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Pathophysiology of Parkinsonism

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Abstract

The motor signs of Parkinson's disease are thought to result in large part from reduction of dopamine in the basal ganglia. Over the last few years, many of the functional and anatomical consequences of dopamine loss in these structures have been identified, both in the basal ganglia and in related areas in thalamus and cortex. This knowledge has contributed significantly to our understanding of the link between degeneration of dopamine neurons in the midbrain, and the development of parkinsonism. This review discusses the evidence that implicates electrophysiologic changes (including altered discharge rates, increased incidence of burst firing, interneuronal synchrony, oscillatory activity, and altered sensorimotor processing) in basal ganglia, thalamus, and cortex, in parkinsonism. From these studies, parkinsonism emerges as a complex network disorder, in which abnormal activity in groups of neurons in the basal ganglia strongly affect the excitability, oscillatory activity, synchrony and sensory responses of areas of the cerebral cortex that are involved in the planning and execution of movement, as well as in executive, limbic or sensory functions. Detailed knowledge of these changes will help us to develop more effective and specific symptomatic treatments for patients with Parkinson's disease.

Keywords

Parkinson's disease; parkinsonism; basal ganglia; dopamine; GABA; glutamate; putamen; globus pallidus; subthalamic nucleus; substantia nigra; bursts; oscillations

Introduction

The term 'Parkinson's disease' refers to a group of neurodegenerative conditions that affect several regions of the brain, including the pigmented nuclei in midbrain and brainstem, the olfactory tubercle, the cerebral cortex, and elements of the peripheral nervous system (e.g., Braak et al., 2006). The earliest and most striking physical disabilities resulting from these changes are motor impairments that, together, are called 'parkinsonism'. These include paucity and slowness of movement (akinesia, bradykinesia), muscle stiffness (rigidity), and tremor at rest. In large part, these problems result from the prominent degeneration of dopaminergic neurons in the midbrain, and the consequent deficiency of dopamine in brain areas that receive dopaminergic inputs from those neurons, specifically the post-commissural putamen and other basal ganglia regions. This review highlights some of the physiologic, anatomical and biochemical consequences of dopamine loss in the basal ganglia, which may be responsible

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for the emergence of parkinsonism. The study of these changes has been greatly facilitated by the availability of toxins with which highly selective dopamine loss can be induced in animals, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys and mice (Burns et al., 1983, Forno et al., 1993, Langston et al., 1983), and 6-hydroxydopamine (6-OHDA) in rats and other animals (Simola et al., 2007, Ungerstedt, 1968, Ungerstedt and Arbuthnott, 1970).

Circuit anatomy of the basal ganglia

Parkinsonism is considered to result primarily from abnormalities of basal ganglia function. The basal ganglia include the neostriatum (caudate nucleus and putamen), the external and internal pallidal segments (GPe, GPi), the subthalamic nucleus (STN), and the substantia nigra with its pars reticulata (SNr) and pars compacta (SNc). They participate in anatomically and functionally segregated loops that involve specific thalamic and cortical areas. These parallel circuits are divided into 'motor', 'associative' and 'limbic' loops, depending on the function of the cortical area involved (Alexander et al., 1986, Alexander et al., 1990, Kelly and Strick, 2004, Middleton and Strick, 2000). The thalamic components of these circuits are largely separate from those engaged by cerebellar outflow pathways (Middleton and Strick, 2000).

Striatum and STN receive glutamatergic afferents from specific areas of the cerebral cortex or thalamus, and transfer the information to the basal ganglia output nuclei, GPi and SNr. The projections between the striatum and GPi/SNr are divided into two separate pathways, a 'direct' (monosynaptic) connection, and an 'indirect' projection, via the intercalated GPe and STN. Output from GPi/SNr goes largely to the ventral anterior and ventrolateral nuclei of the thalamus (VA/VL), which, in turn, project back to the cerebral cortex. Lesser basal ganglia projections reach the intralaminar centromedian and parafascicular thalamic nuclei (CM/Pf) and brainstem structures such as the superior colliculus, pedunculopontine nucleus (PPN), and the reticular formation.

Abnormal activity in the 'motor' loop of the basal ganglia is strongly implicated in the development of parkinsonism. This loop, depicted in figure 1 (left panel), originates in precentral motor areas, and involves the post-commissural putamen and motor regions of GPe, GPi, SNr and STN, as well as VA/VL. CM/Pf receive collaterals of the GPi/SNr projection to VA/VL, and send efferents back to the putamen, specifically targeting the 'direct' pathway, and cholinergic striatal interneurons (Lapper and Bolam, 1992,Meredith and Wouterlood, 1990,Sidibe and Smith, 1996,Sidibe and Smith, 1999).

The striatum also receives prominent dopaminergic input, from the SNc. The nigrostriatal projection terminates predominately at the necks of dendritic spines of the striatal medium spiny output neurons (MSNs). MSN spines also receive corticostriatal terminations. This anatomic arrangement places the dopaminergic inputs in a position to regulate or gate the corticostriatal transmission (see figure 1, left panel). MSNs in the direct pathway carry dopamine D1-receptors, while those in the indirect pathway carry D2-receptors (Gerfen et al., 1990). The direct and indirect pathways are thought to have opposing actions: Direct pathway activation may inhibit GPi/SNr activity, thereby disinhibiting thalamocortical interactions, while indirect pathway activation does the opposite. Put very simply, dopamine release from the nigrostriatal projection appears to facilitate transmission at corticostriatal synapses onto direct pathway-MSNs, and to reduce transmission along indirect pathway-MSNs (see, e.g. DeLong and Wichmann, 2007). Dopamine's net action may thus be to reduce GPi/SNr activity, thereby facilitating activity in thalamocortical projection neurons, and, through greater activation of the cerebral cortex, facilitating movement.

The model outlined above has been very helpful in studies of the anatomy and functions of the basal ganglia circuitry, but it clearly represents a simplified view. Many potentially important

connections between the basal ganglia and brainstem or thalamic nuclei are not included in this model. Furthermore, the separation of striatofugal output pathways into direct and indirect pathways is unlikely to be absolute, considering the results of single-cell tracing studies that showed that at least some striatal output neurons project to both segments of the globus pallidus (Levesque and Parent, 2005, Parent et al., 1995, Wu et al., 2000). The notion that D1 and D2 receptors co-segregate with direct and indirect pathways, respectively, has also been challenged, by studies that demonstrate a high incidence of D1 and D2 receptor co-localization in striatal cells (Aizman et al., 2000, Surmeier et al., 1996). However, more recent studies using transgenic mice in which the cellular expression of green fluorescent protein (GFP) is driven by the D1- or by the D2-receptor promoter showed that GFP-expressing striatal neurons from D1-GFP mice express exclusively the mRNA for the D1 receptor, while GFP-expressing neurons in D2-GFP mice express only D2-receptor mRNA (Day et al., 2006, Wang et al., 2006), underscoring the anatomical separation of D1- and D2 receptors.

Dopamine loss in the striatum

In Parkinson's disease, the degeneration of dopaminergic SNc neurons and their projections to the striatum is a slowly evolving process that may take decades to develop. SNc projections to the putamen degenerate earlier than projections to associative or limbic portions of the striatum. Corresponding to this time course of degeneration, the motor symptoms and signs of Parkinson's disease develop before the non-motor signs.

Recognizable motor or non-motor signs appear only after substantial degeneration of the nigrostriatal neurons (affecting at least 70%, e.g., Bernheimer et al., 1973), testament to the remarkable compensatory capacity within the dopaminergic system, or in the circuits it modulates.

Dopamine loss in the basal ganglia triggers prominent secondary morphological changes. One change that may have pathophysiologic significance is the reduction of the density of dendritic spines on MSNs, particularly in the putamen (e.g., Ingham et al., 1989, Villalba et al., 2006, Zaja-Milatovic et al., 2005), which may greatly alter corticostriatal transmission. Recent studies have suggested that MSNs with D2 receptors (belonging to the indirect pathway) may be preferentially affected by the spine loss, and that the loss of spines may involve the dysregulation of calcium channels (Day et al., 2006).

Dopamine depletion also triggers changes in the density and sensitivity of dopamine receptors. The mRNA expression for dopamine D2-receptors and binding sites in the striatum is increased in patients with Parkinson's disease and parkinsonian animals (Aubert et al., 2005, Bezard et al., 2001, Bokobza et al., 1984, Creese et al., 1977, Guigoni et al., 2005, Lee et al., 1978, Marshall et al., 1989). Changes (increases or decreases) in striatal D1-receptor binding were also reported in some studies (see, e.g., Buonamici et al., 1986, Marshall et al., 1989), but were not seen by other authors (Aubert et al., 2005, Bezard et al., 2001, Guigoni et al., 2005). Gerfen demonstrated that the expression of D1-receptor mRNA was specifically downregulated in direct-pathway MSNs, and that the expression of D2-receptor mRNA was upregulated in indirect pathway-MSNs (Gerfen et al., 1990).

The subcellular locations of dopamine receptors in the striatum may also change. Thus, the proportion of D1-receptors that are bound to the plasma membrane is greater, while the proportion in the cytoplasm is smaller, in parkinsonism than under normal condition (Guigoni et al., 2007). This is not the case at the level of direct-pathway terminations in GPi or SNr in MPTP-treated animals (Kliem et al., 2007b). The subcellular distribution of striatal D2-receptors appears to be only modestly affected by MPTP treatment (Guigoni et al., 2007).

Changes in neuronal activity in the basal ganglia

In the following sections, we will describe abnormalities in basal ganglia firing in parkinsonism, focusing on changes in firing rates, and on the development of abnormal burst patterns, oscillatory activity and synchrony between neurons. Such changes are readily apparent in the single-neuron recordings shown in figures 2 and 3. For clarity, we present these features separately, but it is important to realize that these abnormalities usually do not occur in isolation. For example, increases in burst discharges or increased synchrony often occur together with the development of abnormal oscillations in the basal ganglia-thalamocortical network of connections, and firing rate changes are strongly influenced by changes in burst firing.

Altered firing rates, the 'rate model' of Parkinson's disease

Chronic loss of dopamine results in significant changes in the firing rates of basal ganglia neurons, especially in the extrastriatal basal ganglia. Changes in the firing rates of MSNs have been difficult to identify, perhaps because MSNs are a heterogeneous population of neurons, and because dopamine loss affects corticostriatal transmission rather than directly altering the spontaneous activity of MSNs. Recent recordings in anesthetized 6-OHDA-treated rats, however, have shown less activity among direct pathway MSNs in parkinsonian animals than under normal conditions, while the spontaneous discharge and responses to cortical stimulation in indirect pathway MSNs are greater in dopamine-depleted animals than in normal ones (Mallet et al., 2006). It is not clear whether this is specifically due to changes in the dopaminergic control of corticostriatal transmission, or whether the cortical or thalamic inputs themselves are altered. Of course, the loss of MSN spines, described above, may also impact the activity of these cells.

Studies examining changes in firing rates in the basal ganglia of monkeys in response to MPTP treatment have revealed a combination of increased activity in STN and GPi and reduced activity in GPe (Bergman et al., 1994, Hassani et al., 1996, Miller and DeLong, 1987, Raz et al., 1996, Soares et al., 2004, Wichmann et al., 1999). These studies are also supported by electrophysiologic recordings in parkinsonian patients undergoing neurosurgical interventions (Dogali et al., 1994, Hutchison et al., 1994, Lozano et al., 1996, Taha et al., 1997). Together with measurements of brain metabolism (e.g., Mitchell et al., 1989, Schwartzman and Alexander, 1985a), the changes in firing rates in the extrastriatal basal ganglia led to the development of the 'rate model' of the pathophysiology of parkinsonism (Albin et al., 1989, DeLong, 1990). In its simplest form, this model explains the firing rate changes in the basal ganglia as the result of disturbances of the balance of activity in the direct and indirect pathways (figure 1, right panel). In this model, loss of D2 receptor activation reduces inhibition of corticostriatal transmission at indirect-pathway MSNs, which increases inhibition of GPe activity, disinhibits STN neurons, and therefore leads to excessive activity in targets of STN efferents, including GPi and SNr. In addition, the loss of dopamine decreases activation of striatal D1-receptors, which may disinhibit GPi and SNr neurons along the direct pathway. The resulting increase in activity of GPi and SNr neurons would lead to greater inhibition of neurons in the thalamus and brainstem (Albin et al., 1989, DeLong, 1990). As predicted by this (static) rate model of parkinsonism, inactivation of the overactive STN or GPi by lesioning reverses the motor signs of parkinsonism both in MPTP-treated monkeys and in patients with Parkinson's disease (Alvarez et al., 2005, Aziz et al., 1991, Baron et al., 1996, Bergman et al., 1990, Dogali et al., 1995, Gill and Heywood, 1998, Guridi et al., 1994, Laitinen, 1995, Lozano et al., 1995, Vitek et al., 2003).

The long-term functional changes that are described by the rate model suggest corresponding anatomical and biochemical changes, particularly in the function of GABAergic and glutamatergic pathways in the basal ganglia. Microdialysis studies in parkinsonian animals

showed that the level of GABA is increased in GPe (Galeffi et al., 2003, Robertson et al., 1991), which is compatible with the notion that GPe-projecting indirect-pathway MSNs are overactive, but it is difficult to reconcile with the more recent view that a substantial proportion of the GABA in GPe is released from local collaterals of axons originating in the GPe itself. In the STN, where terminals of axons originating in GPe are the principal source of GABA, the GABA level is decreased (Soares et al., 2004), consistent with the reduction of GPe activity predicted by the 'rate model'. In the SNr, levels of GABA have been reported to be either increased (Windels et al., 2005) or unchanged (Galeffi et al., 2003, Ochi et al., 2004). In postmortem tissue from parkinsonian patients or animals, the level of GABA is unchanged in the extrastriatal basal ganglia (Calon et al., 1999, Kish et al., 1986).

Changes in GABAergic transmission have also been evaluated with measurements of mRNA or protein levels for the GABA-synthesizing enzyme glutamate decarboxylase (GAD), under the assumption that GAD levels reflect the activity of GABAergic pathways. In striatopallidal projection neurons and in GPi and SNr cells there is a selective increase in GAD mRNA in dopamine-depleted animals (Kincaid et al., 1992, Laprade and Soghomonian, 1999, Salin et al., 2002, Soghomonian et al., 1994, Soghomonian and Laprade, 1997). However, in GPe and STN, the level of GAD is unchanged (Pedneault and Soghomonian, 1994, Schneider and Wade, 2003, Soares et al., 2004), contrary to what the rate model would predict.

Finally, changes in GABAergic transmission have been assessed by measuring the binding or density of GABA receptors. Such changes are thought to be compensatory, and therefore opposite in polarity, to the changes in GABAergic activity. Consistent with increased GABA release in GPe, and reduced GABAergic inhibition of GPi and SNr, there are decreases in GABA-A and GABA-B receptor binding or mRNA expression for these receptors in GPe, and increases in GPi/SNr, in parkinsonian patients or animals (e.g., Calon et al., 1999, Chadha et al., 2000, Gnanalingham and Robertson, 1993, Griffiths et al., 1990, Katz et al., 2005, Pan et al., 1985, Robertson et al., 1990).

Besides the GABAergic system, glutamatergic transmission has also been evaluated. There is no consensus regarding changes in the binding or expression of striatal ionotropic glutamate receptors (NMDA- and AMPA-type) in parkinsonism (Bernard et al., 1996, Betarbet et al., 2000, Betarbet et al., 2004, Dunah et al., 2000), but these receptors appear to be down-regulated in the output nuclei of the basal ganglia in parkinsonian patients and in dopamine-depleted animals (Bernard et al., 1996, Betarbet et al., 2000, Dunah et al., 2000). This is, perhaps a compensatory response reflecting increased activity in the glutamatergic STN.

Changes in metabotropic glutamate receptors are less well studied. Compared to the normal state, the mGluR1α subtype of glutamate receptors is reduced in the GPi and SNr of MPTP-treated monkeys (Kaneda et al., 2005, Samadi et al., 2007). Reports of changes of the striatal expression or binding of the metabotropic glutamate receptor subtype mGluR2/3 are inconsistent (Samadi et al., 2007, Testa et al., 1998), and there appear to be regionally specific changes in the binding of mGluR5 receptors, which are increased in the non-motor portions of the striatum, but unchanged in the motor portion in MPTP-treated monkeys (Samadi et al., 2007).

The biochemical and anatomical changes that occur in the basal ganglia in response to dopamine depletion are obviously only partially consistent with the predictions of the 'rate model'. A number of observations indicate that the situation is more complex than suggested by the rate model alone. First, global increases or decreases in GPi activity, produced by local drug injections, do not necessarily produce parkinsonism or involuntary movements, respectively. Second, although the rate model predicts that GPe lesions and lesions of VA/VL should induce parkinsonism, neither type of lesion does so consistently (Canavan et al.,

1989, Soares et al., 2004). Third, the remarkable antiparkinsonian effects of focal electrical 'deep brain' stimulation (DBS) of the STN, a procedure that is thought to increase GPi output to the thalamus (Hashimoto et al., 2003, McIntyre et al., 2004), are contrary to the prediction of the rate model that such increased output should worsen rather than ameliorate parkinsonism. Finally, the reduced density of dendritic spines on indirect pathway-MSNs (described above) should reduce the overall activity along the striato-GPe pathway, contrary to the changes predicted by the rate model. These findings suggest that the rate model of parkinsonian pathophysiology is inadequate, and that other changes in basal ganglia activity, contribute to parkinsonism. These may include changes in the firing patterns of individual neurons, the responsiveness of these neurons to sensory inputs, and altered interactions within ensembles of neurons.

Burst discharges

In dopamine-depleted monkeys, distinct changes in burst firing have been identified in GPe, GPi and STN neurons (Bergman et al., 1994, Filion, 1979, Soares et al., 2004, Wichmann et al., 1999, Wichmann and Soares, 2006). The proportions of spikes within bursts, the proportions of time that the neurons spend in bursting activities, and the length of individual bursts are all increased (Wichmann and Soares, 2006). Likewise, in patients with Parkinson's disease, the incidence of burst firing in the basal ganglia was also reported to be high (Hutchison et al., 1994, Magnin et al., 2000). Bursting activity in the STN develops early in the course of dopamine depletion, along with changes in discharge rates and metabolic markers (Breit et al., 2007, Ni et al., 2001b, Vila et al., 2000).

The mechanism by which neuronal burst firing develops in parkinsonism has been extensively studied. While it is likely that bursting is related to dopamine loss in the striatum, loss of dopamine in other basal ganglia regions (such as the STN) may also be important (Ni et al., 2001a). For instance, dopamine acts locally to reduce inhibitory synaptic input to the STN (Shen and Johnson, 2000, but see Tofighy et al., 2003, Zhu et al., 2002b), and its absence may enhance the impact of synchronous GABAergic inputs on STN activity, resulting in rebound bursting (Bevan et al., 2007, Shen and Johnson, 2005). Activation of D2-receptors normalizes bursting of STN cells in slices obtained from dopamine-depleted animals (Zhu et al., 2002a).

The interplay between GPe and STN may contribute powerfully to the development of burst discharges in both nuclei (Ni et al., 2000a, Plenz and Kitai, 1999). The strongest argument for this hypothesis comes from the observation that, in a dopamine-free co-culture preparation, GPe and STN neurons form connections with one another and generate burst discharges that are abolished if the connections between the two neuronal cell populations are cut (Plenz and Kitai, 1999). In brain slice preparations, synchronous inputs from GPe hyperpolarize STN neurons, leading to rebound bursting in this nucleus (Beurrier et al., 1999, Bevan et al., 2007). The potential role of increased inhibition in the generation of (rebound-) burst discharges in the STN in parkinsonism has also been stressed in computational models of the basal ganglia (Gillies et al., 2002), and was apparent in our recent study of dopamine-depleted monkeys, in which the temporal structure of spike discharges occurring before bursts was found to be significantly altered in parkinsonism, with a lengthening of inter-spike intervals immediately preceding bursts, perhaps indicative of pre-burst inhibition (Wichmann and Soares, 2006).

Although it is likely that the emergence of excessive burst discharges alters information processing in the basal ganglia-thalamocortical circuitry, doubts remain as to whether bursting *per se* has pro-parkinsonian effects, because treatments with antiparkinsonian dopaminergic treatments do not consistently reduce burst firing in the basal ganglia of dopamine-depleted animals or patients. While SNr burst activity was reduced in dopamine-depleted rats that received intrastriatal injections of a D1-like receptor (D1LR) agonist (Tseng et al., 2000), the opposite occurred in other studies in which parkinsonian patients or animals were given

dopaminergic drugs systemically (Lee et al., 2001, Levy et al., 2001). Local injections of a dopamine D1LR receptor agonists into the primate GPi or SNr, or D5 receptor activation in the rodent STN, also increased rather than decreased burst firing in these nuclei (Baufreton et al., 2003, Kliem et al., 2007a). One caveat is that the (potential) behavioral effect of the dopaminergic treatments in these studies was not clear. Further study is therefore needed to examine the effects of dopaminergic treatment on burst discharges *in vivo* specifically in animals in which a satisfactory antiparkinsonian effect has been achieved. It will also be important to monitor the state of arousal in these animals, which has rarely been reported to date: Burst firing in the basal ganglia increases strongly when animals become drowsy (DeLong, 1969), and drowsiness is known to be associated both with parkinsonism and with dopaminergic therapy (the interaction between sleep and parkinsonism-related changes in firing is discussed in Gatev et al., 2006, Gatev and Wichmann, 2004).

Oscillations

Another distinct abnormality in the electrical activity of basal ganglia neurons in parkinsonian animals and patients is the emergence of abnormal oscillatory activity, both at the single-cell level and in larger ensembles of neural elements. At the level of single cells, oscillations in the alpha- and beta- frequency ranges are prominent in recordings in GPe, GPi, and STN of MPTP-treated monkeys, and in parkinsonian patients undergoing functional neurosurgery (see, e.g., Gatev et al., 2006, Levy et al., 2002b, Rivlin-Etzion et al., 2006, Weinberger et al., 2006).

Recent studies have also investigated oscillations in field potential recordings made with DBS electrodes implanted in GPi and STN of parkinsonian patients. Although the process(es) that contribute to the pathological field potential oscillations are not fully understood, it is likely that they reflect oscillatory synaptic or neuronal activities that are generated by large groups of neural elements, separated by considerable distances (millimeters). In fact, the anatomical targets (especially the STN) are often smaller than the spacing of the electrodes used to record the LFP signals, so that structures within and outside the target nuclei likely contribute to the recorded potentials. In several studies, LFP oscillations in the beta frequency band have, however, been shown to be correlated with neuronal activity specifically in the STN of parkinsonian patients (for example, Kuhn et al., 2005, Levy et al., 2002a, Weinberger et al., 2006). In patients in whom dopaminergic medications had been withheld overnight, the spectral power of the recorded LFP potentials in STN and GPi showed peaks in the 10–30 Hz range which disappeared when the patient was treated with dopaminergic agents (Brown et al., 2001, Hammond et al., 2007). The disappearance of the pathological alpha- and beta band oscillations is often associated with the emergence of gamma-band oscillations.

The mechanisms by which oscillations of single cells or groups of neural elements develop in parkinsonism are not clear. It is also not clear why the circuitry involved in the generation of the LFP signals preferentially produces beta-band oscillations (and not oscillations in other frequency ranges). Given the massive dopamine loss in the striatum in Parkinson's disease, it would seem logical that they arise from changes in striatal activity. However, although neural elements in the striatum are capable of generating such oscillations (Berke et al., 2004, Courtemanche et al., 2003, Masimore et al., 2004), the very low and generally non-rhythmic activity of striatal output neurons (MSNs) make it seem unlikely that oscillatory activities originating in the striatum strongly influence the remainder of the basal ganglia circuitry. It is more likely that changes in the extrastriatal basal ganglia, specifically the interplay between GPe and STN, may be important in the development of oscillations. As mentioned above, STN cells generate rebound bursts in response to transient volleys of inhibitory inputs from GPe (Plenz and Kitai, 1999). This, in turn, may trigger additional bursts in GPe, creating a system of self-sustaining oscillatory activity involving both nuclei. The degree to which inputs from the striatum modulate the function of the proposed STN-GPe 'pacemaker' remains unclear

(see, e.g., Bevan et al., 2002, Loucif et al., 2005, Stanford, 2003, Terman et al., 2002). The occurrence of oscillations in the GPe-STN network may be modulated by cortical inputs to the STN (Hartmann-von Monakow et al., 1978, Nambu et al., 2002b) or by thalamic inputs (Castle et al., 2005). Field potential studies in parkinsonian patients have demonstrated that oscillatory activity, once generated in the STN, can be transmitted to the GPi (Brown et al., 2004), and may, presumably, affect the entire basal ganglia-thalamocortical network (see below). A clear caveat with the STN-GPe pacemaker model is that the oscillations in the dopamine-free STN/GPe co-cultures (Plenz and Kitai, 1999) occurred at very low frequencies (< 1 Hz). The relationship between these low-frequency oscillations and the alpha- and beta oscillations seen in patients with Parkinson's disease has not yet been determined.

Although the STN-GPe pacemaker mechanism is an attractive explanation for the generation of oscillatory activity in the basal ganglia, there is no *in vivo* evidence of an STN-GPe pacemaker. An alternative possibility is that the oscillations observed in basal ganglia, thalamus and cortex (see below) are not a primary basal ganglia phenomenon but are generated by other mechanisms and/or at other locations (for instance in thalamus and cortex, as discussed in Gatev et al., 2006, Magill et al., 2000, Magill et al., 2001).

Abnormal synchrony

Under normal conditions, neighboring basal ganglia neurons fire in an uncorrelated fashion (Bergman et al., 1994, Jaeger et al., 1994, Wilson et al., 2004). In the dopamine-depleted state, however, the synchrony between neighboring basal ganglia cells, and even between nuclei, is significantly increased, usually together with the emergence of oscillatory activity (Hammond et al., 2007). These changes are readily seen in the multi-electrode recording examples shown in figure 3. Increased oscillatory synchrony is likely to be a direct result of the loss of dopamine in the parkinsonian brain, as systemically applied dopaminergic agents rapidly reduce the pathological interneuronal synchrony (Heimer et al., 2002, Levy et al., 2002a). Synchronous activities could, for instance, be produced in the striatum through enhancement of electrotonic coupling between striatal cells (Berretta et al., 2001, Cepeda et al., 1989, O'Donnell and Grace, 1993, Onn and Grace, 2000), or through changes in interneuronal or axon collateral activity (Guzman et al., 2003). Alternatively, changes in the general level of striatal inhibition of pallidal activity may act to induce synchrony in the extrastriatal basal ganglia (Terman et al., 2002). While it is also possible in principle that dopamine loss outside of the striatum promotes synchrony, there is, thus far, little evidence for this (see, e.g., Wilson et al., 2004).

Changes in sensory response patterns and changes in task-related activity of basal ganglia neurons

Under normal conditions, many neurons within the motor territory of each of the basal ganglia structures respond to proprioceptive input. Appropriate modulation of basal ganglia activity through such inputs may be important to gate and restrict cortical activities related to specific movements or other activities. Sensory responses in the striatum can be assumed to be the result of direct cortical inputs to this structure, while proprioceptive responses in the extrastriatal basal ganglia are, at least in part, due to inputs reaching the STN via the cortico-subthalamic projection (see figure 1, left panel and, e.g., Hamada and DeLong, 1992,Hartmann-von Monakow et al., 1978,Nambu et al., 2002a). Pallidal recordings in MPTP-treated animals showed a reduction in the specificity of such responses (Rothblat and Schneider, 1995,Schneider and Rothblat, 1996), and an increase in the proportion of neurons with excitatory responses (Boraud et al., 2000). In addition, rodent studies showed that the normal arrangement of striatal neurons into clusters that respond to sensory inputs appears to be fragmented in the dopamine-depleted state (Cho et al., 2002,Prokopenko et al., 2004). These sensory changes may be due to abnormal basal ganglia processing, or may reflect abnormal cortical inputs to the basal ganglia. Through disruption of cortico-subcortical feedback

mechanisms that control the extent and speed of movement, they may contribute to abnormal scaling of movements and bradykinesia in Parkinson's disease (Wichmann and DeLong, 1993).

Changes in thalamic activity

In this section, we will consider parkinsonism-related changes in VA/VL separately from those occurring in CM/Pf, because these thalamic nuclear groups appear to have different physiologic functions. VA/VL are part of the basal ganglia-thalamocortical circuitry, while CM/Pf participate in circuits by which basal ganglia output is fed back into the putamen.

Metabolic studies in MPTP-treated monkeys have suggested that the metabolism in the thalamic VA and VL nuclei is increased in parkinsonism (Mitchell et al., 1989, Rolland et al., 2007), perhaps reflecting increased basal ganglia input to this area. Studies of thalamic firing rate changes in parkinsonism have been inconclusive. Earlier studies in MPTP-treated monkeys reported a small decrease of neuronal activity in basal ganglia-receiving areas of the thalamus (Vitek et al., 1994), but this was not confirmed by later studies in human patients or MPTP-treated monkeys (Molnar et al., 2005, Pessiglione et al., 2005). There is, however, consistency among various reports that changes in thalamic firing patterns generally mirror those found in the basal ganglia output nuclei. In MPTP-treated monkeys, the incidence of burst discharges was found to be increased in VL (Guehl et al., 2003, Kaneoke and Vitek, 1995, Pessiglione et al., 2005, Vitek et al., 1994), and a high level of burst firing in this area has also been documented in human patients with Parkinson's disease (Magnin et al., 2000, Molnar et al., 2005, Zirh et al., 1998). Several authors have reported that the thalamic bursts show characteristics of low-threshold calcium bursting which could indicate that they are generated in the context of hyperpolarization of thalamic neurons, induced by increased GABAergic basal ganglia input (Kaneoke and Vitek, 1995, Magnin et al., 2000), but other authors have failed to find evidence for low-threshold calcium bursting (Molnar et al., 2005, Zirh et al., 1998). A second finding similar to those in the basal ganglia is that pathological oscillations develop in the thalamus (e.g., Guehl et al., 2003, Magnin et al., 2000, Raeva et al., 1999, Zirh et al., 1998). Coherent theta-band oscillations that engage both thalamus and cortex have been identified in studies in which thalamic field potentials were recorded together with cortical EEG in humans (Sarnthein and Jeanmonod, 2007). Finally, there is also an increase in the correlation of the spiking activities of neighboring neurons in VA/VL (Pessiglione et al., 2005). Studies of the sensory response properties of VA/VL neurons have suggested that parkinsonism is associated with reduced specificity of such responses in MPTP-treated monkeys (Pessiglione et al., 2005), a finding that was different from the results of studies in humans (Kiss et al., 2003, Magnin et al., 2000).

With regard to the CM/Pf nuclei, there is indirect evidence that GABAergic basal ganglia output to these nuclei is increased in parkinsonism, in line with predictions of the rate model of parkinsonism (figure 1). Thus, GABA-A receptor subunit expression in Pf is decreased in dopamine-depleted rats (Chadha et al., 2000), and a (transient) decrease in average Pf firing rates has been documented in such animals (Ni et al., 2000b). There is also evidence that MPTP-exposure in monkeys leads to changes in glucose utilization in CM/Pf (Palombo et al., 1990), suggesting changes in synaptic or neuronal activity. The significance of activity changes in CM/Pf in the development of parkinsonism has not been explored in detail. According to the circuitry model in figure 1, parkinsonism may result in a reduction of CM/Pf activity which may, secondarily, result in reduced driving of 'direct' pathway MSNs (Sidibe and Smith, 1996), and worsening of parkinsonism. This pathophysiologic scheme may be too simplistic, however, because the effects of altered patterns of basal ganglia input to CM/Pf, and of CM outputs acting on striatal interneurons are not taken into account.

Interestingly, many of the electrophysiologic changes in the thalamus do not seem to be specific to the thalamic nuclei that receive basal ganglia inputs (VA/VL and CM/Pf). Thus, burst firing, oscillations and abnormal sensory processing have also been found in the nuclei of the thalamus that receive cerebellar input (Guehl et al., 2003, Pessiglione et al., 2005).

In addition to the limited evidence suggesting that neuronal activity in CM/Pf is altered, as a consequence of the loss of dopamine in the basal ganglia, it has been shown in autopsy studies that CM/Pf may also be affected by the neurodegenerative process in Parkinson's disease: more than 50% of CM/Pf neurons have degenerated in patients with (end-stage) Parkinson's disease (Henderson et al., 2000), especially in CM (Henderson et al., 2000, but see ref. Xuereb et al., 1991). Neuron loss has also been seen in the Pf of dopamine-depleted rodents (Aymerich et al., 2006, Henderson et al., 2005). The potential cause(s) and significance of these findings remain(s) unclear.

Changes in cortical activity

Early 2-deoxyglucose studies suggested that cortical activation (at rest) is globally reduced in MPTP-treated monkeys (Schwartzman and Alexander, 1985b). Later studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in parkinsonian patients documented changes in activity both at rest and during the performance of motor or cognitive tasks. The PET studies demonstrated that cortical activation in motor tasks is reduced in parkinsonism, specifically in the supplementary motor area (SMA) and in the anterior cingulate cortex (Brooks, 1997, Haslinger et al., 2001, Jahanshahi et al., 1995, Jenkins et al., 1992, Playford et al., 1992, Samuel et al., 1997, Thobois et al., 2000, Turner et al., 2003).

Besides the obvious motor impairments, parkinsonian patients also show abnormalities in cognitive tasks, perhaps associated with the loss of dopamine in non-motor portions of the striatum (Bruck et al., 2001, Marie et al., 1999). PET studies in such patients have suggested that at least some of the cognitive deficits could be explained by abnormal activation of non-motor areas of the basal ganglia (Dagher et al., 2001).

In parkinsonian patients, the performance of motor and other tasks often recruits brain areas that are not activated in non-parkinsonian individuals, such as areas in the lateral premotor cortex, cerebellum and posterior parietal and occipital lobes (e.g., Samuel et al., 1997, Thobois et al., 2000, Turner et al., 2003). Similarly, cognitive tasks may affect activation in areas that are not normally activated (Dagher et al., 2001, Grossman et al., 2003, Moody et al., 2004). The aberrant patterns of activation are at least partially reversed by dopaminergic and other treatments (Haslinger et al., 2001, Peters et al., 2003). These studies provide evidence that dopamine depletion may not only disturb the function of those frontal areas of the cerebral cortex that receive direct input from the basal ganglia (via the thalamus), but may also result in compensatory shifts in activation towards other areas of cortex.

A small number of electrophysiologic studies have examined changes in cortical activities in MPTP-treated monkeys. These studies found that the activation of motor cortex or the supplementary motor area is reduced in these animals (Watts and Mandir, 1992), and that the synchrony between neurons is increased (Goldberg et al., 2002). EEG studies in patients have shown that parkinsonism may be associated with abnormal beta-band synchronization of cortical networks, (Silberstein et al., 2005), and a failure to modulate frontal and central beta-band activity with movement (Brown and Marsden, 1998, Brown, 2003).

Parkinsonism as a network phenomenon

It is likely that all of the firing rate and pattern changes described in the previous sections occur together and eventually result in the emergence of parkinsonism. A general link between the changes in cortical activity and the previously described subcortical changes emerges from voxel-comparing network analyses of PET images which show that cortical activation patterns relate to activity changes in the basal ganglia in individuals with Parkinson's disease (Antonini et al., 1998, Eidelberg, 1998).

The strongest case for the notion that specific network-wide disturbances of activity are associated with, and may contribute to the development of, parkinsonism has been based on the finding that abnormal and synchronous oscillations appear to permeate the entire basal ganglia-thalamocortical circuitry (Brown, 2003, Hammond et al., 2007). Oscillatory single cell spiking in the basal ganglia has been found to be correlated to oscillatory activity in cortex, and dopamine depletion strengthens the correlation between frontal EEG activity and single cell discharges in STN, GPi, and GPe (Gatev and Wichmann, 2003, Goldberg et al., 2002, Magill et al., 2000, Sharott et al., 2005, Urbain et al., 2000, Wichmann et al., 2002). Many of these studies were done under experimental conditions in which the basal ganglia were the target of synchronous inputs, such as during anesthesia or slow wave sleep (Magill et al., 2000, Urbain et al., 2000). In recent studies in normal and MPTP-treated monkeys, we have extended such observations to the awake resting state, combining EEG recordings with recordings of single neuron activity (Gatev and Wichmann, unpublished). In our experiments, spiking activity in GPe and GPi was associated with shifts from pre-spike synchronization of EEG in primary motor cortex and supplementary motor area, to post-spike desynchronization. STN spiking had the opposite effect, with pre-spike desynchronization and post-spike synchronization. These changes occurred in parallel with shifts in the covariance between beta- and gamma-frequency bands within the EEG-rhythms. In parkinsonism, the spiking-related changes in cortical synchronization were reduced in EEG segments aligned to STN spikes, and increased in segments aligned to spikes in GPe or GPi. Such changes were not limited to the beta-band, but involved a larger spectrum of frequencies, including alpha-, beta- and gamma-bands. Spiking-related changes in beta/gamma band covariance were reduced in all three nuclei (see also, Gatev et al., 2006).

Field potential recordings have also shown that beta-band activity in the STN and GPi is coherent with EEG in unmedicated parkinsonian patients (Brown and Williams, 2005, Fogelson et al., 2005, Gatev et al., 2006), and that beta-band EEG oscillations are reduced by therapeutically effective DBS of the STN (Silberstein et al., 2005).

Do electrophysiologic abnormalities in the basal ganglia-thalamocortical circuitry cause parkinsonism?

There is little doubt that moderate or severe forms of parkinsonism are associated with increased bursting, oscillatory activity, changes in interneuronal synchrony, changes in the processing of sensory information, and perhaps changes in firing rates. The immediate beneficial effects of focal lesions or DBS in the basal ganglia suggests that such changes may contribute to the development of the behavioral manifestations of the disease. However, the importance of specific electrophysiologic features in basal ganglia, thalamic or cortical activity for the development of the behavioral signs of parkinsonism has not been fully worked out yet.

As it seems increasingly doubtful that changes in firing rates or increased bursting are (strongly) pro-parkinsonian, synchronous oscillations within the basal ganglia-thalamocortical circuits are the current lead suspect for a pro-parkinsonian circuit dysfunction (Brown, 2003). However, direct links between these oscillations and specific parkinsonian deficits are still

missing. It may seem logical that the oscillations may result in tremor (Bergman and Deuschl, 2002, Deuschl et al., 2000, Levy et al., 2002b, Wang et al., 2005), but a specific relationship between tremor movements and oscillatory basal ganglia or cortical firing is often difficult to detect, perhaps due to the fact that multiple independent oscillators may be at work at any given time (Ben-Pazi et al., 2001, Bergman et al., 1998b, Levy et al., 2002b, Priori et al., 2004, Raz et al., 2000, Rivlin-Etzion et al., 2008). It is also obvious from primate and human recordings that strongly oscillatory neuronal activity can, in fact, occur without overt tremor (Levy et al., 2002a, Raz et al., 2001, Soares et al., 2004, Wichmann et al., 1999). Another possibility is that the disruption of normal processing in the basal ganglia and associated areas by the excessive alpha- and beta-band oscillations is important for the development of akinesia. This possibility is supported by studies in which 10 Hz- or 20 Hz-stimulation in the STN area with a DBS lead resulted in a moderate increase in akinesia (Chen et al., 2007, Timmermann et al., 2004), and by the finding that anti-akinetic treatments such as levodopa administration or STN-DBS lead to a reduction of beta-band oscillations in the basal ganglia and cortex in patients with Parkinson's disease (Brown et al., 2004, Hammond et al., 2007, Kringelbach et al., 2007, Kuhn et al., 2006, Wingeier et al., 2006).

While the aforementioned studies in moderately or severely parkinsonian patients or animals suggest that synchronous oscillatory activity is associated with parkinsonism, these studies do not prove causality. Thus, it is not known whether 10- or 20 Hz stimulation actually induces low-frequency oscillations in the basal ganglia-thalamocortical network, and, if so, whether the oscillation act through disruption of information processing, or through associated changes in transmitter levels or other biochemical alterations. It is also not known whether levodopa treatments or STN-DBS reduce akinesia because the reduce beta-band activity, or whether the reduction of these oscillations is simply correlated with (but not causal to) the beneficial motor effects.

It is important to keep such caveats in mind, because recent studies in monkeys that underwent a gradual MPTP-treatment protocol that slowly induced parkinsonism cast doubt on the notion that synchronous oscillatory firing truly contributes to (early) parkinsonism (Leblois et al., 2007). In these single-neuron recording studies, synchrony and oscillations in neuronal spiking activity were late phenomena, developing after the first appearance of bradykinesia and akinesia. The authors detected, however, earlier changes in sensory processing. This topic clearly deserves more study. Follow-up studies also need to take advantage of electrophysiologic methods other than single-neuron recordings, such as LFP recordings.

Changes in brainstem activity

Our understanding of the pathophysiologic changes that occur in areas outside of the basal ganglia-thalamocortical loops remains rudimentary. However, there is evidence that abnormalities in brainstem regions, specifically the PPN, may be involved in the development of some of the core signs of parkinsonism. The PPN is tightly connected to the basal ganglia (Mena-Segovia et al., 2004). Animal studies demonstrate that stimulation of the PPN area increases movement (Nandi et al., 2002b), while inhibition or lesioning of the PPN decreases it (Aziz et al., 1998, Kojima et al., 1997, Munro-Davies et al., 2001). In MPTP-treated monkeys, akinesia is reduced by injections of a GABA receptor antagonist into the PPN (Nandi et al., 2002a) or by low-frequency electrical stimulation of the PPN area (Pahapill and Lozano, 2000). Studies in 6-OHDA-treated rats have suggested that PPN activity is increased in the dopamine-depleted state (Breit et al., 2001), and that lesions of the PPN in 6-OHDA treated rats reduce some of the discharge abnormalities in STN and SNr (Breit et al., 2006).

Based on this evidence that PPN may be affected by dopamine depletion, and that PPN interventions may affect movement, several preliminary studies of the effects of PPN

stimulation in parkinsonian patients have been carried out (Mazzone et al., 2005, Plaha and Gill, 2005, Stefani et al., 2007). These (unblinded) studies have reported significant improvements in parkinsonian signs, specifically in gait and postural instability, i.e., symptoms that poorly respond to other antiparkinsonian therapies. These attempts to treat parkinsonism with interventions directed at the PPN are obviously still in their infancy at this time. The mechanisms by which the effects are produced, and the relationship of such movement effects to basal ganglia functions are poorly understood. It has been speculated that manipulation of PPN activity may affect the excitatory input from PPN to SNc neurons, or may act through dopamine-independent mechanisms, perhaps related to the extensive local and spinal connections of this nucleus (see, e.g., Kojima et al., 1997, Mena-Segovia et al., 2004, Nandi et al., 2002a). At this time, it remains uncertain whether the effects of PPN interventions are specific for Parkinson's disease, or whether other forms of gait or postural instability may also respond (see, e.g., Shih and Tarsy, 2007).

Caution is necessary in the interpretation of the effects of surgical PPN interventions in animals or humans, because (1) this nucleus is heterogeneous, (2) it is not well demarcated from surrounding brain regions, and (3) the spread of current of drugs from the site of intervention to surrounding areas cannot be excluded (see, for instance, discussion in Kringelbach et al., 2007). The optimal stereotactic target of surgical interventions in humans has not been determined, and the electrophysiologic properties of the PPN and nuclei around it are not fully defined, rendering electrophysiologic targeting of the surgical procedures more difficult than it is in the basal ganglia (see, for instance, Mazzone et al., 2005, Mazzone et al., 2007, Stefani et al., 2007, Zrinzo et al., 2007a, Zrinzo et al., 2007b)

Conclusion

With clear evidence for concurrent abnormalities in the basal ganglia, thalamus and cortex, parkinsonism is now recognized as a disease of a distributed brain network. Highly specific changes in neuronal activity, produced by dopamine loss in the putamen and other basal ganglia nuclei, or by the loss of dendritic spines on striatal output neurons, appear to severely disrupt the activity of neurons throughout the basal ganglia, thalamus and cortex, and may even lead to the aberrant activation of brain areas that are not part of the immediate basal ganglia-thalamocortical circuitry, eventually resulting in parkinsonism.

There are obvious limitations to our current understanding of this pathophysiologic scheme. First, the specific involvement and changes in striatum, brainstem, thalamus and cortex are less well understood than the changes in GPe, STN and GPi/SNr. Second, dopamine depletion develops very rapidly in the commonly used toxin-based animal models of dopamine-depletion, so that the gradual changes in basal ganglia-thalamocortical activity during the process of dopamine loss in parkinsonism cannot be adequately studied. Third, the lack of methods to identify reliably the 'direct' pathway *in vivo* has led to a (possibly undue) emphasis on the role of abnormalities in the indirect pathway, while the role of the changes in the direct pathway is not clear. Fourth, the involvement of areas outside of the basal ganglia, such as the PPN, in the development of parkinsonism awaits further study. Finally, it remains largely unknown how the development of the behavioral motor signs of Parkinson's disease is specifically related to the aforementioned abnormalities in activity patterns in the basal ganglia and related areas.

While the current dopamine replacement therapies offer excellent symptomatic benefits in many patients with parkinsonism, these treatments are often accompanied by severe side effects, and by wearing-off phenomena and other motor fluctuations. More detailed characterization of abnormalities in brain activity in parkinsonism will help us to develop better and more specific antiparkinsonian treatments. The insight that parkinsonism is a network

disorder has already stimulated the development of local neurosurgical interventions in the basal ganglia to influence the activity of the entire basal ganglia-thalamocortical network of connections, and thereby to ameliorate parkinsonism: Small GPi lesions or focal electrical stimulation of STN or GPi now provide patients with remarkable symptomatic benefits. In the future, a better understanding of the pathophysiologic changes in activity may also help us to develop pharmacologic or genetic treatments by which firing abnormalities in the basal ganglia-thalamocortical circuits can be specifically ameliorated.

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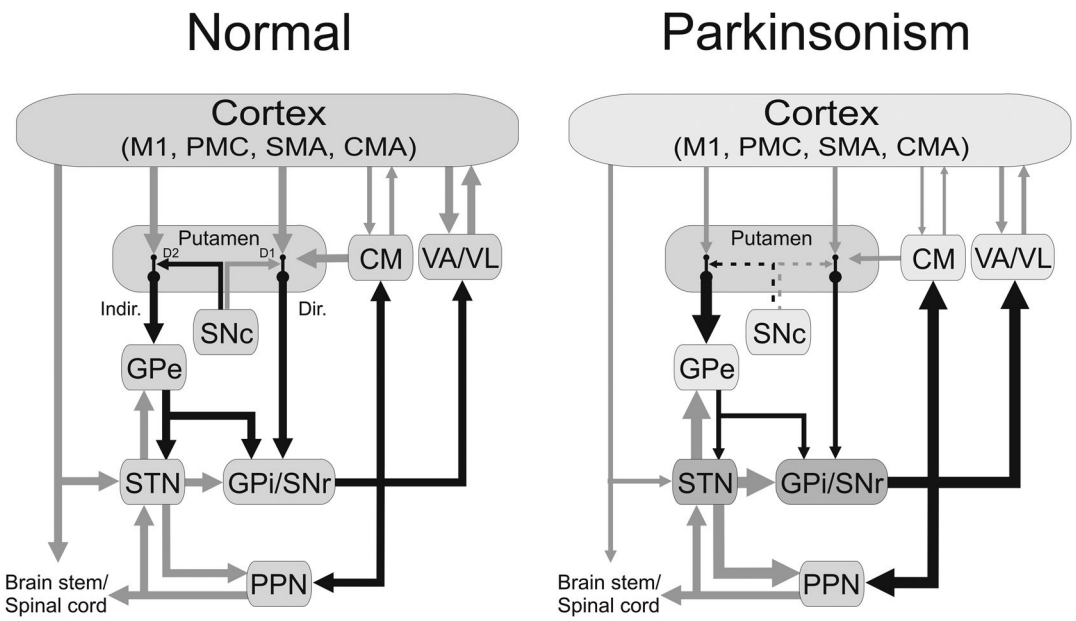

Figure 1.

Parkinsonism-related changes in overall activity (‘rate model’) in the basal ganglia-thalamocortical motor circuit. Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. The thickness of the arrows corresponds to their presumed activity. Abbreviations: CM, centromedian nucleus of thalamus; CMA, cingulate motor area; Dir., direct pathway; D1, D2, dopamine receptor subtypes; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; Indir., indirect pathway; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventral anterior nucleus of thalamus; VL, ventrolateral nucleus of thalamus.

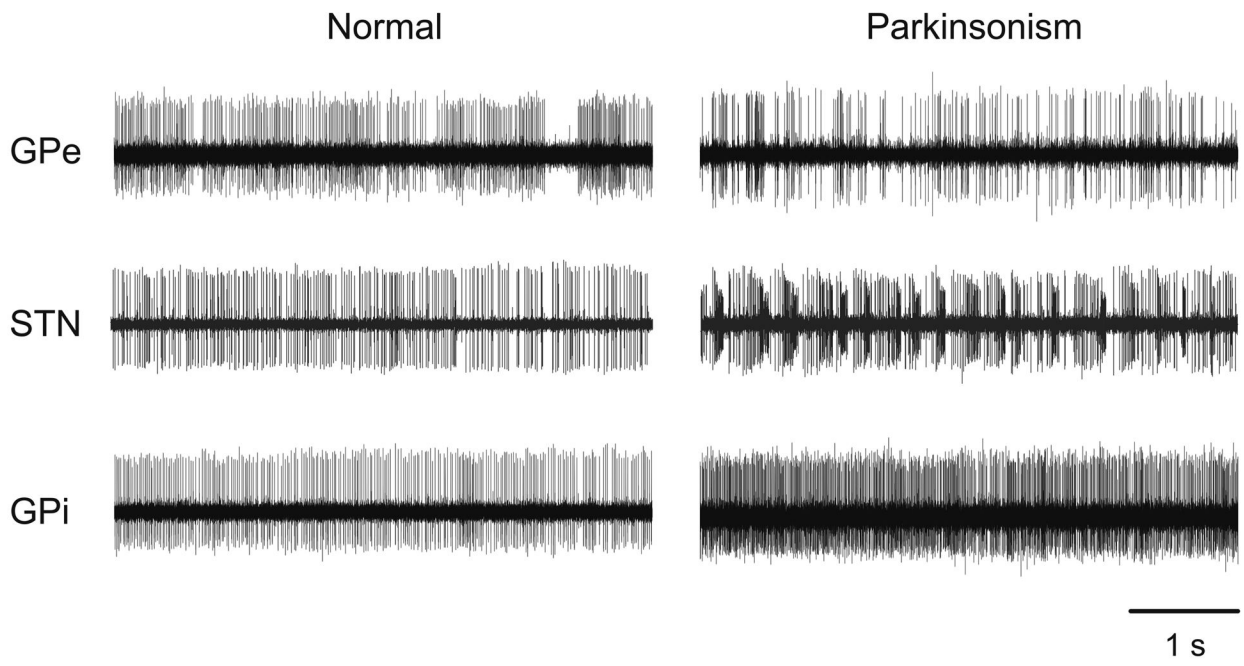

Figure 2.
Changes in the activity of single cells in GPe, STN or GPi of MPTP-treated monkeys. Shown are examples of separate neurons, recorded with standard extracellular electrophysiologic recording methods in normal and parkinsonian animals. Each data segment is 5 seconds in duration.

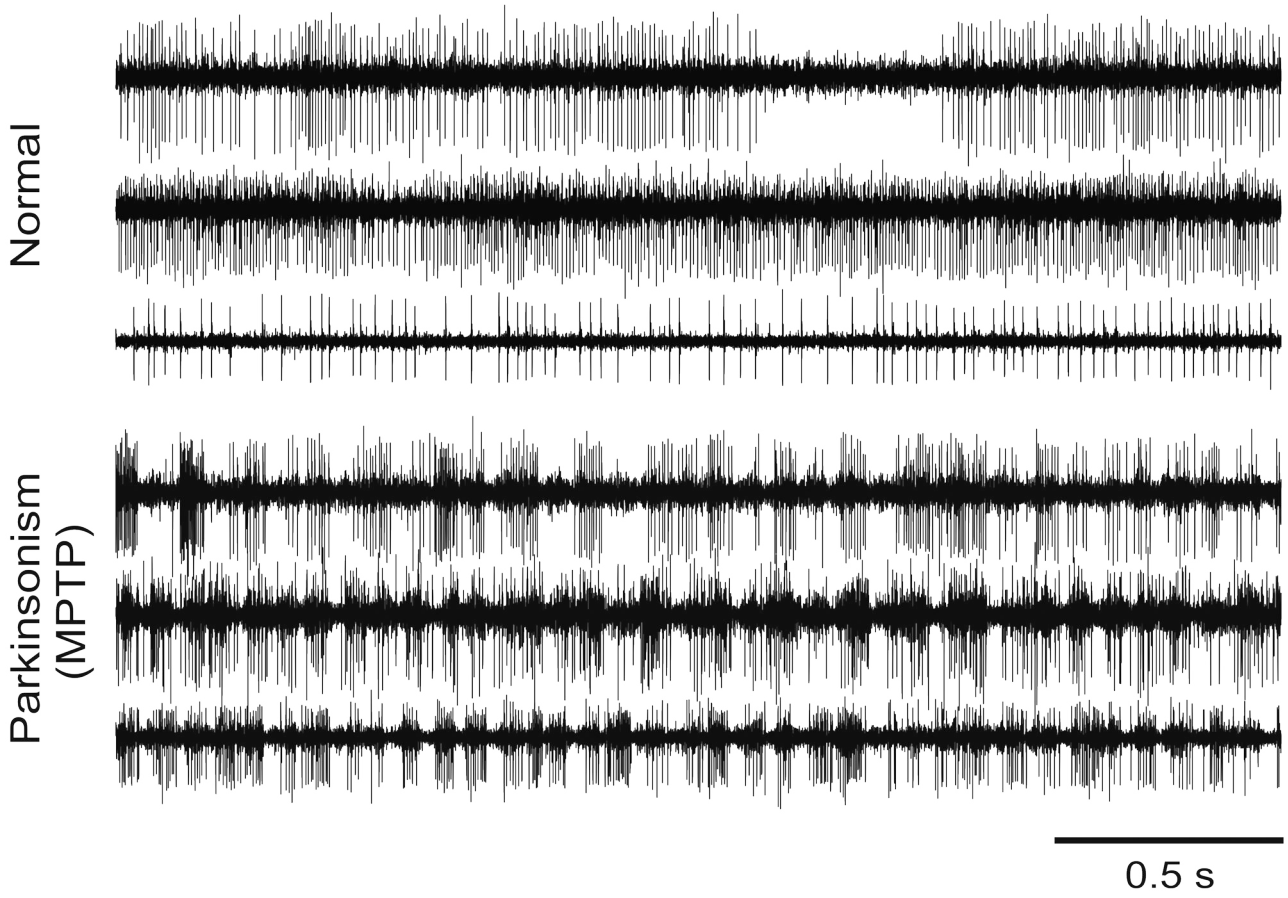

Figure 3.
Simultaneous independent extracellular electrophysiologic recordings of the activity of several neurons in the globus pallidus in a normal (A) and a parkinsonian monkey (B). Traces represent 2.5 s-long example of neuronal activity. In the normal state (A.), the activity of neighboring neurons was not correlated. In the parkinsonian state (B.), however, episodes of synchronous, episodic bursting developed. For abbreviations, see text. The figure is a reproduction of figure 3 in (Bergman et al., 1998a), with permission.