Abnormal Spontaneous Neuronal Discharge and Local Field Potential both in Cortex and Striatum of a Non-human Primate of Parkinson's Disease using Implantable Microelectrode Arrays *

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***Abstract*—Parkinson's disease (PD) is a neurodegenerative disease with the loss of dopaminergic neurons in substantia nigra. This study described abnormal spontaneous neuronal information both in cortex and striatum of a non-human primate of PD using implantable microelectrode arrays. In cortex of PD monkey, Neurons discharged from single-spike mode to burst-firing mode compared to normal monkey; Mean amplitude was 197 μV that was twice of mean amplitude of normal monkey, and mean firing rate was 82Hz; burst-firing activity showed distinctive, stereotypic periods of oscillatory lasted for 20±5 s occurring ever 30-40 seconds, which was consistent with local field potential (LFP) oscillating at 4.79Hz related to PD tremor; neuronal discharge were approximately synchronous from four channels, that were consistent with local field potential fluctuating greatly with a correlation coefficient of 0.99997, and the main frequency of local field potential had a good respond to firing rate of spike with a correlation coefficient of 0.9891. In striatum of PD monkey, two types of neurons were detected with mean amplitude of 102μV and 296μV respectively; the mean firing rate was 62 Hz significantly higher than that in normal monkey; as for one representative type of neurons, with respect to local field potential oscillating at a period in cortex, local field potential continuously oscillated in striatum at low frequency at the range of 4-7Hz which was constituent with neuronal burst firing rate, while single neuron discharged at the range of 10-32Hz, almost at beta frequencies. Abnormal neural information detection by microelectrode arrays with different signals in different position will play an important role in target location in brain of PD patients, especially for treatment.**

I. INTRODUCTION

Parkinson's disease is a neurodegenerative disease with the loss of dopaminergic neurons in substantia nigra in pathological change that massively depletes the dopamine of striatum[1]. The clinical manifestations of Parkinson's disease include mainly static tremor, bradykinesia, muscle rigidity and posture gait disorders that seriously affect the patient's life. Deep brain stimulation (DBS) is an effective treatment for PD[2,3]. Neuronal discharge and local field potential recording by microelectrode arrays play an important role in target location in DBS surgery[4,5]. Non-human primates are most similar to human in function, structure and reaction. Research on abnormal neuronal discharge and local field potential in a non-human primate of PD is significance for the cure of PD.

Traditional neural information detections were based on metal wire microelectrodes or glass micropipettes that could measure single channel information[6-8]. Our group had developed a novel microelectrode array with little damage to tissue based on micro-electromechanical systems(MEMS) could acquiring multichannel neural action potential and local field potential efficiently[9,10].

In this study, spontaneous neuronal discharge and local field potential of cortex and striatum in non-human primate before PD model made (normal monkey) and after PD model made (PD monkey) were acquired based on implantable microelectrode arrays modified by platinum black nanoparticles. Microelectrode arrays with multichannel abnormal neural information could be used for target location for PD patients.

II. EXPERIMENTAL SECTION

A. Implantable microelectrode array

All implantable microelectrode arrays were homemade in our lab based on MEMS. The microelectrode arrays were fabricated by silicon-on-insulator substrates. The length was 25mm that could be implanted into striatum in monkey. There were 16 recording sites on the microelectrode array that were about 20μm in diameter. The microelectrode arrays were modified by platinum black nanoparticles that improved electrophysiological signal to noise ratio.

B. Apparatus

All the electrophysiological signals were recorded by 128-channel neuron data recording system(Cerebus, Blackrock Microsystems, USA). Direct drive micropositioner(Model 2662, KOPF, USA) was used to help implanting microelectrode arrays accurately.

C. In vivo experiment

All animal experiments complied with animal ethics at Wincon TheraCells Biotechnologies Co., Ltd., Nanning, China, accredited by Association for Assessment and Accreditation of Laboratory Animal Care. Male machine monkey used in the research weighed 10kg. Monkey model of PD was formed through injecting MPTP in carotid artery

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unilaterally to the normal monkey. The electrophysiological signals in normal monkey were obtained before model of PD was made. After ketamine hydrochloride(10-30mg/kg, 1M) and atropine(0.04mg/kg, 1M) injection, monkey was anesthetize by isoflurane gas(1-3%). Then monkey was fixed in the primate brain stereotaxic instrument. A rectangular craniotomy was carried out by the cranial coordinates related to bregma. Microelectrode arrays were implanted into the brain by the direct drive micropositioner at speed of 5μm/s. Implantable microelectrode arrays were connected to 128-channel neuron data recording system. There were eight microelectrode sites used for electrophysiological signals. The noise baselines were 20 μV. Action potentials were sampling at 30 kHz, and filtered by high pass filter with cut-off frequency of 250 Hz. Local field potentials were sampling at 1 kHz, and filtered by low pass filter with cut-off frequency of 190 Hz in cortex and 100 Hz in striatum. Experiment procedures on PD monkey and normal monkey were the same.

III. Results and Discussion

A. Comparisons of cortex

Four channels of neuronal discharge and LFPs both in PD monkey (after PD model made) and normal monkey(before PD model made) were recorded as shown in Fig.1(Fig.1a and Fig.1b). In normal monkey, neurons discharged at single-spike mode. While in PD monkey, the discharge pattern changed from single-spike mode to burst-firing mode, especially in ch14. Electrode ch14 with signals of burst-firing mode was closest to the fast discharging neuron than other electrodes. Mean amplitude of PD monkey was 197μV that was twice of mean amplitude of normal monkey(Fig.2a). For firing rate, it had risen sharply in PD monkey, and reached 140 action potentials per second at the fastest time of discharge with mean firing rate of 82Hz (Fig.2b).

As shown in Fig.1c, neurons discharged in typically burst-firing mode during a representative time window. Burst-firing activity in PD monkey showed distinctive, stereotypic periods of oscillatory burst discharge which lasted for 20±5 s. Bursts oscillated at low frequency. The oscillatory activity occurred regularly every 30-40 seconds. LFP during-firing was sampling at 1kHz, and then was filtered by Butterworth band pass filter(1-10Hz). In the local field potential, prominent low frequency oscillations occurred, which coincided with the rhythmic clustering of neuronal discharge. Normalized power spectral density of LFP revealed the main population frequency at 4.79Hz in cortex of Parkinson's disease monkey (Fig.1d). Neurons activity oscillated in cortex in PD monkey at 4.79Hz that was related to Parkinsonian tremor. Parkinsonian tremor is the second most common pathological tremor. Tremor associated with PD occurred at the frequency typically in the range of 3-7 Hz. Tremor-related activity appeared in different parts, such as globus pallidus, subthalamic nucleus, motor thalamus and motor cortex[11-14]. Tremor-related activity was obtained using microelectrode arrays at the depth of 4.36mm which was the typical neurons activity in motor cortex that was not found in normal monkey. The microelectrode arrays can be used as positioning navigation in PD treatment surgery with resolution of single neuron.

For PD monkey, neuronal discharge in each channel was approximately synchronous, that were consistent with LFP fluctuating greatly (Fig3.a). When neurons discharged synchronously, the main frequency of LFP had a good respond to firing rate of spike (Fig3.b), with a correlation coefficient of 0.9891. LFP indicated neuronal population activity.

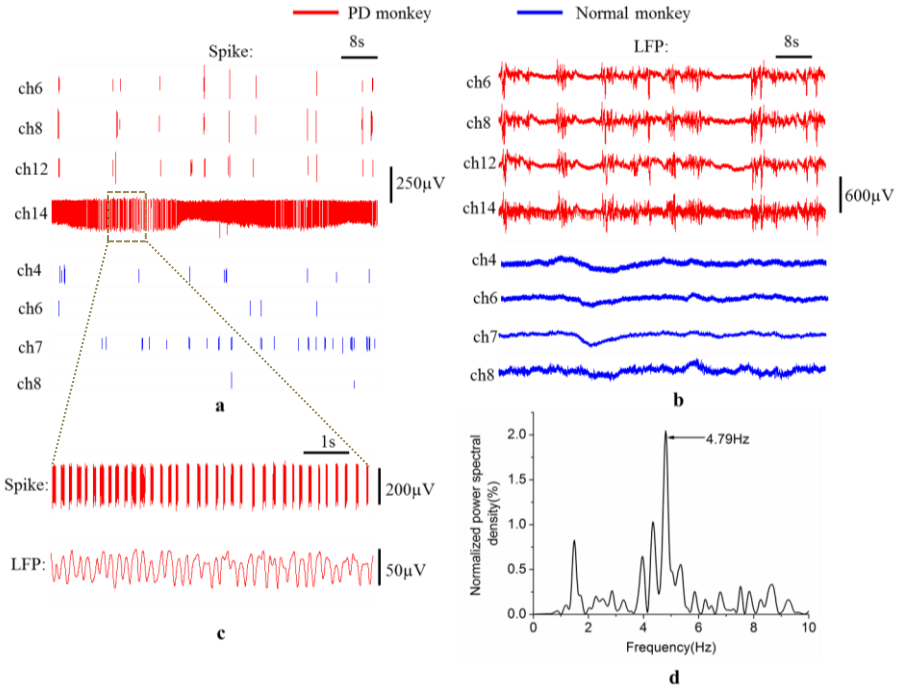

Fig. 1 Multichannel action potentials and LFPs obtained by microelectrode arrays in cortex. (a) Multichannel action potentials detected in PD monkey and normal monkey. (b) Multichannel LFPs detected in PD monkey and normal monkey. (c) A segment of action potential and LFP of ch14. Burst-firing activity in PD monkey showed distinctive, stereotypic periods of oscillatory burst discharge which lasted for 20±5 s. Prominent low frequency oscillations occurred in LFP. (d) Normalized power spectral density of local field potential of c. LFP power spectral density revealed the main population frequency at 4.79Hz.

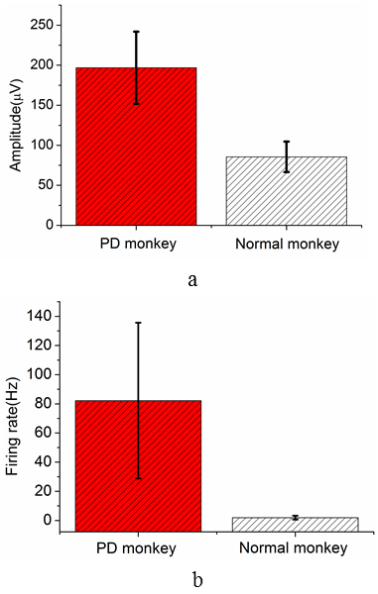

Fig. 2 Comparisons of amplitude and firing rate of cortex in PD monkey and normal monkey. (a) Comparisons of amplitude of PD monkey and normal monkey. (b) Comparisons of firing rate of PD monkey and normal monkey.

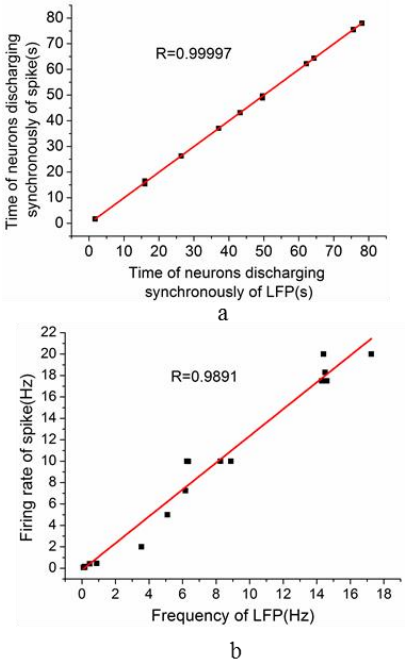

Fig. 3 Relationship of time and frequency between spike and LFP when neurons discharged synchronously. (a) Relationship of time of neurons discharging synchronously between spike and LFP. (b) Relationship of firing rate of spike and main frequency of LFP when neurons discharged synchronously.

B. Comparisons of striatum

Two channels of neuronal discharge and LFPs in striatum of both PD monkey and normal monkey were acquired (Fig.4). In general, neurons discharged more intensive in striatum both of normal monkey and PD monkey than in cortex. Neurons could be classified into two types both in striatum of PD monkey(type AP and type BP) and normal monkey(type AN and type BN) (Fig.4 c). The spike valley-to-peak duration of both type AP and type AN neurons were 0.48ms. With the same valley-to-peak duration and similar shape of spike, type AP neurons and type AN neurons were the same type neurons with a little difference in amplitude. While type BP was totally differently with type BN both in amplitude and shape. Mean amplitude of AP neurons was 102μV that was higher than the mean amplitude of type AN neurons. For BP neurons, the mean amplitude was 296μV that was about triple mean amplitude of type BN neurons (Fig.5a). For firing rate, it was significantly higher in PD monkey than that in normal monkey with mean firing rate of 62Hz (Fig.5b).

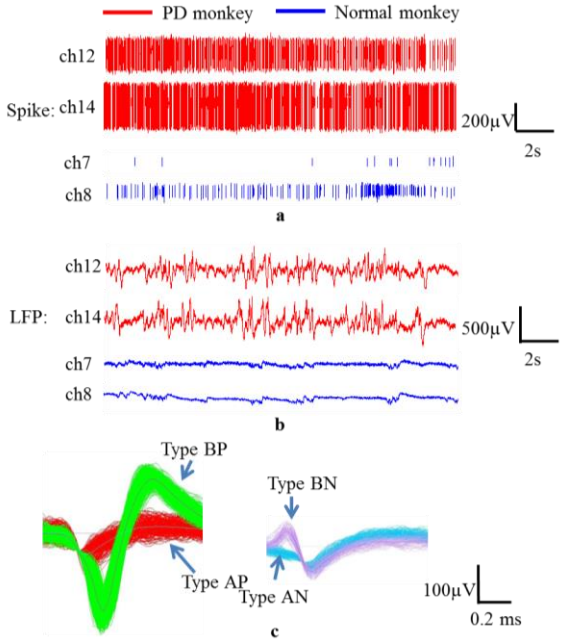

Fig. 4 Multichannel action potentials and LFPs obtained by microelectrode arrays in striatum. (a)Two channels of action potentials detected in PD monkey and normal monkey. (b) Two channels of LFPs detected in PD monkey and normal monkey. (c) Different types of neuronal spikes found in PD monkey (type AP and type BP) and normal monkey(type AN and type BN).

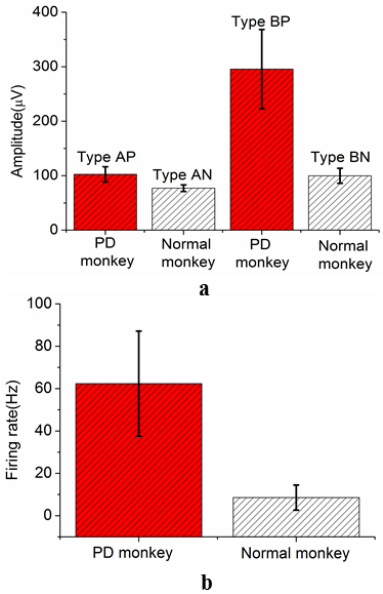

Fig. 5 Comparisons of amplitude and firing rate of striatum. (a) Comparisons of amplitude of PD monkey and normal monkey. (b) Comparisons of firing rate of PD monkey and normal monkey.

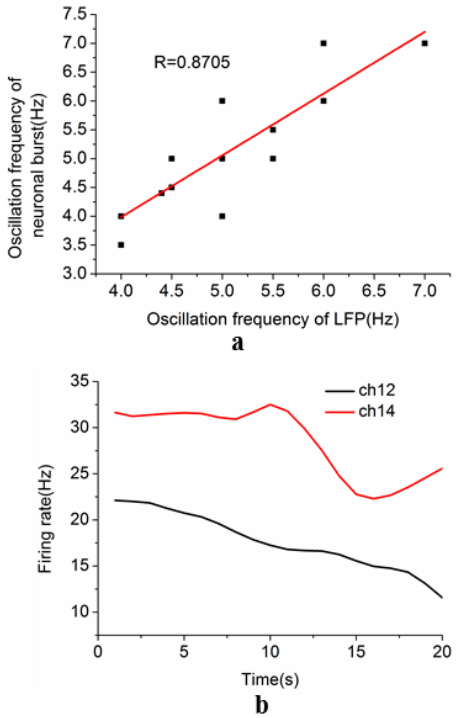

Fig. 6 Oscillation in BP neurons in striatum of LFP and action potential in PD monkey. (a)Relationship between oscillation in LFP and neuronal burst at the range of 4-7Hz. (b)Firing rates of spikes in ch12 and ch14, which were at beta frequencies (8–30 Hz).

BP neurons were representative neurons with high amplitude and high firing rate in PD monkey, discharging at mixed mode (both single spike discharge and burst firing). Rhythmic activity was also found in striatum both in neuronal bursts and LFPs of BP neurons. With respect to LFP oscillating at low frequency at a period in cortex, LFP continuously oscillated at a low frequency at the range of 4-7Hz which was constituent with the oscillating frequency of neuronal burst in striatum (Fig.6a). While for single spike, the firing rate was at the range of 10-32Hz, which was almost at beta frequencies (8–30 Hz). Loss of dopamine in PD monkey excited neurons of dopamine D2 receptors respond to the loss that lead to increasing beta oscillations in striatum[15].

IV. Conclusion

In this study, comparisons of multichannel electrophysiological signals before PD model made (normal monkey) and after PD model made (PD monkey) were obtained using implantable microelectrode arrays. In general, in PD monkey, neurons discharged in burst-firing mode with higher amplitude and higher firing rate. Neurons discharged more synchronously that were consistent with local field potential fluctuating. Tremor related neurons activity was acquired in cortex oscillating at 4.79 Hz. Local field potential continuously oscillated at low frequency consistent with neuronal burst firing rate and single neuron discharged almost at beta frequencies in striatum. Multichannel electrophysiological signals with different signals in different position were studied in this research that would be useful for the cure of Parkinson's disease. Comparisons of electrophysiological signals from same channel for PD monkey and normal monkey will be studied in our further research. The implantable microelectrode arrays in the paper could also be used for electrochemical signal detecting and neural stimulation. We will study both electrophysiological signal and electrochemical signal under stimulating condition that will be significance for mechanism research of Parkinson's disease and precise target location in DBS surgery.

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