Single-Neuron Analysis of Human Thalamus in Patients With Intention Tremor and Other Clinical Signs of Cerebellar Disease

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INTRODUCTION

Intention tremor is defined as tremor that increases in amplitude as the target is approached during visually guided movements (Deuschl et al. 1998). The mechanism of intention tremor after lesions of the cerebellum or cerebellar pathways (cerebellar tremor) is still uncertain, although numerous mechanisms have been proposed (Diener and Dichgans 1992; Flament and Hore 1988; Flament et al. 1984; Gilman et al. 1976b; Goldberger and Growdon 1973; Growdon et al. 1967; Holmes 1922; Hore and Flament 1988; Liu and Chambers 1971; Vilis and Hore 1977, 1980). One such mechanism suggests that cerebellar tremor is the result of a delay in the control signal to antagonistic muscles that brake movements occurring about a joint (Vilis and Hore 1977, 1980). This delayed antagonist activation may be related to delayed motor cortical activity linked to antagonists (Hore and Flament 1988). A second proposed mechanism suggests that cerebellar tremor arises from alternating transcortical stretch reflex activity in antagonist muscle pairs (Diener and Dichgans 1992; Flament and Hore 1988). A third proposed mechanism suggests that cerebellar tremor results from voluntary corrections for errors in following a movement trajectory (Goldberger and Growdon 1973; Growdon et al. 1967; Holmes 1922). These proposed mechanisms of cerebellar tremor all predict that the timing of cerebellar output is altered as a result of cerebellar injury.

Alterations in cerebellar output could be reflected in thalamic activity because some pathways from the cerebellum project to motor cortex (Jones et al. 1979; Kevit and Kuypers 1977; Mehler 1971; Strick 1976; Walker 1938) via the thalamus (Chan-Palay 1977; Kalil 1981; Tracey et al. 1980). To test the hypothesis that the timing of cerebellar output to the thalamus is altered in intention tremor, we examined thalamic single neuron activity during intention tremor.

To our knowledge, thalamic activity has not previously been studied in patients with intention tremor or in a model of intention or cerebellar tremor. We now report the activity of thalamic cells during tremor under isometric conditions in patients with intention tremor and other clinical signs of cerebellar disease (tremor patients). The relationship between thalamic activity and tremor was examined for cells located in a cerebellar relay nucleus of the thalamus (ventral intermediate—Vim) and a pallidal relay nucleus (ventral oral posterior—Vop) (Hirai and Jones 1989). Thalamic activity in tremor patients was compared with that occurring in patients operated on for treatment of chronic pain or movement disorders other than intention tremor. The degree of correlation and relative phase of thalamic single-neuron activity and electromyographic (EMG) activity were compared between Vim and Vop. The results suggest that the cells in Vim were deafferented by


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cerebellar injury. In tremor patients, the activity of many cells in Vim had a phase lag relative to EMG activity during tremor unlike cells in Vop. Some of these findings have been published in preliminary form (Jaeger et al. 1994).

**METHODS**

**Operative techniques**

The data were recorded during the physiologic exploration that preceded either stereotactic thalamotomy for treatment of movement disorders or implantation of deep brain stimulating electrodes for treatment of chronic pain. During these procedures, the stereotactic coordinates of the anterior commissure-posterior commissure (AC-PC) line were determined. A coronal burr hole was made, and the dura and arachnoid were coagulated and cut. A microelectrode was then used to locate the principal somatosensory nucleus of the thalamus (Vc) and to explore the region anterior to it, including thalamic nuclei Vim and Vop (Lenz et al. 1988b, 1990). Standard techniques were used to record EMG activity in wrist flexors, wrist extensors, biceps, and triceps (Lenz et al. 1988c). A multiple-channel tape recorder (Model 4000, Vetter, Rebersburg, PA) recorded the microelectrode signal, the EMG signals, an audio channel describing the active movements and somatic sensory stimulation, and a foot pedal signal marking the onset and duration of somatic sensory stimuli.

**Physiologic techniques**

Physiologic exploration with the microelectrode involved both recording of neuronal activity and constant current stimulation at microampere levels (Lenz et al. 1988a). During recordings, several aspects of neuronal activity were examined: the spontaneous firing pattern at rest, the relationship of spontaneous activity to tremor during maintained posture (pointing), and neuronal activity during somatic sensory stimulation and active movement. The somatosensory examination included stimulation of both cutaneous structures and structures below the skin. Cells were classified as sensory or nonsensory based on their response to somatic sensory stimuli. Cutaneous sensory cells responded to touch or pressure applied to skin. Deep sensory cells responded to joint movement or to squeezing of muscles or tendons in the absence of any response to stimulation of skin deformed by these stimuli.

Microstimulation was delivered through the microelectrode in trains of ~1-s duration at 300 Hz by 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. At each stimulation site, patients were asked to point with the contralateral arm while the effect of the stimulation on tremor was assessed. During stimulation, patients were asked if they felt anything. If any effect was observed, the current was lowered in a series and then raised in a series until a threshold for the effect was established. This technique is called threshold microstimulation (Lenz et al. 1993). The type of effect and location of the projected field (PF) were determined at threshold.

Tremor was produced by having the patient point with the contralateral arm to the corner of the room. The patient was seated in a reclining position with the back at ~20° above the floor. In this position, the shoulder was flexed to ~45° while the elbow, wrist, metacarpophalangeal, and interphalangeal joints all extended to <180°. This pointing task is an isometric task that produces tremor like that evoked by isotonic tasks (Flament and Hore 1988; Mai et al. 1988). The neuronal activity related to tremor was recorded and assessed for between 20 and 60 s.

In patients with tremor, the lesion site was determined by the position of sites anterior to Vc where cells displayed activity related to the tremor and where stimulation evoked changes in tremor. One or more lesions were made at these sites. Lesions were made by introducing a radio-frequency lesioning electrode with an outside diameter of 1.1 mm, an exposed length of 3 mm, and a thermistor at the tip to monitor temperature (TM electrode—Radionics, Burlington, MA). Neurologic examination was carried out before, during, and after each stage of lesioning. To make each lesion, the temperature of the electrode was held for 1 min at 70°C and then for 1 min at 80°C. An egg-white test determined that this technique (Cosman and Cosman 1985) produced a cylindrical lesion with a diameter of 3 mm and a length of 5 mm (Lenz et al. 1995).

**Estimate of nuclear location**

In human studies, nuclear borders must be defined physiologically because radiologic estimates are not reliable (Kelly et al. 1987). Therefore the borders of Vc were defined physiologically and fitted to the atlas maps, which were used to extrapolate locations of other nuclei (Lenz et al. 1990, 1994). Previous studies in humans indicate that sensory cells form the majority of cells in Vc but are the minority in Vim and Vop (Lenz et al. 1988a, 1990, 1994). Vc was defined physiologically as the length of trajectory, bounded by sensory cells, along which the majority of cells were deep or cutaneous sensory cells. The physiologic anterior border of Vc was defined as the most anterior cell along trajectories through Vc (see Fig. 1). The physiologic map of each patient was shifted along the AC-PC line so that the anterior border on the physiologic map coincided with the anterior border of Vc on the atlas map (Lenz et al. 1990, 1994). The borders of Vim and Vop were determined from this transformed physiologic map.

Figure 1 shows an example of the application of this technique to identify the anterior border of Vc. In this figure, 66% of cells along the length of P2 bounded by sites 52 and 57 were sensory cells. Therefore cell 52 was the physiologic anterior border of Vc. The physiologic map (Fig. 1A) would be moved along the AC-PC (horizontal) line in Fig. 1B until site 52 was located at the anterior border of Vc or ventral caudal parvocellular (Vpc), inferior to Vc, in the atlas map.

**Analytic techniques**

After surgery, we examined the tapes made during the operative procedures. Cells analyzed in the present report were located in the region where cells showed activity related to active or passive movements of the upper extremity (Lenz et al. 1990). Action potentials were discriminated by a window discriminator (DDIS-1) and confirmed to arise from a single cell by the criterion of constant shape of the action potential as verified by displaying discriminated action potentials on an oscilloscope. Times of occurrence of action potentials were digitized at a clock rate of 1,000 Hz, and EMG signals were digitized at a rate of 200 Hz on a digital computer (11/73, Digital Equipment) and processed on a workstation (DECstation 3100, Digital Equipment).

To analyze the thalamic and EMG signals, we worked in the frequency domain. For all cells, simultaneous EMG signals for wrist flexors and extensors, as well as elbow flexors and extensors, were digitized. The EMG signal was band-pass filtered to ~6 dB at 20 and 120 Hz to eliminate movement artifact. The signal was then full-wave rectified and filtered to ~6 dB at 20 Hz to produce a signal known as the demodulated EMG. The spike train was converted into an equivalent analog signal by use of the French-Holden algorithm (French and Holden 1971; French et al. 1972; Glaser and Ruchkin 1976; Lenz et al. 1988c). The spike and EMG signals were processed by the 10% cosine rule to minimize artifact related to the finite sampling interval.

Standard techniques were then used to take the spectra of these two signals (Bendat and Piersol 1976; Glaser and Ruchkin 1976; Oppenheim and Schafer 1975). In this study, eight contiguous, nonoverlapping, raw spectral estimates (see Fig. 2B) were averaged to produce a smoothed spectral estimate (Fig. 2C) (Lenz et al. 1988c). Note that the peaks of both the EMG and the spike train signal are seen in the 1.9- to 5.8-Hz range of the smoothed power spectrum.
The signal-to-noise ratio (SNR) was defined as the spike power at tremor frequency (peak EMG activity in the 1.9- to 5.8-Hz range) divided by the mean power across the whole spectrum. The SNR is a measure of the extent to which power is concentrated at tremor frequency. The coherence function (Fig. 2D) was used as a measure of the probability that any two signals were linearly related. The coherence is a function of frequency that has a value of zero if the two signals are not linearly related and one if there is a linear relationship. By the technique used in the present study, a coherence of 0.42 at any frequency indicates that the two signals are linearly related at that frequency with a probability of \( P < 0.05 \) (Lenz et al. 1988c). Phase (Fig. 2D) was calculated by standard techniques (Oppenheim and Schafer 1975) so that a negative phase for the spike X EMG cross-correlation function indicates that the spike signal has a phase lead relative to the EMG signal.

RESULTS

Population of tremor patients

We now report on the activity of 159 cells recorded along 15 trajectories in the seven tremor patients described in Table 1.
All patients had intention tremor (2–6 Hz) (Deuschl et al. 1998) as well as other signs of cerebellar disease. Four patients had clinical signs not related to cerebellar injury, usually clinical signs of pyramidal tract disease (Table 1, column 5). Tremor was proximal (mostly elbow), activated by action and posture, and of frequency (see Table 1, column 4) in the range associated with cerebellar intention tremor (Deuschl et al. 1998). None had tremor at rest. The numbers of epochs of EMG activity during tremor, analyzed in each patient, are included in Table 1 (column 4), and apply to all statistics related to the EMG signal.

Clinical ratings of the severity of tremor were carried out in the last four patients by a standard rating scale of functional disability and a blinded assessment of handwriting and drawing (Fahn et al. 1988). The functional disability scale was scored from 0 (normal) to 28 (total disability). The handwriting and drawing scale was scored from 0 (normal) to 12 (unable to put pencil to paper in any of the 3 tasks).

**Similarities among tremor patients**

Although the diagnoses of the conditions leading to tremor (Table 1, column 5) were different, there were many similarities among tremor patients. Clinical evidence indicated that all tremor patients had intention tremor and other clinical signs of cerebellar disease (Table 1, column 5), and low frequencies of
EMG activity during tremor (Table 1, column 4). The numbers of cells with both a signal to noise ratio >2 and significant coherence at tremor frequency for at least one EMG channel were not significantly different among patients ($\chi^2$, $P > 0.05$). The proportion of stimulation sites were stimulation evoked changes in tremor did not differ significantly in this population ($P > 0.2$, $\chi^2$). Finally, there was no significant difference in surgical outcome (Fisher exact test, $P > 0.05$) between patients with multiple sclerosis (2/4) and those with other etiologies of tremor (2/3—Table 1). Thus tremor was similar in the population of tremor patients as studied by clinical features, thalamic X EMG activity, responses to thalamic stimulation, and response to surgery.

Population of control patients

The control population (control patients) comprised two groups: movement-disorder controls, patients undergoing thalamotomy for the treatment of other movement disorders (essential tremor, 2; parkinsonian tremor, 3; dystonia, 4); and pain controls, patients undergoing implantation of deep brain stimulating electrodes for treatment of chronic pain (3 patients). The present report includes results of neuronal recordings from 316 cells recorded along 31 trajectories in the control population. The pain controls had pain in the lower extremities and served as the control group for studies of thalamic cellular firing because their upper extremity motor function was normal. Both the pain and the movement-disorder controls were used in studies of upper extremity sensory cells.

EMG signal during tremor

As the basis for interpreting the relationship between thalamic activity and tremor, EMG during tremor was studied first. When tremor evoked by the pointing task, the EMG power spectrum often showed a peak in the 1.9- to 5.8-Hz frequency range (Fig. 3). In this example, biceps and triceps showed low frequency modulation of the EMG signal, as seen in the raw record and as indicated by the peak in the lowest frequency range. The low-frequency peak is seen in biceps and triceps spectra and to a lesser degree in the wrist flexor spectrum. The low frequency modulation of EMG activity, which was common in the present results (Fig. 3 and Table 2), was consistent with the irregularity of cerebellar tremor observed in isometric tasks (Flament and Hore 1988), like the pointing task. The percentage of epochs with peaks of EMG power spectra in the lowest frequency, and the tremor-frequency range for all muscles studied is shown in Table 2. Peak power occurred in one of these two frequency ranges for >90% of epochs in triceps, wrist flexors, and wrist extensors. For wrist flexors and extensors, the peak of EMG spectral activity occurred in the tremor-frequency range for the majority of epochs. The peak of EMG activity was commonly found in the low-frequency range (0–1 Hz), however, because of low-frequency variation in EMG activity (Table 2, biceps and triceps). This low frequency modulation of EMG did not correlate with low frequency modulation of thalamic neuronal firing (see following text).

Frequency of EMG activity as a function of severity of tremor

The frequency of peak EMG activity was studied to test the effect of severity on the frequency of tremor (Elble and Koller 1990). Differences in frequency studied by a two-way ANOVA between patient and EMG channel revealed significant differences within this model ($F = 18.22, P < 0.0001$, within groups $df = 576$). The one-way ANOVA of peak frequency in the tremor-frequency range was then carried out among patients 4–7, in whom the severity of tremor was determined by a clinical scale (see METHODS and Table 1). Significant differences among patients were found ($F = 81.49, P < 0.0001$). Mean frequencies for patients with more severe tremor (patients 4 and 5, Table 1) were 3.34 Hz ($n = 19$) and

<table>
<thead>
<tr>
<th>Case</th>
<th>Handedness</th>
<th>Mean Biceps Peak EMG Activity in the Tremor Frequency Range, Hz</th>
<th>Clinical Findings Motor Exam</th>
<th>Diagnosis</th>
<th>Side of Surgery</th>
<th>Age at Surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>3.16 ± 0.26, $n = 15$</td>
<td>Bilat Babinski, right hypotonia and dysdiadochokinesia</td>
<td>Post-traumatic</td>
<td>Left</td>
<td>18 (4)</td>
<td>Unchanged (3)</td>
</tr>
<tr>
<td>2</td>
<td>Right + left</td>
<td>3.06 ± 0.15, $n = 11$</td>
<td>Scanning speech, ataxia</td>
<td>Post-anoxic</td>
<td>Left</td>
<td>25 (3)</td>
<td>Significantly improved (1)</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>3.41 ± 0.23, $n = 19$</td>
<td>Bilat Babinski, dysdiadochokinesia and ataxia</td>
<td>MS</td>
<td>Left</td>
<td>50 (17)</td>
<td>Significantly improved (1)</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>23/9</td>
<td>Dysdiadochokinesia and ataxia</td>
<td>Post-traumatic</td>
<td>Right</td>
<td>27 (17)</td>
<td>Significantly improved (2)</td>
</tr>
<tr>
<td>5</td>
<td>Right + left</td>
<td>25/12</td>
<td>Dysmetria, scanning speech and ataxia</td>
<td>MS</td>
<td>Right</td>
<td>44 (6)</td>
<td>Unchanged (1)</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>20/8</td>
<td>Dysmetria, ataxia and right agraphesthesia</td>
<td>MS</td>
<td>Right</td>
<td>45 (6)</td>
<td>Unchanged (3)</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>21/4.5</td>
<td>Titubation, scanning speech and ataxia</td>
<td>MS</td>
<td>Left</td>
<td>43 (10)</td>
<td>Significantly improved (3)</td>
</tr>
</tbody>
</table>

Values are means ± SD for mean frequency of biceps peak electromyographic (EMG) activity. Parentheses enclose duration and number of lesions, respectively, in the last two columns.
3.20 Hz \((n = 41)\), whereas frequencies for patients with less severe tremor \((\text{patients 6 and 7})\) were 4.10 Hz \((n = 34)\) and 4.32 Hz \((n = 54)\). Thus the frequency of peak EMG activity was lower in patients with more severe tremor, consistent with the observation that the frequency of tremor varies inversely with the severity (Elble and Koller 1990).

**Thalamic signal**

**Firing rates.** Tonic firing rates were studied as an indicator of excitability of thalamic neurons with the arm at rest while the patient was instructed to lie quietly. None of the patients had resting tremor (see preceding text). Tremor patients had a lower neuronal firing rate than did pain controls (Fig. 4A).

**Sensory and nonsensory cells.** Previous studies have demonstrated that sensory input is an important factor in the relationship between cortical cellular activity and cerebellar tremor (Vilis and Hore 1980). Therefore differences between sensory and nonsensory thalamic cells were studied. The number of sensory cells in Vim \((22/121—18\%)\) was significantly higher (Fisher exact test, \(P < 0.05\)) than in Vop \((2/38—5\%)\), as observed in other populations of patients (Lenz et al. 1990, 1999). There was no significant difference (Fisher exact test, \(P > 0.05\)) between the proportion of sensory cells in Vim of tremor patients \((22/121, 18\%)\) and that of pain controls \((9/52, 17\%)\) nor (Fisher exact \(P > 0.05\)) in the proportion of sensory cells in Vop between tremor patients \((2/38, 5.3\%)\) and that in pain controls \((0/9, 0\%)\). Therefore sensory cells were found as

**TABLE 2.** Percentage of epochs \((n = 193)\) of EMG activity having the largest spectral peak in the low- or tremor-frequency range

<table>
<thead>
<tr>
<th>Muscle</th>
<th>EMG Peak in the Low-Frequency Range</th>
<th>EMG Peak in the Tremor-Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>47 ((0.0–0.9 \text{ Hz}))</td>
<td>39 ((1.9–5.8 \text{ Hz}))</td>
</tr>
<tr>
<td>Triceps</td>
<td>54 ((0.0–0.9 \text{ Hz}))</td>
<td>40 ((1.9–5.8 \text{ Hz}))</td>
</tr>
<tr>
<td>Wrist flexors</td>
<td>31 ((0.0–0.9 \text{ Hz}))</td>
<td>62 ((1.9–5.8 \text{ Hz}))</td>
</tr>
<tr>
<td>Wrist extensors</td>
<td>29 ((0.0–0.9 \text{ Hz}))</td>
<td>69 ((1.9–5.8 \text{ Hz}))</td>
</tr>
</tbody>
</table>

Numbers reflect percentage of epochs.
Frequency of spike activity as a function of the severity of tremor

In tremor patients, the spectral peak frequency of thalamic activity in tremor patients varied significantly as a function of the severity of tremor. The frequency of spike power peak was significantly different among the tremor patients in whom the severity of tremor was graded (patients 4–7, 1-way ANOVA, \( P < 0.0006 \)). The frequency of the thalamic peak was significantly lower in the two patients with severe tremor (\( P < 0.05 \), Bonferroni correction), patient 4 (3.34 Hz) and patient 5 (3.20 Hz) than in the two patients with less severe tremor, patient 6 (4.10 Hz) and patient 7 (4.32 Hz). Therefore the frequency of both peak thalamic activity and peak EMG activity in the tremor-frequency range decreased with increasing severity of tremor (see also Frequency of EMG activity as a function of severity of tremor).

Spike X EMG function

It is possible that the EMG activity of some of the muscles studied might be preferentially correlated with the thalamic spike activity. However, differences in the thalamic spike X EMG cross-correlation function were not significant between EMG channels or between patients with tremor. Spike X EMG pairs revealed no significant differences between all possible pairs in terms of mean coherence (1-way ANOVA, \( P > 0.70 \)). Because phase is interpretable solely in linear systems, it was only studied for Spike X EMG pairs with coherence \( \geq 0.42 \). A one-way ANOVA of phase between spike X EMG pairs was not significant (\( P > 0.50 \)). The mean phase of all spike X EMG pairs did not differ significantly from 0 (\( P > 0.2 \), \( t \)-tests).

FIG. 5. Histogram of frequencies of peak activity for neuronal spike spectra in pain controls and tremor patients. Note that the spike activity across muscles occurs in the 1.9- to 5.8-Hz frequency band more commonly in patients with tremor than in pain controls.
Therefore in the analysis of the spike X EMG function that follows, results for any cell are reported for the muscle with EMG activity most coherent with the activity of that cell.

**EFFECT OF CELL TYPE (SENSORY AND NONSENSORY).** Unlike nonsensory cells, sensory cells may have tremor-related activity secondary to sensory inputs. This input might lead to differences in the spike X EMG function between sensory and nonsensory cells. Among tremor patients, the proportion of cells with frequency of peak spike power equal to frequency of peak EMG power in one channel was significantly higher ($\chi^2$, $P < 0.05$) for sensory cells (10/25—40%) than for nonsensory cells (29/134—21.6%). The spike SNR peak in the tremor-frequency range was significantly higher (ANOVA, $F = 4.82$, within groups df = 157, $P < 0.03$) in sensory (2.43 ± 0.21) than in nonsensory cells (1.92 ± 0.09). Thus among cells in tremor patients, sensory cells had a greater concentration of power at tremor frequency than did nonsensory cells.

Although sensory cells had more power at tremor frequency than nonsensory cells, the relationship between thalamic and EMG signals showed only trends toward a significant difference. The proportion of sensory cells with coherence $\geq0.42$ and SNR $\geq2$ (28%—7/25) tended to be higher ($\chi^2$, $P < 0.07$) than that of nonsensory cells (13.4%—18/134). The proportion of sensory cells with positive phase (58%—7/12) was not significantly different from that of nonsensory cells (54%—26/48) with positive phase ($\chi^2$, $P > 0.70$). Thus the spike X EMG signal did not differ between sensory and nonsensory cells.

**EFFECT OF NUCLEAR LOCATION.** To determine whether cells in Vim and Vop could be related to EMG activity by the same mechanism, the spike X EMG function was studied for cells in different nuclei. As shown in Fig. 6A, the tremor-frequency peak SNR was not significantly different (1-way ANOVA, $P > 0.49$) between Vim (2.03 ± 0.100) and Vop (1.89 ± 0.177). Thus the concentration of power at tremor frequency was the same in Vim and Vop.

We next studied the spike X EMG function for the EMG channel with the highest coherence with the thalamic signal. The percentage of cells with coherence $\geq0.42$ and SNR $\geq2$ (Fig. 6, A and B) was not significantly different ($\chi^2 = 0.286$, $P < 0.60$) between Vim (17%, 20/121) and Vop (13.2%, 5/38). The tremor-frequency phase was then compared for neurons in Vim and Vop. There were significantly (Fisher exact test, $P < 0.001$) more cells with phase $>0$ in Vim (65.4%—34/52) than in Vop (10%—1/10; see Fig. 6C). This contrasts with the situation in parkinsonian tremor in which a positive phase is as common ($P > 0.05$, Fisher exact test) in Vim (41%, 9/22) as in Vop (43%, 3/7) (Lenz et al. 1994). Thus cells in Vim and Vop are equally likely to have a concentration of power at tremor frequency and to have a linear spike X EMG function.
ever, cells in Vop are more likely than cells in Vim to have a phase lead relative to EMG.

**DISCUSSION**

The results of this study suggest that cells in Vim have lost their normal input in tremor patients. Cells in Vim of tremor patients had a significantly lower rate of firing than did those in pain controls (Fig. 4). Because input from cerebellum to thalamus is excitatory (Uno et al. 1970), this result suggests that thalamic cells have been deafferented by cerebellar injury. Deafferentation may produce changes in cellular firing as well as changes in the firing rate. The phase of the spike X EMG function with the highest coherence was more likely to be positive in Vim (65.4%) than in Vop (10%), indicating that the spike train was more likely to have a phase lead relative to EMG activity for cells in Vop than for those in Vim. Activity in monkey ventral posterior lateral oral (VPLo), corresponding to human Vim (Hirai and Jones 1989), normally has a phase lead relative to movement (i.e., negative phase) during active oscillations (Butler et al. 1992), unlike the pathologic oscillations reported here. Therefore the present results suggest that cells in Vim are deafferented and, perhaps as a consequence, have a phase lag relative to muscle activity.

**Methodological considerations**

Because we hope to relate our results to cerebellar efferent pathways, we deemed it important to review the evidence that tremor in our tremor patients is similar to cerebellar tremor. Tremor associated with cerebellar lesions is characterized by an intention tremor, which occurs as the target is approached during a visually guided movement, an isometric task (Deuschl et al. 1998). All patients in this study had intention tremor. The pointing task used in the present study is a postural or isometric task. Cerebellar tremor can occur under either isometric or isometric conditions (Flament and Hore 1988; Mai et al. 1988). Although the tremor is similar under both conditions, it is more irregular and of lower frequency in the postural or isometric task. The irregularity is reflected in the present results by the high proportion of epochs of EMG activity with peak frequency in the low-frequency band (see Table 2, column 3, and Fig. 3).

Other characteristics of our tremor patients suggest that the tremor is of cerebellar origin. The frequencies of tremor (Fig. 3 and Table 2) are consistent with the frequency of known cerebellar tremors (Deuschl et al. 1998). All tremor patients had clinical signs of cerebellar disease in addition to intention tremor (see Table 1, column 5), although some patients had clinical signs of lesions in other systems. Nevertheless, the associated cerebellar signs and the frequency of tremor strongly suggest that intention tremor in these patients is similar to cerebellar tremor (Deuschl et al. 1998; cf. Bastian and Thach 1995).

The actual location of cells in the present study is uncertain because stereotactic localization on the basis of the AC-PC line does not have adequate resolution to discriminate nuclei of the thalamic ventral nuclear group (Kelly et al. 1987). The uncertainty in location was minimized in the present study, however, by aligning the anterior border of Vc in the atlas with the anterior physiologic boundary of Vc. This procedure mini-

## Baseline firing rates in Vop and Vim of tremor patients

Lesions other than the loss of excitatory input from the cerebellum to the thalamus could also explain the decrease in firing rates of thalamic cells reported in our tremor patients. Corticothalamic inputs are excitatory (Jones 1985) and may be lesioned in multiple sclerosis or in head injury (see Table 1) (Adams et al. 1996). Alternatively, loss of brain stem inputs to the thalamus may influence the basal firing rates of thalamocortical cells and may result in synchronized oscillations of thalamic systems (Steriade et al. 1990), similar to those found in tremor patients (Fig. 6A). Thus multiple pathways might explain the changes in basal firing rates found in tremor patients.

Our initial explanation for the decreased firing rates in tremor patients was the loss of excitatory cerebellar input. However, this does not explain the decreased firing rates in Vop. Unlike Vim neurons, which might be deafferented by a lesion of the cerebellum or it’s pathways, neurons in Vop are not deafferented because Vop receives input from the pallidum not the cerebellum. There are two connections through which firing rates of cells in Vim might influence those in Vop. First, in monkeys, VPLo, corresponding to human Vim, projects to motor cortex, which sends an excitatory projection to monkey ventral lateral oral (VLo) (Ilinsky and Kultas-Ilinsky 2001), corresponding to human ventral oral (Vo) (Hirai and Jones 1989). Second, inputs to the reticular nucleus from VPLo are probably connected through the diffuse inhibitory interconnections of the thalamic reticular nucleus to VLo (Ilinsky and Kultas-Ilinsky 2001; Ilinsky et al. 1999). Both the cortical and reticular nuclear inputs to the VPLo make connections with relay cells and inhibitory interneurons (Ilinsky and Kultas-Ilinsky 2001). Therefore either of these connections could explain the parallel decrease in firing in the pallidal and cerebellar relay nuclei, that is also observed in parkinsonian monkeys (Vitek et al. 1990).

## Tremor-related activity of sensory and nonsensory cells

The relationship between thalamic and EMG signals was first studied for sensory and nonsensory cells. Both cell types showed activity linearly related to tremor. Studies of cerebellar intention tremor in monkeys have reported that cells with sensory inputs were the only cells in motor cortex displaying activity related to tremor (Flament and Hore 1988; Vilis and Hore 1980), whereas the activity of nonsensory cells was not strongly related to tremor (Flament and Hore 1988). In contrast, in the present study, many thalamic nonsensory cells (22%) showed a concentration of activity at tremor frequency, which was significantly related to tremor. This result may be a consequence of the sensitivity of the present analysis in identifying cellular activity related to tremor (Fig. 2). It also suggests that nonsensory thalamic cells may have a role in the generation of tremor.

Involvement of nonsensory cells in the generation of cerebellar tremor has been suggested by the persistence of cerebellar tremor after deafferentation (Diener and Dichgans 1992; Gilman et al. 1976b; Liu and Chambers 1971). In one of these
studies, kinematic analysis was carried out during visually guided pointing movements of the hand (Gilman et al. 1976b). A “4- to 5-Hz tremor” of the upper extremity was observed in monkeys with cerebellar lesions both with and without deafferentation of the upper extremity. The present data do not identify the central pacemaker that drives thalamic nonsensory cell activity in this situation. This pacemaker could be oscillating cells in the olive, the activity of which is transmitted to the thalamus through the cerebellum (Lamarre 1995). However, recent evidence suggests that the cerebellum does not normally act as a pacemaker for the activity of other neurons (Keating and Thach 1997).

Some of the present results suggest that sensory inputs are as significant in tremor as they are in normal cerebellar function (Thach et al. 1986). For example, peak spike activity tended to occur at tremor frequency and be correlated with tremor more often \( (P < 0.07) \) for sensory (28%) than for nonsensory cells (13%). Moreover, previous studies showed that tremor is influenced by proprioceptive but not visual inputs (Flament et al. 1984) and that the mechanical state of the limb influences the frequency of tremor (Flament et al. 1984; Hore and Flament 1986; Vilis and Hore 1977). In those studies, tremor was measured with cooling of the deep cerebellar nuclei during movements of a handle to a visual target. Tremor frequency and amplitude were altered by changes in the spring stiffness, inertia, and viscosity of the handle, all of which alter sensory input from the limb (Flament et al. 1984; Hore and Flament 1986; Vilis and Hore 1977). Removal of visual feedback of handle position did not influence the tremor (Flament et al. 1984; Gilman et al. 1976a; Mauritz et al. 1981). Thus there is reason to believe that both sensory and nonsensory cells are involved in the mechanism of tremor.

**Other systems that may contribute to thalamic abnormalities in tremor-related activity in Vim and Vop**

The effect of stimulation in Vim on tremor suggests that activity in this nucleus is related to tremor through its connection to motor cortex (Benabid et al. 1996; Buford et al. 1996; Vitek et al. 1996). The activity of 66% of cells in Vim had phase 0, indicating a phase lag with respect to EMG activity during tremor (see Fig. 6). This is in contrast to the activity of cells in monkey VPLo during active wrist oscillations. In those studies, monkeys carried out 2- to 4-Hz alternating flexion/extension movements of the wrist. The activity of cells in VPLo was correlated with and led movement during oscillations (Butler et al. 1992). In the tremor of Parkinson’s disease, the oscillations of cellular activity in both Vim and Vop led tremor (see Spike X EMG Function, EFFECT OF NUCLEAR LOCATION) (Lenz et al. 1994). Thus during physiologic oscillations (Butler et al. 1992) and some pathologic oscillations (parkinsonian tremor) activity in Vim and Vop led EMG activity in tremor, which was not observed in this study.

There are two possible explanations for this result. Normally, the cerebellum contributes to stable posture and accurate movement by feed-forward control of cortical activity to the antagonists of movement about a joint (Hore and Flament 1988). In studies of cerebellar tremor in monkeys, a delay is observed in the feed-forward activation of antagonists that normally brake movement about a joint (Vilis and Hore 1977, 1980). During tremor, corresponding delays in activation are observed in recordings from motor cortical cells with activity related to the antagonists (Hore and Flament 1988). The phase lag of Vim activity relative to EMG is consistent with activity in motor cortex of the monkey because Vim projects to motor cortex (Hirai and Jones 1989).

The second possible explanation focuses on the difference between phase in Vim and Vop. A phase lead in the spike X EMG function was found in almost all cells located in Vop and contrasted with the phase lag for many cells in Vim. The phase difference between these two inputs to cortex may contribute to tremor. Because lesions of axons from deep cerebellar nuclei lead to cerebellar tremor (Carrea and Mettler 1955), it is possible that tremor is not driven by cerebellar output. Rather it may be driven by structures deafferented as a result of the cerebellar injury (e.g., thalamus) under the influence of other inputs to the thalamus, such as pallidal input to cortex through Vop (Holsapple et al. 1991).

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