

Effects of Aging on the Regularity of Physiological Tremor

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Sturman, Molly M., David E. Vaillancourt, and Daniel M. Corcos. Effects of aging on the regularity of physiological tremor. *J Neurophysiol* 93: 3064–3074, 2005. First published February 16, 2005; doi:10.1152/jn.01218.2004. The purpose of this investigation was to determine the effects of healthy aging on the regularity of physiological tremor under rest and postural conditions. Additionally, we examined the contribution of mechanical reflex factors to age-related changes in postural physiological tremor. Tremor regularity, tremor-electromyographic (EMG) coherence, tremor amplitude, and tremor modal frequency were calculated for 4 age groups (young: 20–30 yr, young-old: 60–69 yr, old: 70–79 yr, and old-old: 80–94 yr) under resting and loaded postural conditions. There were 6 important findings from this study: 1) there were no differences between the young and elderly subjects for any of the dependent variables measured under the rest condition; 2) postural physiological tremor regularity was increased in the elderly; 3) postural physiological tremor-EMG coherence was also increased in the elderly, and there was a strong linear relation between peak tremor-EMG coherence in the 1- to 8-Hz frequency band and regularity of tremor. This relation was primarily driven by the increased magnitude of tremor-EMG coherence at 5.85 and 6.83 Hz; 4) enhanced mechanical reflex properties were not responsible for the increased magnitude of tremor-EMG coherence in the elderly subjects; 5) tremor amplitude was not different between the 4 age groups, but there was a slight decline in tremor modal frequency in the oldest age group in the unloaded condition; and 6) despite the increases in postural physiological tremor regularity and the magnitude of low frequency tremor-EMG coherence with age, there was a clear demarcation between healthy aging and previously published findings related to tremor pathology.

INTRODUCTION

In the most general sense, tremor is defined as any involuntary, approximately rhythmic, and roughly sinusoidal movement that can be detected in an oscillating limb (Elble and Koller 1990). Tremor is present in all individuals, occurring at rest (resting tremor) (Brumlik 1962; Marsden et al. 1969a) and during postural maintenance of the limb (postural tremor) (Halliday and Redfearn 1956; Marshall and Walsh 1956; Schaffer 1886). Tremor is also a frequent symptom of movement disorders, such as essential tremor (ET) and Parkinson's disease (PD) (Deuschl et al. 1998; Elble and Koller 1990). These pathologies are more prevalent among elderly individuals (Elble 1998; Kelly et al. 1995; Waite et al. 1996) with prevalence rates for ET reaching 4.8% in individuals >65 yr (Benito-Leon et al. 2003), and the incidence of PD increasing from 0.50/100,000 in individuals aged 30–39 yr to 44/100,000 in individuals >50 yr (Van Den Eeden et al. 2003).

Physiological tremor in healthy individuals is classically characterized as a low amplitude postural tremor with a modal frequency of 8–12 Hz (Elble and Koller 1990). Physiological tremor measured at rest is a normally occurring, low amplitude oscillation determined by mechanical limb properties and cardioballistics (Brumlik 1962; Elble and Koller 1990; Marsden et al. 1969a). In addition to amplitude and frequency, both physiological and pathological tremors can be characterized by the degree of regularity [measured with approximate entropy (ApEn)] in the limb acceleration signal and the amount of coherence between limb acceleration and muscle output [tremor-electromyographic (EMG) coherence]. For healthy physiological tremor, regularity and tremor-EMG coherence <10 Hz are low (Sturman et al. 2004; Vaillancourt et al. 2003). In contrast to healthy physiological tremor, patients with ET have an abnormal postural tremor with increased amplitude, regularity, tremor-EMG coherence <10 Hz, and a modal frequency between 4 and 12 Hz (Elble and Koller 1990; Vaillancourt et al. 2003). Tremor in PD is classified as a resting and/or postural tremor, which also has increased amplitude, regularity, and tremor-EMG coherence <10 Hz. The modal frequency of resting tremor in PD is between 3 and 5 Hz and postural tremor frequency ranges from 4 to 12 Hz (Deuschl et al. 1998; Elble and Koller 1990; Findley et al. 1981).

Previous research on postural physiological tremor has argued that the amplitude and modal frequency of physiological tremor in the elderly could be a form of undiagnosed pathological tremor, such as ET (Elble 1995, 1998; Louis et al. 2000; Moretti et al. 1983). However, recent research has not found changes in the amplitude and modal frequency of tremor with age (Elble 2003; Raethjen et al. 2000). Regularity and tremor-EMG coherence, both of which are markers for tremor pathology, have not been examined in physiological tremor as a function of healthy aging. However, changes in the regularity of physiological output from elderly individuals have been detected in the absence of changes in the mean and variance of the dependent variables used to describe physiological function (Pincus 2001). Recent research has also shown increased motor unit to motor unit coherence <10 Hz among elderly individuals (Semmler et al. 2003).

The first purpose of this study is to investigate the effects of healthy aging on the regularity and tremor-EMG coherence of physiological tremor under resting and postural conditions. In addition, to replicate previous research, we will also investigate the effects of healthy aging on the amplitude and modal frequency of physiological tremor. Due to the decrease in muscle activity in a resting limb state and previous research

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which did not find age-related changes in physiological resting tremor (Kelly et al. 1995; Raethjen et al. 2000), it is hypothesized that age will not affect the neurophysiological characteristics of tremor measured at rest. However, based on previous research demonstrating the sensitivity of regularity in detecting age-related changes in physiological function (Pincus 2001), and the presence of increased motor unit to motor unit coherence among elderly individuals during an active limb state (Semmler et al. 2003), we predict that age will increase postural tremor regularity and the magnitude of tremor-EMG coherence <10 Hz.

The second purpose of this study is to determine whether mechanical reflex oscillations affect physiological tremor in older individuals more so than in young individuals. Both mechanics and reflexes play a role in the peripheral component of physiological tremor, which is described by the mechanical reflex oscillator hypothesis (Stiles and Pozos 1976). According to this hypothesis, the nervous system contributes to physiological tremor by setting the muscle stiffness and driving asynchronous contractions of motor units, with the inertia and stiffness of the limb determining the resonant frequency of tremor. If enhancement of the mechanical reflex component of tremor is contributing to the increased low frequency tremor-EMG coherence with age, we expect to find an age \times load interaction, whereby load is preferentially affecting the magnitude of tremor-EMG coherence <10 Hz in the elderly subjects. Alternatively, if there is no interaction between age and load, then enhanced mechanical reflex oscillations do not play a role in the increased magnitude of tremor-EMG coherence among elderly subjects.

The third purpose of the study is to examine physiological tremor measured under resting and postural conditions using a load manipulation with the same neurophysiological tools that have previously been used for pathological tremors (Sturman et al. 2004; Vaillancourt et al. 2003). This will establish normative data for the regularity of physiological tremor as a function of healthy aging.

METHODS

Subjects

Forty healthy subjects were enrolled in the study. These individuals were assigned to 4 different age groups with 5 females and 5 males in each group: young group [$n = 10$; range 20–30 yr; mean 24.4 (SD = 3.2)], young-old group [$n = 10$; range 60–69 yr; mean 65.8 (SD = 3.6)], old group [$n = 10$; range 70–79 yr; mean 73.5 (SD = 3.0)], and old-old group [$n = 10$; range 80–94 yr; mean 82.8 (SD = 4.4)]. The data from 10 patients with PD and 6 patients with ET are also presented. The data from the ET patients has been published elsewhere (Vaillancourt et al. 2003) as has the data from the PD subjects

(Sturman et al. 2004). Informed consent was obtained from all subjects before the inception of the study, and all study procedures were approved by the local Institutional Review Board (University of Illinois at Chicago, Chicago, IL).

Subject height and weight information for the young and elderly subjects was collected, and a height-to-weight ratio was calculated (cm/kg) for each subject. The Yale Physical Activity Survey for Older Adults (Dipietro et al. 1993) and the Mini-Mental State Examination (Folstein et al. 1975) were administered to all subjects before data collection began. Exclusion criteria were determined a priori and included elite physical condition or extremely frail physical condition, cognitive impairments (scores $<29/30$ on the Mini-Mental State Examination), diabetes, uncontrolled hypertension or angina, alcoholism, or bed rest. Subjects were also excluded from the experiment if they were known to have any neurological pathologies, an apparent resting or postural tremor detectable with clinical tremor rating scales, or a family history of PD or ET. The purpose of the exclusion criteria was to exclude elderly subjects that were tremulous or that had health problems. We excluded one individual from the old group and one individual from the old-old group. The individual considered for the old group had an action tremor that received a 1 on the Tremor Rating Scale (Fahn et al. 1993), and the physical condition of the individual considered for the old-old group was extremely frail because of severe osteoarthritis.

Tremor data are presented in Tables 1 and 2 (mean \pm SD) from 6 individuals with ET and 10 individuals with PD. The data from the patients were collected while they were off treatment. All data analysis procedures and dependent variable calculations were performed in exactly the same way for both the patients and the young and elderly subjects. These procedures are described in detail in the following paragraphs. It is important to note that both patient groups were moderately to severely impaired. The data from both groups of patients are presented to provide a direct comparison between physiological tremor in the elderly and tremor in 2 different pathologies.

Apparatus

Subjects were positioned in a 42-cm-high straight back chair. If necessary, foot support was provided to ensure that the knee and hip angles were both 90° . The arm of the chair served as the supportive surface for the subject's forearm. The supportive surface measured 43 cm in length and was 58 cm from the ground. The subject's dominant forearm was positioned on the supportive surface so that the ulnar styloid process was aligned with the end of the surface. In this position the elbow joint was flexed to about 90° , the shoulder joint was slightly abducted, and the forearm was pronated. A small table was positioned about 30 cm in front of the subject. The height of the table was adjusted to be level with the subject's hand when the wrist and fingers were in a neutral position (0° of flexion and extension) as shown in Fig. 1. The table served as the visual target to enable the subject to maintain the wrist in a neutral position. The width of the table edge was 1.3 cm.

A calibrated Coulbourn type V 94–41 miniature solid-state piezoresistive accelerometer was taped 2 cm proximal to the middle of

TABLE 1. Resting tremor

Dependent Variable	Young	Young-Old	Old	Old-Old	Parkinson's Disease
ApEn	0.70 \pm 0.06	0.69 \pm 0.04	0.71 \pm 0.10	0.69 \pm 0.05	0.53 \pm 0.08
Coherence	0.16 \pm 0.03	0.13 \pm 0.03	0.14 \pm 0.03	0.16 \pm 0.03	0.62 \pm 0.25
Amplitude, cm	0.01 \pm 0.01	0.01 \pm 0.01	0.02 \pm 0.02	0.02 \pm 0.01	9.17 \pm 8.2
Frequency, Hz	8.09 \pm 0.69	7.37 \pm 0.77	7.29 \pm 0.85	7.44 \pm 0.86	6.07 \pm 0.89

Resting tremor regularity [approximate entropy (ApEn)], maximal 1- to 8-Hz tremor-EMG coherence, amplitude (cm), and frequency (Hz) values (mean \pm SD) for young (20–30 yr), young-old (60–69 yr), old (70–79 yr), and old-old (80–94 yr) subjects. For direct comparison between age and disease, values (mean \pm SD) for patients with Parkinson's disease are also given.

TABLE 2. Postural tremor

Dependent Variable	Load, g	Young	Young-Old	Old	Old-Old	Essential Tremor	Parkinson's Disease
ApEn	0	0.72 ± 0.03	0.71 ± 0.04	0.70 ± 0.06	0.68 ± 0.03	0.57 ± 0.05	0.53 ± 0.08
	100	0.71 ± 0.04	0.70 ± 0.03	0.70 ± 0.06	0.69 ± 0.05	0.58 ± 0.04	0.59 ± 0.04
	250	0.72 ± 0.05	0.69 ± 0.02	0.69 ± 0.04	0.66 ± 0.05	0.57 ± 0.05	0.60 ± 0.05
	500	0.74 ± 0.06	0.70 ± 0.04	0.69 ± 0.07	0.67 ± 0.06	0.55 ± 0.04	0.57 ± 0.06
	1,000	0.74 ± 0.06	0.70 ± 0.07	0.68 ± 0.06	0.66 ± 0.03	0.53 ± 0.06	0.58 ± 0.04
Coherence	0	0.16 ± 0.06	0.24 ± 0.10	0.22 ± 0.07	0.27 ± 0.16	0.41 ± 0.16	0.61 ± 0.25
	100	0.16 ± 0.05	0.24 ± 0.11	0.22 ± 0.06	0.27 ± 0.14	0.45 ± 0.26	0.57 ± 0.30
	250	0.15 ± 0.05	0.22 ± 0.08	0.21 ± 0.09	0.26 ± 0.15	0.41 ± 0.26	0.60 ± 0.27
	500	0.14 ± 0.04	0.19 ± 0.09	0.21 ± 0.11	0.24 ± 0.08	0.41 ± 0.24	0.58 ± 0.26
	1,000	0.15 ± 0.04	0.21 ± 0.11	0.20 ± 0.08	0.26 ± 0.11	0.44 ± 0.25	0.57 ± 0.26
Amplitude, cm	0	0.04 ± 0.02	0.06 ± 0.04	0.06 ± 0.05	0.09 ± 0.08	4.67 ± 2.26	10.62 ± 8.97
	100	0.04 ± 0.02	0.06 ± 0.04	0.06 ± 0.06	0.09 ± 0.07	3.49 ± 2.23	5.89 ± 5.79
	250	0.04 ± 0.03	0.05 ± 0.03	0.06 ± 0.06	0.10 ± 0.08	2.05 ± 2.08	6.17 ± 7.62
	500	0.04 ± 0.03	0.05 ± 0.03	0.07 ± 0.06	0.10 ± 0.05	1.97 ± 1.82	4.71 ± 5.36
	1,000	0.06 ± 0.03	0.07 ± 0.04	0.09 ± 0.09	0.11 ± 0.06	1.84 ± 1.77	2.27 ± 0.92
Frequency, Hz	0	8.33 ± 0.74	7.50 ± 1.10	7.45 ± 0.85	7.58 ± 0.50	6.07 ± 0.71	6.15 ± 1.04
	100	7.58 ± 1.10	7.11 ± 0.91	6.93 ± 0.69	7.16 ± 0.59	5.90 ± 0.72	6.20 ± 0.77
	250	7.19 ± 0.93	7.11 ± 0.63	6.64 ± 0.71	6.75 ± 0.62	5.94 ± 0.75	5.81 ± 0.79
	500	6.59 ± 0.75	6.93 ± 1.20	6.30 ± 0.49	6.22 ± 0.29	5.59 ± 0.88	5.86 ± 0.71
	1,000	5.57 ± 0.72	6.09 ± 0.73	6.02 ± 0.59	5.68 ± 0.53	5.42 ± 0.71	5.76 ± 0.56

Postural tremor regularity [approximate entropy (ApEn)], maximal 1- to 8-Hz tremor-EMG coherence, amplitude (cm), and frequency (Hz) values (mean ± SD) for young (20–30 yr), young-old (60–69 yr), old (70–79 yr), and old-old (80–94 yr) subjects. For direct comparison between age and disease, values (mean ± SD) for patients with essential tremor and Parkinson's disease are also given.

the second metacarpophalangeal (MCP) joint (Fig. 1). A Coulbourn Lab Linc V System V72-25A resistive bridge strain gauge transducer with an excitation voltage of ±5 V amplified the changes in electrical resistance of the acceleration signals. The accelerometer's resolution was 0.01 m/s², and a 12-bit A/D converter sampled the acceleration signal at 1,000 Hz. Surface electromyography was used to measure the neuromuscular activity in the extensor digitorum (Fig. 1). Electrode placement was determined by muscle palpation during active wrist and finger extension, and EMG output was inspected by viewing a digital oscilloscope. The EMG signal was amplified (gain = 1,000) and band-pass filtered by the Bagnoli system with a low cutoff of 20 Hz and a high cutoff of 450 Hz (Delsys, Boston, MA). Data from each trial were saved to the hard disk of the data collection computer and analysis and processing was performed off-line.

Protocol

The study examined 2 types of tremor. In the resting tremor condition, subjects were instructed to relax their forearm and hand muscles, and allow the wrist to dangle unsupported over the edge of the supportive surface for 30 s (Fig. 1A) (Burne et al. 1984; Duval et al. 2001; Marsden et al. 1969a; Raethjen et al. 2000). In the postural tremor condition, subjects were asked to maintain their wrist and hand in a neutral, extended position while keeping it level with the target for 30 s (Fig. 1, B–C) (Elble and Randall 1976; Homberg et al. 1987; Raethjen et al. 2000). Loads of 1,000, 500, 250, 100, and 0 g were

suspended from the subjects' hand. A Velcro strap, placed 1 cm proximal to the middle of MCP joints 2–5, secured the weights in their suspended position (Fig. 1C). Subjects performed 3 trials in each condition and at least 3 min of rest was provided between trials. To ensure that fatigue was not present during the recording session, we analyzed the effect of trial in our data. This analysis showed no effect of trial and thus fatigue was not a factor. The resting tremor condition was always performed first followed by the postural tremor experiments. The order of the loaded conditions was randomized. Both verbal feedback and visual feedback were provided to the subjects with respect to the maintenance of the target hand position. Additionally, hand and wrist initial position was checked by the experimenter before each trial.

Data analysis

To quantify the differences in physiological tremor between young and elderly adults, data analysis examined the same 4 dependent measures for resting tremor and for postural tremor with different loads. The independent variables were age and load, and the dependent variables were regularity [measured with approximate entropy (ApEn)], magnitude of tremor-EMG coherence, amplitude, and modal frequency. Before data analyses, the acceleration and EMG signals were processed with the following techniques. The EMG signals were digitally rectified, and both the EMG and acceleration data were downsampled by a factor of 5 to 200 Hz (Vaillancourt and Newell



FIG. 1. Schematic of the experimental paradigm for (A) resting tremor, (B) postural tremor without a load, and (C) postural tremor with a load. An accelerometer was placed 2 cm proximal to the second MCP joint (A–C), surface EMG electrodes were placed over the extensor digitorum muscle (A–C), and a load was suspended from MCP joints 2–5 (C). Target is shown in B and C for the postural tremor conditions.

2000). We analyzed the full-wave rectified EMG signal to maximize the information about the temporal pattern of grouped motor-unit firing potentials (Mima et al. 2001; Myers et al. 2003). This procedure has been used by many different groups when examining physiological and pathological tremor (Elble and Randall 1976; Halliday et al. 1999; McAuley et al. 1997; Vaillancourt and Newell 2000). The acceleration signal was digitally filtered using a 4th-order Butterworth filter with a low-pass cutoff frequency of 30 Hz. For the calculation of tremor-EMG coherence in the 35- to 50-Hz bin, the acceleration signal was filtered at 60 Hz instead of 30 Hz. In addition to the 20- to 450-Hz analog band-pass filter and after rectification, the EMG signal was digitally filtered using a 4th-order Butterworth filter with a low-pass cutoff frequency of 60 Hz (Sturman et al. 2004; Vaillancourt et al. 2003). Data processing and time and frequency analyses were performed using software written in Matlab (The MathWorks, Natick, MA).

Regularity (approximate entropy)

The regularity of tremor was quantified using approximate entropy (ApEn). This algorithm assesses the time-dependent structure of the acceleration signal and returns a value between 0 and approximately 2, which represents the predictability of future values in the time series based on previous values. An ApEn value of zero would correspond to a sine-wave signal that has a high degree of short- and long-term predictability. On the other hand if a highly unpredictable signal, such as white Gaussian noise, is added to a sine wave the ApEn value will increase. If a completely random signal such as pure white Gaussian noise is assessed with ApEn the value returned will be close to 2, which is explained by the fact that, in a completely random signal, future values in the time series are independent and unpredictable based on previous values. The calculation of ApEn requires 2 input parameters: “m” is the window length and “r” is a filter (Pincus 1991). Herein ApEn parameter settings of $m = 2$ and $r = 0.2 \times \text{SD}$ of the signal were used to be consistent with previous work from our laboratory (Sturman et al. 2004; Vaillancourt and Newell 2000; Vaillancourt et al. 2001, 2003) and other laboratories (Pincus and Goldberger 1994).

Tremor-EMG coherence

Cross-spectral analysis was used to analyze the relation between the EMG and acceleration signals (tremor-EMG coherence). The cross-spectrum was calculated using Welch's averaged periodogram method with no overlap between successive segments in the spectral calculation. Coherence between each respective signal was calculated and a 95% confidence interval was determined (Farmer et al. 1993; Rosenberg et al. 1989), which yielded a broadband of coherence that was significantly different from 0. The magnitude of the peak coherence value in the coherence spectrum in the 1- to 8-, 9- to 15-, 15- to 30-, and the 35- to 50-Hz bins was determined. To ensure that the binning method was sufficiently discriminative, we also calculated peak tremor-EMG coherence in 3-Hz bins from 1 to 50 Hz (acceleration signal filtered at 60 Hz). The results were consistent with those in the 1- to 8-, 9- to 15-, 15- to 30-, and 35- to 50-Hz bins and are not presented. The 1- to 8-Hz bin was further divided into 0.976-Hz bins, and the magnitude of tremor-EMG coherence was determined within the smaller bins. Only peak coherence values from the 1- to 8-Hz bin (Tables 1 and 2, Figs. 4 and 6A) are reported because age did not affect the magnitude of peak tremor-EMG coherence in the higher frequency bins.

Amplitude

Autospectral analysis was used to quantify the amplitude of the acceleration signal (Elble and Koller 1990; Jenkins and Watts 1968; McAuley et al. 1997). This method for determining amplitude calcu-

lates the root-mean-square (rms) displacement of the acceleration signal from the modal frequency of tremor (Stiles 1976). The unit of measurement for acceleration before autospectral analysis is m/s^2 . To calculate the rms displacement of the acceleration signal, it is assumed that the tremor spectrum resulted from a periodic oscillation, which is a reasonable assumption for hand tremor. In this case, spectral analysis produces a narrow band of power. The sum of the 3 highest spectral values represents the majority of the variance of the tremor oscillations at the modal frequency (f), and the square root of this sum represents the rms acceleration at this frequency (f). Three spectral values are required to capture the overall variance of the acceleration signal. At this point the unit of measurement for the power spectral density of the acceleration data is m/s^2 divided by Hz (1/s), which gives m/s. By dividing the rms acceleration by the square of ω ($\omega = 2\pi f$) the units are converted to displacement (cm). In this study, units of displacement (cm) are used to quantify tremor amplitude in the elderly in order to directly compare physiological tremor amplitude to pathological tremor amplitude, which is measured clinically in centimeters (Fahn et al. 1993).

Modal frequency–acceleration signal

The modal frequency of the acceleration signal was determined using autospectral analysis of the signal. The spectral resolution was 0.781 Hz. The peak of the tremor acceleration spectrum was designated as the modal frequency (f) of tremor.

Statistical analysis

Data were averaged across the 3 trials for each dependent variable. A one-way ANOVA with a between-subject factor of age (4) was used to determine significant differences in the resting tremor condition. A separate 2-way Age (4) \times Load (5) ANOVA was used to evaluate the significance of the dependent variables for the postural tremor condition. A 3-way Age (4) \times Load (5) \times Bin (9) ANOVA was used to determine which frequency bins within the 1- to 8-Hz band had increased magnitude of tremor-EMG coherence. Tukey's Honestly Significant Difference (HSD) post hoc analysis was used to evaluate which groups were significantly different if a main effect was obtained. Statistical analyses were deemed significant when alpha was <0.05 . All statistical analyses were conducted using Statistica statistical software package (StatSoft, Tulsa, OK).

RESULTS

Resting tremor

There were no significant differences between the 4 age groups in the regularity, magnitude of peak tremor-EMG coherence in any frequency bin, amplitude, or modal frequency for the resting tremor condition. Table 1 provides group means \pm SD of each of the dependent variables for resting tremor.

Postural tremor

REGULARITY AND TREMOR-EMG COHERENCE. Figure 2 quantifies the regularity of postural hand tremor in the 4 age groups calculated with ApEn. There was a main effect of age on ApEn [$F_{(3,36)} = 2.99$, $P < 0.05$]. The age \times load interaction ($P = 0.59$) was not supported nor was the main effect of load ($P = 0.60$). As illustrated by Fig. 2, the ApEn values for the young group were higher than the values for the 3 elderly groups, and ApEn decreased as a function of age. Post hoc analysis using Tukey's HSD revealed that only the ApEn values of the old-old

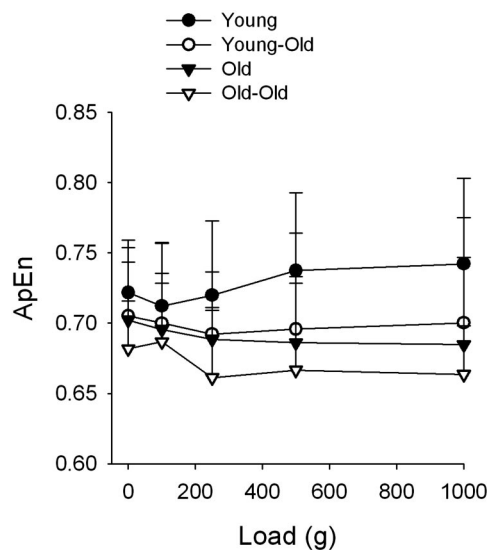


FIG. 2. Tremor regularity [measured with approximate entropy (ApEn)] for the young, young-old, old, and old-old subjects under the postural tremor condition. Each value represents the average across subjects in each age group at each inertial load (mean + SD). $n = 10$ for each age group.

group were significantly different from the young group ($P < 0.05$).

Figure 3 is single-subject data from a young subject (25 yr) and old-old subject (81 yr). This figure depicts the effects of mechanical load on the tremor autospectrum, EMG autospectrum, and the cross-spectrum between the 2 signals. In Fig. 3, *A* and *B*, the addition of mechanical load shifts the accelerometric peak to a lower frequency for both the young and old-old subjects. This suggests that mechanical resonance factors influence the modal frequency of physiological postural tremor. In contrast the frequency of the peaks in both the EMG spectrum (Fig. 3, *C* and *D*) and the tremor-EMG coherence spectrum (Fig. 3, *E* and *F*) are not influenced by mechanical load in the young and elderly subjects, which suggests a central modulation of tremor-EMG coherence. Additionally, a difference exists in the magnitude of peak tremor-EMG coherence between the young and elderly individuals that is most pronounced at or below about 10 Hz (Fig. 3, *E* and *F*). Although significant peak coherence occurred at 40 Hz in this trial for the old-old subject (3*F*), this was not a consistent finding.

The postural tremor condition yielded significant differences in the magnitude of peak tremor-EMG coherence in the 1- to 8-Hz frequency bin between the 4 age groups. This is depicted in Fig. 4. Figure 4 depicts the across subject mean peak tremor-EMG coherence in the 1- to 8-Hz frequency band + SD. There was a main effect of age for the magnitude of peak tremor-EMG coherence in the 1- to 8-Hz frequency band [$F_{(3,36)} = 2.94$, $P < 0.05$]. Post hoc tests confirmed that the main effect of age was attributed to the old-old subjects exhibiting a significantly greater magnitude of peak tremor-EMG coherence in the 1- to 8-Hz frequency band compared with the young subjects ($P < 0.05$). Tremor-EMG coherence analysis was also performed on the 9- to 15-, 15- to 30-, and 35- to 50-Hz frequency bins. There were no differences between the age groups in the magnitude of peak tremor-EMG coherence in the higher frequency bins (values of $P > 0.23$).

To determine the specific frequencies within the 1- to 8-Hz bin that demonstrated an increased magnitude of tremor-EMG

coherence among the elderly, we performed a more detailed analysis of tremor-EMG coherence across load in the 1- to 8-Hz bin, shown in Fig. 5. Results from the 3-way (age \times bin \times load) ANOVA revealed a significant age \times bin interaction [$F_{(24,288)} = 2.77$, $P < 0.01$] and a significant load \times bin interaction [$F_{(32,1152)} = 6.60$, $P < 0.01$]. The age \times load \times bin and age \times load interactions were not significant. To interpret the significant age \times bin interaction, we performed separate one-way, between-group ANOVAs that confirmed a main effect for age at 5.85 Hz [$F_{(3,36)} = 5.26$, $P < 0.01$] and 6.83 Hz [$F_{(3,36)} = 4.03$, $P < 0.01$]. Tukey's post hoc analysis revealed that a significant difference in the magnitude of tremor-EMG coherence existed between the young and old-old groups from 5.85 to 6.83 Hz ($P < 0.01$ for each bin). The old-old subjects also had greater tremor-EMG coherence compared with that of young subjects at 7.81 and 8.78 Hz, and this difference was close to reaching statistical significance (values of $P = 0.07$). To interpret the significant load by bin interaction, we performed separate one-way, within-subject ANOVAs that showed a main effect of load from 4.88 to 8.78 Hz (values of $P < 0.01$), such that the magnitude of tremor-EMG coherence increased with load.

Figure 6 is a summary figure that depicts the relation between the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band and ApEn, and illustrates how these 2 variables change with increasing age. In Fig. 6*A* the relation between the magnitude of peak 1- to 8-Hz tremor-EMG coherence and ApEn is best described by a linear function with a y -intercept of 0.78, a slope of -0.43 , and an R^2 value of 0.70. For Fig. 6, *B* and *C* the magnitude of tremor-EMG coherence at 5.85 and 6.83 Hz is plotted versus ApEn. These 2 frequency bins were chosen because a significant difference in the magnitude of tremor-EMG coherence exists between the young and old-old subjects at 5.85 and 6.83 Hz. As expected, the relation between the magnitude of tremor-EMG coherence and ApEn at 5.85 and 6.83 Hz is linear with R^2 values of 0.59 and 0.57, respectively. These figures suggest that as the amount of squared correlation between the tremor and the muscle output increases, the regularity of tremor also increases as a function of age.

Amplitude and modal frequency

The effect of age on the amplitude of tremor did not reach the 0.05 significance level [$F_{(3,36)} = 2.57$, $P = 0.07$]. Inspection of the data revealed that the old-old subjects had slightly greater tremor amplitudes than those of the young subjects (Table 2). Clinical rating scales for pathological tremor classify tremor amplitude as moderate if it is greater than "slight, but perceivable" and < 2 cm (Fahn et al. 1993). Therefore even though tremor amplitude for the old-old subjects was higher, it did not reach pathological ranges. This is also illustrated in Table 2 where rms values for PD (Table 2) and ET (Table 2) subjects are reported. As expected there was a main effect of load on the amplitude of tremor [$F_{(4,144)} = 6.21$, $P < 0.01$], such that tremor amplitude increased with load. However, an age \times load interaction was not supported ($P = 0.71$).

In line with the increase in amplitude with added load, the modal frequency of tremor decreased with load [$F_{(4,144)} = 86.25$, $P < 0.01$] (Table 2). There was a significant age \times load interaction [$F_{(12,144)} = 3.37$, $P < 0.01$]. Because of the inter-

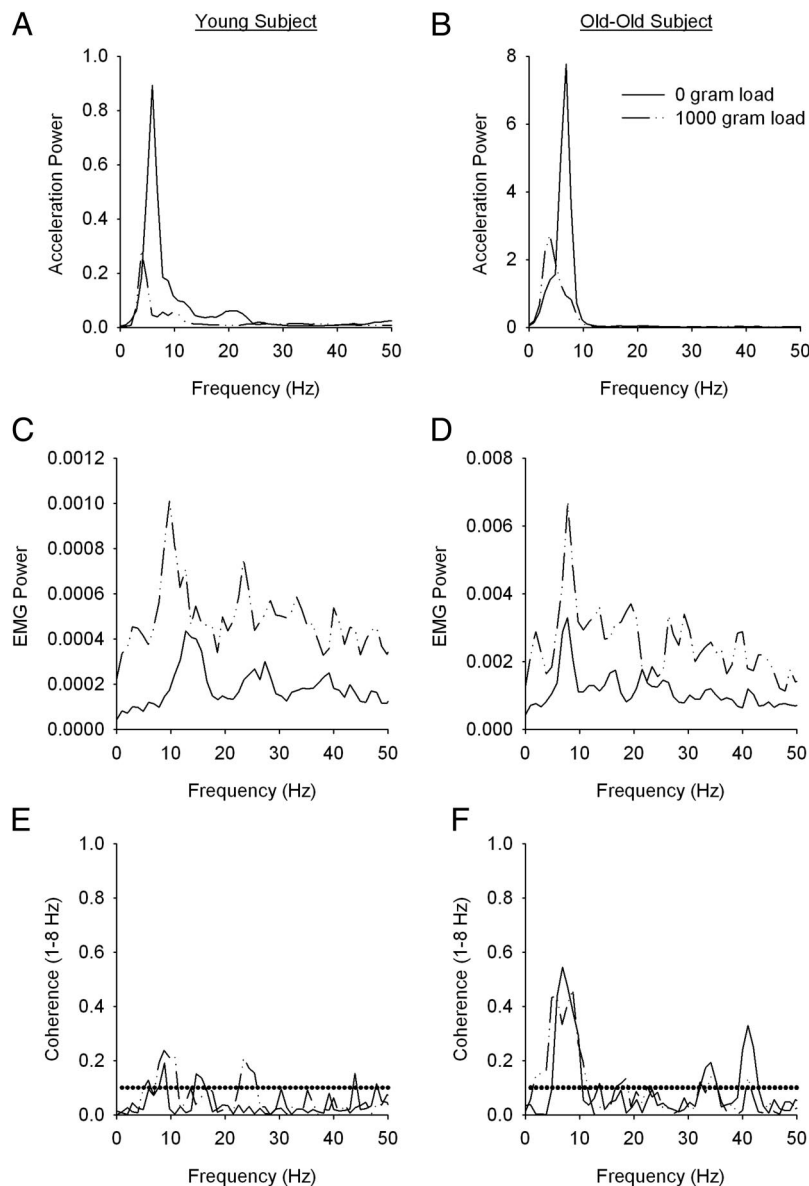


FIG. 3. A: autospectra of tremor for a young subject (25 yr) and (B) an old-old subject (81 yr). C: autospectra of the electromyographic (EMG) signal for the same young subject and (D) the same old-old subject. E: coherence between tremor and EMG for the same young subject and (F) the same old-old subject. Solid line depicts postural tremor-EMG coherence under the 0-g load and the dash-dotted line represents postural tremor-EMG coherence under the 1,000-g load. Thick dotted horizontal line in E and F represents the 95% confidence interval for significant tremor-EMG coherence.

action, separate one-way, between-group ANOVAs were conducted at each load. There was a main effect of age at the 0-g load [$F_{(3,36)} = 2.83$, $P < 0.05$]. However, when loads from 100 to 1,000 g were added to the limb, the tremor frequency was similar in all 4 age groups (values of $P > 0.17$). Independent sample t -tests confirmed a height-to-weight ratio difference between the young and old subjects ($t_{18} = 2.69$, $P < 0.01$) and the young and old-old subjects ($t_{18} = 2.29$, $P < 0.05$). Because the frequency of mechanical oscillations is inversely proportional to the square root of the combined inertia of the oscillating limb, increased limb inertia can reduce the modal frequency of oscillation (Stiles and Randall 1967). Therefore the elderly subjects were heavier than the young subjects, which may account for their lower hand acceleration frequencies at 0 g.

DISCUSSION

The purpose of this study was to investigate the effects of healthy aging on the regularity and tremor-EMG coherence of

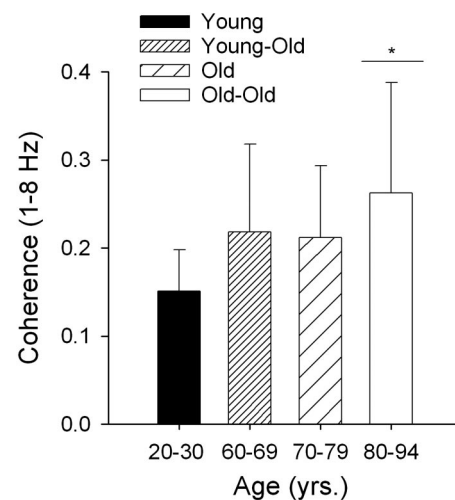


FIG. 4. Maximal postural tremor-EMG coherence in the 1- to 8-Hz band collapsed across load from young, young-old, old, and old-old subjects (mean + SD). $n = 10$ for each age group.

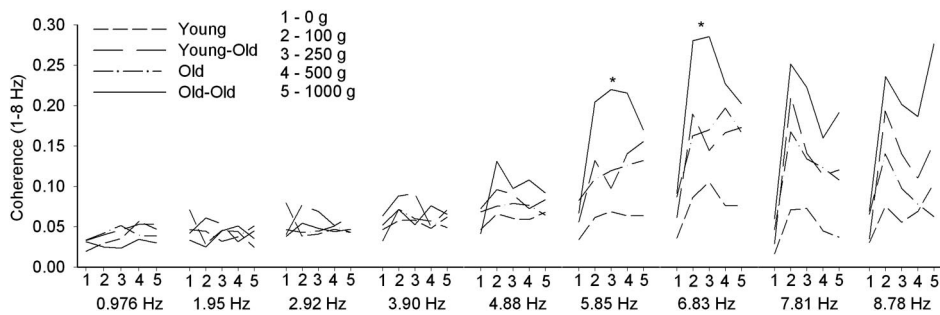


FIG. 5. Tremor-EMG coherence in the low-frequency bins measured under the postural tremor condition from young, young-old, old, and old-old subjects. Frequency bins were subdivided by 0.976 Hz into 9 bins. In each bin, mean tremor-EMG coherence is presented from each age group at each load from 0 g (1), 100 g (2), 250 g (3), 500 g (4), to 1,000 g (5).

physiological tremor under resting and postural conditions using a load manipulation. Additionally, we determined the effects of aging on the amplitude and modal frequency of resting and postural physiological tremor. There were 6 new findings from this study: 1) there were no differences between the young and elderly subjects for tremor regularity and the magnitude of tremor-EMG coherence measured under the rest condition; 2) postural physiological tremor regularity was increased in the oldest group of elderly subjects; 3) the magnitude of peak postural physiological tremor-EMG coherence in the 1- to 8-Hz frequency band was also increased in the oldest group of elderly subjects. There was a strong linear relation between the magnitude of tremor-EMG coherence at 5.85 and 6.83 Hz and tremor regularity; 4) enhanced mechanical reflex properties were not responsible for the increased magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band in the oldest age group; 5) tremor amplitude was not different between the 4 age groups, but there was a slight decline in tremor modal frequency in the oldest age group in the unloaded condition; and 6) despite the increases in postural physiological tremor regularity and the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band with age, there was a clear demarcation between healthy aging and tremor pathology. These findings have important implications for the mechanisms of tremor in the elderly and provide normative aging data that we compare with previous work on ET and PD (Sturman et al. 2004; Vaillancourt et al. 2003).

Resting tremor

The finding that age did not affect the amplitude and frequency of resting physiological tremor is consistent with previous research (Kelly et al. 1995; Raethjen et al. 2000). The

novel results from the present study are that resting physiological tremor regularity and the magnitude of peak tremor-EMG coherence were not different between young and elderly subjects. Resting tremor is one of the cardinal signs of PD (Deuschl et al. 1998; Hughes et al. 1992a,b), and the presence of an obvious resting tremor is associated with pathology. Approximately 20–30% of patients diagnosed with PD do not have a clinically detectable resting or postural tremor (Elble and Koller 1990; Lance et al. 1963; Marsden 1990). However, Vaillancourt and Newell (2000) demonstrated that the ApEn measure was sensitive enough to detect a difference in tremor regularity between mild PD patients who did not have clinically detectable tremor and control subjects. Therefore, if an individual has increased tremor regularity and/or an increased magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band at rest (Table 1), it suggests some form of tremor pathology.

Postural tremor

RELATION BETWEEN TREMOR-EMG COHERENCE AND REGULARITY. The regularity of postural tremor was greater among the elderly subjects compared with the young group. The ApEn measure has been used to assess the effects of aging on other physiological systems (Kaplan et al. 1991; Pincus et al. 1996) and to characterize pathological tremors (Sturman et al. 2004; Vaillancourt and Newell 2000; Vaillancourt et al. 2003). ApEn has also been used to identify an age-related increase in the regularity of force output during a constant, visuomotor, force-production task (Vaillancourt and Newell 2003). In the current study the magnitude of peak tremor-EMG coherence in the 1- to 8-Hz frequency band was increased among the oldest sub-

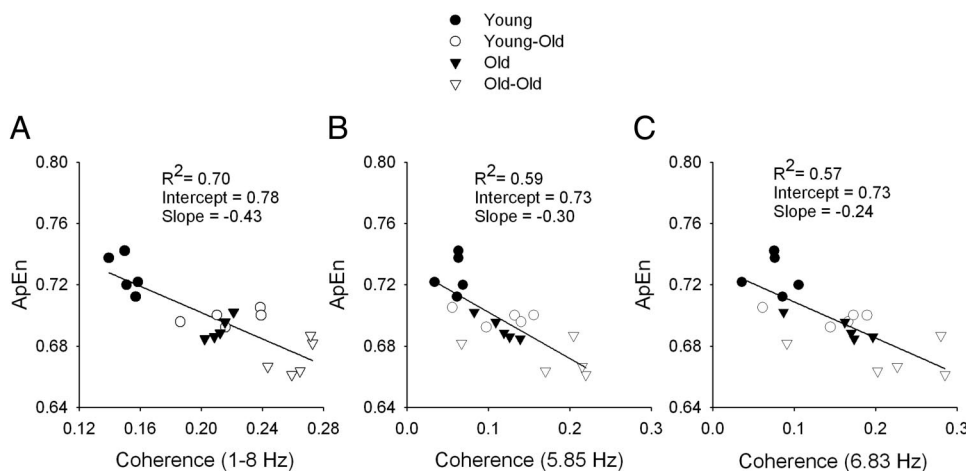


FIG. 6. Relation between regularity (ApEn) and tremor-EMG coherence in the 1- to 8-Hz frequency band measured under the postural tremor condition from young, young-old, old, and old-old subjects. Mean values for ApEn and 1- to 8-Hz tremor-EMG coherence are collapsed across subjects in each age group at each specific inertial load condition. A: tremor-EMG coherence in the 1- to 8-Hz frequency bin plotted vs. ApEn. B: tremor-EMG coherence in the 5.85 Hz frequency bin plotted vs. ApEn. C: tremor-EMG coherence in the 6.83 Hz frequency bin plotted vs. ApEn. Standard deviations for ApEn and 1- to 8-Hz tremor-EMG coherence are presented in Table 2.

jects, and there was a linear relation between the magnitude of low frequency tremor-EMG coherence and tremor regularity. The strong linear relation between low frequency peak tremor-EMG coherence and tremor regularity suggests similar mechanisms behind the age-related changes in these 2 variables. Tremor-EMG coherence provides a predictive measure of motor-unit synchronization (Halliday et al. 1999). Therefore our data suggest that the aging process enhanced motor-unit synchronization, which increased the regularity of tremor measured behaviorally.

Potential mechanisms for increased regularity and 1- to 8-Hz tremor-EMG coherence

During maintained voluntary muscle contraction, pairs of concurrently active motor units exhibit correlated discharge that is postulated to result from common presynaptic input to the motor neuron pool (Datta and Stephens 1990; De Luca and Erim 1994; Dietz et al. 1976; Farmer et al. 1997), and this common drive is thought to have central origins (De Luca and Erim 2002). Both time- and frequency-domain analysis can be used to quantify the correlated discharge of action potentials from motor units (motor-unit synchronization) (Farmer et al. 1993; Halliday et al. 1999). It is known that the common descending input to motor neurons is responsible for motor-unit synchronization in the 1- to 12- and 16- to 30-Hz frequency bands (Conway et al. 1995; Farmer et al. 1993). Due to the established relation between motor-unit synchronization, motor unit to motor unit coherence, and tremor-EMG coherence (Halliday et al. 1999), our finding of an increased magnitude of low frequency tremor-EMG coherence in the elderly subjects was most likely a result of increased motor-unit synchronization. Two potential mechanisms for this age-related change could be increased gain in the mechanical reflex pathway or alterations in the common descending input to the motor neuron pool.

Mechanical resonance tremor of the hand is driven by random, unsynchronized firing of motor units in the forearm muscles, which causes an oscillation at the mechanical resonant frequency. This is the main mechanism for physiological postural tremor (Halliday and Redfearn 1956; Stiles and Randall 1967). However, the stretch reflex is a peripheral neural mechanism that can entrain motor units at the frequency of tremor if the period of tremor oscillation is twice the time delay of the reflex loop. This is a proposed mechanism for enhanced physiological tremor (Hagbarth and Young 1979; Lippold 1970). In enhanced physiological tremor, tremor amplitude, motor-unit synchronization, and motor unit to motor unit coherence are increased (Logigian et al. 1988), while the modal frequency of tremor shifts with changes in the mechanical resonant frequency (Homberg et al. 1987). The oldest group of elderly subjects in this study had physiological tremor with an increased magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band and tremor modal frequencies that followed reductions in the mechanical resonant frequency. If enhanced mechanical reflex oscillations were responsible for these changes, there should have been a significant interaction between age and load affecting the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency bin. In this study there was no evidence for an interaction between age and load on tremor-EMG coherence. Thus increased gain in the mechanical

reflex pathway is not a mechanism that explains the increased magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band in the oldest group of elderly subjects.

The absence of age-related changes in the gain of the mechanical reflex pathway suggests that the mechanism for increased regularity and increased low frequency tremor-EMG coherence may be mediated by common descending input from the cortex to the motor neuron pool. Research examining the effect of aging on the common drive to the motor neuron pool did find differences between young and elderly subjects (Erim et al. 1999). However, other reports in the literature that examined the correlated discharge of action potentials from pairs of motor units in the time domain did not find an age-related increase in motor-unit synchronization (Kamen and Roy 2000; Semmler et al. 2000). In contrast a separate study by Semmler and colleagues (2003), using the same sample of individuals where no differences in motor-unit synchronization were found, did find a difference in the correlated discharge of action potentials from pairs of motor units between young and elderly subjects in the frequency domain (motor unit to motor unit coherence). The authors concluded that frequency rather than time-domain analyses may be more sensitive to subtle, age-related changes in the common descending input to the motor neuron pool (Semmler et al. 2003). Results from the current study support the findings of Semmler and colleagues (2003) by demonstrating increased magnitude of tremor-EMG coherence at 5.85 and 6.83 Hz in the elderly subjects (Fig. 5).

The fact that the frequency of the peaks in the EMG spectrum and tremor-EMG coherence spectrum were unaffected by mechanical load (Fig. 3) supports a centrally driven mechanism for tremor-EMG coherence in the young and elderly subjects in this study. Differences between young and elderly subjects in the ability to modulate the descending inputs to the motor neuron pool may explain the age-related increases in regularity and the magnitude of low frequency tremor-EMG coherence. In young healthy subjects the actions of multiple neural oscillators interact in a coordinated fashion to produce motor output (Sosnoff et al. 2004), and the descending inputs to the motor neuron pool are more random, oscillating at a wide variety of frequencies (Semmler et al. 2003). With aging, the ability to modulate the input from multiple neural oscillators diminishes (Lipsitz 2002; Vaillancourt and Newell 2002), and the descending input to the motor neuron pool becomes more regular, oscillating at a specific frequency (Semmler et al. 2003). These age-related changes may explain the presence of a well-defined peak in the tremor-EMG coherence spectrum between 1 and 8 Hz, which had a greater magnitude for the elderly subjects, and the more distributed pattern of tremor-EMG coherence across a wide range of frequencies with a smaller magnitude for the young subjects. Studies of coherence between motor cortical field potentials and EMG rarely demonstrate significant corticomuscular coherence at or around 10 Hz (Conway et al. 1995; Kilner et al. 2000; Salenius et al. 1997). One explanation for this finding is that a "desynchronizing central mechanism" prevents the motor neuron pool from synchronizing with low frequency cortical oscillations, thereby preventing excess physiological tremor (Baker et al. 2003). Pathological conditions such as epilepsy have been shown to disrupt the "desynchronizing mechanism" producing strong low frequency corticomuscular coherence (Raethjen et al. 2002). With age the ability to desynchronize low frequency

cortical inputs to the motor neuron pool could also diminish, causing increased coherence at or below 10 Hz.

Effects of aging on amplitude and frequency

The amplitude of physiological postural tremor was not statistically different between the 4 age groups. The fact that amplitude did not reach a statistical significance level of 0.05 is consistent with previous literature (Elble 2003; Kelly et al. 1995; Raethjen et al. 2000). In this study tremor frequency was reduced by 1 Hz in the old-old group compared with the young group at the 0-g load. However, when load was added to the limb, tremor modal frequency was the same between young and elderly subjects. This finding for load is congruent with current literature where no difference in modal acceleration frequency was found between young and elderly adults performing loaded abduction movements of the index finger (Burnett et al. 2000). Previous research has demonstrated a decrease in tremor frequency with age (Birmingham et al. 1985; Kelly et al. 1995; Marsden et al 1969b; Marshall 1961; Wade et al. 1982). In these studies the range of decline in frequency with age was about 1–4 Hz (Birmingham et al. 1985; Kelly et al. 1995; Marsden et al 1969b; Marshall 1961; Wade et al. 1982). In contrast, more recent studies have not found any decline in tremor frequency with age in either the presence or the absence of mechanical load (Elble 2003; Raethjen et al. 2000). Differences between the health and functional independence status of subjects in the preceding studies may explain the wide range (0–4 Hz) of age-related declines in tremor frequency reported in the literature. Subjects in the present study were excluded if they showed signs of neurological pathology, were deemed to be extremely frail, and/or resided in a skilled nursing facility.

Aging versus disease

Because of the increased prevalence of movement disorders among elderly individuals (Benito-Leon et al. 2003; Strickland and Bertoni 2004; Van Den Eeden et al. 2003), it is important to distinguish healthy aging from neurological pathologies. Results from this study demonstrated a strong, linear relation between the magnitude of peak tremor-EMG coherence in the 1- to 8-Hz frequency band and ApEn (Fig. 6A), and both of these variables were sensitive enough to detect age-related changes in physiological tremor between the oldest and youngest groups of subjects. Examination of ApEn values in Tables 1 and 2 suggests that healthy physiological tremor in the oldest group of subjects is different from pathological tremor in PD or ET. For resting and postural physiological tremor \pm 3SDs from the mean ApEn value for the old-old subjects yields ApEn scores that range from 0.84 to 0.54 and 0.77 to 0.59, respectively. Therefore it requires an ApEn value that is at least 3SDs below the mean of the oldest group of subjects to approach mean ApEn values of tremor in the PD and ET groups.

The 1- to 8-Hz tremor-EMG coherence data also suggest a demarcation between healthy aging and disease. For resting tremor, there is close to a 4-fold difference between the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band for the old-old subjects and the PD subjects (Table 1). For the unloaded postural tremor condition, the

magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band for the PD patients was between 2- and 2.5-fold greater than the magnitude of 1- to 8-Hz tremor-EMG coherence from the old-old subjects (Table 2). Similarly, the magnitude of the ET subjects' unloaded, postural tremor-EMG coherence in the 1- to 8-Hz frequency band was about 1.5-fold greater than that of the old-old subjects (Table 2). The relation between and sensitivity of ApEn and tremor-EMG coherence in the 1- to 8-Hz frequency band further support their usefulness as biomarkers of tremor for aging and disease.

In summary, the aging process does not affect the neurophysiological characteristics of physiological tremor measured at rest, and the most significant consequences of healthy aging on physiological tremor are found in postural tremor regularity and the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band in the oldest group of elderly subjects. Results from the current study showed that enhanced mechanical reflex properties among elderly adults are not a mechanism that can explain the age-related increases in regularity and tremor-EMG coherence in the 1- to 8-Hz frequency band. A potential mechanism that could explain the changes in these variables is the age-related loss of the ability to modulate descending inputs from multiple neural oscillators (Erim et al. 1999; Sosnoff et al. 2004). This argument is strengthened by the fact that with age the descending inputs to the motor neuron pool become more regular, oscillating at specific frequencies (Semmler et al. 2003). Despite the significant increases in postural tremor regularity and the magnitude of tremor-EMG coherence in the 1- to 8-Hz frequency band with age, there was a clear demarcation between these healthy, elderly individuals and our previous investigations of tremor pathology.

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