

Coherence between low-frequency activation of the motor cortex and tremor in patients with essential tremor

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Summary

Background In healthy people, rhythmic activation of the motor cortex in the 15–30 Hz frequency range accompanies and contributes to voluntarily-generated postural contractions of contralateral muscle. In patients with Parkinson's disease, an abnormal low-frequency activation of the motor areas of the cortex occurs and has been directly linked to the characteristic 3–6 Hz rest tremor of this disease. We therefore investigated whether the motor cortex is involved in the transmission of the rhythmic motor drive responsible for generating essential tremor.

Methods Non-invasive recordings of activity from the hand area of the motor cortex were made from six patients with essential tremor by magnetoencephalography. The recordings were made simultaneously with the electromyogram recorded from contralateral finger muscles during periods of postural tremor. A statistical spectral analysis was done to determine at which frequencies the two signals were correlated.

Findings Spectral analysis of the electromyogram signals showed a significant low-frequency component at the frequency of the tremor bursts. However, there was no coherence between magnetoencephalogram and electromyogram recordings at the tremor frequency, indicating that no correlation existed between the tremor signal and low-frequency activity recorded from the primary motor cortex in individuals with essential tremor. Coherence at frequencies higher than the tremor frequency was similar to that in healthy individuals performing voluntary postural contractions.

Interpretation The absence of significant coherence between the magnetoencephalogram and electromyogram at tremor frequencies suggests that in essential tremor the tremor is imposed on the active muscle through descending pathways other than those originating in the primary motor cortex. These findings challenge the model widely used to explain the efficacy of neurosurgical treatment of essential tremor, are in contrast to those of previous studies of parkinsonian rest tremor, and highlight an important difference in the pathophysiology of essential and parkinsonian tremor.

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Introduction

Essential tremor is the most common movement disorder and has a prevalence of 1–2% in the general population. The disorder can be defined as a low-frequency (4–9 Hz) postural tremor, which is absent at rest and not associated with the clinical signs of parkinsonism or other neurological deficits.^{1,2} The pathophysiology or the neural substrate that contributes to the generation of the tremor is not known.² However, functional imaging studies (positron emission tomography and functional magnetic resonance imaging) have indicated the presence of abnormal activation of the cerebellum and red nuclei in individuals with essential tremor.^{3–6} In addition, these functional imaging studies in patients with essential tremor show cortical activation patterns that cannot be distinguished from those seen in healthy individuals doing the same motor task.^{3–5} However, it is important to note that the limited temporal resolution of functional imaging does not enable abnormal temporal patterns of neural activation to be identified with the precision necessary to confirm or exclude involvement of a particular cortical area in the generation or maintenance of essential tremor.

The findings that lesions of the ipsilateral cerebellum diminish essential tremor and that ventrointermediate thalamotomy or microstimulation reduce tremor suggest an important role for cerebellothalamocortical pathways in its transmission.^{7–9} In this model, a 4–9 Hz oscillatory drive entrains neurons in the primary motor cortex, which then transmit the activity to spinal motor neurons via the corticospinal tract. Ventrointermediate neurons of the thalamus recorded from patients with essential tremor during functional neurosurgery show discharge bursts that correlate with the tremor episodes seen in electromyograms of contralateral arm muscles.¹⁰ However, whether this thalamic activity modulates the activity of neurons of the primary motor cortex remains to be shown.

In healthy individuals performing a voluntary postural contraction, highly localised rhythmic activity of the motor cortex (recorded either by magnetoencephalography or electroencephalography) is correlated with the contralateral electromyogram of the activated muscles within the frequency range 15–30 Hz.^{11–13} This interaction can be seen as significant coherence between the magnetoencephalogram and electromyogram with a peak at about 20 Hz, and is a marker for rhythmic activity in corticospinal pathways^{11,14} and a neurogenic component of physiological tremor.¹¹ A recent study on resting tremor in Parkinson's disease¹⁵ has described the presence of a low-frequency 3–6 Hz oscillatory loop involving the thalamus and motor cortex that results in correlation between magnetoencephalogram and electromyogram bursts at the tremor frequency. This finding indicates that the primary motor cortex contributes to the transmission of rest tremor in Parkinson's disease. If the primary motor cortex also contributes to the generation of essential tremor, there should be significant coherence between the magnetoencephalogram and contralateral electromyogram at tremor frequencies.

Patient	Sex	Age (years)	Duration of essential tremor (years)	Family history of essential tremor	Drug treatment (total daily dose)	Tremor predominance	Peak frequency (Hz) of tremor from electromyogram		Magnetoencephalogram/electromyogram coherence range (Hz)	
							Right	Left	Right	Left
1	F	54	1	Yes	None	Bilateral	6	7	13–28	11–25
2	M	57	16	Yes	Primidone (500 mg)	Asymmetric	..	5	11–26	12–25
3	M	68	3	Yes	Primidone (250 mg)	Asymmetric	..	6	17–23	16–19
4	M	69	20	Not known	Phenytoin (25 mg)	Asymmetric	6	..	11–28	21–28
5	F	65	20	Yes	Propranolol (160 mg)	Bilateral	5	6	..	11–27
6	M	16	1	Yes	None	Bilateral	9	9	24–26	11–13

Data relating to frequency of tremor was determined from the power spectra of electromyogram records; peak frequency, when present, is indicated for left and right recordings of first dorsal interosseous muscle.

Clinical characteristics with essential tremor and summary of the spectral and coherence analysis of magnetoencephalographic and electromyographic data

Our aim was to assess the contribution made to essential tremor by rhythmic activity recorded from the primary motor cortex during voluntary tonic muscle contraction.¹⁶

Methods

We studied six healthy individuals and six patients with essential tremor, whose disorders were diagnosed by an independent neurologist. Our study was approved by the ethics committee of the Southern General Hospitals NHS Trust, Glasgow, UK, and written informed consent was obtained from all participants. Five of the six patients with essential tremor had a positive family history of the disorder. The tremors were of sufficient magnitude to limit the patients' motor ability (eg, unable to hold a full glass of water without substantial spillage) and to give them feelings of embarrassment when in public. Four patients had strong tremor despite medication.

Details of the experimental protocol and a summary of the results for healthy individuals are given elsewhere.¹¹ Activity from the motor cortex was recorded by single-channel magnetoencephalography (BTi model 601, Biotechnology Inc, San Diego, CA, USA; second order gradiometer), with the surface electromyogram from the contralateral first dorsal interosseous muscle. Patients extended their arm, hand, and abducted fingers against gravity and maintained this posture for the duration of each recording. The position of the magnetoencephalography probe was adjusted to record from sites over the hand area of the motor cortex, and 120 s of data were obtained from each site with a sampling interval of 1 ms. Magnetoencephalography signals were filtered at 1–100 Hz, and electromyography signals were filtered at 3–500 Hz and rectified.

We determined whether activity from the primary motor cortex can be directly related to low-frequency bursts (4–9 Hz) of motor-unit firing seen during postural muscle contraction in essential tremor by assessing whether the magnetoencephalogram and electromyogram were correlated at the frequency of essential tremor. The magnetoencephalogram and electromyogram were treated as zero mean stationary time series, and estimates of their power spectra and the coherence between them were obtained by previously described methods.¹⁷

Briefly, each sample record of duration R is divided into L disjoint sections, each of duration T ms. The spectra of the signals is then estimated as the periodogram (1 Hz resolution) of each section averaged over the entire record. The correlation between frequency components of the two signals is given by the coherence, defined as the ratio of the magnitude squared of the cross-spectra of the two signals to the product of their individual autospectra. The coherence is analogous to a correlation coefficient squared at each frequency, and provides a bounded measure of association between components of the magnetoencephalogram and electromyogram at each frequency on a scale from 0 to 1, where 0 at a given frequency indicates that the two processes are independent. The coherence at a given frequency is taken to be significant when its values exceeds the upper 95% confidence limit, calculated under the assumption that the two signals are independent. This level is calculated as $1 - (0.05)^{1/(L-1)}$.

Results

Details of diagnosis for the six patients with essential tremor are shown in the table. Figure 1 shows raw data from magneto-

encephalography and contralateral electromyography of the first dorsal interosseous muscle for a healthy individual and a patient with essential tremor (patient 1, table). The magnetoencephalograms of both participants are similar. In comparison with the more uniform rectified electromyographic activity from the normal individual, the rectified electromyogram of the patient with essential tremor shows characteristic bursts of motor-unit activity at the tremor frequency (~5 Hz).

Analysis of complete magnetoencephalographic and electromyographic records from a healthy individual and a patient with essential tremor are shown in figure 2. The magnetoencephalogram spectra of both individuals are similar, with most power concentrated at low frequencies and with decreasing power at higher frequencies. Significant components at 15–25 Hz are present in both individuals. The electromyogram spectrum for the healthy person has two distinct spectral peaks centred about 12 Hz and 22 Hz with no distinct peaks at essential tremor frequencies. By contrast, the electromyogram spectrum for the patient with essential tremor has a large narrow and discrete peak at the tremor frequency (5 Hz) without distinct harmonics. An additional broader peak centred at 15 Hz is also present.

Importantly, the coherence between magnetoencephalogram and electromyogram is similar for both individuals, with significant values of coherence at 15–25 Hz for the normal person^{11–13} and at 12–25 Hz in the patient with essential tremor. Despite the clear spectral peak in the electromyogram at the tremor frequency (5 Hz), there is no significant coherence at this frequency in the patient with essential tremor. A similar pattern of coherence was seen between right and left first dorsal interosseous muscle electromyograms and contralateral magnetoencephalograms in all six patients. Our findings were similar in patients receiving and not receiving drug treatment and were not affected by the type of drug used (table).

Discussion

In the patients studied, tremor was absent at rest and only present during attempted postural contractions. In all cases there was no coherence between the activity of the motor cortex and the contralateral muscle electromyogram at the tremor frequency despite the presence of strong essential tremor bursts in the electromyogram. In people performing tonic contractions of hand muscles there is coherence of around 20 Hz between magnetoencephalographic or electroencephalographic activity and the electromyogram. Furthermore, cortex-muscle coherence is well localised and follows a somatotopic organisation reflecting the primary motor cortex homunculus.^{11–13} Similarly, primary motor-cortex local field potentials and cortico-motoneuron firing recorded in monkeys performing precision grip tasks show oscillations of about 20 Hz.

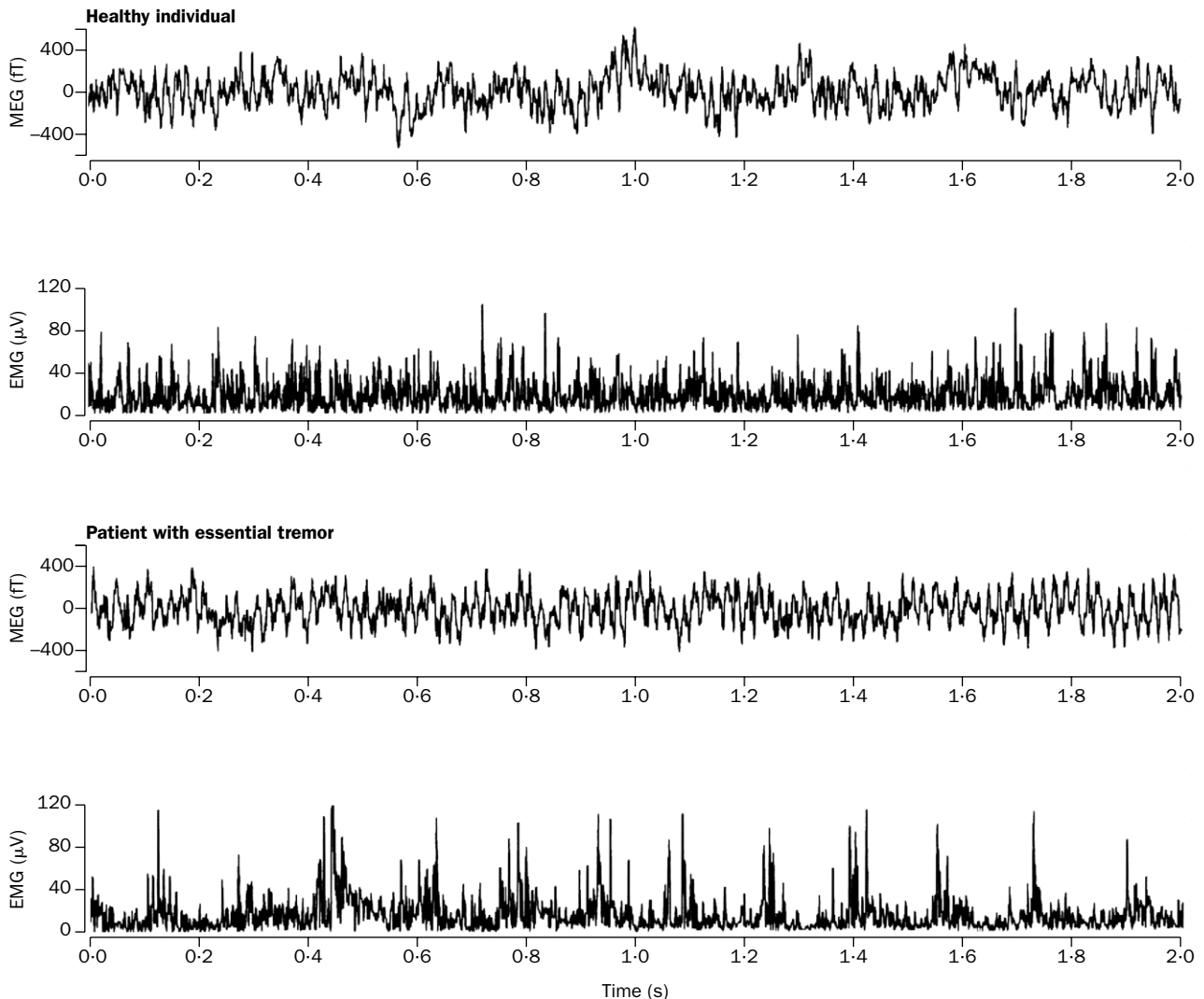


Figure 1: Comparison of magnetoencephalographic and electromyographic recordings from a healthy individual and a patient with essential tremor during voluntary maintained postural contraction of the first dorsal interosseous muscle
EMG=electromyogram; MEG=magnetoencephalogram.

The local field potential oscillations at about 20 Hz are coherent with the hand muscle electromyogram.¹⁸ The patients with essential tremor showed normal coherence of about 20 Hz between the magnetoencephalogram and electromyogram, indicating that the magnetoencephalograms were obtained from the hand area of the primary motor cortex.

The raw electromyograms and their spectra clearly showed the 4–9 Hz frequencies of essential tremor. Although the magnetoencephalogram spectrum encompasses a broad range of frequencies including those at which essential tremor is seen, there was no correlation between the 4–9 Hz components of the electromyogram and similar frequencies identified in the magnetoencephalogram. This implies that 4–9 Hz electromyogram tremor is independent of the magnetoencephalogram at these frequencies.

The normal coherence centred around 20 Hz between magnetoencephalographic and electromyographic activity in patients with essential tremor indicates that, despite tremor, rhythmic interactions between the primary motor cortex and the motor neurons are the same as those detected during non-tremulous tonic muscle contraction in healthy people. The primary motor cortex does not

therefore contribute to the generation or maintenance of essential tremor. On this basis we suggest that the voluntary motor command associated with a maintained muscle contraction is normal in patients with essential tremor, but during postural tasks, an abnormal involuntary non-cortical 4–9 Hz oscillatory drive develops and is imposed on the active motor neuron pools, thus producing the tremor.

Our findings highlight an important difference between essential tremor and the rest tremor of Parkinson's disease. The spectra of primary motor-cortex magnetoencephalographic signals express a 4–6 Hz Parkinsonian rest tremor activity, which is coherent with tremor of the contralateral electromyogram.¹⁵ More generally, the symptoms of Parkinson's disease also include bradykinesia and rigidity. By contrast, in essential tremor patients, with the exception of the tremor, motor behaviour is mostly normal. In Parkinson's disease these additional deficits imply a marked disruption to the organisation of the descending motor command that is not present in essential tremor. Our findings of a normal relation between primary motor cortex and electromyographic activity are in accordance with the clinical differences between Parkinson's disease and essential tremor.

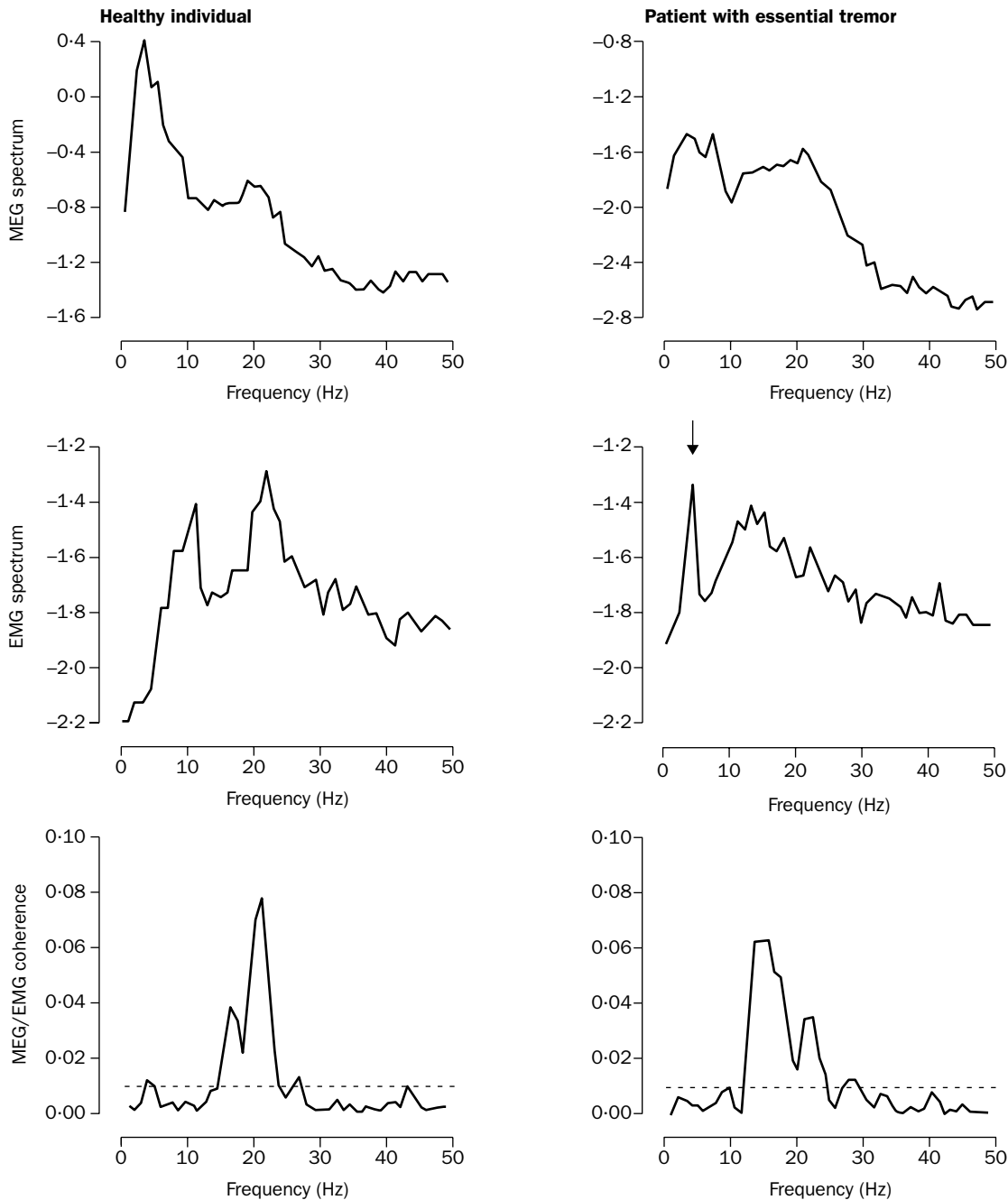


Figure 2: Spectral and coherence analysis of the magnetoencephalogram and contralateral electromyogram recorded from a healthy individual and a patient with essential tremor during voluntary maintained postural contraction of the first dorsal interosseous muscle

The horizontal dashed line indicates the upper level of the 95% CI for coherence. Values of coherence above this level at frequency λ are significant. Arrow indicates peak tremor frequency.

Our findings lead us to question a central component of the most widely accepted model of tremor generation in essential tremor in which the tremor is produced by rhythmic activation of the primary motor cortex by thalamocortical circuits. Neurosurgical ablation or microstimulation of the ventrointermediate nucleus of the thalamus is an accepted treatment for drug-resistant Parkinsonian tremor and severe essential tremor.⁸⁻¹⁰ Our results suggest that the effectiveness of neurosurgery in essential tremor cannot be explained on the basis of thalamic oscillations entraining the activity of neurons in the primary motor cortex.

The ventrointermediate thalamus also projects to premotor areas, including the supplementary motor area. Our findings do not exclude a model of essential tremor generation that involves an oscillatory drive that modulates the activity of non-primary motor areas. Such a model would require non-primary motor areas (eg, the supplementary motor area) to influence spinal-cord motor neurons directly. Recent findings in monkeys have indicated that the supplementary motor area and other premotor areas do project to the spinal cord,¹⁹ raising the possibility of their contribution to the transmission of a tremor signal in people with essential tremor. However,

animal models of essential tremor show that a 6–10 Hz tremor may emerge in decerebrate preparations in which rhythmic activation of cerebellar Purkinje neurons produces synchronisation of spinal motor neurons via vestibulospinal and reticulospinal pathways.^{20,21} Our data also support the view that therapeutic lesions to the thalamus act to interrupt rhythmic activity involving recurrent pathways between thalamus and cerebellum, which then impose the tremor signal on the normal postural motor command via bulbospinal pathways.¹

Coherence analysis can be used to identify features and differences in the pathophysiology of tremor, and is readily applicable within a hospital department of clinical neurophysiology in which electromyograms and electroencephalograms are routinely recorded. We anticipate that future use of this method will be of clinical value in the differential diagnosis of tremor disorders and will lead a better understanding of the pathophysiology of movement disorders.

Contributors

B A Conway, S F Farmer, D M Halliday, and J R Rosenberg were involved in the conception and design of the study. D M Halliday, A J C Russell, and U Shahani completed the experimental work with contribution from B A Conway during initial experimental sessions. Data analysis was done by D M Halliday, and all investigators were involved in discussions on data interpretation. B A Conway, S F Farmer, D M Halliday, and J R Rosenberg wrote the paper with critical input from U Shahani and A J C Russell.

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