Early report

Tremor-correlated cortical activity in essential tremor

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Summary

Background In patients with parkinsonian resting tremor, tremor-correlated activity in the contralateral sensorimotor cortex has been studied by both magnetoencephalography (MEG) and electroencephalography (EEG). In essential tremor, MEG failed to detect cortical involvement. The objective of this study was to investigate whether EEG recording can reveal tremor-correlated cortical activity in patients with essential tremor or enhanced physiological tremor.

Methods Seven patients with essential tremor and three patients with enhanced physiological tremor participated in the study. Unilateral postural tremor was activated by wrist extension on the right or on the left side. Electromyography (EMG) signals arising from the wrist extensor and flexor muscles, and a high-resolution EEG were recorded simultaneously. Coherences between the time series of the rectified tremor EMG and the EEG were estimated.

Findings In five of nine arms with essential tremor, we found highly significant coherences at the tremor frequency between the tremor EMG and the EEG. Isocoherence maps illustrating the topography of significant coherences over the scalp showed that the maximum coherences were located over the contralateral sensorimotor cortex. In the patients with enhanced physiological tremor, we were unable to detect consistent significant corticomuscular coherences at the tremor frequency.

Interpretation Using simultaneous EEG-EMG recordings, we showed that significant corticomuscular coherences at the tremor frequency can be found in essential tremor. This finding contrasts with a recent study based on MEG recordings. The results suggest that the sensorimotor cortex is involved in the generation of essential tremor, in a similar way to that previously shown in parkinsonian resting tremor.

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Introduction

Essential tremor is a common movement disorder characterised by a postural tremor of the arms that can be accompanied by tremor in other body parts such as the head, tongue, larynx, trunk, or legs. Other neurological signs are absent.[1] Essential tremor is generally assumed to be generated by a central oscillatory neuronal network.[2] However, the structural components involved in this network are largely unknown. Two main assumptions about the origin of essential tremor have been put forward: the involvement of the olivocerebellar-spinal loop and the predominant role of thalamic nuclei.

The suggestion that the olivocerebellar system is involved is based on the results of animal experiments with harmaline-induced tremor, which is similar to essential tremor in many respects.[3,4] After injection of harmaline, animals develop oscillatory activity in the inferior olive, which is accompanied by a tremor of the same frequency. In human beings, the olivocerebellar hypothesis is supported by studies that used positron emission tomography or functional magnetic resonance imaging. Patients with essential tremor are characterised by having increased glucose metabolism in the medulla[5] or increased blood flow in the cerebellum.[6,7]

Thalamic involvement in the oscillatory network that generates essential tremor is suggested by neurophysiological and clinical evidence. Neuronal activity in the thalamus is strongly correlated with forearm electromyography (EMG) signals recorded in essential tremor.[8] Moreover, stereotactic lesions or high-frequency stimulation in the nucleus ventralis intermedius of the ventrolateral thalamus have been shown to suppress essential tremor.[9,10]

Given the presence of strong thalamocortical projections in human beings, the cerebral cortex might also contribute to tremor generation in essential tremor. In parkinsonian resting tremor, such cortical involvement has indeed been shown. Coherence analysis has revealed tremor-correlated activity in the contralateral sensorimotor cortex by magnetoencephalography (MEG) and electroencephalography (EEG).[11,12] However, MEG studies in patients with essential tremor have failed to detect cortical involvement in tremor generation.[13] This finding was regarded as evidence that central oscillatory activity related to essential tremor is imposed on the muscles by descending pathways other than the corticospinal tract. Moreover, it was suggested that cortical involvement in the tremor-generating network might be useful in the differential diagnosis between parkinsonian and essential tremor.[14]

We aimed to find out whether EEG recordings assessed by coherence analysis could identify tremor-correlated cortical activity in patients with essential tremor and patients with an enhanced physiological tremor. This enhanced tremor is a physiological tremor with a prominent 8–12 Hz component which has been regarded as a forme fruste of essential tremor.[15]

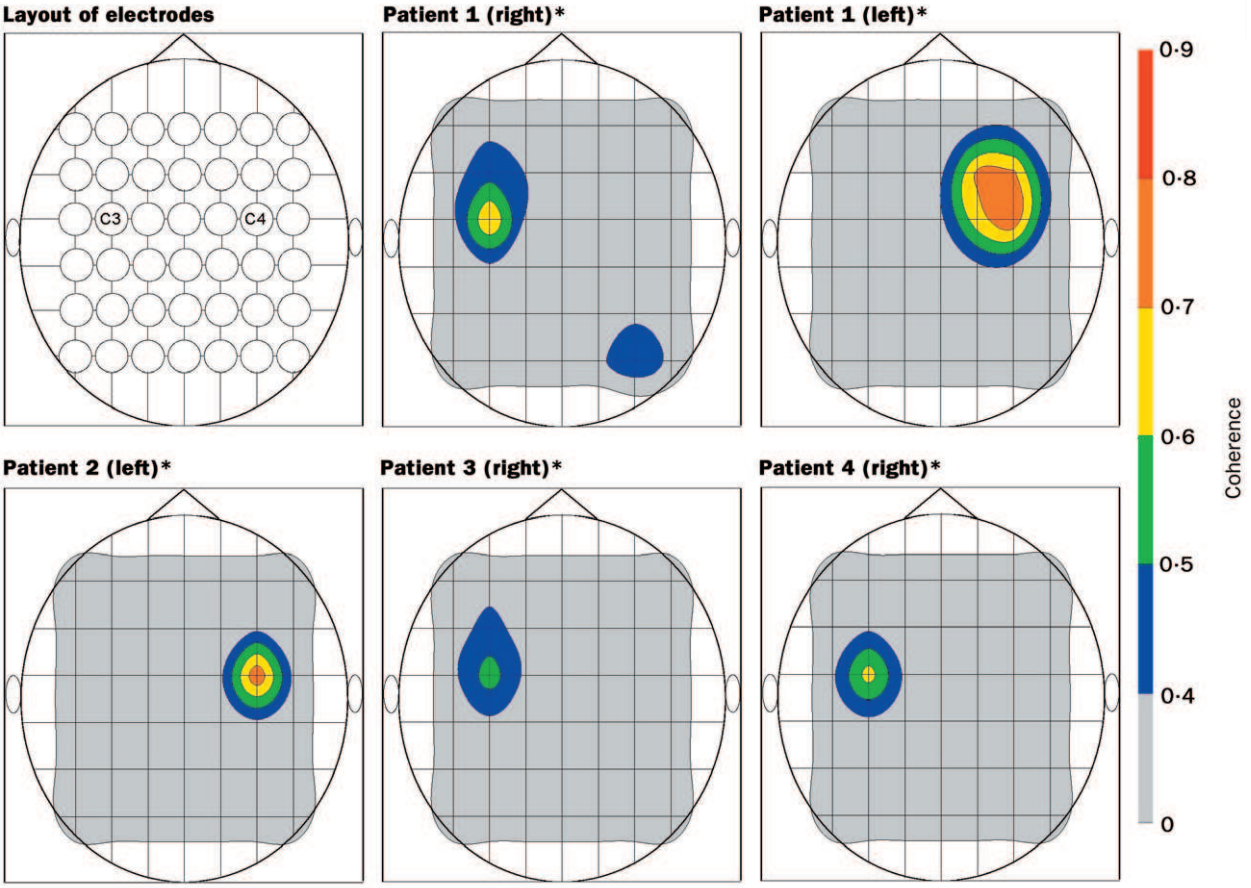

Figure 1: **Schematic layout of the 42 electrodes used in the analysis, and isocoherence maps for patients 1–4**
Grey regions=non-significant coherences. Colours=significant coherences (p<0·01). C3=over left sensorimotor cortex. C4=over right sensorimotor cortex. *Arm with postural tremor.

Methods

Patients

Seven patients (four women, three men) with essential tremor, and three patients (all men) with enhanced physiological tremor participated in the study. All patients were selected because they showed a postural tremor of the arms without significant head tremor. Patients with essential tremor were on average 60·3 years of age (range 45–73 years). Tremor had been present for at least 5 years (mean 18·7 years; range 5–45 years). Apart from the postural tremor in the arms, there was no evidence of further neurological abnormalities, particularly parkinsonian symptoms. Patients with enhanced physiological tremor were on average 39·3 years of age (range 28–47), and tremor had lasted for a mean of 11·0 years (range 6–17). Tremor was the only neurological sign in these patients. The enhanced physiological tremor was defined as a physiological tremor with a prominent 8–12 Hz component visible in the spectra of accelerometer and EMG recordings.[15] This component was preserved when loads were attached to the hands. All patients gave informed consent to participate in the study. Ethical approval was not sought, since the methods used in our study are standard neurological tools which are in no way harmful to the patient.

Recording procedure

Inside a dimly lit room, patients were seated in a comfortable chair with their forearms supported. Surface EMG electrodes were attached to the wrist flexors and extensors of both arms. EEG was done with a 64-channel EEG system (Neuroscan, Herndon, VA, USA). Patients were asked to keep their eyes open and to fix their eyes on a point of light about 1·5 m away. Postural tremor was elicited by unilateral wrist extension on the right or the left side. To increase the tremor amplitude, some patients were instructed to count backwards mentally. EEG and EMG signals were sampled at 1000 Hz and band-pass filtered (EEG 1–200 Hz, EMG 50–200 Hz). Data were stored on a personal computer and analysed off-line. The EMG was full-wave rectified.

In four of seven patients with essential tremor, recordings were done for tremor on the right and the left side. In the remaining three patients, postural tremor was activated only on one side (two on the right, one on the left side), since the tremor on the other side was very weak. Recordings were done on both sides in the patients with enhanced physiological tremor.

Data analysis

In all, 42 electrodes were applied (figure 1). Readings from the electrodes at the edge of the electrode cap were disregarded because of low signal-to-noise ratios. In each recording, high-quality epochs of 80 s were selected. The potential field over the scalp was transformed into the reference free current source density distribution[16] which has been shown to be the optimum basis for EEG-EMG coherence analysis.[17] Coherence estimates the amount of correlation between the frequency components of two processes.[14,18–23] In this study, we used a direct spectral estimation procedure with a Bartlett window of 1 Hz width.[24]

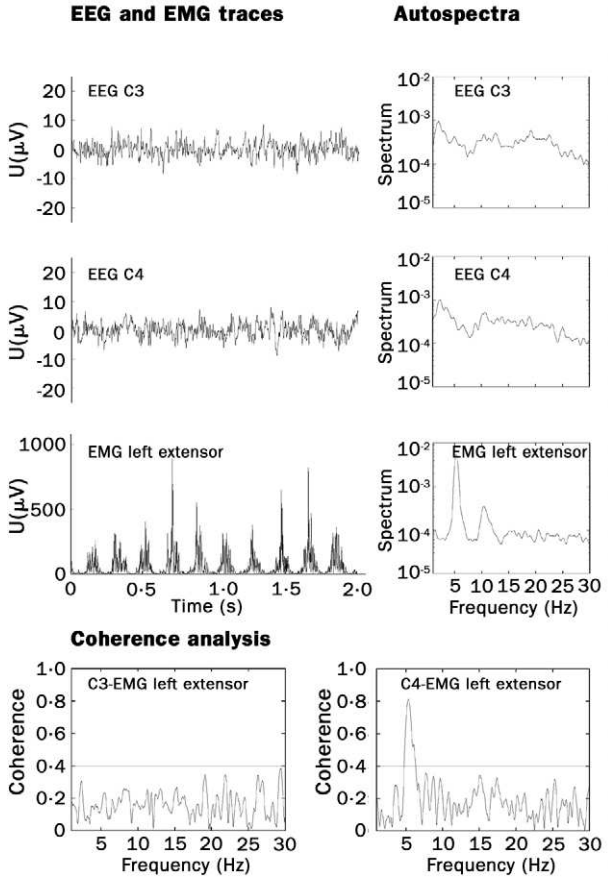

Figure 2: **EEG and EMG traces, their autospectra, and corresponding coherences for patient 1 with activation of postural tremor in the left arm**
Horizontal line at a coherence of 0·4 indicates level of significance (p<0·01).

Signal-to-noise ratios of tremor EMGs were calculated with EMG autospectra by dividing the height of the peak at the tremor frequency above the noise level by the noise level itself.[25]

Results

Figure 2 illustrates results from a patient with essential tremor who activated postural tremor on the left side. Two EEG traces (electrodes C3 and C4), one EMG trace (left wrist extensor), the autospectra of the EEG and EMG traces, and the corresponding coherences are displayed. Inspection of EEG and EMG traces did not reveal any correlation between tremor and cortical activity. Although the autospectrum of the EMG trace showed peaks at the tremor frequency (about 5 Hz) and its higher harmonic, the autospectra of the EEG traces did not reveal such peaks. The coherence analysis revealed, however, a correlation between EEG and EMG. Although there were no significant coherences between the tremor EMG and the ipsilateral EEG electrode C3, a significant coherence peak (p<0·01) at the tremor frequency could be found for the EEG electrode C4 which was located contralateral to the tremor side.

We obtained 11 simultaneous EEG-EMG recordings relating to the arms of the patients with essential tremor (four patients with unilateral tremor activation on the right and the left side, three patients with tremor activation only on one side). Two of these recordings were discarded because inspection of the data revealed continuous

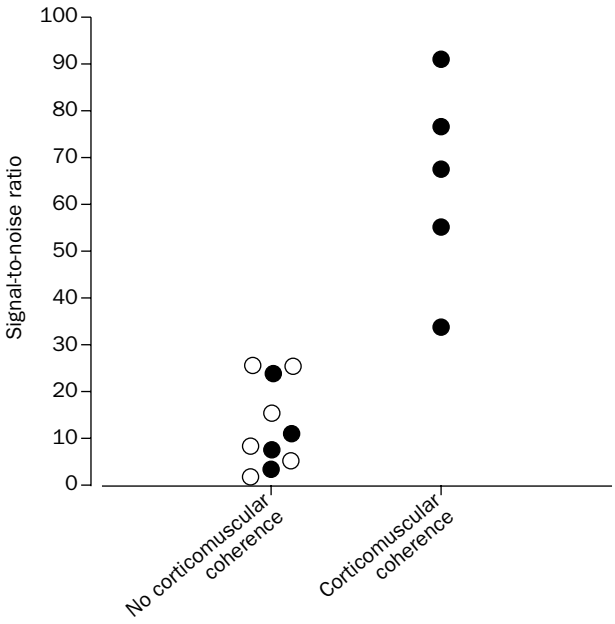

Figure 3: **Signal-to-noise ratios of tremor EMGs of patients with and without significant corticomuscular coherences at the tremor frequency**
Open circles=patients with enhanced physiological tremor; filled circles=patients with essential tremor. Difference between groups was significant (p=0·01, two-tailed Kolmogorov-Smirnov test).

bilateral tremor activation. In the remaining nine arms with unilateral tremor, the amount of coherence was quantified by calculating the mean coherence value over a frequency band of 1 Hz (the width of the direct spectral estimator) at the tremor frequency for each EEG channel. In five of nine arms, we found highly significant (p<0·01) EEG-EMG coherences at the tremor frequency (analysis of 13 high-quality epochs of 80 s duration, mean coherence 0·62, range of significant coherences between 0·45 and 0·76). Figure 1 shows isocoherence maps for these cases in which the topography of significant coherences over the scalp is illustrated. There were highly significant coherences between the tremor EMG and contralateral EEG channels, but not between the tremor EMG and ipsilateral EEG channels. The maximum coherences were located at (or close to) electrodes C3 and C4, which are localised over the sensorimotor cortex.

In four of nine arms with essential tremor, we did not find any significant corticomuscular coherences at the tremor frequency (analysis of 11 high-quality epochs of 80 s duration). This finding also holds for the six arms with enhanced physiological tremor (three patients with unilateral tremor activation on the right and left side). Coherences at the tremor frequency were not consistently significant despite a clear 8–12 Hz peak in the EMG autospectra (analysis of 30 high-quality epochs of 80 s duration, in one case a significant coherence of 0·5). However, in all these arms, tremor amplitudes were relatively low. This was quantified by comparing signal-to-noise ratios of tremor EMGs of arms with significant and non-significant corticomuscular coherences. Figure 3 illustrates that the signal-to-noise ratios were substantially higher in the five arms with significant EEG-EMG coherence at the tremor frequency.

Discussion

Clinical and experimental studies suggest that the central oscillator that generates essential tremor involves the

inferior olive, the cerebellum, and the thalamus. However, the complex pathophysiological mechanisms leading to the clinical expression of essential tremor are still far from being understood. For instance, whether the cerebral cortex contributes to tremor generation via the corticospinal tract is questionable.

In parkinsonian resting tremor, there is clear evidence for the involvement of the sensorimotor cortex in the tremor-generating network. This involvement has been shown by recording directly from the cortical surface,[26] as well as by MEG[11] and EEG recordings.[12] In essential tremor, the situation is less clear. On one hand, stereotactic operations in human beings have shown that the thalamus plays an important part in the generation of essential tremor,[8–10] suggesting that there might also be cortical involvement, considering the strong thalamocortical projections present. On the other hand, there has been no direct proof of a contribution of the cerebral cortex to the central oscillator that produces essential tremor. On the contrary, coherence analysis based on MEG recordings in patients with essential tremor failed to reveal a cortical involvement in tremor generation.[13]

Our findings show that EEG recordings carry information about tremor activity in essential tremor. In five of nine arms studied, coherence analysis revealed highly significant EEG-EMG coherences at the tremor frequency. The topography of significant coherence peaks over the scalp suggests that the contralateral sensorimotor cortex in particular is involved in tremor generation (figure 1).

In four of nine arms with essential tremor, and in the six arms with enhanced physiological tremor, we did not find consistent significant EEG-EMG coherences at the tremor frequency. In enhanced physiological tremor, however, the 8–12 Hz component in the EMG-autospectrum is assumed to be controlled by a central oscillator, since it does not change its frequency after mass loading.[15] Moreover, Köster and colleagues[27] provided evidence for a cortical contribution to the 8–12 Hz component. In drug-induced enhanced physiological tremor of patients with persistent mirror movements, they showed in EMG time series a right-left coherence of the 8–12 Hz component. Such a coherence could not be found in normal controls. This finding was regarded as evidence that the corticospinal tracts (and thus the sensorimotor cortex) were involved in the transmission of the oscillating 8–12 Hz component from the central nervous system to the periphery. Nevertheless, such a cortical component could not be detected by our analysis of corticomuscular coherences in patients with enhanced physiological tremor. This absence could be due to the fact that tremor amplitudes in these patients were relatively low, and is in line with the finding that, in patients with essential tremor, significant EEG-EMG coherences were absent in cases with weak tremor. Figure 3 illustrates that the signal-to-noise ratios of the tremor EMGs were comparatively low in enhanced physiological tremor as well as in essential tremor without significant corticomuscular coherence at the tremor frequency. Timmer and colleagues[22] have shown that the amount of coherence depends indeed on the signal-to-noise ratio. Thus, the failure to detect significant EEG-EMG coherences could be explained by the limited sensitivity of the method, rather than by a real lack of a cortical component. This possibility also means that the question of whether the physiological tremor with a prominent 8–12 Hz component is a separate entity or just a forme fruste of essential tremor[15] cannot be answered by the results of the present study.

Relatively low signal-to-noise ratios in the tremor EMGs could also explain why Halliday and colleagues[13] were unable to find significant corticomuscular coherences at the tremor frequency in their MEG study on patients with essential tremor. In this context, the fact that Halliday and colleagues recorded EMGs from a relatively small muscle, namely the first dorsal interosseus muscle, could also be important. Recordings from the substantially larger wrist extensors and flexors, as in our study, might yield better signal-to-noise ratios. Moreover, the population of cortical neurons oscillating in synchrony with the tremor need not be identical for different muscles, since different muscles may oscillate independently.[28] Thus, a neuronal population coherent with the tremor activity of large muscles might be easier to detect.

Significant EEG-EMG coherences at the tremor frequency over the sensorimotor cortex, as found for essential and parkinsonian tremor, raise the question of whether the underlying tremor-correlated EEG activity is mainly motor, mainly somatosensory, or both motor and somatosensory in nature. The spatial resolution in the isocoherence maps is certainly not precise enough to answer this question. One way to solve this issue, however, is to calculate time delays between cortical and muscular activity by use of phase information. This process might indicate whether tremor-related EEG signals occur before of after tremulous muscular activity. Tremor-coherent cortical activity preceding the tremor would point to activity in the motor cortex, whereas the opposite situation would suggest somatosensory activation via proprioceptive afferences. Hellwig and colleagues,[12] however, have shown that, for parkinsonian tremor, calculations of time delays with phase information lead to results that cannot be interpreted in a meaningful way.

In summary, we have shown that tremor-correlated EEG activity can be detected in essential tremor. The findings suggest that the sensorimotor cortex is involved in the oscillatory neuronal network that generates essential tremor. However, this suggestion does not imply that the thalamocortical loop has an important role in the generation of essential tremor, but not the olivocerebellar system. Oscillatory activity in the olivocerebellar system could conceivably be relayed to the thalamus via the thalamic projections of the cerebellar nuclei, then projected to the sensorimotor cortex, and directed to the periphery via the corticospinal tract.

Results very similar to those presented here have been obtained for unilateral parkinsonian resting tremor.[12] This makes it unlikely that simultaneous EEG-EMG recordings assessed by coherence analysis are useful in the differential diagnosis of essential and parkinsonian tremor. On the contrary, the similarity of results might even indicate that at least part of the basic tremor-generating mechanisms are identical for parkinsonian and essential tremor.[29] The analysis of EEG-EMG coherences seems to be a valuable and widely available tool for further studies on the pathophysiology of tremor disorders.

Contributors

C H Lücking initiated this study. The study design was developed in discussions involving all investigators. B Hellwig and B Guschlbauer carried out the experimental work. Data analysis was done by S Häußler, B Schelter, M Lauk, J Timmer, and B Hellwig. All investigators were involved in discussions on data interpretation. The paper was written by B Hellwig with critical contributions by all investigators.

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