SHORT REPORT

Thalamic neuronal activity correlated with essential tremor

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Abstract

Animal studies suggest that an olivocerebello-bulbospinal pathway mediates harmaline induced tremor, which resembles essential tremor in humans. However, recent evidence suggests that thalamocortical pathways participate in essential tremor. Thalamic single neuron activity has been analysed during thalamotomy for essential tremor. It has been shown by spectral cross correlation analysis that thalamic activity has a significant, linear relation to forearm EMG activity during tremor. The presence of this tremor related activity at the site where a lesion abolishes essential tremor suggests that the thalamus has an important role in the mechanism of essential tremor.

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Keywords: essential tremor; thalamus; spectral cross correlation analysis; thalamotomy

Although essential tremor is the most common movement disorder, its aetiology is unclear. In animals β -carboline drugs such as harmaline produce a tremor which resembles essential tremor.^{1,2} Harmaline tremor has been shown to originate in the inferior olive and to be expressed through cerebellobulbospinal pathways.^{2,3} In humans surgical lesions in the ventralis intermedius (ventralis intermedius-cerebellar relay) nucleus of the thalamus abolish or reduce essential tremor,^{4,5} which suggests that the thalamus is involved in the mechanism of essential tremor. Although thalamic recordings have often been published in parkinsonian tremor,⁶ there are no such reports for essential tremor, which is clearly different from parkinsonian tremor.¹ In this report, we show direct evidence for tremor related single cell activity in the ventralis intermedius of patients with essential tremor.

Methods

The activity of cells in the ventralis intermedius was recorded during physiological localisation of the lesion site to relieve essential tremor in three patients. Thalamic spike trains and contralateral EMG activity were analysed post-operatively for correlation of these two signals.

Detailed operative, microelectrode, analytical, and statistical techniques used in this study were identical to those published elsewhere^{6,7} and so will only be described briefly.

The stereotactic coordinates of the anterior and posterior commissures were determined by CT and were then used to estimate the coordinates of thalamic nuclei.⁸ During the surgical procedure, functional mapping of the thalamus was performed to confirm anatomical boundaries of thalamic nuclei predicted radiologically. Sensory receptive fields as well as the relation between thalamic firing pattern and tremor were assessed for each neuron.

Postoperatively, EMG signals from wrist flexors and extensors as well as the times of occurrence of action potentials were digitised. The EMG was full wave rectified and filtered to produce a signal termed demodulated EMG (figure).⁶ Tremor frequency activity was studied by spectral cross correlation analysis of single neuron activity and EMG activities. Fourier transforms of the EMG signal and spike train were calculated to determine the raw EMG and spike spectra, composed of 256 spectral estimates between zero and 25 Hz. Raw spectra were then filtered by averaging eight contiguous raw spectral estimates. This filtering of the raw spectra decreased both the variability and the resolution of the spectral estimates. The autopower, crosspower, coherence, and phase spectra were calculated by standard methods.⁶

The autopower spectrum measured the intensity of the signal as a function of frequency. The autopower signal to noise ratio was calculated as the power of the spike train at tremor frequency divided by the power averaged over all frequencies and indicated the extent to which power in the spike train was concentrated at tremor frequency. The cross power spectrum indicated the extent to which power in the two signals occurred at the same frequency with a consistent phase relation. The coherence was a statistical function used to estimate the probability that two signals were correlated at a given frequency. A coherence of 0 indicated that the two signals were not linearly related whereas a coherence of 1 indicated that the two signals were identical. As computed in the present study, a coherence of >0.42 indicated that two signals had a significant probability ($p < 0.05$) of a linear

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Figure 1 Simultaneous recording of thalamic single neuron activity (3-1407401) and peripheral EMG during tremor in patient 3-14 with essential tremor. A, Digitised spike train (upper trace) and demodulated EMG channels (lower two traces). B, Smoothed spike autopower spectrum of the spike train illustrated in A. C, D, Smoothed autopower spectra for the two demodulated EMG channels. The dot indicates the frequency at which the maximum spectral component occurs in the EMG autopower spectrum—that is, tremor frequency (5.81 Hz). E, F, G, cross power spectra, H, I, J, coherence spectra, and K, L, M, phase spectra between spike $\times$ EMG1, spike $\times$ EMG2, and EMG1 $\times$ EMG2 respectively. The numbers to the right of the spectra indicate the frequency with highest autopower (B, C, D), and the value at tremor frequency of cross power SNR (E, F, G), coherence (H, I, J), and phase (K, L, M).

Table 1 Description of patients

Patient No	Age	Duration of tremor (y)	Sex	Average preop Fahn score	Average postop Fahn score	Cells (n)	Tremor related cells (n)	Wrist flexor × extensor EMG phase (SEM)	Averaged phase angle spike × EMG
3-14	51	7	M	3.1	1.4	38	14	-16° (10.4°) n=21	-51.1° (24.2°) n=14
3-25	69	30	M	3.7	1.3	16	4	12.5° (15.3°) n=9	-15.1° (56.4°) n=4
5-36	38	18	F	3.4	1.1	19	8	112.6° (4.6°) n=15	NA

relation.⁹ The phase spectrum indicated the relative latency of activity in the spike train and EMG; a negative phase indicated that the spike train led the EMG signal.

Results

Seventy three cells were recorded in the ventralis intermedius and the ventralis oralis posterior during functional mapping before thalamic lesioning in three patients (3-14, 3-25, and 5-36) with disabling, medically intractable essential tremor satisfying Tremor Investigation Group criteria.¹⁰ In all three patients treatment with mysoline and propranolol, both alone and in combination, and treatment with clonazepam were ineffective. The table provides a description of the patients with mean preoperative and postoperative disability scores by the Fahn standard rating scale of tremor in which 0 was normal and 4 was totally dependent for the task being scored.¹¹ Lesions were made in the ventralis intermedius (approximate volume 60 mm³⁻¹²) at the location of tremor related cells, with improvement in the disability scores of all patients (table).

The cell shown in the figure exhibited a periodic firing pattern similar to the pattern of EMG activity in wrist flexors and extensors. The figure (C and D) shows that EMG signals from wrist flexors and extensors had a peak in their autopower spectrum at 5.81 Hz (tremor frequency). The spike autopower spectrum of the spike train (figure B) showed a tremor frequency peak with an SNR of 4.1.

The figure (G, J, and M) shows the cross power, coherence, and phase spectra of EMG 1×EMG 2 signals. The two EMG signals were linearly related to a small phase difference at tremor frequency for patients 3-14 and 3-25 (table), showing cocontraction of wrist antagonists. E and F in the figure also show the cross-power spectrum of the spike×EMG 1 and spike×EMG 2 signals, and H and I show the corresponding coherence. The cell in the figure exhibited a firing pattern that was linearly related to both EMG channels to a significant degree (coherence >0.42). As expected in tremor with cocontraction of antagonists, all cells correlated with both extensor and flexor EMG showed a phase relation with the same sign to both muscle groups.

Patient 5-36 exhibited tremor with reciprocal contraction of wrist flexors and extensors in which the wrist flexor EMG lagged extensor EMG (table). In this patient, the phase of the spike×flexor EMG spectrum had the opposite sign to the spike×extensor spectrum for all tremor related cells.

Tremor related activity, defined by a spike SNR >2.0 and coherence >0.42,⁶ was found for 36% (26 of 73) of cells in the patients stud-

ied. Sensory responses were seen in 37% (27 of 73) of cells, and 33% (nine of 27) of these sensory cells were related to tremor. Tremor related activity had a negative phase angle with respect to EMG for 67% (12 of 18) of cells in patients with cocontraction of antagonists (3-14, 3-25). In patient 5-36, a spike×EMG phase relation could not be established as the phase of thalamic activity was of opposite sign in the antagonists.

Discussion

In this study we have shown that thalamic cells have tremor frequency firing patterns that are linearly related to forearm EMG signals during essential tremor. About one third (26 of 73) of the recorded cells in three patients showed a concentration of power at tremor frequency and a significant linear relation to EMG activity during tremor. Both synchronous and reciprocal antagonist EMG patterns¹³ showed thalamic tremor related activity.

Correlation between thalamic and EMG activity does not prove that thalamic activity causes tremor. Three different models can account for this correlation: thalamic activity drives EMG activity; thalamic activity is driven by sensory input that is generated by tremor movement; or an oscillator outside the thalamus drives both thalamic and EMG activity. The abolition of essential tremor by thalamic lesions⁴⁻⁵ suggests that some population of thalamic cells drives tremor. Therefore, the population of tremor related cells which comprise one in three of all cells and one in three of sensory cells may drive essential tremor. Tremor cells with sensory inputs may mediate the resetting of tremor by peripheral perturbations.¹⁻¹⁴

Animal studies suggest that the olivocerebellar circuit may be a good candidate for the central oscillator in harmaline tremor and so perhaps in essential tremor.²⁻¹⁵ Harmaline tremor is thought to originate in the inferior olive and is transmitted via the cerebellum to vestibulospinal, reticulospinal,²⁻³ or rubrospinal pathways.¹⁶ Recent evidence from human studies suggests that the cerebellothalamocortical pathway is involved in essential tremor. Studies by PET have shown that the cerebellum as well as the contralateral red nucleus, thalamus, and sensorimotor cortex show overactivity during essential tremor.¹⁷ Furthermore, surgical lesions of the ventralis intermedius abolish essential tremor.⁴⁻⁵ In combination with these reports, the present results argue forcefully that thalamocortical connections have an important role in essential tremor.

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