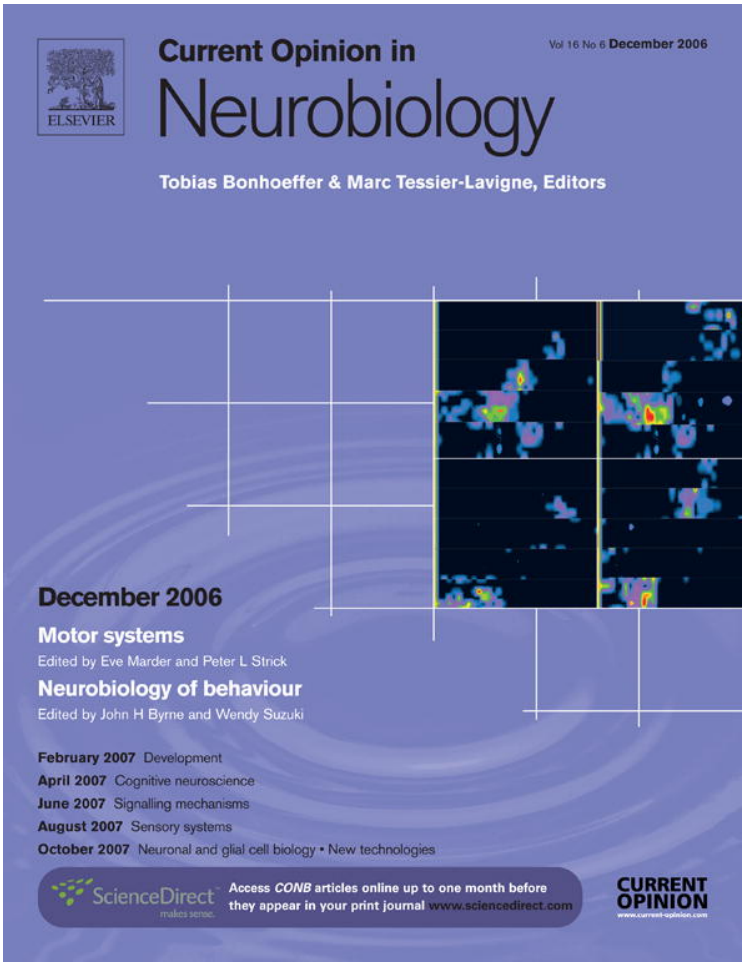

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Basal ganglia oscillations and pathophysiology of movement disorders

Michal Rivlin-Etzion[1,2], Odeya Marmor[1], Gali Heimer[1,4], Aeyal Raz[1,5], Asaph Nini[1,6] and Hagai Bergman[1,2,3]

Low frequency rest tremor is one of the cardinal signs of Parkinson's disease and some of its animal models. Current physiological studies and models of the basal ganglia differ as to which aspects of neuronal activity are crucial to the pathophysiology of Parkinson's disease. There is evidence that neural oscillations and synchronization play a central role in the generation of the disease. However, parkinsonian tremor is not strictly correlated with the synchronous oscillations in the basal ganglia networks. Rather, abnormal basal ganglia output enforces abnormal thalamo-cortical processing leading to akinesia, the main negative symptom of Parkinson's disease. Parkinsonian tremor has probably evolved as a downstream compensatory mechanism.

Addresses
[1] Department of Physiology
[2] The Interdisciplinary Center for Neural Computation
[3] The Eric Roland Center for Neurodegenerative Diseases, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, 91120
[4] Department of Pediatrics, Hadassah – Hebrew University Medical Center, Jerusalem, Israel, 91120
[5] Department of Anesthesia, Rabin Medical Center-Beilinson Campus, Petach-Tikva, Israel
[6] Department of intensive care, Division of Anesthesiology, Shiba Medical center, Tel-Hashomer, Israel

Corresponding author: Bergman, Hagai (hagaibe@ekmd.huji.ac.il)

Current Opinion in Neurobiology 2006, **16**:629–637

This review comes from a themed issue on
Motor systems
Edited by Eve Marder and Peter L Strick

Available online 3rd November 2006

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2006.10.002

Introduction: Parkinson's disease — clinical symptoms and pathology

In 1817, almost two hundred years ago, the English physician James Parkinson wrote '*Essay on the Shaking Palsy*', providing the first clinical description of the motor symptoms of the disease now bearing his name [1]. Today, Parkinson's disease (PD) is the most common basal ganglia movement disorder, and affects from 1% of those aged 65 to 4–5% of the 85 year old population [2].

Only 5% of PD cases can be attributed to specific genetic causes [3•,4]. Most of the remaining cases cannot be attributed to metabolic or toxic causes either, and are, therefore, classified as idiopathic PD. PD is the result of a neurodegenerative process that causes damage to multiple neuronal circuits. The dopaminergic system is the most seriously damaged, but the noradrenergic, serotonergic and cholinergic systems are also affected [5].

On the basis of clinical observations of six patients (including two whom he met on the street and a third he observed at a distance), Parkinson described two of the most important and paradoxically related symptoms of PD: shaking — now defined as a low frequency (4–7 Hz, but higher frequencies, up to 9 Hz, are encountered at early disease stages) tremor at rest (tremor amplitudes decrease during voluntary action and increase during mental stress), a hyperkinetic disorder; and palsy (or akinesia in modern terminology) — characterized by a poverty of voluntary and especially involuntary movements, a hypokinetic disorder. The other cardinal motor symptoms of PD include bradykinesia (slowness of voluntary movements), rigidity (increased muscular tonus), and postural abnormalities. Cognitive and mood (emotional) deficits frequently accompany the motor symptoms. However, in this review we focus on the pathophysiology of the two main motor symptoms of PD as outlined by Parkinson: akinesia and tremor at rest. Note that we consider bradykinesia and related hypokinetic PD clinical features as akinetic symptoms. PD rigidity is characterized by a uniform resistance to passive movements owing to increased muscle response to passive stretch, and is not associated with changes of spinal alpha motor neuron excitability. Thus, and based on the clinical similarities of akinesia and rigidity as outlined below, we associate akinesia and rigidity. Finally, we limit our discussion to tremor at rest, although other non-harmonically related forms (e.g. postural and/or kinetic tremor) are very common in PD [6,7].

Akinesia versus tremor in Parkinson's disease

PD is not a homogenous disease, either across patients or even within a single patient's disease course. Temporally, tremor is not a consistent feature of the disease, but rather is episodic, as opposed to akinesia. Unlike rigidity and akinesia, there is no correlation between the clinical severity of PD tremor and the severity of the dopaminergic deficit in the striatum or the clinical progression of the disease [7].

Human PD covers a broad spectrum of symptoms and can present as a predominant resting tremor (T-subtype) or

Glossary

Direct–indirect rate model of the basal ganglia: The circuitry of the basal ganglia is often divided into two major pathways, the direct pathway and the indirect pathway. The direct pathway directly connects the striatum to the GPi and SNr by GABAergic (inhibitory) projections. The indirect pathway connects the striatum to the GPi and SNr through the GPe and the STN, with net excitatory effects.

Disinhibition: Removal of neuronal inhibition by inhibition. For example, cells in the striatum can inhibit neurons of the GPi and SNr, which in turn removes their tonic inhibition from the thalamus.

Essential tremor: The most common movement disorder (10–20 times more prevalent than PD), characterized by a slowly progressive postural and/or kinetic tremor with no known cause.

Negative symptoms: Normal behaviors or body states that are absent or diminished in a person with a mental or neurological disorder (e.g. akinesia of PD).

Positive symptoms: These are the opposite of negative symptoms and refer to behaviors or body states that are practically absent in people in the general population but are present or enhanced in persons with the neurological disorder (e.g. PD tremor).

Spectral harmonics: Spectral harmonics are other spectral peaks at frequencies equal to integer multiples of the fundamental frequency, usually as a result of distortions to the pure sinus generating the fundamental frequency.

Spectral sidebands: In spectral analysis, a sideband is a band of frequencies higher or lower than the fundamental frequency, usually containing energy as a result of the amplitude modulation process.

primarily as marked akinesia and rigidity (AR-subtype) [8], sometimes defined as the 'postural instability gait difficulty subtype'. As early as 1877, the great French neurologist Jean-Martin Charcot noted that tremor is not always present in human PD patients, and, therefore, suggested changing the name of the disease from 'paralysis agitans' (Latin for shaking palsy) to 'la maladie de Parkinson' (Parkinson's disease). T-subtype PD patients have a better prognosis and slower disease progression than AR-subtype patients [8]. Interestingly, most patients with non-idiopathic PD display akinesia and rigidity but not rest tremor [9]. Anti-cholinergic agents, which were the first drugs available for the symptomatic treatment of PD, tend to have better effects on tremor than on akinetic-rigid symptoms, whereas akinesia might show better and earlier response to dopamine replacement therapy [10]. Several studies have indicated that the pathology of human T-type PD differs from that of the AR-type PD, with the retrorubral area (A8) more severely affected in the tremor-dominant form [11].

The frequency of tremor in a given PD patient is often remarkably similar in different muscles of the extremities and trunk [12]. These observations led to the assumption that a common single central oscillator controls all tremulous muscles. Coherence analysis, however, has shown that although the muscles within one body part (e.g. a limb) are mostly coherent, the tremor in different extremities, even on the same body side, is almost never coherent [13,14], indicating that different oscillators underlie parkinsonian tremor in the different extremities. This absence of tremor coherence could hint at mechanical or spinal reflex mechanisms rather than a single central oscillator. Nevertheless, several studies have failed to demonstrate any frequency reduction of the tremor as a result of load addition to the trembling limb in PD patients [6,7]. Resetting experiments, in which the tremulous limb is reset by mechanical perturbation, have been less conclusive. Initial studies indicated that resetting of tremor is much more easily achieved in essential tremor (see Glossary) than in PD tremor. However, more recent studies have shown that the resetting index varies significantly with the magnitude of the mechanical perturbation and with the tremor amplitude. When these factors were equalized, however, no significant difference was found in mean resetting indexes among PD tremor, essential tremor and normal subjects mimicking tremor. Resetting experiments with electrical stimulation of the median nerve or transcranial magnetic stimulation of the motor cortex did not show consistent resetting of the tremor rhythm when the periphery (median nerve) was stimulated, but did result in complete resetting when the cortex was stimulated [7].

In line with the central nervous system (CNS) hypothesis on the origin of PD tremor, it has long been known that different lesions within the CNS can suppress parkinsonian tremor. Early attempts to remove parts of the motor cortex or its downstream projections were successful in suppressing tremor but produced unacceptable side effects. The cerebellar receiving nuclei of the thalamus (e.g. the ventralis-intermedius, Vim) have traditionally been considered the optimal target for stereotaxic procedures for amelioration of PD and other tremors. Recently, it has been demonstrated that chronic high-frequency stimulation of these same thalamic targets, in addition to subthalamic or pallidal stimulations, are all able to efficiently suppress parkinsonian tremor and other motor symptoms [15••].

In summary, most clinical human studies indicate that PD tremor and akinesia, although they share common origins and similarities, have significantly distinct characteristics. The role of striatal dopamine depletion and the central generators seem to be much more important in akinesia. PD tremor might be modulated by peripheral manipulation and by the activity of other central neuronal systems. It is possible that transmitter systems other than dopamine (e.g. cholinergic, serotonergic), or neural circuits other than the basal ganglia (e.g. cerebellum [16], red nucleus), play a crucial additive role in underlying this symptom.

Parkinson's disease — animal models

Early animal models of PD were based on lesions of midbrain areas in monkeys. These anatomical lesions mainly produce rigidity and only rarely result in a spontaneous, sustained tremor. Careful analysis of the correlation between the clinical symptoms and the extent of the lesion led to the conclusion that experimental rest tremor

is the result of damage to both the nigro-striatal dopaminergic projections and the cerebellar outflow (to the red nucleus and thalamus). Damage to only one of these neuronal systems was not sufficient for reliable generation of tremor [17].

More modern animal models of PD have shifted from anatomical to chemical lesions. Early chemical animal models of PD — for example, the 6-hydroxydopamine (6-OHDA) model — were limited to dopaminergic damage, and mainly reproduced the main negative symptoms of PD; namely, akinesia (see Glossary) [18]. The more recently introduced primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [19] better mimics the clinical and the pathological picture of PD. Post-mortem examination of the brains of MPTP-treated primates reveals that the primary damage is to the dopaminergic system. However, as in human PD, other neuromodulators are also affected [20].

Monkeys treated with MPTP mainly exhibit the akinetic–rigid symptoms of PD [19]. Low frequency (4–7 Hz) resting tremor is not readily replicated in MPTP-treated macaque monkeys, but other species, notably the vervet (African green) monkey, often develop a prominent low-frequency tremor following MPTP injections [21,22]. It is important to note that the tremor usually appears several days after the development of clinical akinesia and rigidity [21,23•]. This reversed order of presentation of clinical symptoms compared with that of the human disease could be due to the fast induction of dopamine depletion in the MPTP model that might impede the development of compensatory processes found in the slow-evolving human disease. Yet, tremor is a much more overt phenomenon than akinesia and rigidity. A human patient or his/her family might first be made aware of the slow development of PD by the more easily recognizable tremor. As in human studies, there is a low coherence between the tremors of the limbs of MPTP-treated vervet monkeys following dopamine replacement therapy [23•].

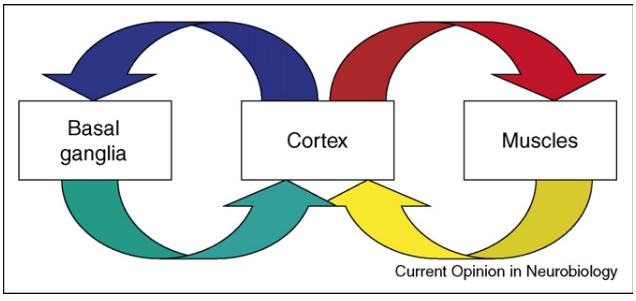
Basal ganglia anatomy

The cumulative clinical and experimental evidence outlined above strongly indicates 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 striatum (composed of caudate, putamen and ventral striatum) is the main input stage of the basal ganglia, receiving inputs from all cortical areas, from many thalamic nuclei and even from the cerebellum [24••]. Therefore, a good grasp of the pathophysiology of PD depends on understanding the anatomy and physiology of the basal ganglia and dopamine networks.

The realization, at the turn of the 20th century, that lesions involving the basal ganglia often result in severe disorders of motor function explains why the basal ganglia were classified as part of the extra-pyramidal system. The pyramidal system starts at the motor cortices, and through the brainstem pyramids projects to α-motoneurons, innervating the distal parts of the limb, and controlling the execution of accurate and voluntary movements. By contrast, it was assumed that the extra-pyramidal system originated at the basal ganglia and the cerebellum, descended parallel to the pyramidal system, and innervated the spinal circuits involved with more axial (postural), automatic non-voluntary movements.

The revolution in anatomical methods during the second half of the 20th century led researchers to the conclusion that the basal ganglia are part of a closed loop connecting all cortical areas sequentially through the striatum, pallidum and thalamus with the frontal cortex (Figure 1). The frontal cortex projects downstream to the spinal level. The direct projection of the basal ganglia to upper brainstem nuclei (e.g. superior colliculus and peduncolopontine nucleus [16]) will be considered here, for the sake of simplicity, as part of this descending system. The new view of the basal ganglia networks assumes that there are two segregated internal pathways that start in the striatum and converge on the output structures of the basal ganglia (the internal segment of the globus pallidus [GPi] and the substantia nigra pars reticulata [SNr]). The 'direct pathway' is a direct GABAergic inhibitory pathway, whereas the 'indirect pathway' is a polysynaptic disinhibitory pathway (see Glossary) through the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). The projection striatal neurons in the direct pathway express D1 dopamine receptors, whereas those in the indirect pathway express D2 dopamine receptors [25]. Midbrain dopamine (DA) has differential effects on the two striato-pallidal pathways: it facilitates transmission along the direct pathway through the D1 receptors and inhibits transmission along the indirect pathway through the D2 receptors [25,26]. Note that in this schematic description the crucial roles of both the cholinergic and the dopaminergic innervation of the striatum on

Figure 1

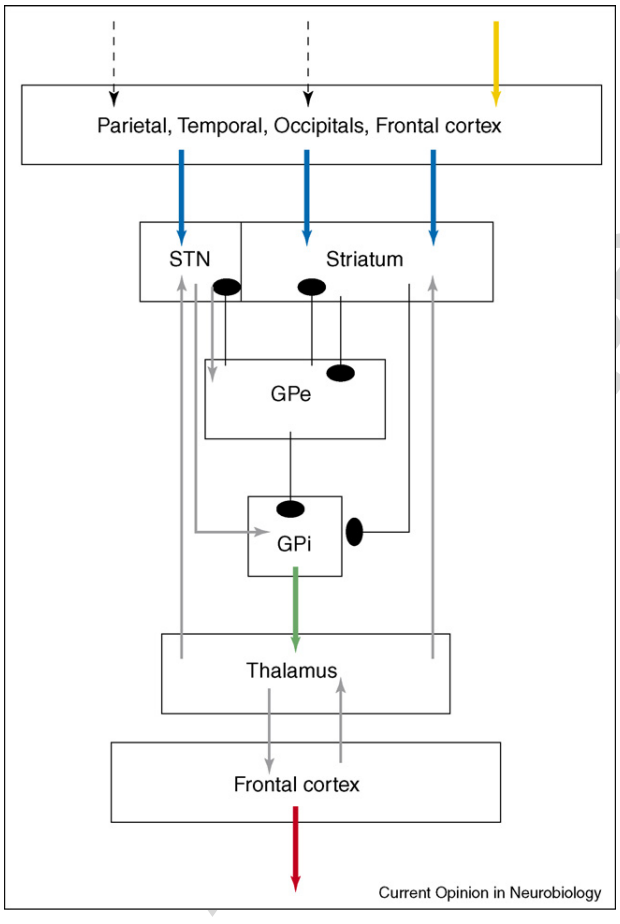


Schematic view of the recurrent connectivity among the cortex, basal ganglia and muscle networks.

plasticity and learning in the cortico-striatal synapse have been neglected [27••,28••].

Recently, single axon tracing anatomical studies have revealed an even more complex map of basal ganglia connectivity. Striatal neurons projecting to GPi and SNr send collaterals to GPe [29••,30]. The physiological evidence for the importance of the direct projections from the motor cortex to the STN (the 'hyper-direct pathway' [31]) indicate that like the striatum, the STN is an input stage of the basal ganglia [32]. Moreover, the recently described feedback projections from the GPe to the striatum [33,34], in addition to the GPe to GPi projection, strongly suggest that the GPe is a central nucleus in the basal ganglia circuitry, rather than a simple relay station in the indirect pathway. Figure 2 summarizes the current view of the complex connectivity among the basal ganglia nuclei.

Figure 2



Detailed linear view of the connectivity of the cortex, basal ganglia and muscle networks. Color coding as in Figure 1. The basal ganglia inter-connectivity is shown in detail, with gray arrows representing excitatory–glutamatergic projections and black round-head arrows for inhibitory–GABAergic projections. Abbreviations: GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; STN, subthalamic nucleus.

Physiological studies of the basal ganglia in normal primates

Single unit recording and analysis of neuronal activity at the level of single spikes of single cells are probably the main ways to study a neuronal network. The different nuclei of the basal ganglia have a diverse background (during a quiet, awake state) spiking activity. The striatal neurons are characterized by a low frequency discharge rate (<1 spikes/s by the projection neurons and 4–10 spikes/s by the tonically active neurons [TANs], the cholinergic interneurons). This slow discharge is striking in contrast to the high (50–80 spikes/s) frequency discharge of the pallidal and SNr neurons. In all these structures the firing rate is irregular (Poisson-like), and neuronal oscillations are seldom observed in normal awake subjects.

Studies exploring the relationship between spiking activity of basal ganglia neurons and body movements have revealed even more unexpected results. The akinesia associated with PD suggests that the basal ganglia play a crucial role in movement initiation. Nevertheless, most basal ganglia neurons change their firing rate after initiation of movements (Putamen: [35,36], GP: [37–39], SNr: [40]), and do not have any exclusive or consistent relationship to movement parameters such as start and/or end, velocity or amplitude [41]. Taken together with the minor impairment of motor control following focal inactivation and lesions of the output structures of the basal ganglia [42–44], the physiological results lead to the surprising conclusion that the basal ganglia do not initiate movements [42,45].

Physiological studies in the dopamine-depleted basal ganglia networks

Early physiological studies of parkinsonian MPTP-treated monkeys reported changes in the discharge rate within the GPe, GPi [46,47] and STN [21]. Reversed trends of pallidal discharge rates in response to dopamine replacement therapy have been reported in both human patients [48,49] and primates [23•,50,51]. The crucial role of these rate changes in the pathophysiology of PD has been verified by the subsequent findings showing that inactivation of STN and GPi could improve the motor symptoms in parkinsonian animals [52] and in human patients [15••].

These findings contributed to the formulation and the popularity of the direct–indirect model of the basal ganglia (see Glossary) [26]. Nevertheless, several studies have failed to find the expected significant changes of firing rates in the pallidum [53], thalamus [54] or motor cortical areas [55] of MPTP monkeys. This and other inconsistencies with the assumptions and the predictions of the direct–indirect rate model have attracted more attention to the potential roles of other aspects of neuronal activity, such as firing patterns and neuronal synchronization, in

the pathophysiology of PD. MPTP monkeys show an increase in the fraction of basal ganglia neurons that discharge in bursts. These bursts are either irregular or oscillatory and have been found in STN, GPe, GPi and primary motor cortex [21,22,46,47,55,56,57•]. In most cases, the cells tend to oscillate at the tremor frequency or at double or even triple the tremor frequency [21]. Nevertheless, these studies repeatedly failed to reveal neurons with oscillations that are consistently coherent with the tremor [22,23•]. Both STN inactivation [58] and dopamine replacement therapy [23•] ameliorate the 4–7 Hz tremor and reduce the GPi 8–20 Hz oscillations, supporting the crucial role of double rather than the tremor frequency oscillations in tremor generation.

Physiological studies and cross-correlation analysis of the activity of simultaneously recorded neurons in the basal ganglia and cortex of monkeys before and after MPTP treatment enable the assessment of the changes in neural synchronization in these areas. These studies have been conducted in the pallidum [22], as well as in the primary motor cortex [55], among striatal TANs and between TANs and pallidal neurons [59,60]. Cross correlation functions become peaked and oscillatory following MPTP treatments, suggesting that striatal dopamine depletion induces abnormal coupling of basal ganglia loops. The abnormal pallidal synchronization decreases in response to dopamine replacement therapy [23•]. In most cases, the maximal power of the synchronous oscillations was at double the tremor frequency [22,23•,59,60].

As in the MPTP primate, single unit studies of the basal ganglia of human PD patients (performed during electrophysiological mapping of the target area for therapeutic implantation of stimulating electrodes) report a high fraction of GPi cells oscillating at the tremor frequency [61]. However, as in the primate, the human studies [62,63••] show that these oscillations are not fully coherent with the simultaneous recorded tremor. The sharp contrast between this transient, inconsistent pallidal-tremor synchronization and the high synchronicity found between thalamic Vim neurons and the tremor [64] suggests that pallidal neurons cannot be viewed as the tremor generators, or as reflecting the proprioceptive feedback of the tremor.

Physiological studies of population neural activity in the dopamine-depleted basal ganglia networks

Synchronization of basal ganglia neuronal activity is also evident in the local field potentials (LFPs) recorded in the subthalamic region of PD patients by the macroelectrodes used for high-frequency stimulation of these structures. These oscillations occur mainly in the β range (15–30 Hz) and following treatment with levodopa shift to higher frequencies in the gamma range [65••]. Another study found that a significant reduction of the β range oscillations preceded the onset of the rest tremor [66•]. In line with both the single unit and the LFP studies, magnetoencephalographic (MEG) studies [67] of T-type PD patients have revealed a strong coherence between the tremor and the activity in the motor and sensory cortices and the cerebellum at tremor frequency, and an even stronger coherency at double tremor frequency. Spectra of coherence between thalamic activity and cerebellum as well as between other brain areas have revealed additional broad peaks around 20 Hz.

Studies of LFPs recorded from frontal cortex and STN of rats following 6-OHDA lesions of midbrain dopamine neurons [68] have revealed significant increases in the power and coherence of β-frequency oscillatory activity. Administration of apomorphine, the dopamine receptor agonist, to these dopamine-depleted animals suppressed the β-frequency oscillations, and increased coherent activity at gamma frequencies in the cortex and STN. Thus, the pattern of synchronization between population activity in the STN and that in the cortex in the 6-OHDA-lesioned rodent model of PD is parallel to that seen in the parkinsonian human.

Recordings of both LFPs and multi-neuronal activity from microelectrodes inserted into STN in PD patients during functional neurosurgery suggest that the discharges of some of the neurons in STN are locked to β oscillations in the LFP [69]. LFP probably represents the synaptic input to a neural structure and its subthreshold slow activity. The discrepancies between LFP oscillatory activity and neuronal activity (in their frequency domain, prevalence and power) are probably due to the fact that even quite strong synchronized inputs can lead to weak neuronal correlations. Alternatively, correlations can be very low at the single-unit level, but still sum and become substantial at the population (LFP) level [70,71].

On correlation, causality and harmonics in spectral analysis

Basal ganglia researchers are aware that depletion of dopamine in the striatum (the input stage of the basal ganglia) is the major event leading to clinical symptoms, including tremor, of PD. It is, thus, tempting to assume a causal relationship between the neural oscillations that are found in the STN and the globus pallidus (output stage of the basal ganglia) and the tremor. However, the closed loop structure of the cortex–basal ganglia–muscle networks (Figure 1), including inputs from other structures (e.g. cerebellum), suggests that basal ganglia oscillations are the result of proprioceptive feedback to the basal ganglia.

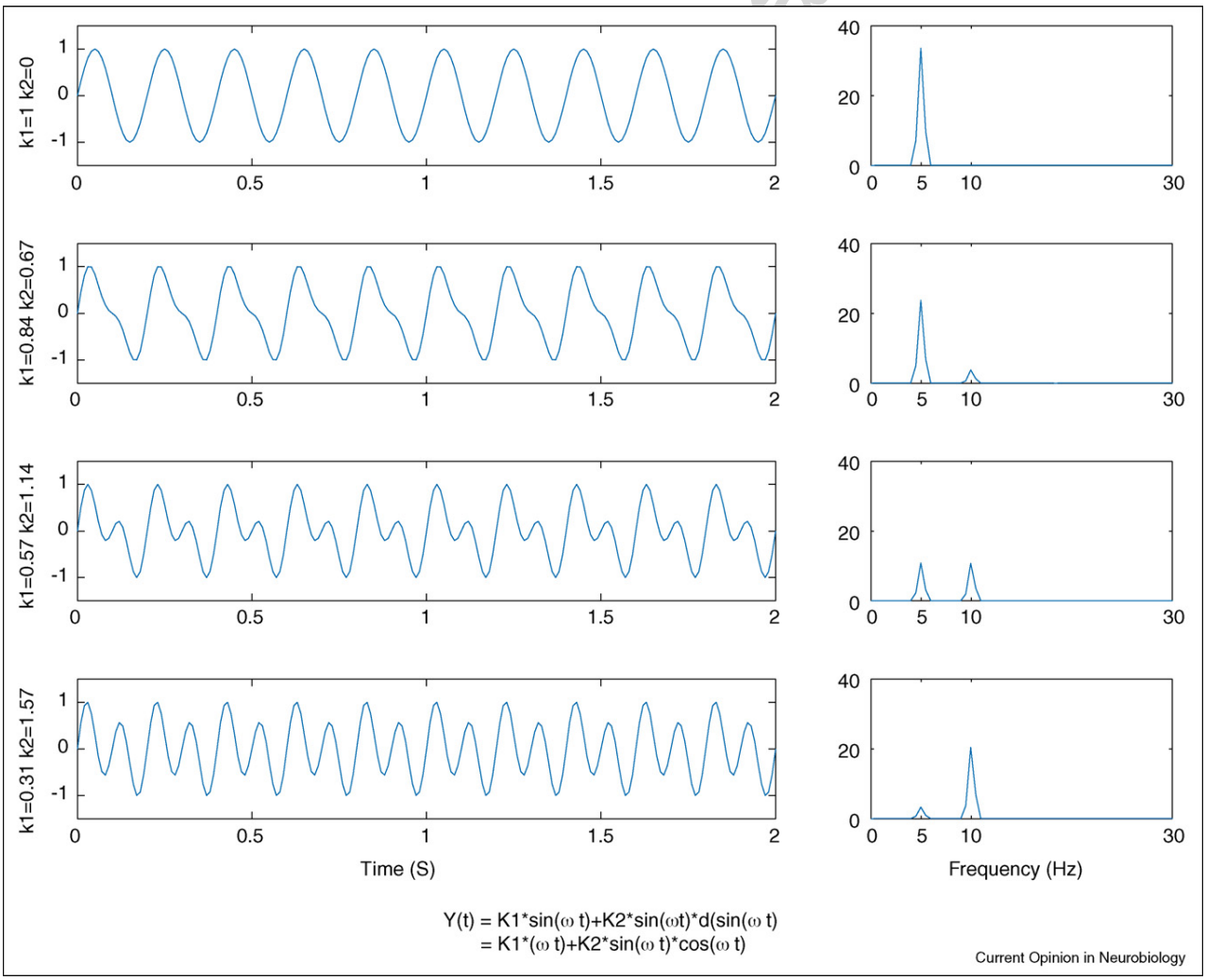
The high-level energy at double the tremor frequency in many single unit correlation studies [22,59] and MEG studies [67] might suggest a 2:1 filtering mechanism downstream of the basal ganglia output [72,73]. However, there are important limitations to spectral analysis

[66•,74–76]. In particular, any non-linear transformation (e.g. the addition of a derivative or high-pass filtered version of the original signal) might add higher harmonics (see Glossary) to the original peak. The amplitude of these higher harmonics can be larger than that of the original peak (Figure 3). Amplitude fluctuation of the tremor or neuronal analog signal (such as LFP) could add 'sidebands' (see Glossary) both above and below the central frequency peak. Moreover, if the amplitude and the frequency fluctuation follow a complex pattern, and enough spectra are averaged (as is the common practice), the additional peaks can be distributed out over a broad frequency domain [77]. Thus, although neuronal oscillations can be detected at several levels of the basal ganglia network subsequent to dopamine depletion and the emergence of clinical PD tremor, there is not enough evidence to support the notion that the tremor follows the basal ganglia oscillations.

Conclusions and future directions

In this review we have explored the possible relationships between basal ganglia oscillatory activity and PD tremor. PD is the result of dopamine depletion in the striatum — the input stage of the basal ganglia. Akinesia and rest tremor are two major symptoms of PD. Nevertheless, cumulative clinical and experimental evidence support the view that akinesia and rest tremor are not generated by identical neuronal mechanisms. Following striatal dopamine depletion, many basal ganglia neurons develop synchronous oscillations at the tremor frequency and at their higher harmonics in addition to in the β range. However, the PD tremor does not strictly follow the basal ganglia

Figure 3



Simulated analog signals and their power spectrums. The analog signal (left column) is composed of a pure sinus wave plus its derivative (cosine function with the same frequency). K1 and K2 are scaling factors of the relative weights of the sinus and its derivate (cosine) function. The scaling factors were chosen to normalize all peak-to-peak amplitudes to the same value.

oscillatory activity. The recent demonstration of anatomical connections between the cerebellum and the basal ganglia, at the cortical, striatal and brainstem levels might suggest that the cerebellum is associated with the movement disorders classically described as basal ganglia disorders. The crucial role of cerebellar output in the generation of PD tremor has been demonstrated by lesion studies and the efficacy of Vim intervention in treatment of PD tremor. These findings, along with the physiological studies of the normal basal ganglia indicating that the basal ganglia do not initiate movements, strengthen the supposition that the abnormal synchronous oscillations in the basal ganglia provide noisy input to the frontal cortex, and hence lead to PD akinesia. In contrast to the akinesia, we suggest that PD tremor (Parkinson's 'shaking') is the result of compensation mechanisms generated downstream of the basal ganglia in order to compensate for PD akinesia ('palsy'). This hypothesis is in accordance with the fact that T-subtype PD is slower to progress than AR-subtype PD, and with the late appearance of the tremor in the MPTP-treated monkeys. Moreover, the peripheral feedback from the tremulous body segments might interrupt the noisy activity of the basal ganglia cortical networks in a similar manner to subcortical DBS or lesions. Future studies of the complex neural network of the basal ganglia and their related neuronal structures will hopefully shed more light on their role and function in health and disease.

Acknowledgements

This research was supported in part by a Center of Excellence grant from the Israel Science Foundation (ISF) and the 'Fighting against Parkinson' Foundation of the Hebrew University Netherlands Association (HUNA). We thank E Singer for critical reading and language editing.

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