

Electrophysiologic Transition From Physiologic Tremor to Essential Tremor

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Abstract: We electrophysiologically examined the transition from physiologic tremor to essential tremor in people at risk for familial essential tremor. Two healthy people from different families with hereditary essential tremor were studied on multiple occasions. A 23-year-old man was studied in 1995, 1997, and 2004, and a 44-year-old woman was studied in 1993, 1995, 1997, and 2003. Hand acceleration and forearm electromyographic readings were measured with and without 300-g loading to determine the characteristic frequency-invariant motor unit entrainment of essential tremor. Clinically and electrophysiologically, the man and woman had normal tremor until the last examination, when both exhibited a fine tremulousness in the outstretched hands and frequency-invariant motor unit entrainment at 7.5 and 6.5 Hz, respectively. At no time did either patient exhibit a prominent 8–12 Hz component of physiologic tremor. Essential tremor in young adults may begin at frequencies less than 8–12 Hz, and this electrophysiologic abnormality is detectable when clinical examinations reveal only questionably abnormal tremor. More young adults at risk for essential tremor must be studied to determine whether initial frequencies less than 8 Hz are the rule or the exception. Nevertheless, the data from our 2 patients demonstrate that a prominent 8–12 Hz component of physiologic tremor does not always precede the development of essential tremor; therefore, the origins of essential tremor and the 8–12 Hz component of physiologic tremor may be different. © 2005 Movement Disorder Society

Key words: tremor; essential tremor; physiologic tremor; accelerometry; electromyography

Physiologic tremor consists of two rhythmic components: mechanical–reflex and 8–12 Hz. The mechanical–reflex component of physiologic tremor is governed by the inertial and elastic properties of the body.¹ These mechanical attributes are such that damped oscillations of the body occur in response to irregularities in motor unit firing and the force of blood ejection during cardiac

systole.^{2,3} The frequency ω of these passive mechanical oscillations depends upon the inertia I and stiffness K of the joint, according to the equation $\omega = \sqrt{K/I}$. Consequently, inertial loads on a joint decrease the tremor frequency, and elastic loads increase tremor frequency. Somatosensory receptors respond to these passive mechanical oscillations, but this response is often too weak to entrain motoneurons at the frequency of tremor.^{4,5} However, the stretch–reflex response to mechanical oscillation can be increased by fatigue, anxiety, and some medications, producing an enhanced reflex modulation and entrainment of motor unit firing. This enhanced mechanical–reflex tremor typically has an amplitude that is 5 to 20 times normal, and the electromyographic (EMG) interference pattern contains bursts of motor unit activity at the frequency of tremor.^{4,6}

The 8–12 Hz component of physiologic tremor is produced by bursts of motor unit discharge at 8–12 Hz. The frequency of this tremor is as low as 6–8 Hz in some elderly people,⁷ but it is unclear whether this lower frequency is due to normal aging or occult neuropathological state. There is a tendency for 8–12 Hz motor unit entrainment to occur in everyone, particularly in the wrist and finger extensors during slow wrist or finger flexion.^{8,9} However, this EMG rhythm is readily detectable in only 8% of normal adults during steady postural contractions.⁷ The frequency of this tremor is independent of reflex arc length and decreases less than 1 Hz when large mass loads are attached to the limb.^{3,10–12} Therefore, this tremor is believed to emerge from a central source of oscillation and is often referred to as the central neurogenic component of physiologic tremor. There is experimental support for the involvement of the inferior olives, cerebellum, ventrolateral thalamus, and sensorimotor cortex in the production of this tremor, but the primary source of oscillation is still uncertain.^{1,13,14}

The significance of a prominent 8–12 Hz tremor in asymptomatic people is unknown. Identical tremor is seen in some young adults with mild essential tremor^{15,16} and enhanced physiologic tremor.³ It is unclear whether the pathophysiological state of essential tremor simply increases a pre-existing physiological 8–12 Hz neurogenic tremor or invariably produces an 8–12 Hz neurogenic tremor as its initial electrophysiological manifestation. The latter scenario would lend support to the hypothesis that physiologic 8–12 Hz neurogenic tremor and essential tremor emerge from the same neural oscillator.¹⁵ Therefore, for more than 10 years, we have periodically examined asymptomatic people at risk for familial essential tremor, hoping to capture the electrophysiological transition from normal to pathological

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tremor. This transition in 2 young adults is now described.

PATIENTS AND METHODS

Both patients underwent the same periodic examinations and electrophysiologic tests, after signing an informed consent, approved by our committee for research involving human subjects. Tremor was assessed clinically with the tremor rating scale of Fahn and coworkers.¹⁷ In the electrophysiologic assessments, tremor and forearm EMG readings were recorded from the dominant hand using methods previously described.⁷ Briefly, postural tremor of the horizontally extended hand was recorded with the hand splinted and the forearm pronated and supported so as to restrict motion to the wrist. A 15-g triaxial piezoresistive accelerometer was secured to a 57-g plastic splint that was fastened to the dorsum of the hand with Velcro straps. The accelerometer was located over the middle finger, 14 cm from the distal wrist fold, and the fingers were splinted in extension. Hand tremor was recorded twice with and twice without a 300-g load distributed over the distal half of the horizontally extended hand. Forearm EMG readings were recorded with 7-mm diameter Ag–AgCl skin electrodes that were positioned in a bipolar arrangement near the motor points of the extensor carpi radialis brevis and flexor carpi radialis. EMG readings were full-wave rectified and low-pass filtered (–3 db at 30 Hz). Hand acceleration and rectified-filtered EMG readings (hereafter EMG) were recorded simultaneously for 62 seconds. Spectral analysis (squared amplitude vs. frequency) and coherence analysis (squared linear correlation vs. frequency) of acceleration and EMG were computed using a fast Fourier transform.¹⁸ Autospectra of six sequential 10.24-second data epochs were averaged to produce smoothed autospectra with a frequency resolution of 0.098 Hz. In addition, tremor in hand writing and figure drawing (Archimedes spirals) was quantified with a digitizing tablet, as previously described.¹⁹ The mean baseline-to-peak tremor acceleration amplitude (cm/sec²) of the unloaded hand was computed by taking the square root of the total power in the tremor spectral peak, and mean baseline-to-peak tremor displacement amplitude was estimated by dividing the acceleration amplitude by the squared peak frequency (radians/sec), as previously described.⁷

Neither patient took any medications, and both enjoyed good health. Patient A was a 23-year-old man who had 36 relatives that had been examined by one of us (R.J.E.), and 7 of these relatives had definite essential

tremor, according to published consensus criteria.²⁰ Patient B was a 44-year-old woman whose only sibling (41-year-old brother) and 72-year-old father were examined by R.J.E. Her father had a 56-year history of hand tremor, and his father reportedly had similar tremor during most of his adult life.

RESULTS

Patient A was examined in 1995, 1997, and 2004, and patient B was examined in 1993, 1995, 1997, and 2003. Their tremors were normal (grade 0) until their last examination, when both exhibited questionably abnormal (grade 1) postural and kinetic tremor in the hands. Both had been experiencing mild tremulousness in the hands when nervous or stressed during the year or so before their last examination. Patient B also experienced transient symptomatic hand tremor when she took terbutaline at age 33 for premature labor.

In 1995 and 1997, patient A exhibited a typical normal mechanical–reflex tremor that decreased 2–3 Hz with inertial loading. EMG in 1995 revealed small, inconsistent spectral peaks that did not reach statistical significance but were coherent with his tremor. EMG in 1997 disclosed tremor-related EMG activity only when the hand was not loaded (Fig. 1). These electrophysiologic characteristics are common in healthy controls.^{7,21} In 2004, at age 23, patient A exhibited prominent 7.5 Hz motor unit entrainment that did not change in frequency with inertial loading, and the amplitude of his postural tremor was much larger than in previous years (Fig. 1). The mean baseline-to-peak tremor amplitudes of his unloaded hand were 15.6 cm/sec² (0.0081 cm), 21.4 cm/sec² (0.0089 cm), and 90.2 cm/sec² (0.042 cm) in 1995, 1997, and 2004, respectively. The mean \pm SD acceleration and displacement values for 100 age-matched controls in our lab are 14.087 ± 7.993 cm/sec² and 0.006 ± 0.003 cm, respectively.⁷

Patient B had normal mechanical–reflex tremor in 1993, 1995, and 1997 (Fig. 2). EMG revealed no spectral peaks in 1993, but in 1995 and 1997, there were small, inconsistent EMG peaks only when the hand was not loaded (Fig. 2). In 2003, at age 44, she exhibited prominent 6.5 Hz motor unit entrainment that did not change in frequency with inertial loading, and the amplitude of her postural tremor had increased considerably (Fig. 2). Her 72-year-old father had advanced essential tremor with a frequency of 5.17 Hz. The mean baseline-to-peak tremor amplitudes of her unloaded hand were 5.5 cm/sec² (0.0035 cm), 28.0 cm/sec² (0.011 cm), 9.5 cm/sec² (0.0042 cm), and 127.9 cm/sec² (0.079 cm) in 1993, 1995, 1997, and 2003, respectively. Neither patient exhibited an 8–12 Hz tremor. Clinical examination and

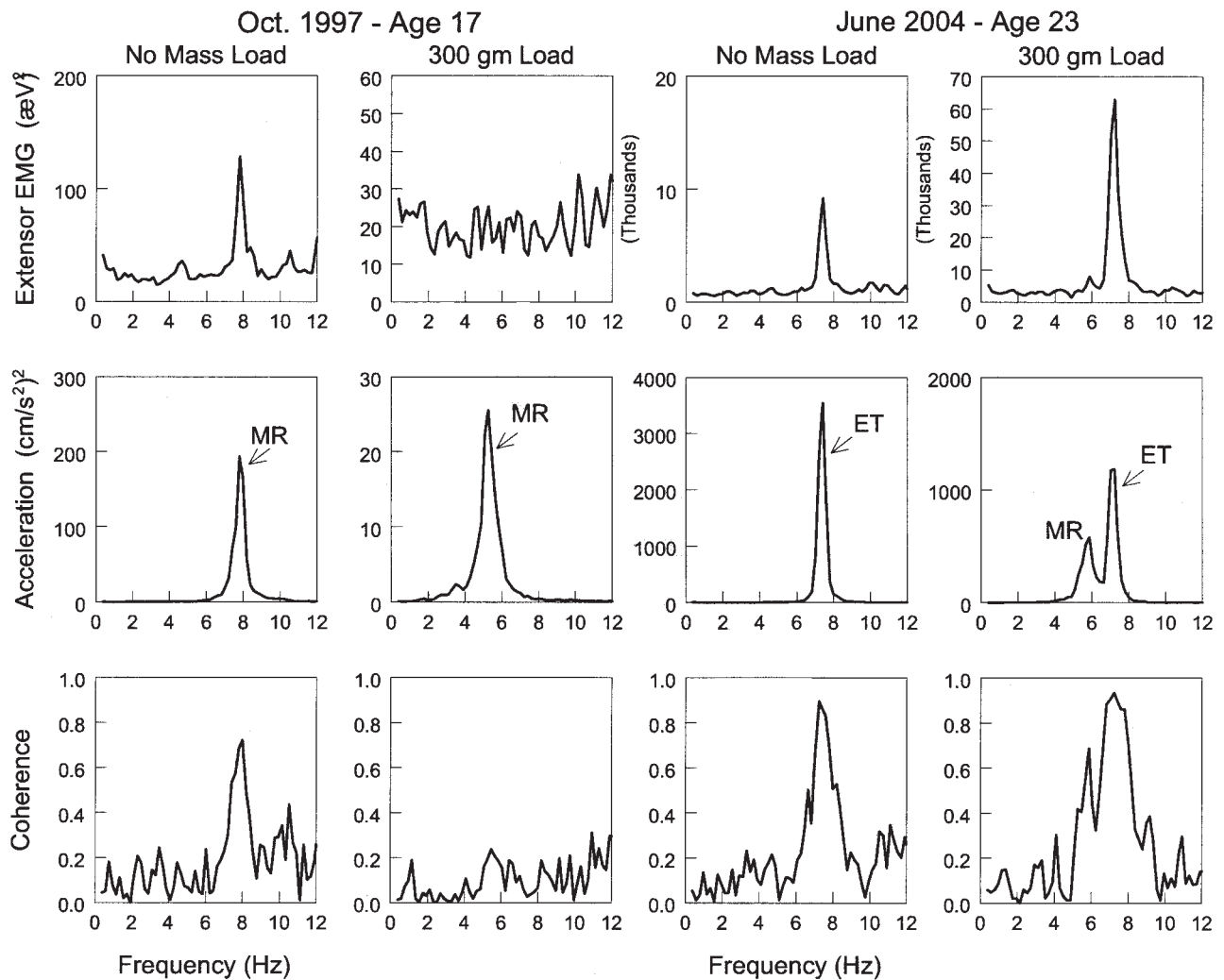


FIG. 1. Electrophysiological studies from Patient A in October 1997 were within normal limits (graphs in first two columns). The mechanical-reflex (MR) oscillation was associated with electromyographic (EMG) modulation (spectral peak at 8 Hz) only when there was no mass load on the hand, and the frequency of oscillation decreased 2.5 Hz with mass loading. In June 2004, the EMG spectra contained prominent spectral peaks at 7.5 Hz, with and without mass loading (graphs in last two columns). The essential tremor (ET) and MR oscillations had the same frequency with no mass loading, and this resonance of the MR and ET oscillations is typical in the absence of inertial loading.¹⁸ The MR frequency decreased to less than 6 Hz when a 300-g load was applied to the extended hand.

tablet analysis revealed no writing or drawing tremor in either patient.

DISCUSSION

The characteristic electrophysiological abnormality of essential tremor is motor unit entrainment at a frequency that is independent of reflex arc length and limb mechanics.^{14,18} The frequency of tremor decreases with time and is inversely proportional to the patient's age.^{16,22} Some young adults with mild familial tremor exhibit motor unit entrainment at 8–12 Hz instead of the more characteristic 4–8 Hz.^{15,16} Only approximately 8% of normal controls 20 to 40 years of age exhibit a prominent 8–12 Hz tremor.⁷

Consequently, we previously hypothesized that a prominent 8–12 Hz tremor could be a *forme fruste* or initial manifestation of essential tremor.¹⁵ We cannot exclude this hypothesis based on the present study of only 2 patients. However, the results of our study clearly show that the pathophysiological condition of essential tremor does not simply increase a pre-existing physiological 8–12 Hz neurogenic tremor, nor does essential tremor invariably produce an 8–12 Hz neurogenic tremor as its initial electrophysiological manifestation. ET may begin at frequencies less than 8 Hz in young adults who never exhibit a prominent 8–12 Hz component of physiological tremor.

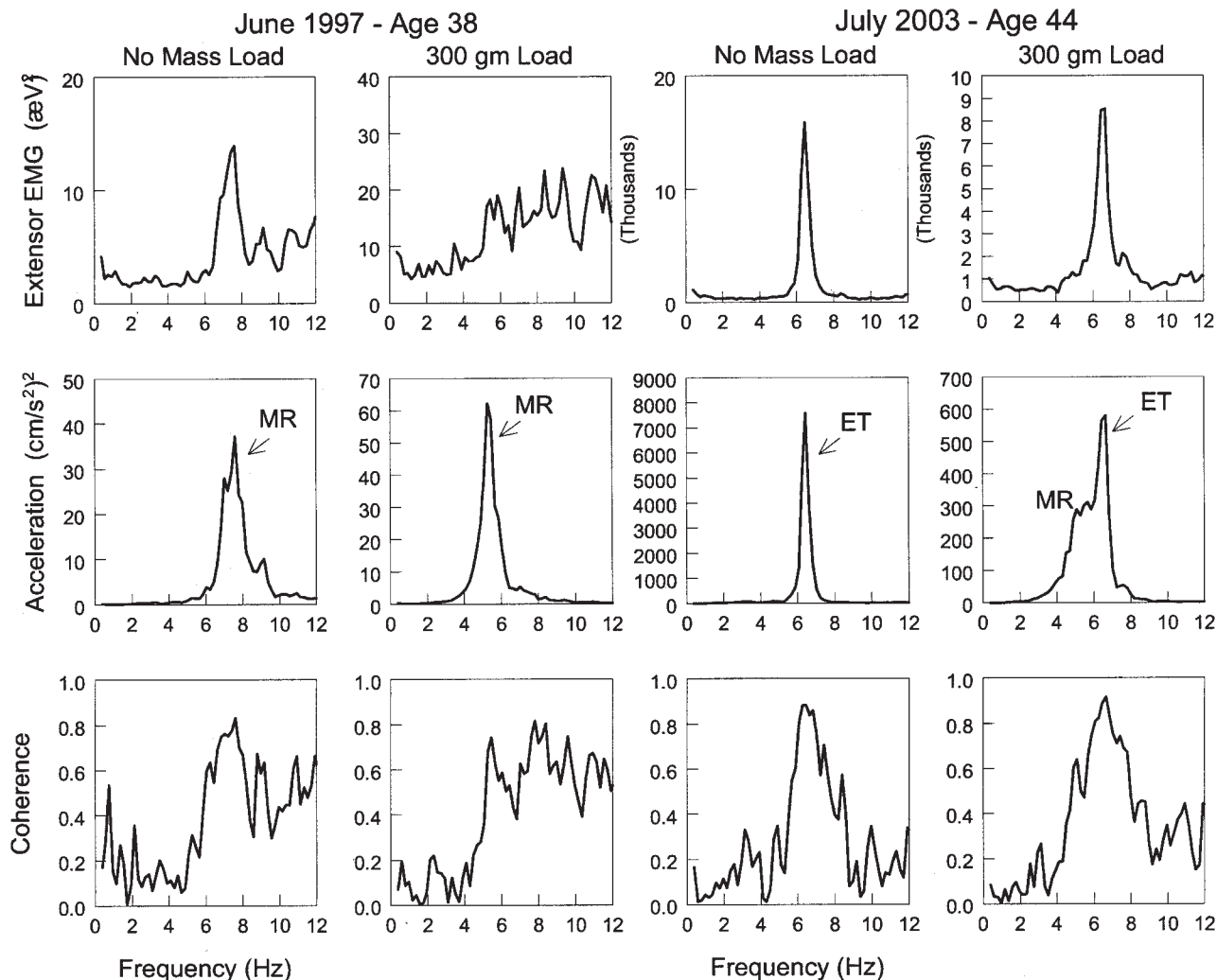


FIG. 2. Electrophysiological studies from Patient B in June 1997 were within normal limits (graphs in first two columns). The mechanical-reflex (MR) oscillation was associated with electromyographic (EMG) modulation (spectral peak at 7.5 Hz) only when there was no mass load on the hand, and the frequency of oscillation decreased more than 2 Hz with mass loading. In July 2003, the EMG spectra contained prominent spectral peaks at 6.5 Hz, with and without mass loading (graphs in last two columns). The essential tremor (ET) and MR oscillations resonated at the same frequency when there was no mass loading, but the MR oscillation moved to a lower frequency when a 300-g load was applied to the extended hand.

We have captured the electrophysiological transition from normal to ET in only 2 people, despite more than 10 years of study. We know from prior cross-sectional studies that some young adults with mild familial ET exhibit a prominent 8–12 Hz tremor and no other frequency-invariant oscillation. It is possible that these people simply had a prominent 8–12 Hz component of physiological tremor that was later enhanced by the pathophysiological condition of ET. According to this scenario, the enhanced 8–12 Hz tremor is ultimately replaced over time by a lower-frequency, larger-amplitude tremor, as previously reported.²² The clinical significance of a prominent 8–12 Hz tremor can only be

determined by additional longitudinal studies. Genetic markers for ET would also be helpful.

In summary, additional people at risk must be studied to determine whether frequencies less than 8 Hz are the rule or the exception for early ET. Nevertheless, it is clear from the present study that the earliest electrophysiological manifestation of ET in young adults can be frequency-invariant motor unit entrainment at frequencies less than 8 Hz. We have not observed frequency-invariant motor unit entrainment at a frequency below 8 Hz in more than 100 normal adults 18 to 40 years of age,^{3,7,12,15} nor was such activity found in the large study by Raethjen and colleagues.²¹ Therefore, 4–8 Hz motor

unit entrainment in this age group has greater diagnostic significance than a prominent 8–12 Hz tremor, which may be a normal variant. Frequency-invariant motor unit entrainment at less than 8 Hz is not specific for essential tremor,^{18,20} but existing data^{7,21} strongly support our interpretation that such entrainment is a useful electrodiagnostic sign of essential tremor in people with a strong family history and questionably abnormal clinical examination results.

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Pallidal Stimulation Reduces Treatment-Induced Dyskinesias in “Minimal-Change” Multiple System Atrophy

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Abstract: Deep brain stimulation therapy is increasingly gaining acceptance in the management of levodopa-induced dyskinesia and fluctuations in idiopathic Parkinson's disease. It is generally not recommended for the other forms of parkinsonism such as progressive supranuclear palsy or multiple system atrophy where the response to levodopa is usually poor and disease progression more rapid, making any benefit short-lived. Here, we present an autopsy-confirmed case of “minimal-change” multiple system atrophy in whom pallidal stim-

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