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Tremor frequency characteristics in Parkinson's disease under resting-state and stress-state conditions

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ABSTRACT

Tremor characteristics—amplitude and frequency components—are primary quantitative clinical factors for diagnosis and monitoring of tremors. Few studies have investigated how different patient's conditions affect tremor frequency characteristics in Parkinson's disease (PD). Here, we analyzed tremor characteristics under resting-state and stress-state conditions. Tremor was recorded using an accelerometer on the finger, under resting-state and stress-state (calculation task) conditions, during rest tremor and postural tremor. The changes of peak power, peak frequency, mean frequency, and distribution of power spectral density (PSD) of tremor were evaluated across conditions. Patients whose tremors were considered more than "mild" were selected, for both rest ($n = 67$) and postural ($n = 25$) tremor. Stress resulted in both greater peak powers and higher peak frequencies for rest tremor ($p < 0.001$), but not for postural tremor. Notably, peak frequencies were concentrated around 5 Hz under stress-state condition. The distributions of PSD of tremor were symmetrical, regardless of conditions. Tremor is more evident and typical tremor characteristics, namely a lower frequency as amplitude increases, are different in stressful condition. Patient's conditions directly affect neural oscillations related to tremor frequencies. Therefore, tremor characteristics in PD should be systematically standardized across patient's conditions such as attention and stress levels.

1. Introduction

Tremor is the rhythmical and involuntary oscillatory movement of a body part with particular amplitude and frequency profiles [7,27]. These profiles provide useful clinical information for the diagnosis and monitoring of tremors [6,7]. For instance, tremor amplitude is directly related to tremor severity and is positively correlated with clinical rating scores. Tremor frequency components are used: (a) to distinguish tremor types in Parkinson's disease (PD); (b) for the longitudinal analyses of tremor characteristics in pathologic tremors including PD and essential tremor (ET); (c) to evaluate the responsiveness to medication(s); (d) to examine the effects of deep brain stimulation on tremor characteristics; (e) to classify diseases such as PD, ET, and physiological tremor [1,2,5–7,9,10,12,22]. Since tremor is one of cardinal features of PD, it is important to investigate the amplitude and frequency profiles of tremor in patients with PD.

The hallmark of PD is dopaminergic cell loss in the substantia nigra and subsequent dopamine depletion in the striatum [8,13,14,16,20]. This causes motor neurons in the basal ganglia to spontaneously misfire, and their synchronization then causes oscillations to be transmitted to the muscles [4]. In addition, Brittain et al. [3] reported that PD tremor is associated with a broadly coupled set of neural oscillators. Therefore, tremor characteristics related to the activation of multiple neural oscillators can be expected to change according to patient's health status, attention, and stress levels. For example, Raethjen et al. [24] demonstrated that stressful situations resulted in increased tremor amplitudes in parkinsonian rest tremor, as well as increases in Unified Parkinson's Disease Rating Scale (UPDRS) scores. Despite this promising work, systematical analyses have not been performed on how different situations affect frequency characteristics of tremor.

Since many patients are exposed to various forms of stress in daily lives [18], it is important to systematically examine the effects of patient's condition under stress-state condition on tremor characteristics. Moreover, since rest tremor is a well-known characteristic of PD, most studies on tremor in PD have focused on analyses for rest tremor. However, many patients with PD have postural tremor that may cause more disability than the typical rest tremor [15]. Therefore, in this

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study, tremor characteristics, such as tremor amplitude, peak frequency, mean frequency, and distribution of power spectral density (PSD) of tremor, were compared between resting-state and stress-state conditions during both rest and postural tremor. We induced stress-states via a calculation task [17,24,26].

2. Materials and methods

2.1. Patients

The study was approved by the Institutional Review Board of Seoul National University Hospital, and all patients provided written informed consent prior to study participation. A total of 114 patients with PD (54 males, 60 females, mean age of 65.1 years) were recruited by experienced movement disorders specialists. Patients with leg tremors or dyskinesias were not recruited. The patients met the diagnostic guidelines of the United Kingdom Parkinson's Disease Society Brain Bank criteria.

Tri-axis-accelerometer sensor (LIS3DSH, STMicroelectronics N.V. Switzerland) was attached over the fingertip of the middle finger of the hand most affected by tremor. The sensor position was altered if the patient displayed more severe tremor symptoms on another finger.

During the measurement of rest tremor, patients were comfortably seated in a chair while their forearms were resting on the arms of the chair for 1 min. During the measurement of postural tremor, patients maintained both arms outstretched forward against gravity for 1 min. Rest and postural tremor measurements were taken under resting-state (no calculation task) and during a calculation task (under conditions of mental stress), whereby patients were asked to quickly count backwards from 100 by 7 out loud (i.e. "100, 93, 86, 79, etc.") for rest tremor and from 100 by 8 out loud (i.e. "100, 92, 84, 76, etc.") for postural tremor. The measurements were presented in a random order. Rest tremor with and without the calculation task was measured in all 114 patients (from 1st to 114th patients). Measurements for postural tremor with and without calculation task were taken in 49 patients (from 66th to 114th patients). In other words, 49 patients performed both rest and postural tremor with and without calculation tasks.

2.2. Data analysis

2.2.1. Basic tremor characteristics and distribution characteristics of normalized power spectral density (NPSD) of tremor

The sampling rate was 125 Hz. Each axis accelerometer signal was filtered with a range of 3–10 Hz using fifth-order Butterworth bandpass filter. After being scaled to cm/s^2, the signals were integrated twice to produce displacements. Power spectral density (PSD) of the displacement signal was computed for 1-minute recording. The PSD in each axis was summated to reflect 3-dimensional tremor movement. Features extracted from each measurement were illustrated in Fig. 1.

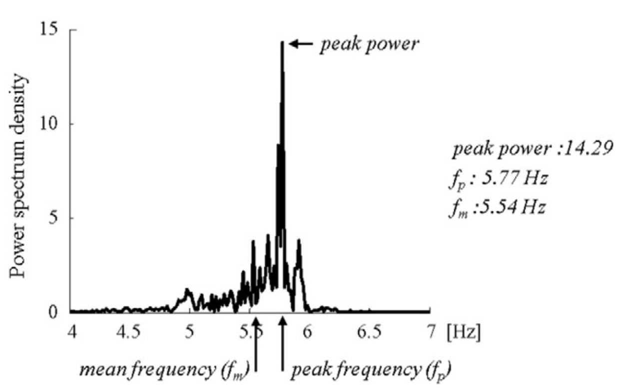

Fig. 1. Description of basic tremor characteristics

- Peak power: the dominant peak amplitude of the PSD in the range of 3 Hz to 10 Hz as a measure of tremor amplitude
- Peak frequency (f_p): the frequency with peak power in the PSD
- Mean frequency (f_m): the frequency with center of the distribution of power across frequencies

$$f_m = \frac{\sum_{i=0}^{n} I_i \cdot f_i}{\sum_{i=0}^{n} I_i}$$

where n is number of frequency bins in the spectrum, I_i is the intensity of the spectrum at bin i of n, and f_i is the frequency of the spectrum at bin i of n.

- Normalized power spectral density (NPSD): Peak powers in the PSD were normalized to have zero mean and unit variance

$$NPSD = \frac{PSD - mean(PSD)}{std(PSD)}$$

where *std* is standard deviation

- Kurtosis: the peakedness of the distribution of NPSD

2.2.2. Data selection

To accurately compare the tremor frequency components between resting-state and stress-state conditions, it was important to determine whether the detected peak frequency was a result of tremor or of unwanted noise. In the spectral analysis of tremor with absent or minimal symptoms, we supposed that the detected peak frequency could only be due to noise. In this study, therefore, data whose peak powers were more than a certain threshold were selected automatically. The threshold was empirically determined as −2.7 power/Hz (= logarithmic of 0.002). All selected peak powers and peak frequencies were checked manually once more to eliminate data having low signal to noise ratio.

2.2.3. Statistical analysis

The differences in tremor characteristics between resting-state and stress-state conditions, for both rest tremor and postural tremor, were evaluated by two-tailed paired samples *t*-test (parametric test or normal distribution) or related-samples Wilcoxon signed ranks test (non-parametric test). The statistical method for each extracted feature was selected according to the result of normality test (Kolmogorov–Smirnov test or Shapiro–Wilk test) that is used to check whether a data set is normally distributed. All statistical results were considered significant if $p < 0.0125$, incorporating Bonferroni correction [11].

All offline analyses were done using MATLAB R2013b (MATLAB, Mathworks, USA) and SPSS version 22 (IBM SPSS Statistic, IBM Corporation, Armonk, NY).

3. Results

3.1. Patient distribution

Of all patients (n = 114), 67 patients whose peak powers were over the threshold on both rest tremor with and without calculation task were selected. Of patients for whom postural data were collected (n = 49), 25 patients whose peak powers were over the threshold on both with and without calculation task were chosen. Table 1 shows the mean age, gender, and mean disease duration of the selected patients.