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Tremor analysis in two normal cohorts

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Abstract

Objective: Quantitative tremor analyses using almost identical methods were compared between two independent large normal cohorts, to separate robust measures that may readily be used diagnostically from more critical ones needing lab-specific normalization.

Methods: Hand accelerometry and surface EMG from forearm flexors and extensors were recorded with (500 and 1000 g) and without weight loading under postural conditions in 117 and 67 normal volunteers in two different specialty centers for movement disorders in Germany.

Results: Tremor amplitude (total power) and frequency fell within a similar range but differed significantly. A significant reduction of tremor frequency under 1000 g weight load (>1 Hz), and a lack of rhythmic EMG activity at the tremor frequency in around 85–90% of the recordings were robust findings in both centers.

Conclusions: The differences in frequency and total power indicate that these measures critically depend on the details of the recording conditions being slightly different between the two centers. Thus each lab needs to establish its own normative data. We estimate that at least 25 normal subjects have to be recorded to obtain normal values. The reduction of tremor frequency under load and lacking tremor-related EMG activity were well reproducible allowing a differentiation of physiological from low amplitude pathological tremor.

Significance: This study provides a framework for more standardized tremor analyses in clinical neurophysiology.

Keywords: Tremor analysis; Standardized; Technique; Physiologic tremor

1. Introduction

Tremor is one of the most common symptoms in clinical neurology. It implies a wide variety of differential diagnoses including monosymptomatic idiopathic and symptomatic forms (Deuschl et al., 1998). Although a careful clinical examination and the history is the most important step towards a diagnostic separation the pathophysiological characteristics of the tremor can help with the diagnosis (Elble, 1998; Hallett, 1998; Louis and Pullman, 2001; Milanov, 2001; Timmer et al., 1993). Therefore, the electrophysiological analysis of tremor using accelerometry and (or) electromyography (EMG) of the affected limbs is considered a valuable complementation of the clinical workup in all tremor patients (Bain, 1993; Findley and Koller, 1987; Koller et al., 1992). Electrophysiological and mathematical methods to analyze human tremor have been described in detail by different authors (Halliday et al., 1995; Timmer et al., 1996) but the electrophysiologic diagnostic tools used for tremor analysis are far from being standardized. Because of the gross methodological differences between labs it has been difficult to define robust measures that can be transferred to other labs using similar methods as opposed to more sensitive measures that will always need lab specific normalization. Therefore, the present study used almost identical tremor analysis algorithms in large samples of normal subjects in two different labs. We will show that robust criteria distinguishing physiologic from early stage, low amplitude pathologic tremors can be defined, whereas

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quantitative measures like frequency and amplitude are very sensitive to the details of the recording condition or technique and therefore need to be normalized for each indiviual lab.

2. Methods

2.1. Subjects

In the movement disorders laboratories of the Departments of Neurology at the Universities of Kiel and Freiburg 117 and 67 normal volunteers were analysed, respectively. The subjects were recruited independently in both centers with the purpose to collect lab specific normative data for tremor analysis. All of them were either hospital staff, their relatives and friends or healthy spouses of patients. Approximately equal numbers in each decade between 20 and 70 and >70 years were recruited in both places. Thus the mean ages and age ranges did not differ significantly between the two normal cohorts. More female than male subjects were examined at both places. This difference was greater in Kiel than in Freiburg (Table 1). All subjects were seen by a neurologist before the tremor recording (J.R/B.K). A general medical history, drug history and family history were taken and a clinical neurological examination was performed. Subjects exhibiting any signs or symptoms of neurological disease, taking tremor active drugs (specifically beta-blocking agents, benzodiazepines, antiepileptics, antidepressants or neuroleptics) or having a positive family history for any kind of tremor were excluded from the study. All subjects were asked to refrain from caffeine intake 2 h before the recording.

All subjects gave informed consent and the study was approved by the local ethics committees at the Universities of Kiel and Freiburg.

2.2. Tremor recording

The setting in which the subjects were recorded was almost identical. They were comfortably seated in an armchair with their forearm supported on the arm rests. Postural tremor was recorded while subjects extended their hands and fingers actively to a 0° position with the resting forearm. This posture was held against gravity only and against an additional weight of 500 and 1000 g in the two loading conditions. Under each of these conditions the tremor was recorded for 30 s. using a piezoresistive accelerometer of about 2 g in both centers and bipolar surface EMG recordings with silver–silver-chloride electrodes from forearm flexors and extensors. In both centers the EMG electrodes were fixed close to the motor points of the ulnar part of the hand extensor and flexor muscles of the forearm thereby preferentially recording the extensor and flexor carpi ulnaris muscles. The accelerometer was fixed on the third metacarpal bone bilaterally. In Kiel it was fixed about 2 cm proximal to the metacarpophalangeal joint, in Freiburg it was attached more distally directly above this joint. The weight was added in 5 by 5 cm flat sacks filled with metal granules which were strapped to the dorsum of the hands covering the accelerometers. In parallel to the differing accelerometer positions the weight load was placed mainly on the metacarpal region of the hands in Kiel and more distally on the distal metacarpals, the metacarpophalangeal joints and the proximal phalanges in Freiburg.

Table 1
Size, age and gender distributions of the two normal populations

	Kiel	Freiburg
n	117	67
Mean age (range)	49,6 (20–94) years	50,3 (23–83) years
Female/male (%)	68/32	57/43

All data were sampled at 800 Hz. The EMG was band-pass filtered between 50 and 350 Hz and full wave rectified. The sampling rate and the filters were identical in both centers (Kiel and Freiburg).

2.3. Data analysis

Spectral analysis was performed using a standard mathematical algorithm implemented in an easy to use commercially available tremor analysis software (Lauk et al., 1999). The exact mathematical procedures are described in detail elsewhere (Lauk et al., 1999). The spectra were calculated between 1 and 30 Hz. The total power of the accelerometrically measured tremor spectra was calculated as a measure of tremor amplitude. Peaks in the power spectra were tested for significance (for mathematical procedure see (Lauk et al., 1999)). In the accelerometry spectra there always was at least one significant peak in all the recordings. In the rare case of more than one significant peak the one with the greatest peak power was considered to reflect the tremor frequency. In the EMG spectra there was a considerable proportion of recordings in which there was no significant peak (see Section 3) indicating a complete lack of rhythmic burst activity. The total power (TP) of the accelerometer spectra was calculated as a measure of the average tremor amplitude in the recorded time series. It is given by the area under the spectral curve in the main frequency band of interest (0–30 Hz). The power of the main peak in the spectrum was also calculated as half-width power. It is given by the area under the curve between two vertical straight lines intersecting the rising and falling edge of the peak at half of the peak power (full-width half maximum). There was a strong linear correlation between total power and half-width power in both centers ($r^2 > 0.9$). This indicates that the spectral tremor peak contains most of the power of the whole spectrum, with narrow peaks only covering a small frequency band but rising to higher power and broad peaks only rising to low power but covering a larger frequency range. Thus total

power and half-width power (power content of the peak) can be regarded as equivalent measures. In the present study we used the total power being more intuitive as a measure of tremor amplitude.

2.4. Statistical analysis

The frequency values and the log-transformed total power values under all conditions and in both places were shown to be normally distributed in the Kolmogorov-Smirnov test ($P < 0.05$). A multifactorial univariate analysis of variance (GLM) was applied to look for significant effects of and possible interactions between recording condition and place (Freiburg or Kiel). Posthoc comparisons were performed using *t*-tests for unrelated (place) and related samples (condition). *P*-values below 0.05 were considered to indicate statistical significance.

3. Results

3.1. Tremor amplitude and frequency are similar but differ significantly between the two centers

The two basic measures characterising a tremor are within the same range in both recording locations but there are significant differences.

Subjects from Freiburg showed a significantly higher total power under all recording conditions ($P < 0.001$). It differed by almost one order of magnitude (Fig. 1). Taking together the results from both places the total power of PT mainly ranged between 0.01 and 0.25 mg^2. Loading the hand did not change tremor total power. There was a slight difference in total power between the left and right side which reached the level of significance ($P < 0.05$) in both places with the left hand showing slightly higher amplitudes in Kiel and the right hand in Freiburg.

The peak frequency of the accelerometer spectrum mainly fell within the 6–12 Hz range in both centers. Although there were some outliers towards higher frequencies there was not a single case in both normal populations with a tremor frequency below 6 Hz. Subjects from Freiburg showed slightly higher frequencies than those from Kiel in the unloaded condition. This difference reached the level of significance ($P < 0.01$). Under 1000 g weight load the frequencies were identical in Freiburg and Kiel (Fig. 2). This interaction between the influence of the recording condition and the influence of the place of recording was significant in the analysis of variance (GLM). It can in effect be explained by the different methods of weight positioning in Freiburg and Kiel (see below).

In both centers the age of the subjects did not have a significant influence on tremor frequency or amplitude. This is discussed in detail in (Raethjen et al., 2000).

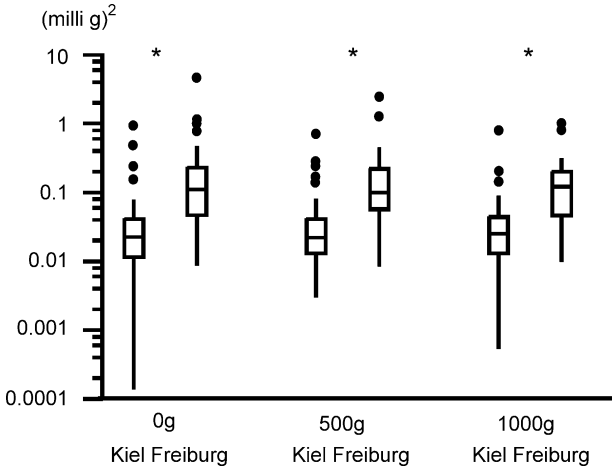

Fig. 1. Distributions of tremor amplitudes as measured by accelerometer total power for both centers under all recording conditions (median, range in $(mg)^2$: 0 g Kiel: 0.02, 0.00014–0.93; 0 g Freiburg: 0.1; 0.0088–4.7; 500 g Kiel: 0.02, 0.003–0.71; 500 g Freiburg: 0.1, 0.0086–2.4; 1000 g Kiel: 0.03, 0.00054–0.8; 1000 g Freiburg: 0.1, 0.01–1.0).The results for the right side are displayed, the results for the left side were almost identical.

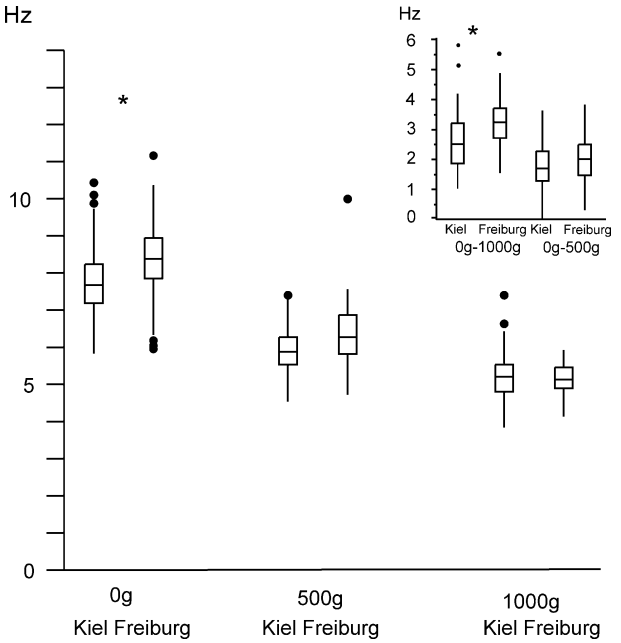

Fig. 2. The main figure shows the frequency distributions in Kiel and Freiburg for all three recording conditions (Mean ± SD/median, range in Hz: 0 g Kiel: 7.8 ± 0.9/7.7, 6.0–10.4; 0 g Freiburg: 8.4 ± 1.0/8.4, 6.0–11.2; 500 g Kiel: 5.9 ± 0.6/5.9, 4.5–7.4; 500 g Freiburg: 6.3 ± 0.8/6.3, 4.7–10.0; 1000 g Kiel: 5.2 ± 0.6/5.2, 3.8–7.4; 1000 g Freiburg: 5.3 ± 1.0/5.1, 4.1–9.7).The small figure at the top right gives the median reduction of tremor frequencies under 1000 and 500 g weight load (Mean ± SD/median, range in Hz: 0 vs. 500 g Kiel: 1.8 ± 0.8/1.7, 0.0–5.4; 0 vs. 500 g Freiburg: 2.0 ± 0.9/2.0, 0.2–3.8; 0 vs. 1000 g Kiel: 2.6 ± 0.9/2.6, 1.0–5.7; 0 vs.1000 g Freiburg: 3.0 ± 1.1/3.2, 1.3–5.6). The asterisks indicate statistically significant differences ($P < 0.05$). Only data from the right side is displayed here. The results on the left were almost identical.

3.2. Reduction of PT frequency under added inertia is a stable phenomenon in both centers

The tremor frequency of PT is highly dependent on limb mechanics. It follows the resonance frequency of the hand. Therefore an additional weight load on the hand reducing its resonance frequency should also lower the tremor frequency. Indeed, this well known effect is equally well visible in both centers as displayed in the inset of Fig. 2. However, the reduction in tremor frequency under 500 and 1000 g load is significantly greater in Freiburg than in Kiel ($P < 0.01$). In 95% of the normal hands examined under 1000 g load the tremor frequency was reduced by more than 2.1 Hz in Freiburg and 1.3 Hz in Kiel. The tremor frequency was reduced by less than 1 Hz only in 3 subjects from Freiburg and 4 subjects from Kiel.

3.3. Rhythmic EMG activity does not differ between centers

In contrast to the accelerometer spectra the EMG spectra only showed a significant peak in a certain proportion of recordings. In both centers there was rhythmic EMG activity in only 50–75% of the recordings depending on the condition and the muscles (flexors or extensors) under study.

In those EMG spectra with a significant peak the frequencies showed very broad distributions between 5 and 25 Hz with the majority of peaks around 12–17 Hz. These distributions did not differ between Freiburg and Kiel (Fig. 3). They were very similar for flexors and extensors. The recording condition did not have a significant influence on the EMG frequencies.

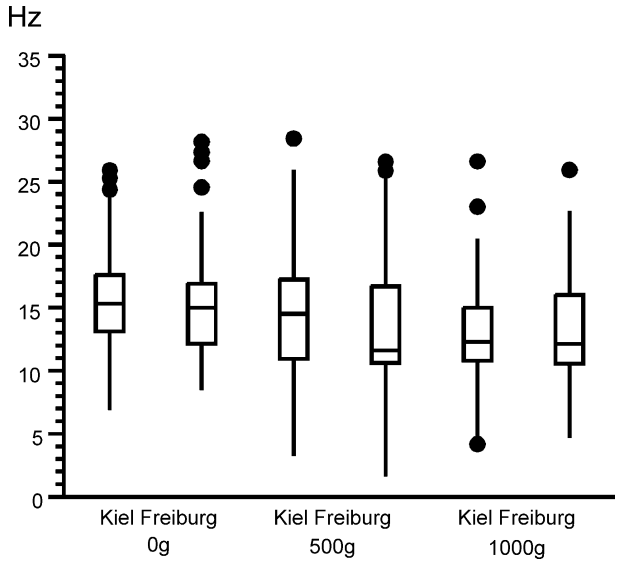

Fig. 3. The medians and distributions of the forearm extensor frequencies are displayed for the right side (Mean ± SD/median, range in Hz:0 g Kiel: 15.7 ± 4.4/15.3, 6.9–25.9; 0 g Freiburg: 15.6 ± 5.2/15.0, 8.6–28.2; 500 g Kiel: 14.3 ± 5.1/14.5, 3.3–28.4; 500 g Freiburg: 14.2 ± 6.3/2.2–26.6; 1000 g Kiel: 12.8 ± 4.4/12.3, 4.2–26.6; 1000 g Freiburg: 13.3 ± 4.7/12.1, 4.8–25.9). Almost identical results were obtained for the left side.

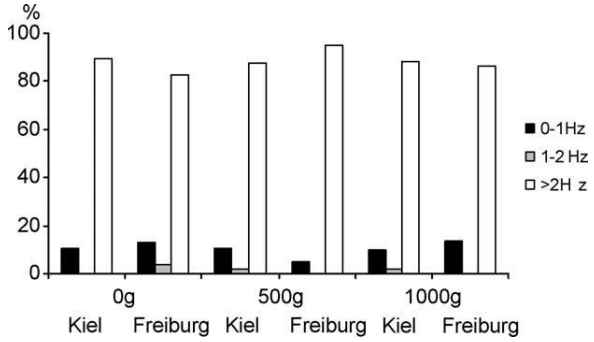

Fig. 4. The proportion of subjects with a significant EMG peak in which the accelerometrical tremor and EMG frequency differ by less than 1 Hz, between 1 and 2 Hz and more than 2 Hz are displayed for the extensor muscles on the right side and the different recording conditions in both centers. Almost identical results were obtained for the left side and the flexor muscles.

3.4. EMG and physiologic tremor frequencies usually differ by more than 2 Hz in both centers

The distribution of the differences between the accelerometrically measured frequency of physiologic tremor and the rhythmic EMG activity (peak frequencies) showed the identical characteristic pattern in the normal populations from Kiel and Freiburg. In the vast majority of recordings with a significant EMG peak (80–95%) the difference was greater than 2 Hz. In those few recordings in which the difference was less than 2 Hz it mostly fell between 0 and 1 Hz. Only in very few recordings did we find a frequency difference between 1 and 2 Hz (Fig. 4). Only in one subject from Kiel did this tremor-related EMG frequency decrease by more than 1 Hz under weight most likely indicating reflex enhancement of physiologic tremor. In the other recordings with tremor-related EMG-activity its frequency often increased but never decreased under weight. The tremor frequency in these cases was close to the mean tremor frequency in both centers and was independent of the subjects' age. Only in one of the recordings with tremor-related EMG activity was the reduction of the acclerometrically measured main tremor frequency under weight less than 1 Hz.

4. Discussion

A great variety of mostly non-standardized accelerometer or EMG recording techniques from tremulous limbs are used as clinical neurophysiological diagnostic procedures in tremor disorders. Widely accepted standards for electrophysiological tremor diagnostic procedures are largely lacking. In the present study we used almost identical methods for tremor recording and analysis using virtually the same hard and software in two distant and independently operating specialty centers for movement

disorders in Germany. It was well applicable in a clinical setting, and the quantitative results were very similar.

However, the mean tremor frequency although within the 6–12 Hz range in both centers was significantly higher in Freiburg than in Kiel. This cannot easily be explained by differences in the recording conditions. The accelerometer was attached to the hand in both centers and the hand frequency should be independent of the position of the accelerometer on the metacarpum which was different in the two centers. One way in which the tremor frequency could be altered systematically would be through differing limb mechanics (Elble and Randall, 1978; Raethjen et al., 2000). Subjects from Freiburg could have had lighter hands than subjects from Kiel. This seems extremely unlikely since the proportion of women was greater in Kiel than in Freiburg. Women generally have smaller hands than men and this has been shown to result in significantly higher physiological tremor frequencies (Raethjen et al., 2000). Another mechanical factor influencing the hand tremor is wrist stiffness. The greater the wrist stiffness the higher is the hand tremor frequency (Elble and Randall, 1978). Only a slightly increased coactivation of forearm muscles may therefore lead to a small increase in tremor frequency. A systematic bias towards more coactivation may be induced by only little differences in the way the hand is held against gravity. Such a difference may be due to different recording chairs and armrests as well as slightly different instructions to the patients. Age has also been discussed to influence physiological tremor frequency. But there was no significant difference in age between the two cohorts. In a previous study we did not find a significant correlation between age and tremor frequency (Raethjen et al., 2000) and we reproduced this finding at both sites in the present study. Other factors like tremor active medication or a history, family history or sign of pathological tremor have been excluded equally in both places before subjects were included in the study.

While the frequency distributions still fell within the same range with a large overlap between the values in Freiburg and Kiel, the total power differed by almost one order of magnitude. This greater difference in total power can be explained by systematic differences in the recording condition. While the accelerometer was placed in the proximal and mid-dorsal metacarpum in Kiel it was positioned on the very distal end of the metacarpal bone in Freiburg. This greater distance between the rotation axis of the wrist joint and the accelerometer position leads to the registration of increased tremor excursions as compared to the more proximal position. The position of the added weight also differed between Kiel and Freiburg as it was placed directly on the accelerometer in both centers. The more distal the weight is placed the greater the moment of the exerted force and the greater the effect on the resonance frequency of the hand. This is why the physiological tremor frequency was significantly more reduced in Freiburg than in Kiel although the weight was the same in both centers.

Thus the details of the recording condition have a clear influence on the normative data for tremor frequency, tremor amplitude and the amount of frequency reduction with weight. As shown in the present study there will always be some differences in the recording conditions between different labs even if almost identical recording procedures are used. Therefore, each lab will have to create its own normative data for tremor frequency (accelerometric peak frequency) and tremor amplitude (accelerometric total power). The variance of the presented data did not differ significantly between the two sites and can be used to calculate the 95% confidence interval of the estimated normal range (± 2 standard deviations) in relation to the number of normal subjects recorded. The present data suggest that $n = 25$ subjects are necessary to obtain normative data with a precison of $\pm 0{,}5$ Hz and $\pm 0{,}15$ log $(\text{mg})^2$.

In contrast to the quantitative measures discussed above there were two characteristics of physiologic tremor which were found very similarly in both places and seem to be diagnostically relevant. Pathological tremors generally are of central origin (Deuschl et al., 2001; Elble, 1996; Hallett, 1998). They typically show constant frequencies under weight load (Deuschl et al., 1996; Elble, 1986) as the central rhythmic drive by definition is largely independent of the peripheral mechanics that is the resonance frequency of the trembling limb. This central rhythmic drive can only cause the hands to tremble through the muscles. Thus another characteristic of pathological central tremors is an EMG burst activity at the tremor frequency driving the rhythmic movements of the tremulous limb (Deuschl et al., 2001). Both of these characteristics of central pathological tremors are lacking in the vast majority of the normal controls analysed in the present study. In both centers we found a clear reduction of the accelerometric tremor frequency under weight load by more than 1 Hz and there were hardly any cases in which we found rhythmic EMG activity at the tremor frequency. These findings were very robust and did not differ between the two centers. Thus they are very reliable markers of physiological as opposed to pathological tremors and can readily be used diagnostically to separate the two. They are diagnostic criteria beyond a mere measurement of the tremor amplitude which will by definition be larger in pathological tremors but definitely needs lab specific normative data before it can be used diagnostically. Rhythmic EMG activity at the tremor frequency as well as a constant tremor frequency under weight load may well be detectable before the tremor amplitude actually rises to pathological values (Elble, 1998). Therefore the tremor analysis method dealt with in the present paper is powerful in the early distinction between an evolving pathological central tremor and normal physiological tremor (Elble, 2003). The recording of surface EMG in parallel to the accelerometric tremor recording is

a crucial factor in electrophysiological tremor analysis largely increasing its diagnostic value.

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