Essential and Aging-Related Tremor: Differences of Central Control

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Essential tremor (ET) is the most common movement disorder in adults, defined as bilateral action and postural tremor, sometimes accompanied by tremor of the head, voice, leg, and trunk.[1,2] Epidemiological studies have suggested a bimodal distribution of age at onset with two peaks, one occurring in adolescence and the other in late adulthood. Studies on ET often include data of mixed ET cohorts, irrespective of the age at onset, albeit whether the two conditions are different manifestations of the same disease or indeed separate entities is unknown. Only rarely is the late-onset group discussed distinctly in the vast existing literature of tremors.[3] Accordingly, little is known about potential pathophysiological differences between early- and late-onset ET. Indeed, these two types of tremor differ with regard to their rate of progression (early-onset ET tends to be more benign), the family history (which is often positive in early-onset ET with an autosomal dominant pattern of inheritance whereas aging-related tremor [ART] typically occurs sporadically), and associated features[4] (eg, coexisiting cognitive impairment and subtle signs of physical aging). Therefore, labeling the late-onset type as ART has been proposed. The latter clinically presents as

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late-onset action tremor, as revealed by the abnormal spirals; decline of aging parameters, including a change of cognition, activities of daily living, and reduction of strength, and thereby faster aging, may be further hallmarks of this condition.[3] The clinical and the pathophysiological separation between classical early-onset ET and ART is important for our understanding of these disorders.

The involved pathophysiological networks in tremor have been discussed in recent studies. An important milestone in this regard has been the detection of electroencephalographic (EEG) or magnetoencephalographic correlates that are coherent with the tremor oscillations in ET.[5] On this basis, the existence of a large-scale oscillating central nervous system network generating peripheral tremor has emerged, mainly in ET. The coherence reflects an involvement of cortical motor areas[6] amongst other network components.[7,8] In a previous study[9] with a similar experimental setup, we were able to show significant coherence and frequency differences even between unaffected relatives of ET patients and healthy controls. The current study now aims at revealing the network topology and the connectivity of early-onset ET and ART.[10,11]

The effects of currently used drugs are often not satisfactory, especially in advanced stages of the disease.[12] In a recent review,[13] we have discussed deep brain stimulation as the most potent available treatment for ET. However, controversy regarding different target locations for deep brain stimulation in these patients is discussed.[12] Therefore, not only understanding the pathophysiology behind these tremors but also detecting possible anatomical targets by looking at network topologies are important.

Considering the available evidence, we hypothesize that cortico-muscular coupling may be different for ET and ART and that the central networks and the connectivity in these two types of tremor may be different.

Methods

Subjects

From a large ET cohort of 847 ET or ART patients evaluated in Kiel since 2002, 61 patients were identified and contacted based on their expressed interest in participating in research studies, a large amount of follow-up information, and their postcode (living nearby), as well as a positive family history in young-onset cases. We started by studying 10 patients with early-onset ET and 10 patients with late-onset tremor (ART). However, after completion, the two groups were noticed to differ in their root-mean-square (RMS) amplitudes. Thus, to exclude that these differences may have influenced our findings, we decided to recruit a second (new) group of patients with early-onset ET and studied them in an identical manner to confirm our findings. This second ET group (ET[C]) was specifically selected to have electromyographic (EMG) amplitudes similar to those of the ART cohort. The overall findings remained the same, strengthening the notion that they are unrelated to the EMG amplitudes.

A thorough medical and family history was taken, and subjects were neurologically examined by a movement disorder specialist (S.S.). The tremor was rated according to the Fahn-Tolosa-Marin (FTM) Tremor Rating Scale,[14] and ET was diagnosed according to the current diagnostic MDS criteria.[1] The muscle strength on both arms was measured twice for each arm with a dynamometer (Smedley digital hand dynamometer).[15] The mean of both measurements was then calculated for further statistical analyses. Cognitive functioning was assessed by using an established four-component cognitive composite score.[16]

EEG Data Acquisition

In all patients with ET and ART, a 256-channel EEG was recorded at a sampling rate of 1 kHz in parallel to surface EMG from first dorsal interosseous (FDI) and forearm extensor muscles under three different activation conditions:

1. Bilateral holding of the hands against gravity
2. Isometric contraction of the FDI at medium strength while gently holding a lightweight tape role (30 g) between the index finger and the thumb with both hands
3. Slow (0.2-0.5 Hz) flexion–extension movements of both hands, watching and following the examiner performing these slow movements at the desired speed

Patients were seated comfortably in an armchair during all recordings, with their head and forearms supported by a headrest and armrest at all times, but the hands were outstretched.

For EEG the reference channel was CZ, and the signals were band-pass-filtered between 0.1 and 100 Hz in parallel surface EMG from extensors, and FDI was recorded depending on the condition. The EMG signal was band-pass filtered between 30 Hz and 500 Hz and was full-wave rectified. Eye blinks were removed by using a regression-based method.[17] Recording length was restricted to 120,000 data points (120 s) in all recordings.

Data Analysis

Coherence spectra were calculated by using the Welch-periodogram method with disjoint segments as previously described.[18] The frequency resolution for this method was 1 Hz. The confidence limit, which indicates the significance of the coherence at a

TABLE 1. Patient demographics

	ET	ET(C)	ART	P_1	P_2	P_3
n	10	10	10	—	—	—
Male/female	5/5	5/5	5/5	—	—	—
Current age	71.3 ± 4.37	67.5 ± 3.51	69.7 ± 4.67	0.24	0.35	0.43
Age at onset	7.6 ± 3.47	6.8 ± 3.46	57.9 ± 6.96	0.003	0.004	0.36
Disease duration	60.4 ± 9.74	58.1 ± 7.65	13.9 ± 4.09	0.0001	0.0002	0.48
Fahn A score	7.4 ± 2.89	7.1 ± 2.10	6.3 ± 3.68	0.45	0.64	0.28
Total Fahn score	23 ± 7.46	24 ± 6.46	22 ± 8.68	0.32	0.41	0.57
Muscle strength (R)	41.9 ± 7.46	40.8 ± 6.45	32.6 ± 12.51	0.009	0.004	0.48
Muscle strength (L)	39.3 ± 8.51	37.8 ± 6.89	27.7 ± 10.09	0.002	0.002	0.54
Cognitive composite	99.8 ± 18.03	97.8 ± 16.2	92 ± 16.70	0.013	0.015	0.63

ET, ET patients; ET(C), ET Control patients; ART, Aging-related tremor patients.
P_1: Level of significance for nonparametric group comparisons (ET vs ART; Mann-Whitney test);
P_2: Level of significance for non-parametric group comparisons (ET(C) vs ART; Mann-Whitney test);
P_3: Level of significance for non-parametric group comparisons (ET vs ET(C); Mann-Whitney test). R, right hand; L, left hand.

particular frequency is given by $1-(1-\alpha)^{1/(M-1)}$, where α was set to 0.99, so the confidence limit was $1-0.01^{1/(M-1)}$.[18,19] This way the estimated coherence reaches a significance level of 99%. The confidence intervals were estimated for the coherence, and the value was 0.0379 for all patients because of the standard data length of 120,000 data points used for the analysis. Maximal EEG-EMG coherence in the contralateral electrode array described was calculated, and its frequency was noted. The signals were prewhitened (amplitude equalized at all frequencies) and normalized before estimating the pooled spectra.[20] Coherence spectra were pooled[21] groupwise for each side and for each recording condition for ET, ET(C), and ART patients separately.

The mean amplitude of the rectified EMG was calculated for the 120,000 data points (RMS amplitude). The total EMG power 2 Hz to 40 Hz, the EMG frequency and the EMG relative signal-to-noise ratio were estimated. The relative signal-to-noise ratio was estimated by taking the signal to be the power at the peak frequency and the noise to be the mean power from the 2 Hz to 40 Hz except the peak scalar value. The peak frequency was estimated by taking the peak amplitude value between 2 Hz and 40 Hz, and the corresponding index in the frequency axis was taken as the peak frequency. Similarly, the EEG signal-to-noise ratio was estimated with the EEG channels, which showed maximal EEG–EMG coherence in each condition and patient, respectively. For all comparisons between the three cohorts, a nonparametric independent samples Mann-Whitney test was performed.

Coherent Source Analysis and Connectivity

Dynamic imaging of coherent sources uses a spatial filter algorithm[22] and estimates the tomographic power and coherence maps, which are based on the standard head models. The forward head model is the computation of the scalp potentials for a set of neural current sources. It is usually solved by estimating the so-called lead-field matrix[23] with specified models for the brain. In this study, the more complex five-concentric-spheres model was used to create the volume conductor model with standard T1 magnetic resonance images.[24] In this study, we have taken the assumption that the source analysis is based on single dipole, which is not linearly correlated to the other dipoles.

Because the coherence between an identified area with itself is always 1, this region was considered as noise for the next run in the coherence matrix, and further coherent areas were identified.[25] The spatial filter was applied to a large number of voxels covering the entire brain, assigning to each voxel a specific value of coherence by taking extensor EMG as the reference signal in the individual frequency band. A voxel size of $5 \times 5 \times 5$ mm was used in this study. In a subsequent analysis, all of the original source signals from each source with several activated voxels were combined by estimating the second-order spectra and employing a weighting scheme depending on the analyzed frequency range to form a pooled source signal estimate for every source as previously described.[21] This analysis was performed for each subject separately, followed by a grand average across all subjects. The significance of the sources was tested by a within-subject surrogate analysis. As a first step, the actual raw data were divided into 1-s segments, and the second step was to estimate surrogates by shuffling them 99 times with a Monte-Carlo random permutation algorithm. The third step for each of the 99 times the coherence values were estimated and the 99th percentile of mean of all these coherence values is taken as the threshold for each individual subject.

To find the effective causality between two signals, the method called renormalized partial directed coherence (RPDC) was used.[26] The pooled source signals were modeled using the autoregressive processes to

TABLE 2. Cortico-muscular coherence

		Coherence Median (range)						Coherence Frequency (Hz) Median (range)					
		ET	ET(C)	ART	P_1	P_2	P_3	ET	ET(C)	ART	P_1	P_2	P_3
Pinch grip (n = 10)	*L*	0.15 (0.09-0.22)	0.15 (0.09-0.20)	0.13 (0.09-0.2)	0.01	0.002	0.32	21 (17-28)	22 (18-28)	22 (17-24)	0.13	0.26	0.19
	R	0.18 (0.12-0.26)	0.17 (0.12-0.26)	0.12 (0.1-0.16)	0.007	0.004	0.28	21 (18-28)	22 (19-27)	22 (17-25)	0.15	0.31	0.20
Slow move (n = 10)	*L*	0.18 (0.1-0.23)	0.17 (0.1-0.21)	0.13 (0.09-0.16)	0.006	0.001	0.36	21 (19-24)	21 (18-25)	22 (17-26)	0.13	0.35	0.21
	R	0.21 (0.09-0.22)	0.21 (0.09-0.22)	0.14 (0.08-0.17)	0.004	0.003	0.29	21 (17-26)	22 (18-27)	19 (16-23)	0.15	0.34	0.19
Hold (n = 10)	*L*	0.26 (0.12-0.29)	0.27 (0.12-0.29)	0.15 (0.11-0.2)	0.0001	0.0002	0.27	5 (3-7)	4 (2-8)	5 (3-8)	0.29	0.36	0.30
	R	0.26 (0.11-0.29)	0.26 (0.10-0.28)	0.16 (0.08-0.18)	0.0002	0.0004	0.38	6 (2-8)	5 (3-8)	5 (2-8)	0.31	0.28	0.38

Pinch grip: First dorsal interosseus muscle; *Slow move:* Forearm extensor muscles during slow up- and down movements of hands; *Hold:* Forearm extensor muscles during steady holding of hands against gravity. *L:* Left muscles; *R:* Right muscles; ET: ET patients; ART: Aging related tremor patients.
P_1: Level of significance for nonparametric group comparisons (ET vs ART; Mann-Whitney test).
P_2: Level of significance for nonparametric group comparisons (ET[C] vs ART; Mann-Whitney test).
P_3: Level of significance for nonparametric group comparisons (ET vs. ET[C]; Mann-Whitney test).

estimate the coefficients of the causality in the specific frequency band with a multivariate approach. The detailed explanation for the estimation of the RPDC values between two signals x and y at a specific frequency f is given in this study.[26] To obtain the coefficients, the optimal order needs to be chosen, which is estimated by minimizing the Akaike information criterion.[27] The bootstrapping method was used to calculate the significance level on the applied data after the estimation of the RPDC values.

Results

Twenty patients with early-onset ET (onset age < 30 years) (10 ET and 10 ET[C]) and 10 patients with late-onset (onset age > 50 years) tremor (ART), all right-handed, were studied. Clinical data are summarized in Table 1. No difference was found in the mean age at assessment or clinical tremor severity as measured by both the total FTM score and the sub score FTM-A between ET and ART patients. The mean age at onset was 7.6 years ± 3.5 and 6.8 years ± 3.5 for the ET groups and 57.9 ± 7.0 in the ART group, which was significantly different by definition of the cohorts. The same applies for disease duration. Two well-established aging parameters were assessed: The muscle strength of the righthand and lefthand measured by a dynamometer and a standardized cognitive test battery consisting of four standardized psychological tests. Hand grip force was significantly lower for the ART group for both hands. The ART

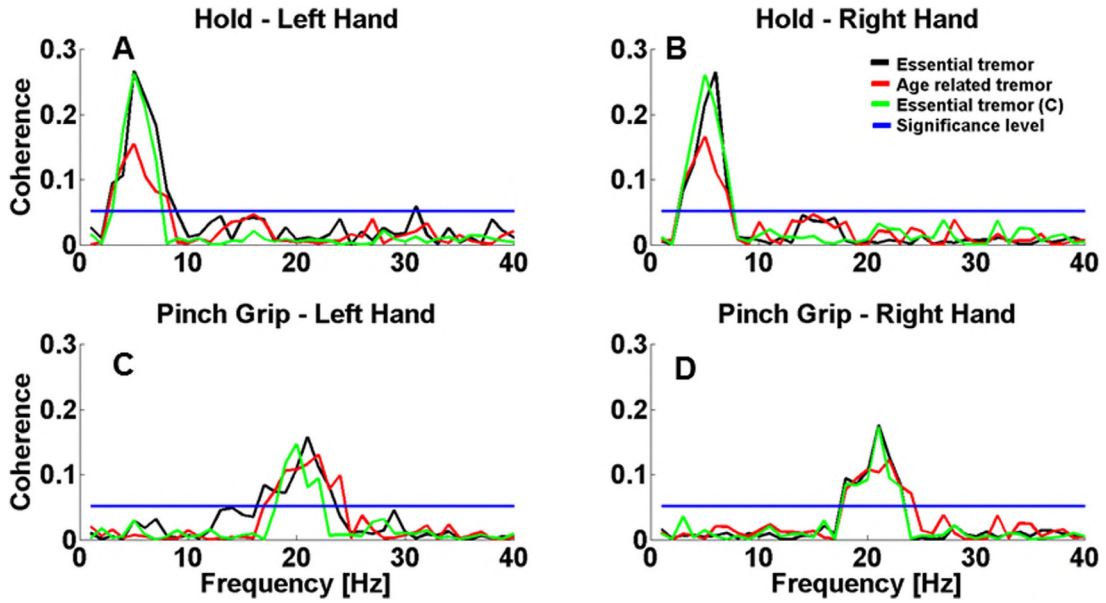

FIG. 1. Pooled cortico-muscular coherence spectra. Bold black lines show the pooled spectra for essential tremor (ET) patients, red bold lines for aging-related tremor (ART) patients, green bold lines for ET control group of patients ET (C), and blue lines indicate the significance level. The upper graphs display the spectra for the holding task for the left (**A**) and right (**B**) forearm extensor muscles. The lower traces show the spectra for the pinch grip tasks with coherence between contralateral EEG and EMG calculated with respect to the first dorsal interosseous muscles on the left (**C**) and right (**D**) side.

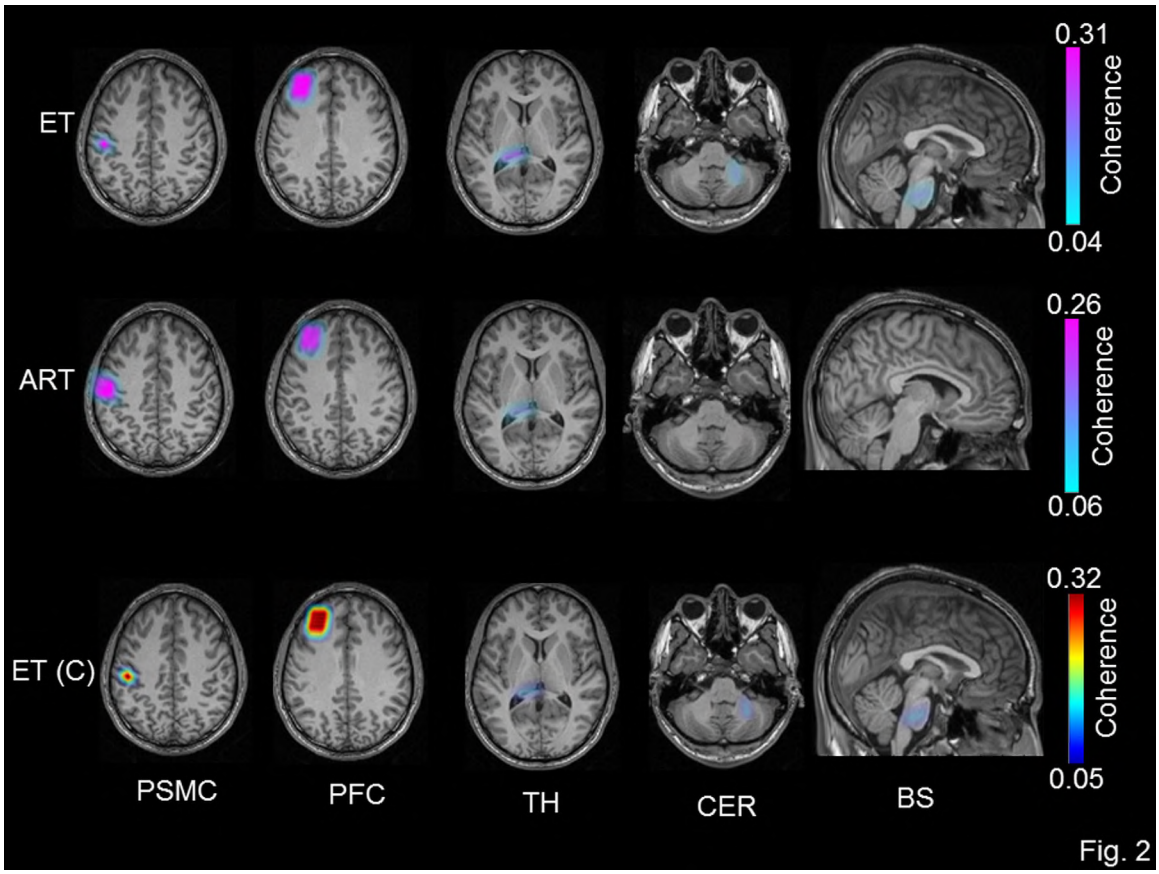

FIG. 2. Shows the grand average of network of sources involved in the tremor frequency for the ET patients in row 1, with the color bar indicating the source coherence values. The second row shows the network of sources involved in the ART patients. The third row shows the network of sources involved in the ET (C) control patients. ET, essential tremor patients; ART, aging-related tremor; ET (C), essential tremor control group patients; PSMC, primary sensory motor cortex; PFC, prefrontal cortex; TH, thalamus; CER, cerebellum; BS, brain stem.

patients also performed significantly worse on cognitive testing than the ET patients. This confirms previous studies that aging parameters are worse for the ART patients.

Table 2 summarizes the results for the corticomuscular coherence analysis, displaying the median and the range of maximal coherence and coherence frequencies. The maximal EEG-EMG coherence was significantly higher (Mann-Whitney test, $P < 0.01$) in ET patients compared with ART patients, when subjects performed the pinch grip task with the FDI recorded as shown in Table 2. Similarly, the maximal EEG-EMG coherence was significantly higher (Mann-Whitney test, $P < 0.01$) in ET during slow up-and-down movements and the holding task with the forearm extensors recorded as shown in Table 2. Evidently the maximal coherence is significantly higher (Mann-Whitney test, $P < 0.01$) in ET patients for both sides. This is displayed as pooled coherence spectra with the significance level for the holding and the pinch grip task in Fig. 1. For both the pinch grip and the slow hand movements tasks, both groups showed coherence peak around 20 Hz. In the holding task, both groups showed peak coherence around 5 Hz. Similar to the first ET group, the second group of ET (ET[C]) patients showed significant differences compared with ART.

The EMG power maxima were distributed broadly between 2 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 (shown in Supplemental Data Table 1) and the EMG signal-to-noise (shown in Supplemental Data Table 2) differed significantly between the ET and ART in none of the three conditions (Mann-Whitney test, $P > 0.05$). However, the RMS mean amplitude of the EMG was significantly (Mann-Whitney-test, $P < 0.05$) greater in ET patients than in ART patients for all recordings because of more power in the higher (100-250 Hz) EMG frequencies (Mann-Whitney test, $P < 0.05$) as depicted in Supplemental Data Table 3 (which led to recruitment of the second ET group to control for this difference). The EEG peak frequencies for all three tasks and three patient groups are demonstrated in Supplemental Data Table 4. The EEG signal-to-noise ratio was estimated for the three tasks and the three cohorts of patients separately for the EEG channels, which showed maximal EEG-EMG coherence. No significant differences

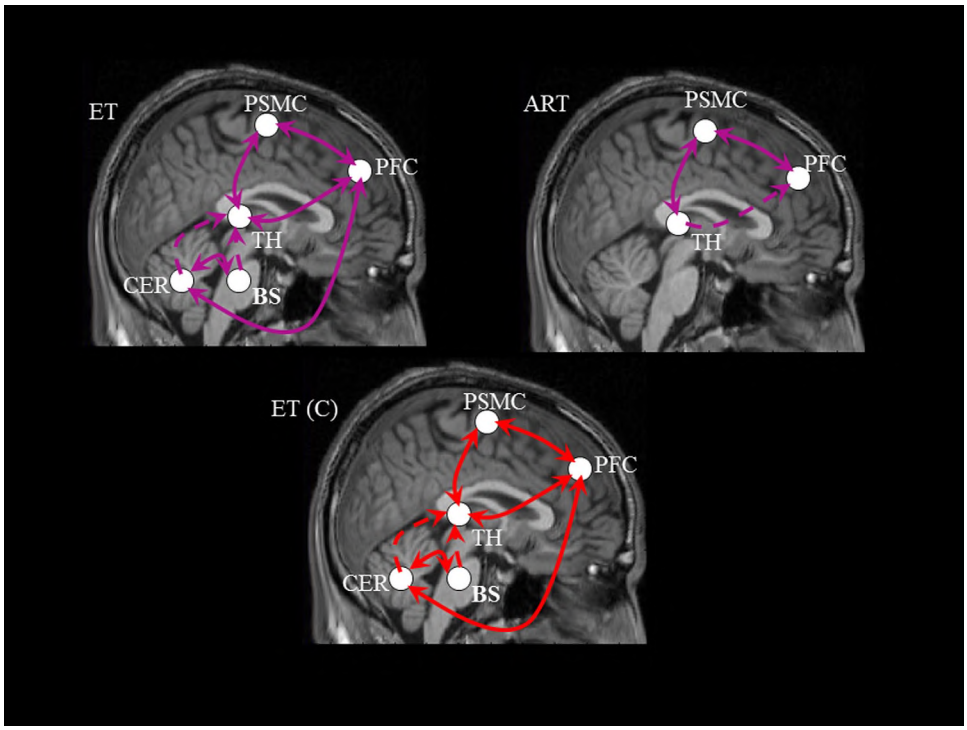

FIG. 3. Significant directionality between the network of sources for ET, ART, and ET (C) control group patients on a template brain (sagittal slice). Dashed lines indicate unidirectional connections, and bold lines indicate bidirectional information flow between the corresponding sources. ET, essential tremor patients; ART, aging-related tremor; ET (C), essential tremor control group patients; PSMC, Primary sensory motor cortex; PFC, Prefrontal cortex; TH, Thalamus; CER, Cerebellum; BS, Brain stem.

were found between the three cohorts of patients in any of the conditions (Mann-Whitney test, $P > 0.05$) as depicted in Supplemental Data Table 5. No significant correlations were found between EMG amplitudes and coherence strength or frequency (Spearman rank correlations).

Because the EMG RMS amplitudes differed between ART and ET patients, we selected a further ET group (ET[C]) with similar RMS amplitudes, and all of the tests were repeated, yielding similar results as depicted in Supplemental Data Table 3. The EMG power spectra were plotted for each task and each group as pooled spectra, and we did not find any changes in the peak frequency as depicted in Supplemental Data Figure 2.

The source analysis was done based on the data for the holding task. The grand average of all 10 patients in each cohort is shown in Figure 2. The network of sources that were involved in the ET patients at the tremor frequency were primary sensory motor cortex (PSMC), prefrontal cortex, thalamus, cerebellum, and brain stem. In ART patients, the network only consisted of primary sensory motor cortex, prefrontal cortex, and the thalamus. All of these identified sources were statistically significant ($P = 0.005$) according to Monte Carlo random permutation across all subjects. The mean source coherence values were also significantly higher ($P = 0.003$) in ET compared with ART. The connectivity between the source signals mostly showed significant ($P = 0.007$) bidirectional connectivity in ET patients except the connection from the cerebellum to the thalamus and the connection from the brainstem to the thalamus, which showed significant ($P = 0.009$) unidirectional information interaction as shown in Figure 3. The second ET group (ET[C]) showed a similar network of activation and directionality between the sources. In ART patients, all of these connections were significant ($P = 0.003$) and mostly bidirectional, except the connection from the thalamus to the prefrontal cortex, which was unidirectional as shown in Figure 3. The renormalized partial directed coherence values for all significant connections are listed in Supplemental Data Table 6.

Discussion

In this study we analyzed the cortico-muscular interaction in patients with different tremor types, that is, early-onset essential tremor and late-onset essential tremor, now also called aging-related tremor, to identify electrophysiological markers separating the two conditions. Our data showed differences in EEG-EMG coupling during simple isometric and isotonic hand motor tasks when comparing patients with ET and ART tremor. For the holding task, we were able to show alterations in the functional source network components involved in these two tremor types as well as differences in network connectivity.

The clinical separation of ART from ET is currently based on the age at onset of tremor, and we have previously in a much larger group[3] found that ART scored worse than ET for standard aging parameters (such as muscle strength and cognitive abilities). The same was found in the relatively small groups of patients studied here, so we believe our subjects are representative of early-onset ET and ART. However, we cannot exclude that changes in age-related parameters (such as cognition) have an effect on tremor physiology. Indeed, one possible explanation for our findings may be that the EEG of a cognitively impaired person may have slower frequencies unrelated to tremor and, therefore, reduced coherence. Tremor patients with a longer disease duration (in our case, patients with early-onset ET) might be less cognitively impaired and, therefore, have little theta and delta range so that all the frequency in that range is related to tremor, resulting in a higher coherence. However, we hypothesize that the electrophysiological findings reflect true differences between these two tremors, unrelated to confounding factors.

We found a lower cortico-muscular coupling for ART than for ET. In manifest ET, cortico-muscular coupling occurs at a tremor frequency in the 4-Hz to 11-Hz band.[28] The current interpretation is that such coupling reflects generation of the tremor oscillation within a motor loop of the central nervous system.[6] Cortico-muscular coupling exists at a similar tremor frequency range in ART and ET patients. Which factors may account for this difference? Tremor frequency is known to be lower in older than in younger healthy subjects.[29,30] The underlying coherence of motor units is well known to shift toward lower frequencies with increasing age.[31] However, this is part of normal aging and not necessarily a pathologic finding.[32,33] Furthermore, age by itself is unlikely to be the reason for the difference, because both cohorts were age-matched, and the frequencies did not differ significantly. Additional indirect evidence against an aging effect comes from a previous study,[9] which showed significant differences of cortico-muscular coupling between healthy subjects and asymptomatic relatives of ET patients. The relatives of ET patients showed higher coherence at the beta band than the healthy subjects, which was interpreted as a subclinical sign for synchronization of motor units, possibly predicting future tremor. Secondly, we found muscle strength to be higher in ET but increased cortico-muscular coupling in ET is not related to muscle strength, as shown previously by looking at motor-unit coherence in ET.[34] Third, the stronger coupling in ET may be attributable to the earlier onset of the disease, and what role genetic factors may play is unclear. Also, possibly in early-onset familial ET, years of constant entrainment of the nervous system result in these EEG or EMG findings. We also performed the calculation of the coherence across a broad range of tremor durations of 20 ET patients and the mean coherence values of the subcortical sources taken from the cerebellum and brainstem. However, no significant correlation ($r = -0.1509$; $P = 0.5027$) was found.

Hopefully, future long-term studies will shed light on this.

Besides the strength of the coupling, the most striking difference, however, is related to the tremor networks for ET and ART. Although in both conditions, the prefrontal cortex, thalamus, and primary sensory-motor cortex are involved, ET patients do have a strong subcortical brainstem and thalamic contribution. The change in coupling cannot be simply related to the strength of the EMG signal because they are not different between the two cohorts. The RMS amplitude was significantly different, but we controlled for this with a second group of ET patients (ET[C]) with similar RMS amplitudes, and the underlying ET network was exactly the same. Therefore, the different RMS amplitude differences cannot account for this difference. The result in ET is in line with EEG[35] and functional MRI studies,[36-38] giving hints on extended network components, especially subcortical brain areas. A similar network of sources involved in ET postural tremor is also shown in earlier magnetoencephalographic[7] and EEG studies.[8] The restriction of this network to the prefrontal cortex, thalamus, and sensorimotor cortex in ART, however, is new. This might reflect a more cortical origin of ART compared with ET. Discussing a possible underlying change of cortical organization in ART such as a loss of inhibition leading to enhanced synchronization of the motor output is speculative. We know that different rhythmic movement disorders can have different cortical loops involved as the motor cortex in the case of mini-asterixis of hepatic encephalopathy,[39] or a more extended network in case of Wilson's disease,[40] orthostatic tremor,[41] or Parkinson's disease.[42,43] Although most of the mentioned tremors can be separated on the basis of their clinical features, ET and ART are clinically similar from the phenomenology of the tremor point of view. Therefore, such differences of their loop may help to uncover the underlying differences.

This first study looking at the difference in EMG, EEG-EMG coherence, involved network components, and connectivity parameters between ET and ART patients has weaknesses. We did not have an estimate of the expected effect size and therefore 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 attributable to the limited number of subjects in this study.

In conclusion, our study demonstrates an easily measurable subclinical alteration of cortico-muscular interaction in ET and ART patients. The next step will be to use these measures in larger cohorts and to follow these subjects long-term to find out whether such physiological measures will be useful as markers for the separation between ET and ART. ■

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