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Cortical Involvement in the Generation of Essential Tremor

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Raethjen J, Govindan RB, Kopper F, Muthuraman M, Deuschl G. Cortical involvement in the generation of essential tremor. *J Neurophysiol* 97: 3219–3228, 2007. First published March 7, 2007; doi:10.1152/jn.00477.2006. Conflicting results on the existence of tremor-related cortical activity in essential tremor (ET) have raised questions on the role of the cortex in tremor generation. Here we attempt to address these issues. We recorded 64 channel surface EEGs and EMGs from forearm muscles in 15 patients with definite ET. EEG and EMG power spectra, relative power of the rhythmic EMG activity, relative EEG power at the tremor frequency, and EEG–EMG and EEG–EEG coherence were calculated and their dynamics over time explored. Corticomuscular delay was studied using a new method for narrow-band coherent signals. Corticomuscular coherence in the contralateral central region at the tremor frequency was present in all patients in recordings with a relative tremor EMG power exceeding a certain level. However, the coherence was lost intermittently even with tremors far above this level. Physiological 15- to 30-Hz coherence was found consistently in 11 patients with significantly weaker EMG activity in this frequency range. A more frontal (mesial) hot spot was also intermittently coupled with the tremor and the central hot spot in five patients. Corticomuscular delays were compatible with transmission in fast corticospinal pathways and feedback of the tremor signal. Thus the tremor rhythm is intermittently relayed only in different cortical motor areas. We hypothesize that tremor oscillations build up in different subcortical and subcortico-cortical circuits only temporarily entraining each other.

INTRODUCTION

Essential tremor (ET) is typically driven by rhythmic EMG bursts remaining constant when the resonant frequency of the oscillating limb is changed, such as by added inertia (Deuschl et al. 1996; Elble 1986). This indicates its relative independence from peripheral mechanical reflex mechanisms and is a sign of a central origin (Deuschl and Elble 2000; Elble 2000).

However, the tremor physiology measured in the periphery cannot determine where in the CNS these oscillations emerge. The strong effect of thalamic lesions on tremor led to the hypothesis that the thalamus may be involved in the generation of ET (Koller et al. 2000; Pahwa et al. 2000; Schuurman et al. 2000). This was supported by recordings of tremor coherent oscillatory activity from the thalamic ventralis intermediate nucleus (Hua and Lenz 2004; Hua et al. 1998), and oscillating thalamocortical loops may be one pathogenetic basis of ET (Deuschl et al. 2001; Elble 1996; Hellwig et al. 2001). However, whereas in Parkinson's disease tremor-related cortical activity was previously found reproducibly in different studies (Hellwig et al. 2000; Timmermann et al. 2003; Volkmann et al. 1996), attempts to demonstrate a cortical correlate of the tremor rhythm in ET led to conflicting results. Halliday et al. (2000) did not find significant coherence between magnetoencephalographically recorded cortical activity and the peripheral tremor, but only around 20 Hz, which is a well-described physiological phenomenon (Baker et al. 1999; Brown et al. 1998; Conway et al. 1995; Halliday et al. 1998). Hellwig et al. (2001) more recently demonstrated clear tremor-related activity in the electroencephalogram (EEG) of a proportion of their patients with ET.

The reasons for these diverging results are not clear and raise questions regarding the role of the cortex in the emergence of ET. Hellwig et al. (2001) suggested that this may be a purely methodological problem because the tremor has to reach a certain intensity before corticomuscular coherence at the tremor frequency can be detected. However, Halliday et al. (2000) were able to detect the physiological coherence around 20 Hz, although the muscle activity at this frequency was not stronger than the activity at the tremor frequency. Another unsolved question is the direction of interaction between cortex and periphery at the tremor frequency. Although the coherence indicates that the cortex is involved in the tremor oscillations it does not necessarily indicate that it is involved in tremor generation (i.e., that the oscillatory activity is transmitted from cortex to muscle).

These issues are addressed in the present study in an analysis of the corticomuscular coherence and its dynamics at the tremor frequency and in the 15- to 30-Hz band in relation to the relative EMG power at the respective frequency in the same ET patients. The delay and direction of interaction between cortex and periphery at the tremor frequency were determined using a newly developed method for delay estimation in narrow-band coherent signals (Govindan et al. 2005, 2006).

METHODS

Patients

In all, 15 patients (three female and 12 male) were included in the study all of whom fulfilled the diagnostic criteria for classical essential tremor (Deuschl et al. 1998) that is definite ET according to Tremor Investigation Group (TRIG) criteria (Findley and Koller 1995). Ages ranged from 26 to 73 yr (mean: 61 ± 13.5). Disease duration was between 4 and 50 yr (mean: 21 ± 15.6). Clinical tremor severity was assessed by the essential tremor rating scale (ETRS) developed by Fahn et al. (1988). Patients covered a broad range between an ETRS total score of 5 and 101 (mean: 32 ± 25.7). All of the patients suffered from bilateral but sometimes asymmetric hand tremor with accelerometric frequencies ranging from 4 to 7 Hz (mean: 5.6 Hz). The hand items of the ETRS differed by <2 points between the left and right hand in 12 of the patients. In the remaining three patients the left–right differences in the clinical hand scores were 3, 8,

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and 14. All of them had bilateral tremor from the onset of the disease. None of them showed any clinically visible head tremor in the recording position at the time of the recordings. Five of the patients had a clear family history of postural tremor in a first-degree relative. Seven of the patients were taking medication directed against their tremor (four only Propranolol, two only Primidon, and one a combination of Primidon and Propranolol). All of these patients reported only a slight alleviation of their tremor by the medication. It was continued at the time of the recordings. The study protocol was approved by the local ethics committee and all patients gave informed consent.

Recordings

Patients were seated in a comfortable chair in a slightly supine position. Both forearms were supported by firm armrests up to the wrist joints. The hands were held outstretched against gravity or an additional weight load of 1,000 g. Patients were asked to keep their eyes open and fix their eyes on a point about 2 m away.

Tremor was recorded by surface EMG from the forearm flexors and extensors using silver chloride electrodes. EEG was recorded in parallel with a standard 64-channel recording system (Neuroscan, Herndon, VA) using a linked mastoid reference. EEG and EMG were sampled at 1,000 Hz and band-pass filtered (EMG 30–200 Hz; EEG 0.05–200 Hz). Data were stored in a computer and analyzed off-line.

Individual recordings were of 1- to 4-min duration. The number of recordings performed in each patient varied between two and eight depending on the way the patient tolerated the experimental setting (cap tautness).

Data analysis

EMG was full-wave rectified and the EEG was made reference free by Hjorth transformation (Hjorth 1975). The combination of band-pass filtering and rectification is the common demodulation procedure for tremor EMG (e.g., Hurtado et al. 2005; Journee et al. 1983; Timmer et al. 1998). Only 49 EEG electrodes were used. The boundary electrodes were used only for the Hjorth transformation and not for the subsequent analysis. Each record was segmented into a number of 1-s-long high-quality epochs from which all the data sections with visible artifacts were discarded. Depending on the length of the recording and the quality of the data, between 40 and 240 segments of 1 s were used for the analysis of one record. Following Halliday et al. (1995) we calculated the periodogram of the power spectra and the cross-spectrum for each of the 1-s segments independently using a Hanning window. These periodograms were then averaged over all the segments to get a reliable spectral and cross-spectral estimate including confidence intervals with a frequency resolution of 1 Hz (Halliday et al. 1995). The coherence was then calculated as the ratio of the squared magnitude of the cross-spectrum to the product of the power spectra. Coherence is a normalized linear measure, taking on a value of one in the case of a perfect linear dependency and zero in the case of complete independence between the two processes. The statistical significance of coherence is assessed by the 99% confidence limit, which is derived under the hypothesis of linear independence (Halliday et al. 1995; Timmer et al. 1998) and is given by

$$1 - (0.01)^{1/(L-1)}$$

where L is the number of disjoint 1-s sections (segments) used in the spectral estimation. Estimated values of coherence lying below this confidence limit are taken as an indication of a lack of linear dependency between the two processes.

The localization of the coherence on the scalp was determined by calculating isocoherence maps taking into account all the electrodes. For this purpose the 99% confidence limit was subtracted from the coherence at the tremor frequency for each of these electrodes, thereby setting the level of significance to zero. These coherence differences were grayscale-coded with black indicating the maximal corticomuscular coherence found in the respective recording and white indicating coherence values below the confidence level. In case of a mechanical transmission of the tremor oscillations from the arm to the head inducing rhythmic movement artifacts in the EEG we found a characteristic pattern of widespread bilateral coherence especially marked in the posterior electrodes. Those recordings were excluded from further analysis. This is in line with the observations and the procedure for movement artifact detection described in earlier work (Timmermann et al. 2003).

In cases that showed two separate coherent areas (“hot spots”) in the isocoherence maps, cortico-cortical coherence was calculated between the electrodes showing maximal coherence with the muscle in the respective hot spot.

A new method was used to determine the direction of interaction between the involved cortical areas and muscle. The traditional way of determining the direction of interaction and time delay between two time series by fitting a line or curve to the phase spectrum in the coherent frequency range (Brown et al. 1998; Lindemann et al. 2001; McAuley et al. 1997; Mima et al. 2000; Muller et al. 2003; Salenius et al. 2002) fails in case of very narrow band signals like pathological tremors. The new method is also based on spectral analysis but overcomes this problem. It takes advantage of the fact that a delay between two signals introduces a time misalignment that slightly reduces the estimated coherence (Carter 1987). To estimate the delay between the time series, one of them is time shifted backward in time, keeping the other constant. The coherence at a selected frequency (here: tremor frequency) is estimated as a function of the shift. If there is a delay in this direction coherence will increase and reach a maximum value at the shift corresponding to the delay. The analysis is repeated by shifting the other time series (which was held constant in time in the preceding analysis) to estimate the delay, if any, in the other direction. Thus we can obtain the nature of coupling and the delay in both directions by this method. The level of significance and the SD of the calculated delays were determined by surrogate analysis. Details of the procedure are given in Govindan et al. (2005). The delays and their SDs for all the coherent electrodes belonging to one hot spot were weighted according to the strength of their coupling with the periphery (coherence) at the tremor frequency and then averaged. This weighted average was taken as a good approximation of the delay between the respective hot spot and the peripheral tremor.

The relative EEG power at the tremor frequency was assessed by dividing the EEG power at the tremor frequency by the mean EEG power at the remaining frequencies between 1 and 100 Hz. For the second broader band around 20 Hz the maximal power in the coherent frequency range was used. The relative EMG powers at the tremor frequency and in the 15- to 30-Hz band were calculated by dividing the height of the peak at the respective frequency by the mean power in the 51- to 100-Hz range. This measure of tremor intensity is similar to the “signal-to-noise ratio” described by Hellwig et al. (2001). It is analogous to the well-known relative power measure for EEG signals, except that the EMG power at the frequency of interest is normalized only by the mean power of higher frequencies to avoid an artificial influence of very high peaks at the lower (e.g., tremor) frequencies. To compare the relative EMG power between the two frequency bands and coherent and noncoherent recordings we performed a receiver operating characteristic (ROC) analysis. The ROC curve is a plot of sensitivity and 1 − specificity. The area under the ROC curve (AUC) gives the degree of separation in the distribution of relative EMG power in two groups and 1 − AUC gives the degree of overlap between the two groups.

Among the recordings that showed a significant coherence at the tremor frequency and/or in the 15- to 30-Hz band, long artifact-free segments and completely artifact free recordings were selected. A dynamic analysis of the corticomuscular coherence, the cortico-cortical

coherence between the two cortical hot spots (if applicable), and the relative EMG power over time were performed for these recordings by calculating power and coherence spectra for moving 30-s windows with an overlap of 28 s, resulting in an apparent time resolution of 2 s. For each of these 30-s windows calculation of the spectral quantities followed the same procedure as that for recording as a whole described earlier (Halliday et al. 1995). However, decreasing the number of data points will inevitably make the coherence estimates noisier and thus one concern is that any intermittent drops in coherence below the significance level may arise from noisy fluctuations in the coherence estimate rather than from an intermittent lack of correlation. Therefore we created a realistic model to test this approach. We considered two coupled AR2 processes (y[n] = a1y[n − 1] + a2y[n − 2] + noise[n]). One version (V1) of AR2 had narrow-band spectral characteristics (a1 = 1.9691, a2 = −0.9753) and the other (V2) had broadband spectral characteristics (a1 = 0.37486, a2 = −0.36788). These two processes were simulated for durations of 150 s at a sampling rate of 1,000 Hz. The narrow-band AR2 (V1) was then band-pass filtered around its spectral peak between 8 and 15 Hz and was then combined by point-by-point summation with the broadband AR2 (V2) as follows: V = V2 + 0.2V1. Independent white noises were added to V and V1 whose amounts were tuned so that the overall coherence between V and V1 was around 0.1, close to what we observe in the biological situation (Fig. 1*A*). In the dynamic analysis of the coherence in this model we found a significant coherence between the data sets at all times (Fig. 1*B*). Also we simulated another different scenario in which the coupling between these signals was introduced only in selected time segments. For this scenario, the dynamic coherence showed coherence between the two signals in the time frames at which the coupling was introduced. However, we did not present these results here for the sake of brevity. These simulation experiences demonstrate that the presence of intermittent versus continuous coupling can be safely captured by our dynamic coherence analysis without attributing the results to methodological pitfalls.

RESULTS

Corticomuscular coherence at the tremor frequency

In all of the 15 patients we found corticomuscular coherence at the tremor frequency. This was reproducible between two to four successive recordings with and without added weight in 12 of the patients, whereas it was seen in only one of the recordings in three of them. The tremor frequency remained constant under weight load in all the patients and the frequency of the corticomuscular coherence also remained unchanged under added inertia in 12 of the patients showing coherence at the tremor frequency under both conditions. Nine patients showed bilateral (albeit slightly asymmetric) tremor activity at the time of the recordings with corresponding corticomuscular coherence at the tremor frequency with the cortex contralateral to the respective tremor hand. Only in one of the patients did we find a significant but weaker corticomuscular coherence also at double the tremor frequency as previously reported for Parkinsonian tremor (Timmermann et al. 2003), although there was a clear peak at double the tremor frequency in the EMG power spectra of 11 patients (Fig. 2).

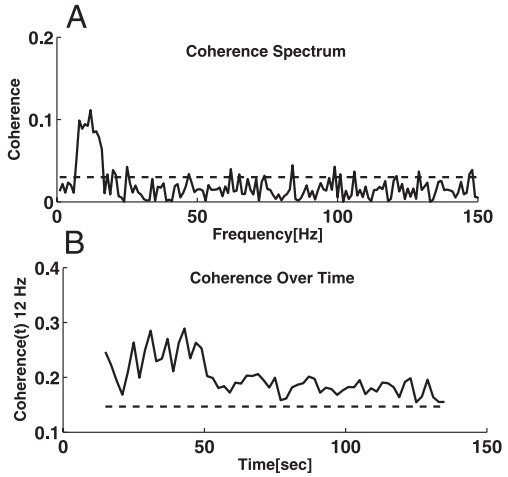

FIG. 1. Performance of the coherence analysis in each 30-s window with a 2-s sliding window over time in a model system. Two AR2 processes (one with a broadband spectrum and one with a narrow-band spectrum) were constructed and coupled by adding a fraction (1/5) of the band-pass filtered narrow-band AR2 to the broadband AR2 (for details see METHODS). Coherence between this compound AR2 process and the narrow-band AR2 is displayed in *A*. Similar to the corticomuscular system in tremor patients there is a narrow-band significant coherence around 0.1. Dynamic coherence estimated is shown in *B*. Although there are some noisy fluctuations of the coherence values they all clearly remain above the significance level at all times.

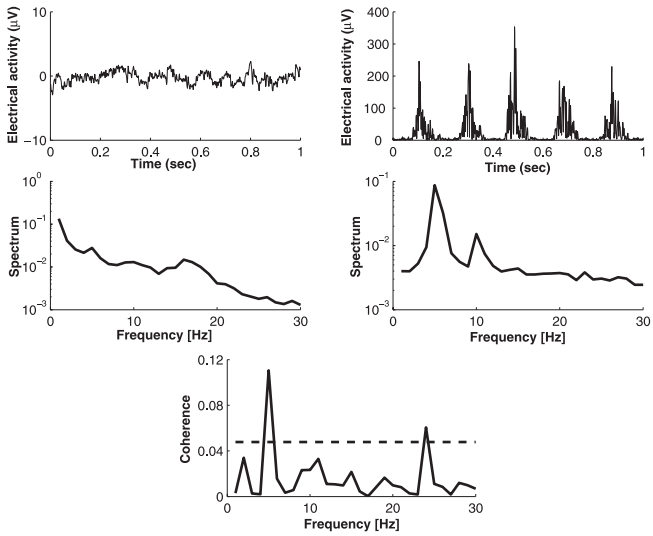

FIG. 2. Representative example of raw data, power, and coherence spectra. A section of Hjorth-transformed electroencephalogram (EEG) raw data and the power spectrum of the whole 2-min time series recorded from electrode C3 is displayed in the *left column*, rectified electromyogram (EMG) and EMG power spectrum of the forearm extensor on the *right*. Corticomuscular coherence spectrum is shown in the *middle* at the *bottom*. Horizontal line in the coherence spectrum indicates the 99% confidence level. Coherence exceeding this level is considered to be statistically significant.

The EMG bursts were not coherent between both sides in the vast majority of the recordings as previously reported for ET (Lauk et al. 1999; Raethjen et al. 2000).

A typical example of Hjorth-transformed EEG and rectified EMG raw data together with the corresponding power spectra and the coherence spectrum is given in Fig. 2. There is strong tremor activity in the EMG resulting in a clear peak in the EMG spectrum. In a number of recordings there was also a peak at the tremor frequency in the EEG spectrum, albeit much less prominent than the EMG peak. The significant EEG–EMG coherence at the tremor frequency indicates tremor-related EEG activity.

Corticomuscular coherence in the 15- to 30-Hz range

In 11 of the patients we also found corticomuscular coherence in the 15- to 30-Hz range the maximum of which was not harmonically related with the tremor frequency in any of them. In nine cases this was seen along with the lower-frequency

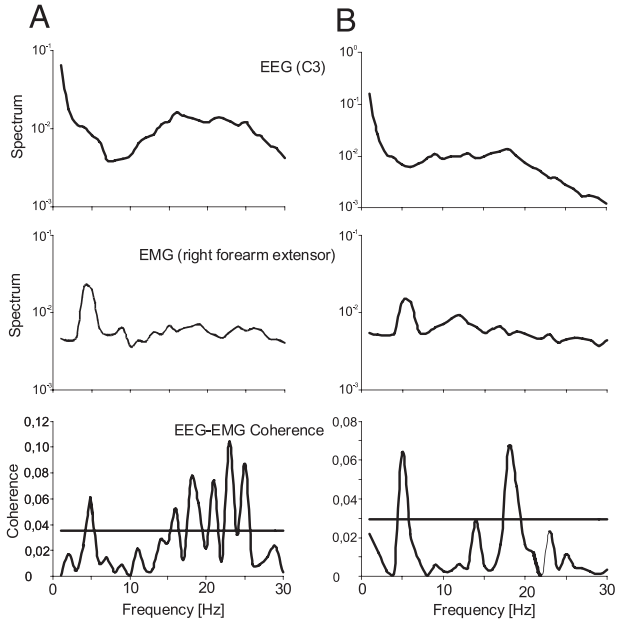

FIG. 3. Two examples of recordings from 2 patients (*A* and *B*) with parallel corticomuscular coherence at the tremor frequency and in the 15- to 30-Hz band. EEG spectra are given at the *top*, the EMG spectra in the *middle*, and the coherence spectra at the *bottom*. Horizontal line in the coherence spectrum gives the 99% confidence limit. Note that the EMG spectra show a clear tremor peak but no discernible peak in the 15- to 30-Hz band.

coherence in the same recordings. Two examples of patients with a coherent lower-frequency tremor activity but an equally strong or even stronger coherence in the 15- to 30-Hz band in parallel are displayed in Fig. 3. Note that the EEG and EMG spectra do not show any discernible peak in the 15- to 30-Hz range. Interestingly, the proportion and the magnitude of this coherence did not differ from a group of normal subjects that were analyzed in the same way (unpublished observations) and it was independent of the strength of the tremor.

This is in contrast to the situation in Parkinson's disease (PD) where the increase in lower-frequency corticomuscular coupling seems to occur at the expense of this normal 15- to 30-Hz coherence (Salenius et al. 2002). Thus our findings in the ET patients may indicate that it is not the tremor but rather the dopamine deficiency that is responsible for the suppression of 15- to 30-Hz coupling in PD; it is not clear, however, whether this is related to the fact that we hardly saw any coherence at double the tremor frequency (around 10–13 Hz) commonly seen in PD tremor (Hellwig et al. 2000; Timmermann et al. 2003).

Topography of corticomuscular coherence

The main coherence is located in the contralateral lateral central area being in keeping with an involvement of the primary cortical areas. Because the isocoherence maps do not allow a distinction between primary motor and sensory cortex we will refer to the "primary sensorimotor cortex" in the following. Three representative examples of isocoherence maps are given in Fig. 4. In five of the patients there was another coherent cortical area in the more frontal (mesial) region in some of the recordings (*A*) and in the patients with bilateral tremor we found very weak coherence just exceeding the level of significance also on the ipsilateral side (*C*) in single recordings in four of the patients, in keeping with a previous report (Hellwig et al. 2003). In three of them the second frontal hot spot included a midline electrode. One of these patients had a strong bilateral tremor and the midline showed coherence with the tremor on both sides. In this patient we also saw a weak but significant coherence between the muscles on both sides. All of the three representative patients displayed in Fig. 4 (*top row*) also showed corticomuscular coherence in the physiological 15- to 30-Hz band in parallel as displayed in the *bottom row*. The hot spot of this higher-frequency corticomuscular coherence covered almost the same electrodes as the main hot spot of the coherence with the tremor in the central region. Because it is well established that the 15- to 30-Hz coherence is generated in the primary sensorimotor cortex (Baker et al. 2003; Brown et al. 1998; Conway et al. 1995; Halliday et al. 1998; Kilner et al. 2000; Salenius et al. 2002) this finding confirms that the sensorimotor cortex is also involved in the ET oscillations. The 15- to 30-Hz coherence was always limited to the one relatively large contralateral area around the central region and we have not seen a second frontal hot spot as seen for the tremor frequency.

Cortico-cortical coherence between the central and the more frontal area was significant at the tremor frequency in all the patients in whom we found a second frontal mesial hot spot.

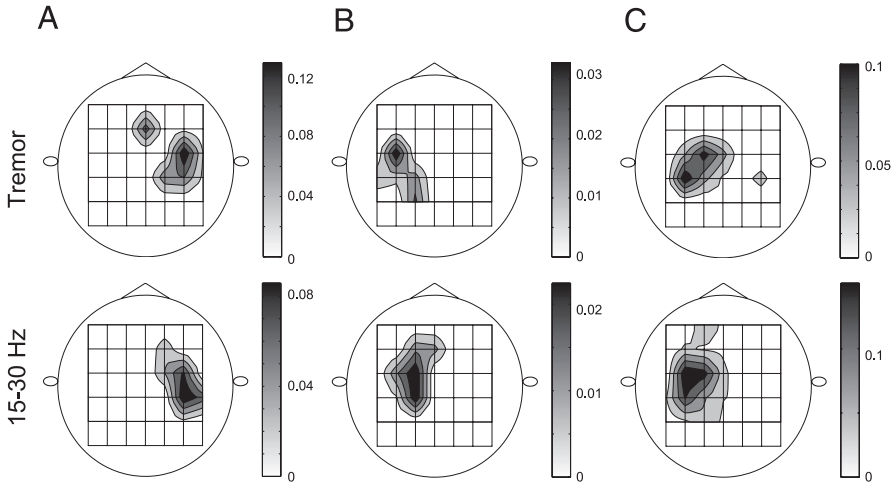

FIG. 4. Isocoherence maps for 3 different patients (*A–C*). *Top row*: cortical areas showing significant coherence with the tremor. *Bottom row*: topographical distribution of the corticomuscular coherence in the physiological 15- to 30-Hz band. Note that there were 2 distinct areas that were coherent with the tremor in some patients as shown in *A*.

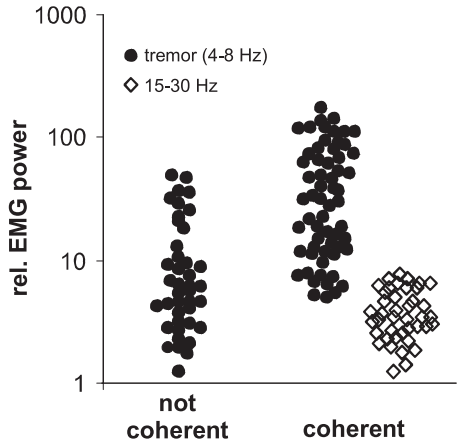

FIG. 5. Relative EMG power at the tremor frequency and in the 15- to 30-Hz frequency. Relative EMG power at the tremor frequency for all extensor and flexor EMGs with a visible tremor peak and for all the recordings from all the patients are displayed separately for recordings with a significant corticomuscular coherence at the tremor frequency and noncoherent recordings (solid dots). Relative power in the 15- to 30-Hz band is given only for muscles and recordings with a significant coherence in this band (open rhombi). Corticomuscular coherence was seen only when the relative EMG power rose above a certain level around 5. Nevertheless, a number of recordings with relative tremor power above this level did not show significant coherence. Relative power of the 15- to 30-Hz EMG activity was below this level for the vast majority of recordings with significant corticomuscular coherence in this band. Receiver operating characteristics analysis confirmed that there was hardly any overlap between the relative power at the coherent tremor frequency and the coherent 15- to 30-Hz band (2.8%), whereas the overlap between coherent and noncoherent tremors was greater (14.5%). Largest overlap was found between noncoherent tremor and coherent 15- to 30-Hz activity (33.1%).

Peripheral tremor intensity and corticomuscular coherence

The relative EMG power of the peripheral extensor and flexor EMG at the tremor frequency bands was compared between recordings with a significant corticomuscular coherence and recordings without a significant coherence at the tremor frequency (4–7 Hz); both of these groups were compared with the 15- to 30-Hz band. Although the relative EMG power was calculated for any distinguishable peak at the tremor frequency, irrespective of whether it was coherent with the EEG, there were hardly any noticeable peaks in the 15- to 30-Hz band. Therefore in this frequency band the maximal power in the coherent frequency band of each individual recording was used, which could be calculated for recordings only with a significant coherence in this frequency band. The relationship-relative EMG power and the incidence of significant coherence did not differ significantly between the flexor and the extensor EMGs. Figure 5 displays the relative EMG power values for the coherent and noncoherent tremor frequencies (black dots, *left two columns*) and the relative EMG power values in the coherent 15- to 30-Hz band (open rhombi, *rightmost column*). Although tremor-related cortical activity is seen only above a certain relative EMG power threshold around 5, the relative EMG power at the tremor frequency in those recordings without significant corticomuscular coherence covered a very broad range reaching up to values at which there was a significant coherence in many other recordings. All the subjects showed corticomuscular coherence at the tremor frequency in at least one of the recordings that disappeared intermittently in single recordings, although the relative EMG power often remained almost unchanged. The relative EMG power values for the coherent 15- to 30-Hz EMG activity were clearly below the threshold for corticomuscular coherence at the tremor frequency in the vast majority of the recordings. Application of ROC analysis (see METHODS) confirmed that there is a good degree of separation between the relative EMG power values at the coherent tremor frequency and those in the coherent 15- to 30-Hz range (overlap is only 2.8%), whereas there is less separation between the noncoherent and coherent tremor recordings (overlap is 14.5%) and least separation between the noncoherent tremor frequency and the coherent 15- to 30-Hz band (overlap is 33.1%). The relative EEG power did not show any difference between the two frequency bands or coherent and noncoherent recordings.

Dynamics of corticomuscular coherence

The corticomuscular coherence does not only vary from recording to recording but it also changes over time within one recording. It was not constantly present during the recording but disappeared intermittently. In only one of our patients did the corticomuscular coherence at the tremor frequency remain throughout the recordings—in this subject we obtained recordings of only 1-min length. As shown in Fig. 6*A* the relative EMG power sometimes seemed to vary in parallel to the coherence, although the corticomuscular coherence was completely lost at times at which the relative EMG power showed only a slight decline on a high level. Figure 6*B* displays the dynamics of the coherence in a patient with less overall tremor intensity. In such cases we often found only very small changes of the relative EMG power over time and they seemed largely independent of the changes in the corticomuscular coherence. The coherence in the 15- to 30-Hz band was generally less variable and dropped below the significance level intermittently in only five of the 11 patients in whom we found corticomuscular coherence in this band. The variations in the two frequency bands were not related in any of the patients. This is shown for one representative patient in Fig. 6*B*. The relative EEG power at the respective coherent frequencies was monitored and did not show any changes in parallel to the coherence.

Both the corticomuscular coherence at the central hot spot and also the coherence between the more frontal area and the tremor activity were variable over time in the majority of the recordings. Figure 7 gives representative examples from three patients with an additional fontal/mesial hot spot. In the first patient (*A*) the rise of coherence in the central hot spot starting at about 60–70 s is clearly not paralleled by the coherence in the frontal hot spot, which starts to rise above the significance level at only about 90 s. The cortico-cortical coherence at the tremor frequency displayed at the bottom became significant only at the time at which both hot spots showed tremor-related activity, but even in this period the coherence between the two hot spots dropped below the significance level intermittently. In the example from the second patient (*B*) the corticomuscular coherence at the tremor frequency ran almost perfectly in parallel and the two hot spots were strongly coupled at the tremor frequency even at the beginning of the recording when both hot spots did not show tremor-related activity. In the third recording from yet another patient (*C*) we again found an intermittent drop in coherence in only one of the hot spots (end of the recording), whereas the other remained coherent. The

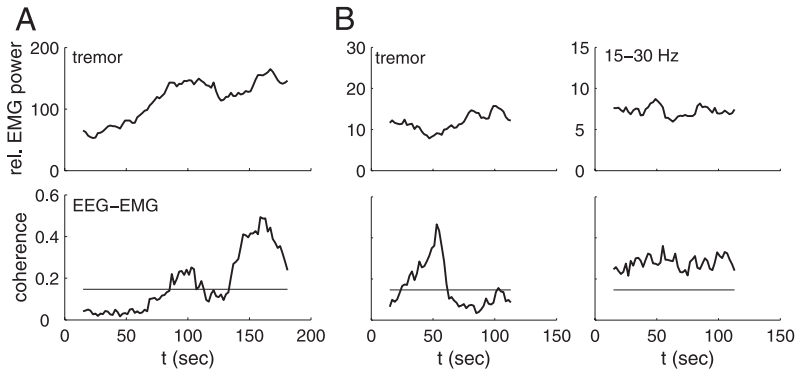

FIG. 6. Corticomuscular coherence at the tremor frequency over time. Two examples from patients (*A* and *B*) are given. *Top row*: relative EMG power (at the tremor frequency) over time. *Bottom row*: corticomuscular coherence, the 99% confidence limit of which is given by the horizontal line. They are calculated for moving windows of 30-s length and an overlap of 28 s (time resolution: 2 s). Example in *A* displays the relative tremor power of the right wrist extensor and its coherence with C3. This patient suffered from a strong tremor at 6 Hz. Corticomuscular coherence and the peripheral tremor intensity seem to change in parallel in this case. However, the coherence intermittently drops below the 99% confidence limit even though the tremor remains strong. *B*: example of a patient with weaker tremor at 7 Hz with parallel 15- to 30-Hz coherence. Relative tremor power is given for the left wrist extensor and its coherence with C4. Although the tremor remained stable over time the coherence varied considerably and dropped below the 99% confidence limit after about 1 min; 15- to 30-Hz coherence remained stable over the whole time.

cortico-cortical coherence also was only intermittently significant and dropped below the significance level even at the time at which both hot spots are coherent with the tremor. These examples show that the tremor-related activity in both hot spots does not necessarily appear in parallel and that the intracortical coupling often disappears intermittently.

Direction of corticomuscular interaction and corticomuscular delay

Two examples of the method for delay estimation (Govindan et al. 2005, 2006) are given for single coherent cortical electrodes in two different patients in Fig. 8 (see METHODS). The coherence is displayed against time shift. There are clearly discernible maxima in both shift directions in Fig. 8*A*, indicating a delay from EEG to EMG as well as an interaction and delay from EMG to EEG. This is a typical example of an electrode in the central hot spot (C3 vs. right forearm extensor in this case). In Fig. 8*B* there is only one coherence maximum in the positive shift direction that makes up for a delay from EEG to EMG. This is a typical example of an electrode from the frontal/mesial hot spot (here: FCz electrode vs. right forearm extensor). The final delay values after weighting by the coherence values (see METHODS) are given in Table 1, which shows that a significant delay could be estimated between the central hot spot and the contralateral forearm extensor muscle in nine of the 15 patients. All of these patients showed a transmission of the tremor frequency from the central hot spot to muscle with delays between 11 and 20 ms (mean 12.1 $\pm$ 2.2 ms) and feedback from muscle to cortex with delays between 9 and 24 ms (mean 15.1 $\pm$ 4.1 ms). In the remaining six patients the coherence maxima did not pass the significance level as determined by the surrogate analysis (Govindan et al. 2005). Thus we could not estimate the corticomuscular interaction reliably in these cases. The frontal/mesial hot spot was coherent in five of our patients and showed a corticomuscular delay between 23 and 27 ms (mean 25 $\pm$ 1.5 ms). In only two of these patients did we find an interaction from muscle to the frontal hotspot with delays around 10 ms (mean 10.2 ms) and in one of these patients we could not reliably estimate the delay for the frontal hot spot in either direction. Overall the delays between the

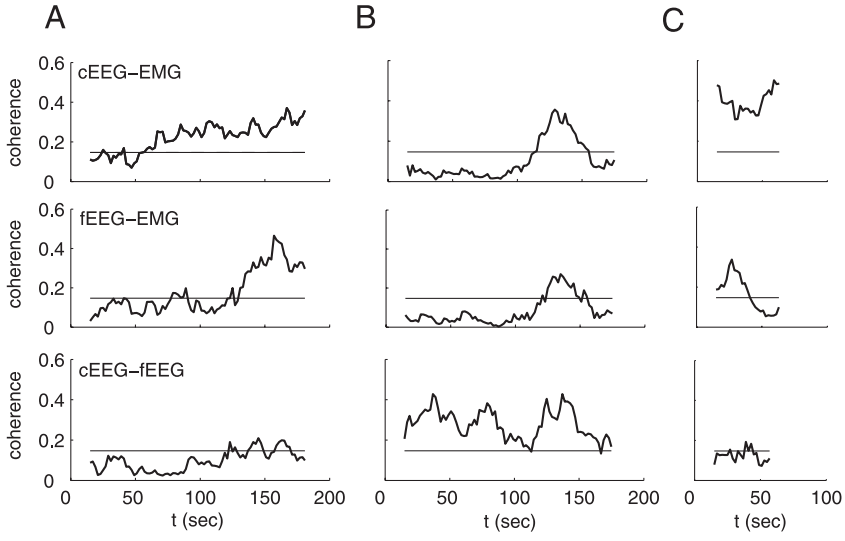

FIG. 7. Corticomuscular coherence for both hot spots and cortico-cortical coherence over time. Corticomuscular coherence at the tremor frequency is given for the central (*top row*) and the more frontal hot spot (*middle row*) and the cortico-cortical coherence between the two hot spots (*bottom row*) is displayed for 3 recordings from 3 different patients (*A*–*C*). Horizontal lines represent the 99% confidence limit. Plots show that the corticomuscular coherence is variable for the frontal hot spot as well (*A*–*C*). These variations often do not occur in parallel (*A*, *C*), however, and the 2 hot spots may become intermittently independent (not coherent) even while both hot spots are coupled with the peripheral tremor (*A*, *C*).

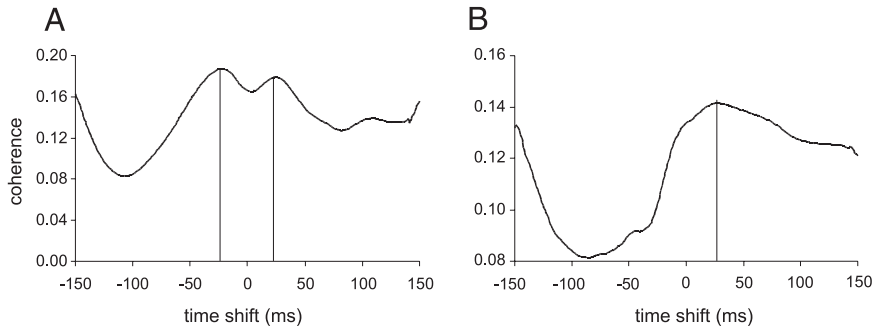

FIG. 8. Example of delay estimation for representative individual cortical electrodes in 2 patients. Corticomuscular coherence at the tremor frequency (ordinate) is plotted against the time by which one time series is shifted while the other remains constant. Positive time shifts make up for delays from EEG to EMG and negative ones for EMG–EEG delays. In case of a delay the coherence increases from its value at zero shift and reaches a maximum when the delay has been made up for completely. In *A* there is a clear coherence maximum in both directions indicating transmission of the signal at the tremor frequency from cortex to muscle and from muscle to cortex. Delay times of 22 ms from EEG to EMG and 23 ms from EMG to EEG are marked by the vertical lines. This is a typical example of an electrode from the central hot spot (C4). In *B* there is only one peak at (+)27 ms. This peak indicates a corticomuscular transmission and is a typical example of an electrode from the more frontal hot spot (FC2). Coherence peaks displayed here all exceeded the 95% confidence limit as determined by the surrogate analysis for every single step of the time shift (for details see Govindan et al. 2005).

frontal area and muscle were slightly longer than those from the central area and the feedback from the periphery was less consistent.

In five of the 11 patients with coherence in the 15- to 30-Hz band we also found a corticomuscular interaction in this frequency band (mean delay: 19.4 ± 6 ms), satisfactorily in keeping with previously published data (Gross et al. 2000; Mima et al. 2000b). In four of these patients there was also feedback from muscle to cortex in this band (mean delay: 17.3 ± 7.9 ms), in line with recent findings (Riddle et al. 2005) in normal subjects.

DISCUSSION

In the present study we could show that the corticomuscular delay times at the tremor frequency would be in keeping with transmission of oscillatory activity from cortex to muscle, which is in turn fed back to the cortex. However, involvement of the sensorimotor cortex is more complex than previously envisaged. The corticomuscular coherence at the tremor frequency is seen only in higher-amplitude tremors and it disappears intermittently, albeit continuously strong peripheral tremor activity. By contrast, the physiological 15- to 30-Hz coherence is present even without any visible peak at this frequency in the power spectra.

TABLE 1. *Corticomuscular delay*

	Delay, ms			
	Central Hot Spot		Frontal/Mesial Hot Spot	
Patient	EEG–EMG	EMG–EEG	EEG–EMG	EMG–EEG
1	12.0 ± 6.6	16.2 ± 2.6	25.0 ± 10.4	n.s.
2	14.0 ± 4.4	9.0 ± 4.4	23.0 ± 7.9	10.0 ± 2.3
3	11.0 ± 3.7	9.0 ± 3.8	27.3 ± 12.7	n.s.
4	10.5 ± 5.1	9.1 ± 4.0	26.1 ± 12.9	10.5 ± 5.0
5	n.s.	n.s.	n.s.	n.s.
6	16.0 ± 7.7	24.0 ± 9.0	—	—
7	11.3 ± 6.1	15.0 ± 3.8	—	—
8	11.0 ± 0.8	17.6 ± 1.2	—	—
9	20.4 ± 6.2	18.0 ± 1.3	—	—
10	11.2 ± 3.2	11.6 ± 3.2	—	—
11	n.s.	n.s.	—	—
12	n.s.	n.s.	—	—
13	n.s.	n.s.	—	—
14	n.s.	n.s.	—	—
15	n.s.	n.s.	—	—
Mean*	12.1 ± 2.2	15.1 ± 4.1	25.0 ± 1.5	10.2 ± 0.3

n.s., not significant; —, no coherence; *, average weighted by the error bars.

Bidirectional interaction between cortex and peripheral tremor rhythm

For the corticomuscular coherence in the 15- to 30-Hz band it has been convincingly shown that it is transmitted from the cortex to the periphery by fast conducting corticospinal fibers (Gross et al. 2000; Mima and Hallett 1999) and also fed back to the cortex (Riddle et al. 2005). We found similar results in some of our patients. The direction of interaction between the tremor and its cortical correlate has not been assessed for ET, although (Hellwig et al. 2001) one of the reasons is that the established methods for delay estimation do not work in narrow-band tremor signals (Lindemann et al. 2001; Muller et al. 2003). By means of a newly developed method we were able to estimate the delay between cortex and muscle in essential tremor. All the patients in whom a significant delay could be calculated showed a bidirectional interaction between primary sensorimotor area and peripheral tremor. The delay times for corticomuscular interaction were principally compatible with a transmission in fast-conducting corticospinal pathways, although slightly lower than the corticomusucular latencies described in cortical stimulation studies (Rothwell et al. 1991). The delay times from muscle to cortex were more variable between subjects, but on average they were also in keeping with somatosensory conduction delays from the distal arm to the sensory cortex as measured in somatosensory-evoked potentials. This variability and the differences to cortical stimulation studies may be attributable to factors influencing the delay estimation other than the pure corticomotoneuronal conduction delay (e.g., capacitance or impedance of neurons and neuronal assemblies). Feedback to the primary motor cortex, the primary sensory cortex, or other parietal areas cannot be separated as a consequence of the limited spatial resolution of the EEG; thus the coherent central area most likely represents a mixture of efferent connections from

motor cortex to muscle and its afferent feedback to different (motor and) sensory areas.

Thus our results would be in keeping with transmission of the tremor rhythm in ET from the cortex to the peripheral muscle (Elble 2000; Hellwig et al. 2001), which is in turn fed back to the cortex, although other explanations cannot be ruled out. In fact, the tremor-related activity in the cortex may merely be an efference copy of a subcortically generated oscillatory signal reaching the muscle by bulbospinal pathways. In this case the estimated corticomuscular delay should reflect the difference between the subcortico-muscular delay and short subcortico-cortical latencies. Because we do not know which subcortical system is involved and there are hardly any human data on the conduction velocity of these systems this point remains speculative. In studies on monkeys, however, the latencies of forearm muscle facilitation after stimulation of the reticular formation were found to be very similar to the latencies after corticospinal tract stimulation on the brain stem level (e.g., Davidson and Buford 2004, 2006). If this applied similarly to the systems involved in essential tremor generation the resultant delays may indeed resemble fast corticomotoneuronal transmission time.

The bidirectionality of corticomuscular interaction would be in keeping with contributions of the whole feedback loop between CNS and periphery, as previously proposed on the basis of mechanical resetting experiments (Britton et al. 1992).

The intermittent nature of cortical involvement

In accordance with the results of Hellwig et al. (2001) we found that the tremor intensity in ET as given by the relative EMG power has to exceed a certain threshold before we see corticomuscular coherence at the tremor frequency. On the other hand there were a number of recordings without coherence and the vast majority of recordings showed an intermittent loss of corticomuscular coherence at the tremor frequency despite strong peripheral tremor, whereas the coherence in the 15- to 30-Hz range was more constantly present (albeit much weaker) EMG signal (relative power) than at the tremor frequency. This is principally in keeping with the results obtained by Halliday et al. (2000) in a small number of ET patients.

If the tremor remains even when the corticomuscular coherence at the tremor frequency has vanished one may ask whether the tremor-related cortical activity is connected to tremor at all. The corticomuscular delays seem to be in favor of a direct corticomuscular transmission. Nevertheless, the intermittency of cortical involvement draws attention to other subcortical mechanisms, possibly bypassing transcortical pathways.

There is converging evidence from functional imaging studies and studies on motor function that the cerebellar system is strongly involved in the pathophysiology of ET (Bucher et al. 1997; Colebatch et al. 1990; Deuschl et al. 2000; Jenkins et al. 1993; Louis et al. 2002; Pagan et al. 2003; Stolze et al. 2001). The cerebellum projects not only to the thalamus, which was previously shown to be involved in the oscillations in ET (Hua and Lenz 2004; Hua et al. 1998), but also to brain stem centers. These centers may at least intermittently function as an output station, transmitting the tremor oscillations by bulbospinal pathways, and may be at least similarly important as the thalamo-cortico-spinal projections (Deuschl et al. 2001; Elble 1996). Whether the oscillatory activity reaches the cortex may depend on the state of the thalamic neurons or the whole physiological cerebello-thalamo-cortical motor circuit as recently suggested by Hua and Lenz (2005) on the basis of thalamic recordings in ET patients.

However, because cerebellar and brain stem centers are difficult to access in humans the evidence remains indirect. On the one hand, the intermittent loss in corticomuscular coherence need not necessarily reflect a complete lack of cortical contribution to the peripheral tremor and may be explained by other reasons (e.g., intermittent nonlinear corticomuscular interaction or modulating influences from other cortical areas); on the other hand, even the phases with significant coherence could mainly reflect cortical input from subcortical tremor generators (efference copy) rather than an important causal role of the cortical output.

The strong oscillatory EMG activity at the tremor frequency showing only loose and intermittent coupling with the cortex is clearly contrasted by corticomuscular coherence in the physiological 15- to 30-Hz band even without any visible rise in the EMG power spectrum in the same patients. Whereas the broader 15- to 30-Hz coherence may reflect a mainly cortical activity transmitted through relatively hard-wired corticospinal projections the corticomuscular coherence at the tremor frequency possibly represents only one output relay of a more widely distributed oscillatory network.

The frontal (mesial) hot spot

Given the poor spatial resolution of the isocoherence maps in the present study it was not possible to draw any conclusions on the exact anatomical area generating the separate frontal (mesial) hot spot in five of our patients. It is tempting to interpret the separate midline coherence in terms of an involvement of the supplementary or cingulate motor area possibly related to the corticomuscular coherence at around 10–15 Hz found over the SMA in electrocorticographic recordings of epileptic patients (Ohara et al. 2000; Raethjen et al. 2004). Other premotor areas, however—the cortex adjacent to the lateral sulcus and the sensorimotor cortex—are equally likely to generate tremor-related activity in the mesial/frontal electrodes. Thus it is possible that this coherence does not reflect the involvement of any other separate cortical motor center at all but may be the result of a complex field distribution of activity generated in the lateral central area. Nevertheless, some of our results seem to separate these frontal (mesial) electrodes from the main lateral central hot spot: First, there is less consistent feedback of the tremor rhythm to the frontal electrodes. This would be in keeping with the sparse direct sensory input to premotor areas (Geyer et al. 2000). Second, the delay is clearly longer between the frontal/mesial electrodes and muscle than between central lateral electrodes and muscle, which would be in accordance with longer corticomuscular conduction times from premotor areas demonstrated in primates (Cerri et al. 2003; Maier et al. 2002). Third, the corticomuscular coherence in the frontal/mesial and central lateral electrodes behaved differently over time in that there were phases in which one of the areas showed tremor-related activity, whereas the other did not. If they were both generated by the same underlying structure one would rather expect a parallel time course of the coherence.

On the basis of these considerations one may speculate that different cortical areas are involved in the tremor oscillations possibly being different cortical targets of putative subcortical (e.g., cerebello-thalamic) projections (Dum and Strick 1991; Macpherson et al. 1982; Porter and Lemon 1993) carrying the tremor oscillations. There is good evidence in the nonhuman primate (Rouiller 1996; Strick 1985; Strick et al. 1993) and first hints in humans (Hurtado et al. 1999; Marsden et al. 2000; Williams et al. 2002) that these projections are dynamically organized (Hurtado et al. 2005) in different, somewhat independent channels exchanging information mainly through cortico-cortical connections (Houk 2001; Rouiller 1996). The intermittent loss of cortico-cortical coherence between the lateral central and the frontal/mesial electrodes in our data may reflect such transiently coupled subcortico-cortical channels being involved in the tremor oscillations in ET.

However, coherence is a linear measure and therefore most sensitive to linear associations and we cannot rule out nonlinear interactions in noncoherent phases. Further, there is only a small number of patients with separate tremor-coherent activity in frontal/mesial electrodes. Thus if this frontal coherence has a separate generator at all it seems to be dispensable for tremor generation and at the most represents one part of a variable and dynamically organized tremor-generating network (Hurtado et al. 2005).

In conclusion, the corticomuscular coherence and delay times seem to support the notion that the motor cortex is involved in generating ET. In the dynamic coherence analysis, however, coherence becomes insignificant intermittently, although the peripheral tremor remains almost with the same amplitude. Further, the dynamic corticomuscular coherence analysis of the frontal (midline) region and cortico-cortical dynamic coherence analysis show that the central and the frontal coherent regions are not coupled at all times to cause peripheral oscillations. Based on these facts, to explain the observed peripheral tremor in the phases of insignificant coherence, we hypothesize that at least intermittently subcortical centers come into play and directly maintain the external tremor. However, addressing the exact nature of these pathways is beyond the scope of the current work. Nevertheless our findings would conform with a widely spread oscillatory network keeping up tremor oscillations for longer periods of time, although the participation of individual network components seems to be variable. A similar view was recently put forward for the small-scale oscillatory network of Parkinsonian tremor in the GPi (Hurtado et al. 2005) and may thus also be a common property of large-scale tremor-generating networks. In search of new targets for therapeutic interventions future studies will have to address whether there are core structures in these dynamic networks that are more important than others for sustaining tremor oscillations.

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