganglia must take into account the series of parallel and somatotopically segregated but highly collateralized projection systems that are regulated by several internal circuits[103–105]. In addition, the dopaminergic system has several characteristics that permit it to serve a stabilizing function[42] (Fig. 3). In normal monkeys, dopaminergic neurons of the SNc discharge tonically at a low frequency, but fire in robust and highly synchronous bursts under some circumstances, such as reward or anticipation of movement[110]. Stable firing of SNc neurons probably plays a key role in maintaining continuous delivery of dopamine to the striatum[111]. This can be achieved through mechanisms which involve both renewal and non-renewal regulatory processes. The former is involved primarily with firing rate, and implies that cell excitability is influenced by the duration of the inter-spike interval or the time elapsed since the last action potential. This process is a general feature of neuronal activity, including basal ganglia neurons and, therefore, implicitly assumed in the classic model of the basal ganglia. Non-renewal activity applies to neuronal systems that use patterned codes to provide signaling information. Here, the excitability of a given neuron is influenced by its previous firing behavior over periods of hundreds to thousands of milliseconds[112]. This leads to stable levels of neuronal activity. Both types of regulatory processes are found in dopaminergic neurons of the SNc (Fig. 4). The internal, 'horizontal' circuits within the basal ganglia (Fig. 3) seem ideally suited to support non-renewal activity, thereby forming a complex neuronal network for motor function that remains stable except in extreme circumstances.

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[113]. In the early stages of learning, a complex task is executed by relying on the associative prefrontal cortex and the anterior basal

ganglia[93,96]. However, as the sequence becomes routine, premotor and primary motor areas and the posterior basal ganglia are predominantly engaged in the task[113]. The nigrostriatal dopamine system plays an essential modulatory role during this learning process[110,114]. These plastic changes are likely to reflect the macro-organization of the network, rather than changes in individual loops and synapses[115]. Indeed, present evidence suggests that the basal ganglia is not only involved in movement control, but also in planning, 'working memory' and emotion[93,115], 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[6], 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[56]. 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[32,116]. In the dopamine-depleted state, intermittent L-dopa administration might act as a destabilizing stimulus by alternately exposing the basal ganglia to large concentrations of unregulated, mainly extrasynaptic L-dopa on the one hand and severe dopamine deficiency on the other. These oscillations between periods of extremely low and excessively high dopaminergic activity mi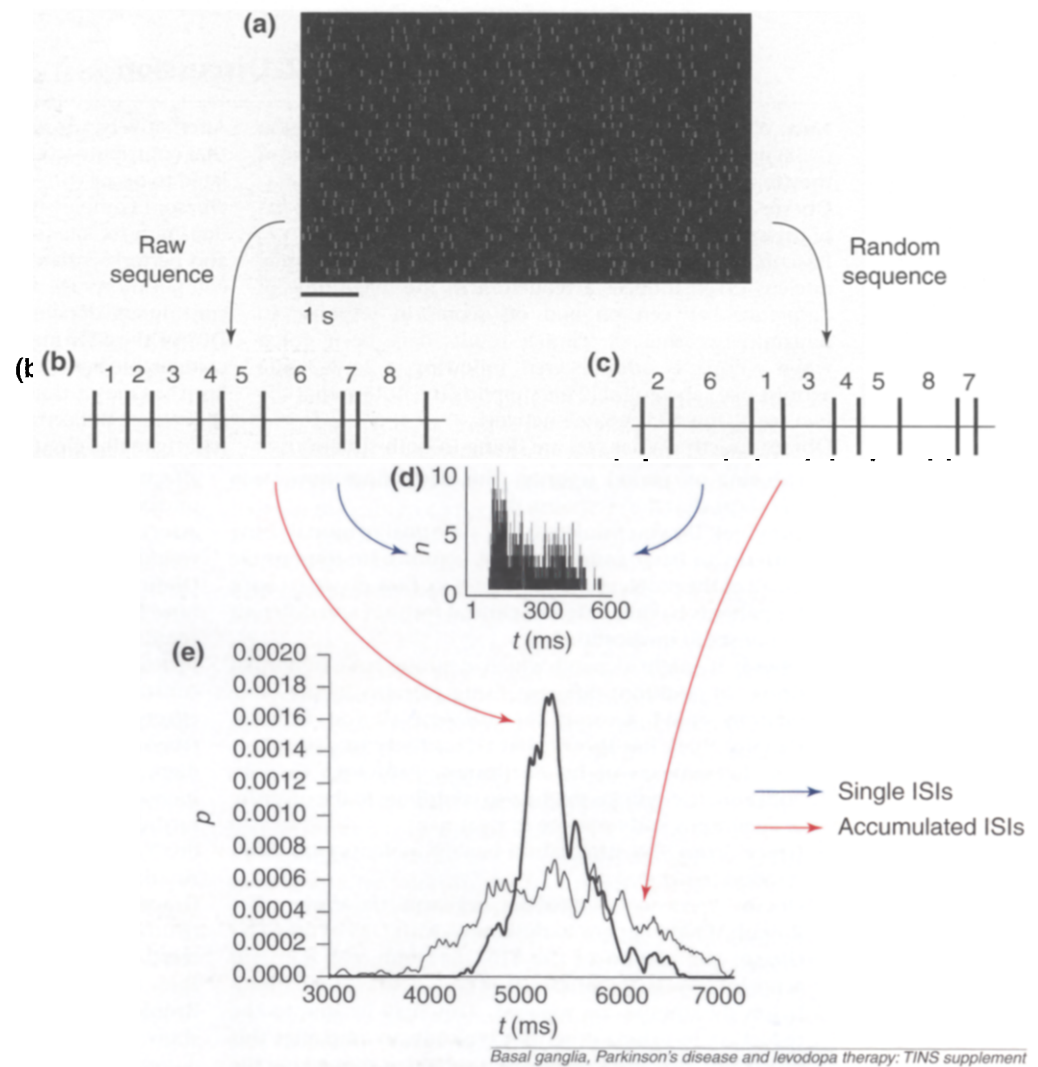ght force an already abnormal network to adapt to an even more stressful situation. How dopamine depletion and chronic pulsatile stimulation with L-dopa combine to induce plastic changes in the basal ganglia needs to be more precisely defined[14,88,117,118]. We, and others, have postulated that intermittent use of short-acting dopaminergic agents such as L-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[7,88,119,120]. 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[118,121], by agents that interfere with intracellular signals that promote abnormal phosphorylation of glutamate receptors[120], or by surgical lesions that eliminate the communication of altered firing patterns from the basal ganglia to cortical motor areas[85,86]. This hypothesis

Fig. 4. *Assessment of non-renewal firing activity of dopaminergic neurons in the rat.* Measurement of (a) *the rate of firing of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the rat. The* (b) *original interspike interval (ISI) sequence (raw sequence) was* (c) *randomized (random sequence) and the distribution of the interspike intervals analyzed using two different statistical procedures: (1) the* (d) *single-ISI histogram, which represents the interval distribution between two successive spikes; and (2)* (e) *the accumulated-ISI histogram, which is a probability density function of the time elapsed between two potentials separated by the number of spikes (20 spikes in this instance). The single-ISI histogram (d) is the same for the raw and random sequences. However* (e), *the accumulated-ISI histogram shows a larger dispersion for the random than for the raw sequence, which has a greater probability (P) of intervals around 5000 ms. These findings indicate that long-lasting intervals are followed by short-lasting intervals (and vice versa), compensating for previous variations of ISIs. This is a form of non-renewal activity and supports the existence of stable firing patterns in SNc neurons.*

Box 2. Discussion

Nutt: Why is the maximal benefit of deep-brain stimulation (DBS) no better than the benefit of L-dopa? Does this mean they're acting in the same way?

Obeso: It could be that they are acting on different parts of the same network.

Rascol: You showed that chronic DBS of the subthalamic nucleus (STN) induces a reduction in the magnitude of difference between on and off scores in response to dopaminergic therapy. Similar results have been noted when L-dopa is administered following a long-acting agonist like cabergoline. This supports the notion that the two are acting on the same network.

Obeso: Exactly. What you are doing in both situations is reducing off period severity. This determines how steep the short-duration response is.

Graybiel: Do you think that the abnormal neuronal firing patterns in basal ganglia output neurons are responsible for all of the problems in PD? And if so, how do we account for patients having different clinical features and different responses to medication?

Obeso: It might depend which neurons have abnormal firing. In addition, different firing patterns in the same neurons could account for different clinical features. Dr Jerry Vitek has shown that GPi activity in dystonia is not the same as in hemiballismus. Pathology in non-dopaminergic systems might also contribute to the diversity of symptoms and response to treatment.

Grace: Does STN stimulation benefit patients who don't respond to L-dopa?

Obeso: Experience is limited but, in general, the answer is no.

Rascol: What happens to dyskinesia with DBS of the STN?

Obeso: Stimulation of the STN may induce a transient acute increase in dyskinesia. However, with chronic stimulation dyskinesias are reduced. This may be due to the reduction in L-dopa dose that typically accompanies this procedure. It is also possible that surgery is mimicking the effects of continuous dopaminergic stimulation, and thereby stabilizing the system in a manner similar to what can be accomplished with infusion of a dopaminergic agent.

Rascol: But it is hard to establish this if you have lowered the dose of L-dopa.

Olanow: We found that dyskinesias were diminished or disappeared with chronic STN stimulation in cases where we deliberately held the dose of L-dopa constant. It may be that with constant stimulation you are avoiding or reversing the downstream changes induced by pulsatile stimulation of the dopamine receptor, and in this way mirror what occurs with continuous dopaminergic stimulation.

Alternatively, we might be disrupting abnormal signals that contribute to the expression of dyskinesia as is postulated to occur with pallidotomy.

Obeso: I completely agree. It is possible that intermittent dopamine receptor stimulation induces downstream changes and perturbs striato–pallidal firing so as to induce motor complications. Disruption of these abnormal patterns with continuous dopamine receptor stimulation or chronic DBS of the STN might stabilize the network and provide comparable benefits with respect to motor applications.

Smith: One of the problems in interpreting this data is that we are not certain how DBS works and what it does to basal ganglia circuits. We assume that it simulates the effects of a lesion, but Sebasta *et al.* recently showed, using microdialysis, that high frequency STN stimulation is associated with glutamate release. This is not what you would expect if you were making a lesion.

Olanow: We are at an early stage in understanding of how DBS works. The experiments you describe employ acute and not chronic stimulation. Even if it does drive neurons, it doesn't dispel the notion that DBS provides a constant effect and thereby obviates the deleterious effects of pulsatile receptor stimulation.

Obeso: There is also data in the same experimental paradigm showing that DBS of the STN is associated with increased dopamine release in the striatum, which could further stabilize the system. The bottom line is that we don't know how DBS works, but at all sites tested so far it simulates the effects of a lesion.

Grace: When you stimulate, even if you inactivate the neurons you are still going to be driving the axons. So, the result of stimulation could be related to either or both of these effects.

Brooks: PET activation studies following STN stimulation show activation of the motor cortex, in support of the current model. I agree with including the PPN in the model, although its role in the parkinsonian state has not been clearly defined. Do you think that benefits of STN stimulation could be mediated, at least in part, through its connections to the PPN.

Obeso: This is certainly possible. First, there are major projections between STN and PPN and GPi and PPN. Further, PPN provides a major input to the SNc. Second, PPN lesions in monkeys are associated with parkinson-like features including gait dysfunction, postural disturbances and akinesia. Third, there is cell loss in the PPN in PD. Finally, the PPN is thought to be involved in REM behavior disorder which is commonly seen in PD patients. What is not clear is what

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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[122].

For further discussion on this topic see Box 2.

Selected references
1 Wilson, S.A.K. (1912) Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* 34, 295–507
2 Purdon-Martin, J. and Alcock, N.S. (1934) Hemichorea associated with a lesion of the corpus Luysii. *Brain* 57, 504–516
3 Denny Brown, D. (1966) *The Basal Ganglia*, Oxford University Press
4 Marsden, C.D. (1982) The mysterious motor function of the basal ganglia: The Robert Watenberg lecture. *Neurology* 32, 514–539
5 DeLong, M.R. and Georgopoulos, A.P. (1981) Motor functions of the basal ganglia. In *Handbook of Physiology. The Nervous System II*, pp. 1017–1061, American Physiological Society
6 Marsden, C.D. and Obeso, J.A. (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 117, 877–894
7 Obeso, J.A. *et al.* (2000) Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model. *Ann. Neurol.* 47 (Suppl. 1), 22–34
8 Penney, J. and Young, A.M. (1986) Striatal inhomogeneities and basal ganglia function. *Mov. Disord.* 1, 3–15
9 Albin, R.L. *et al.* (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 12, 366–375
10 DeLong, M.R. (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 13, 281–285
11 Crossman, A.R. (1987) Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. *Neuroscience* 21, 1–40
12 Obeso, J.A. *et al.* (1997) Surgery for Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 62, 2–8
13 Obeso, J.A. *et al.* (1997) Basal ganglia pathophysiology: a critical review. *Adv. Neurol.* 74, 3–18

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.

Olanow: 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 concept we found increased levels of 3-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.

Parent: In considering the role of the STN in PD you 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 ganglial nuclei. What we need to do now is to take advantage of this in order to determine how dopamine should be replaced in order to obtain the best therapeutic response.

Graybiel: Do you think that grafted dopaminergic neurons can restore dopaminergic function and normalize this basal ganglia network? Do implanted neurons re-establish normal connectivity in the basal ganglia of PD patients?

Olanow: We found dramatic clinical benefit with increased on time and decreased dyskinesia in 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, and connections of nigral dopaminergic neurons to targets such as SNr and STN were not re-established, but we were impressed by 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?

Olanow: 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. I envision that there are a variety of different firing patterns and that what happens with dyskinesia is that you go from one altered firing pattern to another. I wanted to emphasize that the pattern comprises many different components, and that clinical features cannot be explained exclusively by firing rate. The improvement in dyskinesia that is seen with pallidotomy suggests that it is better to eliminate basal ganglia input than to have transmission of abnormal signal patterns.

Obeso: In addition, patterns of neuronal activity have to be considered in terms of time and space domains that reflect both the specific firing characteristics and the precise anatomic distribution of the specific basal ganglia-cerebral cortex circuits that are involved. We have to take into account, not only what is happening, but where it's happening and what it is 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 receptors are extra-synaptic. Most G-protein-coupled receptors, including dopamine receptors, muscarinic receptors, and metabotropic glutamate receptors are primarily found extrasynaptically 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 taking place at the synapse.

Graybiel: I want to emphasize what Yoland 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.

14 Wichmann, T. et al. (2000) Pathophysiological considerations in basal ganglia surgery: Role of the basal ganglia in hypokinetic and hyperkinetic movement disorders. *Prog. Neurol. Surg.* 15, 31–57

15 Alexander, G.E. et al. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381

16 Chevalier, G. and Deniau, J.M. (1990) Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci.* 13, 277–280

17 Alexander, G.E. and Crutcher, M.D. (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* 13, 266–271

18 Cepeda, C. et al. (1993) Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. *Proc. Natl. Acad. Sci. U. S. A.* 90, 9576–9580

19 Gerfen, C.R. et al. (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 250, 1429–1432

20 Gerfen, R.C. et al. (1991) Dopamine differentially regulates dynorphin, substance P, and enkephalin in striatal neurons: *in situ* hybridization histochemical analysis. *J. Neurosci.* 11, 1016–1031

21 Engber, T.M. et al. (1991) Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats. *Brain Res.* 552, 113–118

22 Herrero, M.T. et al. (1995) Effects of L-dopa on preproenkephalin and preprotachykinin gene expression in the MPTP-treated monkey striatum. *Neuroscience* 68, 1189–1198

23 Mitchell, I.J. et al. (1989) Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 32, 213–226

24 Vila, M. et al. (1997) Consequences of nigrostriatal denervation on the functioning of the basal ganglia in human and nonhuman primates: an *in situ* hybridization study of cytochrome oxidase subunit I mRNA. *J. Neurosci.* 17, 765–773

25 Herrero, M.T. et al. (1996) Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum. *Neurology* 47, 219–224

26 Filion, M. and Tremblay, L. (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP induced parkinsonism. *Brain Res.* 547, 142–151

27 Bergman, H. et al. (1990) Reversal of experimental parkinsonism by lesion of the subthalamic nucleus. Science 249, 1436–1438

28 Aziz, T.Z. et al. (1991) Lesion of the subthalamic nucleus for the alleviation of MPTP-induced parkinsonism in the primate. Mov. Disord. 6, 288–293

29 Lonser, R.R. et al. (1999) Convection-enhanced selective excitotoxic ablation of the neurons of the globus pallidus internus for treatment of parkinsonism in nonhuman primates. J. Neurosurg. 91, 294–302

30 Guridi, J. et al. (1996) Subthalamotomy in parkinsonian monkeys: Behavioural and biochemical analysis. Brain 119, 1717–1727

31 Wichmann, T. et al. (1994) The primate subthalamic nucleus III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J. Neurophysiol. 72, 521–530

32 Limousin, P. et al. (1999) The effects of posteroventral pallidotomy on the preparation and execution of involuntary hand and arm movements in Parkinson's disease. Brain 122, 315–328

33 Ceballos-Baumann, A. et al. (1994) Restoration of thalamocortical activity following posteroventral pallidotomy in Parkinson's disease. Lancet 344, 814

34 Crossman, A.R. et al. (1984) Experimental hemichorea-hemiballismus in the monkey. Brain 107, 579–596

35 Crossman, A.R. et al. (1988) Chorea and myoclonus in the monkey induced by gamma-aminobutyric acid antagonism in the lentiform complex. Brain 111, 1211–1233

36 Mitchell, I.J. et al. (1989) The role of the subthalamic nucleus in experimental chorea. Evidence from 2-deoxyglucose metabolic mapping and horseradish peroxidase tracing studies. Brain 112, 1533–1548

37 Crossman, A.R. (1990) A hypothesis of the pathophysiological mechanism that underlie levodopa or dopamine agonist-induced dyskinesia in Parkinson's disease. Mov. Disord. 5, 100–108

38 Filion, M. et al. (1991) Effects of dopamine agonists on the spontaneous activity of the globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 547, 152–161

39 Lozano, A.M. (2000) Neuronal recordings in Parkinson's disease patients with dyskinesias induced by apomorphine. Ann. Neurol. 47 (Suppl. 1), 141–146

40 Aizman, O. et al. (2000) Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. Nat. Neurosci. 3, 226–230

41 Koetter, R. (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. Prog. Neurobiol. 44, 163–196

42 Joel, D. and Weiner, I. (2000) The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 96, 451–474

43 Smith, Y. and Kieval, J.Z. (2000) Anatomy of the dopamine system in the basal ganglia. Trends Neurosci. 23 (Suppl. Basal ganglia, Parkinson's disease and levodopa therapy), S28–S33

44 Yung, K.K.L. et al. (1995) Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. Neuroscience 65, 709–730

45 Abercrombie, E. and DeBoer, P. (1997) Substantia nigra D1 receptors and stimulation of striatal cholinergic interneurons by dopamine: a proposed circuit mechanism. J. Neurosci. 17, 8498–8505

46 Betarbet, R. et al. (1997) Dopaminergic neurons intrinsic to the primate striatum. J. Neurosci. 17, 6761–6768

47 Eblen, F. and Graybiel, A.M. (1995) Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. J. Neurosci. 15, 5999–6013

48 Graybiel, A.M. et al. (2000) Levodopa-induced dyskinesias and dopamine-dependent stereotypies: a new hypothesis. Trends Neurosci. 23 (Suppl. Basal ganglia, Parkinson's disease and levodopa therapy), S71–S77

49 Parent, A. (1990) Extrinsic connections of the basal ganglia. Trends Neurosci. 13, 254–258

50 Sato, F. et al. (2000) Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. J Comp. Neurol. 417, 17–31

51 Parent, A. et al. (2000) Organization of the basal ganglia: the importance of axonal collateralization. Trends Neurosci. 23 (Suppl. Basal ganglia, Parkinson's disease and levodopa therapy), S20–S27

52 Berardelli, A. et al. (1996) Single-joint rapid arm movements in normal subjects and in patients with motor disorders. Brain 119, 71–77

53 Morris, M.E. et al. (1996) Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain 119, 551–568

54 Hanakawa, T. et al. (1999) Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 122, 1271–1282

55 Obeso, J.A. et al. (2000) Functional models of the basal ganglia: Where are we? Prog. Neurol. Surg. 15, 58–77

56 Bergman, H. et al. (1998) Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci. 21, 32–38

57 Rodriguez, M.C. et al. (1998) The subthalamic nucleus and tremor in Parkinson's disease. Mov. Disord. 13 (Suppl. 1), 111–118

58 Guridi, J. et al. (1999) Stereotactic targeting of the globus pallidus internus in Parkinson's disease: Imaging versus electrophysiological mapping. Neurosurgery 45, 278–289

59 Plentz, D. and Kitai, S.T. (1999) Organotipic cultures reveals intrinsic oscillatory activity in the basal ganglia. Nature 400, 677–682

60 Bevan, M.D. and Wilson, C.J. (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J. Neurosci. 19, 7617–7628

61 Wichmann, T. and DeLong, M.R. (1999) Oscillations in the basal ganglia. Nature 400, 621–622

62 Kimber, T.E. et al. (1999) Voluntary movement after pallidotomy in severe Parkinson's disease. Brain 122, 895–906

63 Gross, R.E. et al. (1999) Relationship of lesion location to clinical outcome following microelectrode-guided pallidotomy for Parkinson's disease. Brain 122, 405–416

64 Levy, R. et al. (1997) Re-evaluation of the functional anatomy of the basal ganglia in normal and parkinsonian states. Neuroscience 76, 335–343

65 Chesselet, M. and Delfs, J.M. (1996) Basal ganglia and movement disorders: An update. Trends Neurosci. 19, 417–422

66 Delf, J.M. et al. (1995) Glutamate decarboxylase messenger RNA in rat pallidum: comparison of the effects of haloperidol, clozapine and combined haloperidol-scopolamine treatments. Neuroscience 66, 67–80

67 Vila, M. et al. (2000) Evolution of changes in neuronal activity in the subthalamic nucleus of rats with unilateral lesion of the substantia nigra assessed by metabolic and electrophysiological measurements. Eur. J. Neurosci. 12, 1–8

68 Bezard, E. et al. (1999) Involvement of the subthalamic nucleus in glutamatergic compensatory mechanisms. Eur. J. Neurosci. 11, 2167–2170

69 Filion, M. (2000) Physiologic basis of dyskinesias. Ann. Neurol. 47 (Suppl. 1), 35–41

70 Parent, A. and Hazrati, L.N. (1995) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res. Rev. 20, 128–154

71 Ryan, L.J. and Clark, K.B. (1992) Alteration of neuronal responses in the subthalamic nucleus following globus pallidus and neostriatal lesions in rats. Brain Res. Bull. 29, 319–327

72 Feger, J. et al. (1997) The subthalamic nucleus and its connexions: New electrophysiological and pharmacological data. Adv. Neurol. 74, 31–43

73 Orieux, G. et al. (2000) Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. Neuroscience 97, 79–88

74 Cossette, M. et al. (1999) Extrastriatal dopaminergic innervation of human basal ganglia. Neurosci. Res. 34, 51–54

75 Hassani, O.K. and Feger, J. (1999) Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: An electro-physiological and c-fos study. Neuroscience 92, 533–543

76 Rodriguez, M.C. et al. (1998) Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: A target for neuroprotection. Ann. Neurol. 44, 175–188

77 Onn, S.P. and Grace, A.A. (1999) Alterations in electrophysiological activity and dye coupling of striatal spiny and aspiny neurons in dopamine-denervated rat striatum recorded in vivo. Synapse 31, 1–15

78 Piallat, B. et al. (1996) Subthalamic nucleus lesion on rats prevents dopaminergic nigral neuron degeneration after striatal 6-OHDA injection: Behavioral and inmmunohistochemical studies. Eur. J. Neurosci. 8, 1408–1414

79 Takada, M. et al. (2000) Protection against dopaminergic nigrostriatal cell death by excitatory input ablation. Eur. J. Neurosci. 12, 1771–1780

80 Papa, S.M. et al. (1999) Internal globus pallidus discharge is nearly suppressed during levodopa-induced dyskinesia. Ann. Neurol. 46, 732–738

81 Maneuf, Y.P. et al. (1994) On the role of enkephalin cotransmission in the GABAergic striatal efferents to the globus pallidus. Exp. Neurol. 125, 65–71

82 Brotchie, J.M. (2000) The neural mechanisms underlying levodopa-induced dyskinesia in Parkinson's disease. Ann. Neurol. 47 (Suppl. 1), 105–114

83 Verhagen, L. et al. (2000) Apomorphine-induced dyskinesia and single-cell discharges in globus pallidus internus of parkinsonian subjects. Neurol. 54 (Suppl. 3), 456–457

84 Matsumura, M. et al. (1995) Activity of pallidal neurons in the monkey during dyskinesia induced by injection of bicuculline in the external pallidum. Neuroscience 65, 59–70

85 Baron, M.S. et al. (1996) Treatment of advanced Parkinson's disease by posterior pallidotomy: 1-year results of a pilot study. Ann. Neurol. 40, 355–366

86 Lang, A.E. *et al.* (1997) Posteroventral medial pallidotomy in advanced Parkinson's disease. *New Engl. J. Med.* 337, 1036–1042

87 Vitek, J. and Giroux, M. (2000) Physiology of hypokinetic and hyperkinetic movement disorders: Model for dyskinesia. *Ann. Neurol.* 47 (Suppl. 1), 131–140

88 Olanow, C.W. and Obeso, J.A. (2000) Preventing L-dopa induced dyskinesia. *Ann. Neurol.* 47 (Suppl. 1), 167–178

89 Alexander, G.E. *et al.* (1990) Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog. Brain Res.* 85, 119–146

90 Hoover, J.E. and Strick, P.L. (1993) Multiple output channels in the basal ganglia. *Science* 259, 819–821

91 Middleton, F.A. and Strick, P.L. (1997) New concepts abut the organization of basal ganglia output. *Adv. Neurol.* 74, 57–68

92 Nambu, A. *et al.* (1996) Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformation from the primary motor cortex and the supplementary motor area. *J. Neurosci.* 16, 2671–2683

93 Middelton, F.A. and Strick, P.L. (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res. Rev.* 31, 236–250

94 Mushiake, H. and Strick, P.L. (1995) Pallidal neuron activity during sequential arm movements. *J. Neurophysiol.* 74, 2754–2758

95 Brotchie, P. *et al.* (1991) Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. *Brain* 114, 1685–1702

96 Nambu, A. *et al.* (1990) Discharge patterns of pallidal neurons with input from various cortical areas during movement in monkey. *Brain Res.* 519, 319–327

97 Brotchie, P. *et al.* (1991) Motor function of the monkey globus pallidus. 1. Neuronal discharge and parameters of movement. *Brain* 114, 1667–1683

98 Hikosaka, O. *et al.* (1989) Functional properties of monkey caudate neurons. II. Visual and auditory responses. *J. Neurophysiol.* 61, 799–813

99 Nambu, A. *et al.* (2000) Excitatory cortical input to pallidal neurons via the subthalamic nucleus in the monkey. *J. Neurophysiol.* 84, 289–300

100 Hikosaka, O. and Wurtz, R.H. (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. *J. Neurophysiol.* 49, 1254–1267

101 Berretta, S. *et al.* (1997) Local release of GABAergic inhibition in the motor cortex induces immediate-early gene expression in indirect pathway neurons of the striatum. *J. Neurosci.* 17, 4752–4763

102 Parthasarathy, H.B. and Graybiel, A.M. (1997) Cortically driven immediate-early gene expression reflects modular influence of sensorimotor cortex on identified striatal neurons in the squirrel monkey. *J. Neurosci.* 17, 2477–2491

103 Mengual, E. *et al.* (1999) Thalamic interaction between the input and output systems of the basal ganglia. *J. Chem. Neuroanat.* 16, 187–200

104 Fénelon, G. *et al.* (1990) Topographic distribution of pallidal neurons projecting to the thalamus in macaques. *Brain Res.* 520, 27–35

105 Joel, D. and Weiner, I. (1997) The organization of the basal ganglia-thalamocortical circuits: Open interconnected rather than closed segregated. *Brain Res. Rev.* 23, 62–78

106 Shink, E. *et al.* (1996) The subthalamic nucleus and the external pallidum: Two tightly interconnected structures that control the ouptput of the basal ganglia in the monkey. *Neuroscience* 73, 335–357

107 Kojima, J. *et al.* (1997) Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. *Neurosci. Lett.* 226, 111–114

108 Jimenez-Castellanos, J. and Graybiel, A.M. (1987) Subdivisions of the dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix. *Neuroscience* 23(1), 223–242

109 Gonzalez, T. and Rodriguez, M. (2000) Compartmental organization and chemical profile of dopaminergic and GABAergic neurons in the substantia nigra of the rat. *J. Comp. Neurol.* 427, 107–135

110 Suri, R.E. and Schultz, W. (1999) A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task. *Neuroscience* 91, 871–890

111 Grace, A.A. and Bunney, B.S. (1985) Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. *Brain Res.* 333, 271–284

112 Eggermont, J.J. (1990) *The Correlative Brain*, pp. 60–62, Springer-Verlag

113 Hikosaka, O. *et al.* (1999) Parallel neural networks from learning sequential procedures. *Trends Neurosci.* 22, 464–470

114 Matsumoto, N. *et al.* (1999) Role of (corrected) nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. *J. Neurophysiol.* 82, 978–998

115 Beiser, D.G. and Houk, J.C. (1998) Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. *J. Neurophysiol.* 79, 3168–3188

116 Jahashani, M. *et al.* (2000) The impact of deep brain stimulation on executive functions in Parkinson's disease. *Brain* 123, 1142–1154

117 Mitchell, I.J. *et al.* (1992) A 2-deoxyglucose study of the effects of dopamine agonists on parkinsonian primate brain. Implications for the neural mechanisms that mediate dopamine agonist-induced dyskinesia. *Brain* 115, 809–824

118 Calon, F. *et al.* (2000) Molecular basis of levodopa-induced dyskinesias. *Ann. Neurol.* 47 (Suppl. 1), S70–S78

119 Obeso, J.A. *et al.* (1994) The role of pulsatile versus continuous dopamine receptor stimulation for functional recovery in Parkinson's disease. *Europ. J. Neurosci.* 6, 889–897

120 Chase, T.N. and Oh, J.D. (2000) Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications. *Ann. Neurol.* 47 (Suppl. 1), 122–129

121 Rascol, O. *et al.* (2000) A five-year study of the incidence of dyskinesia in patients with early Parkinson's diseaes who were treated with ropinirol or levodopa. *New Engl. J. Med.* 342, 1481–1491

122 Sealfon, S.C. and Olanow, C.W. (2000) Dopamine receptors: from structure to behavior. *Trends Neurosci.* 23 (Suppl. *Basal ganglia, Parkinson's disease and levodopa therapy*), S34–S40