Corticomuscular Coherence in Asymptomatic First-Degree Relatives of Patients With Essential Tremor

Jan Raethjen, MD, Muthuraman Muthuraman, PhD,* Achim Kostka, MD, Martin Nahrwold, DEng, Helge Hellriegel, MD, Delia Lorenz, MD¶ and Günther Deuschl, MD

Department of Neurology, University Hospital Schleswig, Holstein, Campus Kiel, Germany

Essential tremor (ET) is the most common adult movement disorder. From clinical experience and epidemiological studies, we know that it follows an autosomal dominant type of inheritance in the majority of patients.[1,2] Twin studies clearly confirm the importance of genetic factors in the etiology of ET.[3,4] Although this has stimulated a number of genetic studies, different loci have been identified in linkage analyses, and genome-wide association studies have identified genetic risk factors,[5,6] the responsible genes remain elusive.[7,8] These are highly desirable, because the effects of currently used drugs are unsatisfactory in a large number of patients, especially those in the advanced stages of disease.[9]

A large-scale oscillating central nervous system network generating the peripheral tremor has emerged from a number of recent studies. The basis of these studies has been the detection of electroencephalogram (EEG) or magnetoencephalogram (MEG) correlates that are coherent with the tremor oscillations in ET,[10] and it also is well established that this coherence reflects an involvement of cortical motor areas[11] among other network components.[12] Whereas, in healthy individuals, the dominant frequency at which the EEG or MEG exhibit coherent activity is in the (upper) α and lower β (8–30 Hz) range,[13,14] and the dominant coupling frequency in ET is the tremor frequency (3–11 Hz). Taking the available evidence together, we hypothesize that an alteration in corticomuscular coupling maybe present in asymptomatic relatives.

Patients and Methods

Participants

We contacted all 121 patients from our database with definite ET who were living in Kiel or within the surrounding area (< 50 km). In the next step, we contacted 37 relatives from 32 families who were interested in the study. Finally, 37 first-degree relatives (children) of patients with ET were selected from our data base for the study. Each of the affected index patients had been examined by a movement disorder specialist (D.L.), and ET was diagnosed according to the criteria of Bain et al.[15] The mean age ($\pm$ standard deviation [SD]) of ET relatives (25 females and 12 males) was 41.8 ± 12.9 years. On average, individuals in the control group (23 women and 14 men) were aged 42.7 ± 12.4 years. All individuals were right-handed except for 1 of the ET relatives. Both groups were neurologically examined, and a careful medical and family history was taken by two movement disorder specialists (D.L., J. R.). There were no signs of any neurological disease in either group; in particular, there was no hint at a pathological tremor in a structured examination according to the Fahn-Tolosa-Marin tremor scale.[16]

*Correspondence to: Dr. M. Muthuraman, Department of Neurology, University Hospital Schleswig Holstein, Campus Kiel, Schittenhelmstraße 10, 24105 Kiel, Germany; m.muthuraman@neurologie.uni-kiel.de

Funding agencies: Drs. J. Raethjen, M. Muthuraman, H. Hellriegel, and G. Deuschl received support for the research presented in this article from the German Research Council (Deutsche Forschungsgemeinschaft [DFG]; SFB 855) Project D2.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Delia Lorenz and Günther Deuschl contributed equally to this work.

Data Acquisition

In all ET relatives and controls, a 64-channel EEG was recorded in parallel with a surface EMG from the first dorsal interosseus (FDI) and forearm extensor muscles in 3 different activation conditions: (1) bilateral holding of the hands against gravity (all ET relatives and controls); (2) isometric contraction of FDI at medium strength while gently holding a light weight tape role (30 g) between index finger and thumb on both sides (all ET relatives and controls); and (3) slow (0.2–0.5 Hz) flexion-extension movements of both hands, with ET relatives watching and following the examiner performing these slow movements at the desired speed (subgroup of 25 ET relatives and matched controls).

All recordings were done with a Neuroscan 64-channel EEG system at a sampling rate of 1 kHz. A linked mastoid reference was used, and the EEG signals were band pass-filtered between 0.1 Hz and 100 Hz in parallel surface EMG from extensors and FDI were recorded, depending on the condition. The EMG signal was band-pass filtered between 30 Hz and 500 Hz. Recording length was restricted to 97,000 data points (97 seconds) in all recordings.

Data Analysis

Current source densities were calculated for each EEG electrode using the Hjorth transformation.[17] EMG data were full-wave rectified.

Power spectra of the Hjorth-transformed EEG signal recorded from C, FC and CP electrodes in the 3 paramedian rows (2, 4, and 6 for the right hemisphere and 1, 3, and 5 for the left hemisphere) and the rectified surface EMG were calculated, and the coherence with contralateral Hjorth-transformed EEG signals was computed. Coherence spectra were calculated using the Welch-periodogram method with disjoint segments as described by Halliday et al.[18] The confidence limit that indicated the significance of the coherence at a particular frequency was calculated at a 100% α as follows: $1-(1-\alpha)^{1/(M-1)}$, where α is set to 0.99, so the confidence limit is $1-0.01^{1/(M-1)}$.[18,19] The confidence intervals were estimated for the coherence, and the value was 0.0511 for all controls and ET relatives because of the standard data length of 97,000 data points used for the analysis. Maximal EEG-EMG coherence in the contralateral electrode array described above was calculated, and its frequency was read out. The signals were prewhitened (amplitude equalized at all frequencies) and normalized before estimating the pooled spectra.[20] Coherence spectra were pooled[21] group wise for each side and recording condition separately for ET relatives and controls.

The mean amplitude of the rectified EMG was calculated for the 97,000 data points (root-mean-square amplitude). For all comparisons between the 2 cohorts, a nonparametric independent samples Mann-Whitney test was performed.

Results

The maximal EEG-EMG coherence and its frequency were significantly higher in ET relatives compared with controls when participants performed a pinch grip and the FDI was recorded or when they performed slow up-and-down movements with the forearm extensors recorded. When the hand was only held against gravity, there was no significant difference in coherence strength or frequency between the 2 groups. This is displayed as pooled coherence spectra with the significance level in Figure 1. It can be seen that the main coherence in the pinch-grip task and the slow hand movements was in the 10 to 20 Hz range in controls and from 20 Hz to 30 Hz in the ET relatives. In the hand-holding task, both groups had similar coherence, mainly around 20 Hz. It is evident that both the maximal coherence and its frequency were significantly higher (Mann-Whitney test; $P<0.01$) in the ET relatives and for both sides. However, there was some overlap between the 2 groups that was more pronounced on the right side. Very similar and also significant differences (Mann-Whitney test; $P<0.01$) could be observed for the slow up-and-down movement paradigm, again more clearly on the left than the right side. Table 1 summarizes the results from the corticomuscular coherence analysis, displaying medians and ranges of maximal coherence and coherence frequencies.

The EMG power maxima were distributed broadly between 2 Hz and 30 Hz, and neither the frequency of these maxima nor the total power (area under the curve) in the 2 to 40 Hz range differed significantly between the 2 groups in all conditions (Mann-Whitney test; $P>0.05$). However, the root-mean-square mean amplitude of the EMG was significantly greater (Mann-Whitney-test; $P<0.05$) in ET relatives than in controls for all recordings because of higher power in the higher EMG frequencies (100–250 Hz; Mann-Whitney-test; $P<0.05$). There were no significant correlations between EMG amplitudes and coherence strength or frequency (Spearman rank correlations).

Discussion

Our data demonstrate alterations in EEG-EMG coupling during simple isometric and isotonic hand motor tasks in asymptomatic first-degree relatives of patients with ET. If we consider an autosomal dominant mode of inheritance, then we would expect such an alteration only in those 50% of the relatives who will go on to develop ET in the future. We did not observe such a bimodal distribution in our measures, but the distributions were relatively broad with considerable

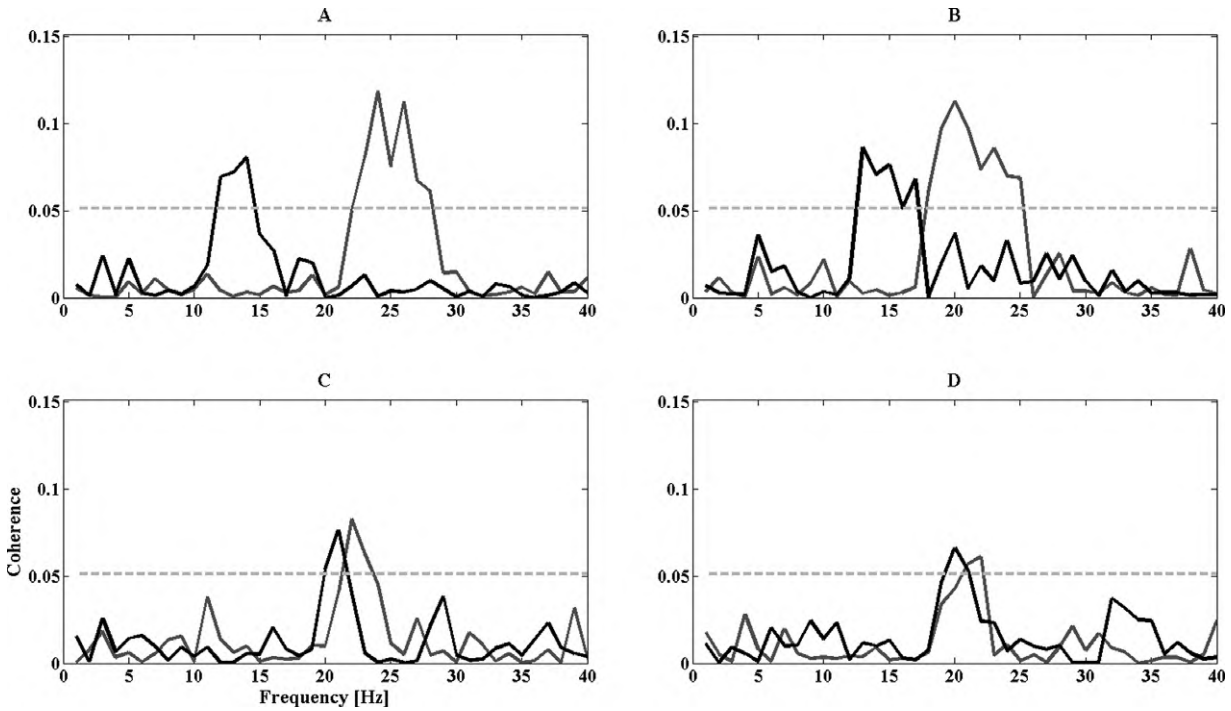

FIG. 1. Pooled corticomuscular coherence spectra are illustrated. *Grey lines* indicate the pooled spectra for relatives with essential tremor (ET), *black lines* indicate the pooled spectra for normal individuals, and *dashed grey lines* indicate the significance level. The upper traces show spectra for the pinch grip tasks with coherence between contralateral electroencephalogram and electromyogram tremor bursts calculated with respect to the first dorsal interosseus muscles on the (**A**) left side and (**B**) the right side. The lower graphs display the same measurements from the holding task for the (**C**) left and (**D**) right forearm extensor muscles.

overlaps between both groups, and the number of participants in this pilot study was relatively small.

In manifest ET, there is corticomuscular coupling at the lower tremor frequency in the 4-Hz to 11-Hz band.[10] Whereas the physiological coupling is in the higher α and lower β band (10–30 Hz),[13] it was surprising to see that the ET-relatives did not have abnormally low coupling frequencies that came closer to the ET frequency range but abnormally high coupling frequencies that were even further away from the ET frequencies than in the controls. Thus, our findings do not simply reflect subclinical tremor but may be due to other physiological/pathophysiological processes (eg compensatory mechanisms). However, this remains very speculative, and the meaning of our present findings in the context of ET pathophysiology and genetics currently is not clear. This is a first pilot study in looking at the difference in EMG and EEG-EMG coherence parameters between ET relatives and controls. Because we did not have an estimate of the expected effect size, we could not perform a meaningful power analysis before the start of the study. Nevertheless, we have to take into account that the lack of significant differences for some of the EMG measures could be

TABLE 1. Corticomuscular coherence

	Maximum coherence: Median (range)			Coherence frequency: Median (range), Hz		
Measure	ET	NS	*P*	ET	NS	*P*
Pinch grip, n = 37						
Left	0.11 (0.05–0.27)	0.07 (0.01–0.24)	0.0001	22 (12–40)	13 (2–27)	0.0002
Right	0.11 (0.03–0.26)	0.06 (0.02–0.14)	0.0002	22 (8–28)	14 (8–25)	0.0004
Slow move, n = 25						
Left	0.11 (0.04–0.28)	0.07 (0.04–0.11)	0.0004	22 (9–38)	13 (2–28)	0.0003
Right	0.11 (0.05–0.21)	0.07 (0.05–0.15)	0.0006	22 (13–32)	15 (6–25)	0.008
Hold, n = 37						
Left	0.06 (0.02–0.22)	0.06 (0.03–0.34)	0.84	24 (7–35)	21 (9–33)	0.21
Right	0.05 (0.02–0.24)	0.05 (0.02–0.33)	0.95	23 (9–35)	21 (11–34)	0.45

ET, essential tremor; NS, normal subjects.

caused by the limited number of individuals in this study.

In conclusion, our study demonstrates an easily measurable subclinical alteration of corticomuscular interaction in as yet unaffected relatives of ET patients. The next step will be to use these measures in larger cohorts and to follow these patients long-term to determine whether such physiological measures could be useful as presymptomatic markers of ET.

Acknowledgements: We gratefully acknowledge support from the German Research Council to Drs. J. Raethjen, M. Muthuraman, H. Hellriegel, G. Deuschl is from the German Research Council.

References

1. Busenbark K, Barnes P, Lyons K, Ince D, Villagra F, Koller WC. Accuracy of reported family histories of essential tremor. Neurology 1996;47:264–265.
2. Louis ED, Ottman R. How familial is familial tremor? The genetic epidemiology of essential tremor. Neurology 1996;46:1200–1205.
3. Lorenz D, Frederiksen H, Moises H, Kopper F, Deuschl G, Christensen K. High concordance for essential tremor in monozygotic twins of old age. Neurology 2004;62:208–211.
4. Tanner CM, Goldman SM, Lyons KE, et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. Neurology 2001;57:1389–1391.
5. Stefansson H, Steinberg S, Petursson H, et al. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet 2009;41:277–279.
6. Thier S, Lorenz D, Nothnagel M, et al. LINGO1 polymorphisms are associated with essential tremor in Europeans. Mov Disord 2010;25:717–723.
7. Gasser T, Bressman S, Durr A, Higgins J, Klockgether T, Myers RH. State of the art review: molecular diagnosis of inherited movement disorders. Movement Disorders Society Task Force on Molecular Diagnosis. Mov Disord 2003;18:3–18.
8. Jasinska-Myga B, Wider C. Genetics of essential tremor. Parkinsonism Relat Disord 2012;18(suppl 1):S138–S139.
9. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol 2011;10:148–161.
10. Hellwig B, Haussler S, Schelter B, et al. Tremor-correlated cortical activity in essential tremor. Lancet 2001;357:519–523.
11. Raethjen J, Govindan RB, Kopper F, Muthuraman M, Deuschl G. Cortical involvement in the generation of essential tremor. J Neurophysiol 2007;97:3219–3228.
12. Schnitzler A, Munks C, Butz M, Timmermann L, Gross J. Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. Mov Disord 2009;24:1629–1635.
13. Conway BA, Halliday DM, Farmer SF, et al. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol 1995;489(pt 3):917–924.
14. Halliday DM, Conway BA, Farmer SF, Rosenberg JR. Using electroencephalography to study functional coupling between cortical activity and electromyograms during voluntary contractions in humans. Neurosci Lett 1998;241:5–8.
15. Bain P, Brin M, Deuschl G, et al. Criteria for the diagnosis of essential tremor. Neurology 2000;54(11 suppl 4):S7.
16. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and Movement Disorders. Baltimore, MD: Williams & Wilkins; 1993:225–234.
17. Hjorth B. An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr Clin Neurophysiol 1975;39:526–530.
18. Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data–theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 1995;64(2–3):237–278.
19. Muthuraman M, Govindan RB, Deuschl G, Heute U, Raethjen J. Differentiating phase shift and delay in narrow band coherent signals. Clini Neurophysiol 2008;119:1062–1070.
20. Baker SN. "Pooled coherence" can overestimate the significance of coupling in the presence of inter-experiment variability. J Neurosci Methods 2000;96:171–172.
21. Amjad AM, Halliday DM, Rosenberg JR, Conway BA. An extended difference of coherence test for comparing and combining several independent coherence estimates: theory and application to the study of motor units and physiological tremor. J Neurosci Methods 1997;73:69–79.