# Pathophysiology of Parkinson's Disease: The MPTP Primate Model of the Human Disorder

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**ABSTRACT: The striatum is viewed as the principal input structure of the basal ganglia, while the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr) are output structures. Input and output structures are linked via a monosynaptic "direct" pathway and a polysynaptic "indirect" pathway involving the external pallidal segment (GPe) and the subthalamic nucleus (STN). According to current schemes, striatal dopamine (DA) enhances transmission along the direct pathway (via D1 receptors), and reduces transmission over the indirect pathway (via D2 receptors). DA also acts on receptors in GPe, GPi, SNr, and STN. Electrophysiologic and other studies in primates rendered parkinsonian by treatment with the dopaminergic neurotoxin MPTP have demonstrated a reduction of neuronal activity of GPe and an increase of neuronal discharge in STN, GPi. and SNr. These findings are compatible with the view that striatal DA loss results in increased activity over the indirect pathway. Prominent bursting, oscillatory discharge patterns, and increased synchronization of neighboring neurons are found throughout the basal ganglia. These may result from changes in the activity of local circuits (e.g., the GPe-STN "pacemaker") or from more global abnormalities of the basal ganglia-thalamocortical network. These findings have been replicated in human patients undergoing microelectrode-guided stereotactic procedures targeted at GPi or STN. PET studies in patients with Parkinson's disease have lent further support to the proposed circuit abnormalities. The current models of basal ganglia function have recently been criticized. For instance, the strict separation of direct and indirect pathways and the segregation of D1 and D2 receptors have been questioned, and the almost complete absence of motor side effects of pallidal or thalamic lesions in human patients and animals is inconsistent. These results suggest that changes in discharge patterns and synchronization between basal ganglia neurons, abnormal network interactions, and compensatory mechanisms are at least as important in the pathopohysiology of parkinsonism as changes in discharge rates in individual basal ganglia nuclei. Lesions of GPi or STN are effective in treating parkinsonism, because they reduce or abolish abnormal basal ganglia output, enabling remaining circuits to function more normally.**

**KEYWORDS: MPTP; primate; pathophysiology; pallidum; subthalamic nucleus; substantia nigra**

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## INTRODUCTION

Recent progress in neuroscience research has led to major insights into the structure and function of the basal ganglia and into the pathophysiologic basis of disorders of basal ganglia origin, such as Parkinson's disease.[1–3] The availability of suitable animal models, in particular the MPTP model of primate parkinsonism, has been crucial in this progress.[4,5] In addition, the renaissance of stereotactic surgery for Parkinson's disease and other movement disorders has provided valuable neuronal recording and imaging data from human subjects. In the following, we summarize, from a systems perspective, the pathophysiologic concepts that have arisen from the animal models and from work in patients with Parkinson's disease.

## PATHOLOGIC SUBSTRATE IN PARKINSON'S DISEASE

Idiopathic Parkinson's disease is characterized by the cardinal signs of akinesia (impaired movement initiation and poverty of movement), bradykinesia (slowness of movement), muscular rigidity, and tremor at rest. The etiology of the disease is most likely multifactorial, with both genetic and environmental/toxic factors resulting in a relatively selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), which project to the striatum (e.g., Ref. 6), and, to a lesser extent, to other basal ganglia nuclei such as the external and internal segments of the globus pallidus (GPe, GPi, respectively), the subthalamic nucleus (STN), and the substantia nigra, pars reticulata (SNr).[6] In early phases of the disease, dopamine loss affects particularly the sensorimotor portion of the striatum, the putamen, resulting in the appearance of motor disturbances early in the disease (e.g., Ref. 7). In later stages, more widespread dopamine loss affecting other regions of the basal ganglia (such as the caudate nucleus and the pallidum) and extrabasal ganglia areas (such as cortex, hypothalamus, and thalamus) as well as spread of neuronal degeneration to nondopaminergic systems (such as the locus coeruleus and the raphe nuclei) may cause the development of additional signs and symptoms (such as cognitive disabilities, sleep disorders, and mood disturbances).

## ANATOMICAL SUBSTRATE FOR CIRCUIT DYSFUNCTION IN PARKINSONISM

In order to understand how the loss of dopamine in the basal ganglia leads to the signs and symptoms of parkinsonism, it is necessary first to consider some of the anatomic and physiologic details of the basal ganglia and related structures.

The basal ganglia are a group of functionally related subcortical nuclei that include the neostriatum (comprised of the caudate nucleus and the putamen), ventral striatum, GPe, STN, GPi, SNr and SNc. They are anatomically related to large portions of the cerebral cortex, thalamus, and brain stem. The corticobasal ganglia-thalamocortical circuits appear to be organized in an orderly arrangement of segregated reentrant circuits that is thought to significantly enhance the efficiency and speed of cortical processing (see left half of FIG. 1). Most authors believe, however, that the range of behaviors seen in humans, nonhuman primates, and other species

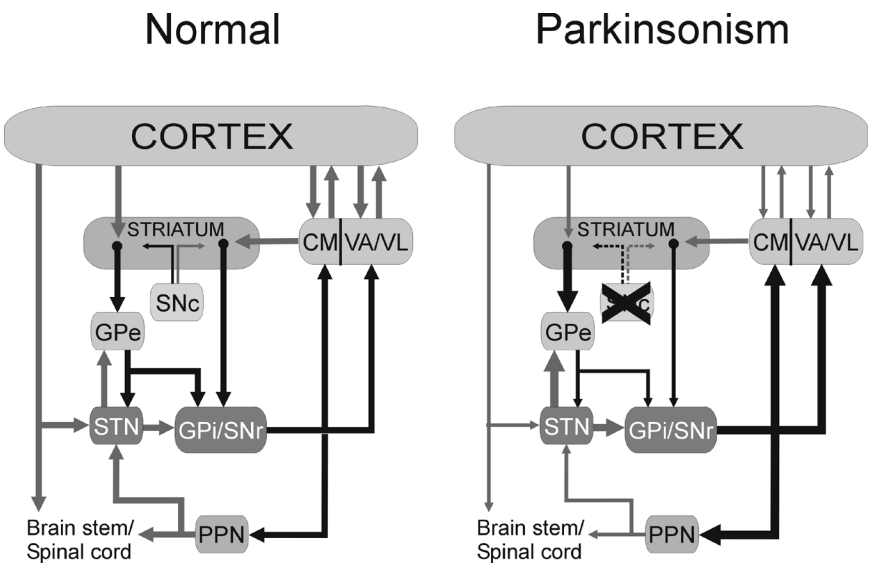


**FIGURE 1.** Simplified schematic diagram of the basal ganglia–thalamocortical circuitry under normal conditions **(left)** and rate changes in parkinsonism (**right)**. Inhibitory connections are shown as *filled arrows*, excitatory connections as *open arrows*. The principal input nuclei of the basal ganglia, the striatum and the STN, are connected to the output nuclei, GPi and SNr. Basal ganglia output is directed at several thalamic nuclei (VA/VL and CM) and at brain stem nuclei (PPN and others). In parkinsonism, dopaminergic neurons in the SNc degenerate, which results, via a cascade of changes in the other basal ganglia nuclei, in increased basal ganglia output from GPi and SNr. This, in turn, is thought to lead to inhibition of related thalamic and cortical neurons. In addition to the changes shown here, there are prominent alterations in discharge patterns (see text). For abbreviations, see text.

requires some intermodular transfer of information. Such cross-talk may occur through interactions of the basal ganglia with some of the brain stem areas or the SNc, which are not as distinctly organized into functional territories.

In primates, projections from the somatosensory, motor, and premotor cortices terminate in the postcommissural putamen, the "motor portion" of the striatum;[8,9] while associative cortical areas project to the caudate nucleus and the precommissural putamen;[10,11] and projections from limbic cortices, amygdala, and hippocampus terminate preferentially in the ventral striatum (e.g., Ref. 12). Cortical inputs also terminate in the STN.[13,14] This projection originates in the primary motor, prefrontal, and premotor cortices.[13,14]

A second major group of inputs to striatum and STN arises from the intralaminar thalamic nuclei, the centromedian nucleus (CM) and the parafascicular nucleus (Pf) (e.g., Refs. 15–17). In primates, CM projects to the motor portions of putamen and STN, whereas Pf projects largely to the associative and limbic territories.[18–20]

Topographically segregated cortical information is conveyed from the striatum to the output nuclei of the basal ganglia (GPi and SNr). Striatofugal projections main-

tain the striatal organization into motor, limbic, associative, and oculomotor territories.[21] The connections between the striatum and the basal ganglia output nuclei are thought to be organized into a *direct* and an *indirect* pathway.[2,22,23] The direct pathway arises from striatal neurons that project monosynaptically to neurons in GPi and SNr, whereas the indirect pathway arises from a different set of neurons that projects to GPe (see Ref. 24 for a review). Some striatofugal neurons may also collateralize more extensively, reaching GPe, GPi, and SNr.[25] GPe conveys the information it receives either directly to GPi/SNr or via the STN.

The population of striatal neurons that gives rise to the direct pathway can be further characterized by the presence of the neuropeptides substance P and dynorphin, by the preferential expression of the dopamine D1 receptors, and by the fact that these neurons (as well as most striatal interneurons) appear to be the targets of thalamic inputs from the centromedian nucleus.[26,27] The population that gives rise to the indirect pathway expresses preferentially enkephalin and dopamine D2 receptors[28,29] and may be the principal target of cortical inputs.[26,27] The functionally important segregation of D1 and D2 receptors between the direct and indirect pathways has been most clearly demonstrated in dopamine-depleted animals, while several studies in normal animals have supported the existence of a degree of overlap between D1- and D2-positive cell populations (e.g., Refs. 29, 30). However, the D1/D2 dichotomy may still serve to explain the apparent dual action of dopamine, released from the nigrostriatal pathway arising in the substantia nigra pars compacta, on striatal output. Dopamine appears to modulate the activity of the basal ganglia output neurons in GPi and SNr by *facilitation* of transmission over the direct pathway and *inhibition* of transmission over the indirect pathway (e.g., Ref. 31). The net effect of striatal dopamine release appears to be to reduce basal ganglia output. A reduction of dopamine release as is seen in Parkinson's disease will therefore result in a net increase in basal ganglia output.

Basal ganglia output arises from both GPi and SNr. The division of GPi into a caudoventral "motor" portion and rostromedial associative and limbic areas[32] is maintained in the pallidothalamic projections.[33] The motor territory of GPi projects almost exclusively to the posterior part of the ventrolateral nucleus (VLo in macaques), which in turn sends projections towards the supplementary motor area (SMA),[34,35] the primary motor cortex (M1),[35–37] and the premotor (PM) cortical areas.[37] Associative and limbic areas project preferentially to the parvocellular part of the ventral anterior (VA) and the dorsal VL nucleus (VLc in macaques)[33] and may be transmitted in turn to prefrontal cortical areas,[38,39] as well as to motor and supplementary motor regions[35]).

The SNr can be broadly subdivided into a dorsolateral sensorimotor and a ventromedial associative territory (e.g., Refs. 40, 41). Projections from the SNr to the thalamus terminate in the magnocellular division of the ventral anterior nucleus (VAmc) and in the mediodorsal nucleus (MDmc). These nuclei, in turn, innervate anterior regions of the frontal lobe, including the principal sulcus (area 46) and the orbital cortex (area 11),[42] as well as premotor areas and the frontal eye field.[42]

Both GPi and SNr also send projections to the noncholinergic neurons of the PPN[43–45] and the CM/Pf nuclei.[20,33] Additional projections from the SNr reach the superior colliculus; these may play a critical role in the control of saccades and orienting behaviors.[46]

## MOVEMENT-RELATED BASAL GANGLIA ACTIVITY IN NORMAL AND PARKINSONIAN ANIMALS

Voluntary movements appear to be initiated at the cortical level of the motor circuit, with output to brain stem and spinal cord, and to multiple subcortical targets including the thalamus, putamen, and the STN. Cortical activation of an ensemble of striatal motor territory neurons that give rise to the direct pathway leads to a reduction of inhibitory basal ganglia output and subsequent disinhibition of related thalamocortical neurons[47] and facilitation of the movement. In contrast, activation of striatal neurons that give rise to the indirect pathway will lead to increased basal ganglia output and, presumably, to suppression of movement. Since the majority of neurons in GPi increase their firing rate with movement,[48,49] it has been speculated that the main role of the basal ganglia is to inhibit and stabilize the activity of the thalamocortical network. As far as motor function is concerned, the basal ganglia may play a role in the control of specific kinematic parameters, such as amplitude, velocity, and direction (see, e.g., Refs. 47, 50–52) or may "focus" movements,[53] allowing intended movements to proceed and suppressing unintended movement (see discussion in Ref. 1). Besides these elemental functions in motor control, a multitude of other motor functions have been proposed, such as a role in self-initiated (internally generated) movements, in motor (procedural) learning, and in movement sequencing (e.g., Refs. 54–56). The functions of the nonmotor portions of the basal ganglia may be analogous to the motor functions but are less well explored.

### *Global Activity Changes in the Basal Ganglia*

The study of pathophysiologic changes in the basal ganglia that result from loss of dopaminergic transmission has been greatly facilitated by the discovery that primates treated with MPTP develop behavioral and anatomic changes that closely mimic the features of Parkinson's disease in humans.[5,57,58] Early studies in this model suggested that the metabolic activity (as measured with the 2-deoxy-glucose technique) is increased in both pallidal segments (e.g., Refs. 59, 60). This was interpreted as evidence for increased activity of the striatum-GPe connection and the STN-GPi pathway; or, alternatively, as evidence for increased activity via the projections from the STN to both pallidal segments. It was then shown with microelectrode recordings of neuronal activity that MPTP-induced parkinsonism in primates is associated with reduced tonic neuronal discharge in GPe and increased discharge in STN, GPi, and SNr, as compared to normal controls (see example recordings in FIG. 2 and Refs. 61–64). In parkinsonian patients undergoing pallidotomy it has been shown that the average discharge rate in GPe is significantly lower than that in GPi.[65–67]

The changes in discharge rates in the basal ganglia nuclei have been interpreted as indicating that striatal dopamine depletion leads to increased activity of striatal neurons of the indirect pathway, resulting in inhibition of GPe, and subsequent disinhibition of STN and GPi/SNr. In addition, loss of dopamine in the striatum should also lead to reduced activity via the inhibitory direct pathway. Increased basal ganglia output to the thalamus and increased inhibition of thalamocortical neurons have been corroborated by 2-deoxy-glucose studies in which increased (synaptic) activity in the VA and VL nucleus of thalamus was demonstrated.[59,60] PET studies in parkinsonian patients

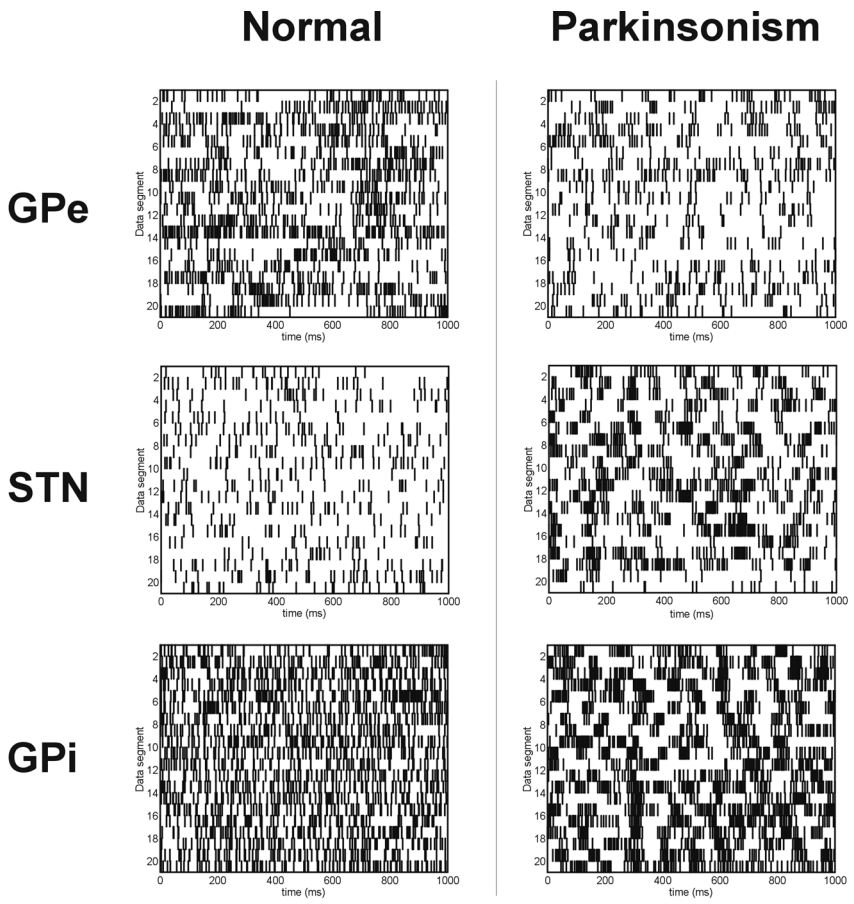


**FIGURE 2.** Raster displays of spontaneous neuronal activity recorded in different basal ganglia structures within the basal ganglia circuitry in normal and parkinsonian primates. Shown are 20 consecutive 1000-ms segments of data from GPe, STN, and GPi. The neuronal activity is reduced in GPe and increased in STN, GPi, and SNr (not shown). In addition to the rate changes, there are also obvious changes in the firing patterns of neurons in all four structures, with a marked prominence of burstiness and oscillatory discharge patterns in the parkinsonian state. For abbreviations and further explanation, see text.

have shown that the activation of motor and premotor areas in parkinsonian patients is reduced (e.g., Refs. 68, 69) although no changes have been seen in the thalamus. Alterations of cortical activity in motor cortex and supplementary motor areas have also been demonstrated with single-cell recording in hemiparkinsonian primates.[70] The proposed pathophysiologic model of changes in the level of activity in the basal ganglia–thalamocortical motor circuit is summarized in FIGURE 1.

The basal ganglia circuitry incorporates multiple negative and positive feedback loops, which may play a prominent role in the development and maintenance of ab-

normal discharge in the basal ganglia output structures. Some of the primary feedback loops that may directly affect GPi activity involve intrinsic basal ganglia structures such as GPe and STN, or structures outside of the basal ganglia, such as the thalamic nucleus CM, or the pedunculopontine nucleus (PPN).[71,72] Positive feedback loops, for instance those involving PPN and STN and the pathway through CM and the putamen, tend to enhance the abnormalities of discharge in the basal ganglia output nuclei associated with Parkinson's disease; whereas negative feedback circuits, such as a feedback involving CM and STN, will act to normalize neuronal discharge in the basal ganglia output nuclei.

Conceivably, increased tonic inhibition of thalamocortical neurons by excessive output from GPi/SNr may reduce the responsiveness of cortical mechanisms involved in motor control. Increased tonic inhibition of thalamocortical neurons by increased basal ganglia output in parkinsonism may also render precentral motor areas less responsive to other inputs normally involved in initiating movements or may interfere with "set" functions that have been shown to be highly dependent on the integrity of basal ganglia pathways.[22] All of these effects may lead to akinesia.

Brain stem areas such as the PPN may also be involved in the development of akinesia. It has been shown that lesions of this nucleus in normal monkeys can lead to hemiakinesia, possibly by reducing stimulation of SNc neurons by input from the PPN or by a direct influence on descending pathways.[73,74] It remains unclear, however, whether the motor abnormalities seen after PPN inactivation are, in fact, related to parkinsonism, or represent changes in behavioral state or other disturbances that have no direct relation to Parkinson's disease. It is noteworthy that these animals do not manifest rigidity or tremor, which appear to be critically dependent on thalamic circuitry.

Due to the fact that parkinsonism is a *network* or circuit disease, surgical or pharmacologic interventions at a variety of targets within the network could be successful. This can, indeed, be appreciated when considering the results of lesion studies in parkinsonian primates. One of the most important and dramatic in this regard was the demonstration that lesions of the STN in MPTP-treated primates reverse all of the cardinal signs of parkinsonism, presumably by reducing GPi activity.[75,76] Similarly, GPi and SNr inactivation have been shown to be effective against at least some parkinsonian signs in MPTP-treated primates.[77–79]

Over the last decade, these results from animal studies have rekindled interest in functional neurosurgical approaches to the treatment of medically intractable Parkinson's disease. This was first employed in the form of GPi lesions (pallidotomy)[80–84] and, more recently, with STN lesions (see, e.g., Ref. 85). In addition, high-frequency deep-brain stimulation (DBS) of both the STN and GPi have been shown to reverse parkinsonian signs, probably by multiple modes of action—for instance, by inhibition of STN neurons through "depolarization block" or activation of inhibitory afferents, or by true activation of STN efferents to the pallidum. PET studies in pallidotomy and DBS patients performing a motor task have shown that frontal motor areas whose metabolic activity was reduced in the parkinsonian state became active again after the procedure.[81,86]

### *Altered Discharge Patterns*

Several important findings in lesion patients are not compatible with the rate-based model presented in FIGURE 1. For instance, in contrast to the prediction of sim-

ple rate-based models, lesions of the "basal ganglia–receiving" areas of the thalamus (VA/VL) do not lead to parkinsonism and are, in fact, beneficial in the treatment of both tremor and rigidity (see, e.g., Ref. 87). Similarly, lesions of GPi in the setting of parkinsonism lead to improvement in all aspects of Parkinson's disease without any obvious detrimental effects. Furthermore, they are effective against both parkinsonism and drug-induced dyskinesias (see, e.g., Refs. 88, 89). Dyskinesias are thought to arise from pathologic *reduction* in basal ganglia outflow[1,90] and should, thus, not respond positively to further reduction of pallidal outflow (see, e.g., Ref. 91). These findings suggest that factors other than changes in the discharge rates may be important in the development of Parkinson's disease.

Alterations in discharge patterns and synchronization between neighboring neurons have been extensively documented in parkinsonian monkeys and patients. For instance, neuronal responses to passive limb manipulations in STN, GPi, and thalamus (e.g., Refs. 61–63, 92) have been shown to occur more often, to be more pronounced, and to have widened receptive fields after treatment with MPTP. There is also a marked change in the synchronization of discharge between neurons in the basal ganglia (see example in FIG. 3). Cross-correlation studies have revealed that a substantial proportion of neighboring neurons in globus pallidus and STN discharge in unison in MPTP-treated primates.[63] This is in contrast to the virtual absence of synchronized discharge of such neurons in normal monkeys (e.g., Ref. 93). Finally, the proportion of cells in STN, GPi, and SNr with discharge in oscillatory or nonoscillatory bursts is greatly increased in the parkinsonian state.[62,63,94,95]

It has been argued that some of these abnormal discharge patterns may develop as a reflection of abnormal, proprioceptive input. This is particularly obvious for tremor, in which proprioceptive input to the basal ganglia would be expected to be oscillatory. However, tremor could also be *caused* by synchronized oscillations in the basal ganglia arising from changes in local pacemaker networks, such as a feedback circuit involving GPe and STN,[96] perhaps through loss of extrastriatal dopamine (see, e.g., Refs. 97, 98). In addition, intrinsic membrane properties of basal ganglia neurons are conducive to the development of oscillatory discharge.[99,100] Increased inhibitory basal ganglia output may also contribute to the generation of oscillatory discharge in the thalamus,[1,101] which may then be transmitted to the cortex. Finally, and perhaps most likely, oscillations throughout the entire basal ganglia-thalamocortical network may be tightly related to each other, so that no one "oscillator" can be identified as their sole source (see, e.g., Ref. 102).

While tremor is perhaps the most obvious example of a parkinsonian sign that may develop as a consequence of abnormally patterned basal ganglia output, certain aspects of akinesia or bradykinesia may also be related to altered neuronal activity. Thus, increased phasic activity in the basal ganglia may erroneously signal excessive movement or velocity to precentral motor areas, leading to a slowing or premature arrest of ongoing movements and to greater reliance upon external clues during movement. Alternatively, phasic alteration of discharge in the basal ganglia may simply introduce noise into thalamic output to the cortex that is detrimental to cortical operations. The polarity and exact nature of the abnormal patterning and overall activity in the basal ganglia–thalamocortical pathways may determine the nature of the resulting movement disorder.

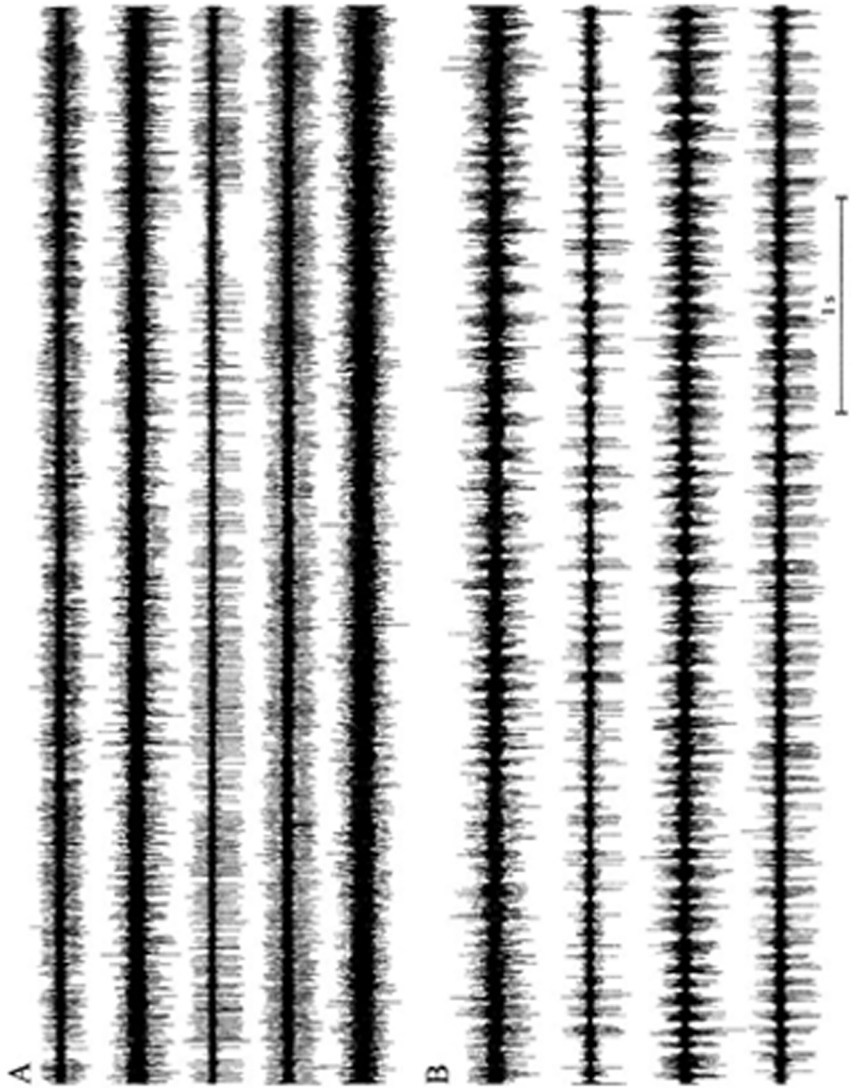


**FIGURE 3.** Examples of simultaneous recordings of the activity of neurons in the globus pallidus in a monkey before **(A)** and after treatment with MPTP **(B)**. (Reprinted from Raz *et al.*[108] with permission.)

Consistent with the notion that changes in basal ganglia discharge may result in tremor, lesions of the STN or GPi significantly reduce tremor in MPTP-treated African green monkeys and in patients with parkinsonism.[23,80,101]

Besides the skeletomotor abnormalities, parkinsonism is also associated with oculomotor abnormalities, such as hypometric and slow saccades (e.g., Ref. 103), autonomic dysfunction, depression, anxiety, sleep disturbances, impaired visuospatial orientation, and cognitive abnormalities (e.g., Ref. 104). It is likely that at least some of these abnormalities rely on abnormal discharge in nonmotor circuits of the basal ganglia, which may be affected by dopamine loss in much the same way as the motor circuit. This is particularly true for oculomotor abnormalities that may directly result from dopamine depletion in the caudate nucleus (see, e.g., Refs. 105, 106). Similarly, some of the cognitive and psychiatric disturbances seen in parkinsonian patients are reminiscent of syndromes seen after lesions of the dorsolateral prefrontal cortex (problems with executive functions) or of the anterior cingulate (apathy, personality changes) and may be the result of loss of dopamine in the dorsolateral or ventral caudate nucleus, respectively.[107]

## CONCLUSIONS

From the considerations above, a complex model of parkinsonism emerges in which relatively selective dopamine depletion in the striatum and other basal ganglia nuclei results in increased and disordered discharge and synchronization in motor areas of the basal ganglia thalamocortical motor loops. In fact, the motor circuit in Parkinson's disease may be "taken hostage" by widespread discharge abnormalities that greatly interfere with its normal functions. Abnormal activity in the basal ganglia feedback loops may contribute to the development of parkinsonism. Individual parkinsonian motor signs appear to be caused by distinct abnormalities in basal ganglia discharge. It is probable that progressive loss of dopamine in nonmotor areas of the striatum and other basal ganglia nuclei may underlie the nonmotor abnormalities of Parkinson's disease. The development of the different signs of movement disorders may be the consequence of changes in the rate, patterns, and degree of synchronization of discharge; of altered proprioceptive feedback; and of the appearance of "noise" in the basal ganglia output signal.

The current models of basal ganglia pathophysiology are incomplete and should be taken as a first draft of basal ganglia dysfunction in the different disease states. Most pertinently, changes in phasic discharge patterns and new anatomical connections need to be better incorporated into any new concept of basal ganglia function, and greater emphasis needs to be placed on the manner in which thalamic, brain stem, and cortical neurons utilize basal ganglia output.

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