The Basal Ganglia in Parkinson's Disease: Current Concepts and Unexplained Observations

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The pathophysiology of Parkinson's disease is reviewed in light of recent advances in the understanding of the functional organization of the basal ganglia (BG). Current emphasis is placed on the parallel interactions between corticostriatal and corticosubthalamic afferents on the one hand, and internal feedback circuits modulating BG output through the globus pallidus pars interna and substantia nigra pars reticulata on the other. In the normal BG network, the globus pallidus pars externa emerges as a main regulatory station of output activity. In the parkinsonian state, dopamine depletion shifts the BG toward inhibiting cortically generated movements by increasing the gain in the globus pallidus pars externa-subthalamic nucleus-globus pallidus pars interna network and reducing activity in "direct" cortico-putaminal-globus pallidus pars interna projections. Standard pharmacological treatments do not mimic the normal physiology of the dopaminergic system and, therefore, fail to restore a functional balance between corticostriatal afferents in the so-called direct and indirect pathways, leading to the development of motor complications. This review emphasizes the concept that the BG can no longer be understood as a "go-through" station in the control of movement, behavior, and emotions. The growing understanding of the complexity of the normal BG and the changes induced by DA depletion should guide the development of more efficacious therapies for Parkinson's disease.

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The hallmark feature of Parkinson's disease (PD) is degeneration of dopamine neurons in the substantia nigra pars compacta (SNc) and a consequent striatal dopamine deficiency. This dopamine deficiency leads to a cascade of functional changes in basal ganglia circuitry, which are ultimately responsible for the development of the cardinal features of PD.[1–3] The essential pathophysiological characteristic of the PD state is increased neuronal firing activity in the output nuclei of the basal ganglia (globus pallidus pars interna [GPi] and substantia nigra pars reticulata [SNr]) leading to excessive inhibition of thalamocortical and brainstem motor systems. This was initially proposed to arise as a consequence of increased firing in basal ganglia output

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neurons resulting from reduced inhibition in the "direct" striatal pathway and increased excitation of subthalamic neurons consequent to increased activity in striatopallidal GABAergic neurons in the "indirect" pathway[1–3] (Fig 1A).

A determination of the functional state of the basal ganglia network after nigrostriatal denervation has been achieved by electrophysiological, metabolic, and biochemical studies (Table). Results in PD patients have produced somewhat conflicting results because of confounding factors such as the use of antiparkinsonian drugs, and variability in the clinical state and the degree of striatal dopamine depletion in different individuals. To avoid these influences, this review primarily relies on results obtained in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–intoxicated monkeys and 6-hydroxydopamine (6-OHDA)–lesioned rats.

The basal ganglia has traditionally been considered to be a "go-through" system, where cortical afferent activity is modulated by the basal ganglia and is then sent back to the cortex to modify motor activity ("the motor loop"). Current thinking has been somewhat modified, and emphasis is now placed on the parallel interactions between corticostriatal and corticosubthalamic afferents on the one hand, and internal feedback circuits modulating basal ganglia output through the GPi and SNr on the other hand (Fig 2). The basal ganglia are functionally subdivided into motor, oculomotor, association, limbic, and orbitofrontal loops based on their relationship to the relevant cortical projection area.[4–6] Thus, in addition to the well-known role of the basal ganglia in motor control, it is now appreciated that functions such as attention and time estimation, implicit learning and habit formation, reward-related behaviors and emotions are all associated with activation of cortical loops that connect with the caudate nucleus, the anterior putamen, or the ventral putamen.[7–9] Dopamine denervation is thus now appreciated to be associated with a variety of different clinical manifestations in addition to parkinsonism such as impaired executive functions (ie, working memory), reduced motivation, depression, and apathy. Importantly, a variety of motor and behavioral disorders (ie, dyskinesia, dopamine dysregulation syndrome, and impulse-control disorders) can be seen in association with the chronic use of dopaminergic drugs, and may well be caused by abnormal modulation of these subcircuits and their connections. Whether each of these different cortico-striatal-pallidal loops is functionally organized and operates in an identical and parallel manner is not yet known. Most studies in PD and animal models have focused on the motor features associated with dopamine depletion and replacement, and have not addressed the molecular and physiological changes that occur in the different subcir-

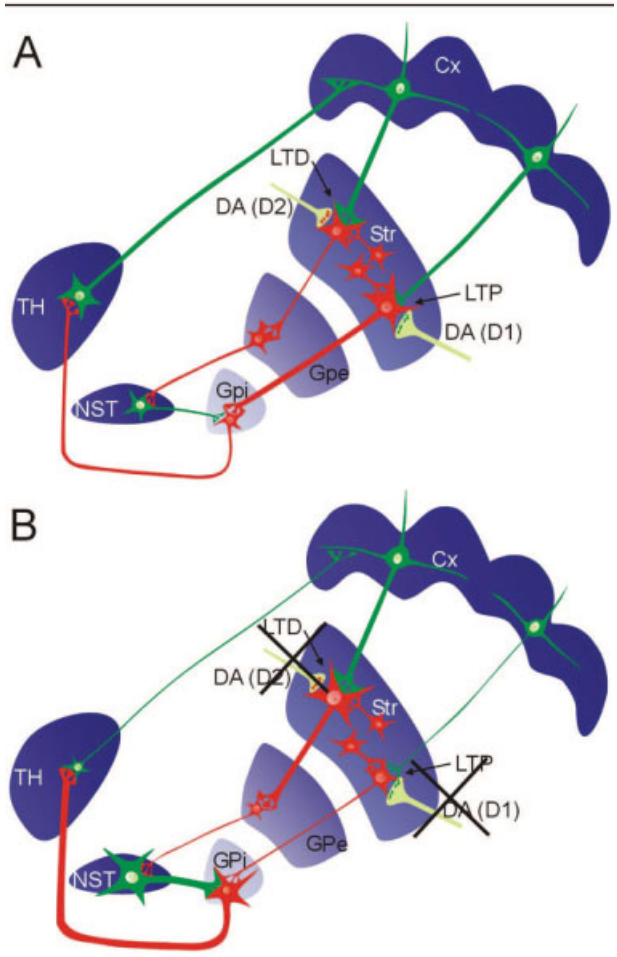


Fig 1. Classical model of the basal ganglia. (A) Normal state. Corticostriatal activity (yellow lines) *excites medium spiny neurons (MSN), causing the "direct" striato-globus pallidus pars interna (GPi) pathway and the "indirect" (green) striato-globus pallidus pars externa (GPe)-subthalamic nucleus (NST) pathway. The former inhibits, whereas the latter activates the GPi, which, in turn, provides inhibitory innervation to thalamocortical projections. Thus, the direct and indirect pathways serve to respectively facilitate or inhibit movement. Also, notably, D2-expressing neurons in the "indirect" pathway (green) primarily mediate long-term depression (LTD), whereas long-term potentiation (LTP) depends on D1 receptor activation. Repeated cortical activation could conceivably lead to enhanced synaptic transmission in the "direct" pathway (red), thereby facilitating learned movements. (B) In the parkinsonian state, dopamine depletion leads to increased activity in the "indirect" pathway and reduced activity in the "direct" pathway. This results in excessive GPi inhibitory output to the thalamus (TH). LTP and LTD are also disturbed, and there is a net shift to increased activity in the "indirect" pathway. These changes lead to reduced (parkinsonian) movements. Increased activity is shown in red, and reduced activity is shown in green for any circuit; yellow indicates no change in activity in the parkinsonian state compared with control subjects. Cx = cortex; Str = corpus striatum.*

Table. **Summary of Studies Assesing the Basal Ganglia in the Parkinsonian State as Compared with Control Values in Monkeys.**

Analytic Method	Model	Globus pallidus pars externa	Globus pallidus pars interna	Subthalamic nucleus	Substancia nigra pars reticulata	Striatum
2-DG	**MPTP**	↑ ↑	↑	↓	=	↑
	MPTP+ DA agonist	↓	↑ ↑	↑ ↑	↑	↓
GAD_{67}	**MPTP**	↑ / =	↑	↑	↑	↑
	MPTP+ DA agonist	↓	=	=	=	↑
Neuronal Firing Rate	**MPTP**	↓	↑	↑	↑	↑
	MPTP+ DA agonist	↑	↓ ↓	↓	↓	↑ ↑

↑ Indicates above normal and ↓ Below normal values; = Indicates no differences from normal control.
2-DG, 2-deoxi-glucose autoradiography. GAD_{67}, Glutamic acid decarboxylase. GAD_{67} and CO-I are measured by "in situ" hybridization.

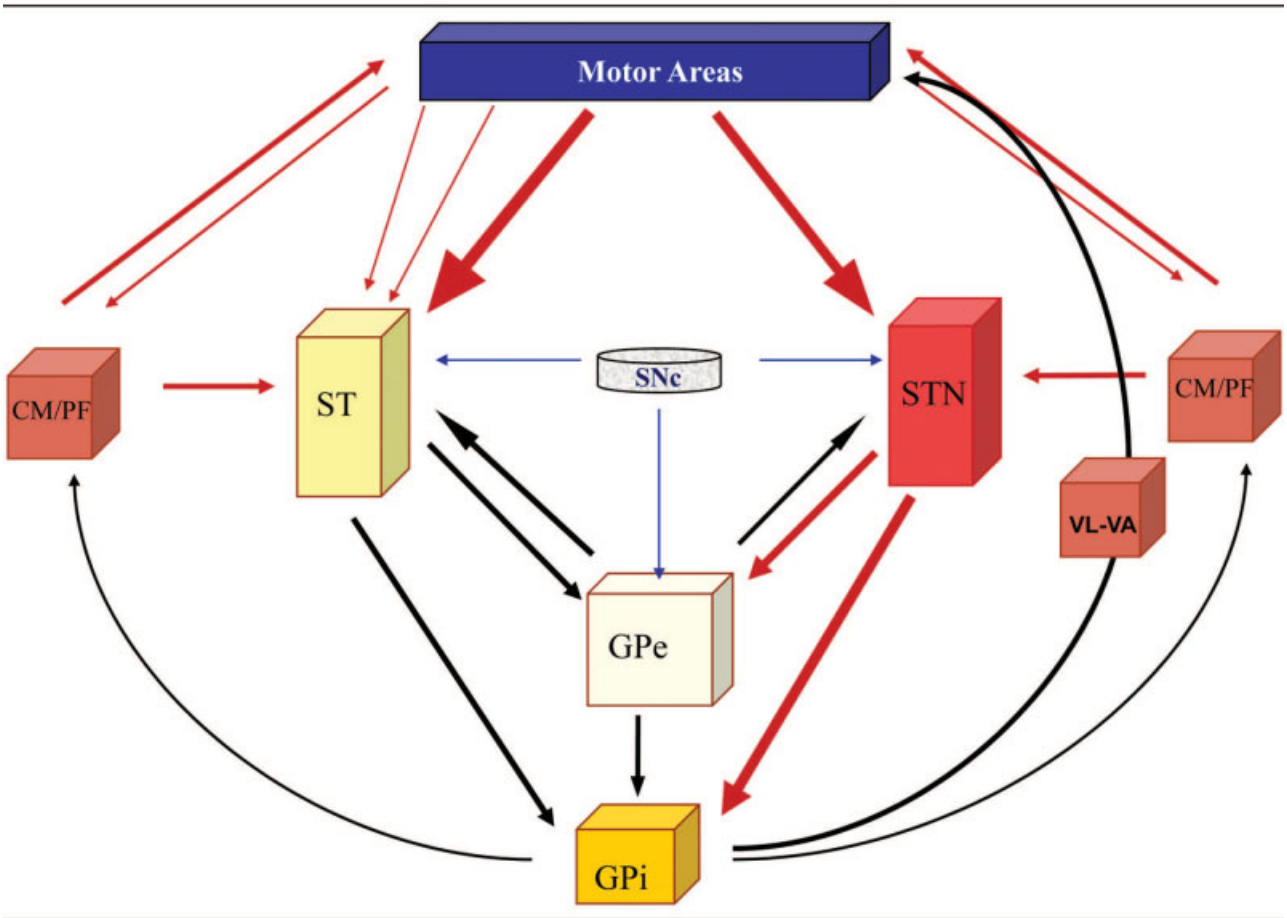


Fig 2. New model of the basal ganglia based on Nambu's work.[160] Cortical innervation to the basal ganglia is primarily by way of corticostriatal and corticosubthalamic projections. The primary basal ganglia projections back to the cortex originate in the GPi (and SNr) and pass through the ventral nuclei of the thalamus (VL-VA). Several "internal" or "horizontal" circuits control basal ganglia excitability. These include substantia nigra pars compacta (SNc) dopaminergic projections to the striatum and other basal ganglia nuclei, centromedian-parafascicular (CM/Pf) thalamic projections to the striatum and subthalamic nucleus (STN), and reciprocal connections between the globus pallidus pars externa (GPe) and the STN and striatum. In this model, the GPe appears to be strategically placed to modulate basal ganglia output.[162]

cuits that are now appreciated to be incorporated within the basal ganglia.

Clearly, the classical model of the basal ganglia[1–3] has provided a conceptual framework for better understanding the pathophysiology of PD and other movement disorders. Indeed, it had a paramount role in revitalizing functional surgery for PD[10,11] and in defining the subthalamic nucleus (STN) as a target.[12–14] Over the years, many observations made in the laboratory and in PD patients have highlighted some limitations of the original model.[15–18] Furthermore, there have been numerous advances in our understanding of the anatomic and physiological state of the basal ganglia in the normal and dopamine-depleted state. This new information is summarizedin this article, together with new hypotheses as to how the basal ganglia may be organized in these different conditions. We hope this will allow for a more comprehensive understanding of the pathophysiology of PD and a more coherent approach to the treatment of PD.

Functional Organization of the Basal Ganglia in the Normal and Parkinsonian State

Input to the Basal Ganglia

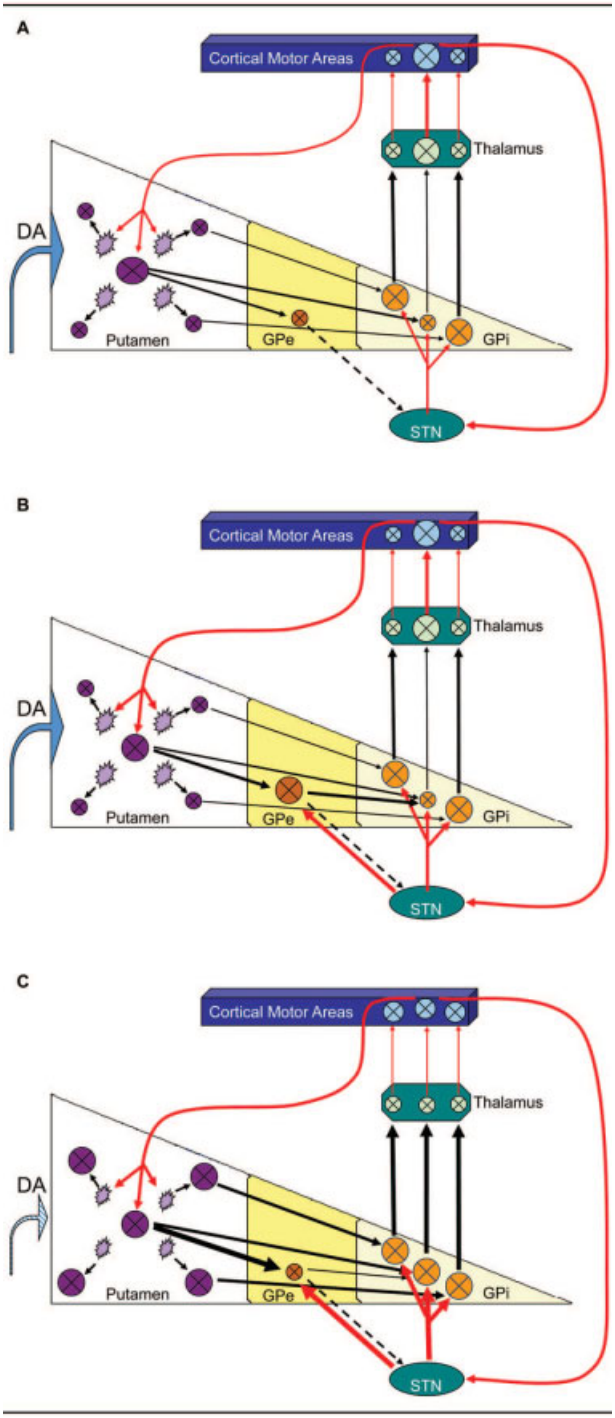
CORTICOSTRIATAL ACTIVITY: NORMAL STATE. Most striatal neurons are medium spiny GABAergic neurons (MSNs). These neurons receive huge numbers (tens of thousands) of glutamatergic inputs from the cortex and thalamus, which predominantly form asymmetric contacts on the heads of dendritic spines.[19] Input to MSNs also comes from dopaminergic, cholinergic, and GABAergic neurons, which tend to form thousands of symmetric synaptic contacts.[19] In the rat, approximately 5,000 glutamatergic afferents project to each striatal MSN, and 100 MSNs project onto each pallidal neuron. This arrangement requires a precise selection mechanism to filter incoming and outgoing signals to perform precise movements. This activity is largely mediated by dopamine and, to some extent, by GABAergic interneurons. To date, no somatotopic arrangement has been found in nigrostriatal projections. However, dopamine has been shown to modulate (both presynaptically and postsynaptically) the effects of afferent glutamatergic terminals on MSNs.[20]

The capacity of the striatum to filter the enormous number of incoming signals is facilitated by the functional anatomic and physiological organization of the striatum: (1) Cortical motor areas project in a somatotopically organized fashion to the striatum,[21] and indeed throughout the entire motor loop.[22] The leg is represented in the posterodorsal region of the putamen, the face ventrally, and the arm in-between. Cortical afferents from area 4 are placed laterally in the putamen with respect to projections from the supplementary motor area, which is more medially represented.[23] (2) Corticostriatal projections to MSNs that express D1 receptors are distinct from those projecting to MSN-expressing D2 receptors.[24] Moreover, as described in the rat,[25] D2-expressing MSNs in the "indirect" circuit receive glutamate inputs that originate in cortical layer V and have large synaptic contacts (mean diameter, 0.61μm). In contrast, cortical neurons projecting to MSNs in the "direct" circuit arise from layer III and upper layer V of the motor cortex and make thinner contact (mean, 0.45μm). This arrangement may enhance corticostriatal transmission in the "direct" pathway, which facilitates movement. (3) Most MSNs express either D1 or D2 receptors (see Fig 1A); it is generally accepted that the majority of D1-expressing neurons comprise the "direct" pathway and project to the GPi/SNr, whereas D2-bearing neurons project to the globus pallidus pars externa (GPe) and are part of the "indirect" pathway.[26,27] (4) Dopamine exerts a dual effect on MSNs,[27] inhibiting striatal D2-bearing neurons and exciting striatal neurons that express D1 receptors through L-type calcium channels.[28] (5) Activation of selected nigrostriatal projections leads to increased dopamine levels in innervated striatal regions in parallel with a marked reduction in dopamine concentration in adjacent zones.[29] This "sink and source" represents a signaling function of dopamine that may be related to reward, habit formation, and motor learning.[30] (6) The striatum contains large numbers of interneurons.[19] These include tonically active neurons (TANs), which are thought to be cholinergic, and fast-spiking interneurons, which are GABAergic. TANs have been recently shown to play a critical role in mediating the dopaminergic mechanisms associated with the plastic synaptic changes that induce long-term depression[31] and learning.[32] TANs receive glutamatergic excitatory innervation from the thalamus and the cortex,[33] and exert a complex effect on MSN excitability. One preponderant mechanism of these neurons is presynaptic inhibition of cortical glutamatergic input onto MSNs, an effect mediated by activation of muscarinic M1 and M2 receptors.[34] Thus, firing of cholinergic interneurons reduces MSN excitability to cortical afferents.[34] On the other hand, the phasic release of dopamine as typically occurs with reward stimuli induces firing pauses of TANs, which, in turn, facilitates corticostriatal transmission.

GABAergic interneurons mediate, together with axon collaterals from MSN neurons, a powerful intrastriatal inhibition.[35] This is thought to provide a mechanism to facilitate firing of a given pool of MSNs when performing a specific motor task (Fig 3A). This is based on the physiological principle of lateral inhibition.[35] The activity of these fast-spiking interneurons is also modulated by dopamine, which induces depolarization through activation of D1 receptors on their

cell surface and inhibition by acting at presynaptic D2 receptors.[36,37]

Collectively, these mechanisms permit cortical activity corresponding to a given movement to be facilitated at the striatopallidal level, whereas competing stimuli are canceled (see Fig 3A). This is supported by experimental evidence indicating that dopamine enhances synchronous corticostriatal afferent volleys whereas simultaneously inhibiting other inputs.[38]



CORTICOSTRIATAL ACTIVITY IN PARKINSON'S DISEASE. In the parkinsonian state, there is a general increase in striatal neuronal activity and particularly, an increment in the proportion of MSNs responding to stimulation of individual body parts. This translates into a reduction in somatotopic specificity.[39] However, these changes in striatal excitability are not uniform. There is decreased excitation of D1-bearing striatal neurons leading to reduced activity in the "direct" pathway. In contrast, there is reduced inhibition of D2-bearing striatal neurons resulting in increased activity in striatopallidal (GPe) projections. Mallet and colleagues[40] describe different responses of corticostriatal neurons to dopamine depletion, that is, a reduction of firing rates in the subpopulation of cortical neurons that project to MSNs in the "direct" pathway, but no effect on the activity of corticostriatal neurons projecting to MSNs, which cause the "indirect" pathway. Furthermore, voltage-clamp recordings demonstrate that, in the dopamine-depleted state, cortical terminals that project to MSNs in the "indirect" pathway are more likely to release glutamate and activate their target neurons.[41] In keeping with these observations, increased mRNA expression for enkephalin,[42,43] D2 receptors,[44,45] and

Fig 3. Schematic diagram of main corticobasal ganglia circuits and prevailing physiological concepts. (A) The "direct" and "hyperdirect" pathways. In the normal state, a movement-related corticostriatal signal excites a pool of medium spiny GABAergic neurons (MSNs) (large circle) *in the target area of the motor striatum. At the same time, there is a parallel inhibition of surrounding MSNs* (small circles) *that are unrelated to the desired action mediated by dopamine and interneurons* (small rough circles). *Transmission in activated neurons in the "direct" pathway subsequently inhibits the concomitant pool of globus pallidus pars interna (GPi) neurons, resulting in facilitation of thalamocortical activity underlying the desired action. The cortical volley also activates neurons in the subthalamic nucleus (STN; "hyperdirect" pathway), which increases excitation of surrounding neuronal pools in the GPi, thereby inhibiting the corresponding region of the thalamus and the selection of unwanted movements. This combination of effects allows for specific activation of thalamocortical fibers subserving a given motor action coupled with inhibition of surrounding neurons that promote undesired movements. (B) Globus pallidus pars externa (GPe)-STN-GPi circuit. STN activation leads to excitation of the GPe, which in the normal state leads to further inhibition of the GPi neuronal pool associated with the desired movement, thereby facilitating the effect of the "direct" pathway and the selection of the appropriate motor activity. (C) In the parkinsonian state, there is impaired capacity to filter cortical inputs and to specifically activate MSN pools responsible for a desired motor activity. In addition, the STN-GPi pathway is hyperactive and responds excessively to input signals, which reduces the signal-to-noise ratio in the GPi. Altogether, these changes make precise movement selection and execution difficult.*

glutamic acid decarboxilase (GAD67)[46–48] are found in the striatum in the parkinsonian state. In contrast, markers of cellular activity in the "direct" circuit such as mRNA expression of preprotachykinin, the gene precursor of the neuropeptide substance P, and preprodynorphin mRNA, the gene precursor of dynorphin, are decreased after dopamine lesion in the rat[41,43,49] and in the MPTP monkey.[42,50] Curiously, expression of mRNA for D1 receptor is decreased in 6-OHDA–lesioned rats[49] but increased or unchanged in MPTP monkeys.[44,45] These differences may be related to variations in the degree of dopamine depletion and the capacity for motor recovery between the rats and monkeys.

Dopamine depletion can also impair synaptic plasticity in several ways. Long-term depression or potentiation (LTP) induced on MSNs by cortical high-frequency stimulation[51,52] is eliminated by dopamine blockade or lesions. Corticostriatal synapses also exhibit bidirectional synaptic plasticity, which means that they can be either potentiated or depressed depending on the information arriving from the cortex. Cortical low-frequency stimulation reverses previously induced corticostriatal long-term potentiation and evokes long-term depression, in a process known as *depotentiation,* which appears to be crucial for the storage of memory and the elimination of incorrect or useless information.[53] This plasticity and the capacity to express depotentiation is lost in rats with 6-OHDA lesions that have developed dyskinesias in response to L-dopa.[54]

Loss of nigrostriatal dopaminergic activity in rodents, MPTP monkeys, and PD patients is associated with a significant loss in the number and length of dendritic spines of MSNs.[55,56] This occurs rapidly after dopamine depletion and was described in mice to specifically affect D2-bearing MSNs in the "indirect" pathway through activation of L-type, voltage-gated calcium channels.[55] This finding is not easy to fit with the above data that point to enhanced activity of MSNs in the "indirect" pathway. A profound loss of dendritic spines on D2-bearing MSNs should lead to reduced glutamatergic activation and reduced excitability. A recent study in MPTP monkeys confirmed a 50% loss of dendritic spines, particularly in the motor putamen where dopamine depletion is greatest, but failed to demonstrate a differential reduction between D1- and D2-bearing MSNs (R. Villalba, personal communication).

Dopamine depletion also affects the activity of striatal interneurons. Fino and colleagues,[57] in a series of in vitro experiments, showed that membranes of fast-spiking GABAergic interneurons became less excitable after dopamine depletion. However, in vivo recordings from dopamine-depleted rats show that these neurons do not change their firing rate in response to cortical stimulation.[39] These seemingly contradictory results may be related to the effects of dopamine depletion on MSNs and TANs, which, in turn, may affect fast-spiking interneuron excitability.

The effect of dopamine depletion on cholinergic interneurons is also somewhat controversial. Activation of D1 and D5 receptors on cholinergic neurons produces membrane depolarization,[37] but activation of presynaptic D2 receptors reduces acetylcholine postsynaptic potentials.[58] In monkeys, MPTP lesions cause an increase in oscillatory (approximately 16Hz) activity of TANs,[59] but no change in their basal firing rate[60] or in their degree of synchronization.[61] Overall, it has generally been found that dopamine depletion is associated with an increase in the excitability of cholinergic (ie, TANs) interneurons and inhibition of GABA interneurons. These changes result in impaired corticostriatal transmission and reduced feed-forward intrastriatal inhibition. Together, these findings may be directly related to the difficulty PD patients have in selecting and generating movement amplitude and speed.

In summary, dopamine depletion caused a bias in corticostriatal transmission toward activating GABAergic MSNs in the "indirect" circuit leading to excess inhibition of neurons in the GPe (see Fig 1B).

CORTICOSUBTHALAMIC ACTIVITY: NORMAL STATE. The STN is now appreciated to be subdivided into a motor, associative, and limbic region. The dorsolateral STN corresponds with the motor region and is further subdivided based on site of origin of afferent fibers. Fibers from the primary motor area (area 4) project to the lateral tip of the STN, whereas afferents from the supplementary motor area are more medially placed.[61] In the monkey, STN neurons fire at a rate of approximately 30Hz and provide tonic excitatory input to both the GPe and GPi. Thus, a lesion or blockade of the STN is associated with a significant reduction in the mean firing rate of pallidal neurons.[62,63]

Initial studies recording STN activity in awake monkeys who were performing a task indicated that neuronal firing occurred after or coinciding with movement initiation.[64] This finding suggests that the STN was not involved with movement onset, in keeping with the then prevailing idea that the STN was primarily related to inhibition of movement. However, recent studies recording single-cell activity and local field potentials in patients with PD have shown clear evidence of activation of STN neurons up to 1 second before initiation of a movement.[65–67] It thus appears that when a voluntary movement is to be performed, cortical volleys are simultaneously dispatched to the putamen and the STN. Indeed, microstimulation of the motor cortex in the monkey evokes a short latency excitatory response in the STN (approximately 6 milliseconds) followed by a brief inhibition and a second excitatory response at approximately 19 milliseconds.[63]

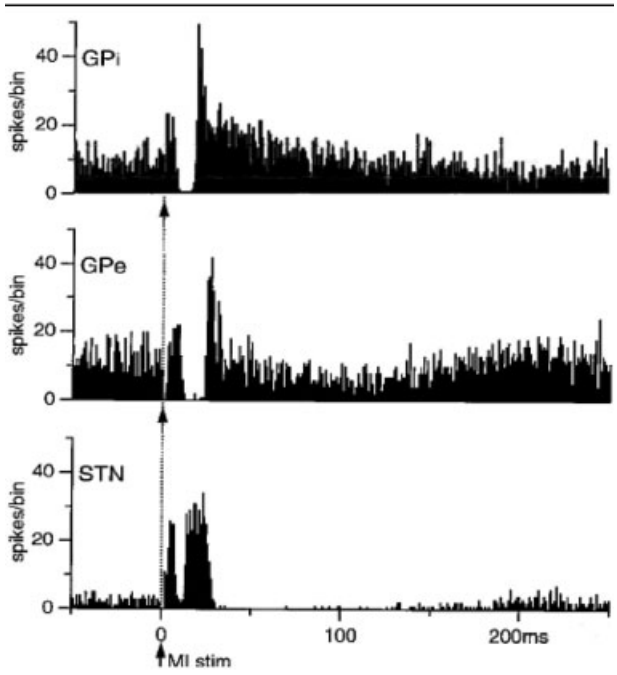


Fig 4. Response of subthalamic nucleus (STN), globus pallidus pars externa (GPe), and globus pallidus pars interna (GPi) neurons to motor cortex microstimulation. The cortical volley first excites the STN with a short latency (5–7 milliseconds), which, in turn, leads to excitation of the GPe and GPi. This is followed by a short period of inhibition in the STN caused by reciprocal firing of GABAergic neurons in the GPe and then by a period of relatively robust excitation. The initial discharge in GPe together with the inhibitory activity in the "direct" pathway mediate the inhibition in the GPi, which facilitates movement. Adapted from Tachibana and colleagues[68] and Kita and coauthors,[102] by permission.

The same response pattern is recorded in the GPe and GPi[63,68] some 2 to 3 milliseconds later (Fig 4). Accordingly, it is now thought that cortico-STN-GPe/GPi projections represent a fast-conducting system that is well placed to modulate basal ganglia output. Indeed, a recent functional magnetic resonance imaging study found that STN activation was specifically associated with stopping an ongoing movement.[68,69] Such action engages a network comprising the inferior frontal cortex, STN, GP, and pre-supplementary motor area. Interestingly, experiments in the rat with STN lesions showed premature responses to a cue signaling reward and impairment in the capacity to suppress competing responses.[70] These results are in keeping with findings indicating that deep brain stimulation (DBS) of the STN impairs the capacity to stop making wrong decisions.[71] These types of findings have led to the hypothesis that the STN normally reduces the excitability of the basal ganglia and the cortical circuitry involved in decision making, thus allowing extra time to consider the best option when confronted with conflicting choices.[72] These findings have important pathophysiological implications. First, they suggest that PD patients will take a longer time but perhaps perform more efficiently when posed with difficult decision making. Second, it suggests that patients with a lesion of the STN should perform poorly in similar situations and fail to suppress making bad choices. Indeed, STN-DBS has been shown to trigger behavioral and mood disorders such as hyperactivity, increased suicidal ideations, and abnormal control of impulses, euphoria, and laughing, but also apathy, crying, and depression,[73,74] which is in keeping with the involvement of the STN in the control of behavior and emotions. In summary, the old idea that the STN is exclusively involved in inhibiting movement[75,76] must now be revisited.

CORTICOSUBTHALAMIC ACTIVITY: PARKINSONIAN STATE. STN neuronal activity is increased in the parkinsonian state leading to excessive neuronal recruitment and augmented inhibitory output of the GPi and SNr. This has been shown by neuronal recordings in vivo and by molecular markers of increased metabolic activity such as cytochrome oxidase (CO) and 2-dexoyglucose (see the Table). Indeed, STN hyperactivity may be considered as the best defined functional feature of the parkinsonian state.[77] It is now well recognized that blockade or lesion of the STN in the dopamine-depleted state is associated with functional restoration of basal ganglia and thalamocortical activity, and improvement in parkinsonian features in both animal models[78] and PD patients.[79]

Interestingly, the origin of the STN hyperactivity in PD has not been completely ascertained. The classical model of the basal ganglia portrays that GPe hypoactivity (caused by excessive striatopallidal inhibition) is the key factor leading to disinhibition of the STN (see the next section), but this interpretation has been questioned by studies in the 6-OHDA rat and MPTP monkey showing normal levels of CO and GAD in the GPe.[80,81] Furthermore, STN has reciprocal connections with the GPe. It would be expected that if STN overactivity after a dopamine lesion was due to inhibition of GPe neurons, this feedback loop would serve to reactivate the GPe and stabilize the system unless other as yet unappreciated factors are at play. It is now known that STN neuronal activity can also be influenced through other mechanisms. The cortex, thalamus, and pedunculopontine nucleus (PPN) all send excitatory projections to the STN[82] and potentially could induce increased firing independent of the activity state of the GPe. The corticosubthalamic pathway was found to be underactive in the 6-OHDA–lesioned rat,[83] but the centromedian/parafascicular complex and the PPN are overactive in the same model (Fig 5) and could cause a state of hyperactivity in the parkinsonian brain (presumably through activation of the STN).[84] Indeed, lesions of the PPN reverse hy-

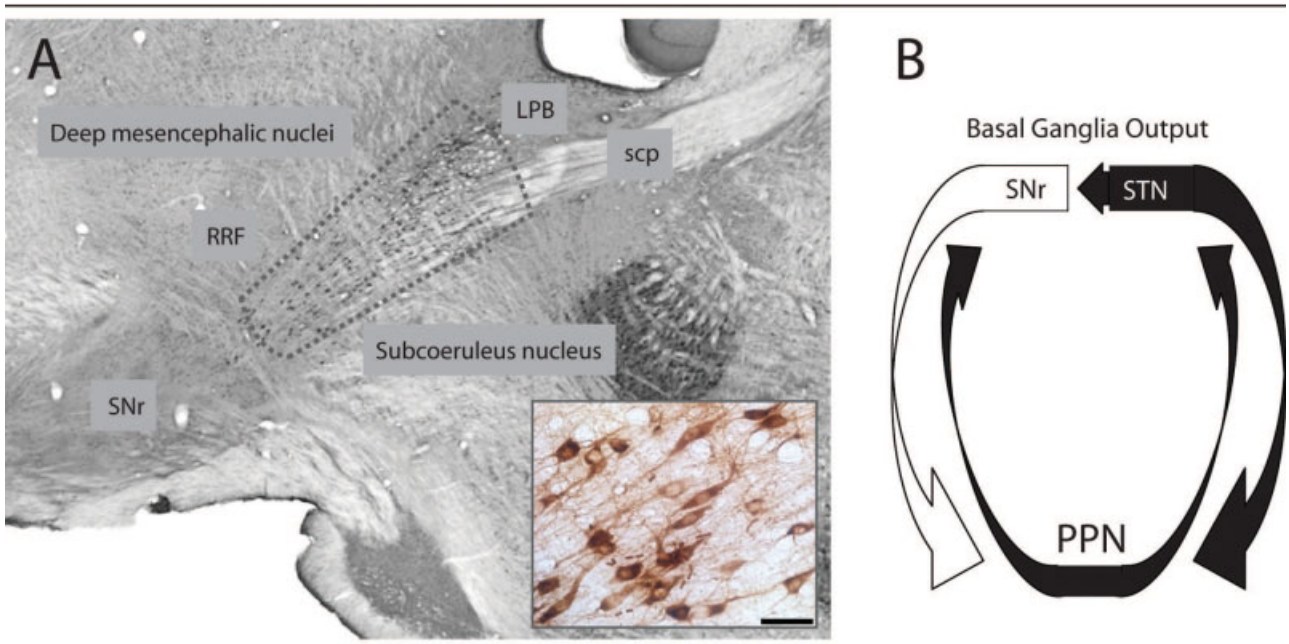


Fig 5. Anatomy of the pedunculopontine nucleus (PPN) and its main relation to the basal ganglia in the rat. (A) The boundaries of the PPN are typically defined by the borders of the cholinergic population (dotted line), *stained in this example using immunohistochemistry for choline acetyltransferase (inset). Scale bar = 50μm. Adjacent structures include the deep mesencephalic nuclei and retrorubral field (RRF) dorsally, the subcaeruleus nucleus ventrally, the substantia nigra pars reticulata (SNr) rostrally, and the lateral parabrachial nucleus (LPB) caudally. The PPN is crossed by the subcerebellar peduncle (scp). (B) The PPN receives afferents from all of the basal ganglia, particularly inhibitory fibers from the basal ganglia output nuclei (SNr in the rat;* white arrow*) and excitatory fibers from the subthalamic nucleus (STN;* black arrow*). PPN projections to the basal ganglia are predominantly excitatory.*

peractivity in the STN in 6-OHDA–lesioned rodents.[85] Dopamine depletion also has a direct effect on STN activity.[84,86] Local interruption of dopamine terminals directed to the STN increase its activity, indicating a direct modulatory effect of dopamine on the STN.[84] We have postulated that early denervation of the STN in PD may act as a compensatory mechanism that maintains the basal ganglia output within normal limits despite a progressive loss of striatal dopamine,[87] thus potentially explaining why clinical features do not emerge until there is a 70 to 80% reduction in striatal dopamine levels.

THALAMOSTRIATAL AND THALAMOSUBTHALAMIC PROJECTIONS IN THE NORMAL AND PARKINSONIAN STATES. The centromedian-parafascicular (CM-Pf) is an important source of glutamatergic innervation of the basal ganglia, with major projections to the striatum,[88,89] STN,[90] globus pallidus, and substantia nigra.[90] The CM-Pf forms two "internal" or "transverse" loops within the basal ganglia (see Fig 2), which suggests it has a modulatory effect on the striatum and STN.

In rats with 6-OHDA lesions, Pf neurons that innervate the STN and the striatum are hyperactive,[91,92] and Pf ablation reverses the increase in STN metabolic activity associated with the parkinsonian state.[93] However, we found neither antiparkinsonian benefit nor amelioration of L-dopa–induced dyskinesias after chemical ablation of the CM nucleus in MPTP-treated monkeys.[94] This casts doubts on the likelihood that this intralaminar nucleus plays an important role in the pathophysiology of PD. It is still possible, though, that the CM is involved in more complex aspects of movement and behavioral control.

Output of the Basal Ganglia

The main output of the basal ganglia for movement control of the face and limbs stems from the GPi/SNr, which project to the thalamocortical and brainstem motor regions. Considerable evidence indicates that the excitability and the firing pattern of GPi/SNr neurons play a key role in determining normal function, parkinsonism, and motor complications such as dyskinesia. The excitability and firing pattern of GPi/SNr neurons is influenced and controlled by several key projections: (1) the striatopallidal circuit ("direct" pathway), (2) the cortico-STN-GPi/SNr projection, (3) dopaminergic and serotoninergic afferents, and (4) the GPe-GPi/SNr projection. Movement facilitation is associated with a pause or a reduction in neuronal firing rate in the GPi (or the SNr), which, in turn, facilitates thalamocortical activation.[1,3] This has classi-

cally been interpreted as being mediated by the "direct" pathway (see Fig 1), which caused the inhibition, whereas activation of the "indirect" pathway leads to thalamic inhibition and stops unwanted movements[95] (see Figs 1A and 3A). Recording of neuronal activity in monkeys indeed shows changes in firing rate in GPe and GPi in keeping with this general assumption,[96] but also shows that individual neighboring neurons can express a decrease, increase, or both in firing frequency depending on the characteristics of the task.[97,98] This can be taken to indicate that activation of corticoputaminal-GPi activity ("direct" pathway) is not necessarily the predominant or the only mechanism involved in facilitating movement. Rather, facilitation of movement is now known to principally involve GPe and STN connections with the GPi.

GLOBUS PALLIDUS PARS EXTERNA-SUBTHALAMIC NUCLEUS-GLOBUS PALLIDUS PARS INTERNA-THALAMIC NETWORK: NORMAL STATE. The GPe, STN, and GPi form a highly organized network that exhibits a precise anatomic correspondence.[99] For example, reciprocally interconnected areas of the GPe and STN converge on the same region of the GPi. The GPe projection to the GPi is important and accounts for about half of GPi afferents.[100] Importantly, about 40% of GPe neurons also project to the striatum where they predominantly synapse with interneurons.[101] The GPe is therefore perfectly placed to exert a powerful impact on basal ganglia information processing (see Fig 2).

In the normal monkey, Kita and coauthors[102] show that 10Hz stimulation of the STN induced strong excitation of the GPe and a shorter latency brief excitation of the GPi, which is followed by an inhibitory response (see Fig 4). This inhibition is mediated by the GPe (local blockade of GABA afferents onto the GPi eliminate it) and predominates over the initial short-latency STN-GPi excitatory response. This implies that, after cortical activation, the incoming excitatory volley onto the STN predominantly leads to inhibition of the GPi via activation of the inhibitory GPe disynaptic connection with the GPi (see Fig 3B).

Cortical activity associated with movement initiation leads to parallel activation of two afferent loops to the basal ganglia, that is, the striatum and the STN (see Fig 2). Subsequently, the GPe receives an inhibitory volley from GABAergic-enkephalin MSNs in the indirect pathway and excitation via STN projections. Both projections onto the GPe are disynaptic, and it is likely that the cortically derived signals arrive close in time. Simultaneously, the GPi receives a disynaptic short-duration excitation via the cortico-STN-GPi projection and inhibition from the GABAergic-substantia P-dynorphin "direct" pathway (see Fig 2). Under these series of events, the third synaptic component of the circuit, the GPe-GPi inhibitory synapse, can modulate GPi neuronal excitability and directly influence its output effect on thalamocortical projections. This organization is ideal for assisting in the performance of motor activities such as repetitive, sequential, and switching movements, which require precise spatial and temporal selection of different muscle groups.

The GPe also has connections with the reticular nucleus of the thalamus, the SNc, and the PPN.[103] It is perhaps also important to appreciate that both the GPe and GPi receive dopaminergic innervation by a nigropallidal projection, as well as from collaterals of nigrostriatal axons.[103] Indeed, D2-expressing neurons are found in about 40 to 50% of all pallidal neurons,[104] and local administration of dopamine into the GP (in the rat) modifies the neuronal firing rate.[105] Thus, dopamine exerts a direct physiological effect on pallidal activity that may be physiologically relevant and relevant to the pharmacological effects of dopaminergic drugs in PD.

GLOBUS PALLIDUS PARS EXTERNA-SUBTHALAMIC NUCLEUS-GLOBUS PALLIDUS PARS INTERNA-THALAMIC NETWORK: PARKINSONIAN STATE. The functional state of the GPe in the parkinsonian state has been a matter of discussion[106,107] (see the Table). Studies have reported a low firing rate in the GPe of parkinsonian animals,[108] no change,[109] or slight increase at the time of onset of parkinsonian signs.[110] More recently, a detailed study[111] in the MPTP monkey showed that GPe firing is significantly lower than normal and the GPe/GPi discharge rate is well below 1 (the normal ratio). In addition, GABA release (measured by microdialysis) was reduced in the STN and GAD (measured by immunoradiography) was increased in the GPe, in keeping with previous findings.[105,106] This study[110] supports the original model contention that the GPe is functionally hypoactive in the parkinsonian state leading to reduced inhibition of the STN and GPi. However, it also demonstrates a dissociation between neuronal electrophysiological activity and GAD expression in the GPe, which had been at the base of previous questioning of the functional state and role of this nucleus in PD.[80,87] It is possible that these discrepancies are related to changes in GPe excitability and activity throughout the evolution of PD.[87] This idea is supported by a recent study of the time course of CO-I activity after a unilateral intrastriatal injection of 6-OHDA in the rat.[112] This approach induces a slower and less complete SNc degeneration than the classical approach where the toxin is injected directly into the nigrostriatal fascicle. Although CO-I activity was ultimately increased in all basal ganglia nuclei examined (GP, STN, SNr, and the entopeduncular nucleus = GPi in primates), the temporal pattern varied among the different nuclei throughout the evolution of damage. In the GP, an immediate decrease in CO-I activity

was observed at day 1, followed by a modest (+10%) increase that peaked (+25%) by the fourth week after lesion developed. The STN showed a moderate increase in CO-I activity at day 1 and remained increased throughout the 4 weeks after lesion developed. The output nuclei (SNr and entopeduncular nucleus, EP) exhibited a triphasic metabolic response with a significant increase at day 1, reduction at 3 and 7 days after injection, and a permanent increase after the third week. Basal ganglia output was, therefore, kept within normal limits during the initial 2 weeks probably through compensatory mechanisms in the GPe-STN-GPi circuitry. It has been shown that GPe activity (or GP in the rat) remains within normal limits during the initial (presymptomatic) period of nigrostriatal dopamine loss[113] and maintains basal ganglia output within normal limits,[87] which likely accounts for why animals are asymptomatic during this stage. In addition, dopamine innervation of the GPi is higher in MPTP monkeys who exhibit clinical recovery after MPTP,[114] and F-dopa positron emission tomography shows increased uptake in the GPi in the early but not advanced stages of PD.[115] Thus, the basal ganglia network adapts to the functional effects of dopamine depletion in several ways beyond the nigrostriatal system, and changes are not concatenated in an orderly manner as was suggested by the original pathophysiological model.

In summary, the GPe-STN-GPi network has the capacity to modulate basal ganglia output to a greater extent than is widely appreciated, and it may compensate for the functional consequences of striatal dopamine loss and the initial changes in the "indirect" and "direct" pathways. Once the dopaminergic deficit surpasses the threshold for the available compensatory mechanisms, the GPe-STN-GPi network becomes hyperactive and loses its normal physiological tuning. It may be said that the symptomatic parkinsonian state is characterized by a shift in the internal excitability of the BG (see Fig 3C). Here, overactivity in the excitatory STN-GPi pathway predominates and overwhelms the inhibitory effects of GPi afferents from the GPe (which is hypoactive) and the "direct" pathway.[116] This leads to excessive firing of the GPi in response to afferent signals[117] and a decreased signal-to-noise ratio,[118] thereby impeding the normal facilitation of a desired movement.

BASAL GANGLIA-BRAINSTEM ACTIVITY: NORMAL AND PARKINSON'S DISEASE STATES. The basal ganglia projects to the brainstem and, therefore, is in a position to influence excitability of several brainstem centers and functions. These include the control of saccadic movement of the eyes, the blink reflex and startle reaction, up-righting, postural reflexes, and locomotion. Gait and balance are important sources of disability in PD and are generally not adequately controlled with available therapies. Among the brainstem centers that are linked to the basal ganglia, the PPN has attracted particular attention because of its relation to sleep disorders and gait dysfunction seen in PD.

The PPN is composed of a heterogeneous population of neurons with long-range axonal projections that target primarily the basal ganglia[119] (see Fig 5). The PPN is implicated in a wide variety of functions, such as locomotion, inhibition of motor activity during REM sleep, and possibly attention.[120,121] By means of a mixture of cholinergic, glutamatergic, and GABAergic fibers, PPN neurons project preferentially to two main targets in the basal ganglia, the STN and the SNr/GPi.[122,123] PPN also projects to the SNc and the ventral tegmental area. In turn, PPN neurons receive dense glutamatergic and GABAergic projections arising from the STN and SNr/GPi, respectively.[123,124, 125]

A role of the PPN in PD has been suspected since the late 1980s. In a postmortem study, Hirsch and colleagues[126] identified a decrease in the number of cholinergic neurons in the PPN in PD patients. Recently, a reduction in CO-I activity (measured by in situ hybridization) of acetylcholine neurons in the PPN of MPTP monkeys has also been reported,[127] but this was not associated with cell loss. These findings could be explained by increased GABAergic input from the SNr and GPi. On the other hand, in the parkinsonian state, the PPN receives an increased glutamatergic input originating from the STN that should drive PPN neurons to increase their basal firing rate, which, in turn, could further increase STN firing. This dual excitatory connection between the PPN and STN could form a positive feed-forward loop that could perpetuate abnormal basal ganglia hyperactivity (see Fig 5). Theoretically, one would expect that reducing the activity in one of them could lead to a decrease in the activity of the others. Indeed, lesions of the PPN have been reported to induce parkinsonism in monkeys.[128]

Low-frequency DBS in the PPN has been recently proposed as a novel target for the surgical treatment for PD.[129] This is based on the idea that the massive outflow from the GPi in PD has overinhibited the PPN. Indeed, one study in the MPTP monkey model showed improvement in akinesia after local infusion of a GABA antagonist into the PPN,[130] and low stimulation of the PPN led to improvement of parkinsonian features in MPTP monkeys.[131] A pilot study of DBS of the PPN has shown promising results particularly with respect to locomotion that could not be obtained with stimulation of the STN.[132] Recently, it has also been shown that stimulation of the PPN improves H-reflex excitability in PD patients[133] arguing in favor of a direct effect on spinal cord physiology. Despite all these clues, the functional state of the PPN in the parkinsonian state is not well defined, and this may prove difficult to define given its heterogeneous cell popula-

tion and the possibility that its neuronal activity may change over the course of the disease.

Pathophysiology of Parkinson's Disease: Current Concepts and Therapeutic Consequences

ORIGIN OF CARDINAL FEATURES AND UNEXPLAINED PROBLEMS. Poverty of spontaneous movements (hypokinesia) and slowness of voluntary movement (bradykinesia) are fundamental features of the general phenomenon of akinesia in PD. The evidence summarized earlier indicates that dopamine depletion shifts the balance of basal ganglia activity toward the "indirect" circuit where the GPe-STN-GPi microcircuit plays a paramount role (see Fig 3C).

Increased output from the GPi overinhibits the thalamocortical projection reducing cortical neuronal activation associated with movement initiation. In addition, the putamen, STN, and GPi show an abnormal augmented neuronal response to peripheral stimulation with synchronous firing of neighboring neurons. This could impair the normal selection or filtering of incoming signals that characterizes normal basal ganglia physiology (see Fig 3C). Thus, the basal ganglia is shifted toward inhibiting cortically aided movements by an increased gain of the STN-GPi network and reduced excitability in the "direct" cortico-putaminal-GPi projection.[116,134] Typical features in PD also include an alteration of automatic movements with reduced blinking rate, a positive Meyerson's sign, decreased arm swing, and short stride length when walking. All of these are probably mediated by brainstem mechanisms, which are also functionally impaired by excessive basal ganglia inhibitory outputs. This has been elegantly shown experimentally for the excitability of the blink reflex.[135] Presumably, a similar mechanism underlies the impairment of other automatic movements in PD. However, the current understanding of basal ganglia pathophysiology does not provide an adequate explanation for other essential characteristic motor abnormalities in PD.[136] These include difficulty in performing simultaneous and sequential movements, a progressive reduction in amplitude while performing a repetitive movement, and the striking improvement in gait freezing induced by visual cues. A newer outlook to understand some of these problems has arisen by the study of neuronal populations as a complement to single-cell recordings.

The several loops connecting the BG internally and also with the thalamus and brainstem provide ample possibilities for neuronal synchronization and network oscillations. Animal studies have shown that DA depletion is associated with increased synchronization of neuronal activity throughout the BG.[137,138] The standard application of DBSs of the internal part of the globus pallidus (GPi) or STN to treat PD currently allows the recording of local field potentials on a routine basis. There is general agreement that in the "off" medication state, the STN shows a predominant activity in the high alpha-low beta range (11–30Hz), which is attenuated when parkinsonian signs abate during the "on" medication state.[139,140] The latter is also characterized by a peak around 60 to 80Hz in the power spectrum and by an increase in the theta band when L-dopa–induced dyskinesias are present. Voluntary movements lead to a significant reduction of the alpha-beta activity starting about 1 second before movement initiation and continuing until movement is ended. This sequence occurs both in the "off" and "on" states, although the beta band reduction in the "on" state is less overt because activity (ie, energy power) is already reduced. In healthy subjects, movement-related changes in oscillatory activity in the motor cortex are similar to those found in the STN.[141] All of the above have led researchers to suggest that PD patients may have greater difficulty than healthy individuals in reducing beta activity before movement, which could provide a better explanation of several akinetic/bradykinetic features.

The current basal ganglia model does not provide any explanation for the two other cardinal features of PD, that is, rigidity and tremor. Regarding the latter, it is now realized that the parkinsonian state is characterized not only by neuronal hyperactivity in basal ganglia output neurons but also by increased neuronal synchronization of cell firing leading to oscillations,[18] which are particularly evident when tremor is present. Recording neuronal activity in patients with PD[142] has shown a definite correlation between tremor in the limbs and rhythmical 4 to 6Hz firing in basal ganglia nuclei (GPe, GPi, STN), as well as in the ventralis intermedius nucleus (Vim) of the thalamus.[143] Lesion or DBS of the STN, GPi, and Vim are all well known to stop tremor in PD. However, the Vim is a cerebellar receiving area and is not directly connected with the BG. Studies in organotypic cultures showed that the GPe and STN in the dopamine deficient state have an enhanced tendency to rhythmical and reciprocal firing, causing 4 to 5Hz bursting activity.[144] It is therefore tempting to suggest that the complex organization of basal ganglia circuits has a tendency to generate oscillatory activity that produces tremor in PD. It remains to be elucidated whether mechanisms engaging tremor are primarily mediated and depend on striatal dopamine deficiency or are the consequence of impairment of direct dopaminergic projection to the STN, GPe, and GPi or the thalamus.[145] On the other hand, a recent study in vervet monkeys shows a low-pass filter capacity of the motor cortex for stimulation of the GPi at more than 5Hz.[146] This led the authors to suggest that the 4 to 6Hz tremor-related activity seen in PD is not really driving the motor system, but that tremor in

PD primarily originates outside the basal ganglia (ie, brainstem motor nuclei or spinal cord). This is indeed a challenging proposal. How dopamine deficiency leads to abnormal oscillatory activity in an extensive motor network that involves the basal ganglia, cerebellum, thalamus, and motor cortex is not well understood. It is equally not well understood why some PD patients have tremor and some do not, and why lesions in the Vim improve tremor but not rigidity and bradykinesia, whereas all of these features are improved with lesions of the STN or GPi.

Rigidity is essentially an increase in resistance to passive movement. Accordingly, it has been thought for decades that rigidity should be related to an enhancement of stretch reflex excitability. The tonic stretch reflex, as well as the phasic long-latency stretch reflex, is facilitated in PD patients.[147,148] How the basal ganglia changes associated with dopamine depletion modify the excitability of stretch reflex mechanisms has not really been explored. It is well known that basal ganglia surgery (ie, pallidotomy, subthalamotomy, and DBS of either GPi or STN), as well as thalamotomy involving the anteroventral thalamic nucleus (receiving the pallidal projection) has a marked antirigidity effect. But the precise mechanism responsible for this effect is not known. One interesting point is that primary cortical excitability is enhanced in the parkinsonian state,[149] unlike premotor and prefrontal areas, which are hypoactive, and it is conceivable that projections to the STN from area 4 might have increased reflex gain. This would allow afferent impulses from muscles and joints during movement to excite the "hyperdirect" cortico-STN-GPi pathway. In keeping with this concept, STN and GPi neurons respond readily to muscle stretching and vibration (which selectively activates Ia afferent fibers) in the MPTP monkey and PD patients. However, how such increased GPi responses would lead to facilitation of the stretch reflex is not apparent.

THERAPEUTIC CONSEQUENCES. In the presymptomatic phase of PD, the functional consequences of a slow decline in striatal dopamine content are compensated for by changes in the remaining nigrostriatal dopamine neurons and by adjustments in the basal ganglia and cortical circuits that keep "motor loop" activity within normal limits despite progressive neurodegeneration.[150] Eventually, the equilibrium is lost and the cardinal features of PD begin to emerge. Compensatory mechanisms remain active, however, explaining the subtle clinical manifestations that are present in the early stages of the disease (ie, cardinal features are limited to one body part or hemibody) despite massive striatal dopamine depletion. Thus, in the parkinsonian state, the basal ganglia are no longer operating normally, but the network is still able to function in a relatively stable manner. This essential feature of basal ganglia functional organization and compensation is totally disrupted by standard L-dopa therapy.[151] Progressive neurodegeneration and loss of nigrostriatal fibers leads to an inability to maintain tonic dopamine receptor stimulation, which is the basic mechanism regulating striatal neuronal excitability.[152] Intermittent doses of standard L-dopa lead to oscillations in plasma L-dopa that are translated into pathological fluctuations in striatal dopamine levels and intermittent dopamine receptor activation. Physiologically, this discontinuous or pulsatile stimulation of striatal dopamine receptors is translated into abnormal firing patterns in basal ganglia output neurons that lead to motor complications. Thus, apomorphine or L-dopa given as a bolus can reduce the increased firing rate of GPi neurons that characterize the "off" state and improve motor function in a PD patient, but does not normalize basal ganglia output.[17] The "on" state continues to be associated with hypoactivity of the STN and GPi so that the GPe/GPi firing rate ratio (normal, approximately 1) is markedly increased[153]; in addition, there is a marked modification in the prevailing oscillatory activity, that is, reduction of beta rhythm and increment of theta band with the onset of dyskinesias.[139,140] Furthermore, L-dopa reduces but does not normalize the percentage of correlated pairs of neurons with synchronous firing in the GPi and GPe of MPTP monkeys.[153] Thus, intermittent doses of standard L-dopa do not normalize the physiology of the basal ganglia and may, in fact, act as a "destabilizing" stimulus by repeatedly exposing the denervated basal ganglia, over a few hours, to large, unregulated, extrasynaptic levels of dopamine alternating with a state of severe dopamine deficiency. We believe that such intermittent dopaminergic induces abnormal "pulsatile" stimulation of striatal dopamine receptors leading to dysregulation of intracellular signals and plastic changes in MSNs ultimately associated with motor complications, particularly dyskinesias.[154] This concept suggests that delivery of L-dopa in a more continuous manner might be more physiological and reduce the risk for inducing motor complications.[154] Indeed, L-dopa infusion is associated with a highly significant reduction in both "off" time and dyskinesia in advanced PD patients in comparison with standard intermittent L-dopa doses.[155]

A final therapeutic consideration concerns the issue of when to initiate symptomatic treatment in PD. The common medical practice has been to delay pharmacological treatment until warranted by the severity of symptoms and signs. In PD, this practice has been strongly influenced by experience indicating that L-dopa treatment is eventually associated with motor complications. However, one can argue that early, and adequate, intervention enhances basal ganglia compensatory mechanisms and contributes to better clinical control.[156] The TEMPO (TVP-1012 in Early Mono-

therapy for Parkinson's Disease Outpatients) study demonstrated that early introduction of the monoamine oxidase B inhibitor rasagiline provided long-term benefits that could not be equaled by later introduction of the same drug.[157] Furthermore, the ELLDOPA (Earlier versus Later Levadopa Therapy in Parkinson Disease) study[158] showed that de novo PD patients treated with L-dopa soon after diagnosis had significantly less deterioration on the Unified Parkinson's Disease Rating Scale than did placebo-treated patients, even when examined 2 weeks after stopping L-dopa therapy. Such observations cannot be explained by means of L-dopa pharmacokinetics and in all probability are related to changes in basal ganglia circuitry induced by symptomatic treatment. In fact, the long-duration response to L-dopa in the 6-OHDA rat[159] is paralleled by a gradual return of basal ganglia (STN, SNr) activity toward parkinsonian levels. With the availability of dopaminergic agents that are well tolerated, have a low adverse effect profile, and are not likely to induce motor complications, we now advocate introducing dopaminergic therapy to PD patients as soon as feasible, and possibly even at the time of diagnosis.

Conclusions

Current concepts about the organization of the basal ganglia emphasize the existence of several "internal" mechanisms that modulate input/output activity, and sustain normal selection and execution of movement.[160,161] In the parkinsonian state, this filtering mechanism is deranged and precise neuronal tuning is lost. The current model provides a reasonable explanation for the origin of akinetic features in PD and the response to drugs and surgery.[162] However, we are still in need of a more comprehensive model that accounts for the other cardinal features such as rigidity and tremor, as well as gait dysfunction, attention and learning deficits, emotional disturbances, and cognitive disorders, which are all now realized to form part of the global clinical picture of PD. Further understanding of the intimate pathophysiological mechanisms underlying the different manifestations of PD could potentially lead to more refined and more effective treatments that more completely restore the physiological balance of the basal ganglia.[162] Currently, effort should be made toward using this type of information to introduce dopaminergic therapies in as physiological a manner as possible and to avoid where possible the use of nonphysiological discontinuous dopaminergic stimulation that provokes newer abnormalities and further destabilizes an already abnormal basal ganglia network.

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References

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–375.
2. Crossman AR. Primate models of dyskinesias: the experimental approach to the study of basal ganglia-related involuntary movement disorders. Neuroscience 1987;21:1–40.
3. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–285.
4. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.
5. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266–271.
6. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev 2000;31: 236–250.
7. Buhusi CV, Meck WH. What makes us tick? Functional and neural mechanisms of interval timing. Nat Neurosci Rev 2005;6:755–765.
8. Hikosaka O, Nakamura K, Sakai K, et al. Central mechanisms of motor learning. Curr Opin Neurobiol 2002;12:217–222.
9. Yin HH, Knowlton B. The role of the basal ganglia in habit formation. Nat Neurosci Rev 2006;7:464–476.
10. Obeso JA, Guridi J, DeLong MR. Surgery for Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62:2–8.
11. Olanow CW. Pallidotomy: have we made a dent in Parkinson's disease? Ann Neurol 1996;40:341–343.
12. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436–1438.
13. Aziz TZ, Peggs D, Sambrook MA, et al. Lesions of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl, 1, 2, 3, 6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 1991;6:288–292.
14. Guridi J, Herrero MT, Luquin MR, et al. Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis. Brain 1996;119:1717–1727.
15. Obeso JA, Rodríguez MC, DeLong MD. Basal ganglia pathophysiology: a critical review. Adv Neurol 1997;73:3–18.
16. Obeso JA, Rodríguez-Oroz MC, Rodríguez M, et al. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000;23(suppl):S8–S19.
17. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, et al. Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with current model. Ann Neurol 2000; 47(suppl 1):22–32.
18. Montgomery EB. Basal ganglia physiology and pathophysiology: a reappraisal. Parkinsonism Relat Disord 2007;13: 455–465.
19. Wilson CJ. Basal ganglia. In: Sphepherd GM, ed. The synaptic organization of the brain. Oxford: Oxford University Press, 2004:361–414.
20. Bamford NS, Robinson S, Palmiter R, et al. Dopamine modulates release from corticostriatal terminals. J Neurosci 2004; 24:9541–9552.

21. Takada M, Tokuno H, Nambu A, et al. Corticostriatal projections from the somatic areas of the frontal cortex in the macaque monkey: segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the promotor cortex. Exp Brain Res 1998;120:114–128.
22. DeLong MR, Crutcher MD, Georgopoulos AP. Primate globus pallidus and subthalamic nucleus functional organization. J Neurophysiol 1985;53:530–543.
23. Miyahi S, Lu X, Imanishi M, et al. Somatotopically arranged inputs from putamen and subthalamic nucleus to primary motor cortex. Neurosci Res 2006;56:300–308.
24. Lee FJ, Wang YT, Liu F. Direct receptor cross-talk can mediate the modulation of excitatory and inhibitory neurotransmission by dopamine. J Mol Neurosci 2005;26:245–252.
25. Lei W, Jiao Y, Del Mar N, et al. Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats. J Neurosci 2004;24: 8289–8299.
26. Onn SP, West AR, Grace AA. Dopamine-mediated regulation of striatal neuronal and network interactions. Trends Neurosci 2000;23(suppl):48–56.
27. West AR, Grace AA. Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining in vivo intracellular recordings and reverse microdialysis. J Neurosci 2002;22:294–304.
28. Hernandez-Lopez S, Bargas J, Sumeier DJ, et al. D1 receptor activation enhances evoked discharge in neostriatal medium spiny neurons by modulating an L-type Ca2+ conductance. J Neurosci 1997;17:3334–3342.
29. Rodriguez M, Morales I, Gomez I, et al. Heterogeneous dopamine neurochemistry in the striatum: the fountain-drain matrix. J Pharmacol Exp Ther 2006;319:31–43
30. McHaffie JG, Stanford TR, Stein BE, et al. Subcortical loops through the basal ganglia. Trends Neurosci 2005;28:401–407.
31. Wang Z, Kai L, Dopaminey M, et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. Neuron 2006;50:443–452.
32. Morris G, Arkadir D, Nevet A, et al. Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons. Neuron 2004;43:133–143.
33. Calabresi P, Centonze D, Bubellini P, et al. Acetylcholine-mediated modulation of striatal funtion. Trends Neurosci 2000;23:120–126.
34. Pakhotin P, Bracci E. Cholinergic interneurons control the excitatory input to the striatum. J Neurosci 2007;27:391–400.
35. Tepper MJ, Koós T, Wilson CJ. GABAergic microcircuits in the neostriatum. Trends Neurosci 2004;27:662–669.
36. Bracci E, Centonze D, Bernardi G, Calabresi P. Dopamine excites fast-spiking interneurons in the striatum. J Neurophysiol 2002;87:2190–2194.
37. Centonze D, Grande C, Usiello, et al. Receptor subtypes involved in the presynaptic and postsynaptic actions of dopamine on striatal interneurons. J Neurosci 2003;23: 6245–6254.
38. Bamford NS, Zhang H, Schmitz Y, et al. Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals. Neuron 2004;42:653–663.
39. Cho H, Duke D, Manzino L, et al. Dopamine depletion causes fragmented clustering of neurons in the sensorimotor striatum: evidence of lasting reorganization of corticostriatal input. J Comp Neurol 2002;452:24–37.
40. Mallet N, Ballion B, Le Moine C, Gonon F. Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats. Neurobiol Dis 2006;26: 3875–3884.
41. Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature 2007;445:643–647.
42. Morissette M, Grondin R, Goulet M, et al. Differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists. J Neurochem 1999;72:682–692.
43. Marin C, Aguilar E, Mengod G, et al. Concomitant short- and long-duration response to levodopa in the 6-OHDA-lesioned rat: a behavioural and molecular study. Eur J Neurosci 2007; 25:259–269.
44. Betarbet R, Greenamyre JT. Regulation of dopamine receptor and neuropeptide expression in the basal ganglia of monkeys treated with MPTP. Exp Neurol 2004;189:393–403.
45. Herrero MT, Augood SJ, Asensi H, et al. Effects of l-dopa therapy on dopamine D-2 receptor mRNA expression in the striatum of MPTP-intoxicated parkinsonian monkeys. Mol Brain Res 1996;42:149–155.
46. Soghomonian JJ, Chesselet MF. Effects of nigrostriatal lesions on the levels of messenger RNAs encoding two isoforms of glutamate decarboxylase in the globus pallidus and entopeduncular nucleus of the rat. Synapse 1992;11:124–133.
47. Carta AR, Pinna A, Cauli O, et al. Differential regulation of GAD67, enkephalin and dynorphin mRNAs by chronic intermittent L-Dopa and A2A receptor blockade plus L-Dopa in dopamine-denervated rats. Synapse 2002;44:166–174.
48. Katz J, Nielsen KN, Soghomonian JJ. Comparative effects of acute or chronic administration of levodopa to 6-hydroxydopamine-lesioned rats on the expression of glutamic acid decarboxylase in the neostriatum and GABA-A receptors subunits in the substantia nigra, pars reticulata. Neuroscience 2005;132:833–842.
49. Gerfen CR, Engber TM, Mahan LC, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidopaminel neurons. Science 1990;250:1429–1432.
50. Herrero MT, Augood SJ, Hirsch EC, et al. Effects of L-Dopa on prepronekephalin and preprotachykinin gene expression in the MPTP-treated monkey striatum. Neuroscience 1995;68: 1189–1198.
51. Calabresi P, Maj R, Pisani A, et al. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosci 1992;12:4224–4233.
52. Calabresi P, Pisani A, Mercuri NB, Bernardi G. Long-term potentiation in the striatum is unmasked by removing the voltage-dependent magnesium block of NMDA receptor channels. Eur J Neurosci 1992;4:929–935.
53. Fino E, Glowinski J, Venance L. Bidirectional activity-dependent plasticity at corticostriatal synapses. J Neurosci 2005;25:11279–11287.
54. Picconi B, Centonze D, Hakansson K, et al. Loss of bidirectional striatal synaptic plasticity in L-Dopa-induced dyskinesia. Nat Neurosci 2003;6:501–506.
55. Day M, Wang Z, Ding J, et al. Selective elimination of glutamatergic synapses on striatopallidopaminel neurons in Parkinson disease models. Nat Neurosci 2006;9:251–259.
56. Stephens B, Mueller AJ, Shering AF, et al. Evidence of a breakdown of corticostriatal connections in Parkinson's disease. Neuroscience 2005;132:741–754.
57. Fino E, Glowinski J, Venance L. Effects of acute dopamine depletion on the electrophysiological properties of striatal neurons. Neurosci Res 2007;58:305–316.
58. Pisani A, Bonsi P, Centonze D, et al. Activation of D2-like dopaminergic receptors reduces synaptic inputs to striatal cholinergic interneurons. J Neurosci 2000;20:RC69.

59. Raz A, Frechter-Mazar V, Feingold A, et al. Activity of pallidal and striatal tonically active neurons is correlated in mptp-treated monkeys but not in normal monkeys. J Neurosci 2001;21:128.
60. Aosaki T, Kimura M, Graybiel AM. Temporal and spatial characteristics of tonically active neurons of the primate's striatum. J Neurophysiol 1995;73:1234–1252.
61. Nambu A, Takadopamine M, Inase M, Tokuno H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci 1996;16:2671–2683.
62. Wichmann T, Bergman H, DeLong MR. 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 1994;72:521–530.
63. Nambu A, Tokuno H, Hamadopamine I, et al. Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. J Neurophysiol 2000;84:289–300.
64. DeLong MR, Crutcher MD, Georgopoulos AP. Primate globus pallidus and subthalamic nucleus functional organization. J Neurophysiol 1985;53:530–543.
65. Rodriguez-Oroz MC, Rodriguez M, Guridi J, et al. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. Brain 2001;124: 1777–1790.
66. Paradiso G, Saint-Cyr JA, Lozano AM, et al. Involvement of the human subthalamic nucleus in movement preparation. Neurology 2003;61:1538–1545.
67. Alegre M, Alonso-Frech F, Rodriguez-Oroz MC, et al. Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. Eur J Neurosci 2005;22:2315–2324.
68. Tachibana Y, Kita H, Chiken S, et al. Motor cortical control of internal pallidal activity through glutamatergic and GABAergic inputs in awake monkeys. Eur J Neurosci 2008; 27:238–253.
69. Aron AR, Poldrack RA. Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 2006;26:2424–2433.
70. Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. Nat Neurosci 2005;8:484–489.
71. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318:1309–1312.
72. Frank MJ. Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 2006;19:1120–1136.
73. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–839.
74. Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci USA 2007;104:10661–10666.
75. Purdon Martin J, Alcock NS. Hemichorea associated with a lesion of the corpus Luysii. Brain 1934;57:504–516.
76. Carpenter MB, Whittier JR, Mettler FA. Analysis of choreoid hyperkinesia in the rhesus monkey. J Comp Neurol 1950;92: 293–322.
77. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, et al. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000;23(suppl):8–19.
78. Guridi J, Herrero MT, Luquin MR, et al. Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis. Brain 1996;119:1717–1727.
79. Trost M, Su S, Su P, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. Neuroimage 2006;31:301–307.
80. Levy R, Hazrati LN, Herrero MT, et al. Re-evaluation of the functional anatomy of the basal ganglia in normal and parkinsonian states. Neuroscience 1997;76:335–343.
81. Obeso JA, Rodríguez-Oroz MC, Rodríguez M, et al. Current problems in understanding the basal ganglia model for Parkinson′s disease and levodopa-induced dyskinesias. Ann Neurol 2000;47(suppl 1):22–32.
82. Hassani OK, Mouroux M, Feger J. Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience 1996;72: 105–115.
83. Orieux G, Francois C, Feger J, Hirsch EC. Consequences of dopaminergic denervation on the metabolic activity of the cortical neurons projecting to the subthalamic nucleus in the rat. J Neurosci 2002;22:8762–8770.
84. Kreiss DS, Anderson LA, Walters JR. Apomorphine and dopamine D(1) receptor agonists increase the firing rates of subthalamic nucleus neurons. Neuroscience 1996;72:863–876.
85. Breit S, Lessmann L, Unterbrink D, et al. Lesion of the pedunculopontine nucleus reverses hyperactivity of the subthalamic nucleus and substantia nigra pars reticulata in a 6-hydroxydopamine rat model. Eur J Neurosci 2006;24: 2275–2282.
86. Smith Y. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and parkinsonian brains. Mov Disord 2008;23:708–715.
87. Obeso JA, Rodriguez-Oroz MC, Lanciego JL, Rodriguez M. How does Parkinson's disease begin? The role of compensatory mechanisms. Trends Neurosci 2004;27:125–127.
88. Sidibe M, Smith Y. Differential synaptic innervation of striatofugal neurones projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey. J Comp Neurol 1996;365:445–465.
89. Castle M, Aymerich MS, Sanchez-Escobar C, et al. Thalamic innervation of the direct and indirect basal ganglia pathways in the rat: ipsi-and contralateral projections. J Comp Neurol 2005;483:143–153.
90. Tande D, Feger J, Hirsch EC, Francois C. Parafascicular nucleus projection to the extrastriatal basal ganglia in monkeys. Neuroreport 2006;17:277–280.
91. Orieux G, Francois C, Feger J, et al. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. Neuroscience 2000;97:79–88.
92. Aymerich MS, Barroso-Chinea P, Perez-Manso M, et al. Consequences of unilateral nigrostriatal denervation on the thalamostriatal pathway in rats. Eur J Neurosci 2006;23: 2099–2108.
93. Bacci JJ, Kachidian P, Kerkerian-Le Goff L, Salin P. Intralaminar thalamic nuclei lesions: widespread impact on dopamine denervation-mediated cellular defects in the rat basal ganglia. J Neuropathol Exp Neurol 2004;63:20–31.
94. Lanciego JL, Rodriguez-Oroz MC, Blesa FJ, et al. Lesion of the centromedian thalamic nucleus in MPTP-treated monkeys. Mov Disord 2008;23:708–715.
95. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 1996;50: 381–425.
96. Turner RS, Anderson ME. Pallidopaminel discharge related to the kinematics of reaching movements in two dimensions. J Neurophysiol 1997;77:1051–1074.

97. Matsumura M, Tremblay L, Richard H, Filion M. Activity of pallidal neurons in the monkey during dyskinesia induced by injection of bicuculline in the external pallidum. Neuroscience 1995;65:59–70.
98. Turner RS, Anderson ME. Context-dependent modulation of movement-related discharge in the primate globus pallidus. J Neurosci 2005;25:2965–2976.
99. Smith Y, Bevan MD, Shink E, Bolam JP. Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 1998;86:353–387.
100. Smith Y, Wichmann T, DeLong MR. Synaptic innervation of neurones in the internal pallidal segment by the subthalamic nucleus and the external pallidum in monkeys. J Comp Neurol 1994;343:297–318.
101. Billings LM, Marshall JF. Glutamic acid decarboxylase 67 mRNA regulation in two globus pallidus neuron populations by dopamine and the subthalamic nucleus. J Neurosci 2004; 24:3094–3103.
102. Kita H, Tachibana Y, Nambu A, Chiken S. Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. J Neurosci 2005;25:8611–8619.
103. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 1995;20:91–127.
104. Floran B, Floran L, Sierra A, Aceves J. D2 receptor-mediated inhibition of GABA release by endogenous dopamine in the rat globus pallidus. Neurosci Lett 1997;237:1–4.
105. Galvan A, Floran B, Erlij D, Aceves J. Intrapallidal dopamine restores motor deficits induced by 6-hydroxydopamine in the rat. J Neural Transm 2001;108:153–166.
106. Delfs JM, Anegawa NJ, Chesselet MF. Glutamate decarboxylase messenger RNA in rat pallidum: comparison of the effects of haloperidol, clozapine and combined haloperidol-scopolamine treatments. Neuroscience 1995;66:67–80.
107. Herrero MT, Levy R, Ruberg M, et al. Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum. Neurology 1996;47:219–224.
108. Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991;547:142–151.
109. Benazzouz A, Boraud T, Feger J, et al. Alleviation of experimental hemiparkinsonism by high-frequency stimulation of the subthalamic nucleus in primates: a comparison with L-Dopa treatment. Mov Disord 1996;11:627–632.
110. Bezard E, Boraud T, Bioulac B, Gross CE. Involvement of the subthalamic nucleus in glutamatergic compensatory mechanisms. Eur J Neurosci 1999;11:2167–2170.
111. Soares J, Kliem MA, Betarbet R, et al. Role of external pallidal segment in primate parkinsonism: comparison of the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism and lesions of the external pallidal segment. J Neurosci 2004;24:6417–6426.
112. Blandini F, Levandis G, Bazzini E, et al. Time-course of nigrostriatal damage, basal ganglia metabolic changes and behavioural alterations following intrastriatal injection of 6-hydroxydopamine in the rat: new clues from and old model. Eur J Neurosci 2007;25:397–405.
113. Hassani OK, Mouroux M, Feger J. Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience 1996;72: 105–115.
114. Mounayar S, Boulet S, Tande D, et al. A new model to study compensatory mechanisms in MPTP-treated monkeys exhibiting recovery. Brain 2007;130:2898–2914.
115. Whone AL, Moore RY, Piccini PP, Brooks DJ. Plasticity of the nigropallidal pathway in Parkinson's disease. Ann Neurol 2003;53:206–213.
116. Rubchinsky LL, Kopell N, Sigvardt KA. Modeling facilitation and inhibition of competing motor programs in basal ganglia subthalamic nucleus-pallidopaminel circuits. Proc Natl Acad Sci USA 2003;100:14427–14432.
117. Filion M, Tremblay L, Bedard PJ. Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Res 1988;444:165–176.
118. Boraud T, Bezard E, Bioulac B, Gross CE. Ratio of inhibited-to-activated pallidal neurons decreases dramatically during passive limb movement in the MPTP-treated monkey. J Neurophysiol 2000;83:1760–1763.
119. Mena-Segovia J, Bolam JP, Magill PJ. Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? Trends Neurosci 2004;27:585–588.
120. Takakusaki K, Saitoh K, Haradopamine H, Kashiwayanagi M. Role of basal ganglia-brainstem pathways in the control of motor behaviors. Neurosci Res 2004;50:137–151.
121. Inglis WL, Olmstead MC, Robbins TW. Selective deficits in attentional performance on the 5-choice serial reaction time task following pedunculopontine tegmental nucleus lesions. Behav Brain Res 2001;123:117–131.
122. Woolf NJ, Butcher LL. Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. Brain Res Bull 1986;16:603–637.
123. Bevan MD, Bolam JP. Cholinergic, GABAergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J Neurosci 1995;15: 7105–7120.
124. Hammond C, Rouzaire-Dubois B, Feger J, et al. Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat. Neuroscience 1983;9:41–52.
125. Spann BM, Grofova I. Nigropedunculopontine projection in the rat: an anterograde tracing study with Phaseolus Vulgaris-leucoagglutinin (PHA-L). J Comp Neurol 1991;311:375–388.
126. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci USA 1987;84:5976–5980.
127. Gomez-Gallego M, Fernandez-Villalba E, Fernandez-Barreiro A, et al. Changes in the neuronal activity in the pedunculopontine nucleus in chronic MPTP-treated primates: an in situ hybridization study of cytochrome oxidopaminese subunit I, choline acetyl transferase, and substance P mRNA expression. J Neural Transm 2007;114:319–326.
128. Kojima J, Yamaji Y, Matsumura M, et al. Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. Neurosci Lett 1997; 226:111–114.
129. Mazzone P, Lozano A, Stanzione P, et al. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport 2005;16: 1877–1881.
130. Nandi D, Aziz TZ, Giladi N, et al. Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. Brain 2002;125: 2418–2430.
131. Jenkinson N, Nandi D, Miall RC, et al. Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. Neuroreport 2004;15:2621–2624.
132. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596–1607.

133. Pierantozzi M, Palmieri MG, Galati S, et al. Pedunculopontine nucleus deep brain stimulation changes spinal cord excitability in Parkinson's disease patients. J Neural Transm 2008; 115:731–735.
134. Leblois A, Boraud T, Meissner W, et al. Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. J Neurosci 2006;26:3567–3583.
135. Basso MA, Powers AS, Evinger C. An explanation for reflex blink hyperexcitability in Parkinson's disease. J Neurosci 1996; 16:7308–7317.
136. Marden CD. The mysterious motor functions of the basal ganglia. Neurology 1982;32:514–539.
137. Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 1994;72:507–520.
138. Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion. J Neurophysiol 2008;100:385–396.
139. Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003;18:357–363.
140. Alonso-Frech F, Zamarbide I, Alegre M, et al. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. Brain 2006;129:1748–1757.
141. Alegre M, Labarga A, Gurtubay IG, et al. Movement-related changes in cortical oscillatory activity in ballistic, sustained and negative movements. Exp Brain Res 2003;148:17–25.
142. Rodríguez MC, Guridi J, Mewes, et al. The subthalamic nucleus and tremor in Parkinson's disease. Mov Dis 1998; 13(suppl 1):111–118.
143. Ohye C, Shibazaki T, Hirai T, et al. Tremor-mediating thalamic zone studied in humans and in monkeys. Stereotact Funct Neurosurg 1993;60:136–145.
144. Bevan MD, Magill PJ, Terman D, et al. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. Trends Neurosci 2002;25:525–531.
145. Garcia-Cabezas MA, Rico B, Sanchez-Gonzalez MA, Cavadopamine C. Distribution of the dopamine innervation in the macaque and human thalamus. Neuroimage 2007;34: 965–984.
146. Rivlin-Etzion M, Marmor O, Saban G, et al. Low-pass filter properties of basal ganglia cortical muscle loops in the normal and MPTP primate model of parkinsonism. J Neurosci 2008; 28:633–649.
147. Andrews CJ, Burke JD, Lance JW. The response to muscle stretch and shortening in parkinsonian rigidity. Brain 1972; 95:795–812.
148. Rothwell JC, Obeso JA, Traub MM, Marsden CD. The behavior of the long-latency stretch reflex in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1983;46: 35–44.
149. Reis J, Swayne OB, Vandermeeren Y, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 2008; 586:325–351.
150. Bezard E, Gross MC, Brotchie JM. Presymptomatic compensation in Parkinson's disease is not dopamine-mediated. Trends Neurosci 2003;26:215–221.
151. Obeso JA, Rodriguez-Oroz M, Marin C, et al The origin of motor fluctuations in Parkinson's disease: importance of dopaminergic innervation and basal ganglia circuits. Neurology 2004;62(suppl 1):S17–S30.
152. Grace A. Physiology of the normal and dopamine-depleted basal ganglia: insights into L-DOPA pharmacotherapy. Mov Disord (in press).
153. Heimer G, Bar-Gad I, Goldberg JA, Bergman H. Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. J Neurosci 2002;22:7850–7855.
154. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006;5:677–687.
155. Stocchi F, Vacca L, Ruggieri S, Olanow CW. Infusion of levodopa methyl ester in patients with advanced PD: a clinical and pharmacokinetic study. Arch Neurol 2005;62:905–910.
156. Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: a need for reappraisal? Ann Neurol 2006;59: 559–562.
157. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson's disease. Arch Neurol 2004;61:561–566.
158. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351: 2498–2508.
159. Marin C, Aguilar E, Mengod G, et al. Concomitant short- and long-duration response to levodopa in the 6-OHDA-lesioned rat: a behavioural and molecular study. Eur J Neurosci 2007;25:259–269.
160. Nambu A. A new dynamic model of the cortico-basal ganglia loop. Prog Brain Res 2004;143:461–467
161. Obeso JA, Rodriguez-Oroz MC, Blesa J, Guridi G. The globus pallidus pars externa and Parkinson's disease: ready for prime time? Exp Neurol 2006;202:1–7.
162. Brown P, Eusebio A. Paradoxes of functional neurosurgery: clues from basal ganglia recording. Mov Disord 2008;23: 12–20.