Tremor cells in the human thalamus: differences among neurological disorders

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Object. Thalamic neurons firing at frequencies synchronous with tremor are thought to play a critical role in the generation and maintenance of tremor. The authors studied the incidence and locations of neurons with tremor-related activity (TRA) in the thalamus of patients with varied pathological conditions—including Parkinson disease (PD), essential tremor (ET), multiple sclerosis (MS), and cerebellar disorders—to determine whether known differences in the effectiveness of thalamic stereotactic procedures for these tremors could be correlated to differences in the incidence or locations of TRA cells.

Methods. Seventy-five operations were performed in 61 patients during which 686 TRA cells were recorded from 440 microelectrode trajectories in the thalamus. The locations of the TRA cells in relation to electrophysiologically defined thalamic nuclei and the commissural coordinates were compared among patient groups.

The authors found that TRA cells are present in patients with each of these disorders and that these cells populate several nuclei in the ventral lateral tier of the thalamus. There were no large differences in the locations of TRA cells among the different diagnostic classes, although there was a difference in the incidence of TRA cells in patients with PD, who had greater than 3.8 times more cells per thalamic trajectory than patients with ET and approximately five times more cells than patients with MS or cerebellar disorders.

Conclusions. There was an increased incidence of TRA in the thalamus of patients with PD. The location of thalamic TRA cells in patients with basal ganglia and other tremor disorders was similar.

Key Words • movement disorder • Parkinson disease • tremor • thalamus

MICROELECTRODE recordings during stereotactic surgery have shown that tremor disorders are characterized by the presence of neurons in the ventral thalamus that have a spontaneous rate of discharge synchronous with peripheral tremor. These neurons are known as TRA cells or tremor cells. Although the pathogenesis of tremor remains unclear, a large body of evidence indicates that TRA cells play an important role. Indeed, the aim of surgical interventions for the treatment of tremor disorders is to disrupt the activity of TRA cells in the region of the Vim.

Although lesioning and high-frequency stimulation of the Vim have been performed for different clinical conditions, outcomes of surgical procedures in this region vary with the reason for the procedure. Patients with PD and those with ET have better responses to surgery than patients with MS or cerebellar disorders.

We used microelectrode recordings to assess the locations and incidence of TRA neurons in the thalamus and to determine possible variations associated with different tremor disorders.

Clinical Material and Methods

This study was based on a retrospective review of the records of 61 patients who had undergone 75 thalamic operations for the treatment of upper ET between March 21, 1985, and August 24, 1995, at the Toronto Western Hospital, University of Toronto. We included all patients treated during that period in whom the diagnosis was MS, ET, or tremor caused by cerebellar disorders (cerebellar tremor) and randomly chose a comparable number of patients with PD. Nineteen patients had PD, 15 had ET, 19 had MS, seven had tremor of cerebellar origin, and one patient had post-traumatic tremor (Table 1). Because the tremor experienced by one patient with posttraumatic tremor was similar to that associated with cerebellar lesions, we combined these two groups.

Stereotactic Procedure

Ventriculography was used as the imaging modality in 15 operations before November 1987. After this, surgical procedures were guided by either computerized tomography or magnetic resonance images (60 operations). Following administration of a local anesthetic, a Leksell frame (mod-
el D or G; Elekta Instruments, Atlanta, GA) was applied to the patient’s head. The coordinates of the AC and PC were obtained using computerized tomography scanning (Highlight Advantage [GE Medical Systems, Milwaukee, WI]; 1.5-mm-thick nonoverlapping axial slices) or magnetic resonance imaging (Signa 1.5-tesla magnet [GE Medical Systems]; 1-mm-thick nonoverlapping axial T2-weighted slices). The intercommissural line was calculated and transcribed onto a digitized sagittal stereotactic map obtained from either the Schaltenbrand and Bailey14 or Schaltenbrand and Wahren15 atlas. Using a personal computer, the atlas map was stretched or shrunk in the anteroposterior direction to match the intercommissural distance in a particular patient. The initial target was located just above the intercommissural line, 15 mm lateral to the midline or 11 mm lateral to the wall of the third ventricle, and 3 to 5 mm anterior to the PC, based on the configuration of the redrawn atlas diagrams.

After administration of local anesthesia, either twist drill holes (for lesions) or burr holes (for DBS) were made at the level of the coronal suture, approximately 2 cm from the midline. The dura mater was penetrated and the electrode assembly was introduced into the brain. Physiological studies were begun after the electrode had reached 10 mm above the intended target.

**Microelectrode Recording**

Details of microelectrode recordings and signal processing at our center have been previously described.1,11 Extraacellular single- and multiunit recordings were made with gold- and platinum-plated tungsten microelectrodes (exposed tips measured 15–40 μm and impedances were < 1 MΩ). Cell activity was amplified (DAM 80; World Precision Instruments, Inc., Sarasota, FL) with a gain of 1000 and was initially filtered to 0.1 to 10 kHz. Additional filtering (model 3700 filter; Krohn–Hite Corp., Avon, MA) was done to remove unwanted frequencies. The signal was displayed on oscilloscopes and directed to a window discriminator (Winston Electronics, Millbrae, CA) and an audio monitor (AM 8 [Grass Instruments, Quincy, MA] with a noise-clipping circuit).

**Data Acquisition**

The records and thalamic maps of physiological data for each patient were reviewed to obtain the stereotactic coordinates of each thalamic target, the stereotactic frame angles, and the depth at which the TRA cells were located. Data were entered into a computerized database (Access, version 2; Microsoft Corp., Redmond, WA). During surgery, neural activity was displayed on an oscilloscope and fed to an audio speaker. The relationship between neuronal bursting and tremor frequency was determined using audio and visual monitoring of the patient and online recording. Cells with TRA were identified intraoperatively according to the following criteria: 1) isolated single thalamic unit; 2) bursts of action potentials (5–10 in a train) occurring at frequencies similar to those of peripheral tremor (3–10 Hz), which fired in synchrony with the patient’s tremor; and 3) units oscillating at a tremor frequency when no tremor was apparent. Surface activity from contralateral wrist extensors and flexors was recorded on EMG (Fig. 1). We did not systematically analyze the peripheral receptive field of the TRA cells and, therefore, did not categorize TRA cells as voluntary, kinesthetic, or autonomous, as previously described.5,8,9

**Neuroimaging and Physiological Landmarks**

The neuroimaging-derived positions of the AC and PC were used as landmarks. Thalamic TRA neurons were described according to their positions (in millimeters) lateral to the PC, anterior to the PC, and above the AC–PC line. To standardize measurements, the length of the intercommissural line was determined for each operation and the y values were scaled to correspond to a standard length of 24 mm.

**FIG. 1.** Correlation between thalamic neuronal activity and tremor. Upper: Trace obtained from a single thalamic unit in a patient with ET, correlating to a trace of arm tremor recorded using an accelerometer (Acc). Lower: Traces showing the correlation between thalamic tremor cell activity in a patient with PD and contralateral arm on EMG recordings.

<table>
<thead>
<tr>
<th>Cause of Tremor</th>
<th>No. of Ops</th>
<th>No. of Males</th>
<th>No. of Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>60.5</td>
<td>14</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>ET</td>
<td>53.3</td>
<td>9</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>MS</td>
<td>35.5</td>
<td>4</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>cerebellar &amp; trauma</td>
<td>42.9</td>
<td>5</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

**TABLE 1**

Patient demographics and general characteristics of surgical procedures
The tactile border of the Vc, characterized by the presence of neurons with tactile receptive fields, was assigned as the anterior–posterior physiological landmark. The physiological base of the thalamus, defined as the transition zone between the thalamic nuclei and the medial lemniscus, was assigned as the dorsal–ventral physiological landmark. Paresthesias of corresponding parts of the body were evoked by applying low-threshold microstimulation (300 Hz to 1–10 μA) to the tactile border of the Vc. Microstimulation of the ventral border of the thalamus and the medial lemniscus induced paresthesias in large projected fields.

Standard geometric methods were used to convert the location of the TRA cell relative to the tactile border of the Vc and the physiological base of the thalamus into cartesian coordinates.

Statistical Methods

Univariate one-way analysis of variance (SPSS, version 11.0; SPSS, Inc., Chicago, IL) was performed on data for each coordinate plane by using the diagnostic group as the independent variable. The location of all TRA cells was used as the dependent measure. Post hoc comparisons were conducted using the Student and Newman–Keuls tests (α = 0.05). An effect size (η²) was also computed for each analysis to determine the magnitude of variance.

Results

Sixty-one patients underwent 75 surgeries (Table 1). Thalamotomies had been planned in 47 patients and DBS electrode (model 3287; Medtronic Inc., Minneapolis, MN) implantation in 28 patients. Fifty-nine operations were performed on the left side and 16 on the right side. A total of 686 TRA cells were identified while examining 440 microelectrode trajectories. Five hundred seventy-two TRA cells were located on the left side and 114 on the right side (Table 2).

Two operations were performed in 14 patients. In one patient bilateral procedures were performed. Repeated surgery was a consequence of technical difficulties with the electrophysiological equipment in four patients. Nine thalamotomies had to be repeated because the first procedure failed to improve the patient’s tremor sufficiently.

In 13 surgeries (17%), TRA cells were not identified due to either technical difficulties with the physiological equipment or targeting inaccuracies. In these instances, lesions and DBS electrode sites were chosen on the basis of microstimulation-induced tremor arrest (300 Hz, 100-μsec pulse widths, < 100 μA, and 1-second trains).

Incidence of TRA Cells

As shown in Table 2, on average patients with PD had 3.8 times more TRA cells than patients with ET per unit length of thalamus, and approximately five times more TRA cells than patients with cerebellar tremor or MS. This may account for the lower number of trajectories necessary to target the Vim in patients with PD.

Position of Cells in Relation to Anatomical Landmarks

The location of TRA cells relative to the PC and the intercommissural line is shown in Table 3. Even though the overall distribution of TRA cells was widespread through the ventral lateral thalamus, most of these cells were concentrated in the lower half of the Vim (Fig. 2).

The analysis of the location of TRA cells across patients

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Incidence of tremor cells*</th>
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<tbody>
<tr>
<td><strong>No. of TRA Cells</strong></td>
<td><strong>Cause of Tremor</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>113 (4.5 ± 3.0)</td>
</tr>
<tr>
<td>ET</td>
<td>116 (6.6 ± 3.2)</td>
</tr>
<tr>
<td>MS</td>
<td>151 (6.4 ± 3.8)</td>
</tr>
<tr>
<td>cerebellar &amp; trauma</td>
<td>60 (6.7 ± 2.4)</td>
</tr>
</tbody>
</table>

* Mean values are expressed as the means ± standard deviations.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Location of tremor cells relative to the PC, midline, and AC–PC line*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Distance</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cause of Tremor</strong></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>16.5 ± 2.1</td>
</tr>
<tr>
<td>ET</td>
<td>15.8 ± 1.1</td>
</tr>
<tr>
<td>MS</td>
<td>16.1 ± 1.0</td>
</tr>
<tr>
<td>cerebellar &amp; trauma</td>
<td>14.5 ± 2.7</td>
</tr>
</tbody>
</table>

* Distances are expressed as the means ± standard deviations.
with different diagnoses revealed small but significant differences (Fig. 3). There was a group effect for the x (medi-al–lateral) \(F(3,682) = 19.35, p < 0.001, \eta^2 = 0.078\) and y (anterior–posterior) \(F(3,682) = 3.14, p < 0.03, \eta^2 = 0.014\) coordinates. A post hoc analysis revealed that TRA cells were located slightly more medially in patients with cerebellar tremors and more posteriorly in the ET group (Table 3). No significant group effect emerged in the dorsal–ven-tral axis (z coordinate).

**Position of Cells in Relation to Physiologically Defined Borders**

The mean position of TRA cells in the sagittal plane (y plane) relative to the tactile border of the Vc and in the vertical plane (z plane) relative to the physiological base of the thalamus is shown in Table 4. There was a group effect for the y \(F(3,662) = 7.54, p < 0.0001, \eta^2 = 0.033\) and z \(F(3686) = 10.67, p < 0.0001, \eta^2 = 0.045\) coordinates. A post hoc analysis indicated that TRA cells in patients with PD were located more anteriorly and those in patients with MS more ventrally than in other groups (Fig. 4). Differences in the mean location along the y and z planes were less than 1 and 2 mm, respectively.

**Discussion**

The results of this study confirm that TRA cells are present throughout the ventral lateral thalamus. Based on stereotactic atlas landmarks, TRA cells populated the Vc, Vim, Vop, and Voa.\(^3\)\(^,\)\(^7\)\(^–\)\(^10\)\(^,\)\(^12\)\(^,\)\(^19\) Despite the previous identification of these cells in patients with PD, ET, and cerebellar tremor,\(^3\)\(^,\)\(^7\)\(^–\)\(^10\)\(^,\)\(^12\)\(^,\)\(^19\) this is the first study in which the incidence and locations of these cells have been compared among these different clinical conditions. We found that the number of TRA cells recorded per trajectory was much greater when they were associated with PD compared with other forms of tremor, and that patients with different clinical entities had tremor cells in slightly different locations.

Differences in the incidence of TRA cells between patients with PD and those with other clinical entities may have been caused by particularities of each clinical condition as well as by differences in the pattern of tremor. A simpler hypothesis is that the resting state during surgical procedures may have favored recording of TRAs during conditions in which the tremor was at rest, such as in patients with PD. Most likely, however, differences in neuropathological features, in involved brain circuits, and in the pattern of cerebral reorganization may have been important contributors to the differences in the incidence of TRA cells observed among different conditions. In addition, bias related to the location of the microrecording mapping also may have accounted for some of the differences in this study; recordings were mostly done close to the thalamic representation of the hand. In this sense, the incidence of TRA may have been underestimated in patients with clinical entities that are characterized by more proximal or widespread patterns of tremor, such as cerebellar diseases or MS.

Errors in stereotactic imaging and frame systems approximate 1 to 2 mm. Although statistically significant differences were found in the locations of TRA cells among patient groups, on average the differences were less than 2 mm. As a result, the clinical impact of these differences in driving the decision of what should be the optimal thalamic target will likely be low.
Conclusions

In patients with tremor from a variety of causes, the ventral lateral thalamus is populated by neurons with TRA. When different clinical entities were compared regarding the incidence and locations of TRA cells, two main differences were noticeable. First, the incidence of TRA cells in patients with PD was higher than the one observed in patients with other clinical entities. Second, there was a small difference (a mean < 2 mm) in the location of tremor cells in the ventral thalamus among the various forms of tremor.

Acknowledgments

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References


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