Posture-Related Oscillations in Human Cerebellar Thalamus in Essential Tremor Are Enabled by Voluntary Motor Circuits

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INTRODUCTION

Essential tremor (ET) is the most common movement disorder (Brin and Koller 1998; Louis et al. 1998). It is a bilateral, symmetric, postural, and/or action tremor that is often familial and is attenuated by alcohol (Elble and Koller 1990). Although ET appears to be a mono-symptomatic illness, its etiology and pathophysiology have been elusive. In humans, surgical lesions or deep brain stimulation (DBS) of a cerebellar recipient thalamic nucleus, Vim, abolish ET (Goldman et al. 1992; Wilms et al. 1999). Ipsilateral cerebellar activity is increased an additional 5% during unilateral postural tremor (Bucher et al. 1997; Jenkins et al. 1993; Wills et al. 1994). If this abnormal cerebellar activity during rest results from abnormal olivary oscillations, then the cerebellum and cerebellar efferent structures such as Vim should display oscillatory activity during rest and during postural tremor.

It has been suggested that oscillations originating in the inferior olive (IO) and transmitted through the cerebellum are responsible for ET (the olivary model) (Lamarre 1995). Electrotonic coupling predisposes IO neurons to synchronous activity (Llinas et al. 1974; Llinas and Yarom 1981). Furthermore, the β-carboline drug harmaline produces both continuous olivary oscillations and a fine, generalized 8- to 12-Hz tremor during rest and movement that has been compared with ET (Elble and Koller 1990; Wilms et al. 1999). If the two are comparable, then abnormal oscillatory activity in ET should be present in the olive, cerebellum, and efferent structures during rest as well as posture and action, consistent with the imaging studies (Wilms et al. 1999).

We now provide a detailed analysis of human neuronal activity in ET. Specifically we demonstrate that thalamic activity exhibited oscillatory activity only during postural tremor and not at rest. Thalamic tremor activity was strongest among cells related to voluntary movement as compared with other functional classes and was highest in Vim as compared with pallidal recipient, Vop, and the principal sensory nucleus, Vc. These results demonstrate that human thalamic activity in ET is different from that predicted by the olivary model of ET and by recent functional imaging studies.
electromyographic (EMG) activity in the contralateral wrist flexors, wrist extensors, biceps, and triceps (Lenz et al. 1988b). The micro-
electrode and EMG signals were recorded on a multiple-channel tape
recorder (Model 4000, Vetter, Rebersburg PA) along with an audio
channel describing procedures and a foot pedal signaling the onset and
duration of somatosensory stimuli.

Physiologic techniques

Physiologic exploration with the microelectrode involved both
recording of neuronal activity and stimulation at microampere current
levels (microstimulation) (Lenz et al. 1988a). During recordings,
several aspects of neuronal activity were examined including: the
spontaneous firing pattern, the relationship of spontaneous activity to
tremor, and neuronal activity during somatic sensory stimulation and
during active movement. The somatic sensory examination included
stimulation of both cutaneous structures (Fig. 1 during active movement. The somatic sensory examination included
stimulation of both cutaneous structures (Fig. 1C, neurons at sites
22–24) and structures deep to the skin (Fig. 1C, neurons at sites 10,
14, 21). Cutaneous sensory neurons responded to touch or pressure
to skin, whereas deep sensory neurons responded to joint movement and
squeezing of muscles or tendons in absence of any response to
stimulation of skin deformed by these stimuli. Cells not responding to
sensory stimulation were a separate category, i.e., nonsensory cells.

Voluntary neurons were identified by activity during active move-
ments such as making a fist, flexing or extending the wrist, elbow, or
shoulder (Fig. 1C, neuron at site 47). Cells not responding during
active movement were also a separate category, i.e., nonvoluntary
cells. In the case of voluntary neurons with sensory (deep) receptive
fields (combined neurons), voluntary neurons were defined by activity
preceding the onset of active movement as indicated by EMG activity
(Fig. 1C, neuron at site 46) (Lenz et al. 1990). Therefore the neuronal
response during active movement could not be the result of afferent
activity generated by the movement.

Microstimulation was delivered through the microelectrode in
trains of ~1-s duration at 300 Hz using a biphasic pulse consisting of
a 0.2-ms anodal pulse followed in 0.1 ms by a 0.2-ms cathodal pulse
of the same magnitude. Patients were asked during stimulation if they
felt anything. If any sensory effects were observed, then the current
was lowered in a series then raised in a series until a threshold for the
effect was established-threshold microstimulation, TMS (Lenz et al.
1993). The nature of the effect and the location of the projection field
(PF) were determined at threshold.

Initially, the activity of some neurons (n = 52) was measured with
the arm at rest by the patient’s side as they reclined. Thereafter, tremor
was produced by asking patients to elevate the arm. Patients were
seated in a reclining position with the back at ~20° above the floor
and were asked to point to the corner of the room. In this position, the
shoulder was flexed to ~45° with the elbow, wrist, metacarpophalan-
geal, and interphalangeal joints all extended to ~180°. Tremor was
provoked by this maneuver, and the neuronal activity related to tremor
was assessed for a period of between 10 and 30 s. During this interval,
we attempted to judge whether neuronal activity was related to the
tremor.

FIG. 1. Receptive field (RF) and projected field (PF) maps for trajectories in the region of ventral caudal (Vc) in a tremor patient (81 in Table 1). Results
from trajectories in the 15.0 mm lateral parasagittal (right) plane through the thalamus. In A and B, the anterior commissure-posterior commissure (AC-PC)
line is indicated by the horizontal line and the trajectories are shown by the oblique lines in each panel. The position of nuclei is inferred from the AC-PC line as
described under METHODS and thus is only a first approximation of nuclear location. A: anatomic map. The physiologic map shown in B has been shifted along
the AC-PC line so that the physiologic data shown in C best fit the anatomic map. The oval outline is an estimate of the lesion location and size based on this
map. B: physiologic map. Locations of neurons are indicated by ticks to the right of the trajectory and stimulation sites are indicated by ticks to the left of the
trajectory. Neurons or stimulation sites where no response was observed are indicated by the short ticks. Sites where recording or stimulation or both were carried
out are numbered sequentially from the top left in each trajectory, starting with trajectory P4. Scales as indicated. C: paired figurines for sites as numbered in
B are shown their projections to the right of the vertical line indicate the RF; NB indicates that the neuron had no RF. The label “tremor” indicates that the neuronal
activity was subjectively related to tremor, as assessed in the operating room. The figurines to the left indicate the part of the body where a sensation (PF) was
evoked by stimulation at that site. The number below the figure indicates the threshold in μA. A decrease in tremor with stimulation is indicated by dec tremor.
RESULTS

Recordings from 152 neurons were obtained during mapping of Vim thalamus prior to lesioning in seven patients (5, 6, 14, 25, 36, 81, and 148). All seven patients had medically intrac

table ET and have all been followed for >5 yr (Deuschl et al. 1998; Findley and Koller 1995). All patients failed treatment with myoline, propranolol, and clonazepam, both alone and in combination. Table 1 provides a description of the patients and shows that the age of the patients ranged from 35 to 75 yr (mean: 52). Five patients (5, 6, 14, 25, and 148) displayed primarily synchronous contraction of forearm antagonists during intraoperative recording of tremor (i.e., ~0° phase difference), and two patients exhibited reciprocal contraction of antagonists (i.e., ~180° phase difference). Both synchronous and reciprocal varieties have been reported in ET (Deuschl et al. 1987; Shahani and Young 1976).

The patients had lesions involving both Vim and Vop (see Fig. 1A), and most showed a significant postoperative improvement in tremor disability as measured by the Fahn standard rating scale of tremor (Fahn et al. 1988). In this rating scale, a score of 0 represents normal function, whereas a score of 4 represents total disability for that task. On average patients improved 1.3 points after surgery (Table 1).

Examples of the digitized spike trains for neurons exhibiting tremor-related activity are shown in Fig. 2. When patients held elevated the arm contralateral to the recording site, rhythmic patterns in the spike train were obvious for many of the tracings, as shown in Fig. 2A. There was marked variability of rhythmic activity during tremor ranging from distinct periodic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Duration of Tremor, yr</th>
<th>No. of Neurons</th>
<th>Preoperative Fahn Rating</th>
<th>Postoperative Fahn Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>F</td>
<td>35</td>
<td>23</td>
<td>5</td>
<td>0 Synch</td>
<td>2.1 Synch</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>46</td>
<td>14</td>
<td>45</td>
<td>16 (36) Synch</td>
<td>3.4 Synch</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>51</td>
<td>2</td>
<td>38</td>
<td>14 (37) Synch</td>
<td>3.1 Synch</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>69</td>
<td>30</td>
<td>16</td>
<td>4 (25) Recip</td>
<td>3.7 Synch</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>38</td>
<td>18</td>
<td>19</td>
<td>8 (42) Recip</td>
<td>3.4 Recip</td>
</tr>
<tr>
<td>81</td>
<td>F</td>
<td>49</td>
<td>2</td>
<td>14</td>
<td>12 (86) Recip</td>
<td>0.9 Recip</td>
</tr>
<tr>
<td>148</td>
<td>F</td>
<td>75</td>
<td>6</td>
<td>15</td>
<td>7 (47) Synch</td>
<td>1.4 Synch</td>
</tr>
<tr>
<td>Total/Average</td>
<td></td>
<td>51.9</td>
<td>13.6</td>
<td>152</td>
<td>61 (40) Synch</td>
<td>2.6 ± 0.42 1.3 ± 0.11</td>
</tr>
</tbody>
</table>

Parentheses enclose percentages. Synch, synchronous; recip, reciprocal.

Standard computational techniques (fast Fourier transform) (Oppenheim and Schafer 1975) were then used to take the raw spectral estimate of these two signals (Bendat and Piersol 1976; Glaser and Ruchkin 1976; Lenz et al. 1988b; Oppenheim and Schafer 1975). This estimate is unreliable because it has a high degree of variability that can be decreased by averaging the spectral estimate across time or frequency windows. In this study, eight contiguous, nonoverlapping, raw spectral estimates were averaged together to produce one smoothed spectral estimate, thus decreasing the variability. The autospectra were divided by the product of the averages of the two autospectra to produce the coherence of the signals at a particular frequency. By the technique used in the present study, coherence is defined as the autopower at that frequency divided by a statistically significant degree (Jenkins and Watts 1968; Lenz et al. 1988b; Oppenheim and Schafer 1975). This estimate is unreliable because it has a high degree of variability that can be decreased by averaging the spectral estimate across time or frequency windows. In this study, eight contiguous, nonoverlapping, raw spectral estimates were averaged together to produce one smoothed spectral estimate, thus decreasing the variability. The autopower of a signal is the square of the magnitude of the signal at a particular frequency and indicates the amount of activity occurring at that frequency in the signal. The signal-to-noise ratio (SNR) for a particular frequency was defined as the autopower at that frequency divided by the mean autopower throughout the spectrum and indicates the extent to which power is concentrated at tremor frequency. A SNR of greater than two indicates that power is concentrated at that frequency to a statistically significant degree (Jenkins and Watts 1968; Lenz et al. 1988b; Oppenheim and Schafer 1975).

The cross-spectrum of the two signals is composed of the magnitude (cross-power) and phase spectra. The cross-power squared is often divided by product of the averages of the two autospectra to produce the coherence. The coherence is used to estimate the probability that the two signals are linearly related, which is to say that one signal could be described as a linear function of the other (Lenz et al. 1988b). The coherence has a value of 0 if the two signals are not linearly related and 1 if there is a perfect linear relationship between the signals at a particular frequency. By the technique used in the present study, coherence >0.42 indicates that two signals are linearly related at the level of P < 0.05 (Benignus 1969), and SNR >2 indicates a significant concentration of power at a particular frequency (Jenkins and Watts 1968; Lenz et al. 1988b).

The phase was calculated as the arc-tan of the negative value of the average real component of the cross-spectrum divided by the average imaginary component (Oppenheim and Schafer 1975). A given phase angle (e.g., 60°) may equally be the value which is 360° (or 720°, 1,080°, etc) out of phase with that given angle (e.g., 60° and 300°/etc.) (Bendat and Piersol 1976). In this study, we have arbitrarily identified the phase angle with the smallest absolute value as the phase. If the phase for the spike × EMG cross-spectrum is negative, then the spike train leads the EMG signal. In Fig. 3K, the spike × EMG 1 phase angle is ~144° (or +216°), indicating that the spike signal leads the EMG signal at tremor frequency, according to our assumption. Because the tremor frequency is ~5.8 Hz and the period of one oscillation (360°) is ~170 ms, i.e., the EMG leads the spike signal by 69 ms.
“bursts” (e.g., Fig. 2A, lines 2 and 3) to continuous modulation without distinct bursts (e.g., Figure 2A, lines 4 and 5). When the arm was at rest, without EMG evidence of tremor, each neuron exhibited an aperiodic firing pattern, shown in the line of Fig. 2B corresponding to that in Fig. 2A, e.g., the same cell is represented in the third line from the top in A and B. The rest condition resembled Vim thalamic spike trains recorded in patients without movement disorders undergoing sensory thalamic procedures for treatment of pain (Fig. 2C).

To demonstrate a correspondence between thalamic spike train and EMG signals directly, we calculated the coherence between each spike train and the simultaneously recorded EMG signals. Figure 3A shows an example of simultaneous recordings of thalamic spike train, contralateral wrist flexor (EMG 1), and wrist extensor (EMG 2) signals during tremor. The autopower spectra for the spike train, EMG 1, and EMG 2 are shown in Fig. 3, B–D, respectively. In each of the three EMG autopower spectra, a distinct peak occurred at 5.8 Hz, which was therefore identified as tremor frequency. Figure 3G shows that the cross-power spectrum between EMG 1 × EMG 2 also exhibited a distinct peak at tremor frequency. These two signals were related with a significant coherence of 0.63, demonstrating that wrist extensor and wrist flexors were significantly correlated. These two signals had a phase difference of 3° at tremor frequency (Fig. 3M), indicating synchronous contraction of wrist antagonists (as opposed to a 180° difference for reciprocal contraction).

Figure 3, E and F, shows the cross power spectrum for spike × EMG 1 and spike × EMG 2 signals, and H and I show the corresponding coherence spectra. Both cross power spectra and both coherence spectra demonstrated distinct peaks at tremor frequency, i.e., 5.8 Hz. Additionally, the spike × EMG 1 coherence at tremor frequency was 0.71, whereas the spike × EMG 2 coherence at tremor frequency was 0.90. These findings demonstrate that the spike train was linearly related to both EMG signals to a significant degree. Furthermore, the spike signal demonstrated a negative phase with respect to both EMG signals at tremor frequency as shown in Fig. 3, K and L, suggesting that the spike train had a phase lead on both EMG signals.

Previously, the periodic firing of a neuron was judged to be significant if the SNR was >2 in the spike autopower spectrum (Jenkins and Watts 1968; Lemstra et al. 1999; Lenz et al. 1988b) and to be linearly related to the EMG to a significant degree if the coherence between the two signals was >0.42 (Benignus 1969). A neuron meeting both of these criteria at tremor frequency was said to show tremor-related activity. Thus the neuron shown in Fig. 3 was tremor related as were 78 (51%) of the 152 neurons studied.

Tremor activity related to functional class and nuclear location

As described under methods, neuronal responses to sensory stimulation and that preceding voluntary movement were determined. Responsiveness to sensory stimulation was not mutually exclusive of responsiveness to voluntary movements, i.e., the two categories were independent. Therefore each neuron was classified as either sensory or nonsensory and also as either voluntary or nonvoluntary. Cells could also be classified as combined, i.e., sensory and voluntary, or no response, i.e., neither sensory nor voluntary. Table 2 shows the distribution of neurons among three functional classes (sensory, nonsensory, and voluntary) and according to coherence, phase, SNR, and percentage of tremor relatedness. Voluntary neurons had the largest proportion of tremor-related neurons (75%, 15/20) as well as the largest percentage of neurons with significant coherence with EMG (95%, 19/20). Voluntary classification included 40% (8/20) sensory or combined and 60% (12/20) nonsensory neurons. The group of voluntary neurons had a significantly higher proportion of tremor-related neurons (75%, 15/20) than did the group of nonvoluntary neurons (48%, 63/132) (P = 0.03, 2-tailed Fisher’s exact test).

The proportion of tremor-related activity was not significantly different between sensory and nonsensory neurons (50%, 29/58 and 52%, 49/94, respectively, P = 0.87, 2-tailed Fisher’s exact test). On average, the spike × EMG coherence of sensory neurons (0.58 ± 0.03, mean ± SE; P = 0.01, 2-tailed t-test assuming unequal variances) and nonsensory neurons (0.55 ± 0.03, P = 0.001, 2-tailed t-test assuming unequal variances) were significantly lower than that of voluntary neurons (0.72 ± 0.04).

Combined neurons exhibited tremor-related activity (75%, 6/8) as often as neurons other than combined neurons (nonsensory neurons: 50%, 72/144, P = 0.3, Fisher’s exact test) (Lenz et al. 1990). Furthermore, the average coherence of combined neurons (0.71 ± 0.07) was not significantly different from that of nonsensory neurons (0.55 ± 0.02, P = 0.07, 2-tailed t-test assuming unequal variances).

The location of each neuron in specific thalamic nuclei was estimated as described under methods. This analysis identified that most of the neurons (61%, 92/152) were located in Vim, followed by Vc (18%, 27/152) and Vop (12%, 19/152). Fourteen neurons were located outside these three nuclei. Of the three nuclei, Vim had the highest percentage of tremor-related neurons (64%, 59/92) followed by Vc (41%, 11/27) and Vop (16%, 3/19). There were significant differences in the number of tremor neurons among the three nuclei (P = 0.0002, Fisher’s exact test). Vim had significantly more tremor-related neurons than Vc (P = 0.04, 2-tailed Fisher’s exact test) and Vop (P = 0.0002, 2-tailed Fisher’s exact test). The number of tremor-related neurons did not differ significantly between Vc and Vop (P = 0.1, 2-tailed Fisher’s exact test). The finding that cerebellar recipient thalamus, Vim, demonstrated the highest proportion of tremor neurons supports the hypothesis that ET is related to cerebellar efferent activity.

Thalamic activity at rest and during tremor

Abnormal cerebellar activity has been demonstrated during rest and tremor in functional imaging studies of ET (Boecker et al. 1996; Colebatch et al. 1990; Jenkins et al. 1993; Wills et al. 1995) and in the harmaline model of ET (Milner et al. 1995; Wilms et al. 1999). These results predict abnormal thalamic oscillatory activity in ET during both rest and tremor. Fifty-two neurons were studied with the contralateral arm at rest without tremor and during posture with tremor (Fig. 2). The mean firing rate increased significantly from rest (21.9 ± 5.0 spikes/s) to postural arm tremor (26.8 ± 5.3 spikes/s, P = 0.00001, pairwise 2-tailed t-test). Thirty-nine of the 52 (75%) neurons increased their firing rates when moving from a rest condition to tremor.
Spectral analysis of thalamic tremor neurons revealed very different frequency profiles between rest and tremor conditions. Of the 52 neurons studied at rest and during tremor, 16 were tremor-related neurons. The averaged normalized autopower spectrum in these 16 tremor neurons, shown in Fig. 4, demonstrated that tremor neuron autopower was distributed evenly among the frequencies at rest. In contrast, during postural arm tremor, there was a concentration of power.
functionally identified thalamic activity in ET

Distribution of neurons among functional classes

<table>
<thead>
<tr>
<th>Coherence</th>
<th>All</th>
<th>Sensory</th>
<th>Nonsensory</th>
<th>Voluntary</th>
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<tr>
<td>&lt;0.42</td>
<td>49 (32)</td>
<td>19 (33)</td>
<td>30 (32)</td>
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</tr>
<tr>
<td>0.42-0.6</td>
<td>37 (24)</td>
<td>10 (17)</td>
<td>27 (29)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>0.6-0.8</td>
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<td>12 (21)</td>
<td>19 (20)</td>
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<tr>
<td>0.8-1.0</td>
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<td>17 (29)</td>
<td>18 (19)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>&gt;0.42</td>
<td>103 (68)</td>
<td>39 (67)</td>
<td>64 (68)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>58</td>
<td>94</td>
<td>20</td>
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Phase

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<tr>
<td>–180° to –90°</td>
<td>22 (28)</td>
<td>5 (20)</td>
<td>17 (34)</td>
<td>6 (60)</td>
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<td>–90° to 0°</td>
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<td>10 (40)</td>
<td>14 (28)</td>
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<td>16 (21)</td>
<td>9 (32)</td>
<td>8 (16)</td>
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<td>2 (8)</td>
<td>11 (22)</td>
<td>2 (20)</td>
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<tr>
<td>Negative phase</td>
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<td>15 (60)</td>
<td>31 (62)</td>
<td>8 (80)</td>
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<td>Total</td>
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SNR

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<td>28 (48)</td>
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<tr>
<td>2-3.5</td>
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<td>21 (36)</td>
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<td>Total</td>
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<td>58</td>
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Tremor related

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<td>Non-tremor</td>
<td>74 (49)</td>
<td>29 (50)</td>
<td>45 (48)</td>
<td>5 (25)</td>
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</table>

Percentages are in parentheses.

Hz. This finding demonstrated that thalamic neurons did not exhibit rhythmic activity during rest as predicted by functional imaging studies and by the harmaline model of tremor. Instead, thalamic neurons switched to a rhythmic firing pattern at tremor frequency during postural tremor.

Sensory neurons with nonsinusoidal tremor activity

During spectral analysis, a single peak in the frequency domain represents a sinusoidal signal in the time domain with a single frequency. Multiple peaks in the frequency domain represent either concurrent signals at different frequencies or a signal with a nonsinusoidal waveform. We examined the coherence spectrum for significant peaks in the 8- to 25-Hz range. We identified 20 neurons with activity in the 8- to 25-Hz range that was related to EMG in that range as defined by spike SNR >2.0 and coherence >0.42 at the frequency of the peak in the 8- to 25-Hz range. Nineteen of these 20 tremor-related neurons were tremor-related (i.e., tremor frequency activity), and in 18 of these 19 the 8- to 25-Hz peak occurred at multiples (harmonics) of tremor frequency. These cells were more commonly found in Vim (n = 14), than in Vc (n = 4) or Vop (n = 1), or regions outside these three nuclei (n = 1).

For each of these neurons, we constructed an autocorrelogram of the spike train, i.e., a histogram of interspike intervals (ISIs) between every pair of spikes in the spike train. A composite autocorrelogram for all 20 neurons was constructed by normalizing each individual autocorrelogram by the total number of ISIs for each neuron and averaging each bin across 20 neurons (Fig. 5). Figure 5 shows that there was a paucity of ISIs in the 83 ms to 125-ms range, i.e., the range corresponding to 8- to 25-Hz oscillatory activity. In contrast, there was a peak in the 200-ms range, which corresponded to ~5-Hz tremor frequency activity. The distribution of ISIs demonstrated that the 8- to 25-Hz coherence peaks did not result from 8- to 25-Hz signals carried concurrently in the spike train. Instead, neurons with 8- to 25-Hz harmonic peaks had nonsinusoidal spike trains during tremor, i.e., spike trains were more square wave or burst-like than sinusoidal.

Among neurons with 8- to 25-Hz harmonics, 60% (12/20) were sensory neurons, a significantly higher number than that among neurons without harmonics (36%, 47/132) (P = 0.05, 2-tailed Fisher’s exact test). In contrast among neurons with harmonics, the number with activity related to voluntary movement (15%, 3/20) was not different from neurons without harmonics (13%, 17/132, P = 0.7, Fisher’s exact test). This relationship is exactly opposite to the general population of tremor neurons [compare Fig. 6, A and D (harmonics) with B and E (tremor neurons)], even though 19 of 20 neurons with 8- to 25-Hz harmonics were tremor related. Thus the subset of tremor neurons with 8- to 25-Hz harmonics was associated with proprioceptive feedback rather than voluntary movement, a relationship reversed from that for the general group of tremor neurons.

Tremor cells with harmonics had higher spike × EMG coherence (mean: 0.87 ± 0.021 SE) at tremor frequency than tremor cells without harmonics (0.77 ± 0.016, P = 0.0003, 2-sample t-test assuming unequal variances). However, this difference did not account for the reversed receptive field qualities of neurons with harmonics as compared with tremor cells in general. Figure 6, C and F, shows that the 39 tremor neurons with high coherence levels (>0.8) were significantly related to voluntary movement but not to sensory receptive fields (P = 0.01, 2-tailed Fisher’s exact test), similar to the general population of tremor cells. In summary, neurons with 8- to 25-Hz harmonics have proprioceptive inputs, nonsinusoidal tremor activity, and high tremor frequency coherence and represent a subset of tremor neurons that may allow sensory feedback direct access to the central tremor oscillator in ET.

Discussion

This study reports that thalamic neurons exhibited periodic activity that was coherent with EMG during posture but not during rest. These results are not consistent with a model of continuous oscillatory drive generated in the olivo-cerebellar circuit and transmitted to the periphery without modulation by limb position or movement as predicted by functional imaging studies and animal models. Our results further demonstrate that among thalamic nuclei, Vim had the highest percentage of tremor neurons. Among functional classes, voluntary neurons had the highest proportion of tremor neurons. These findings suggest that the activity of the central oscillator in ET is both mediated through...
and modulated by voluntary neurons in Vim. Thus ET may be the result of motor circuits involving the thalamus that elevate tremor-related inputs to the thalamus above threshold levels and so enable tremor during posture or movement.

Mechanism of ET

Mechanical studies suggest that ET results primarily from a central oscillator (Elble 1996; Elble and Koller 1990). The identity of the central oscillator has been elusive, although the inferior olive is the leading candidate. Recent imaging studies have attempted to delineate the location of the central oscillator in ET. In patients with ET, PET scanning at rest without tremor using $^{18}$F-fluoro-2-deoxyglucose to measure regional resting glucose metabolism demonstrated increased activity in the thalamus and medulla, perhaps in the olive (Hallett and Dubinsky 1993). Furthermore, PET scanning at rest using $H_2^{15}$O and $C^{15}$O$_2$ to measure regional blood flow demonstrated increased activity in the cerebellar vermis and hemispheres, red nuclei, and thalamus bilaterally in patients with ET (Boecker et al. 1996; Colebatch et al. 1990; Jenkins et al. 1993; Wills et al. 1995). Unilateral postural tremor was associated with an additional 5% increase in blood flow in the same areas bilaterally as well as in the contralateral sensorimotor cortex (Bucher et al. 1997; Jenkins et al. 1993; Wills et al. 1994). Although this constellation of results does not identify a specific neuronal network as the central oscillator, these results do indicate that an altered neuronal substrate is present bilaterally in the cerebellum and in its connections with the red nucleus and thalamus, both at rest and during tremor.

The olivary model of ET is also suggested by harmaline tremor that has been proposed to mimic ET and that occurs during rest, posture, and action (Elble 1998; Lamarre 1995; Wilms et al. 1999). Harmaline induces continuous oscillatory activity in the inferior olive (Llinas and Yarom 1986), which suggests that similar activity occurs in ET. This activity may descend through bulbospinal pathways en route to spinal motor neurons in cats (Lamarre 1984; Weiss 1982). In monkeys, the olivary and cerebellar activity may be transmitted through a pathway involving cerebellum, thalamus, cortex, and corticospinal tract (Lamarre 1995).

If ET originates from continuous olivary cerebellar oscillations as predicted by functional imaging studies, oscillatory activity should be present in cerebellar efferent structures during rest and tremor. However, in the present study, we did...
not find evidence for oscillatory behavior at rest in Vim. Instead we found a dramatic change in the pattern of Vim activity from nonoscillatory activity at rest to tremor frequency oscillations during arm tremor. Although the single-unit techniques used in this study do not detect the presence of subthreshold potentials, local field potentials (LFPs) may detect membrane potentials. Marsden et al. (2000) have demonstrated the presence of LFPs in the thalamus that are coherent with EMG only during isometric contraction but not during rest in one patient with ET. The absence of thalamic oscillations during rest is in contrast to the significant resting cerebellar activity seen in functional imaging studies (Bucher et al. 1997; Jenkins et al. 1993; Milner et al. 1995; Wills et al. 1994).

For the present results to comply with an olivary model of tremor and with functional imaging studies, olivary activity should switch from an nonoscillatory pattern during rest to an oscillatory pattern during tremor (Welsh and Llinas 1995; Welsh et al. 1995). Mechanisms for such a switch in the context of tremor have not been proposed, and direct evidence for oscillatory activity in the olivary cerebellar system during normal movement has been difficult to demonstrate (Keating and Thach 1995, 1997).

Alternately, the switching could occur in the thalamus. The present results demonstrate that 50% of neurons in Vim or Vop are not activated either during sensory stimulation or during a range of active movements, yet many of these cells have tremor-related activity. A similar group of tremor-related cells have been described in patients with parkinsonian tremor (Lenz et al. 1990, 1994). The determinants of the activity of these neurons are unclear. It may be that the powerful cortical inputs not phase locked to voluntary movement can depolarize thalamic neurons. These “energizing” inputs (Jasper and Bertrand 1942) might not produce activity related to active movement but might elevate subthreshold tremor-related inputs from the deep cerebellar nuclei above threshold so enable the thalamic tremor-related activity (Butler et al. 1998; Sherman and Guillery 2001).

Another hypothesis for the generation of posture-dependent thalamic oscillations involves the activation of reverberating cerebellar thalamic cortical circuits during posture (Deuschl and Bergman 2002; Elble 1998). Recurrent premotor circuits involving the cerebellum, thalamus, cerebral cortex, and pons have been proposed to carry an efference copy and to mediate motor learning (Horne and Butler 1995; Houk and Wise 1995; Hua and Houk 1997). This and other recurrent feedback connections with the cerebellar nuclei are thought to exhibit reverberatory premotor activity that is modulated by Purkinje cell inhibition of the cerebellar nuclei (Allen and Tsukahara 1974; Houk et al. 1993). Activation of these recurrent premotor circuits during movement in the context of abnormal cerebellar cortical activity may lead to the generation of tremor activity during posture and movement but not at rest. This hypothesis is supported by the clinical findings that lacunar strokes in the cerebellum as well as the pons (both parts of the cortico-cerebellar circuit) have been reported to eliminate essential tremor (Dupuis et al. 1989; Nagaratnam and Kalasabail 1997). Our finding that voluntary neurons in the thalamus have the highest proportion of tremor activity supports the involvement of premotor circuits in the mechanism of ET.

Sensory entrainment of the central oscillator

Although the exact location of the central oscillator in ET is still in debate, mechanical studies suggest that the oscillator in ET is of a nonlinear limit cycle variety (Elble and Koller 1990). Limb-perturbation studies have shown that the amplitude and phase of ET can be reset with large limb perturbations at particular frequencies (Elble et al. 1992; Lee and Stein 1981). Thus the central oscillator may be influenced by peripheral inputs, perhaps through a stretch-reflex arc (Lenz et al. 1983a, 1994). Although we found that voluntary neurons had the highest proportion of tremor activity, we also found a subset of proprioceptive neurons that exhibited high coherence with tremor and nonsinusoidal, burst-like, tremor-related activity.
The burst-like activity of these sensory neurons may result in harmonic frequencies in the coherence spectrum. These sensory tremor neurons with harmonic coherence peaks may allow peripheral inputs to modulate the central oscillator in ET.

The presence of harmonics in the tremor-related activity of sensory cells means that their activity is not purely sinusoidal. The nonsinusoidal pattern may reflect the transformation of the tremor-related EMG signal either by coupling of EMG to muscle or of muscle to movement or by the sensory receptor which transduces the tremor sensory signal (Johnson et al. 2000; Mathews 1981). Alternately, this pattern may reflect the nature of essential tremor, the EMG of which can have harmonics (see Fig. 3, B and C). Whatever the mechanism, these results suggest that both voluntary activity and sensory feedback, both tremor and harmonic related, may play important roles in the generation of ET.

Comparison of ET with Parkinson’s Disease

While ET and parkinsonian tremor are both treated effectively by thalamic lesions or DBS, they are believed to have different mechanisms. The most obvious difference is that ET is primarily a postural tremor, whereas parkinsonian tremor is primarily a resting tremor. The postural component of ET may arise from tremor-related inputs to thalami that are enabled by active movement, whereas the best evidence indicates that tremor in PD is the result of reflex mechanisms. Studies using the present techniques demonstrate that thalamic neurons in PD exhibit strong tremor-related activity with the arm at rest (Lenz et al. 1988b) in contrast to the present findings in ET (Fig. 4) and intention tremor (Lenz et al. 2002). Furthermore, sensory neurons in PD had significantly higher proportions of tremor-related activity than neurons without sensory inputs (Lenz et al. 1994). There was also no difference in the proportion of tremor neurons between cerebellar recipient Vim and pallidal recipient Vop thalamus. Compared with the present findings in ET, these studies suggest that the role of the thalamus in PD tremor is different from in ET. The thalamus in PD may be involved in a sensory feedback mechanism of tremor, perhaps through long loop reflex arcs (Cheney and Fetz 1984; Desmedt 1978; Lenz et al. 1983b).

G R A N T S

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R E F E R E N C E S


FUNCTIONALLY IDENTIFIED THALAMIC ACTIVITY IN ET


