ABSTRACT: We investigated the electromyographic activity (EMG) of flexor and extensor muscles with different hand positions in patients with essential (ET) and parkinsonian (PD) tremor. Using a previously developed bootstrap method and standard cross-spectral analysis, we performed statistical tests to assess the effect of hand position on: (1) the frequency of the EMG; and (2) the phase between the EMGs recorded from antagonistic muscle pairs. Frequency as well as phases changed significantly with different positions of the hands but not during the recordings when the position was left unchanged. Besides confirmation that frequency and phase are stationary and reliable parameters during short-term recordings under controlled laboratory conditions, these results are of particular interest for ambulatory long-term tremor measurements. A higher variability of the estimated parameters reported in long-term recordings may perhaps reflect a patient's mobility only. Our study shows that long-term recording systems should have the means to monitor the patient's movements to provide reliable results.

 Muscle Nerve **24:** 1365–1370, 2001

VARIABILITY OF FREQUENCY AND PHASE BETWEEN ANTAGONISTIC MUSCLE PAIRS IN PATHOLOGICAL HUMAN TREMORS

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Accepted 14 April 2001

Spectral and cross-spectral analysis are powerful tools in investigating human tremors, but it is not clear to what extent diurnal changes and changes in experimental settings influence tremor frequency, power, or phase relationships between different muscles. One reason for this is that most studies do not distinguish between biological variability and variability originating from a statistical error in the estimation process.

Numerous studies have investigated the variability of tremor frequencies in short-term recordings in different experimental settings and in long-term recordings.[1,3,5,8,12,17,18,23,25] None of these studies considered statistical tests or confidence intervals for the estimated peak frequencies in deciding on the significance of the results. The value of a study investigating the variability of frequencies without taking a statistical test into account is limited in cases where the peak frequencies do not differ substantially.

One other prominent application of phase-spectral analysis in short- and long-term tremor recordings is estimation of the phase between antagonistic muscle pairs.[3,7,11,23,25] Here also it is not clear to what extent the phase between the muscles depends on mechanical parameters, such as hand and arm position, and whether the phase varies within a short-term recording in controlled experimental settings.

Methods of estimating confidence intervals are available for frequency and phase.[2,4,20,28,29,31] These methods allow separation of the two possible variation sources and a decision whether a biologically significant change has occurred or whether the difference lies in the range of the error of estimation.

In this study we investigate short-term electromyographic (EMG) recordings of different experimental settings obtained from patients with essential

Abbreviations: EMG, electromyography; ET, essential tremor; PD, parkinsonian tremor; TRIG, Tremor Investigation Group
Key words: human tremor; cross-correlation analysis; phase-spectral analysis; Fourier analysis; contraction pattern; electromyogram (EMG);
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(ET) and parkinsonian (PD) tremor to test for: (1) the effect of the position of the hand on the frequency of the EMG; and (2) the effect of the position of the hand on the phase between EMGs recorded from antagonistic muscle pairs. Furthermore, we investigated whether these parameters differ significantly within a recording if the position is not changed. The study is particularly relevant to ambulatory long-term recording systems, which are gaining increasing attention,[1,3,22–25,33] because it is not clear whether a movement monitoring system is needed or whether EMG recordings alone are sufficient to calculate reliably the frequency and phase of tremor.

MATERIALS AND METHODS

Subjects. All subjects underwent detailed clinical evaluation by trained, experienced movement disorder specialists. Informed consent was obtained from each subject prior to participation. Subjects were classified according to the criteria of the Tremor Investigation Group (TRIG).[10] Only patients with a definite diagnosis of the respective tremor disorder were included. Ten patients with typical ET and six patients with PD of a similar amplitude entered the study.

Data Recordings. During the recording, subjects were seated in a comfortable, heavy chair with their arms supported. The forearms were fixed proximal to the wrist with a strap. To measure postural tremor, subjects were asked to hold their hands outstretched and to avoid any voluntary movement. To provoke or increase tremor, mental stress was induced by counting backwards. The duration of each record was 30 s; therefore, muscular fatigue effects can be excluded.

Surface EMGs were recorded from the wrist flexors and extensors of the right and left forearm. To this end, bipolar surface electrodes were placed at the site of maximum muscle contraction elicited by voluntary wrist extension or flexion. The distance between the bipolar electrodes was about 5 cm. EMGs were bandpass filtered to avoid aliasing effects and undesired slow drifts (80–500 Hz). All data were simultaneously sampled at 1000 Hz and stored on a computer using special software for offline analysis.[16] The mean was subtracted from each time series. Finally, the series were tapered with a Bartlett window and normalized to unit variance. In addition, EMGs were digitally full-wave rectified for spectral and cross-spectral analysis.[9,13]

Three recordings were done for each patient. The first was recorded in a pronated position, in the following referred to as "condition 1." The second, "condition 2," was recorded while turning the outstretched hand 90°, the right hand clockwise, and the left hand counterclockwise. The third was recorded while holding the outstretched hand with the palm up; that is, with the flexor acting against gravity ("condition 3").

We included both severe and mild tremors in the study. The tremor power ranged from about 0.1 $(mm/s^2)^2$, which corresponds to the amplitudes of an enhanced physiological tremor up to 400 $(mm/s^2)^2$. Therefore, some EMGs of mild tremors did not exhibit a significant peak at all. Only EMGs showing a significant peak at the same frequency in flexor as well as extensor EMG were considered, as discussed in what follows in the section on data analysis.

Altogether, for each of the described experimental conditions, we examined 15 flexor and extensor EMGs of ET (8 on the right side, 7 on the left side, and 5 excluded) and 8 flexor and extensor EMGs of PD (5 on the right side, 3 on the left side, 4 PDs had unilateral tremor). Note that, based on the results of our recently study,[15] it is possible to investigate tremor on the right side and the left side as independent processes. Therefore, in the following, we have used the term "cases" instead of patients, as some patients served as two cases, with their left- and right-sided tremor. As stated earlier three recordings were done for each of the EMG pairs, so that the total number of investigated pairs was 45 (three recordings, 15 cases) in ET, and 24 (three recordings, 8 cases) in PD.

To investigate whether the frequencies and phases change significantly within the 30-s recordings, we separated each recording into two segments of 15 s each and compared the frequencies and phases between the segments.

Data Analysis. All data analysis was performed using special software for tremor analysis.[16] Power spectra were estimated by a direct spectral estimation procedure.[27] In short, the squared magnitude of the Fourier transform of the time series is convolved by a window function to get an estimate of the spectrum.[2,4,27] A bootstrap method[28,31] is used to obtain confidence intervals for the peak frequencies and to test for a significant difference in peak frequencies.

A significant peak is defined by a method that has been described in detail by Timmer et al.[27] Briefly, a peak is considered significant if it exceeds the 95% confidence level of the spectral estimation; that is, if the value at the peak minus the confidence level

exceeds the value of the two nearest-neighbor valleys plus the confidence level. The confidence level for a spectrum estimated by a direct spectral estimation procedure is given by a chi-square distribution.[27]

The cross-spectrum of two time series is defined as the Fourier transform of the cross-correlation function.[4,29] The coherency spectrum is defined as the modulus of the cross-spectrum normalized by the autospectra.[4,29] The phase-spectrum denotes the phase of the complex cross-spectrum. The coherency can be interpreted as a measure of linear predictability[4,20]—it equals 1 whenever the two time series under investigation are a linear function of each other. In general, phase-spectra are more difficult to interpret.[29] However, we were only interested in the phase lag between the antagonistic muscle pairs at the tremor frequency.

At frequencies exhibiting a significant coherency, the confidence interval of the phase-spectrum is inversely proportional to the coherency spectrum.[4,20,29] The error is high if the coherency is low, and vice versa. A significant difference of the phase is detected if the confidence intervals for the phases at the tremor frequencies do not overlap.

For the investigation of phases we also considered the problem of EMG crosstalk[14] that complicates the estimation of phases between antagonistic muscle pairs. Crosstalk describes the effect of volume conduction of the measured EMG potentials. In fact, the EMG measured at a muscle is always a sum of the signal originating from this muscle and from other neighboring muscles. The magnitude of crosstalk depends on different parameters such as muscle volume, skin resistance, and placement of the electrodes, which cannot be fully controlled. The amount of crosstalk can be estimated from the discontinuity at lag zero of the cross-correlation function estimated between the unrectified EMGs (see Fig. 1 for an example). It is not possible to estimate reliably the amount of crosstalk directly as a percentage of the total variance because of the part of the cross-correlation not originating from the crosstalk. We therefore use this method only for detection of strong crosstalk. If the amount of crosstalk is not negligible, a phase of zero is measured between the muscles, regardless of the true situation. In this study, we considered the problem of crosstalk by visually inspecting the cross-correlation function of the unrectified EMG time series.[21] Two recordings showing a high amount of crosstalk were excluded.

For all statistical tests we used a level of significance of $\alpha = 0.01$.

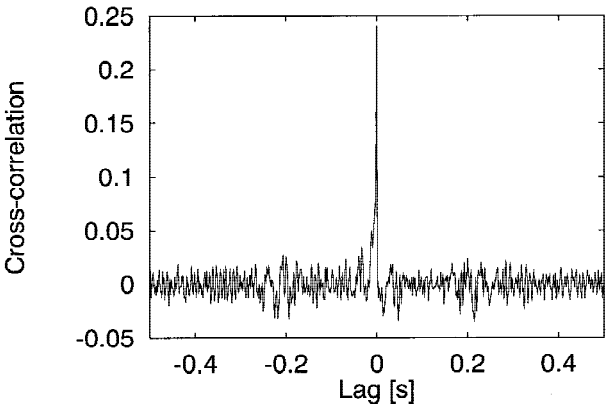

FIGURE 1. Cross-correlation function between an unrectified extensor and flexor EMG of a patient with ET. The sharp discontinuity at lag zero indicates that strong crosstalk (a volume conduction effect) is present between the two recorded EMGs.

RESULTS

Variability of Frequency. Within the recordings, our results clearly show that the frequencies do not change significantly if subjects are examined under controlled laboratory conditions. The frequencies differed significantly in the second 15-s segment compared to the first 15 s in only 3 recordings out of 45 single EMG time series of ET. Similarly, for PD, the null hypothesis was rejected in only 3 of the 24 EMG trials.

The frequencies of flexor and extensor activity did not change significantly across the different settings of the recordings in one of the PD cases (unilateral tremor). In all other cases the frequencies changed significantly for at least one of the recording conditions. No consistent pattern could be seen; for example, sometimes the frequencies were higher for condition 2 than for condition 1, whereas in other instances they were lower. In one patient with bilateral PD, the frequency even increased on the left side for condition 2 but, at the same time, decreased on the right side.

Similarly, for all of the ET cases, the frequency changed significantly across the different recording conditions. Here also, no correlation could be seen between the direction of change and the recording conditions. Table 1 summarizes the results for the test across the different recording settings. The largest differences measured were around 1 Hz.

Figure 2 shows an example of a patient with ET. Here the frequency does not change significantly within the recordings (Fig. 2a,b), whereas it differs across the recording conditions (Fig. 2c).

Note that the frequencies of extensor and flexor EMGs as well as the tremor frequency determined by

Table 1. Variability of frequencies for different recording conditions.

	Recorded muscle	Number of recordings	Cases without changes
Parkinson's disease (PD)			
	Flexor	8	3
	Extensor	8	2
Patients without changes	1 of 6		
Essential tremor (ET)			
	Flexor	15	5
	Extensor	15	0
Patients without changes	0 of 10		

The results of the comparisons of each investigated muscle are shown. Altogether, 60 comparisons were performed for ET and 32 for PD. The last column contains the number of cases where the frequency did not change between conditions 1 and 2 or between conditions 1 and 3.

accelerometry did not differ significantly within the recordings.

Variability of Phases. The phase remained constant over all three conditions in only 3 of the investigated 15 ET cases and in 2 of the PD cases. In all other cases, the phase changed significantly in at least two of the three recording conditions. For 5 cases (1 PD and 4 ET) the phase changed by π (i.e., the pattern changed from cocontracting to alternating). For 6 cases, the phase changed between $\pi/2$ and π, and for 7 cases it changed less than $\pi/2$. There was no consistent direction of change across the different recording conditions. Table 2 summarizes the results for the test across the different recording settings.

Comparing the phase of the first 15-s segment of each recording with that of the second segment, the phase only changed for 2 of the 45 recordings of ET, and for 1 of the 24 recordings for PD. The changes were rather moderate: around $\pi/6$ for the two ET cases and $\pi/10$ for the case of the patient with PD. Such small differences in phase were still significant due to the high coherency levels of up to 0.98.

To illustrate these findings, Figure 3 shows examples of cross-correlation functions for a patient with ET. The two 15-s segments of the conventional postural recording (Fig. 3a) show exactly the same phase. This is also true with the recording done under the second condition (Fig. 3b, hand turned 90°). In Figure 3c, which displays the recordings of Fig 3a, b in one plot, the phases are different.

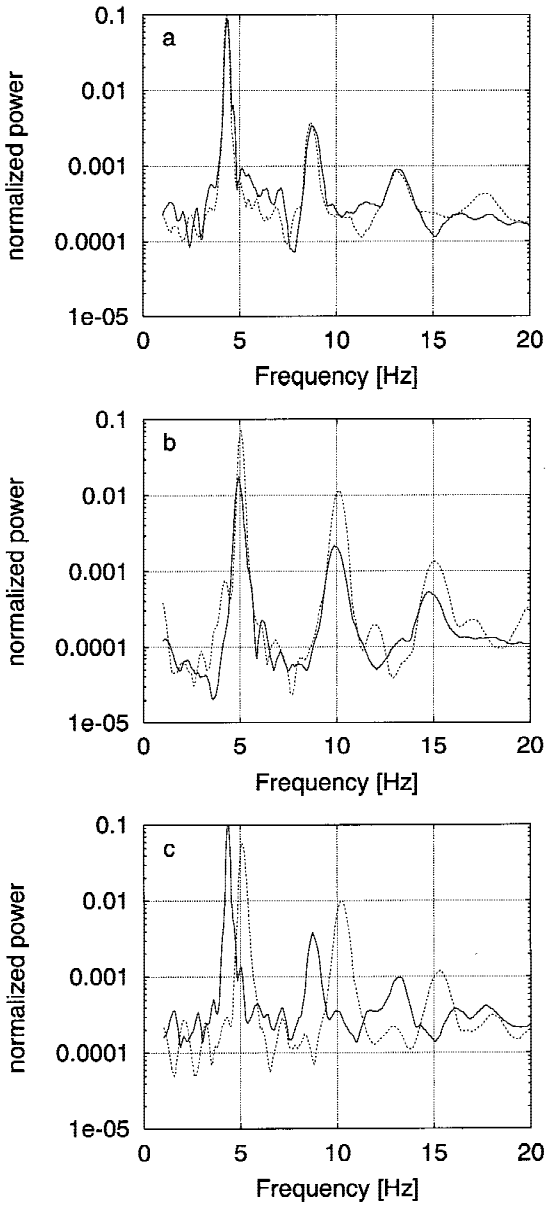

FIGURE 2. Power spectra for a patient with ET. The results for the extensor muscle of the right hand are shown. **(a)** Normal postural recording (hand outstretched, extensor muscle acting against gravity), and **(b)** hand turned 90°, showing the estimated spectra of the first 15 s (solid line) and the second 15 s (dashed line). **(c)** the estimated spectra of all 30 s of the two recordings of **(a)** (solid line) and **(b)** (dashed line) in one plot. The differences in **(a)** and **(b)** are only one frequency bin, and the null hypothesis of zero difference could not be rejected. For **(c),** the null hypothesis has been rejected at a level of $\alpha = 0.01$.

DISCUSSION

The phase between EMGs recorded from antagonistic muscle pairs and also the frequency of the EMG depend on posture. We could show, however, that the parameters do not change significantly within a

Table 2. Variability of phases between antagonistic muscle pairs.

	Number of investigated muscle pairs	Number of cases without changes
Parkinson's disease	8	2
Patients without changes	1 of 6	
Essential tremor	15	3
Patients without changes	0 of 10	

The results of the comparisons of each investigated muscle pair are shown. The last column contains the number of cases where the phase did not change between conditions 1 and 2 or between conditions 1 and 3.

short recording when the position is not changed. These findings should be considered in the interpretation of the results of long-term recordings when it is not possible to monitor movements.[3,23–25] For example, greater variability of the phase between flexor and extensor muscles or the frequencies recorded during a period of certain hours could perhaps reflect the mobility of the patients. This could explain the finding that the phase varies more in ET patients than in PD patients[23] who are generally less mobile. It would be of interest to investigate whether the reported variance of the distribution of frequencies and phases between antagonistic muscle pairs in ambulatory long-term recordings[3,23–25] correlates with the mobility of patients.

To obtain reliable results in long-term EMG recording systems, monitoring of the position of the investigated limb is necessary.[33] Also, assessment of tremor severity by EMG recordings alone[3,22,23–25] is difficult, because the relationship between EMG and tremor severity is still unclear.[19]

Long-term recordings, particularly to determine the distribution of phases between antagonistic muscle pairs over certain hours, may be a means of differentiating between PD tremor and ET.[23] Because position of the limb was not recorded in this study, the reported results raise the question of whether the differentiation was successful only because a small sample of typical examples was investigated and a PD patient is typically less mobile due to bradykinesia. In small retrospective studies, it is often the case that only a small part of the true parameter distribution is measured. Other approaches have discriminated PD and ET based on measured time series in small-sample studies.[6,26] However, none of these methods has revealed a similar good discrimination power in prospective, large-sample studies.[32] The value of a new method as a diagnostic tool can only be estimated in a large, multicenter, prospective study.

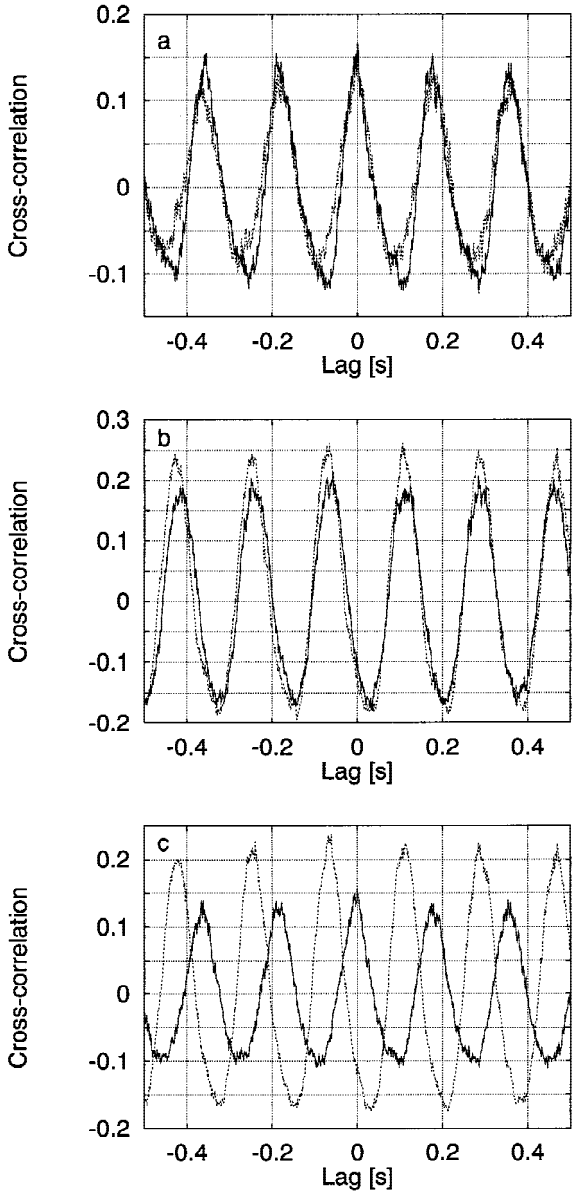

FIGURE 3. Cross-correlation functions for a patient with ET. Shown is the crosscorrelation between the extensor and flexor muscle of the right hand. **(a)** Normal postural recording (hand outstretched, extensor muscle acting against gravity), and **(b)** hand turned 90°, showing the resulting cross-correlation for the first 15 s (solid line) and the second 15 s (dashed line). **(c)** Cross-correlation of all 30 s of the two recordings of **(a)** (solid line) and **(b)** (dashed line) in one plot.

Bearing in mind that the phases and frequencies did not change within recordings during a stable position, two possible reasons remain for the changes that occur with change in position. First, if the subject turns the hand, the electrodes may no longer record from the same muscle. Second, phase and frequency may be modified by a change of activity in spinal reflex loops.

In a simulation study, Timmer et al.[30] showed that sensory feedback exerts a complex influence on the frequency of a centrally driven resonant physiological hand tremor. Depending on the latency of the spinal response and the resonance frequency of the hand, the resulting frequency of the hand tremor was altered by more than 1 Hz. Thus, it is conceivable that different positions of the hands lead to tremor modification by activating different proprioceptive Ia afferents. However, this simulation study did not investigate an appropriate model for pathological tremors, in which the hand tremor is not a resonant oscillation of the hand.

A reliable long-term recording system is certainly one goal in the development of methods for recording tremor. However, the first step toward such an application is an understanding of the effects of the biomechanical system, the corticospinal system, and diurnal rhythms on tremor under controlled laboratory conditions.

This work was supported by the German Federal Ministry of Education, Science, Research and Technology (BMBF) by the grant Verbundprojekte auf dem Gebiet der Mathematik (M.L.).

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