Thalamic stimulation reduces essential tremor but not the delayed antagonist muscle timing

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Abstract—Background: Electrical stimulation of the thalamus dramatically reduces essential tremor (ET). It has been hypothesized that the cerebellum and inferior olive are involved in the generation of ET, and thalamic stimulation is presumed to dampen ET through interactions with cerebellar output to the thalamus. Evidence suggests that abnormal timing of agonist and antagonist muscle responses contribute to cerebellar tremor (CbT); however, this relationship has not been investigated for ET. The mechanisms of the tremor and improvement are unknown. Objective: To measure the effect of ventral intermediate thalamic stimulation in controlling the ET response to sudden stretch of an agonist muscle and to determine whether, in ET, the timing relationships between the initial agonist and antagonist electromyography (EMG) responses show abnormalities similar to those seen in CbT. Methods: The authors studied ET subjects (with implanted thalamic stimulators turned off and on) and normal controls as they responded to mechanical torque pulses given at the wrist joint. The wrist joint angle, wrist agonist, and antagonist EMG were recorded. Results: Like CbT, patients with ET showed delayed onsets of antagonist EMG and excessive rebound. Thalamic stimulation reduced the tremor but did not alter the antagonist delay or the rebound. Conclusions: In ET, antagonist muscle responses to a torque pulse are similar to that in CbT. However, benefit from thalamic stimulation did not alter these EMG responses; therefore, suppression of tremor must be caused by mechanisms other than the re-establishment of normal agonist–antagonist timing.

The fundamental mechanism causing essential tremor (ET) is unknown. One possibility is a pathologic periodic synchronized discharge generated in the inferior olive and relayed through the cerebellum and out over excitatory pathways to cerebellar motor targets. Another is an increased propensity for reciprocal thalamocortical circuits to oscillate. Recently, deep brain stimulation of the ventral intermediate (VIM) thalamic nucleus has been shown to substantially reduce ET. However, the mechanism by which thalamic stimulation suppresses tremor remains unknown.

The current study first quantifies the effect of VIM thalamic stimulation in controlling the ET response to sudden stretch of an agonist muscle, and, second, examines in ET the timing relationships between the initial agonist and antagonist electromyography (EMG) responses, which are known to be abnormal in cerebellar tremor (CbT). We found that ET, like CbT, has a normal agonist but a delayed antagonist EMG response that results in excessive rebound on the return toward the initial position. Thalamic stimulation improved the tremor. Nonetheless, thalamic stimulation did not improve the delayed antagonist response and the excessive rebound. We discuss the similar abnormalities in ET and CbT and how thalamic stimulation may improve tremor without restoring antagonist timing.

Preliminary accounts of some of these results were published previously.

Methods. Subjects. Eight ET subjects and eight control subjects matched for age and sex, all right-hand dominant, participated in this study (table 1). The mean age ± the SD of ET subjects was 70.1 ± 9.9 years. Magnitude and constancy of right upper extremity tremor was graded by a neurologist on a scale of 0 to 4 (see table 1): six of eight were 3 (moderate) and two of eight were 4 (marked) in severity. All ET subjects had a single implanted thalamic stimulator and, with stimulator “off,” visible postural tremor at the wrist. The mean age ± SD of healthy adult controls was 70.7 ± 8.4 years. Informed consent was obtained from all subjects before testing in accordance with the Institutional Review Board at Washington University School of Medicine.
Thalamic stimulator information. Each ET subject had a single left-side thalamic stimulator implanted from 1 month to 3 years before testing (mean, 16 months). The stimulating electrode for each subject had been implanted in the left VIM nucleus of the thalamus using standard stereotaxic methods. The electrode then was connected to a pulse generator that was implanted subcutaneously in the subclavicular area and was programmed to yield the greatest tremor suppression with the fewest side effects (e.g., paresthesia). At the time of testing, all subjects verbally reported that when the stimulator was turned on, it provided dramatic relief from tremor symptoms.

Protocol. Subjects were seated with their forearm supported and right hand placed, fingers extended, in a manipulandum device that was attached to a torque motor (figure 1). In all trials, the manipulandum restricted arm movements to wrist flexion and extension in the horizontal plane. The agonist muscles were the wrist flexors, and the antagonist muscles were the extensors. The torque motor provided a maintained flexor load of 0.25 nm, sufficient to activate forearm flexors and (in ET) result in tremor in the hold position. An oscilloscope screen was placed in front of the subject, displaying a target hold area with two vertical cursors and (in ET) result in tremor in the hold position. An oscilloscope screen was placed in front of the subject, displaying a target hold area with two vertical cursors, displaying a target hold area with two vertical cursors placed about 1 inch apart (approximately 20° of wrist flexion or extension). A third vertical cursor represented the manipulandum. Subjects were instructed to keep the manipulandum (i.e., the third cursor) in the target hold area during all trials. Voluntary movements were cued by movement of the target hold area to the right of center, requiring subjects to flex the wrist in the manipulandum. The voluntary movement periods served as a break between the hold periods and were not further analyzed. ET subjects were tested under two different conditions: 1) thalamic stimulator turned off (Stim Off), and 2) stimulator turned on (Stim On), each consisting of 10 trials. Each trial began with a constant, flexor load, hold period of 800 to 1200 ms, immediately followed by a 2000-ms voluntary movement period (against the same load), and ended with a return to the hold position. In five randomly ordered trials within each condition, a torque-pulse perturbation was given during the hold period. The perturbation consisted of a 1.0-nm and 100-ms duration load stretching the wrist flexors and displacing the wrist and manipulandum in extension. In practice trials, the subject had been previously instructed to return the manipulandum to the initial hold position as quickly as possible. Subjects were instructed to keep the manipulandum in the cued hold position during all trials. Physical assistance was given if subjects could not return the manipulandum to the hold window at the completion of each trial.

Apparatus. Kane and Thach previously described the details of the manipulandum apparatus. Silver–silver chloride patch electrodes were used for the surface EMG recordings from the wrist flexors and from the wrist extensors. Wrist flexor EMG likely included the activities of the flexor digitorum superficialis and profundus muscles; it also may have included the activities of the flexor carpi

Table 1 Information on subjects with essential tremor

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Time with stimulator implanted, mo</th>
<th>Length of symptoms, y</th>
<th>UE tremor scale</th>
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<tr>
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<td>M</td>
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<td>25</td>
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<tr>
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<td>M</td>
<td>49</td>
<td>1.5</td>
<td>28</td>
<td>4</td>
</tr>
</tbody>
</table>

Tremor scale: 1 = slight and infrequently present; 2 = mild in amplitude, or medium in amplitude but only intermittently present; 3 = moderate in amplitude and present most of the time; 4 = marked in amplitude and present most of the time.

ET = essential tremor; UE = upper extremity.
radialis and ulnaris muscles. Wrist extensor EMG likely included the activity of the extensor digitorum; it also may have included the activities of the extensor carpi radialis longus and brevis and extensor carpi radialis ulnaris. EMG signals were amplified (1000×) using a differential amplifier (DAM 80, World Precision Instruments, Inc., Sarasota, FL), bandpass filtered (10Hz-1kHz), and digitally sampled at 2 kHz. The signal then was filtered using digital high-pass filtration (140 Hz) and rectified using Spike Two Software (Cambridge Electronics Design, Cambridge, UK).

Analysis. We analyzed wrist position data and EMG activity during the initial hold period of the trials in which a torque-pulse perturbation occurred. To estimate tremor damping, we fit the wrist position data obtained during the first 100 to 1000 ms (900 ms per trial) after the torque-pulse perturbation to the following equation using a least square method:

\[ \theta = - (A \cdot e^{-\lambda t} \cdot \cos(\omega t + \phi) + B) \]

where \(A\) represents displacement from equilibrium, \(\lambda\) is the damping coefficient (1/ms), \(t\) is the time in milliseconds from the onset of the torque pulse, \(k\) is the scaling constant, \(\omega\) is the angular oscillation frequency, \(\phi\) is the phase angle, and \(B\) is the bias term. The 900-ms period reflects the time after the 100-ms torque-pulse perturbation and continues up to the point where physical assistance could be given for subjects to return the manipulandum to the initial hold position (shortly after 1000 ms). Analysis of variance (ANOVA) was done to determine significant differences among the three groups (controls, ET Stim On, and ET Stim Off) for the amplitude, the damping coefficient, and the angular frequency. Only the results for the damping coefficient \(\lambda\) are reported here because the other variables did not show any consistent patterns across subjects or groups.

Prior work has shown that postperturbation antagonist EMG activity that is delayed in onset and prolonged in duration accompanies CbT. To test if subjects with ET had a similar disturbance, we calculated the following regarding postperturbation: 1) the onset latency of the first agonist (wrist flexor) and antagonist (wrist extensor) EMG bursts, and 2) the duration of the first agonist and antagonist EMG burst. In many of the EMG traces, one can distinguish two peaks, the latencies corresponding to those of the so-called “M1 and M2” components of the initial agonist burst. In this analysis, the two peaks, when apparent, were lumped together and considered as one burst. In addition, we quantified the number of EMG bursts after
the torque pulse along with the number of wrist position peaks in amplitude.

To compute the EMG latencies, we first determined a baseline for EMG activity. The baseline was chosen as a quiet period of 100 ms within the 500-ms period just before the torque pulse. The time of onset of EMG activity then was chosen as the point when the activity increased at least three SD above baseline measure for a minimum of 20 ms after the torque pulse.

To analyze the duration of the first agonist and antagonist bursts after a torque-pulse perturbation, onset and offset times of EMG activity for each burst were chosen systematically. Onset times were chosen as previously described. Offset times were chosen as the point when an EMG burst returned to baseline level after an onset.

To quantify the number of repetitive EMG bursts, we counted the number of agonist–antagonist burst pairs after the torque pulse. Criteria for onset and offset of an EMG burst were the same as that used for the latency and duration measurements. In this analysis, the area of each EMG burst after torque-pulse perturbation was compared with the area of the first burst in that trial; agonist bursts were compared separately from antagonist bursts. As a systematic means of counting EMG bursts that maintained an appreciable magnitude, each burst was counted only if its area remained at 50% of the area of its respective first burst (e.g., the second and third agonist bursts had to be at least 50% of the first agonist burst). A pair of EMG bursts was defined as one agonist and one subsequent antagonist burst. Counting was stopped if 1) one of a burst pair did not reach its 50% criteria for two successive bursts, or 2) 12 burst pairs were counted (this often was the case in ET subjects with Stim Off).

To analyze the amplitude of the corrective wrist response after a torque-pulse perturbation, the first maximum wrist flexion position relative to its baseline was chosen systematically. Baseline is the wrist position immediately before onset of the torque pulse. All five of the torque pulse trials from each subject were analyzed. The amplitude of the corrective wrist response was of primary interest because it should correlate with latency findings in the antagonist EMG responses.

ANOVA was used to test for significant differences in latencies of muscle activity, duration of first agonist and antagonist bursts, number of burst pairs, peak wrist flexion amplitude between control subjects, and ET subjects with Stim On and Stim Off.

**Results.** Thalamic stimulation reduced tremor in our ET subjects and improved the damping of their response to a torque-pulse perturbation. Figure 2 shows single-trial position traces from one representative control and matched ET subject (ET05) with Stim Off, and (C) the same essential tremor (ET) subject with stimulator turned on (Stim On). Ordinate: ordinate: time before and after onset of torque-pulse perturbation in milliseconds. Vertical line represents the onset of the 100-ms torque-pulse perturbation. EMG traces show the agonist muscle displayed above the abscissa and corresponding antagonist muscle inverted on the same axis. Arrows represent the time of antagonist muscle onset for each trial. The control subject had a latency of 141 ms. The ET subject, both with stimulator turned off (Stim Off) and Stim On, had a significant delay in onset of antagonist muscle burst (185 ms and 183 ms, respectively) and an excessive rebound.

![Figure 4. Single trial of electromyography (EMG) and corresponding wrist position traces for (A) one control subject, (B) one ET subject (ET05) with Stim Off, and (C) the same essential tremor (ET) subject with stimulator turned on (Stim On). Ordinate: for EMG is microvolts (MicV), for position is degrees (DEG). Abscissa: time before and after onset of torque-pulse perturbation in milliseconds. Vertical line represents the onset of the 100-ms torque-pulse perturbation. EMG traces show the agonist muscle displayed above the abscissa and corresponding antagonist muscle inverted on the same axis. Arrows represent the time of antagonist muscle onset for each trial. The control subject had a latency of 141 ms. The ET subject, both with stimulator turned off (Stim Off) and Stim On, had a significant delay in onset of antagonist muscle burst (185 ms and 183 ms, respectively) and an excessive rebound.](image-url)
Thalamic stimulation improves ET, increasing damping coefficient more than twofold. The ET subjects had higher damping coefficients during the Stim On condition compared with the Stim Off condition ($p < 0.01$). All three groups (controls, ET Stim On, and Stim Off) were different from one another ($p < 0.01$). Figure 3A illustrates the method of determining the damping coefficient where the exponential curve follows the contour of the tremor over time. The damping coefficient represents how quickly the oscillations returned to their baseline amplitude and frequency. Figure 3B illustrates summary data for subjects in the three groups: control, ET with Stim On, and ET with Stim Off. The controls had the highest damping coefficient of the three groups with a mean ± SEM of 14.7 ± 1.7, ET subjects with Stim On had a mean of 9.22 ± 1.2, and ET subjects with Stim Off had a mean of 4.0 ± 0.9. A large damping coefficient shows that control subjects minimized the number and size of oscillations after a torque-pulse perturbation, as seen in figure 2B. Damping coefficients calculated for ET subjects during the Stim On condition were not normal but were closer to control.

Thalamic stimulation does not change the delayed antagonist response and excess rebound. In CbT, after sudden agonist muscle stretch, there is a delayed antagonist muscle response and excess rebound of the perturbed limb segment. This imbalance in stretch reflexes could, in turn, cause the tremor. We wanted to see if there were similar imbalances of agonist–antagonist stretch reflexes in ET. If so, might thalamic stimulation correct them in such a way as to “explain” improvement of tremor?

Agonist and antagonist onset latencies. Figure 4 shows a single trial of EMG and wrist angular position from one control subject and one ET subject with Stim Off and Stim On. Each trace shows a 500-ms period aligned on torque-pulse perturbation (vertical line). The onset latencies of the initial agonist EMG response (wrist flexor) after the perturbation showed no differences between the control and the ET subject with Stim Off and Stim On. By contrast, the onset of the first antagonist EMG for the control subject was 141 ms, whereas that for the ET subject was delayed during both the Stim Off (185 ms) and the Stim On (183 ms) conditions.

In all ET subjects, the timing of the stretched agonist response was normal and the antagonist response was delayed. Figure 5A summarizes the EMG onset times across subjects. Agonist EMG mean onset times are shown for individual subjects (small open symbols) and group means (large open symbols). Antagonist EMG onset times are shown as filled symbols. The group mean latency of the first antagonist EMG burst in ET subjects with Stim On was significantly delayed compared with the control group ($p < 0.0001$) and with ET subjects with Stim On ($p < 0.001$). Antagonist muscle responses were not significantly different when comparing ET subjects with Stim On and Stim Off. (B) Individual subject mean number (± SEM) of agonist–antagonist muscle burst pairs for the control, ET Stim Off, and ET Stim On groups after a torque-pulse perturbation. ET subjects during the Stim Off condition had more muscle burst pairs ($p < 0.0001$) compared with ET subjects in the Stim On condition and with control subjects. There was no significant difference in number of muscle burst pairs between control subjects and ET subjects with Stim On.
and Stim Off was delayed compared with that of control subjects ($p < 0.001$). This also was true for individual ET subjects, with the exception of ET04. In this subject, the antagonist EMG response time was within the normal range, but surprisingly, only with Stim Off. During Stim On, this subject’s latencies fell back into the group range with a mean delay of 144 ms.

**Duration of first agonist and first antagonist bursts.** Control subjects overall had a shorter first agonist EMG burst duration than ET subjects with Stim Off ($p < 0.01$) and Stim On. However, the duration of the agonist EMG activity in ET subjects did not change with thalamic stimulation. Control subjects had a mean duration ± SEM of 46.8 ± 4.0; ET subjects with Stim On, 71.4 ± 8.6; and ET subjects with Stim Off, 82.8 ± 6.4 ms. The duration of the first burst of antagonist EMG activity in ET subjects with Stim On and Stim Off was not significantly different than in control subjects. Control subjects had a mean duration ± SEM of 90.2 ± 7.3 ms; ET subjects with Stim On, 76.0 ± 7.1 ms; and ET subjects with Stim Off, 76.7 ± 6.5 ms.

**Antagonist rebound.** As shown previously, the delay in antagonist EMG activity was accompanied by a larger than normal wrist flexion corrective response. Table 2 shows individual and group peak amplitude measures for the first corrective response. Compared with the control group, after perturbations, ET subjects with both Stim Off and Stim On rebounded with greater peak amplitudes ($p < 0.01$). In ET subjects, the amplitude of the corrective response increased with stimulation. However, ET subjects as a group showed no significant difference in the amplitude of the rebound with Stim Off vs Stim On.

**Number of post-torque pulse EMG bursts.** Improvement of ET by thalamic stimulation was quantitated by counting the post-torque pulse EMG bursts with Stim On and Stim Off compared with controls. Figure 6 illustrates representative EMG and position traces aligned on torque-pulse perturbation for one control subject and one ET subject. Figure 6A shows that the control subject responded with two oscillations of wrist position and one burst pair of EMG. With Stim Off, the ET subject had persistent oscillations in wrist position and corresponding EMG bursts that continued for more than 12 burst pairs before returning to the target area (only four burst pairs are shown in figure 6B). With Stim On, the ET subject responded with three oscillations of wrist position and three burst-pairs of EMG (see figure 6C).

Group data are shown in figure 5B as the mean number of burst pairs for each subject. As a group, ET subjects during the Stim Off condition had a markedly increased number of EMG burst pairs ($p < 0.0001$) compared with during the Stim On condition and controls. The number of muscle burst pairs required for ET subjects with Stim On to return to baseline levels was not significantly different from controls.

**Time of torque-pulse perturbation.** The phase of the tremor at which the torque pulse was delivered may have affected the response. For example, trials in which the torque pulse was given during the flexion phase of tremor might differ from trials in which the torque pulse was given during the extensor phase of tremor. To correct for this possibility, we analyzed all wrist position traces at the moment immediately preceding the torque pulse and sorted trials into one of four phase angle categories: I, 0 to 90°; II, 91 to 180°; III, 181 to 270°; and IV, 271 to 360°. We then assessed EMG latency (ms), duration (ms), and tremor amplitude (degrees) for each of the categories. Our results show that in 77% of all ET trials with a torque-pulse perturbation, the manipulandum was held in a neutral position (i.e., no displacement greater than four degrees in the flexor or extensor direction) such that no tremor was evident at least in the position of the manipulandum. In all other trials in which tremor was present and the torque pulse was delivered, the phase did not systematically affect any of our response measures (i.e., EMG latency, duration, number of bursts, or amplitude).

**Tremor resetting.** Previous investigations report that the oscillations in ET can be reset by torque-pulse perturbations if the magnitude is high enough (0.75 to 1.5 mm). This suggests that the stretch reflex may be uncoupled to the ET oscillator. In our preliminary data, we found that the tremor rhythm was resettable in ET subjects without thalamic stimulation during the first 1000 ms after the torque pulse. However, several studies argue that brief mechanical perturbations have an intrinsic problem in the measurement of resetting in that the post-perturbation mechanical-reflex transients interfere with the regular tremor rhythm and result in inaccurate measures of resetting. In addition, a few of our ET sub-

### Table 2 Peak amplitude of first corrective response

<table>
<thead>
<tr>
<th>ET subjects</th>
<th>Stim Off</th>
<th>Stim On</th>
<th>Controls</th>
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<tr>
<td>ET01</td>
<td>14.7 (5.6)</td>
<td>25.8 (3.8)</td>
<td>CO 01 10.6 (5.1)</td>
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<tr>
<td>ET02</td>
<td>15.5 (8.9)</td>
<td>27.3 (5.2)</td>
<td>CO 02 13.7 (5.6)</td>
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<td>8.7 (4.8)</td>
<td>13.6 (6.6)</td>
<td>CO 03 14.0 (7.6)</td>
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<td>34.2 (12.1)</td>
<td>23.6 (3.1)</td>
<td>CO 04 11.9 (2.3)</td>
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<tr>
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<tr>
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<td>5.1 (6.0)</td>
<td>19.1 (5.4)</td>
<td>CO 06 7.66 (1.60)</td>
</tr>
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<td>22.7 (2.8)</td>
<td>CO 07 15.8 (5.7)</td>
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<tr>
<td>ET08</td>
<td>31.8 (8.3)</td>
<td>26.8 (11.1)</td>
<td>CO 08 10.8 (4.5)</td>
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<tr>
<td>Mean</td>
<td>17.2</td>
<td>23.4</td>
<td>Mean 11.5</td>
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All values are in degrees ±SD. Peak amplitude is significantly greater for essential tremor (ET) subjects both with stimulator turned off (Stim Off) and stimulator turned on (Stim On) relative to controls (CO). * $p < 0.01$. 

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jects (Stim Off) had a variable tremor rhythm at baseline, making it difficult to distinguish between a transient disruption of the tremor and true resetting.

**Discussion.** Patients with ET showed normal timing of the stretched agonist EMG, a delayed antagonist response, and excessive rebound after a mechanical perturbation at the wrist joint. Thalamic stimulation did not eliminate the antagonist delay: indeed, in subject ET04, thalamic stimulation paradoxically increased the antagonist delay. Nevertheless, thalamic stimulation did reduce the ET subjects' wrist oscillations during a held posture and after a perturbation. This improvement resulted from a general reduction in the propensity for reciprocal agonist–antagonist bursting during both a maintained wrist posture and when the wrist posture was perturbed.

Previous studies suggest that the mechanism for ET may involve coupled oscillators, or at least some type of interaction between mechanical components and central components driving the tremor. Some investigators emphasize the central component, showing that weighting the limb does not influence ET and that "resetting" of the tremor occurs only with a specific amplitude or frequency of perturbation. The central generator of ET has been proposed to be a pathologically periodic and excessively synchronized output from the inferior olive. Evidence considered to support this view has been the whole-body 10-Hz tremor caused by harmaline in laboratory animals, the correlated 10-Hz discharge in the olive, and the abolition of the tremor by olivary ablation. Also in apparent support, PET studies in human ET have shown increased olivocerebellar blood flow. A report of a single case study showed a reduction in ET symptoms at onset of a cerebellar infarct.

Another possible cause of ET points to abnormalities at a thalamic level. The VIM nucleus receives inputs primarily from the contralateral cerebellar nuclei and also from ascending somatosensory pathways before projecting to higher cortical centers. Thalamotomy of the VIM nucleus suppresses both CbT and ET. High-frequency electrical stimulation of the VIM nucleus greatly improves ET. Tremor suppression by stimulation could be caused by a depolarization block, giving a result similar to thalamotomy. However, thalamic lesions also are known to cause (usually after a delay of years) a cerebellar-like tremor. One functional imaging study with ET patients shows that thalamic stimulation activated motor cortex and supplementary motor area, suggesting that the stimulation activates rather than blocks thalamocortical output.

The interplay of mechanical and central components could attenuate or exacerbate the characteris-
tics of the tremor. Because physiologic wrist tremor has a similar frequency to that of ET, the improved damping coefficient that we report may have occurred as a result of reduced resonance between the mechanical components related to the wrist joint and central components related to ET.

Mechanical perturbation studies of ET have not previously measured agonist–antagonist EMG timing or reported antagonist delay. Our finding of a delayed antagonist response has been seen previously in macaque monkeys with CbT from cooling the deep cerebellar nuclei. In that study, a delay in onset and a prolonged duration of the first antagonist EMG response was reported. The authors argue that the antagonist EMG onset must be correctly timed and of the appropriate duration to damp oscillations. They propose that the cerebellum provides the feed-forward control signal to time the antagonist response mechanism.

Our finding of a delayed first antagonist response in ET (seven of eight Stim Off, eight of eight Stim On) was associated with increased rebound amplitude, similar to that seen in a study of CbT. In this study, the authors show a delay that is similar to the average delay of 40 ms that we report. Comparison of these results suggests that the antagonist delay in ET may result from cerebellar disease. Indeed, other investigators report movement abnormalities in ET similar to those after cerebellar damage, including prolonged movement time and target overshoot.

Therefore, it is interesting that we did not see a change in the timing of the first agonist or antagonist muscle responses with thalamic stimulation. Yet, thalamic stimulation did damp tremor. If the delayed antagonist response were the proximate mechanism in ET, as suggested for CbT, we would have expected the delay in the antagonist response to improve with thalamic stimulation. Instead, what changed was the propensity for reciprocal agonist–antagonist bursting during a maintained posture and after a mechanical perturbation.

Stiffening the limb or co-contracting agonist and antagonist muscles can damp some types of tremor. ET most likely involves a central source that is uninfluenced by somatosensory reflex pathways. Therefore, it would not be expected that co-contraction would damp tremor to the extent that we demonstrated. Our data did not show an increase in baseline EMG activity, nor was there a change in the latency or duration of either the initial agonist or antagonist EMG bursts with thalamic stimulation. In addition, the EMG traces do not show consistent overlap of agonist and antagonist bursts. Whereas the traces used in figure 5 do show some overlap, this was not a consistent response in any of our subjects. Our data do not support the idea that co-contraction is the means by which ET subjects damp tremor in the wrist.

Stimulation of the VIM thalamus improves tremor of various types, including ET, Parkinson, and CbT. However, how the VIM nucleus generates or mediates tremor and how its anatomic connections to the motor cortex influence its function remain unclear. Thalamic stimulation could engage local inhibitory systems, such as local circuit neurons in the thalamus, thalamic reticular neurons, or inhibitory fibers from the globus pallidus. Some investigators speculate that the reticular nucleus may gate activity transmitted from the thalamus to cortex during the generation of movement. Single pulses of thalamic stimulation inhibited voluntary muscle activity for up to 200 ms, and a continuous train of stimulation reduced this inhibition, suggesting that thalamic stimulation increases local inhibition leading to activation of muscle activity during the early phases of a voluntary movement. However, our findings are not consistent with this mechanism. We found a general reduction in agonist and antagonist bursting throughout the postural hold and 1000 ms after the torque-pulse perturbation. This reduction was not limited to a 200-ms time window or to the voluntary corrective movement after the torque-pulse perturbation. We also did not observe a change in the latency of agonist or antagonist muscle responses with thalamic stimulation. In sum, our behavioral data during thalamic stimulation cannot be explained adequately by an inhibitory mechanism that gates voluntary movement at the level of the thalamus.

The mechanism of thalamic stimulation could be mediated by habituation of inhibitory thalamic influences through repeated stimuli. In this scheme, continuous thalamic stimulation might disrupt thalamic oscillations associated with ET by diminishing the inhibitory phase that underlies the silent period of muscle activity associated with tremor. It then might be predicted that the thalamic stimulation would result in a reduction in the silent phases of muscle activity associated with tremor (i.e., more muscle co-contraction might be seen). Our data do not support the idea that muscle co-contraction is mediating the change in tremor expression by people with ET (see previous section).

Other investigators suggest that the thalamocortical loop may facilitate tremor through neuronal entrainment and reverberation. In this scheme, the VIM thalamocortical loop may work as a resonator for ET and other types of tremor. One study in cats shows evidence that normal thalamocortical relay cells directly activate the antagonist while inhibiting the agonist muscle pyramidal tract neurons. Our data also show evidence of two different effects on antagonist and agonist muscles. We found a delayed first antagonist response with no change in the agonist response, both with and without thalamic stimulation in subjects with ET. If tremor resonance interfered with normal VIM thalamocortical function then a delayed first antagonist activation would be a reasonable result. However, we would have expected that the onset of thalamic stimulation would have systematically changed the antagonist response latency or duration: it did not. Therefore, our data
cannot be completely explained by resonance of a tremor signal within a VIM thalamocortical loop.

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References