

## Physiology and pathophysiology of the basal ganglia–thalamo–cortical networks

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### Abstract

Low-frequency resting tremor is one of the cardinal signs of Parkinson's disease (PD) and occurs also in some of its animal models. Current physiological studies and models of the basal ganglia indicate that changes of discharge pattern and synchronization of basal ganglia neurons rather than modification in their discharge rate are crucial to the pathophysiology of PD. However, parkinsonian tremor is not strictly correlated with the synchronous oscillations in the basal ganglia networks. We therefore suggest that abnormal basal ganglia output enforces abnormal thalamo–cortical processing leading to akinesia, the main negative symptom of Parkinson's disease. The parkinsonian positive motor signs, such as tremor and rigidity, most likely evolve as a downstream compensatory mechanism.  
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### 1. Pathophysiology of Parkinson's disease

Based on clinical observations of six patients, James Parkinson described two of the most important and paradoxically related symptoms of Parkinson's disease (PD): shaking – low-frequency (4–7 Hz) tremor at rest; and palsy, or akinesia in modern terminology – a hypokinetic disorder. The other cardinal motor symptoms of PD include rigidity and postural instability. PD is not a homogenous disease, either across patients or even along the natural course of a single patient. Temporally, tremor is not a consistent feature of the disease, but rather is episodic, as opposed to akinesia. Unlike rigidity and akinesia, the clinical severity of PD tremor is not correlated with the severity of the dopaminergic deficit in the striatum or the clinical progression of the disease. Interestingly, most forms of non-idopathic PD and most animal models of PD display akinesia and rigidity but not resting tremor.

Many studies indicate that PD tremor is due to abnormal central oscillator(s) rather than mechanical or spinal reflex mechanisms. Early attempts to remove parts of the motor cortex or its downstream projections were successful in suppressing tremor but produced unacceptable side effects. The ventralis intermediate nucleus of the thalamus (Vim), the cerebellar receiving nucleus of the thalamus has tradi-

tionally been considered the optimal target for stereotaxic procedures to ameliorate PD and other tremors. Recently, it has been demonstrated that chronic high-frequency stimulation of this thalamic target, as well as of the subthalamic nucleus (STN) and the pallidum can efficiently suppress parkinsonian tremor and other motor symptoms [1].

### 2. Basal ganglia anatomy

There is a consensus that the major pathological event leading to the motor symptoms of PD, and especially to akinesia, is the death of midbrain dopaminergic neurons and their striatal projections. The basal ganglia are part of a closed loop connecting all cortical areas sequentially through the striatum, pallidum and thalamus with the frontal cortex. The frontal cortex projects downstream to the spinal level. Recently, single axon tracing anatomical studies [2] have revealed the complexity of the map of basal ganglia connectivity. Striatal neurons projecting to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) have been shown to send collaterals to the external segment of the globus pallidus (GPe). The physiological evidence for the importance of the direct projections from the motor cortex to the STN – the “hyperdirect” pathway [3] – indicates that, like the striatum, the STN is an input structure of the basal ganglia. Moreover, the recently described feedback projections from the GPe

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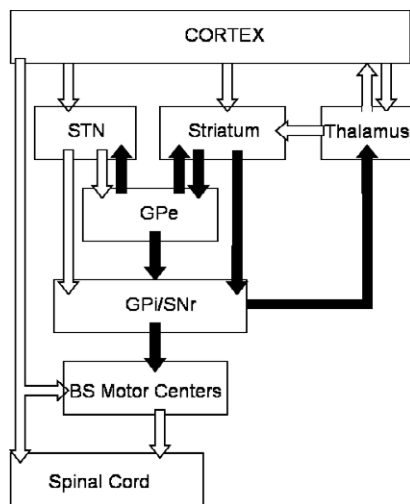


Fig. 1. Schematic view of the internuclear connectivity of the basal ganglia neuronal networks. Black arrows represent GABAergic inhibitory projections, white arrows mark glutamatergic excitatory connections. BS: Brainstem; GPe: globus pallidus, external segment; GPi: globus pallidus, internal segment; SNr: substantia nigra pars reticulata, STN: subthalamic nucleus.

to the striatum [4], as well as the GPe to GPi projection, strongly suggest that the GPe is a central nucleus in basal ganglia circuitry rather than a simple relay station in the indirect pathway. Figure 1 summarizes the current view of the complex connectivity among the basal ganglia nuclei.

### 3. Physiological studies of the basal ganglia in normal and dopamine depleted primates and human patients

The firing rate of basal ganglia neurons is irregular (Poisson-like) and neuronal oscillations are seldom observed in normal subjects. Most basal ganglia neurons change their firing rate after initiation of movements, and do not have any exclusive or consistent relationships to movement parameters such as start/end, velocity and amplitude. Early physiological studies of parkinsonian MPTP-treated monkeys reported changes in the discharge rate within the GPe, GPi and the STN [5–7]. Reversed trends of pallidal discharge rates are observed in response to dopamine replacement therapy [8]. Subsequent findings showing that inactivation of STN and GPi improve the motor symptoms in parkinsonian animals and human patients [1,9] supported the view that modulations of discharge rate play a critical role in the pathophysiology of PD.

More recent studies have emphasized the role of firing patterns and neuronal synchronization in the pathophysiology of PD [10]. MPTP monkeys show an increase in the fraction of basal ganglia neurons that discharge in oscillatory and non-oscillatory bursts. These bursts have been found in STN, GPe, GPi and also in primary motor cortex [11]. In most cases, the cells tend to oscillate at tremor frequency as well as at higher frequencies. Nevertheless, these studies have failed to reveal a significant fraction of neurons with oscillations that are consistently

coherent with the simultaneous recorded tremor. Both STN inactivation [12] and dopamine replacement therapy [8] significantly ameliorate the 4–7 Hz tremor and simultaneously reduce the GPi 8–20 Hz oscillations, supporting a critical role of high-frequency oscillations rather than tremor frequency oscillations in the generation of parkinsonian tremor.

Physiological studies in MPTP-treated monkeys of simultaneously recorded neurons in the pallidum, as well as in the primary motor cortex, among striatal tonically active neurons (TANs) and between TANs and pallidal neurons demonstrate that their pair-wise cross-correlograms become peaked and oscillatory, suggesting that striatal dopamine depletion induces abnormal coupling of basal ganglia loops. This abnormal pallidal synchronization decreases in response to dopamine replacement therapy. In most cases, the maximal power of the synchronous oscillations was found at double the tremor frequency [8]. Our recent preliminary analysis of human STN neurons recorded during electrophysiological mapping of the target area for therapeutic implantation of stimulating electrodes, also revealed significant synchronization of STN neuronal oscillations at the higher frequency, but not at the tremor frequency. The sharp contrast between this transient and inconsistent basal ganglia-tremor synchronization and the high synchronicity found between thalamic Vim neurons and the tremor [13] suggest that basal ganglia neurons cannot be viewed as the direct tremor-driving elements.

Synchronization of basal ganglia neuronal activity is also evident in the local field potentials recorded in the subthalamic region of PD patients by means of macro-electrodes used for high-frequency stimulation of these structures. These oscillations occur mainly in the beta range (15–30 Hz) and shift to higher frequencies in the gamma range following treatment with levodopa [14]. Magneto-encephalographic studies of PD patients have revealed a strong coherence between tremor and activity in the motor and sensory cortices and the cerebellum at tremor frequency. However, even stronger coherence was found at double the tremor frequency and around 20 Hz [15].

### 4. Summary and conclusions

Depletion of dopamine in the striatum (the main input structure of the basal ganglia) is the major event leading to PD clinical symptoms, including tremor. It is thus tempting to assume a causal relationship between the neural oscillations that are found in the basal ganglia and the tremor. The prominent power at double the tremor frequency in many single unit and MEG studies may suggest a 2:1 filtering mechanism downstream of the basal ganglia output. However, there is not enough evidence to support the notion that the tremor follows the basal ganglia oscillations. Akinesia, rigidity and resting tremor are the major motor symptoms of PD. Cumulative clinical and experimental

evidence support the view that these symptoms are not generated by identical neuronal mechanisms. We therefore suggest that the abnormal synchronous oscillations in the dopamine-depleted basal ganglia networks provide noisy input to the frontal cortex, hence leading to PD akinesia. Tremor is generated by neuronal networks downstream to the basal ganglia struggling to compensate for PD akinesia. Future studies of the complex network of the basal ganglia and their related neuronal structures will hopefully shed more light on their role and function in health and disease.

### Conflict of Interest statement

None declared.

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