Neurophysiological changes in the primate basal ganglia following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism

Yaara Erez[1] and Izhar Bar-Gad[1,2]

[1] Gonda Brain Research Center and [2] Goodman Faculty of Life Sciences, Bar Ilan University, Ramat Gan, Israel

Abstract

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that impairs mostly motor skills. Extensive research of the disease is conducted using a common primate model which is based on the administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In order to characterize the abnormal neuronal activity during PD, we performed electrophysiological recordings in the globus pallidus external (GPe) and internal (GPi) segments of an MPTP treated primate. We analyzed both the single neuron activity and the interactions of multiple neurons, and found major effects of Parkinsonism. Single unit firing patterns in the normal state were characterized by a Poissonian irregular firing, and were not correlated to the background activity. In the Parkinsonian state, autocorrelation and spectral analysis revealed that the firing patterns became bursting and the activity was oscillatory. The discharge of the neurons was correlated with the oscillatory background activity and the cells tended to fire at different phases of the background cycle of oscillations. Multi unit activity was synchronized in the Parkinsonian state compared to the independent activity in the normal state. The cells tended to oscillate synchronously, with phase differences between them. Our results support other evidence that suggests multifaceted changes in the firing pattern and interaction in PD, instead of mere changes in firing rate. These complex changes reflect a substantial effect on the whole motor system through the loop of the cortex-basal ganglia-thalamus-cortex. We suggest that the projections from the globus pallidus during PD interfere with the thalamic activity that relays information to the cortex, instead of

modulating it as in the normal state. This disturbance to the information flow is enhanced by burst firing as well as correlated oscillatory activity of multiple neurons that causes large and simultaneous post-synaptic effects on thalamic neurons at a temporal micro-scale. This activity eventually results in abnormal thalamic and cortical activity that leads to the typical clinical motor symptoms of the disease. Characterizing and understanding the changes in neuronal activity patterns form a crucial step towards treatments that are aimed at reversing this abnormal activity, offering new hope for PD patients.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that impairs primarily motor skills. The disease was first described as "Shaking Palsy" ("paralysis agitans") in 1817 by the British physician James Parkinson, after which the disease was later termed. He described the symptoms as "Involuntary tremulous motion, with lessened muscular power … with propensity to bend the trunk forwards ... the senses and intellects being uninjured" (1). The most ancient description of Parkinsonian symptoms is probably a clinical syndrome termed Kampavata in Sanskrit described in the Indian Ayurvedic texts over 3000 years ago, including symptoms such as tremor and akinesia. The syndrome was treated using an extraction from seeds of a plant called Mucuna Pruriens. This plant was found in the 20th century to contain a substance which is the most common modern pharmacological treatment for PD (2;3).

The prevalence of PD is about 1% of the population over age 65 and 5% of the population over age 85 (3). It is typically a disease of the middle to late years, beginning at a mean age of 50-60 years and progressing slowly, with mean lifespan with the disease of 20 years (4). The age of onset has a broad distribution, with about 5 percent of cases beginning before age 40 ("young-onset PD).

The cardinal symptoms of PD are rest tremor (4-7 Hz), akinesia (reduction in spontaneous movement, 'freezing'), bradykinesia (slowness of movement), rigidity (stiffness, or resistance of the limb to passive movement), and postural instability. Other non-motor characteristics include autonomic dysfunction, cognitive, mood and sleep disturbances (5).

The most remarkable pathophysiological sign of PD is the degeneration of dopaminergic neurons in a deep brain nucleus called the substantia nigra pars compacta (SNc) (6;7). These cells project to the striatum, and the loss of the nigro-striatal projectoins leads to dopamine depletion in the striatum and subsequently affects the activity of neurons throughout other nuclei connected to the striatum (8). The clinical symptoms appear when the neuropathology has already reached an advanced state which is estimated to be about 50-60% of SNc cells loss and about 70% of dopamine depletion in the striatum (9). Intracytoplasmic inclusions called Lewy bodies in the surviving SNc cells are another fundamental pathological hallmark of PD. The main component of the Lewy bodies is aggregations of the presynaptic protein α-sinuclein (3;10-15). In addition to these hallmark changes, extensive brain damage appears gradually through the course of the disease, including the brain stem, primary motor and sensory cortices, sensory association and premotor areas, and the olfactory nucleus (14).

The most common pharmacological treatment for PD is dopamine replacement therapy (DRT). It is mainly based on the dopamine precursor levodopa (L-dopa) (16), but other agents involved in the dopaminergic system such as catechol-O-methyltransferase (COMT) inhibitors and monoamine oxidase B (MAO-B) inhibitors are used as well. The dopaminergic agents affect the pre-synaptic dopaminergic cells thus enhancing the efficacy of the remaining SNc neurons in terms of dopamine level. Dopamine agonists, which act directly on post-synaptic dopamine receptors, comprise another branch of DRT. Other pharmacological treatments include anticholinergics and glutamate antagonists (17). Non-pharmacological treatments include surgical interventions such as lesions and electrical deep brain stimulation (DBS) in the STN, GPi and thalamus (18-22).

The etiology of PD is mostly unknown. Though it can be attributed to genetic factors or be induced by toxins, drugs or infections, most of the cases (around 95%) are idiopathic, or sporadic, meaning that the cause is unknown. Toxin-induced Parkinsonism involves various toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Fig. 1A), manganese, carbon monoxide, carbon disulfide, cyanide and methanol (23). Whilst the clinical symptoms following MPTP intoxication are similar to those of PD, the other

toxins lead to varied neuropathologies and diverse behavioral, psychiatric and motor symptoms, among which are PD-like symptoms such as rigidity and bradykinesia (23).

The first case of MPTP-induced Parkinsonism in humans was reported in 1976, when a chemistry student injected himself with incorrectly synthesized 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), a synthetic opiod with effects similar to those of heroine and morphine (Fig. 1B), contaminated with MPTP (24). A few years later, in 1982, several young drug users from Northern California developed Parkinsonian-like symptoms after using MPPP. These symptoms were found to be caused by MPTP that was accidentally produced during the illicit manufacture of MPPP (25). Further research revealed that MPTP reaches the brain within minutes after the injection and starts a cascade of events that leads to its toxic effect. MPTP is metabolized by the enzyme MAO-B in glial cells to 1-methyl-4-phenyl-2,3,-dihydropyridinium (MPDP+), which is then oxidized to 1-methyl-4-phenylpyridinium (MPP^+) (Fig. 1C). The MPP^+ that is released into the extracellular space is taken up by dopamine transporters of the dopaminergic neurons. MPP+ then accumulates in the mitochondria, inhibiting the mitochondrial respiratory enzyme complex I, and eventually leading to a selective death of the dopaminergic neurons in the SNc (26-28).

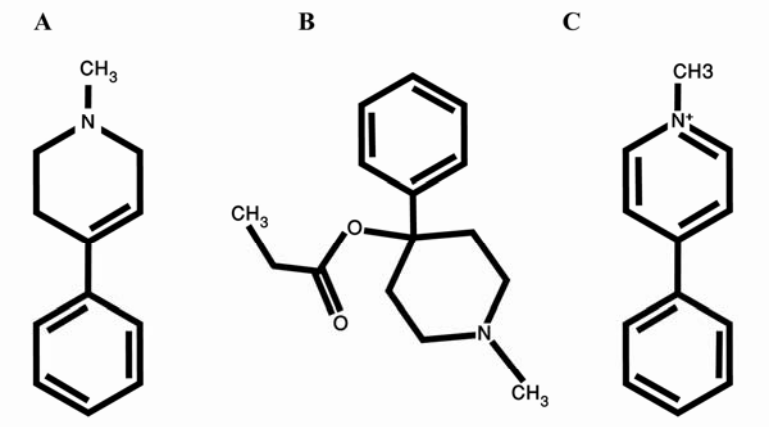

Figure1: Chemical structures. A: MPTP. B: MPPP. C: MPP^+

Following the discovery of MPTP-induced human Parkinsonism, the first animal model based on MPTP was developed, using squirrel monkeys (29;30). The monkeys exhibited the major Parkinsonian symptoms such as akinesia and rigidity. Since then, the MPTP animal model for PD has developed and is broadly used with different species including cats, dogs, rats, pigs and goldfish, but mostly nonhuman primates and mice (28;31-34).

Other toxins, such as the 6-hydroxydopamine (6-OHDA), are also used for PD animal models (31).

Various primate species have been used in research as preparations for PD animal model, among them are squirrel monkeys, Macaca fascicularis (cynomolgus), Macaca mulatta (rhesus), African green monkey (vervet), Macaca fuscata (Japanese macaque) and others. The symptoms produced as a result of MPTP administration in the primates resembles human PD: akinesia, rigidity, postural instability, and bradykinesia. However, resting tremor was observed only in the African green monkey (35), while some of the other species express only action (also termed intention) tremor.

The MPTP primate model is comprised of multiple models that differ from each other by the administration protocol. High-dose MPTP administration during a short time period of a few consecutive days leads to irreversible moderate to severe parkinsonism, affecting the state of the animal within a few days (19;36;37). Other models emphasize the long term degeneration of the nervous system and its similarity to the slow time scale of the pathological neurodegenerative processes that take place in human PD by low-dose MPTP injections given 2-3 times a week over prolonged time periods, ranging from weeks to months (38-40). Hemiparkinsonian syndrome is achieved by unilateral internal carotid artery infusion of MPTP (41-43) that leads to manifestation of symptoms primarily on the side contralateral to the injection. The main advantage of this model is that it enables the animal to eat, drink and maintain itself, unlike the full Parkinsonian state.

The neuropathological damage to MPTP-treated monkeys is a selective degeneration of SNc dopaminergic neurons and dopamine depletion in the striatum, similar to human PD pathophysiology (29;44). Yet, the Lewy bodies typical to PD are absent in MPTP-treated monkeys, though other inclusion bodies that lack the morphological and immunocytochemical features of the Lewy bodies are observed in aged monkeys treated with MPTP (45;46). Pharmacologically, MPTP-induced Parkinsonian monkeys respond to DRT and exhibit peak-dose hyperkinetic distortions of movement called dyskinesia after long-term DRT, similarly to humans (47-50). This resemblance of the MPTP-induced Parkinsonism in primates to human PD has enabled extensive research of the

impairment in information processing in PD and led to the development of new therapies for the disorder (51).

The SNc, whose neurons degenerate during PD, is part of a group of interconnected nuclei called the basal ganglia (BG). The idea that the basal ganglia is involved in PD was first raised in 1912 by S. A. Kinnier Wilson, who described symptoms similar to PD and related them to pathophysiology of the BG (52). The BG receive input mainly from the cortex and thalamus and project their output primarily to the thalamus and thereafter back to the cortex, hence constructing the cortico-basal ganglia loop. The Albin & DeLong 'Box and Arrow' model shown in Fig. 2A (53;54) describes the anatomy of the basal ganglia. The input nuclei of the basal ganglia are considered to be the putamen and caudate, together comprising the striatum. From the striatum there are two complementary pathways. The GABAergic inhibitory projections from the striatum to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), which together comprise the output nuclei of the BG, are termed the *direct pathway*. The GABAergic inhibitory projections from the striatum to the external segment of the globus pallidus (GPe), then inhibitory projections to the subthalamic nucleus (STN) and finally excitatory projections to the GPi and SNr are termed the *indirect pathway* (53;55). The disinhibition in the indirect pathway creates a net effect of excitation on the output structures of the BG which is opposite to the net inhibitory effect of the direct pathway. Recent evidence revealed another input pathway from the cortex directly to the STN, termed the *hyperdirect pathway* (56). Reciprocal connections within the BG nuclei also exist, thus creating a complex feed-forward and feed-back connectivity (Fig. 2B) (57-62).

The nigro-striatal dopaminergic neurons modulate the activity of the striatal projection neurons (also called medium spiny neurons - MSNs) via D1 and D2 receptors, affecting the direct and indirect pathways respectively (63;64). The effect of dopamine on D1 receptors is excitatory, and the effect on D2 receptors is inhibitory. Additional modulation of striatal activity by the dopaminergic projections occurs due to the dopaminergic synapses on GABAergic and cholinergic interneurons.

The death of the SNc cells in the pathological state of PD disrupts the balance between the direct and indirect pathways. Dopamine depletion in the striatum leads to reduced

inhibition on the GPi and SNr via the direct pathway, leading to an increased firing rate in these two nuclei. At the same time, via the indirect pathway, it leads to enhanced inhibition on the GPe, reduced inhibition on the STN and enhanced excitation on the GPi and SNr, such that the total effect is increased inhibition on the thalamus and decreased excitation of the cortex (Fig. 2C). This total effect was considered as responsible for the hypokinetic effects in PD (54).

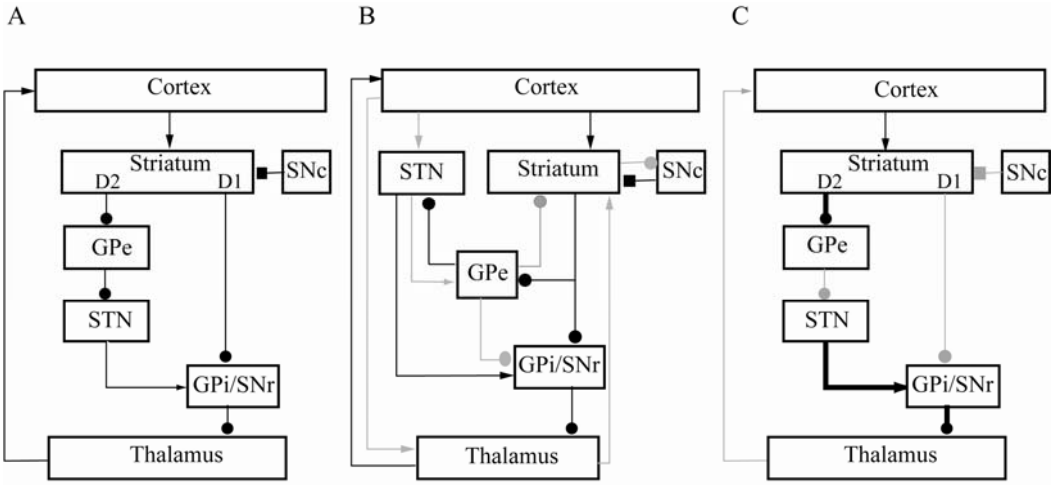

Figure 2: The box and arrow network of the different pathways of the basal ganglia. (A) The original network. (B) The up-to-date network. The original network is in black and later additions are in gray. (C) The activity of the original network in PD. Increased firing rate in thick black and decreased firing rate in gray. Glutamatergic synapses are denoted by arrows, GABAergic synapses by circles and dopaminergic synapses by squares. Adapted from (63).

Some experimental results support these predictions of changes in firing rate in the BG. It was found that the activity of the GPi increased and the activity of the GPe decreased in MPTP-treated monkeys (37). Furthermore, lesions of the STN and GPi caused improvement in clinical state and reduction of motor symptoms in both human PD patients (65) and Parkinsonian monkeys (66). However, other studies found contradicting evidence. Anatomically, striatal neurons were found to contain dopamine receptors of both D1 and D2 classes, projecting to both direct and indirect pathways (67), and innervating both GPe and GPi (57). Clinically, GPi lesions were found to ameliorate hyperkinetic disorders and not just hypokinetic disorders such as PD (68), though a mere reduction in the firing rate (caused by lesion) and its effect on the total disinhibition of the cortex cannot account for opposites clinical changes (54). Additionally, some studies

revealed that the changes in firing rates are not so significant as expected according to the model (69-73).

The abnormal activity of the cortico-basal ganglia loop in PD represents a major change in information processing that is reflected in the disease's clinical symptoms. Characterizing the neurophysiological changes that take place in PD is essential to understanding and treating this disorder. In this study, we quantitatively assess the electrophysiological changes in the GPe and GPi of an MPTP-treated monkey relative to the activity in the normal state.

Material and Methods

Animal. A cynomolgus monkey (*Macaca fascicularis*; male; weight, 3.7 kg) was used in this study. The monkey was trained and engaged in a simple behavioral paradigm of a visual–motor response task as part of a study of the normal GP before this study. After these experiments were completed, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections were started (see below). A second set of recordings was performed on the animal in its Parkinsonian state. The monkey's health was monitored by a veterinarian, and its fluid consumption, diet, and weight were followed daily. All procedures were in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and *Bar-Ilan University guidelines for the use and care of laboratory animals* in research and were approved and supervised by the *Institutional Animal Care and Use Committee (IACUC)*.

Surgery and induction of Parkinsonism. After training, a 27 mm square cilux recording chamber (Alpha Omega Engineering, Nazareth, Israel) was attached to the skull to allow access to both segments of the GP. The recording chamber was tilted 40˚ in the sagittal plain, with its center targeted at the stereotaxic coordinates A12, L7 and H4 (74) of the right hemisphere. In addition, a head-holder connector and two electroencephalogram (EEG) screws (Crist Instrument, Hagerstown, MD, USA) were attached to the skull. All surgical procedures were performed under general anesthesia [induced by intramuscular ketamine hydrochloride (10 mg/kg) and Domitor (0.1 mg/kg) and maintained by isoflurane and N_2O ventilation] and aseptic conditions. After a period of recording in the normal state, Parkinsonism was induced by five intramuscular injections of 0.4 mg/kg

MPTP hydrochloride neurotoxin (Sigma, Rehovot, Israel). The MPTP injections were given under intramuscular ketamine hydrochloride (10 mg/kg) anesthesia and over a period of 4 days (two injections on the first day). The monkey developed severe Parkinsonism 6 days after initiation of MPTP injections, and recordings were resumed 4 days after the last injection. The monkey's Parkinsonian state was assessed daily using the Schneider scale (75) and was stable throughout the recording period (Mean ± SD: 45.75 ± 3.37).

Recording. During recording sessions, the monkey's head was immobilized, and eight glass-coated tungsten microelectrodes (impedance, 0.25–0.7 MΩ at 1 kHz) confined within a cylindrical guide (1.7/2.15 mm inner/outer diameter) were advanced separately [EPS (Electrode Positioning System) 4.10, Alpha–Omega Engineering] into the GP. The vertical location of each electrode was set independently to optimize the recording of single units, and the range of vertical distances was 0–2500 μm. The horizontal distance between the different electrodes was 450–1000 μm, defined by the spatial arrangement of the electrodes within the guide. In addition to these known variables in the location, the electrodes may not follow a straight trajectory during their extension from the guide to the deep brain structure, thus leading to an unknown change in the horizontal location (typically <1mm). The electrode signal was amplified with a gain of 1000 and bandpass filtered with a 2–8000 Hz four-pole Butterworth filter [MCP (Multi Channel Processor)-Plus 4.10, Alpha–Omega Engineering]. The signal was continuously sampled at 40 kHz with 14-bit resolution (Alphamap 10.10, Alpha–Omega Engineering). Thus, the analog-to-digital (A/D) range of ±5 V enabled a ~0.5 μV recording amplitude resolution.

Data analysis. The digitized continuous signal of each electrode was offline sorted [OFS (Offline Sorter)-2.8.4, Plexon, Dallas, TX]. Further analysis was performed both on the continuous digitized signal and on the point process representing the spike train. The analysis process included measures for assessing the individual neuron firing pattern and measures for identifying interactions between two or more neurons. Identification numbers of the example neurons appear in each figure.

Results

Single unit activity

The neuronal activity of the GPe and GPi in the normal state is characterized by high frequency discharge. The discharge roughly follows a Poisson process, in which the occurrences of spikes are independent from previous spikes at every point in time. This process is limited by the refractory period that reduces the probability of firing after each spike for a few milliseconds. Thus, intuitively this process can be viewed as a random, unordered discharge, which partially depends on the time of the last spike. A typical characteristic of GPe cells is pauses of firing, in which no spikes occur for a period of hundreds of milliseconds (Fig. 3A). These pauses are absent in GPi cells, that fire persistently without such breaks (Fig. 3C).

In the Parkinsonian state, this activity undergoes a significant modification: GPe cells tend to decrease their firing rate, whereas GPi cells tend to increase their firing rate. Moreover, the discharge pattern becomes bursting and oscillatory (Fig. 3B and D). Burst is a change in a temporal micro-level, in which the firing rate greatly increases and spikes appear grouped together. Oscillations are repetitive modulations in firing rate, usually at a larger time scale.

The differences in discharge patterns in the normal and Parkinsonian states were reflected in various measures used to characterize the neural activity. The *autocorrelation function* of a neuron represents the probability to find two spikes with a specific time interval between them (76). If spikes are independent of each other, then the probability for a spike is equal at every offset, and the autocorrelation function is expected to be flat. As a result of the refractory period, there is some dependency between spikes at the range of a few milliseconds, in which the probability of a spike is reduced. Hence, the typical autocorrelation of a neuron that fires as a Poisson process with a refractory period is flat with a trough at small lags from time zero, such as the typical GPi neuron in the normal state (Fig. 3C). Time zero in the autocorrelation is the time in which each spike was fired. Therefore, the probability at this time is 1 and usually removed from the display. A slight increase in probability of firing is often observed right after the refractory period. This increase may reflect bursts activity or be an artifact that results from the refractory period itself (77). The pauses in firing in the GPe in the normal state further affect the autocorrelation by a much wider peak in the autocorrelation (Fig. 3A). This wide peak is a result of decreased probability of firing at larger offsets due to absence of spikes during

the pauses. The autocorrelation functions of GPe and GPi neurons in the Parkinsonian state reveal the oscillatory activity of these neurons, at a frequency of approximately 12 Hz, as well as its bursting property. The bursts of firing is evident by the peak around the zero lag, that reflects increased probability for very short ISIs, meaning that spikes fired very close in time to each other (Fig. 3B). The oscillatory activity is seen in the semi-sinusoidal modulations of firing rate (Fig. 3B and D). The oscillations are most evident closer to the zero lag, and become smaller in amplitude and broader in time when moving away from zero, as a result of accumulations of ISI jitters and reduced accuracy of spike time intervals at long ISIs.

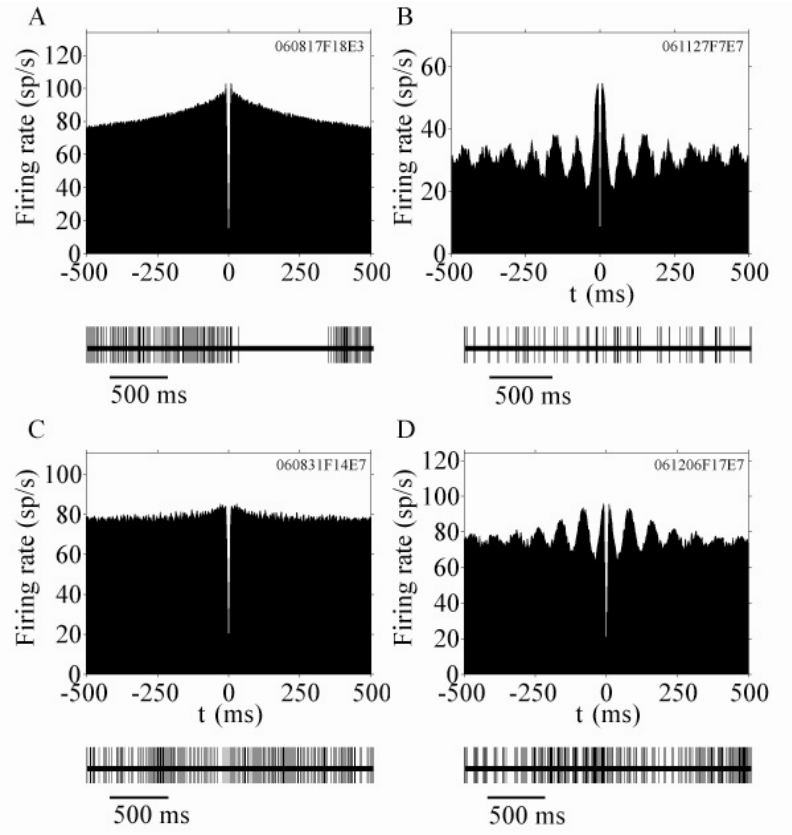

Figure 3: Examples of traces and autocorrelation functions of neurons in the globus pallidus in the normal and Parkinsonian states. GPe neurons in (A) normal state, (B) Parkinsonian state. GPi neurons in (C) normal state, (D) Parkinsonian state. Autocorrelation functions were calculated using 1 ms bin size and smoothed by a 9 bins Gaussian window.

The oscillations revealed by the autocorrelation functions were further analyzed using spectral analysis. Spectral analysis is commonly used to characterize the properties of a

signal, or relations between two signals, in the frequency domain and identify frequency dependent processes that underlie the neural activity. The *power spectral density (PSD) function* of a signal describes the amount of power of the signal at each frequency. The PSD is defined as the square of the magnitude of the discrete Fourier transform of the signal. If the signal is not comprised of frequency dependent processes then the shape of its PSD is expected to be flat. The PSD of a Poissonian neuron with a refractory period is typically distorted and characterized by low magnitude at the low frequencies that results from the refractory period (78) (Fig. 4A and C). Oscillations in the Parkinsonian state are reflected in the PSD as a peak at the frequency of the oscillations (Fig. 4B and D).

The PSD function characterizes the signal over all the recording time. In order to inspect the changes in the frequency spectrum over time, a *spectrogram* was used. The spectrogram calculates the PSD of the signal at windowed frames in time, thus enabling the simultaneous examination of time dependent and frequency dependent processes in the signal. The spectrogram may be displayed as a 3D graph in which the axes are time and frequency, and the power of the signal is color (or in this case gray scale) coded. The intersection of the spectrogram at a certain point in time over all the frequencies is the PSD of the signal around that time. The oscillations of the GPe and GPi neurons in the Parkinsonian state are stable over time, as shown in the spectrogram, in which the spectrum is similar over time (Fig. 4E).

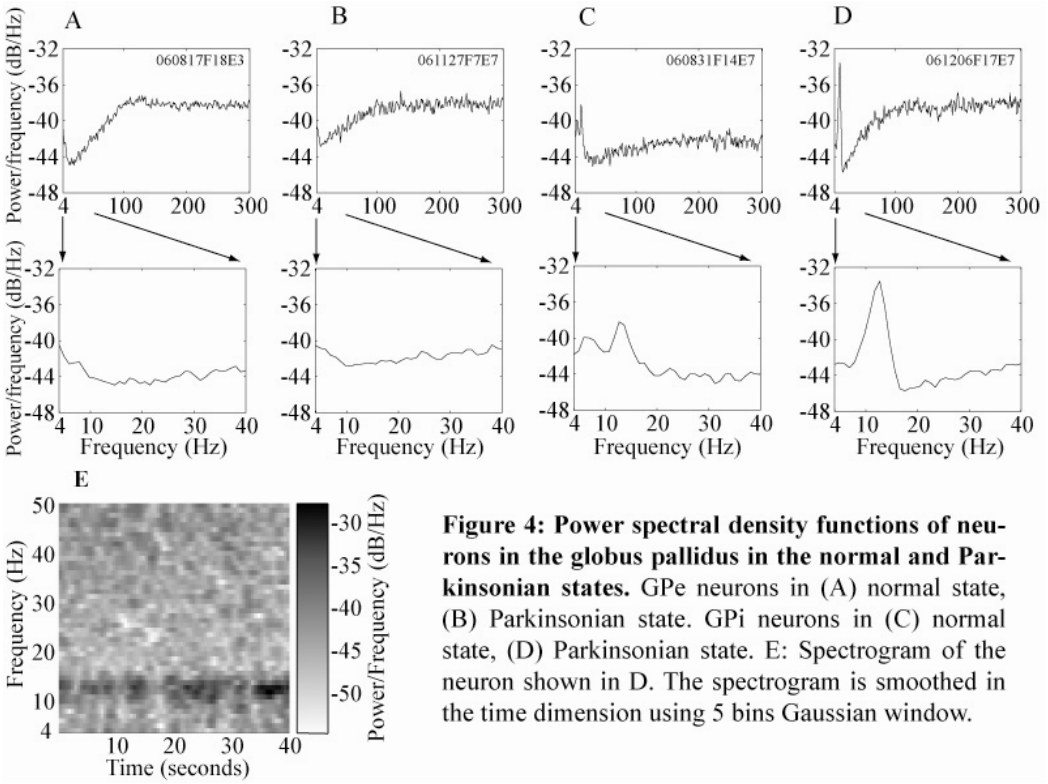

Figure 4: Power spectral density functions of neurons in the globus pallidus in the normal and Parkinsonian states. GPe neurons in (A) normal state, (B) Parkinsonian state. GPi neurons in (C) normal state, (D) Parkinsonian state. E: Spectrogram of the neuron shown in D. The spectrogram is smoothed in the time dimension using 5 bins Gaussian window.

A measure used to analyze the relation between the spiking activity of the cell and the background activity at its vicinity, as was recorded in the raw signal, is the reverse *correlation function*. Reverse correlation, also termed '*spike triggered average*', describes the average signal that precedes a spike. It is calculated by extracting the signal at a certain period of time that preceded each spike, and averaging over all the signals at these time periods. The reverse correlation is displayed backward in time from time 0, which is the time of a spike. A flat reverse correlation function means that the cell tends to fire independently from the recorded background activity. Reverse correlation that includes peaks or troughs whose amplitude is significantly different from random implies that the cell tends to fire in time dependency with the background. The reverse correlation typically displays low frequency background activity, which is usually viewed as synaptic input. Therefore, the reverse correlation provides a measure to the sensitivity of the cell to a certain synchrony in its input. In the normal state, GPe and GPi cells do not show any relation to the background activity, as seen in the flat reverse correlation (Fig. 5A). However, in the Parkinsonian state, the cells tend to fire in relation to a synchronous oscillatory background activity, with a certain phase relative to these oscillations (Fig. 5B and C). The oscillations are largest in amplitude close to time zero,

and get smaller and broader when moving away from the spike backward in time. Similarly to the autocorrelation functions, this phenomenon is a result of spike time jitters that accumulate over time and flatten the reverse correlation.

Reverse correlation between the cells to the background activity recorded by a difference electrode was calculated as well. It was found to be similar to the relation between the cell to the background activity recorded by the same electrode, in both pattern and amplitude (data not shown), implying that the activity throughout the nucleus oscillates together, and cells are sensitive to this activity in different ways.

The significance of the reverse correlation was tested using bootstrapping heuristics. The ISIs of the signal were shuffled and a reverse correlation function based on the shuffled ISIs was calculated. This process was repeated 100 times and two parameters were calculated for the original reverse correlation and for each shuffled reverse correlation: standard deviation and amplitude (the difference between the maximal and minimal voltage). The significance of each of the parameters was tested using one-tailed t-test. For the two GPe and GPi neurons shown in Fig. 5B and C, both parameters were significantly larger from the shuffled population ($p<<0.01$), meaning that the reverse correlation is not due to chance but reflects a property of the firing pattern of the cell.

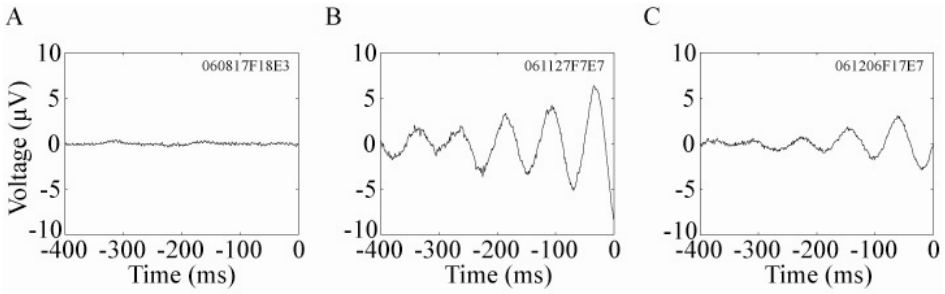

Figure 5: Reverse correlations of neurons in the globus pallidus in the normal and Parkinsonian states. (A) GPe neuron in normal state, (B) GPe and (C) GPi neurons in Parkinsonian state.

Multi unit activity

Exploration of multi unit activity enables the characterization of relations between neural activities of two (or more) cells, and sheds light on the activity of populations and ensembles of neurons. In the normal state, cells in the GPe and GPi tend to fire independently of each other, and the background activity can be described as white noise without special temporal characteristics.

In the Parkinsonian state, the activity of multiple cells becomes more correlated and synchronized in both segments of the GP (Fig. 6).

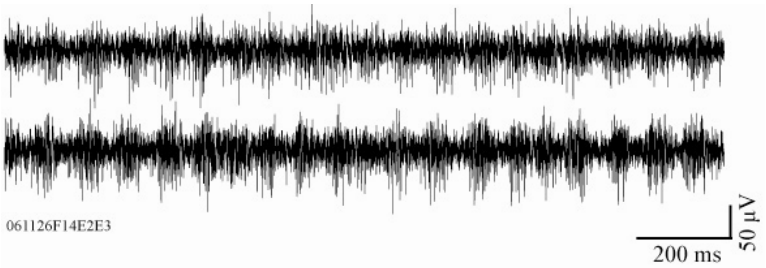

Figure 6: Multi unit activity in the GPi in the Parkinsonian state. Raw signal recorded from two adjacent electrodes.

The dependency of firing activity of firing of two neurons was measured by the *cross-correlation function* (79). The cross-correlation function between two neurons is calculated by counting ISIs of all orders between the spikes of one cell ('reference') to the other ('target'). A flat cross-correlation function implies no dependency between the spiking activities of the neurons, i.e., the probability of firing of one cell is independent of the firing of the other cell (Fig. 7A). A dependency between the neural activities is expressed by peaks (increased probability of firing) or troughs (reduced probability of firing) in the function. The correlated activity in the GP in the Parkinsonian state is demonstrated in the oscillations in the cross-correlation around, and mainly before, time lag zero (Fig. 7B). The target neuron tends to fire in relation to an oscillatory activity of the reference neuron, after the trough of the oscillations cycle.

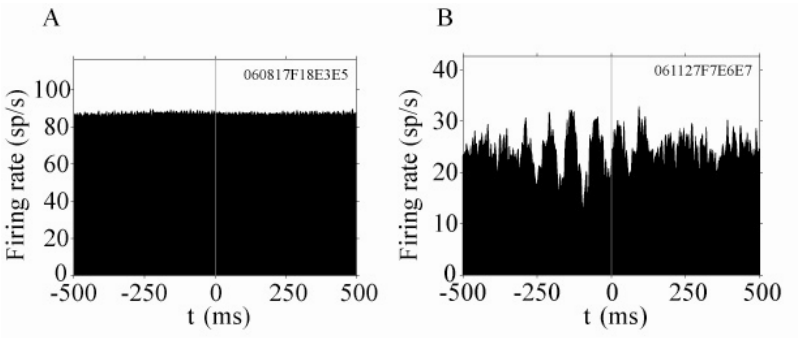

Figure 7: Cross-correlation function of neurons in the globus pallidus in the normal and Parkinsonian states. Cross-correlation between 2 GPe neurons in (A) Normal state and (B) Parkinsonian state. In both cases the cross-correlation function is calculated using 1 ms bin size and smoothed by 9 ms Gaussian window. A vertical line is added to mark lag zero.

The nature of this oscillatory spike timing dependency was further analyzed by calculating the *cross spectral power density (CPSD) function*. The cross spectral density

function is the Fourier transform of the cross-correlation function of two neurons, and is used to reveal common frequencies shared by the two signals. If the two signals are unrelated and do not share enhanced power in any common frequency, then their CPSD is flat, except for the refractory period artifact of low power at low frequencies (78) (Fig. 8A). The peak in the CPSD of two GPe neurons in the Parkinsonian state (Fig. 8C) at 12.7 Hz reveals the frequency that underlies the correlation between them.

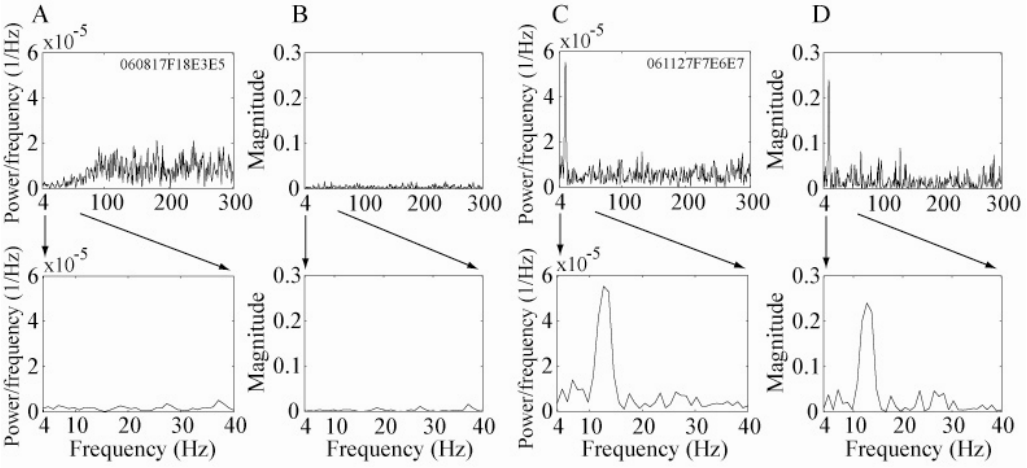

Figure 8: Spectral relation of neuronal activity in the globus pallidus in the normal and Parkinsonian states. (A) Cross spectral density (B) coherence functions of 2 GPe neurons in the normal state. (C) Cross spectral density and (D) coherence function of the same 2 GPe neurons as in the cross-correlation in Fig. 7B, in the Parkinsonian state. The lower figures are enlargements of the upper figures.

The spectral characteristics of the relation between neurons depend on the correlation between their activities, but also on the independent activity of each of them. In order to find the spectral properties relation of the neurons apart from the structure of their single activity, the CPSD was normalized to the power spectrum of the two neurons, yielding the *coherence function* (80). The values of the coherence function range from 0 (no coherence) to 1 (full coherence) for each frequency, and describe the spectrum of the spike time dependency between two neurons. Flat coherence with low values implies spike time independency between the neurons, typical to the neuronal activity in the GP during the normal state (Fig. 8B). The tendency of the neurons to oscillate synchronously at the same frequency in the Parkinsonian state is shown in Fig. 8D. The coherence is high around 12 Hz which is the same frequency shown in the power spectrum of the individual neurons, meaning that both neurons oscillate at similar frequency in a phase locked manner. The relative phase of the oscillations, which is the timing relation of the

cycles of oscillations, was further extracted using the phase spectrum (80). It was found to be 120° at 12.7 Hz, similar to the phase seen in the cross-correlation.

	GPe		GPi	
	Normal	**Parkinsonian**	**Normal**	**Parkinsonian**
Single unit activity				
Firing rate	High frequency	↓	High frequency	↑
Bursts	Slight	↑	Slight	↑
Oscillations	-	↑	-	↑
Relation to background activity	-	↑	-	↑
Multi unit activity				
Correlations	-	↑	-	↑
Coherence	-	↑	-	↑

Table 1: Properties of GP activity in the normal and Parkinsonian states. Legend: (+): existence, (-): absence, (↑): increase, (↓): Decrease.

Conclusion

Our results demonstrate that the neural activity in both segments of the globus pallidus undergoes major changes in the Parkinsonian state compared to the normal state. This abnormal activity is reflected in both single neuron firing pattern and the interaction between multiple neurons. At the single unit level, the firing pattern of the neurons becomes more bursting and oscillatory, with a total effect of less 'random' firing compared to the Poissonian firing pattern typical to the normal state. The tendency for oscillations is much more evident in the GPi (data not shown). At the multi unit level, neurons become more correlated and tend to fire in synchronous oscillations (See summary in Table 1).

Based on the 'Box and Arrow' model (53;54), changes in firing rate in the BG during PD were the main focus of attention. Increase in firing rate in the GPi and decrease in firing rate in the GPe in the Parkinsonian state were reported (37). Nevertheless, our results, as well as many others (57;67-73), imply that the change in the firing pattern of the neurons are salient and go far beyond mere changes in the rate. A fundamental characteristic of

the firing pattern in the Parkinsonian is the oscillatory activity. In humans, oscillatory activity within the basal ganglia has been observed in patients undergoing surgery for treating PD (71;81;82). Oscillatory activity was also observed in multiple species of MPTP-treated monkeys such as vervet and rhesus (70;83), and was found to be partially correlated with tremor (70;82;84). Our monkey, in line with other studies of MPTP treated cynomolgus monkeys, was not tremulous during the sessions depicting the oscillations (data not shown).

Other changes in firing patterns in the GP were reported, such as increased bursting activity in the GPi (19;69) as opposed to its typical irregular firing (70), and correlated neuronal activity (70;85). Changes were also observed in other parts of the cortico-basal ganglia loop, such as the striatum (85), STN (19) and SNr (69). In the thalamus, a primary target of GPi and SNr projections, no rate changes were found, but rather correlated activity and loss of receptive fields specificity (73). In the primary motor cortex, the neurons were found to display reduced firing rate, irregular discharge patterns and enhanced synchrony between neurons (86;87).

This extensive body of evidence suggests a major effect on the whole motor system and an impairment in information processing of the cortico-basal ganlgia loop in the Parkinsonian state at the neuronal and network levels, which are reflected in the severe clinical symptoms. The mechanism by which the observed abnormal activity affects the behavioral clinical symptoms is enigmatic. Rate based model such as the Albin & DeLong model can account for some of the symptoms of PD such as akinesia due to inhibition of the cortex. This reduced cortical activity is caused by excessive inhibitory activity of the GPi that leads to decreased firing rate in the thalamus, which consequently causes less excitation of the cortex. However, the picture seems to be more intriguing. The complexity of this impairment was demonstrated when changes in correlated activity but not in firing rate were found in the thalamus of Parkinsonian primates (73), though the thalamus receives input from the GPi.

The action-selection model of the BG (88) views the direct pathway as responsible for the enhancement of a specific action required by the cortex, while the indirect pathway inhibits all the other competing motor programs. This model attributes the symptoms of PD, such as bradykinesia, rigidity and akinesia, to the imbalance of the direct and indirect

pathways leading to loss of specificity of the active motor program. Loss of functional segregation in the BG in the Parkinsonian state was suggested (89) and supported by excessive correlations in the GP (70;90). However, the dopamine signal transmission through D1 and D2 receptors was found to affect both direct and indirect pathways without complete segregation (67), thus the imbalance between the two pathways should be further explored. Furthermore, no evidence was found for the negative cross correlation between neurons in the output nuclei of the BG as expected from the model (62;70).

The lack of changes in firing rate in the thalamus (73), which receives its input from the BG, further challenges the roll of the BG in PD. The thalamus is considered as a relay station, receiving extensive inputs and projecting to the cortex. The BG may be viewed as modulating the activity of the thalamus that serves as a control gate for its other sources of input. In the Parkinsonian state, the increased firing rate in the GPi, an output nucleus of the BG that projects directly to the thalamus, might lead to a weakening of the GP-thalamic synapses strength by a homeostatic plasticity mechanism (91;92), thus delimiting the effect and preserving the homeostasis in the macro-level. However, when a GPi neuron oscillates instead of firing in a Poissonian manner, there are fast changes in firing rate in a temporal micro-scale (for example, around 12 Hz as described above) that affect the post-synaptic cells. The post-synaptic effects of bursts, in which spikes rapidly occur over a short period of time, is greater than the effect caused by single spikes. It increases the probability that the post-synaptic cell will fire (or will not fire, in this case of an inhibitory effect) in accordance with the bursts firing of the pre-synaptic cell. Correlated and synchronous activity of pre-synaptic cells that affect the same post-synaptic cell increases this non-linear effect as well, as the post-synaptic cell gets the same input simultaneously and strongly modulates its firing accordingly. Synchronous oscillatory activity of a few neurons, in which spikes are concentrated in time at the same phase of the cycle sparser at another phase combines these two effects and enhances the correlation between the firing of the pre-synaptic and post-synaptic cells.

Thus, during PD the BG output is no longer just a modulator of the thalamic activity, but rather significantly disturbs it. Pallidal cells interfere with the activity of the thalamic neurons and determine their firing pattern, due to the synchronized and correlated

activity. Indeed, excessive correlations in the thalamus, as well as lack of specificity in the Parkinsonian state compared to the normal state were observed (73). This abnormal activity in the thalamus might impair the recruitment of cortical neurons for the initiation or execution of motor actions, which might account for the akinesia and bradykinesia symptoms of PD. The neuronal activity and the reciprocal effects in the cortico-basal ganglia loop should be further characterized and explored in order to understand the information processing in both normal and pathological states. As these will be achieved, treatments that are aimed at reversing this abnormal activity might be developed, offering new hope for PD patients.

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