Reduced information transmission in the internal segment of the globus pallidus of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced rhesus monkey models of Parkinson's disease☆

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Abstract

Rhesus monkey models of Parkinson's disease were induced by injection of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Neural firings were recorded using microelectrodes placed in the internal segment of the globus pallidus. The wavelets and power spectra show gradual power reduction during the disease process along with increased firing rates in the Parkinson's disease state. Singular values of coefficients decreased considerably during tremor-related activity as well as in the Parkinson's disease state compared with normal signals, revealing that higher-frequency components weaken when Parkinson's disease occurs. We speculate that the death of neurons could be reflected by irregular frequency spike trains, and that wavelet packet decomposition can effectively detect the degradation of neurons and the loss of information transmission in the neural circuitry.

Key Words

Research Highlights

(1) Wavelet package decomposition and power spectrum analysis were adopted to analyze neural firings and information transmission. We found that a Parkinson's disease group could be separated from a control group on the basis of related wavelet coefficients.
(2) Based on the combination of the inference of wavelet coefficients, the activities of globus pallidus neurons were weakened.
(3) Microelectrode recording of neural firing signals could help us understand the pathogenesis of Parkinson's disease. As well as detecting changes in neural firing before and after disease attack, this method could help distinguish targets for stimulation from the neighborhood of the globus pallidus, and confirm the target location precisely.

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INTRODUCTION

Parkinson's disease is an age-related progressive neurological disorder that brings a heavy burden to patients and societies all over the world. It is believed to be a circuit disorder of the basal ganglia[1]. The basal ganglia circuit consists of the following four parts: striatum, globus pallidus, substantia nigra and subthalamic nucleus. The basal ganglia are thought to execute projections and transfer information among diverse cortical areas, *via* the thalamus to the motor cortex. The internal segment of the globus pallidus (GPi) is an output component, whereas its output may regulate the overall amount of movement[2-3]. There are direct and indirect pathways from the striatum to the substantia nigra pars reticulata and the GPi[4]. Dopamine regulates the gamma amino butyric acid level to inhibit the GPi/substantia nigra pars reticulata and facilitate movement *via* D1 dopamine receptors through the direct pathway, and increases excitability of the GPi/substantia nigra pars reticulata *via* D2 dopaminereceptors to inhibit motor behavior through the indirect pathway[5]. The balance between the inhibition and facilitation produced by dopamine and acetylcholine is very important for the motor cortex to keep normal function and imbalance can induce disorder.

In the normal basal ganglia, the globus pallidus relays GABAergic inhibition to subthalamic nucleus neurons, whereas, in Parkinson's disease, the lack of dopamine amplifies the feedback inhibition, leading to the pathological expression of cortical oscillations in the subthalamic nucleus and external segment of the globus pallidus such that information flow is exaggerated around the subthalamic nucleus-external globus pallidus circuit[6]. Therefore, the detection of damage occurring to dopamine neurons under the Parkinson's disease condition would help us to uncover the pathology and offer further therapy.

Many researchers have focused on the mechanisms underlying encoding of neural signals utilized by neurons to uncover pathology. Previous studies have considered the correlations between pairs of neurons with increasing spiking rate, and found that they are nearly independent of the spiking variance in response to fluctuating afferent input currents with fixed correlations[7]. It is the same with heterogeneously tuned cells. Related patterns of firing rate and population correlations are key components for heterogeneously tuned cells to encode sensory stimuli[8-9]. Rate and synchrony of neural firings play an important role in information processing under

time-varying stimuli[10]. Lempel-Ziv complexity and deviation-from-Poisson index have been employed for feature extraction from neurons. Power spectrum is another popular method for ordinary analysis. An increased neuronal firing rate in the GPi is a key feature of the parkinsonian state[11]. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in model of parkinsonism[12]. Some GPi neural pairs oscillate synchronously at the tremor frequency, whereas other neural pairs oscillate independently[13]. Could we detect the degradation of related neurons through neural spike trains using this process? What could be inferred from the spike trains in the relevant cortical region under the Parkinson's disease condition? Researchers have presumed that the appearance of a gamma band oscillation would impede proper motor behavior. What happens to the frequency sub-bands under pathological conditions? In this study, we adopted an N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced model[14-15] to search for an effective technique for detecting changes occurring because of the loss of dopamine neurons.

RESULTS

Quantitative analysis of experimental animals

Four rhesus monkey models of Parkinson's disease were established by bilateral carotid artery injection of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. One monkey died of intracranial infection during the microelectrode recording process at 3 weeks after model establishment. One monkey failed the apomorphine test. The remaining two models were eligible during exprimentation.

Spectral analysis of the original neural signals

For the spectral analysis, a pathological neuron spike was assumed to be a significantly irregular higher frequency oscillation compared with normal ones. Figure 1 shows the results of power spectral analysis of the three representative original neural signals. Figure 2 shows the normalized wavelet spectrum of the dominant neural signals. Under the normal state, the neural signals have lower power and less burst firing compared with pathological neurons.

Quantitative analysis of wavelet packet decomposition

As shown in Figures 3 and 4, the largest singular values of wavelet packet decomposition coefficients under the

pathological and normal conditions were quite different, and the pathological ones as well as the tremor-related ones were lower than those of the normal ones, especially for the low-level wavelet coefficients that correspond to the high frequency components of the signal.
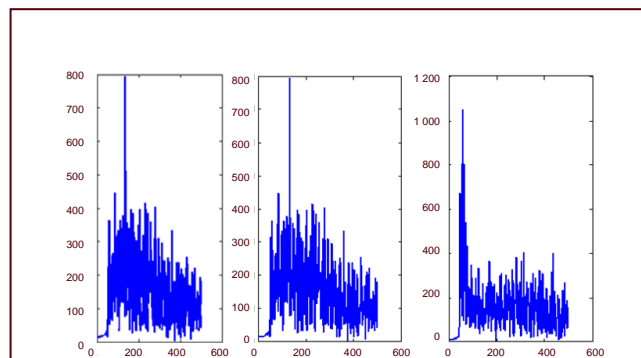

Figure 1   Fourier spectrum of the three representative signals.

From left to right: power spectrum illustrations of pathological signals, tremor-related signals and normal signals. The vertical axis represents the amplitude of the power spectrum of the corresponding frequency and the horizontal axis represents the frequency (Hz) component of the neural firing spike trains.
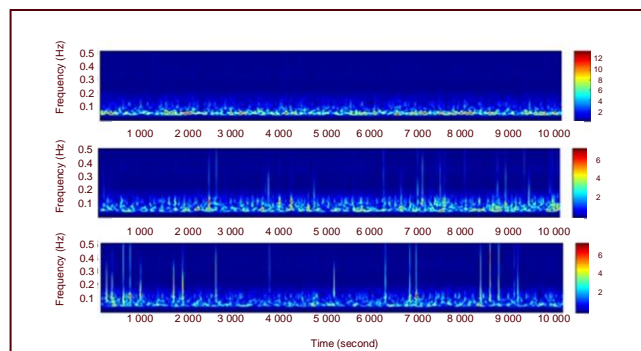

Figure 2   The normalized wavelet spectrum of the dominant neural signals.

Wavelet spectrum of neural signals under normal, Parkinson's disease and tremor state from top to bottom individually. The different colors of the points correspond to the amplitude of the power spectrum. Accordingly, from blue to red, the value increases from 0 to 8.

More details are provided in Table 1. The reconstructed decomposed wavelet coefficients reveal energy distribution of the original signal. The energy of special sub-bands and corresponding coefficients of wavelet packet decomposition, especially the largest singular values, were selected as features as they have maximal discriminability judged by the Fisher distance criterion

and can describe the main features of the processed signals based on the quantification of energy found in specific frequency bands at specific time locations during each spike profile. These irregular frequency oscillations have a close relationship with the loss of energy and the miscarriage of information, which reflect some of the Parkinson's disease symptoms. In our study, the lower-scale coefficients (D1–D4 from this figure) had the most energy among the original signals and the pathological signals are typically smaller than the normal ones, which further suggest that the correspondingly higher frequency domain oscillations are impeded, and that oscillations like gamma oscillations may be disturbed affecting long-range information transmission.
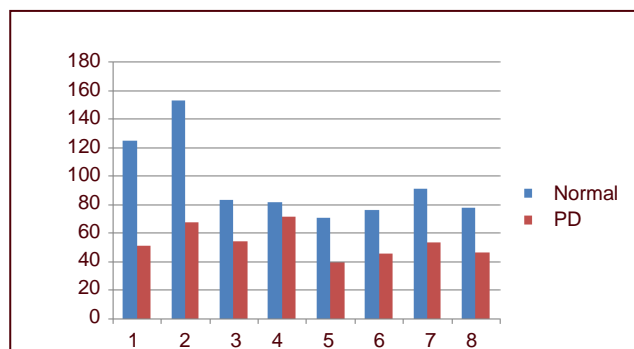

Figure 3   The largest singular values from wavelet packet decomposition of the neural signals under the normal state and Parkinson's disease (PD) activity.

As we adopted three-level decomposition, there are eight values (D1–D8 scale) for one spike train. The horizontal axis represents the scale level of the wavelet packet decomposition and the vertical axis indicates the corresponding magnitude of the largest singular value.
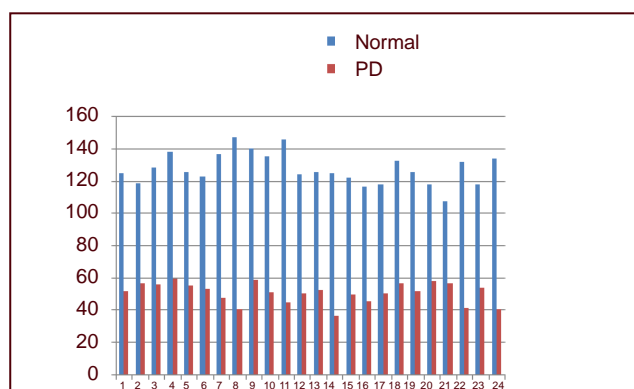

Figure 4   Largest singular values of the fourth-level wavelet coefficient (D4) of 24 neural signals.

The vertical coordinate represents the magnitude of the value. PD: Parkinson's disease.

Table 1   Paired-sample *t*-tests for the largest singular values from the neural signals under the Parkinson's disease (PD) and normal states

PD-Normal	Paired difference					*t*	Degree of free-dom	*Sig.*
	Mean	Std.deviation	Std.error mean	95% confidence interval of the difference				
				Lower	Upper			
D1	76.047 63	12.938 81	2.697 93	70.452 47	81.642 80	28.187	22	0.000
D2	57.743 68	24.270 94	5.060 84	44.248 13	65.239 22	10.817	22	0.000
D3	17.151 55	10.334 53	2.154 90	12.682 57	21.620 54	7.959	22	0.000
D4	9.598 30	14.957 97	3.118 95	3.118 95	16.066 61	3.077	22	0.000
D5	27.868 26	4.931 79	1.028 35	25.735 59	30.000 92	27.100	22	0.000
D6	27.680 20	5.656 22	1.179 40	25.234 27	30.126 13	23.470	22	0.000
D7	21.224 81	8.060 33	1.680 69	17.739 27	24.710 36	12.629	22	0.000
D8	23.738 51	5.670 70	1.182 42	21.286 31	26.190 70	20.076	22	0.000

D1–D8 are the largest singular values of wavelet coefficients in the corresponding nodes (3, 0) to (3, 7) after wavelet packet decomposition.

DISCUSSION

All neurodegenerative diseases share the common phenomenon that neurons, and usually relatively specific groups of neurons, are lost progressively as the disease develops[16]. Irregular spontaneous neural activity may prevent normal rhythmicity[17]. It has been argued that the strong power and correlations of β-band activity are general features of basal ganglia oscillations and, when no movement is performed, the replacement of β- with γ-band activity during movement occurs[18]. However, based on the results of our study, this might not be true. Pairs of neurons transfer translated relevant currents into correlated spikes. Over short time scales, correlation transfer increases with both spike time variability and rate[19]. Neurophysiological studies report an absence of linear correlation between single neurons in normal animals, suggesting a segregated parallel processing scheme[18]. Spillover of disruptive brain oscillations arise from the basal ganglia to the cortex in Parkinson's disease patients when patients do not take their medication, and patients who take L-DOPA show fewer areas of spillover[20]. Correlated neural activity in the subthalamic nucleus has been shown to be related to the destruction of dopaminergic neurons in Parkinson's disease[21-22]. Dopamine can modulate connections between different cortico-striatal modules and facilitate independent activity of striato-pallidal modules in the normal state. Disturbances in dopaminergic transmission to the prefrontal cortex is linked to pathogenesis of brain disorders[23]. Synaptic inputs[24] and dendritic sodium channels[12] are affected by dopamine depletion and then destroy neurons. However, the firing pattern[25] shift alone would not induce distinctive oscillatory activity in the Parkinson's disease state, and more attention should be paid to the spatial organization of the sub-cortex and information transfer among regions.

In this study, we examined the fluctuations of neural activity in the GPi during the transition from the healthy state to parkinsonism. We found that microelectrode recording could detect dynamic changes in neural signals. The decreased coefficients suggested a lessened capability of information processing and transmission. The declined neural fluctuation combined with the smaller wavelet coefficients may be a reflection of the loss of specific dopamine neurons and particular neuronal death in line with previous studies, and it could be taken as an alarm for the onset of the disease. Intriguing results have suggested that deteriorated neural oscillations under the pathological state[26-27] could be detected by a simple but efficient method, namely, wavelet packet decomposition of the original signal. We deduced that the singular values of the coefficients are the signature of the information loss and incidence of the disease. This might be taken as an assistant measurement for further evaluation and diagnosis. Appropriate motor control requires the cooperation of large-scale neural networks through neuronal spikes. In the normal brain, some nerve cells produce the chemical dopamine, which transmits signals within the brain to produce smooth movement of muscles. In Parkinson's disease patients, 80% or more of these dopamine-producing cells are damaged, dead, or otherwise degenerated. This causes the nerve cells to fire wildly or become dysfunctional, leaving patients unable to control their movements. The deterioration of the motor control appears to relate directly to the neuron and neural circuit dysfunction. N-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine interferes with neuronal circuits, and clusters of neural firing bursts emerge with irregular frequency oscillations becoming significant along with

the hampering of normal information processing and exacerbated symptoms of Parkinson's disease. Studies of the fluctuations in the brain's neural activity combined with studies of information flow during the process will help us to understand the pathology of Parkinson's disease[2-3] and how dopamine loss is involved. Interference using medicine will alter this situation[5, 20]; however, medicines become ineffective and have side effects in Parkinson's disease patient after long-term use. Therefore, deep brain stimulation is another popular therapy for Parkinson's disease patients to relieve their symptoms. External stimulation of the globus pallidus might reactivate the silent or disabled neurons and bring the circuit back to life, which could alleviate symptoms to some extent. We deduce that wavelet packet decomposition produces a suitable representation of neural signals for Parkinson's disease recognition, and that it could help us to discriminate basal ganglia neurons from cortical neurons and thereby help surgeons locate the best target for deep brain stimulation.

The information processing mechanism in the basal ganglia system is critical for the development of Parkinson's disease. Further research using multi-micro-electrode array techniques and large-scale neural network modeling on super computers is necessary to uncover the pathology mechanism.

MATERIALS AND METHODS

Design
This is a neural electrophysiology study.

Time and setting
Experiments were performed at the Tangdu Hospital Affiliated to The Fourth Military Medical University, China from June 2007 to July 2008.

Materials
Four healthy adult rhesus monkeys were chosen for this experiment, including three males and one female. They were all older than 10 years (13, 10, 12, and 13 years old) and their weights were 7.5, 6.7, 7.3, and 7.1 kg respectively. The width at the front and the height of the cranium were greater than 45 mm, and the face angle was greater than 100 degrees. The monkeys were provided by the Experimental Animal Center of The Fourth Military Medical University (License No. SCXK (Shaan) 2008-002). Each monkey lived in a separate cage in a standard animal house and fruit was added after operation. All the experiments met the *Guidance Suggestions for the Care and Use of Laboratory Animals*,

formulated by the Ministry of Science and Technology of China [28].

Methods
N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced Parkinson's disease model
The day before surgery, water and food were stopped. Anesthesia was induced by intramuscular injection of ketamine and diazepam. Two minutes later, the animal was placed on the couch for digital subtraction angiography. A puncture was performed in the right femoral artery using the Seldinger technique. The guide wire could reach the internal carotid artery and 0.5 cm above the bifurcation point; N-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine saline solution (0.2 mg/mL; Sigma, St. Louis, MO, USA) was then injected through the common carotid artery at 1.2–1.5 mg/kg in each rhesus monkey. If an animal failed the apomorphine test, an additional injection was given at 1.0 mg/kg 5 weeks following the surgery. Four days later, the contralateral limbs showed reduced activity and slow movement, and the subject showed postural tremor. Three weeks later, these symptoms stabilized. The animals had no difficulties in swallowing, digestion and pronunciation. All symptoms were very close to those in clinical Parkinson's disease patients. Apomorphine (Sigma) is a postsynaptic membrane dopamine D2 receptor agonist, and eight weeks after the operation, apomorphine was injected intramuscularly at a dosage of 0.2 mg/kg. Ten minutes later, the primate demonstrated left-side abnormal rotation with 6–10 circles per minute, and this got worse under stimulation. If the motion rating scale score remained 6–8 and the apomorphine test[29] gave the same result after 12 weeks, then the Parkinson's disease model would be used in microelectrode recordings for further analysis. In our research, two monkeys successfully modeled the disease and underwent the microelectrode recording process.

Microelectrode recording of neural firing in the GPi
In addition to reference to a stereotaxic atlas for anatomical structure, the boundary of the GPi was set with the assistance of the microelectrode (FHC, Bowdoinham, ME, USA) as basal ganglia nuclei have representative neural firing patterns. A combination of anatomical and functional orientation helped us to locate the recording point precisely, including discrimination between the recording target and the internal capsule and optic tract, since these are not only important structures but also close to the GPi anatomically. Microelectrode recording began when the electrode was set in the correct position and stable neuronal firing was

observed. Each recording lasted for several minutes with the electrode remaining in the GPi, and the whole experiment lasted more than 6 months. The diameter of the microelectrode was 1–2 μm with an impedance value of about 70–300 kΩ to counteract environmental noise. Signals from the microelectrode were amplified 5 000-fold and band-pass filtered between 0 and 2 000 Hz along with a 50-Hz notch to minimize interference from industrial frequencies. The signals were then sampled at 10 kHz. We selected three dominant kinds of representative neural spiking trains recorded from the primate model as follows: (1) rest spontaneous spike trains of GPi neurons from normal healthy monkey before modeling; (2) rest spontaneous spike trains from GPi neurons under the Parkinson's disease condition after successful modeling; and (3) tremor-related neural firings after N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment when the animal trembled severely. The spike trains are illustrated in Figure 5.
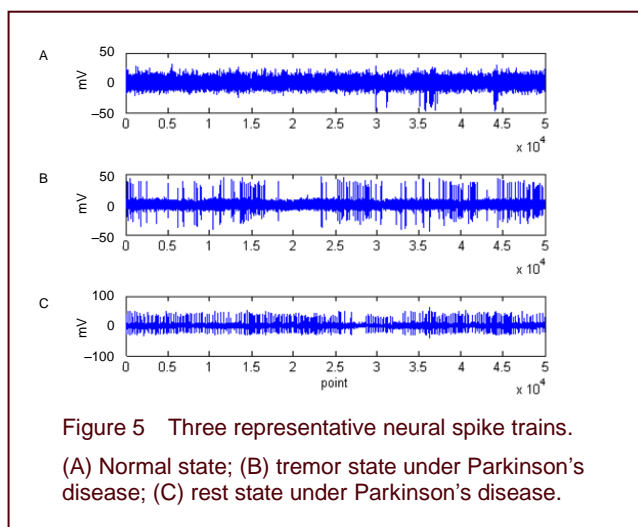

Figure 5   Three representative neural spike trains.
(A) Normal state; (B) tremor state under Parkinson's disease; (C) rest state under Parkinson's disease.

Wavelet analysis

Because we choose third-order wavelet packet decomposition, the derived eight wavelet coefficients were chosen as the basis matrix. Wavelet-based analysis is a good fit for neural signals ranging from magnetoencephalograms[30] and electroencephalograms[27, 31-33] to neural spike trains[34-37]. We adopted this technique to detect alterations in the activity of the neural circuits to see if it could identify pathological changes to the GPi neurons and offer an alarm for the onset of the disease. Intuitively, wavelet analysis can be understood as a way of decomposing/atomizing the total energy and variance of a spatial process or time series by an orthonormal basis of wavelets, each of which is weighted by a coefficient[38] representing the amount of energy in the data at a particular scale and location. Wavelet packet

decomposition comprises more filters than the digital wavelet transform. In the wavelet transform, an appropriate basis is chosen so that fewer vectors could represent more information relating to the original signals. Wavelet transforms can locate the signals in both time and frequency simultaneously; in other words, most of the energy of the signal could be represented by very few coefficients. Lower-level wavelet coefficients are related to the high-frequency domain and higher-level coefficients are related to the low-frequency domain[39]. Wavelet coefficients are chosen according to their correlation with the original signal. The energy content for each level is plotted to see the composition; then we determine which coefficients have most of the energy from the signal. Thus, the decomposition of neural signals by wavelet packet decomposition is more delicate and fine than wavelet transform. The coefficients derived from temporal spike profiles could be taken as feature extraction parameters[40-42]. For n levels of wavelet packet decomposition it produces $2n$ ($n = 1, 2, 3…$) different sets of coefficients as opposed to $3n + 1$ set of discrete wavelet transforms. We abstracted the singular values from the wavelet coefficients. For A is an $m \times n$ real valued matrix of rank r, there exist matrix U and $V,$ which establishes the following equation:

$$U \times AV = \begin{bmatrix} \Sigma_r & 0 \\ 0 & 0 \end{bmatrix}$$

where $\Sigma_r = \text{diag}(\sigma_1, \sigma_2, …… \sigma_r)$, $\sigma_1 \geq \sigma_2 \geq …… \geq \sigma_r > 0$. Since A is a real value matrix, U and V could be real orthogonal matrices. Although U and V could be different, Σ_r is exclusive for one signal. Such a singular value decomposition is believed to abstract the main information from original signal.

The objective of feature extraction is to produce a suitable representation of neural signals for pathology recognition. We adopt the Daubechies 4 wavelet in a one-dimensional case with three-scale level decomposition for feature extraction. The db4 wavelet has good adaptability to the wave shape of the spikes while keeping as much energy as possible, and the optimization criteria are set as the entropy.

Statistical analysis

We adopt the paired samples *t*-test for statistical analysis using Excel (WPS Office 2012, Kingsoft, Beijing, China).

signal processing.

Author contributions: Yan He analyzed the data and wrote the manuscript. Jue Wang and her group conceived and designed this study and obtained funding. Guodong Gao provided the laboratory and contributed to animal experiment and technical discussions. Guangjun Zhang provided technical suggestions and obtained funding.

Conflicts of interest: None declared.

Ethical approval: The project received full ethical approval from the Animal Committee of the Xi'an Tangdu Hospital in China.

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