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A longitudinal study of tremor frequencies in Parkinson's disease and essential tremor

B. Hellwig [a,*], P. Mund [a], B. Schelter [b], B. Guschlbauer [a], J. Timmer [b], C.H. Lücking [a]

[a] Neurologische Universitätsklinik, Neurozentrum, Breisacher Strasse 64, 79106 Freiburg, Germany
[b] Zentrum für Datenanalyse und Modellbildung, Eckerstrasse 1, 79104 Freiburg, Germany

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ABSTRACT

Objective: There is evidence that the tremor frequency in essential tremor (ET) decreases with time. Longitudinal studies on the evolution of tremor frequencies in Parkinson's disease (PD) have so far not been published. Here, we present a longitudinal analysis of tremor frequencies in PD and ET.
Methods: We analyzed the standardized accelerometric and electromyographic tremor recordings of 53 patients with PD and 38 patients with ET who underwent repeated routine tremor recordings between 1991 and 2002.
Results: In an average follow-up period of 44.9 months in PD and 50.6 months in ET, the average number of tremor recordings was 3.3 in PD and 3.7 in ET. In both disorders, tremor frequencies tended to decrease with time. The average annual decrease of the tremor frequency was 0.09 Hz/year in Parkinsonian rest tremor, 0.08 Hz/year in Parkinsonian postural tremor and 0.12 Hz/year in ET.
Conclusions: The tremor frequency decreases with time in both PD and ET. The similarity of this decrease in PD and ET may point to a common underlying pathophysiological mechanism.
Significance: Decreasing tremor frequencies with time may be functionally important by inducing larger tremor amplitudes due to the low-pass filtering properties of muscles and limbs.

1. Introduction

Tremor is defined as an involuntary oscillatory movement of a body part. It occurs in many neurological disorders including essential tremor (ET) and Parkinson's disease (PD). According to the 'Consensus Statement of the Movement Disorder Society on Tremor' (Deuschl et al., 1998), ET is characterized by a bilateral postural and kinetic tremor of the upper limbs. Other body parts may also be tremulous, for instance the head, the chin, the trunk or the lower limbs. Cerebellar signs such as intention tremor or slight ataxia may be present, other focal neurological abnormalities do not occur. Parkinsonian tremor is most commonly a combination of rest and postural tremor. The frequency of the postural tremor may be identical with or higher than that of the rest tremor. Parkinsonian tremor is typically associated with other clinical signs of PD such as bradykinesia, rigidity or postural instability (Deuschl et al., 1998).

In ET, there is evidence that the tremor frequency decreases with time (Elble et al., 1992; Elble, 2000). This is likely to influence the tremor strength, since decreasing tremor frequencies should lead to increasing tremor amplitudes due to the low-pass filtering properties of muscles and limbs (Elble, 2000). A negative correlation between tremor frequency and amplitude has indeed been found in a number of studies on ET (Calzetti et al., 1987; Elble, 1986; Elble et al., 1992, 1994).

Since 1991, patients with tremor admitted to the Department of Neurology of the University Hospital of Freiburg, Germany, have been routinely investigated using a standardized neurophysiological recording procedure. Accelerometric and electromyographic data acquisition as well as data analysis using spectral and cross-spectral methods have been performed with a software developed in our tremor laboratory (Lauk et al., 1999). Many patients with PD or ET were followed up, and they underwent more than one tremor recording over the years. Thus, a large data base has accumulated which allows a longitudinal analysis of the clinical progression of tremor disorders. In the present study, we used this data base to investigate the evolution of tremor frequencies in ET and PD. As to ET, our study complements previous results by Elble et al. (1992, 2000). We used, however, a different approach by studying the evolution of tremor frequencies in individual patients as compared to the group analysis in Elble's work. In PD, the development of tremor frequencies with time has previously not been investigated.

* Corresponding author. Tel.: +49 761 389060; fax: +49 761 3890617.
E-mail address: hellwig@npi-freiburg.de (B. Hellwig).

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2. Methods

2.1. Patients

Patients who were considered for this study were investigated between the years 1991 and 2002 in the Department of Neurology of the University Hospital of Freiburg, Germany. All patients underwent a clinical evaluation by experienced neurologists who were well trained in the differential diagnosis of tremor disorders. Tremor recordings were done as part of the clinical routine. All patients gave informed consent to participate.

In all, 53 patients with PD (19 female, 34 male) and 38 patients with ET (18 female, 20 male) were included in this study. The diagnosis of ET or PD conformed to the criteria given in the 'Consensus Statement of the Movement Disorder Society on Tremor' (Deuschl et al., 1998). Only patients with an unequivocal diagnosis were included. None of the ET patients developed signs of PD during the period of observation. The average age at the first recording was 62.1 years (range 48–77) in PD and 64.1 years (range 38–82) in ET. Tremor duration before the first recording was on average 4.0 years in PD and 11.9 years in ET. Note that this information is probably imprecise due to the insidious disease onset in ET and PD.

A standardized tremor recording was done at least twice in each of the patients. The number of recordings done in each patient was on average 3.3 (range 2–9) in PD and 3.7 (range 2–10) in ET. The average time span between the first and the last recording in each patient was 44.9 months (range 6–109) in PD and 50.6 months (range 6–107) in ET.

2.2. Recording procedure

Patients were seated in a comfortable, heavy chair with their forearms supported. Hand acceleration was measured using piezoresistive accelerometers (ACCs) attached to the dorsum of both hands between the 3rd and 4th metacarpophalangeal joints. Surface electromyographies (EMGs) were recorded from the wrist flexors and extensors of both arms. ACCs and EMGs were bandpass filtered to avoid aliasing effects and undesired slow drifts (ACC: 0.5–50 Hz; EMG: 80–500 Hz). All data were simultaneously sampled at 1000 Hz and stored for off-line analysis.

For the measurement of rest tremor, patients were asked to relax and to avoid any voluntary muscle contraction. The hands were flexed and pronated. In order to increase tremor amplitudes, mild mental stress was induced by instructing the patients to count backwards. Postural tremor was elicited by bilateral wrist extension, the hands being pronated. In all patients, postural tremor was measured before and after weight loading (500 g and 1000 g) to the outstretched hands. The duration of each recording was 30 s. The medication was not modified before the tremor recordings.

2.3. Data analysis

EMGs were full wave rectified. Power spectra were estimated for each EMG and ACC time series following the mathematical methods described by Timmer et al. (1996). A neurologist experienced in the analysis of tremor recordings (B.H.) checked all recordings for a clear pathological tremor pattern. First, narrow peaks at the tremor frequency in both the ACC and EMG spectra were required. Second, the frequency of postural tremor had to be constant after weight loading to the hands in order to exclude enhanced physiological tremor. Recordings which did not conform to the above two criteria were excluded. In all, the present study is based on tremor recordings from 73 arms in Parkinsonian rest tremor, from 62 arms in Parkinsonian postural tremor and from 60 arms in ET. In ET, only postural tremor was considered. The data analysis concerning postural tremor was based on recordings without weight loading in both PD and ET.

Data analysis was based on ACC time series. It depended on whether two or more time series were recorded per arm. If only two time series were available, a test for the difference between spectral peak frequencies was applied (Timmer et al., 1999). This test ($p < 0.05$) was calculated for 32 arms in Parkinsonian rest tremor, 24 arms in Parkinsonian postural tremor and 18 arms in ET. In patients, who underwent more than two tremor recordings, confidence regions for the spectral peaks at the tremor frequency were determined (Timmer et al., 1997). Linear least-squares regression of tremor frequencies versus time of recording was performed for each individual arm. The null hypothesis that the slope of the regression line was compatible with 0 was tested ($p < 0.05$). Such a regression analysis was done for 41 arms in Parkinsonian rest tremor, for 38 arms in Parkinsonian postural tremor and for 42 arms in ET.

Tremor amplitudes were not considered for analysis, since most patients were under tremor medication at the time of recording. In some patients, tremor medication varied in successive recordings. Thus, unbiased measurements of tremor amplitudes were not available in the present study in which recordings were obtained as part of the clinical routine.

3. Results

3.1. Significant changes of the tremor frequency with time

The average tremor frequency at the time of the first recording was 5.6 Hz in Parkinsonian rest tremor, 5.9 Hz in Parkinsonian postural tremor and 5.6 Hz in ET. Fig. 1 displays the percentage of significant changes ($p < 0.05$) of the tremor frequency over time. In Fig. 1a, c and e, data of all tremulous arms are pooled, irrespective of the time span between the first and the last recording and irrespective of the type of statistical evaluation (direct comparison or regression analysis, see Patients and Methods). It is illustrated for rest and postural tremor in PD as well as for postural tremor in ET that a significant decrease of the tremor frequency occurs distinctly more often than an increase, the decrease being 2.7–5.0 times more frequent. In Fig. 1b, d and f, the results are shown in more detail. The data are analyzed in subgroups which were formed according to duration of the follow-up (see Table 1). This more detailed analysis confirms that tremor frequencies tend rather to decrease than to increase, the time span between the first and last recording being without a clear-cut influence.

The question arises whether the few patients with *increasing* tremor frequencies over time form a specific subgroup. This does not seem to be the case. For all types of tremor investigated here, there is no statistically significant difference between patients with increasing and decreasing tremor frequencies, at least as far as age and tremor frequency at the time of the first recording are concerned (exact Wilcoxon rank sum test, $p > 0.05$).

The results illustrated in Fig. 1 remain essentially unchanged when only the tremor-dominant arms are considered. Moreover, the type of statistical analysis that had to be applied (direct comparison versus regression analysis) is without major impact. There is a higher percentage of significant tremor frequency changes in case of direct comparison of two recordings. However, the predominance of decreasing tremor frequencies with time is present in both types of statistical analysis.

3.2. Average change of the tremor frequency per year

So far, the analysis focussed on the mere presence or absence of significant tremor frequency changes with time. However, the

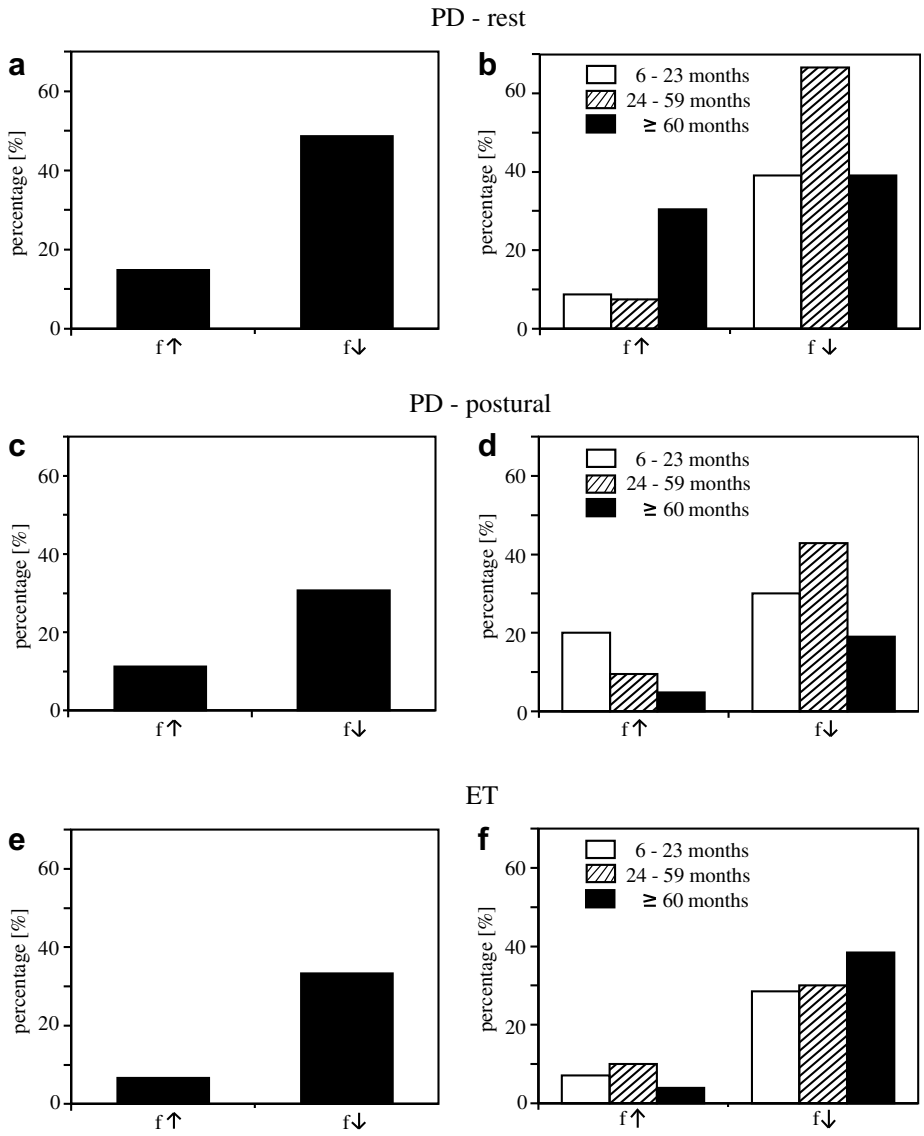

Fig. 1. (a, c, and e) The percentage of significant increases (f↑) and decreases (f↓) of the tremor frequency with time in PD and ET ($p < 0.05$). (b, d, and f) The results illustrated in (a, c, and e) analyzed in more detail for different periods of follow-up.

Table 1
Numbers of tremulous arms in PD and ET analyzed for different periods of follow-up.

Duration of follow-up	Number of tremulous arms		
	PD-rest ($n = 73$)	PD-postural ($n = 62$)	ET ($n = 60$)
6–23 Months	23	20	14
24–59 Months	27	21	20
>59 Months	23	21	26

magnitude of the tremor frequency changes is also an important point. In the case of just two recordings per individual arm, the change of the tremor frequency per year can be directly estimated. If more than two recordings were available for an arm, the slope of the regression line is a measure of the change of the tremor frequency per year. Fig. 2 illustrates the results. As expected from Fig. 1, the change of the mean tremor frequency per year obtains a negative value. In Parkinsonian rest tremor, the tremor frequency decreases on average by 0.09 ± 0.05 Hz/year, in Parkinsonian postural tremor by 0.08 ± 0.04 Hz/year and in ET by 0.12 ± 0.04 Hz/year. Table 2 shows the average decrease of the tremor frequency per year for different periods of follow-up. Note that in ET the tremor frequency decrease per year tends to become smaller with increasing duration of the follow-up. This tendency was, however, not statistically significant.

3.3. Tremor frequency versus age

To test for a linear correlation between tremor frequency and age at the time of the first recording, a Kendall's tau rank correlation test was performed. In ET, there was a significant negative correlation between tremor frequency and age ($p = 0.0002$), i.e. tremor frequencies decreased with increasing age. In Parkinsonian rest and postural tremor, Kendall's tau suggested a negative correlation which was, however, not statistically significant ($p > 0.05$).

4. Discussion

This study provides evidence that the tremor frequency decreases with time in both PD and ET. As far as ET is concerned, our investigation confirms previous longitudinal studies by Elble

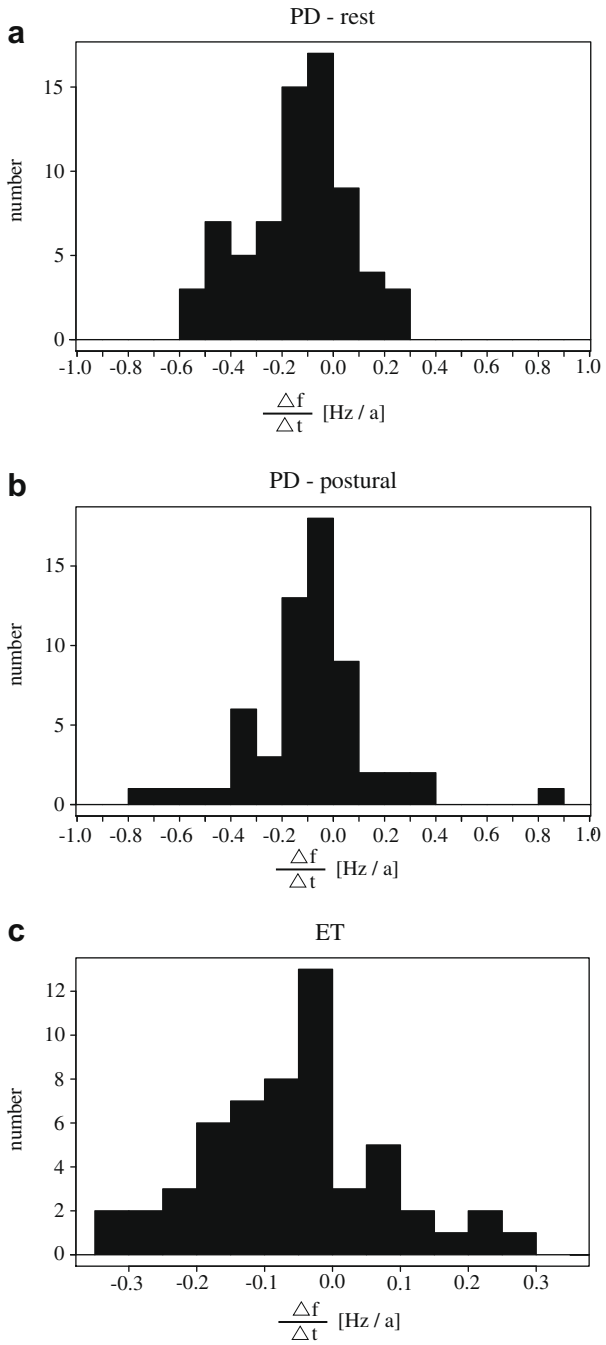

Fig. 2. Histograms illustrating the frequency distribution of the annual decrease of the tremor frequency $\Delta f/\Delta t$ in PD and ET.

Table 2
Average annual change of the tremor frequency for different periods of follow-up (bottom row: total average).

Duration of follow-up	Average change of tremor frequency (Hz/year)		
	PD-rest	PD-postural	ET
6–23 Months	−0.12 ± 0.09	−0.09 ± 0.10	−0.26 ± 0.15
24–59 Months	−0.08 ± 0.10	−0.12 ± 0.07	−0.13 ± 0.06
>59 Months	−0.08 ± 0.05	−0.03 ± 0.03	−0.05 ± 0.02
⩾6 Months	−0.09 ± 0.05	−0.08 ± 0.04	−0.12 ± 0.04

et al. (1992, 2000). Our results were, however, obtained with different methods. While Elble's work was based on a group analysis, we were able to investigate the evolution of tremor frequencies in the individual arm (Timmer et al., 1997, 1999). The evolution of tremor frequencies in Parkinson's disease has been investigated here for the first time. As in ET, tremor frequencies tend to decrease with time in Parkinsonian rest and postural tremor.

The average decrease of the tremor frequency per year was very similar in ET and PD. The value obtained here for ET (0.12 ± 0.04 Hz/year) is close to the estimate given by Elble (2000) (0.06–0.08 Hz/year). Inspection of Table 2 suggested in ET that the decrease of the tremor frequency per year becomes less prominent with increasing duration of the follow-up. This might indicate that tremor frequencies do not decrease in a linear way. A larger data base is, however, needed to clarify this issue.

The recordings on which the present study is based were done in a routine clinical setting. This means that most patients were under medication which was not necessarily constant during the whole follow-up period. Discontinuing the medication before the tremor recordings would have been hardly tolerable for most of the patients, in particular for patients with long-standing PD. Furthermore, a short-term discontinuation of the medication does not guarantee a complete drug washout. For L-Dopa and bromocriptine, it has been shown, for instance, that the washout period after withdrawal of the medication may be longer than two weeks (Nutt et al., 1995; Hauser et al., 2000; Hauser and Holford, 2002).

Nevertheless, the question arises whether the tremor frequency can be influenced by drug intake. This issue has not received much attention in the literature. There are, however, a number of studies on ET showing that the tremor frequency was not changed by the administration of beta blockers, while the tremor amplitude was clearly reduced (Teravainen et al., 1977; Larsen et al., 1982; Calzetti et al., 1983a,b; Koller, 1986). As to PD, most studies report that levodopa does not change the frequency of rest and postural tremor (Scholz et al., 1988; Tedeschi et al., 1990; Henderson et al., 1994; Blahak et al., 2007) or leads even to a tremor frequency increase (Sturman et al., 2004). There is only one report by Kulisevsky et al. (1995) indicating that levodopa slowed down rest tremor, while postural tremor was accelerated. Other drugs investigated in the treatment of PD tremor (dopamine agonists, amantadine, entacapone, propranolol, primidone, clonazepam) did not reduce the tremor frequency (Koller and Herbster, 1987; Henderson et al., 1994; Sturman et al., 2004). Thus, the overwhelming majority of studies indicate that the decrease of the tremor frequency in ET and PD reported in this study is not an effect of drug intake.

The underlying pathophysiological mechanism that causes tremor frequencies to decrease with time is as yet unclear. One might speculate that this unknown pathophysiological mechanism is common to both ET and PD, since the annual decrease of the tremor frequency is very similar in both disorders. Our data and a study by Elble et al. (1994) on ET demonstrate that age is negatively correlated with tremor frequency. More specifically, Elble (2000) suggested that age-related changes of the cerebellum may contribute to decreasing tremor frequencies in ET (Elble, 2000). This may also be true for PD: in a single case study of a PD patient whose cerebellum was unilaterally resected, the tremor frequency was markedly lower on the side of cerebellar lesion (Deuschl et al., 1999).

The handicap induced by tremor is more related to the tremor amplitude than to the tremor frequency. In the present study, tremor amplitudes were not considered, since the data were obtained in a routine clinical setting. Thus, most patients were under medical treatment for tremor which is supposed to influence tremor amplitudes. Nevertheless, the analysis of the temporal evolution of tremor frequencies has a functional significance. There are several studies demonstrating that tremor amplitudes are negatively correlated with tremor frequencies (Calzetti et al., 1987;

Elble, 1986; Elble et al., 1992, 1994). In other words, low tremor frequencies are associated with high tremor amplitudes and vice versa. It has been argued that this is due to the low-pass filtering properties of muscles and limbs (Elble, 2000). Thus, the decrease of the tremor frequency with time shown here could be an important factor leading to a deterioration of PD or ET by inducing an increase of the tremor amplitude.

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