CHANGES IN BILATERAL PHASE SYNCHRONIZATION IN PARKINSONIAN TREMOR RELATED TO AMPLITUDE DIFFERENCE

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ABSTRACT
Tremor, which is a manifestation of the Parkinson’s disease, is rhythmic and involuntary oscillation in the frequency range from 3 to 8 Hz. Physiological mechanisms of parkinsonian tremor have not been clearly revealed even though there have been many related studies. In this study, we attempted to analyze bilateral phase synchronization between both hands in order to interpret parkinsonian tremor dynamics which can be helpful to speculate the mechanisms of parkinsonian tremor. Eighteen subjects with Parkinson’s disease participated in this study. Tremor was measured for 30 seconds by three axis accelerometer placed over the middle finger with sampling frequency of 64Hz and 12 bit A/D converter while subjects were resting on a chair and relaxing both hands on their knees. Three kinds of synchronization indexes, ρ, γ and λ, were employed to assess the synchronization strength for tremor between both hands. As a result, when bilateral difference of tremor amplitude became larger than specific value, phase synchronization strength was significantly increased. Therefore, we may suppose that the dynamics of parkinsonian tremor have two modes of the non-phase synchronization and phase synchronization between both hands.

KEY WORDS
Parkinson’s Disease, Tremor, Phase, Synchronization

1. Introduction
As a manifestation of the Parkinson’s disease, tremor is rhythmic and involuntary oscillation of which frequency generally ranges from 3 to 8 Hz. Symmetric movements in Patients with Parkinson’s disease have been important research topic. They have characteristics of moving asymmetrically, so that they could be classified with symmetry index from the normal [3]. In case of tremor, characteristics related to symmetry or coupling have been usually used to analyze dynamics of tremor and to investigate the mechanism of tremor. Mechanism of tremor generation has not been identified clearly even though it has been reported that central nervous system oscillator affects rest tremor. In addition, how central nervous system oscillator has an effect on the multiple limbs has not been established [2,8]. Therefore, many studies have been attempted to investigate the mechanism of different types of tremor, which could be distinguished by analyzing the tremor dynamics [5]. It has been reported that symmetry of intensity and frequency has been different between parkinsonian tremor and essential tremor [6] and that limb tremor has been coupled with body sway [4]. Furthermore, bilateral coherence has been significantly larger in orthostatic tremor than other types of tremor. Bilateral coherence, however, has not been appeared in other types of tremor [7]. On the other hands, it has been also examined that phase synchronization strength between both hands’ tremor has been decayed by time delay, that is, there are phase synchronization in both hands in parkinsonian tremor with time delay [9]. In contrast, it has been also reported that finger has been coupled with hand within same limb, whereas tremors in both limbs have not been coupled to each other, so that both limbs have oscillated independently [10]. In this study, we investigated that bilateral phase synchronization in parkinsonian tremor in order to speculate the effects of central oscillator and mechanical oscillator.

2. Methods
2.1 Subjects
Eighteen subjects with Parkinson’s disease participated in this study. In all subjects, tremor was more remarkable than other symptoms such as rigidity, bradykinesia and akinesia. They were evaluated by movement-disorder neurologist with Unified Parkinson’s disease rating scale (UPDRS), followed by being measured with tremor recording device. All participants signed informed consent forms approved by Seoul National University Hospital Review Board.

2.2 Measurement
Three axis accelerometers were placed over the most distal phalanx of the both middle finger. Acceleration
signal was measured with sampling rate of 64 Hz and 12-bit A/D converter while video was recorded with frame rate of 30 at the same time. The frequency of the parkinsonian tremor is known to range from 3 to 8 Hz, so that the sampling frequency was sufficient to measure the tremor. The accelerometer with plastic enclosure was light-weight (6.5g), which did not disturb the dynamics of the hand tremor. Rest tremor was measured for 30 seconds while subjects were sitting on a chair.

2.3 Preprocessing

Tremor acceleration was filtered with band-pass filter of frequency band from 0.1 to 1 Hz in order to remove noise. Then the filtered signal was detrended as subtracted by the mean of every 1 second signal. Next, it was moving-averaged for 5 samples. For the purpose of phase synchronization analysis we used the concept of analytic signal which was appropriate to find the phase in periodic and semi-periodic signals. Then the instantaneous phase \( \phi(t) \) was derived by constructing the analytic signal,

\[
\zeta(t) = s(t) + i s_H(t) = A(t)e^{i \phi(t)}
\]

where \( s_H(t) \) is the Hilbert transform of \( s(t) \). Then we calculated the cumulative sum of each instantaneous phase series. In sequence, phase difference of each instantaneous phase series was obtained.

\[
\phi(t) = n\phi_1(t) - m\phi_2(t)
\]

Next, cyclic relative phase was derived from the phase difference.

\[
\psi_{n,m} = \text{mod}_{2\pi} \phi(t)
\]

Amplitude of the tremor was obtained by the difference between upper envelope and lower envelope which were fitted to the upper extrema and the lower extrema with cubic spline. Amplitude difference was derived from the log of absolute value of amplitude difference multiplied by 10, then multiplied by 10.

\[
A = \text{Envelope}_{\text{UPPER}} - \text{Envelope}_{\text{LOWER}}
\]

\[
d = A_{\text{Right}} - A_{\text{Left}}
\]

\[
AD = 10 \log 10|d|
\]

Figure 2(a-b) represented the tremor acceleration in left and right hand, respectively. Upper envelope was depicted in red line, while lower envelope was described in green line. The absolute values of differences between upper envelope and lower envelope were depicted in Figure 2(c-d). The trends of amplitude were generally similar in both hands. The absolute values of amplitude differences were shown in Figure 2(e).

2.4 Synchronization index

Synchronization indexes were employed to quantify the synchronization strength between right and left hand tremor. There were three kinds of synchronization indexes which were generally used for phase synchronization analysis such as \( \rho, \gamma \) and \( \lambda \). Synchronization index, \( \rho \), was defined as following equation.

\[
\rho_{n,m} = \frac{S_{\text{max}} - S}{S_{\text{max}}}
\]

where \( S = -\sum_{k=1}^{N} p_k \ln p_k \), and maximal entropy is represented by \( S_{\text{max}} = \ln N \). \( N \) is the number of bins and \( p_k \) is the probability of locating \( \psi_{n,m} \) within k-th bin. The optimal number of bins was reported as \( N = \exp(0.626 + 0.41\ln(M - 1)) \) where M was the number of samples. Synchronization index, \( \gamma \), was derived by following equation.
where the brackets stand for the average over time. Synchronization index, $\lambda$, was obtained by using the following equation.

$$\eta = \phi_2 \bmod 2\pi |\phi_1, \phi_2, \phi_3|$$

$$\Lambda_i = M_i^{-1} \sum_{i=1}^{M_i} \exp[i(\eta_{i,1} / \lambda)]$$

$$\lambda_{n,m} = N^{-1} \sum_{n=1}^{N} |\Lambda_i|$$

where the $\lambda_{n,m}$ is conditional probability for $\phi_2$ to have a certain value when $\phi_1$ is located in a certain bin. All synchronization indexes vary from zero to one where zero was interpreted as no synchronization and one was regarded as complete synchronization. The indexes were calculated in the 5 second window which slide every 0.5 second. Therefore change of the synchronization strength was obtained over time. The characteristics of all indexes were different. Index, $\rho$, has relative small values compared to the other indexes. Indexes, $\gamma$ and $\lambda$ have quite high values within certain range of phase difference. Index, $\rho$, however, had high values when the phase difference have constant values [1].

2.5 Data analysis

Three kinds of synchronization indexes which were calculated in 5 second sliding window were compared with absolute value of the difference between amplitudes of the both hands. Fifty one values of synchronization indexes were calculated in tremor signal which were recorded for 30 seconds. Average of each index and maximum of each index were compared with absolute value of the amplitude difference between both hands.

3. Results

Table 1 depicted UPDRS and mean of amplitudes of the both hands. When difference between both hands’ UPDRS were high, amplitude difference tended to be increased. However, it was not significant because tremor was variably provoked, so that severity of tremor during recording could be different from that of during clinician assessment. Figure 3 showed the relationship between three kinds of synchronization index and amplitude difference. Trends of all indexes, which tended to be increased as the amplitude difference became larger, were similar to one another. Index, $\rho$, had the largest variability among all the indexes, which ranged from 0 to 0.6 whereas other indexes have the values over the 0.75. When amplitude was over 22, the synchronization indexes were abruptly increased. However, synchronization indexes were not linearly increased as the amplitude difference became much larger. Figure 4 represented mean of synchronization indexes in small amplitude difference and large amplitude difference. Amplitude difference was split into two groups at the amplitude difference 22. Independent samples T-test was applied to verify the statistical significance between two groups. Mean values of $\rho$ and $\lambda$ were significantly different between two groups ($\rho$: $P=0.002$, $\lambda$: $P=0.003$). Maxima of indexes $\rho$, $\gamma$ and $\lambda$ were significantly increased at higher amplitude difference ($\rho$: $P=0.001$, $\gamma$: $P=0.032$, $\lambda$: $P=0.001$)

<table>
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<th>Patient No.</th>
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<tr>
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4. Discussion

In this study, parkinsonian tremor was measured with three axis accelerometer attached on the both middle finger. Amplitude of tremor was calculated by difference between upper envelope and lower envelope. Three kinds of synchronization indexes were compared with the amplitude difference. As a result, when amplitude difference became higher than 22, all kinds of synchronization indexes had larger values than those in small amplitude difference. Therefore, we may suppose that phase synchronization of parkinsonian tremor has two modes where inter-limb relationship occurs or not.
according to amplitude difference. It was reported that tremor intensity, frequency, frequency dispersion were asymmetric in parkinsonian tremor [6] and that bilateral independence of tremor was preserved in different conditions [10]. In addition, it was demonstrated that coherence between tremors in different limb was low [2].

![Figure 3](image1.png)

**Figure 3.** Relationship between three kinds of synchronization index (a) $\rho$ (b) $\gamma$ (c) $\lambda$ and mean amplitude difference. When amplitude difference were increased and reached to the certain value, synchronization indexes abruptly became larger.

Independence of different limbs in parkinsonian tremor was described in these studies. Frequency and coherence analysis were used to investigate relationship in different limbs in these studies. In contrast, there were studies which represented synchronization in different limbs [9] and synchronization between tremor and body sway [4]. These studies used phase synchronization and coherence analysis in order to investigate the relationship between dynamics of different limbs. In this study, three kinds of phase synchronization indexes were employed to examine coupling strength between both hands in tremor.

![Figure 4](image2.png)

**Figure 4.** Mean and standard deviation of synchronization index in the small amplitude difference and the large amplitude difference. Difference synchronization indexes were shown in (a) $\rho$ (b) $\gamma$ (c) $\lambda$, respectively. (n=18, * P < 0.05, ** P < 0.01)

Our results showed that both of interdependency and dependency appeared within certain range and that occurrence of phase synchronization was closely related to the amplitude difference between both hands. Therefore, it is possible that conflicting results of previous studies can be explained by our results. Thus, mechanical oscillator of dominant hand tremor may have an effect on the entrainment of non-dominant hand’s oscillation. However, it is not sufficient to convince the mechanical
oscillator because neuronal signal was not investigated by acquisition for EMG signal. Therefore, for further study, EMG would be also measured with accelerometer in order to investigate phase synchronization in neuronal signal whether the results would be the same as the results of this study or not. Additionally, we would validate the specific range where the synchronization index would be abruptly changed for more subjects.

5. Conclusion

In this study, we examined the acceleration of parkinsonian tremor on both hands in order to investigate bilateral dynamics relationship. As a result, when the amplitude difference was larger than specific value, phase synchronization strength was higher. Therefore, we may suppose that the dynamics of tremor have two modes of which the non-phase synchronization and phase synchronization between both limbs.

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References