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Determinants of physiologic tremor in a large normal population

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Abstract

Objectives: It has been well established that peripheral mechanical resonant factors as well as central mechanisms may play a role in the generation of physiological tremor (PT). Furthermore it has been postulated that subject's attributes like age and sex might influence PT. The present study was designed to quantify these influences on PT in a large normal population.

Methods: Physiological hand and finger tremors were measured in a group of 117 normal subjects between 20 and 94 years of age using accelerometry and surface EMG recordings from the forearm flexor and extensor muscles. The hand tremor was measured in a postural position with and without weight, and the finger tremor was recorded with the arm outstretched, forearm supported and hand supported. Hand volume and grip force were measured in each subject.

Results: Hand tremor frequency (mean 7.7 Hz) was reduced significantly by added inertia (mean 5.2 Hz) and it was negatively correlated with hand volume while there was no correlation with grip force. Finger tremor showed, subject to the arm position, maximally 3 and at least two distinct frequency bands (1–4, 6–11 and 15–30 Hz) reflecting the resonance frequencies of the whole arm, the hand and the finger, respectively. A significant EMG peak was found in 50–80% of the recordings. This EMG synchronization gave rise to a corresponding accelerometer peak or a significant EMG-EMG coherence in about one-third of the population indicating a central component of PT because its frequency was unaffected by mechanical changes in the periphery. We did not find a significant influence of age on the tremor frequency, while the sex of the subjects slightly but significantly changed the frequency range of hand tremor. Multiple partial correlations revealed, however, that the only direct influence on hand tremor frequency is the hand volume indicating that the influence of sex on hand tremor frequency is an indirect effect produced by the significantly larger hands of male subjects.

Conclusions: In conclusion, the main determinants of PT are the mechanical properties of the oscillating limb. Apart from the dominating peripheral resonance mechanism we found indications of an additional central component of PT in about one-third of the normal population. There was no age dependence of tremor frequency and it was shown that the influence of the subjects' sex on tremor frequency only represents an indirect mechanical effect.

Keywords: Physiologic tremor; Peripheral resonance; Central generation; Age; Sex; Accelerometry; EMG

1. Introduction

Physiological tremor (PT) of the hands and fingers has been extensively studied (Schäfer et al., 1886; Friedlander, 1956; Halliday and Redfearn, 1956; Marshall and Walsh, 1956; Brumlik, 1962; Marsden, 1978; Elble, 1995) but an overall quantification of the different influences determining the properties of PT is still lacking. Two main mechanisms were shown to drive physiologic tremor: Mechanical resonance at the Eigenfrequency of the oscillating limb is one of the sources of PT. It has been postulated that those motor units firing coincidentally at this resonant frequency cause the limb to oscillate (Stiles and Randall, 1967; Elble and Randall, 1978); additionally, this rhythm is fed back into spinal reflex loops which can in turn further enhance the tremor (Hagbarth and Young, 1979). The second influence on PT is a central drive originating from hypothesized oscillators within the CNS (Elble and Randall, 1976; Elble, 1996). This central component of PT is reflected by synchronized EMG bursts mainly in the 7–13 Hz band which can be found in some normal subjects in addition to the unsynchronized background EMG activity (Allum et al., 1978). Both of these mechanisms have been well established and are widely accepted to play a role for the generation of PT. However, the question as to which degree peripheral mechanisms determine PT compared to the central drive remains unclear as most of the previous studies were aimed only at characterizing one of the two mechanisms in a small number of subjects.

Apart from these direct factors the subjects' attributes like

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age and sex might act as more unspecific and indirect determinants (Lakie, 1995). The results of the studies addressing these issues gave rise to conflicting results. While several authors found a clear age dependence of tremor frequency (Marsden et al., 1969; Birmingham et al., 1985) another study could not reproduce this (Elble, 1986). One of the problems of these studies is the limited number of recording conditions and accelerometric recording sites which makes a comparison between different studies and an overall interpretation of the currently available data extremely difficult.

The present study is aimed at overcoming these problems by analyzing physiological hand and finger tremors in a large sample of normal subjects from all age groups under a number of different conditions using a statistical time series analysis algorithm (Timmer et al., 1996; Lauk et al., 1999a). The mechanical properties of the oscillating system (hand) and the driving system (forearm muscles) are monitored by measuring the individuals' hand volume and grip force at the time of the recording.

We will show that the characteristics of normal physiological tremor are highly dependent on the posture and mechanics of the oscillating system indicating strong peripheral resonance mechanisms. The EMG spectrum is largely independent of such peripheral factors and at least partly reflects rhythmic central input which is strong enough to give rise to an additional centrally driven component of PT in a proportion of normal subjects. In the vast majority of subjects we did not find any evidence of reflex loops enhancing the mechanical resonance. There was no consistent correlation between age and tremor frequency. It will be shown that this is in good accordance with the mechanics of the oscillating system as the main influence on PT in all age groups. Preliminary results have been published in abstract form (Raethjen et al., 1998).

2. Methods

2.1. Subjects

One hundred and seventeen healthy volunteers from different age groups between 20 and 94 years (for age distribution see Table 1) were recruited from hospital staff, their friends and relatives and from old people's homes close to the hospital. Exclusion criteria were medication with centrally acting drugs or with drugs known to induce tremor and the presence of neurological or systemic disease or orthopedic forearm or hand problems. The subjects were asked to avoid caffeine intake for at least 2 h prior to the investigation. A thorough medical history was taken and a neurologic examination was performed to be sure not to miss an exclusion criterion. The protocol was approved by the local ethical committee of the University of Kiel and informed consent was given by all subjects.

Table 1
Age and sex distribution of the normal population of the present study

Age group (years)	Mean (years)	Range (years)	*n*	Male	Female
20–29	25	23–29	20	8	12
30–39	33.4	30–38	20	6	14
40–49	43.4	40–49	20	7	13
50–59	53.8	50–59	20	5	15
60–69	62.7	60–68	19	7	12
>70	83.4	71–94	18	5	13

2.2. Tremor recording

Hand and finger tremors were recorded in all subjects. They were seated comfortably in an armchair. Hand tremor was recorded with the subjects' forearms on the armrests of the chair under rest and postural conditions. In the case of the rest condition subjects were asked to relax their arm and let their hand hang freely from the arm rest. Under the postural condition they were asked to hold their hands in a 0° position with the supported forearm. The postural hand tremor was recorded unloaded and with 500 and 1000 g weights fixed on the dorsum of the hand. Finger tremor was recorded with the hands supported and the fingers extended to the level of the hands, with the forearms supported and the hands and fingers stretched out and with both arms held out straight at shoulder level. The duration of each recording was 30 s.

The actual mechanical tremor was measured by two unidirectional piezoelectric accelerometers weighing 2.5 g each. They were fixed on the dorsum of both hands on the distal part of the third metacarpal bone or on the dorsum of the index finger on the distal phalangeal joint. The acceleration of the hand was measured in gravities and it was displayed as milli-gravities^2 in the power spectra. The corresponding tremor activity of the muscles was recorded by bipolar surface EMG from the hand flexors (Flexor carpi ulnaris) and extensors (Extensor carpi ulnaris) or index finger flexors (index finger portion of the Flexor digitorum sublimis) and extensors (Extensor indicis), respectively. Silver-chloride electrodes were fixed 2–3 cm apart close to the motor points of the muscles. The EMG amplitudes were measured in μV and they were displayed as $(\mu V)^2$ in the power spectra. The sampling rate was 800 Hz and the EMG data were band pass filtered between 50 and 500 Hz on-line. Before the analysis the EMG was full wave rectified.

2.3. Data analysis

Power spectra were calculated for each of the EMG and accelerometer channels using a stochastic time series analysis method (see Timmer et al., 1996 for a detailed description of the mathematical methods). The accelerometer and the EMG peak frequencies were calculated and the total power of the spectra was analyzed as a measure of tremor amplitude.

EMG-EMG coherence spectra were calculated on the basis of the cross-spectrum and the individual autospectra of the flexor and extensor muscles of the same forearm (Timmer et al., 1996). Before calculating the coherence those pairs of EMG data containing an amount of mutual cross-talk which was critical to the coherence estimate were excluded from further analysis. Cross-talk was estimated from the cross-correlation function on the basis of a special mathematical model which was verified by extensive simulation studies published previously (Raethjen et al., 2000). A significant coherence between extensor and flexor muscles from the same arm reflects a common multivariate process underlying the respective power content of the EMG spectra at the peak frequency most likely indicating a common central origin of the oscillation (Lauk et al., 1999b).

With this interpretation of coherence in mind one might assume that the coherence between EMG and accelerometer recordings from the same limb could be regarded as an estimate of the causal relationship between EMG synchronization and the power content of the tremor spectrum at the EMG frequency even in the absence of a significant accelerometer peak. On theoretical grounds, however, this assumption does not hold true as we know that the main sources of the power in the accelerometer spectrum are rhythmical and non-rhythmical muscle contractions as measured by the surface EMG (Timmer et al., 1998). Therefore, the theoretical coherence between EMG and tremor (accelerometer) should be very high across all frequencies and only the high noise level in the EMG recordings breaks down this theoretically strong coherence. Therefore, a peak in the coherence function between EMG and accelerometer at the EMG peak frequency merely reflects the substantially higher signal to noise ratio at this frequency and cannot be interpreted as an indication of a significant influence of the EMG rhythm on the tremor unless there is a coincident significant accelerometer peak. Therefore, we did not calculate EMG accelerometer coherence and estimated the overall influence of the EMG frequency on the tremor spectrum in our normal population by the incidence of a significant accelerometer peak at the EMG frequency.

2.4. Measurement of mechanical hand properties

The hand volumes were measured by collecting the water displaced by the subjects' hands which were dunked into a container filled with water. The maximal hand grip power was measured with a hand dynamometer (Martin Vigorimeter). These measurements were performed after the tremor recording to avoid an enhancement of the physiological tremor by hand exertion. They were repeated 3 times and the maximal value was used.

2.5. Statistical analysis

All sets of data were tested for normal distribution by the Kolmogorov–Smirnov test. In the case of a normal distribution Student's t test for unpaired or paired samples or an ANOVA for the comparison of more than two groups was performed. In the case of not normally distributed sets of data the Mann–Whitney U test, the Wilcoxon matched pairs signed ranks test or the Kruskal–Wallis test was used. In the case of more than two paired groups the Friedman two way ANOVA was utilized. Dichotomous paired data were compared using the McNemar χ^2 test. Statistical analysis of linear correlations was performed by the Pearson's correlation coefficient when the analyzed data were normally distributed and by the Spearman's rank correlation coefficient in the case of not normally distributed data. Multiple partial correlations were used to estimate multivariate interrelations. Partial correlation analysis allows a distinction between direct and indirect relationships and can disclose hidden dependencies. P values below 0.05 were considered to indicate statistical significance.

3. Results

3.1. Peripheral mechanical influences on PT

The intrinsic mechanical hand properties were correlated with the tremor frequency and the effect of deliberate modifications of those hand properties by adding inertia or changing the posture of the arm was analyzed in all subjects. While most of the accelerometer data described here were recorded from the hand, the effect of changing arm postures was analyzed for the index finger tremor because the influence of arm posture should be most pronounced in the most extreme part of the limb. Apart from the tremor frequency we also analyzed total power as a measure of tremor amplitude which showed a logarithmic distribution with a median of 0.026 milli-gravities^2 and was largely independent of the postural recording condition. The total power under the resting condition, however, was about one order of magnitude lower than under the postural condition. This finding is in line with the definition of PT as a postural tremor (Fig. 1). Therefore, only the postural recording conditions were subsequently analyzed. Postural tremor amplitude was slightly higher on the left than on the right side and this difference reached the level of significance under all conditions (Wilcoxon test, $P < 0.05$).

3.1.1. Hand tremor frequency changes with added inertia

The main frequency band of classical physiological postural hand tremor was normally distributed between 6 and 11 Hz with a mean frequency of 7.7 Hz and there was no significant difference between the left and right sides. When adding weight to the hand the mean frequency dropped highly significantly (t test, $P < 0.0001$) to 5.9 Hz under 500 g and to 5.2 Hz under 1000 g weight load. The difference between the 500 and 1000 g conditions was also highly significant (t test, $P < 0.0001$). Fig. 2 illustrates the frequency distribution under different recording conditions. Only significant peaks were displayed including the largest, load-dependent peak, a remaining peak around 10 Hz and

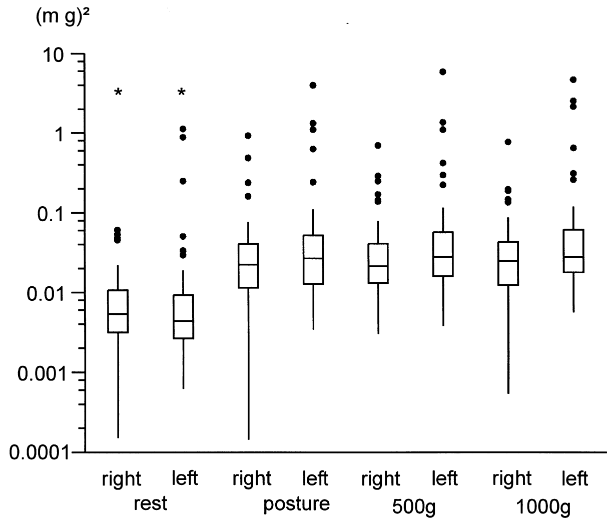

Fig. 1. Total power as a spectral measure of tremor amplitude under the different hand tremor conditions. The total power distribution is displayed by box and whisker plots for the right and left hand separately. The horizontal lines of the boxes represent 25th, 50th (median) and 75th percentiles of the distribution. The whiskers show the extremes of the distribution except for the outliers displayed separately. The total power is given in milli-gravities. The difference between the postural conditions and the rest condition was significant (Friedman ANOVA + post-hoc comparisons, $P < 0.001$ for both sides) as indicated by the asterisks. The difference between the left and right sides also reached statistical significance, the left hand showing more tremor under the postural conditions and the right hand exhibiting stronger tremor under the rest condition.

very rare higher frequency peaks in the 20–30 Hz range (Fig. 2A). These higher frequency bands largely consisted of spectral peaks occurring in addition to the main peak in the 6–11 Hz range. An example of such a spectrum with an additional peak under weight load is given in Fig. 2D. These additional 10 Hz peaks usually occurred at the frequency of significant EMG synchronization which will be dealt with in detail in a later section of this paper.

3.1.2. Finger tremor frequency is dependent on arm posture

When recording the physiological finger tremor by accelerometer the distribution of peak frequencies was highly dependent on the recording condition. When the hand and forearm were supported and only the outstretched index finger which carried the accelerometer could move freely, two frequency bands could be separated. The lower frequency band in the 6–13 Hz range appeared to be equivalent to the frequency bands which were detected when measuring the hand tremor and it was in the range of the hand's resonant frequency; the much broader higher frequency band around 16–30 Hz is specific to the finger tremor and lay within the finger's resonant frequency band (Halliday and Redfearn, 1956; Lippold, 1970) (Fig. 2B).

When the hand was stretched out and only the forearm remained supported the 16–30 Hz band was clearly attenuated while the 6–13 Hz band became much more prominent. This is illustrated by the frequency distribution in Fig. 2B for the right side. The mean frequencies of the prominent 6–13 Hz peak (8.3 ± 1.9 Hz on the right and 8.2 ± 1.5 Hz on the left) fell within the same frequency band as the postural hand tremor.

When neither the hand nor the forearm were supported and the whole arm was held outstretched the frequency distribution of the accelerometry showed two clear peaks (Fig. 2B). The 6–13 Hz peak remained unchanged compared to the previous two conditions. The second peak appeared in a lower frequency band between 2 and 4 Hz while the higher frequency component in the 16–30 Hz range was further attenuated compared to the condition with the forearm supported. As the 2–4 Hz frequency range was not seen under the other two conditions it is most likely linked to the freely oscillating arm around the shoulder joint which again is supported by the fact that the resonant frequency of the arm has been reported to be in this range (Fox and Randall, 1970).

In most subjects only one frequency peak in one of the different concurrent bands reached the level of significance and was therefore included in the distribution. There were some subjects, however, who exhibited frequency peaks in more than one of the bands at the same time, an example of which is shown in Fig. 2C.

3.1.3. Hand tremor frequency is correlated with hand volume but not with grip force

The mechanical hand properties were correlated with the tremor characteristics. There was a clearly significant albeit relatively weak negative correlation between the accelerometer frequency and the hand volume which was present equally on both sides (Pearson's correlation coefficient: right, $r^2 = 0.0926$, $r = 0.3$, $P < 0.001$; left, $r^2 = 0.1064$, $r = 0.33$, $P < 0.001$) in the unloaded postural hand tremor condition and the forearm supported finger tremor condition. It disappeared when the hands were loaded with extra weight. The correlation between postural tremor frequency and hand volume is illustrated in Fig. 3 for the right hand.

The grip force did not show any significant correlations with the accelerometric hand and finger tremor frequencies. As the hand volume is directly proportional to hand weight this result is in line with the strong influence of resonance on the hand tremor frequency. The grip force is a more complicated measure reflecting the active muscular mechanics of the hand muscle oscillator which obviously does not have as direct an influence on tremor frequency.

There was no consistent correlation between the mechanical hand properties and the total power (TP) of PT.

3.2. EMG synchronization and its influence on PT

The power spectra of the surface EMG recorded in parallel with accelerometry from the forearm flexors and extensors were calculated and significant peaks indicating an EMG synchronization at the peak frequency were determined. As the surface EMG is recording multiple single

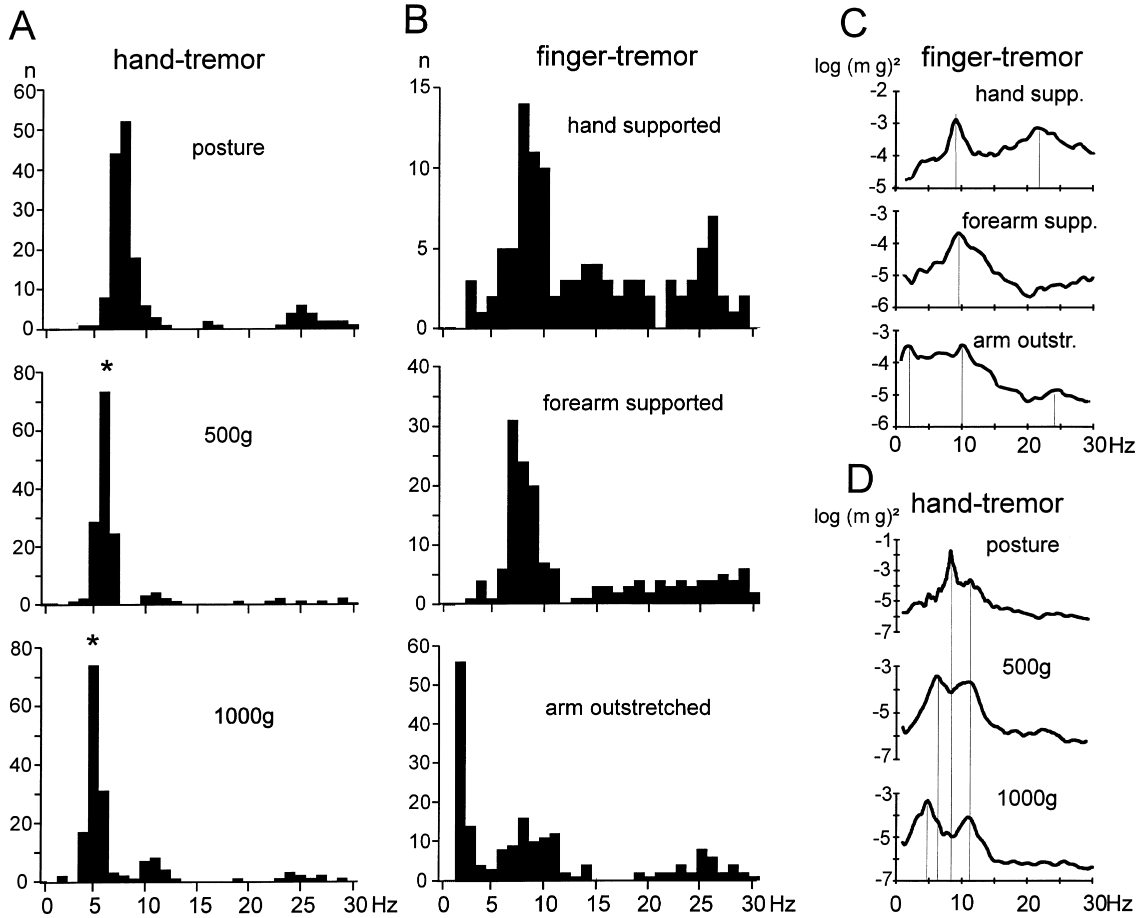

Fig. 2. Distributions of accelerometric peak frequencies under the different recording conditions. The frequencies are displayed representatively for the right side but the results of the other side were essentially the same. (A) The main frequency band of the hand in the 6–12 Hz band clearly dropped under added weight (Wilcoxon test: posture 500 g, $P < 0.001$, 500–1000 g, $P < 0.001$). There was a small amount of remaining peaks in the 10 Hz range under weight load of the hand. (B) Finger tremor showed 3 distinct frequency bands (2–4, 6–12 and 15–30 Hz) which strongly depend on the arm position. (C) Examples of coincident occurrence of the different peaks within the same spectra. (D) Example of an additional hand tremor peak around 10 Hz which is not influenced by weight.

motor units its synchronization allows the best estimate of a possible central rhythmic drive to the muscles, that is the central component of PT. As the EMG amplitude measured by the total power of the EMG spectra is highly dependent on parameters like skin resistance, muscle and electrode location we concentrated on the peak frequencies to characterize the EMG spectra.

3.2.1. Significant EMG synchronization is only found in 50–80% of the recordings

In contrast to the accelerometer spectra only a certain proportion of the EMG spectra showed significant peaks. We found a burst synchronization with significant spectral peak only in 50–80% of the EMG recordings. The occurrence of significant peaks was more frequent in the flexors as compared to the extensor muscles on both sides. As illustrated in Fig. 4A the extensor muscles showed significant peaks in 55% when taking into account all the recording conditions of hand and finger tremors compared with 63% for the flexor muscles. This difference between flexors and extensors was statistically significant under all the hand tremor recording conditions and the first two finger tremor conditions on the left and under one hand tremor and one finger tremor condition on the left. In the finger tremor recording with the arm outstretched this relationship was

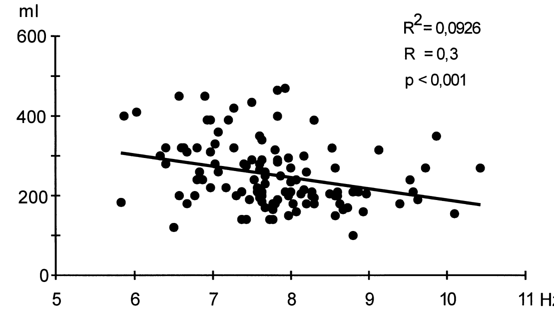

Fig. 3. Correlation between hand volume and frequency of physiological hand tremor. Hand tremor frequency is plotted against hand volume for the right side.

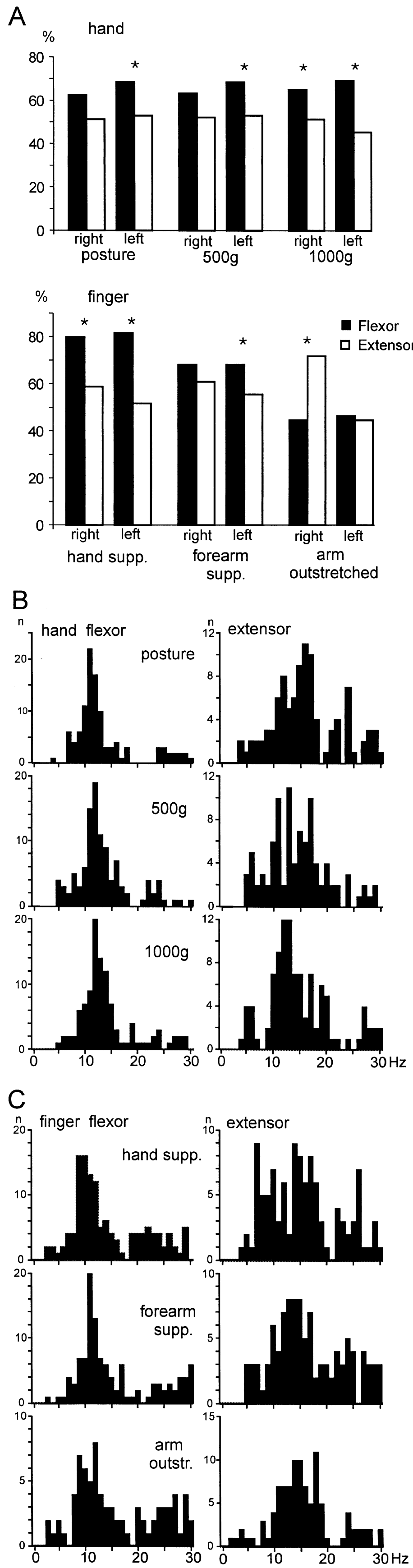

Fig. 4. The EMG synchronization in PT. (A) Percentage of subjects in whom we found significant EMG peaks in the respective muscles. Significant peaks were found slightly more often in the flexor than in the extensor muscles. Asterisks indicate statistical significance of this difference (McNemar test, $P < 0.05$). (B) Distributions of the significant EMG peak frequencies of the hand muscles under the 3 different recording conditions. (C) EMG peak distributions of the finger muscles.

reversed with the extensors showing significantly more frequent EMG peaks than the flexors (McNemar test, $P < 0.05$). While the proportion of significant EMG peaks did not differ between the different postural hand tremor recordings there was a slight decrease of significant flexor and extensor EMG peaks when the hand and arm were stretched out compared with the hand supported recording condition of finger tremor (Fig. 4A).

We found significant EMG peaks in the same muscle under all 3 hand or finger tremor conditions in only between 17 and 25% of the subjects depending on the muscle and the side of the body. Only around 5% of all the analyzed subjects showed a significant EMG synchronization in both the extensor and flexor muscles under all the postural hand tremor and finger tremor recording conditions. These percentages indicate that the EMG synchronization is neither very stable across different subjects of the normal population nor across different muscles and recordings within the same subject.

3.2.2. EMG peak frequency is variable but shows a clear preference of the 8–18 Hz band

The EMG peak frequencies showed a greater scatter than the accelerometer frequencies indicating a greater variability. This variability in EMG synchronization became evident when comparing the EMG frequencies between flexor and extensor muscles from the same side in those 35% of subjects with coincident EMG peaks in both muscles. In only 6–12% of those subjects did we find differences of less than 1 Hz between both muscles and the majority showed differences of more than 3 Hz. However, the EMG peak frequency histograms of the whole population (Fig. 4B,C) showed a close to normal distribution within a specific main frequency range between 8 and 18 Hz for the hand (Fig. 4B) and finger tremor recordings (Fig. 4C). The extensor frequency distribution was broader than the flexor distribution and extended to higher frequencies across all recording conditions with the main frequency band remaining in the 8–18 Hz band, however (Fig. 4B,C). The frequency distributions are only displayed for the right side in Fig. 4 as they were in exactly the same range on both sides of the body.

3.2.3. Mechanical limb properties do not affect the EMG peak frequencies

Although the EMG peak frequencies differed considerably between different recordings and different conditions there was no effect of the recording condition on the EMG frequencies. In contrast to the decrease of the accelerometer frequency under weight load or the different accelerometric frequency bands appearing under the different finger tremor recording conditions, the EMG peak frequencies did not show any systematic changes under different recording conditions. When comparing the different rows of Fig. 4B,C it is evident that the flexor and extensor frequencies remain in exactly the same range. This constancy of EMG frequencies was seen bilaterally. It demonstrates that the EMG synchronization is largely independent from peripheral mechanical influences. On the single case level we found a parallel decline of EMG and accelerometer frequency under weight in only two out of the 117 subjects.

3.2.4. EMG synchronization causes significant tremor in about 20% of subjects

When comparing the distributions of the accelerometric frequencies and the EMG peak frequencies it is obvious that the EMG peak frequency band is much higher than the actual tremor frequency as measured by accelerometry. However, there was a small proportion of subjects with an additional higher frequency accelerometric peak which remained constant under weight load (Fig. 2A,D). Most of these higher frequency peaks occurred at the EMG frequency. Two examples of such cases are given in Fig. 5A displaying the EMG and tremor spectra for two different subjects under the 500 g hand tremor recording condition. We found an additional significant higher frequency accelerometer peak corresponding to the EMG peak (differing by less than 1 Hz) in 13–28% of the population depending on the side and the recording condition (Fig. 5B). The proportion of coincident accelerometer and EMG peaks at the same frequency was slightly higher for the finger tremor recordings than the hand tremor recordings. In the case of finger tremor, synchronization between EMG and accelerometer was encountered more regularly on the right than the left side (Fig. 5B). The frequencies of the EMG peaks leading to an additional accelerometer peak fell within the main frequency band between 8 and 18 Hz (see Fig. 4) with some preference of the frequencies between 10 and 14 Hz as can be seen by the additional peak in the accelerometer frequency distribution in Fig. 2A. The proportion of subjects with an additional accelerometer peak at the EMG frequency slightly decreased when the resonant frequency of the oscillating system was lowered by added weight or a different arm posture (Fig. 5B).

This comparison between the accelerometric and EMG data shows that the EMG synchronization which mostly

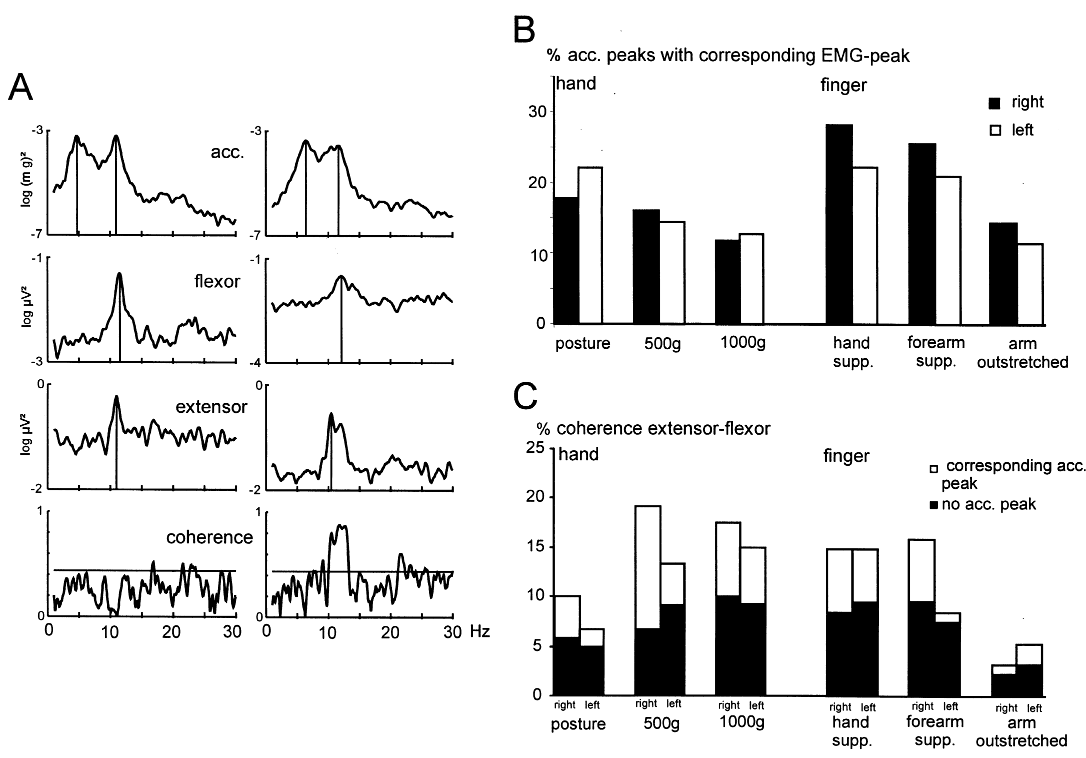

Fig. 5. Central mechanisms in PT. (A) Two single case examples of hand tremor spectra recorded under 500 g weight are given. In both cases a strong influence of the EMG peaks on the accelerometer spectrum is demonstrated by a significant accelerometric peak at the EMG frequency. This peak appears in addition to the peripheral peak which has been lowered by the 500 g load already. The bottom traces show the coherence between flexor and extensor muscles. Although the EMG and accelerometer spectra look very similar in both cases only one shows a clearly significant EMG-EMG coherence. (B) Percentage of subjects showing an EMG influence on PT under the different recording conditions. (C) Percentages of significant coherences between flexors and extensors, the black part of the columns representing those cases with no concurrent corresponding accelerometer peak at the EMG frequency, and the white part of the columns representing cases with such an additional accelerometer peak.

occurred at higher frequencies than the tremor frequency and which was independent of mechanical influences gives rise to a significant tremor only in a certain small proportion of subjects.

3.2.5. Significant coherence between flexor and extensor muscles is found in about 10% of the subjects

After the exclusion of recordings with significant myoelectrical cross-talk (see Section 2) the coherence spectra between flexors and extensors were calculated for all recordings with a significant spectral peak in at least one of the two muscles in the main frequency range of the EMG between 8 and 18 Hz. Only 5% of the recordings had to be excluded from the analysis because of excessive mutual cross-talk which could artifactually influence the coherence spectrum. As displayed in Fig. 5C the proportion of subjects with a significant flexor–extensor coherence differed considerably between different recording conditions between 5 and 20%. Two examples of coherence spectra between flexor and extensor muscles are given at the bottom of Fig. 5A, the right exhibiting a highly significant coherence, and the left no coherence. In the case of hand tremor the number of coherent EMG recordings increased with added inertia (Fig. 5C, left). In finger tremor the number of coherent recordings decreased when the hand or arm was not supported. The question as to how much the proportion of subjects with a significant coherence between extensor and flexor muscles overlap with the group of subjects with a significant higher frequency accelerometer peak at the EMG frequency is addressed in Fig. 5C as well. The white part of the columns indicates the proportion of subjects exhibiting both the coherence and higher frequency accelerometer peak at the EMG frequency. It becomes clear that the majority of subjects with a significant coherence do not show a corresponding accelerometer peak although there obviously is a considerable overlap. As illustrated in Fig. 5A both phenomena seem to be relatively independent from each other. Both examples in Fig. 5A show very similar EMG and accelerometer spectra with close to equal frequencies in flexors and extensors and a significant accelerometer peak at the EMG frequencies, but only in one case is there a highly significant coherence between flexors and extensors at the EMG frequencies while in the other case flexors and extensors are not coherent at all. This striking finding will be discussed later.

3.3. Additional independent influences on PT

Apart from direct passive and active influences of the oscillating system on the oscillation itself physiological tremor may depend on the subjects' characteristics like age and sex. Such indirect influences on PT may be secondary to age- or sex-dependent changes in the mechanics of the oscillating system. This will be tested by correlating the subjects' age and sex with the tremor characteristics and the measures of mechanical hand properties described above.

3.3.1. PT frequency is lower in male than in female subjects due to larger hands in males

The frequencies of the physiological hand tremor in the male subjects was significantly lower than in the females (t test, $P < 0.01$). The median frequency was 7.83 Hz on both sides for the females and only 7.4 Hz on the right and 7.3 Hz on the left for the males. The frequency distributions for the male and female subjects are displayed in the same histogram in Fig. 6A for both sides. The tremor frequencies of the male subjects mainly occurred at lower frequencies. With added inertia this difference was not as clear and failed to reach the level of significance. The tremor amplitude as measured by total power only showed a tendency towards slightly higher values in male subjects but failed to reach the level of significance. The EMG frequencies and the extent of EMG synchronization and coherence as well as tremor amplitude were independent from sex.

As illustrated in Fig. 6B the hand volumes and the grip force were significantly greater (Mann–Whitney U test, $P < 0.005$) in the male than in the female subjects (hand volume: male right hand mean, 334.5 ± 70.1 ml; male left hand mean, 328.5 ± 66.9 ml; female right hand mean, 215.6 ± 55.1 ml; female left hand mean, 207 ± 55 ml; grip force: male right hand mean, 106.7 ± 30.8 kPa; male left hand mean, 103.2 ± 26.9 kPa; female right hand mean, 73.1 ± 22.9 kPa; female left hand mean, 63.6 ± 22.1 kPa). In the multiple partial correlation analysis between hand volume, grip force, sex and hand tremor frequency the correlation between sex and frequency disappeared as soon as it was controlled for hand volume, indicating that sex does not have a direct influence on frequency but only acts through the difference in hand volume between male and female subjects.

3.3.2. PT frequency is independent from subjects' age

The results from the different finger and hand tremor recording conditions did not show a consistent change with increasing age of the subjects. This was tested by bivariate correlation analyses (Pearson's correlation coefficient) and multiple group comparisons between the different age groups and is shown for hand and finger tremors in Fig. 7A,B. To test for a hidden dependency between age and frequency we again performed multiple partial correlations between the mechanical hand properties, sex, age and frequency. This analysis confirmed the results of the bivariate correlation in that there was no hidden age dependence of frequency on both sides.

The amplitude of PT as measured by accelerometer total power did not show significant differences between different age groups nor did the extent of the EMG synchronization or coherence and the EMG frequency show any consistent changes with age.

3.3.3. Frequency determining mechanical hand property remains constant across age groups

In multiple partial correlations we found that of all the

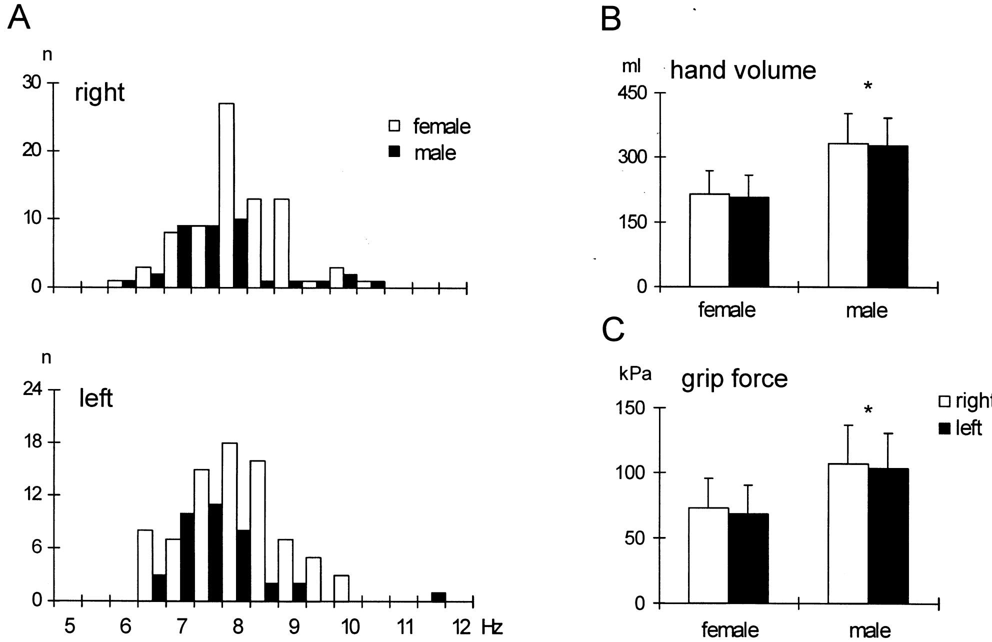

Fig. 6. PT frequency and mechanical hand properties in relation to the sex of the subjects. (A) Frequency distributions for the postural hand tremor superimposed for the male and female subjects. The frequency difference between male and female subjects was significant (t test, $P < 0.01$). (B) Difference in hand volume (Mann–Whitney U test, $P < 0.001$). (C) Difference in grip force between male and female subjects (Mann–Whitney U test, $P < 0.001$). The columns show the mean, and the error bars show the standard deviation.

parameters (mechanical hand properties, sex and age) only the hand volume has a direct significant influence on tremor frequency. However, only the grip force showed a strong dependence on the subjects' age. As displayed in Fig. 7D the grip force decreased continuously from age group to age group, starting with a population mean of 105 ± 26.2 kPa on the right in the youngest age group and going down to a mean of 41.8 ± 14.4 kPa in the oldest age group (Friedman-

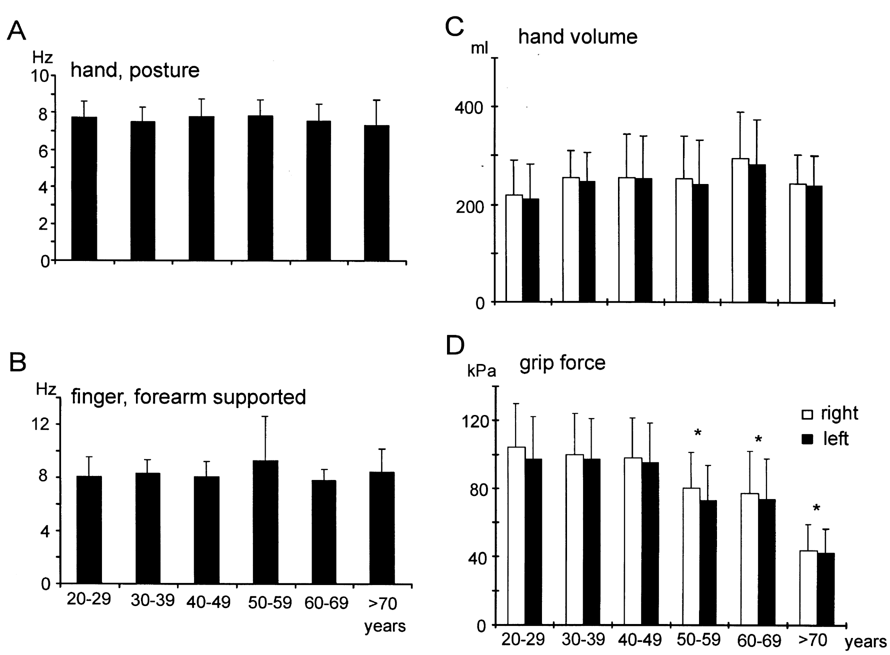

Fig. 7. Influence of age on tremor frequency and mechanical hand properties. (A) Lacking influence of age on postural hand tremor frequency. (B) Lacking influence on finger tremor frequency with the hand supported. There was no change of tremor frequency with increasing age under any of the other hand or finger tremor conditions. (C) Constancy of hand volume across the different age groups. (D) Decrease of grip force with increasing age (Friedman ANOVA, $P < 0.001$). The error bars give the standard deviation.

ANOVA, $P < 0.005$), whereas hand volume remained constant across all the age groups of the present study (youngest age group right hand mean, 251 ± 61.9 ml; oldest age group right hand mean, 238.6 ± 40.7 ml) (Fig. 7C).

4. Discussion

The hand tremor frequency band around 8 Hz contains both the peripherally driven tremor which is dominated by the natural frequency of the hand (7–12 Hz) (Stiles and Randall, 1967; Allum et al., 1978) and a central component in the 8–12 Hz range which was demonstrated convincingly by Elble and Randall (1976). The extent to which both of these mechanisms contribute to the normally encountered physiological tremor is not clear, however. This is one of the questions addressed in this paper.

The postural tremor of the hand is strongly influenced by changing the hand mechanics as has been known for some time (Wertheim-Solomonsen, 1897; Kuhnke, 1952), the finger tremor frequency distribution substantially changed with varying arm postures allowing different parts of the arm to take part in the oscillation measured at the index finger tip and the measured hand volume negatively correlated with the hand tremor frequency in normal subjects. These 3 results strongly support the view that normal physiological tremor is a peripheral tremor arising from a resonant oscillation in the vast majority of our normal population. In earlier studies it was shown that this resonance is driven by randomly firing motor units in the respective muscles (Dietz et al., 1976; Allum et al., 1978; Timmer et al., 1998). In the present study we were able to demonstrate that a resonant oscillation is the predominant mechanism which is responsible for normal physiological tremor in a large normal population, regardless of the EMG spectrum which showed significant peaks at a higher frequency in more than 50% of the subjects. Such resonant oscillations are obviously not restricted to the wrist joint but they are also present in the metacarpophalangeal joints in the 15–30 Hz band corresponding to the higher resonant frequency of the finger (Halliday and Redfearn, 1956) and in the proximal shoulder joint in the 2–4 Hz band according to the much lower resonant frequency of the arm (Fox and Randall, 1970). Similar frequency bands under comparable recording conditions were recently found by Morrison and Newell (1999). The hand tremor is the most dominant tremor, however, and it was detected under all the arm postures in a considerable proportion of normal subjects, whereas the finger and arm tremors disappeared or were markedly attenuated as soon as the arm was supported or when the more proximal joints were involved in the oscillation. The dominance of the 7–12 Hz frequency band when recording physiological finger tremor which has a much higher resonant frequency has been related to the central component of PT which has the same frequency as the mechanical hand frequency (Elble and Randall, 1976, 1978). Therefore, it is not possible to distinguish between a mechanical transmission of the resonant hand tremor on the finger (Stiles and Randall, 1967) and a central generation on the grounds of the accelerometer data alone. In the case of a centrally driven tremor one would expect an EMG synchronization at the same frequency (Deuschl et al., 1996). The EMG peak frequencies were distributed in a much higher frequency range (9–18 Hz) than the accelerometer frequencies in the 7–12 Hz band. This lack of corresponding EMG peaks is a strong argument against the 7–12 Hz component in the finger tremor recordings being of central origin. It rather reflects the optimal anatomy of the wrist joint oscillating mainly in the sagittal plane which is the direction measured by the uniaxial accelerometers used in this study. The hand oscillations are further exaggerated in comparison to the actual finger oscillations because the distance between accelerometer and wrist joint is much greater than the accelerometer MCP-joint distance, so even with the hand supported a transmission of the peripheral hand tremor to the finger seems likely (Stiles and Randall, 1967).

In order to estimate the influence of the central component on physiological tremors, we analyzed the flexor and extensor EMG spectra for all patients. A significant peak in the EMG spectrum reflects rhythmic EMG activity at the peak frequency (Timmer et al., 1996). Such rhythmic EMG activity was present in more than 50% of the patients for most recorded muscles. This percentage was higher in the flexor than the extensor muscles but relatively independent of the recording condition. The fact that the EMG frequency differed considerably from muscle to muscle and recording to recording might cast some doubt on the notion that such a rhythmic EMG activity represents the correlate of a rhythmic central drive constituting the central component of physiological tremors. It is well known from pathological tremors which are now consistently proven to involve and arise from central structures (Hua et al., 1998; Volkmann, 1998; Deuschl et al., 1999) that EMG synchronization at the accelerometric tremor frequency remaining constant under changing mechanics of the limb (Elble, 1995; Deuschl et al., 1996) and a significant coherence at the respective frequency between muscles within the same limb (Raethjen et al., 2000) are characteristic features of central tremors. In our normal population we only rarely found a tremor frequency in the accelerometer spectrum which corresponded to the flexor or extensor frequency and only in a small minority of subjects did we find an equal or close to equal frequency in flexor and extensor muscles. Those subjects with a significant coherence between flexors and extensors also represent only a minority within the normal population. So the comparison of our results to the characteristics of pathological central tremors seems to argue against regarding the variable EMG peaks solely as a sign of a weak motor unit synchronization by rhythmic central input, that is the central component of PT. As has been postulated previously by other authors surface EMG peaks may be produced by randomly firing unfused late recruited motor units in the absence of actual motor unit synchronization (Taylor, 1962; Fox and Randall, 1970; Dietz et al., 1976; Erimaki and Christakos, 1999). If the EMG peaks arose only by randomly firing motor units, though, one might expect a more widespread frequency distribution as opposed to the close to normal distribution within the same frequency band (Halliday et al., 1999) for all recorded muscles and conditions. But the frequency range in which we found the majority of the EMG peaks corresponded well to the physiological range of motor unit firing rates (Allum et al., 1978; Fuglevand et al., 1993). The fact that the frequency distributions extended to higher frequencies in the extensor than in the flexor muscles (Fig. 4) might be due to the physiological increase in the motor unit firing rate with increasing strength of the contraction, as the extensor muscles are primarily active under the postural hand tremor recording conditions. So there are clear indications of the EMG peaks being at least partly determined by independently firing motor units. However, the additional significant accelerometer peaks at the EMG frequency in a small proportion of subjects indicates a clear influence of the EMG frequency on the tremor spectrum. Such an effect of the EMG frequency reflects synchronized firing of a larger number of motor units leading to a rhythmic movement and cannot be explained by a small number of motor units randomly firing at the respective frequency. Another indication of a common central drive at the EMG frequency is the significant coherence we found between flexor and extensor muscles in another proportion of subjects. A significant coherence reflects a common origin of the two rhythmic oscillations under consideration (Amjad et al., 1997; Lauk et al., 1999b). Such a common origin could either lie in the periphery, that is coupling of the two muscles through the rhythmic peripheral feedback (Hagbarth and Young, 1979; Erimaki and Christakos, 1999), or within the CNS as a central oscillator transmitting its rhythmic signal to both muscles in parallel (Elble, 1996). If the reflex activation played a relevant role in tremor generation one would expect the EMG frequencies to change under load in parallel with the tremor frequency. This was the case in only two out of the 117 subjects and the EMG frequencies were generally not influenced by added inertia, so this mechanism seems very unlikely. However, the coherence could still be a secondary phenomenon to the central component of PT produced by a strong most likely centrally driven motor unit synchronization in the 8–18 Hz range on the single muscle level. The stronger the synchronization of the motor units in one muscle the more likely a peripheral entrainment via reflexes could lead to coupling between the flexor and extenser muscles producing a significant coherence. This mechanism might be responsible for the coherence in some of the subjects. But the cases with strong EMG synchronizations leading to a clear higher frequency tremor peak without a significant coherence between flexors and extensors indicate that the coherence is more likely to reflect a common central input. This is in line with numerous other examples in which we found no tremor at the EMG frequency that could lead to a peripheral coupling but a clearly significant coherence between flexors and extensors.

Taking together the results indicating a centrally driven component of physiological tremors we found a clear effect of the EMG synchronization on physiologic tremors in about 15–20% of the subjects and the coherence function between flexor and extensor muscles reached the level of significance at the EMG frequency in about another 10–15% of subjects in whom we did not find a corresponding accelerometer peak at the same time. So we found an indication of a central component of PT in about one-third of the normal population.

Although the central component is relatively weak in normal PT and it was only detected in a minority of subjects it is of great interest as it very likely constitutes the basis for the development of pathological tremors like ET or enhanced physiologic tremors (Elble, 1986). Thus, subjects with a central tremor component might be more prone to develop a pathological tremor than others. However, such a transition from physiologic via enhanced physiologic to pathologic central tremor is far from being understood and is one central question of tremor research (Elble, 1995).

Another question addressed in the present study is the role of indirect influences on physiologic tremor. In particular, the subjects' age has been reported to influence the tremor frequency. Several studies found either a gradual decline (Marshall, 1961; Birmingham et al., 1985; Kelly et al., 1995) of frequency with age or a reduction of tremor frequency beyond a certain age (60 or 70 years) (Marsden et al., 1969; Wade et al., 1982). The detailed results of these studies were quite heterogeneous. Kelly et al. (1995) found an age dependence only under some recording conditions and Birmingham et al. (1985) were only able to demonstrate a reduction of tremor frequency on one side of the body. Together with the previous studies by Wade et al. (1982) and Marsden et al. (1969) which only employed a single recording condition, these ambiguous results were interpreted as a confirmation of the tremor frequency reduction with age, albeit having been already discussed as a more complex phenomenon (Birmingham et al., 1985). Another paper (Elble, 1986) did not find any statistically significant alterations of physiological hand tremor frequency with increasing age. In the present study we tried to resolve these contradictory results by analyzing all the different hand and finger tremor conditions reported in the literature and using a special time series analysis tool (Lauk et al., 1999a) to determine the exact tremor frequency. Under none of the recording conditions reported in the literature did we find a change in tremor frequency with age. Thus, our study argues against an overall reduction of tremor frequency with age. The conflicting results in the previous studies already made a general change in PT physiology with old age questionable, and it might rather reflect an increase in systematic errors when measuring tremors in elderly subjects, like instationarities of the tremor time series because of difficulties in holding the hands in a steady position, or accidental inclusion of elderly subjects with mild pathological tremors, which are much more common in the older population (Elble, 1998). We controlled very strictly for such factors by testing our data off-line for instationarities and by performing a thorough neurological history and examination including special questions concerning any disability because of trembling hands. However, we did notice that the tremor recordings were more prone to show artifacts in the elderly subjects.

Wade et al. (1982) speculated on what the physiological basis for a reduction of tremor frequency with age could be. They postulated that alterations in the mechanics of the oscillating limb with increasing age reducing the resonant frequency of the limb are the most likely mechanism of a decline in frequency. To control for these peripheral mechanical factors we analyzed the grip force and hand volume of our normal population. While the grip force decreased significantly with increasing age the hand volume remained constant across all age groups. The decrease in grip force with age is in keeping with the results of Kelly et al. (1995), but they found a parallel decline of tremor frequency in the older subjects. This was the basis for their postulate that this mechanical change leads to the change in tremor frequency. We were able to show, however, that the grip force did not correlate with tremor frequency, so it obviously does not covary with the resonant frequency of the hand and its change with age is not likely to produce a concurrent reduction in tremor frequency. Unlike the grip force the hand volume did correlate negatively with the tremor frequency, but it did not show any changes with increasing age. So our result of a lacking age dependence of the tremor frequency is in good keeping with the constant hand volume across all age groups. In the partial correlation analysis, including all putative direct and indirect influences on tremor frequency, we were able to also exclude a hidden dependency between age and tremor frequency which might be missed in multiple bivariate correlations. A change in the central component of PT with increasing age was not found in our data either. The EMG synchronization was very variable but it did not show any systematic differences between different age groups.

The slightly lower frequencies in male as compared to female subjects are in line with the results of Lakie (1995) who also found significantly higher frequencies in female subjects. Partial correlation analysis revealed that these results are only due to an indirect mechanical effect as the female subjects had significantly smaller hands than the males and hand volume and tremor frequency clearly correlated negatively. None of the other tremor characteristics (EMG frequency and synchronization, tremor total power and frequency reduction with added inertia) were influenced directly or indirectly by the sex of the subjects. Therefore, our results concerning the percentage of subjects with a central component of PT are independent of the sex distribution of our normal population, although it included more female (roughly two-thirds) than male (roughly one-third) subjects.

Tremor amplitude was not influenced by any of the direct or indirect factors. Only the slightly but significantly higher total power in the left than the right hand under all postural conditions was striking but should not be overestimated. It is difficult to explain at present but as only 3 out of the 117 subjects were left-handed these data indicate that the dominant hand generally does not exhibit dominant physiological tremor.

In conclusion, we found in a large normal population that the main component of normal physiological tremors is a resonant oscillation depending on the limb's mechanics. Such a mechanical resonance is not restricted to the distal joints but also occurs in the more proximal parts of the arm at a lower frequency which is dependent on the passive mechanical properties of the oscillating system and not the contractile properties of the driving muscles. A reflex enhancement of this peripheral component was only found in two out of 117 subjects. It was shown that the comparison between the EMG and accelerometer spectra and the calculation of the coherence between flexors and extensors allow an estimate of the central mechanisms in PT; we found a clear indication of a central component in the 8–16 Hz range in about one-third of the subjects. There was no age dependence of the tremor frequency or EMG frequency, while the sex of the subjects had a small but clear influence on the tremor frequency, which corresponds to the hand volume also lacking any age dependence but clearly depending on sex. This shows that such indirect influences also act through changes of the peripheral mechanics and again confirms the predominance of peripheral mechanisms in PT.

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