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Research report

Complex analysis of neuronal spike trains of deep brain nuclei in patients with Parkinson's disease

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been used to alleviate symptoms of Parkinson's disease. During image-guided stereotactic surgery, signals from microelectrode recordings are used to distinguish the STN from adjacent areas, particularly from the substantia nigra pars reticulata (SNr). Neuronal firing patterns based on interspike intervals (ISI) are commonly used. In the present study, arrival time-based measures, including Lempel-Ziv complexity and deviation-from-Poisson index were employed. Our results revealed significant differences in the arrival time-based measures among non-motor STN, motor STN and SNr and better discrimination than the ISI-based measures. The larger deviations from the Poisson process in the SNr implied less complex dynamics of neuronal discharges. If spike classification was not used, the arrival time-based measures still produced statistical differences among STN subdivisions and SNr, but the ISI-based measures only showed significant differences between motor and non-motor STN. Arrival time-based measures are less affected by spike misclassifications, and may be used as an adjunct for the identification of the STN during microelectrode targeting.

1. Introduction

Deep brain stimulation (DBS) has been applied for the treatment of various neuropsychiatric disorders (Parkinson's disease, epilepsy, dystonia, tics, neuropathic pain, and major depression). The subthalamic nucleus (STN) is the most common target of DBS to alleviate Parkinsonian symptoms including tremor, rigidity, and bradykinesia. Preoperative anatomical landmarks to guide localization of the targeted brain nuclei can be determined by X-ray computed tomography (CT) and magnetic resonance imaging (MRI) [10,17,20]. However, the targeted brain areas must be further confirmed during the electrode placement process by identifying the characteristic electrophysiological activity of specific brain areas. The targeted area can be identified through cooperation between the neurophysiologist and neurosurgeons via listening to the auditory representation of cellular activity, visually analyzing the record of background and single unit signals, and inspecting the motor/perception-related neurophysiological responses along the trajectories of microelectrode recordings (MERs) [3,15]. When targeting the STN, one important step is to identify the border between the STN and substantia nigra pars reticulata (SNr) which lies slightly ventral and medial to STN.

Increased electrophysiological background noise and single cell activity are observed in STN along the electrode trajectory [3]. STN can be localized by the visualization of energy, autocorrelations, power spectral density and marginal probability density functions of the MER signals at different depths [6]. A Bayesian inference system based on estimated distance to target and normalized root-mean-square of the MER signals was developed to refine the location of STN [18]. In addition, the feasibility of STN localization based on spikeless neurophysiological signals was also demonstrated [5,19]. The high-frequency neuronal background (>500 Hz) of the MER signals increased in the STN [19]. The local field potential activity (13–35 Hz) recorded from the DBS electrode can be used to confirm placement within the STN [5].

Neuronal spikes are the most direct description of neuronal activities. Firing rate is defined as the number of neuronal spikes within a defined period of time and is the simplest measure to delineate the global firing activity of various brain nuclei. Nevertheless, neuronal discharge is often irregular, and may have various duration periods of bursts (series of consecutive spikes within a short period) and pauses (temporary cessation of spik-

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ing) [3,7,15,21]. Interspike intervals (ISI) histogram is commonly used to delineate regular/irregular firing activity [7,15,21]. Burst and pause indexes derived from interspike intervals (ISIs) can be used to quantify the occurrences of these patterns [7,11]. However, the ISI-based measures may be subject to incorrect spike annotations including erroneous detections and misclassifications. For example, when a pseudo-spike is annotated, the original ISI is replaced by two shorter, false ISIs. When a spike is missed in annotation, the surrounding two ISIs appear merged as a longer, false ISI. Although spike sorting can help aggregate neuronal spikes with similar morphologies and which are expected to be generated from the same neurons, this method can still result in ambiguous classifications.

Delineating neuronal activity based on spike arrival time has been used to determine the entropy of neuronal discharge responses to stimuli [2,23]. By dividing the time axis into discrete bins, a spike train is transformed into a sequence of symbols where "1" denotes at least one spike and "0" denotes no spike in the bin [23]. Accordingly, false spike annotations will just alter corresponding symbols in the sequence and may thus have a smaller effect on entropy estimation. We expected that the entropy measure would be useful in differentiating neuronal activity of the STN from SNr as well as the ISI-based measures. The robustness of the entropy measure to spike misclassifications was also investigated.

2. Materials and methods

2.1. Microelectrode recordings

Neural activities were obtained from 13 tracks in 7 patients with Parkinson's disease through a MER system (Medtronic, Minnesota, MN, USA) during implantation of targeting electrode (Table 1). The patients were under local anesthesia with 1% Lidocaine only. As shown in Fig. 1, a tungsten microtargeting single-electrode with Epoxylite insulation (FHC, Bowdoinham, ME, USA; impedance $1.0 \pm 0.2\,M\Omega$) attached to a microdrive was guided to the STN according to preoperative brain MRI findings. The STN neurons were distinguished from cells of the zona incerta (Zi) or internal capsule by a sudden increase of neuronal activity. The movement-related cells within the STN (motor STN indicated by the dashed-line ellipse) were specified by the presence of simultaneous neuronal response to passive or voluntary movements of the arms or legs, e.g., leg movement in Fig. 1. The exit of the microelectrode tip out of the STN corresponds to a decrease of neuronal activity. The penetration of the microelectrode tip into the SNr was identified by increased neuronal activity, typically regular discharges. 148 MERs (48 at non-motor STN, 60 at motor STN, and 40 at SNr) under spontaneous neuronal activity (no limb movement) along the electrode trajectories were selected for analysis. Each MER signal was amplified with a total gain of 1000 and filtered (passband from 300 Hz to 10 kHz and notch filter at 60 Hz). The filtered signal was digitized for 10 s at a sampling rate of 24 kHz. The digitized data were retrieved via the Leadpoint Export Utility 1.0.10.0 (Medtronic, Minnesota, MN, USA).

2.2. Data processing

Fig. 2 depicts a flowchart of the data processing protocol. Neuronal spikes were detected from each MER signal and the detected spikes were subsequently sorted. The spikes belonging to the major aggregated cluster were retrieved for spike-train analysis due to their neuronal-activity dominance. The ISI-based measures, including burst and pause indexes, and the arrival time-based measures, including Lempel-Ziv complexity and deviation-from-Poisson index were computed. In addition, all detected spikes (without applying spike classification) were also retrieved for spike-train analysis. When non-dominant spikes in neuronal firing measures are included, this measure is used to simulate spike misclassifications. All data processing, including spike detection, classification, ISI-based and arrival time-based analyses was performed using MATLAB 7.0 (MathWorks, Natick, MA, USA).

2.2.1. Spike detection

Neuronal spikes in each MER were detected by an adaptive threshold that uses proportional feedback to estimate the root-mean-square (RMS) value of near spike-free background noise by keeping the duty cycle (defined as the portion of data with a larger magnitude than the estimated RMS value in a 100-ms running window) at 15.85% [8]. The detection threshold was set as 3 times the estimated background RMS. As the waveform amplitude exceeded the adaptive threshold, searching for largest-amplitude wave in the subsequent 1 ms was continued to prevent the detection of small, connected wave as a separate spike.

2.2.2. Spike classification

The classification of neuronal spikes was performed over the reconstructed phase space [4]. In each MER, spike waveforms from −15 to 22 points around the maximum-magnitude position were transformed into a two-dimensional phase space portrait with a time delay of 0.125 ms. The phase space portrait was quantified by one-dimensional major portrait radii (MPR) defined as the largest radii at 25 equally spaced phases from 0 to 2π. In each MER, the MPR of all detected spikes were analyzed by principal component analysis. Based on the first 5 principal components, the detected spikes were divided into ten initial clusters by *k*-means clustering. The initial clusters were subsequently merged when the normalized RMS difference between mean MPR of every 2 clusters was less than 0.36.

In our data, the aggregated clusters can be categorized by major-spike clusters, secondary-spike clusters or minor-spike clusters. The secondary spikes are different from the major spikes in morphology or amplitude. The minor spikes are small in amplitude and mixed with background activities but they are also detected. Through the validation and correction by a domain expert by inspecting waveforms, phase space portraits, and principal components of the MPR, the major-spike clusters were confirmed and used for spike-train analysis.

2.2.3. Burst and pause measures

The burst and pause indexes, proposed by Favre et al., were used to quantify regular and irregular and/or short-burst activities of deep brain nuclei [7]. The burst index (BI) was defined as the number of ISI < 10 ms divided by the number of ISI > 10 ms. The pause index (PI) was defined as the number of ISI > 50 ms divided by the number of ISI < 50 ms.

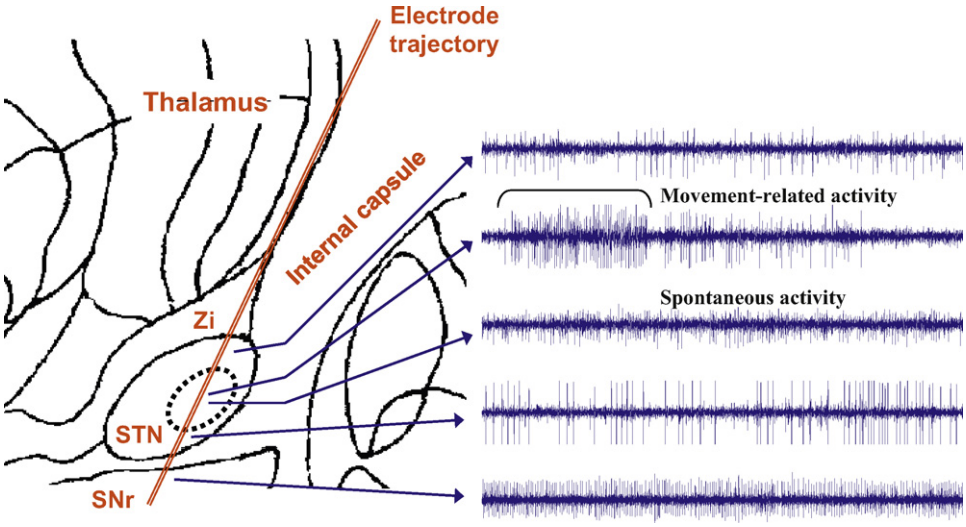

Fig. 1. The geometrical map of deep brain nuclei and microelectrode trajectory. Distinct neuronal firing patterns are presented at different neurons.