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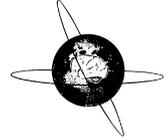Sharifi, S.; Luft, F.; Potgieter, S.; Heida, T.; Mugge, W.; Schouten, A. C.; Bour, L. J.; van Rootselaar, A. F.

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Directionality of corticomuscular coupling in essential tremor and cortical myoclonic tremor

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ARTICLE INFO

HIGHLIGHTS

- Renormalized partial directed coherence is a suitable approach to investigate corticomuscular directionality in tremor.
- An efferent cortical drive is lacking in the majority of essential tremor (ET) patients; corticomuscular coupling in ET has predominantly an afferent direction.
- ET might be associated with a non-linear (rate-dependent) cortical transmission.

ABSTRACT

Objective: A role of the motor cortex in tremor generation in essential tremor (ET) is assumed, yet the directionality of corticomuscular coupling is unknown. Our aim is to clarify the role of the motor cortex. To this end we also study 'familial cortical myoclonic tremor with epilepsy' (FCMTE) and slow repetitive voluntary movements with a known cortical drive.
Methods: Directionality of corticomuscular coupling (EEG-EMG) was studied with renormalized partial directed coherence (rPDC) during tremor in 25 ET patients, 25 healthy controls (mimicked) and in seven FCMTE patients; and during a self-paced 2 Hz task in eight ET patients and seven healthy controls.
Results: Efferent coupling around tremor frequency was seen in 33% of ET patients, 45.5% of healthy controls, all FCMTE patients, and, around 2 Hz, in all ET patients and all healthy controls. Ascending coupling, seen in the majority of all participants, was weaker in ET than in healthy controls around 5–6 Hz.
Conclusions: Possible explanations are that tremor in ET results from faulty subcortical output bypassing the motor cortex; rate-dependent transmission similar to generation of rhythmic movements; and/or faulty feedforward mechanism resulting from decreased afferent (sensory) coupling.
Significance: A linear cortical drive is lacking in the majority of ET patients.

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1. Introduction

Essential tremor (ET), characterized by a postural and intentional tremor predominantly of the hands, is a highly prevalent and disabling movement disorder of unknown cause (Hopfner et al., 2016). In addition to the cerebellum, other structures within this tremor network are suggested to be involved in sustaining or even in generating tremor in ET (Hopfner et al., 2016). A common hypothesis regarding the origin of ET involves dysregulated neuronal signaling within the cerebello-thalamo-cortical network, or "tremor network" (Raethjen and Muthuraman, 2015). A prominent role of the central sensorimotor cortex was suggested following several EEG-EMG and MEG-EMG studies that demonstrated corticomuscular coupling at tremor frequency (Hellwig et al., 2001; Raethjen et al., 2007; Schnitzler et al., 2009). Previous studies that investigated corticomuscular coherence over time have shown intermittent coherence despite a constant tremor power (Raethjen et al., 2007; Sharifi et al., 2017). Thus, over time despite a strong tremor intensity there was a loss of significant corticomuscular coherence at tremor frequency. This might suggest that

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motor cortex activity is not directly driving the tremor in ET, and might even solely reflect an afferent input. The purpose of our study was to enlighten on the controversies concerning cortical involvement in ET and to differentiate between afferent and efferent corticomuscular flow in ET; to investigate directionality of corticomuscular coupling in ET at tremor frequency.

We hypothesize that there may be parallels between ET and voluntary movement, which also involves the cerebello-thalamo-cortical network. Up until now, studies into corticomuscular coupling in tremor did not consider rate-dependency of cortical involvement, a phenomenon seen in voluntary movement. In locomotion mainly activation, and not the preservation of rhythmical movement, is associated with cortical output (Klarner et al., 2014; Zehr, 2005). Cortical activity has been suggested to have a linear efferent association with repetitive movements at increasing rates until ~ 4 Hz and saturate at higher frequencies (Riecker et al., 2003). Above approximately 4 Hz, cortical activity has been shown not to increase with movement rates in a perfect parallel. This might suggest a linear cortical drive only for lower frequencies and not for frequencies above 4 Hz, possibly also in ET.

On the other hand, efferent coupling around tremor frequency might be present in ET, similar to the cortical drive in 'familial cortical myoclonic tremor with epilepsy' (FCMTE). FCMTE can clinically mimic ET, but has a completely different pathophysiology (Van Den Ende et al., 2018; Florian et al., 2019). This autosomal-dominant familial syndrome is characterized by distal cortical myoclonic tremor, and later in life epileptic seizures (van Rootselaar et al., 2005). In fact, the cortical myoclonic tremor consists of fast jerky movements (8–20 Hz) fulfilling the electrophysiological criteria of cortical myoclonus (Sharifi et al., 2012; Shibasaki and Hallett, 2005). Rhythmic cortical myoclonus or cortical myoclonic tremor has a degree of rhythmicity that is detectable in its EMG power spectrum (Bhatia et al., 2018; Latorre et al., 2020; Van Rootselaar et al., 2020).

Conventional methods to establish corticomuscular coupling, using EEG-EMG coherence analysis, are unable to reveal the relative contributions of efferent and afferent information flows. Among methods to detect directionality of EEG-EMG coupling, (renormalized) partial directed coherence (PDC, rPDC), has been indicated to be a reliable measure (Campfens et al., 2014). However, rPDC has not yet been applied systematically to investigate directionality of corticomuscular coupling in tremor. This method yields insight into the directionality by evaluating asymmetrical causal interactions between the spectral content of the 2 signals based on Granger causality derived from multivariate autoregressive models (Schelter et al., 2006, 2009). In order to investigate corticomuscular directionality with rPDC, the first premise is to establish significant corticomuscular coherence.

We examined corticomuscular directionality during tremor in ET, FCMTE and in healthy controls while mimicking tremor, as well as during 'slower' voluntary movement (~2 Hz) in ET and in healthy controls. Note that, in the context of the current study, tremor is defined as 'fast' (>4 Hz) movements (although ET is not considered a fast tremor, (Bhatia et al., 2018)). Confirmation of a cortical drive in FCMTE will also validate the rPDC method to investigate directionality of (myoclonic) tremor related neuronal activity. During slow (~2 Hz) self-paced movement, we expect to confirm an efferent information flow, which may be absent during faster (~6 Hz; mimicked) tremor.

2. Materials and methods

Data was collected in the Amsterdam UMC, Academic Medical Center Amsterdam (AMC, center I) and the University Medical Center Groningen (UMCG, center II), two academic hospitals in the Netherlands. The study conformed with the Declaration of Helsinki and was approved by the AMC and the UMCG Medical Ethical Committee. All participants provided written informed consent.

Demographic and clinical characteristics of the participants are summarized in Table 1.

2.1. Inclusion at center I – ET patients and healthy controls

From the AMC outpatient movement disorders clinic 17 patients (13 men; mean age, 59.8 ± 16.5 years) with ET were recruited. Patients were diagnosed according to the criteria of the Tremor Investigation Group, displaying bilateral postural arm tremor without other neurological disorders (Bain et al., 2000; Bhatia et al., 2018). All subjects were aged 18 years or older, were right-handed according to the Annett handedness questionnaire, had a positive family history in the immediate family, and reported a positive effect of propranolol and alcohol on tremor. Also, 18 healthy right-handed controls (10 men; mean age, 57.1 ± 12.6 years) were included without any known neurological disorders. Exclusion criterion for both groups was cognitive dysfunction established with Mini-Mental State Examination < 26. All recordings in the tremor patients were performed off medication. A movement disorders specialist (J.D. Speelman, JDS) rated the tremor severity from recorded videos according to the TRG ET Rating Assessment Scale (TETRAS)(Elble et al., 2012). The mean score for tremor severity was 18.8 (SD 8.1).

2.2. Inclusion at center II – ET patients, healthy controls and FCMTE

From the UMCG outpatient department, eight ET patients (seven men; mean age, 55.5 ± 15.7 years) were included, participants were diagnosed and screened by a movement disorders specialist (AFvR). Unfortunately, TETRAS scores were not collected. Seven healthy controls (5 men; mean age, 47.1 ± 12.3 years) without any neurological disorders were included, and seven FCMTE patients (five men; mean age, 44.7 ± 9.7 years). Myoclonic tremor severity in FMCTE was scored by a movement disorders specialist (JDS) using the Unified Myoclonus Rating Scale (UMRS) (Frucht et al., 2002). The mean score for tremor severity was 10.4 (SD 8.4).

2.3. Experimental procedure, motor tasks including tremor task and slow repetitive task

Participants were seated and instructed to fixate with their eyes on one point during recordings. Before recordings, participants were instructed and the researchers demonstrated the two motor tasks.

Tremor task: simultaneous EEG-EMG measurements were recorded for two periods of 1 minute alternated with 30 seconds of rest to avoid fatigue. ET and FCMTE patients were asked to extend their right arm, inducing (myoclonic) tremor. Healthy controls were asked to mimic tremor by performing self-paced rhythmic extension-flexion wrist movements during arm extension around 6 Hz.

Slow repetitive task: ET patients and healthy controls who were included in center II additionally performed slow paced extension-flexion wrist movements of about 2 Hz for two 1-minute periods.

2.4. Recordings

The experimental setup performed in center I is previously reported in detail (Sharifi et al., 2017). EEG was captured with a 64-channel cap and amplifier, and EMG was recorded using a 6-channel amplifier (Refa8 and Porti7, Twente Medical Systems International B.V., Oldenzaal The Netherlands). The sampling rate was 2048 Hz with resolution of 0,01839 μV (24 bits). The input

Table 1
Characteristics of participants.

	Center I	Center II	n
ET			
Number (male)	17 (13)	8 (7)	25
Age in years	59.8 ± 16.5	55.5 ± 15.7	
Disease duration in years	32.2 (4–61)	23.5 (5–52 y)	
Healthy controls			
Number (male)	18 (10)	7 (5)	25
Age, years	57.1 ± 12.6	47.1 ± 12.3	
FCMTE			
Number (male)		7 (5)	7
Age, years		44.7 ± 9.7	
Disease duration in years		18.1 (7–34)	

Categorical data are presented as the number of patients and continuous data as mean ± standard deviation or as median (range). ET essential tremor; FCMTE familial cortical myoclonic tremor with epilepsy.

impedance was high > 100 MΩ. The influence of electrode impedance is therefore very small, impedance values were kept below 20kΩ. The connectors were active shielded micro coaxer channels. All signals were amplified and referenced against the average of all connected unipolar EEG inputs. The patient ground electrode was required (between FPZ-FZ), but was not an active input. Tremor activity was recorded by placing bipolar surface EMG electrodes on the wrist flexors (recorded over flexor carpi radialis), on the wrist extensors (recorded over extensor carpi ulnaris), and on the index finger abductor (first dorsal interosseous) of the right hand. Eye movements and heart rate were registered with additional electrodes to correct for EOG and ECG artifacts.

The experimental setup performed in center II is previously reported in detail (van Rootselaar et al., 2006). In summary, simultaneous EEG-EMG recordings were performed with a similar high-quality system as center I but using a 128-channel cap and headbox (Twente Medical Systems BV, Oldenzaal The Netherlands) and two bipolar EMG surface electrodes placed on the wrist extensors and first dorsal interosseous of the right hand (Silicon Biomedical Instruments BV, Westervoort, The Netherlands). The sampling frequency was 1000 Hz.

2.5. Data processing

All data were processed in MATLAB software (MathWorks, Inc., 2014, Natick, MA, USA). Filters for movement artifact removal described here were selected to avoid introduction of filtering artifacts that could contaminate Granger-based causality estimations (Florin et al., 2010). The EEG was band-pass filtered (zero-phase, 2–250 Hz, fourth order Butterworth filter). The EMG was band-pass filtered (zero-phase, between 10 and 750 Hz, fourth order Butterworth filter) and full-wave rectified which is the common method to demodulate tremor from EMG (Journée, 1983). Furthermore, line-noise artifact (48–52 Hz) was removed via a notch filter. To identify focal patterns of specific cortical activity, EEG derivations were composed: the average of the four nearest electrodes was taken as the reference for a given electrode (Hjorth, 1991).

2.6. Coherence analyses

The coherence analyses methods have been reported elsewhere (van Rootselaar et al., 2006; Sharifi et al., 2017) and are summarized here. The coherence analyses were performed with help of the NeuroSpec toolbox (Halliday et al., 2000). Briefly, each recording was segmented in L epochs (2 seconds). Subsequently, the spectra and coherence values were estimated for each epoch. Per participant per task, the EMG channel with the most distinct tremor peak on visual inspection and in power spectral density was

chosen for further analyses. Also, we determined the 'EEG hotspot': the EEG electrode with the strongest corticomuscular coherence (Sharifi et al., 2017). Coherence maps derived from EEG-EMG signal do not have an optimal spatial resolution to separate between primary motor and sensory cortex; it is not possible to associate efferent or motor output specifically with motor areas and afferent input specifically with neighboring sensory areas (Hellwig et al., 2001; Mima et al., 2001; Raethjen et al., 2007). For this reason, we selected the electrode over the central (sensorimotor) cortical area contralateral to the tremor with strongest corticomuscular coherences (FC3 and C3) per participant to calculate directionality (Bourguignon et al., 2015). A 95% confidence limit was set for statistical significance of coherence, determined by the number of epochs used for the spectral estimation $[1 - (0.05)^{1/(L - 1)}]$. Epochs showing significant corticomuscular coherence around the frequencies of interest, i.e. (mimicked) tremor frequency and the slow movement frequency, were selected for further analysis with rPDC.

2.7. rPDC analyses

RPDC, which is based on Granger causality, is a robust technique to investigate directionality with statistical endorsement (Schelter et al., 2006, 2009). It starts from the premise that causes must precede their effects in time; thus, information in a cause's past must improve the prediction of the effect and cross-correlation. With standard corticomuscular coherence analysis, a common (exogenous) cause may synchronize two signals revealing coherence, however, without having a directional causal relationship (Mullen, 2010). Also, the corticomuscular loop consists out of multiple relays including afferent and efferent pathways. Therefore, bidirectional coupling or a 'simultaneous' information flow in both directions is likely to exist. In case of a bidirectional signal, phase differences cannot be calculated reliably. RPDC includes a multivariate-autoregressive (MVAR) model with an appropriate order p fitted to both signals in a bidirectional way.

The coefficients of the coupling are calculated in two directions: the afferent information flow (EMG → EEG) and the efferent information flow (EEG → EMG). Fourier transformation of the vector autoregressive model coefficients yields the PDC. Finally, the PDC is renormalized, leading to the rPDC values. Previous method studies have performed extensive analyses investigating the optimal MVAR settings (Schelter et al., 2006, 2009). In light of those results, we applied an in-house developed rPDC toolbox specific for EEG and EMG activity around tremor frequency. The toolbox was based on published theories and is described below in more detail (Schelter et al., 2006, 2009).

The preprocessed recordings were first divided into overlapping segments of 4 second periods. The amount of overlap between segments was set at 50%. All segments were decimated to 256 Hz (data from center I) or 250 Hz (data from center II). Segments were further processed by demeaning and tapered with a Tukey window. Only segments with sufficient power in the frequency band of interest (i.e., maximum in power spectral density at the frequency of interest ± 3 Hz rising 2.5 times the median of the total power) were used for further analysis (Sharifi et al., 2017). This selection was made to ensure to establish directionality of information flow solely in the presence of tremor or intended movement (motor tasks).

Corticomuscular directionality is only meaningful in case of significant corticomuscular coupling. RPDC estimations were calculated for epochs with significant coherences in the frequency band of interest. MVAR parameters were estimated for each segment using the 'direct method', which produces more accurate estimations than alternatives, especially for relatively small sample sizes (Franaszczuk et al., 1985). The selection of MVAR order p was estimated by minimizing the Akaike information criterion,

where the optimal order for recordings depended on the length of useful available data (Akaike, 1974). With the assumption that qualitative data for at least 2 minutes were available, the model order was set at 100. MVAR parameters were calculated for each segment, averaged across all segments and then used for the rPDC calculation. Spectral and MVAR-based coherence estimations were compared to ensure correctly estimated parameters. The frequency resolution was set to 0.25 Hz, and adjusted with zero padding if necessary. Simulations where performed and showed that this form of interpolation did not affect the strength of interaction over the frequencies (SP). Renormalization in the calculation of rPDC results in an approximately noncentral χ^2 distribution with two degrees of freedom (Schelter et al., 2009). The significance level was set at 95% and was dependent on the number of epochs used, calculated with analytical confidence level $\chi^2_{df,}$ 1 – α/N.

2.8. Between-group comparison

First, the statistical differences between groups for 1) presence of efferent and 2) presence of afferent coupling were tested per task with the Fisher-Freeman-Halton exact test using dichotomous rPDC categories; that is, significant/insignificant afferent and significant/insignificant efferent coupling. Tasks are the tremor task and the slow repetitive task. Subsequently, continuous rPDC values representing the coupling strength were compared between groups per task with Kruskal-Wallis one-way analysis. For this, the maximum afferent and maximum efferent rPDC value in the frequency band of interest per group per task was noted. Post hoc analyses of the continuous rPDC values were performed with follow-up Mann-Whitney *U* tests between pairs of groups. A Bonferroni adjustment was applied to adjust multiple tests (0.05/3). Lastly, frequency-dependency of cortical involvement was tested with Spearman rank order correlation based on the rPDC values per task per direction.

We refrained from statistical testing of within-group rPDC values representing afferent and efferent information flow because the strength of the rPDC directional coupling is strongly dependent on the signal-to-noise ratio (SNR) (Florin et al., 2011). Here, the SNR in the EMG compared to the EEG is presumed to be disproportionally represented (as EEG data is less selective for tremor related information from the motor cortex), which results in misleading within-group comparisons.

3. Results

3.1. Corticomuscular coherence

3.1.1. Corticomuscular coherence tremor task

The CMC results for ET, healthy controls and FCMTE, described in detail elsewhere (van Rootselaar et al., 2006; Sharifi et al., 2017), are summarized here. The data of the participating hospitals were pooled as the same inclusion criteria were applied, and recordings and analyses were done by the same group following the same protocols. Frequency peaks in the EMG power spectrum indicated satisfactory task performance. The power spectrum showed a dominant (4.5–8.5 Hz) tremor peak in the EMG signal in all ET patients and healthy controls (Fig. 1). Peak frequency per participant varied less than 1 Hz during a task indicating constant task performance. In the FCMTE group, the power spectra from the EMG recorded during myoclonic tremor showed a broad 'tremor' band, with the highest power ranging from 12 to 25 Hz (Fig. 1). In ET, corticomuscular coherence at tremor frequency was present in 18 out of 25 ET patients (Table 2), most often with the hotspot (strongest corticomuscular coherence) over C3 (Hjorth derivation). Three patients revealed the strongest corticomuscular coherence

over FC3. All but three healthy controls demonstrated significant corticomuscular coherence between C3 and contralateral EMG around mimicked tremor frequency. All FCMTE patients revealed a dominant coherence peak between C3 and the right wrist extensor muscle. In appendix A (supplementary material) the results are described for each center separately.

3.1.2. Corticomuscular coherence slow repetitive task

In the slow repetitive task, the EMG power spectra in all participants showed a dominant peak around 2 Hz. In all ET patients, the self-paced movements resulted in a significant corticomuscular coherence around the movement rate (in one patient hotspot over FC3, all others C3). All but one of the healthy participants exhibited corticomuscular coherence around the frequency of interest (two participants hotspot over FC3, all others C3).

3.2. Directionality of corticomuscular coherence: rPDC

An example of rPDC analyses output, depicting asymmetrical coherence values for both directions, is shown in Fig. 2. Table 3 summarizes presence of significant rPDC efferent and afferent coupling in the frequency band of interest per group per task (dichotomous rPDC categories). Fig. 3 shows the continuous rPDC values representing the average strength of the corticomuscular coupling per group per task (model order set at 100, which resulted in rPDC graphs resembling MVAR-based coherences).

3.2.1. rPDC tremor task

In general, 57 good-quality segments were extracted with sufficient tremor power (>2.5 × median of total EMG power in the tremor band) per condition. Two segments were excluded, because these were lacking sufficient tremor power, in two ET patients' recordings and in one healthy control recording. The rPDC analyses of the tremor task showed in 33% of the ET patients and in 46% of the healthy controls a significant efferent coupling (EEG → EMG) with clear peaks at (mimicked) tremor frequencies. Significant afferent coupling (EMG → EEG) around (mimicked) tremor frequency was present in all except one ET patient and all healthy controls. Thus, the direction of information flow associated with tremor in ET and mimicked tremor in healthy controls was efferent in less than half of the participants and afferent in almost all of the participants.

The rPDC analyses of the myoclonic tremor in FCMTE revealed significant efferent coupling in all patients and afferent coupling in all but one FCMTE patient.

3.2.2. rPDC slow repetitive task

Similar to the tremor task, 57 segments were selected from the EEG and EMG recorded during slow repetitive task in healthy controls and ET because of sufficient tremor power. In the slow repetitive task, in all healthy controls and all ET patients an efferent information flow (EEG → EMG) was seen. There was a significant afferent coupling in five out of eight ET patients and in all healthy controls.

3.3. Between-group comparison

3.3.1. Tremor task

The Fisher exact test, investigating the proportion of significant rPDC values dichotomously, indicated a significant difference in efferent coupling between the groups (*p* = 0.008). No difference was observed in the proportion of presence of significant rPDC in afferent coupling between the different groups (*p* = 0.136). However, analyzing continuous rPDC values (Fig. 3), the Kruskal-Wallis analysis revealed a statistically significant difference in
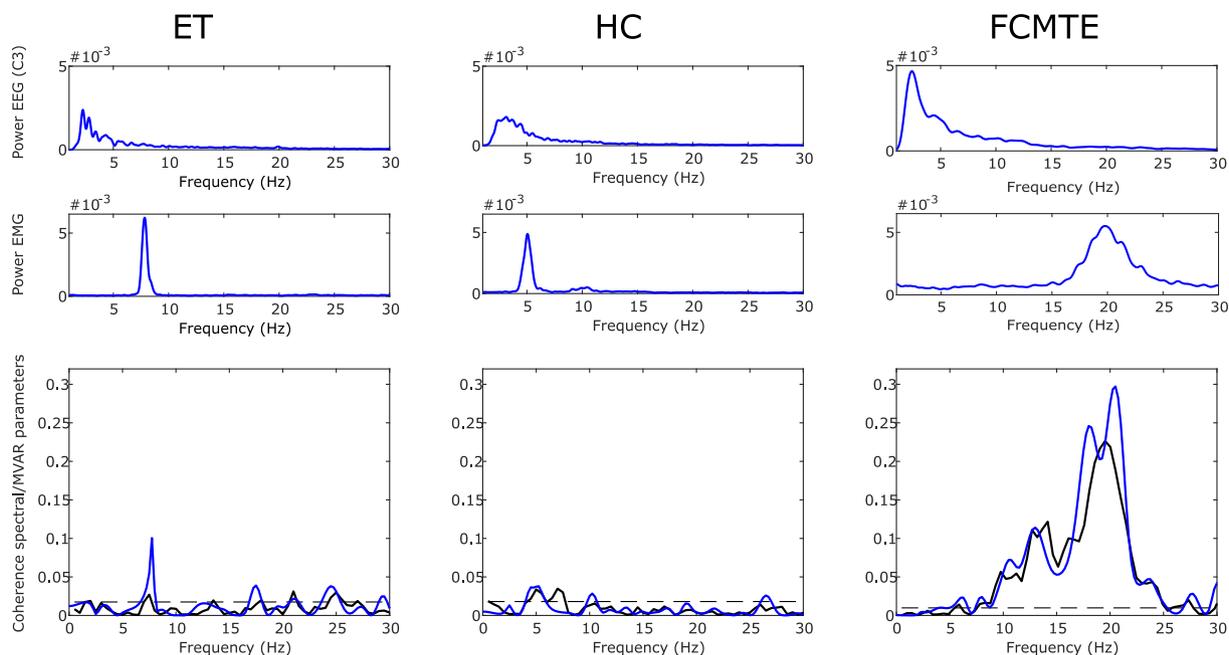
Fig. 1. Representative examples in individual essential tremor (ET) patient, healthy control (HC) and in familial cortical myoclonic tremor with epilepsy (FCMTE) patient of power spectra derived from two minutes EEG (upper panels, C3 Hjorth derivation, after filtering) and EMG (middle panels, from right wrist extensors during tremor and mimicking tremor in HC, after filtering and rectification), and coherence plots (lower panels) derived from spectral (black) and multivariate autoregressive (MVAR) parameters (blue) with a renormalized partial directed coherence (rPDC) analytical confidence limit (dotted line).

Table 2
Significant corticomuscular coherence (CMC) between EMG and contralateral sensorimotor cortex around frequency of interest.

	Tremor task Significant CMC /total	Tremor Frequency, Hz mean (sd)	Slow repetitive task Significant CMC /total	Tremor frequency, Hz mean (sd)
ET	18/25 (72%)	6.4 (1.1)	8/8	1.9 (0.3)
Healthy controls	22/25 (88%)	5.2 (1.0)	6/7	2.1 (0.5)
FCMTE	7/7 (100%)	16.6 (3.9)	-	-

ET essential tremor; FCMTE familial cortical myoclonic tremor with epilepsy.

the strength of the afferent coupling across the three groups (FCMTE, n = 6; ET, n = 17; healthy control, n = 22; $\chi^2_{[2, 45]}$ = 10.58, p = 0.0005). In the post-hoc analyses, the Mann-Whitney U test revealed a significant difference in strength of the afferent coupling between healthy controls (median = 0.0005) and ET patients (median = 0.0022: U = 75, z = –3.17, p = 0.002). The strength of the information flow in ET was less than in healthy controls.

3.3.2. Slow repetitive task

With respect to the slow repetitive flexion–extension task, there were no significant differences in the proportion of significant rPDC values or in the strengths of the efferent or afferent coupling between healthy controls and ET.

3.3.3. Rate-dependency

The relationship between rPDC values, for both directions, and the frequency of the flexion–extension movements below and above 4 Hz was investigated (Fig. 4). A best fit-regression showed a different trend between the slow repetitive task and the tremor task. Using the nonparametric Spearman rank order correlation coefficient there was a significant negative correlation between the EMG to EEG direction and its tremor frequencies (r = -0.30,

p = 0.048, n = 45) with higher tremor frequencies associated with a less strong rPDC connectivity.

4. Discussion

Our results show a predominantly afferent (EMG to EEG) signal flow at tremor-frequency in ET, although less prominent in patients than in healthy controls during mimicked tremor. Remarkably, there is no convincing efferent corticomuscular coupling in ET during tremor in the majority of patients, although, with rPDC, a cortical drive could be identified in FCMTE. Our findings are inconsistent with a, generally presumed, linear cortical drive in ET. However, these are in accordance with previously reported, seemingly contradictory findings including absence of corticomuscular coherence around tremor frequency, intermittent coupling, and afferent cortical coupling (Muthuraman et al., 2018; Sharifi et al., 2017).

Placing our results in the context of current knowledge regarding the pathophysiology of (essential) tremor and of voluntary movement, possible non-mutually exclusive explanations for tremor generation in ET include: 1) a subcortical output of faulty oscillatory activity bypassing the motor cortex; and/or 2) a mechanism similar to generation of rhythmic movements including a
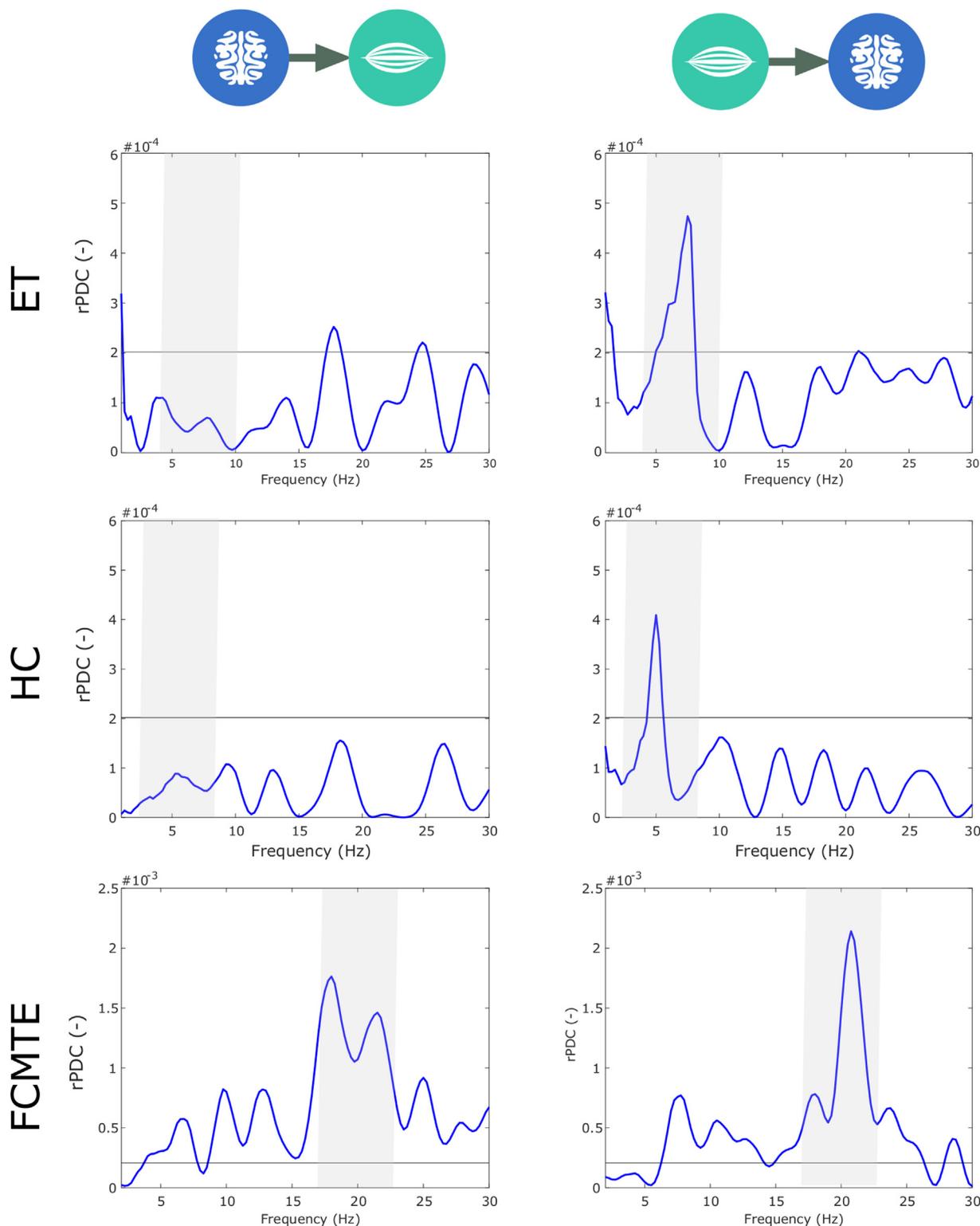
Fig. 2. Representative examples of renormalized partial directed coherence (rPDC) plots and their predefined tremor band (shaded area) during 2 minutes (mimicked) tremor in an essential tremor (ET) patient (top), a healthy control (middle), and a familial cortical myoclonic tremor with epilepsy (FCMTE) patient (bottom). Information flow in the FCMTE patient is bidirectional, whereas it is afferent only in the ET patient and in the healthy control.

non-linear or rate-dependent transmission and/or 3) a faulty feed-forward mechanism resulting from decreased sensory coupling. These hypotheses are discussed below.

  1) a subcortical output of faulty oscillatory activity bypassing the motor cortex

In ET there is increasing evidence of abnormal functioning of the cerebellum and its outflow tracts (Hopfner et al., 2016). Our findings are consistent with a subcortical (cerebellar) origin involved in driving ET and a disrupted connectivity with the motor cortex within the tremor network (Buijink et al., 2015; Nicoletti et al., 2020). Moreover, cerebellar faulty oscillatory activity could

Table 3
Significant rPDC coupling for efferent and afferent direction.

| | Tremor task | | Slow repetitive task | |
| | Efferent | Afferent | Efferent | Afferent |
	EEG → EMG	EMG → EEG	EEG → EMG	EMG → EEG
ET	6/18 (33.3%)	17/18 (94.4%)	8/8 (100%)	5/8 (62.5%)
Healthy controls	10/22 (45.5%)	22/22 (100%)	6/6 (100%)	6/6 (100%)
FCMTE	7/7 (100%)	6/7 (85.7%)		

ET essential tremor; FCMTE familial cortical myoclonic tremor with epilepsy.
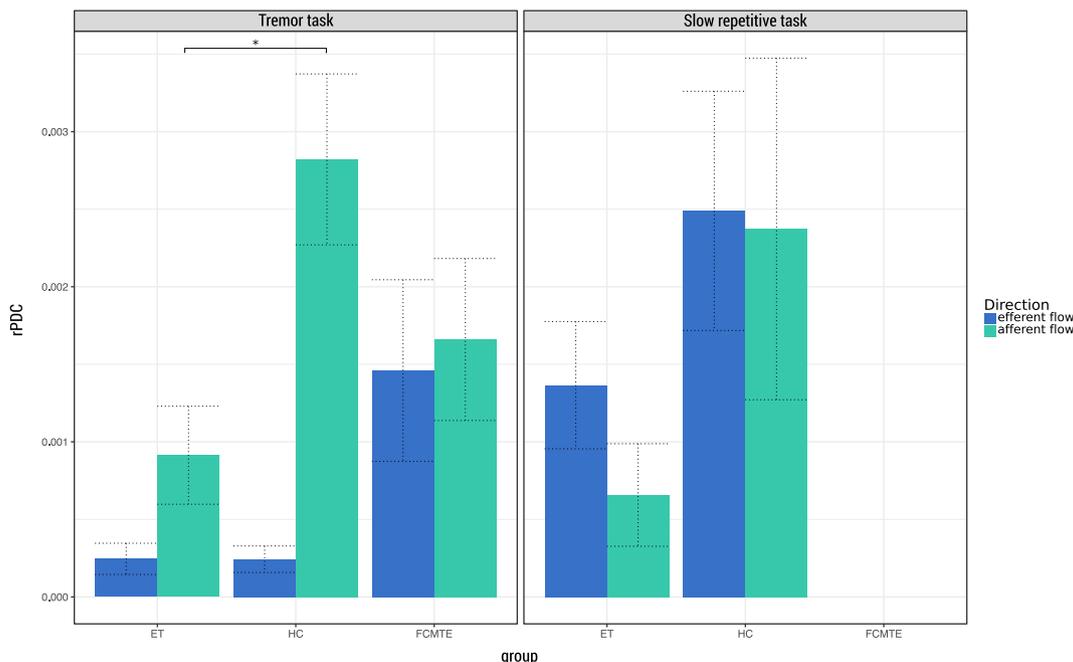

Fig. 3. Histogram with renormalized partial directed coherence (rPDC) values (mean, standard deviation) representing the strengths of the corticomuscular coupling in both efferent and afferent direction for all groups and conditions. The mean efferent rPDC values of essential tremor (ET) and healthy controls in the tremor task do not reach the confidence level which is given by the horizontal dashed line. Post-hoc analyses: the strength of the afferent coupling in ET is significantly less strong than in healthy controls. In the slow-paced task the difference between groups was not significant. FCMTE familial cortical myoclonic tremor with epilepsy; * <0.05/3 tested post-hoc Mann-Whitney U tests.

lead to augmented inhibitory activity between thalamus and cerebral cortex (Buijink et al., 2015). Alternatively, subcortical output of faulty oscillatory activity could directly project to spinal neurons. In animal studies, ~10 Hz oscillations of the deep cerebellar nuclei were not only coherent with oscillations recorded in the periphery but also indicated an efferent coupling (Williams et al., 2010, 2009). These studies suggested that the bulbospinal pathways are likely to provide (partial) descending oscillatory activity leading to physiological tremor. In this context, the afferent flow might be an epiphenomenon, a result of the fast movements of the hand.

2) a mechanism similar to generation of rhythmic movements including a non-linear or rate-dependent transmission

Both in ET and in healthy controls the presence and the strength of efferent coupling differed per task (slow vs fast movement). And, although based on limited data, movements up to 4 Hz appear to be associated with an increase in the strength of the coupling, whereas - at increasingly higher rates - the strength seemed to decrease. Similar rate-dependent engagement of the sensorimotor system has been described previously (Riecker et al., 2003). Parametric fMRI analyses resulted in a linear increase of the hemodynamic response in the sensorimotor cortex up to a movement

frequency range of 4 Hz (Blinkenberg et al., 1996; Jäncke et al., 1998), albeit developing a plateau phase at higher rates (Riecker et al., 2003). In human locomotor studies, it has been hypothesized that only the activation of rhythmic movements is attributed to supraspinal cortical output. The preservation of rhythmic movements is thought to rely little on cortical output but to be based on subcortical and mainly spinal mechanisms (Klarner et al., 2014; Zehr, 2005). Considering the different engagement of sensorimotor cortex during the different voluntary repetitive movement rates, one could hypothesize comparable non-linear or rate dependent cortical involvement during involuntary movement. In ET, the cortical areas might still be involved in activation of tremor, but not the preservation of tremor.

3) A faulty feedforward mechanism resulting from decreased sensory coupling

Based on the finding of decreased afferent coupling in ET compared to healthy controls, it can be hypothesized that cortical misprocessing of sensory feedback may play a role in tremor generation in ET. Normally, the cerebellar forward model precomputes expected sensory information and compares it to actual sensory information from the sensory system (Pisotta and Molinari, 2014). Subsequently, if necessary, the cerebellum adjusts the
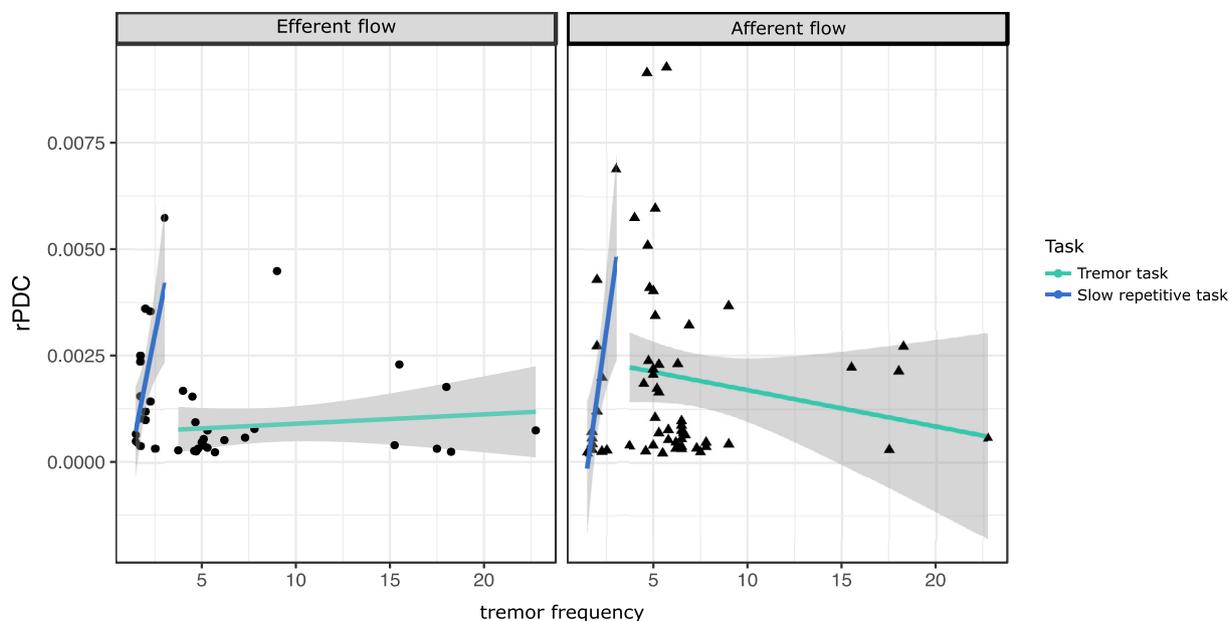
Fig. 4. Scatterplot with best-fit regression per task displays the relationship between frequency of movements and renormalized partial directed coherence (rPDC) values. Groups are pooled: the slow-pace task contains data points from essential tremor and healthy controls, and the tremor task contains data points from familial cortical myoclonic tremor with epilepsy, healthy controls, and essential tremor. The scatterplot suggests a strong positive trend associated with slow (<4Hz) movement and the rPDC values, whereas a virtually flat/negative trend is seen during fast (>4Hz) movement (including both involuntary and voluntary movement).

motor activity in the cortex and the brainstem during the execution of a movement. When normal feedforward mechanisms fail, because of faulty afferent input, this might lead to faulty output and thus tremor. Alternative explanations for the difference in afferent coupling between ET and HC, include a (sub)cortical compensatory mechanism with dampening of afferent oscillatory input, habituation due to constant tremor input, and/or differences in amplitude of movement between ET and HC.

This study is the first to apply the rPDC method to investigate directionality of corticomuscular coupling in tremor. The analyses confirmed efferent coupling in FCMTE around 16 Hz (12–25 Hz), consistent with the cortical drive of the myoclonic tremor in FCMTE (Sharifi et al., 2012). Slow, self-initiated movements (<4 Hz) revealed a prominent efferent information flow, where faster voluntary movements did not, as expected (Riecker et al., 2003). These findings, in line with previous findings, indicate that the current rPDC method is suitable to investigate directionality of corticomuscular flow, recorded with EEG and EMG, around tremor frequency.

Of importance, when applying rPDC analysis, is that MVAR Granger causality is limited to detection of linear connections. Second, SNR is of importance for rPDC analyses. Differences in signal strength might potentially hamper detection (of direction) of corticomuscular coupling. In the current study, the strength of the signal of interest, the tremor band, is conceivably stronger in the EMG (>SNR) than it is in the EEG (<SNR). If the signal of interest is disproportionally represented in the two signals, the coupling originating from the signal with the lowest SNR theoretically might be overshadowed. Also, an absolute low SNR might lead to a low sensitivity (Florin et al., 2011). Nevertheless, our results demonstrate that the rPDC method applied here can capture an efferent information flow present during fast and slow movements. Also, we focused on improving the EEG SNR during the preprocessing because our simulations showed that after a certain SNR threshold (>10 dB), between-signal differences in SNR are less influential. To enhance the underlying cortical activity, we applied a Hjorth derivation identifying focal cortical activity, as opposed to other

experimental studies exploring corticomuscular directionality in tremor that did not apply EEG derivations (Schelter et al., 2006, 2009). Furthermore, the quality of the data was visually inspected, and the SNR of all tasks between participants was assessed to be equal. The SNR issue mostly pertains to the height of the rPDC coupling. A direct comparison of strength between afferent and efferent direction within subjects must be made with caution. Between-subject comparisons are not thought to be affected.

A drawback of our study is that we collected data at 2 centers. However, the results from both locations were comparable. We do not expect this to have affected our results.

In future investigations into tremor pathophysiology frequency of tremor, rate dependency and other analogies with voluntary movement might be important factors to consider. Further identification of how the motor and sensory information is processed, can help to improve and develop treatment options. To further investigate these hypotheses, we suggest investigations with high-density EEG/EMG integrated with fMRI and effective connectivity studies to distinguish primary motor cortex involvement from SMA and sensory motor cortex involvement.

4.1. Conclusion

The rPDC results, showing a cortical drive in FCMTE and during slow voluntary repetitive movements, seem to be a reliable technique to investigate directionality of corticomuscular coupling in tremor, both high and low frequencies. Tremor in ET seems not to be attributed to a linear cortical drive. The lacking efferent output might be part of the pathophysiological mechanism in ET, for instance the occurrence of a descending subcortical faulty activity bypassing the motor cortex consistent with a cerebellar origin, concerning a non-linear (rate-dependent) transmission, or in case normal (cerebellar) feedforward mechanisms fail. Understanding the origin of tremor in movement disorders, for example, with help of electrophysiological features, might help diagnosis and therapy in the future.

Declaration of Competing Interest

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.04.011.

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