CHAPTER 3

CAN WE DIFFERENTIATE POSTURAL TREMOR USING INTERMUSCULAR COHERENCE AND CUMULANT ANALYSIS?

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ABSTRACT

OBJECTIVE: To investigate the potential value of two advanced EMG measures as additional diagnostic measures in the polymyographic assessment of postural upper-limb tremor.

METHODS: We investigated coherence as a measure of dependency between two EMG signals, and cumulant analysis to reveal patterns of synchronicity in EMG activity in muscle pairs. Eighty datasets were analysed retrospectively, obtained from four groups: essential tremor (ET), Parkinson's disease (PD), enhanced physiological tremor (EPT), and functional tremor (FT). We used strict diagnostic inclusion criteria combining clinical, neurophysiological and imaging information

RESULTS: Intermuscular coherence was highest in the PD group (0.58), intermediate in FT (0.43) and ET (0.40), and weakest in EPT (0.16) (p=0.002). EPT patients could be distinguished by low coherence: coherence<0.18 in the wrist + elbow extensors differentiates EPT in this sample with a sensitivity of 86% and specificity of 84%. Cumulant analysis showed predominantly alternating activity between wrist and elbow extensor in ET patients, while a more synchronous pattern was predominant in PD, EPT and FT (p=0.008). EMG activity in wrist and elbow flexors tended to be more synchronous in PD (p=0.059).

CONCLUSION: Our results suggest that coherence and cumulant analysis may be of additional value in the diagnostic work-up of postural tremor.

SIGNIFICANCE: These additional measures may be helpful in diagnosing difficult tremor cases.

INTRODUCTION

Although tremors are the most common movement disorders, distinguishing one type of postural tremor from another can be challenging (1). History taking and clinical examination by a movement disorders specialist are of primary importance. Additionally, a clinician can request polymyography. Unfortunately, this general work-up of choice does not always lead to a conclusive diagnosis (2).

In the outpatient clinic, accurate diagnosis can be challenged by the fact that not all patients have a classic presentation. Tremors that present as a postural tremor could mainly be essential, enhanced physiological, dystonic, parkinsonian, or functional. However, not all parkinsonian tremors start of as a typical pill-rolling rest tremor, and not all essential tremor is symmetrical, action-induced and with a slight intention component (3). Neither does every essential tremor patient have a positive family history or a positive response to alcohol (4, 5). Organic tremor patients can present with a story that seems 'functional', whereas functional tremor patients might be hard to distract from their symptoms, making their tremor appear organic.

In more difficult cases, a clinician can request polymyography to help establish a diagnosis (6). These tests are usually of great value: for instance, a prospective study by Gironell and colleagues proposed a set of six neurophysiological criteria for essential tremor with very high sensitivity and good specificity for this type of tremor (7). However, this has not been done for all types of tremor, and interpretation is not always straightforward. For example, although tremor frequency can be of help, the typical frequencies of different types of tremor overlap and as a result frequency is not always a distinguishing feature (8). Other tremor characteristics, such as frequency change at loading in enhanced physiological tremor, or entrainment in functional tremor (9) are not present in all patients and sensitivity and specificity are generally poorly known.

In the current study, we sought to add to the diagnostic power of routine polymyography, by investigating the potential additional diagnostic value of two advanced EMG measures: coherence and cumulant analysis. Coherence analysis is a method to detect a common input for the generation of two signals, and is therefore relevant for the study of relationships between the activities of tremulous muscles (10). Coherence is a normalized measure, which takes on a value of 1 in case of absolute dependence, and 0 in case of complete independence between two signals. Applied to two tremulous EMG signals, this implies that high coherence indicates a common drive from a generator mechanism. While coherence analysis provides a measure in the frequency domain, cumulant analysis is informative of the relationship between two signals over time. Applied to two tremulous EMG signals, cumulant analysis can be used to assess the timing relations between EMG bursts in pairs of muscles, in a more objective way than by visual inspection of the EMG signals.

Previous studies have investigated intermuscular coherence (11-13) or muscle activity patterns (11, 14, 15), but generally without direct comparison between commonly encountered tremor types. In this study, we compared four groups of carefully selected patients with essential tremor (ET), parkinsonian tremor (PD), enhanced physiological tremor (EPT) and functional tremor (FT). Our aim was to examine whether intermuscular coherence and cumulant analysis might be of help as additional diagnostic measures in polymyographic assessment of postural tremor.

TABLE 3.1. INCLUSION AND EXCLUSION CRITERIA.

ESSENTIAL TREMOR	PARKINSONIAN TREMOR
Bilateral postural tremor Developed before the age of 65 Present for >3 years Absence of rest tremor, or if present, frequency approx. 1.5 Hz lower than the postural tremor and without tremor latency No other neurological signs/symptoms	Unilateral or asymmetrical tremor Postural tremor + resting tremor Partial or complete suppression during movement FDOPA-PET positive
ENHANCED PHYSIOLOGICAL TREMOR	FUNCTIONAL TREMOR
Postural + rest and/or action tremor Positive electrophysiological report: • Frequency variability >1 Hz • High frequency (>7 Hz, not mandatory) • Effect of loading (frequency decrease >1 Hz, not mandatory)	Postural + rest and/or action tremor Positive electrophysiological report: • Frequency variability >1 Hz • Effect of mental distraction
EXCLUSION CRITERIA	
Occurrence of entrainment, in all groups except FT Decrease of tremor on mental distraction, in all groups except FT History of stroke or co-existing neurological disease	

METHODS

SUBJECTS

We analyzed 80 polymyography datasets that were obtained as part of the diagnostic work-up in patients suffering from postural tremor. The patients were equally distributed over the four tremor groups most commonly encountered in our clinic: ET, PD, EPT and FT. We used strict inclusion criteria (Table 3.1), combining clinical, neurophysiological and imaging information, to ensure that the diagnosis was as reliable as possible. Inclusion criteria for ET are in accordance with the TRIG criteria (16) and the neurophysiological criteria proposed by Gironell et al (7).

POLYMYOGRAPHY RECORDINGS

EMG was recorded with Ag/AgCl surface electrodes placed over flexor and extensor muscles in the fore- and upper arm, using palpation and maximal voluntary contractions to identify the muscles. Four muscle pairs were studied; 1) wrist flexor + extensor, 2) elbow flexor + extensor, 3) wrist + elbow extensors, 4) wrist + elbow flexors. We selected parts of the recording where patients sat with their most affected arm stretched out parallel to the ground, with the palm of the hand facing the floor and a neutral (no flexion, no extension) wrist position. Note that the included PD patients had a postural tremor in this specific position, in addition to classic tremor at rest. This group is a relevant and important addition to our study, as action tremor in PD can complicate distinction from other tremor disorders. All selected patients showed tremor bursts in the EMG of at least two of the assessed muscles during this postural task. The selected sections of the EMG signal were extracted using BrainRT software (OSG BVBA, Rumst, Belgium) and exported to ASCII format. The mean duration of the sections was 32.7 s (range: 21-57 s). As classic tremor characteristics, we documented tremor frequency (mean of maximal and minimal tremor frequency throughout the polymyography recording)

and frequency variability (maximal – minimal tremor frequency) for each patient from their clinical neurophysiology reports.

COHERENCE AND CUMULANT ANALYSIS

Data was analyzed in MATLAB R2007a (MathWorks, Natick, MA, USA), using the signal processing toolbox and NeuroSpec 2.0 (www.neurospec.org) to calculate power spectra, coherence, phase and cumulant density for each patient and each of the muscle pairs (17) (Figure 3.1 A-E). Our script is available as supplementary material online. Sample frequency was 1 kHz. A Butterworth 10 Hz highpass filter was used to remove drift and movement artefacts. Next, the data was full-wave rectified, thereby enhancing the firing rate information of the signal (17). Segments were selected to contain 2¹⁰ datapoints (1.024 sec). We did not apply smoothing or tapering.

The quality of the EMG signals was judged based on the 95% confidence interval of the individual power spectra for each muscle; signals with a dominant (first) tremor peak smaller than the confidence interval were excluded. Moreover, signals where the amplitude of the dominant tremor peak was smaller than   were excluded because this was assumed to reflect poor signal-to-noise ratio. For each patient and muscle pair, we registered the presence or absence of significant coherence (as reflected in at least one coherence value above the confidence limit), and coherence values at the dominant tremor peak were used for statistical analysis.

Cumulant density plots were classified manually for each patient and muscle pair. Plots were classified as 1) a broad positive peak around zero, indicating tremor burst activity that was more in-phase and synchronous, 2) a broad negative peak around zero, indicating tremor burst activity that was more out-of-phase and alternating, and 3) a narrow central peak close to zero, indicating short-term synchronization with tremor bursts consistent with a common presynaptic drive (18-

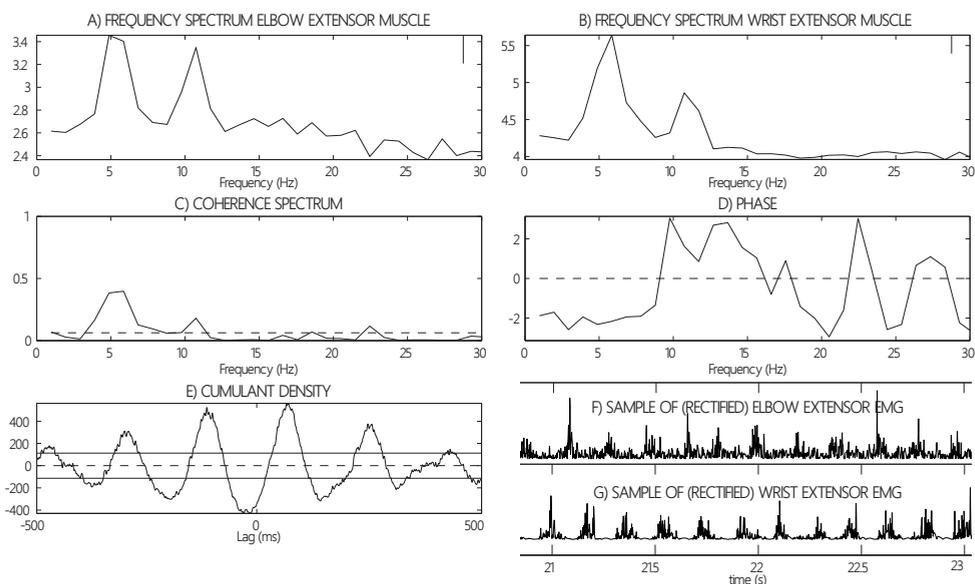Figure 3.1. Example of output of the coherence and cumulant analysis for an ET patient. Note the appearance of two peaks in the coherence spectrum (C), at the dominant tremor frequency and its first harmonic. The cumulant (E) shows a broad negative peak around zero for muscle pair 3: wrist + elbow extensors and indicates an alternating pattern of muscle activity, as can be verified in the EMG (F and G).
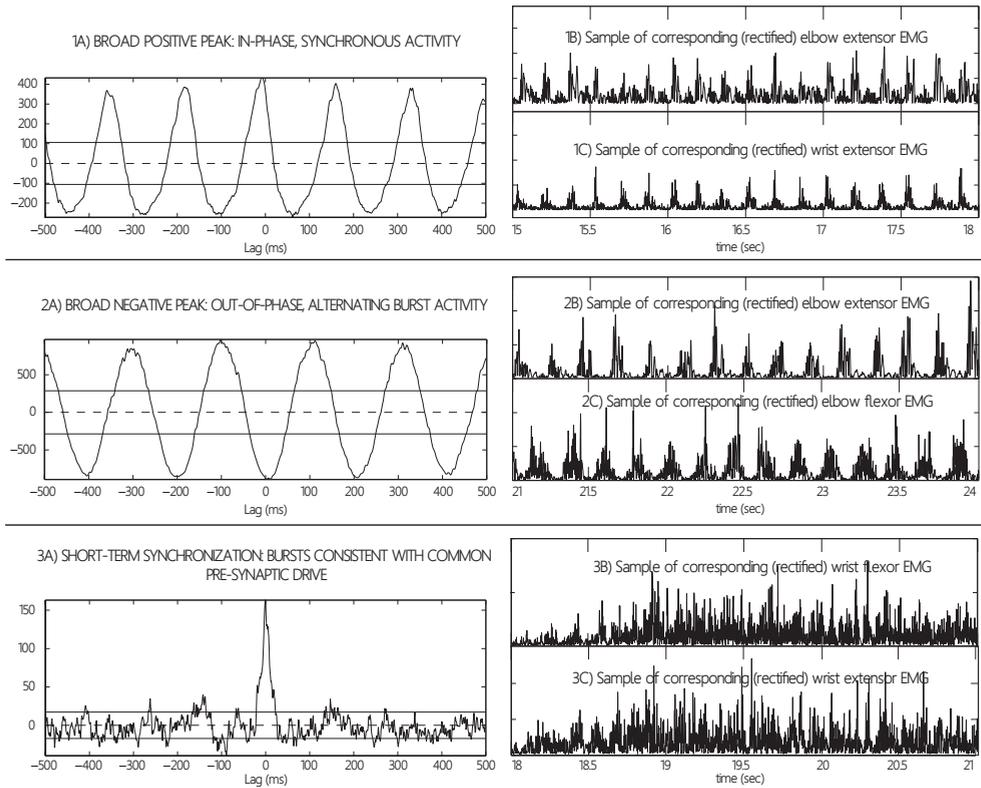
Figure 3.2. Examples of the three types of cumulant density plots; a broad positive peak around zero (1A), a broad negative peak around zero (2A), and a narrow peak around zero indicating short-term synchronization (3A), with their corresponding EMG signals (1-3B&C).

20)(see Figure 3.2 for typical examples). We chose cumulant density as a measure over phase, because it is the direct counterpart of coherence, in the time domain.

In some data sets, cumulant analysis did not reveal any significant correlation structure between EMG bursts. In addition, when data was contaminated by EMG cross-talk as identified by the combination of a sharp narrow central peak (<10 ms) in the cumulant, broadband coherence (>0.5 above 30 Hz) and flat phase (21, 22), the related data sets were excluded from further analysis.

STATISTICAL ANALYSIS

Patient characteristics including classic tremor characteristics, were compared between groups using Chi-square tests for categorical data, one-way ANOVAs for normally distributed data and Kruskal-Wallis tests for non-normally distributed data in SPSS 20 (SPSS, Chicago, IL). Normality of distributions was tested using the Shapiro-Wilk test. In case of significant effects, post-hoc testing was performed using Games-Howell-corrections because of unequal variances (post-ANOVA) or Mann-Whitney tests (post-Kruskal-Wallis), with Bonferroni correction for multiple comparisons.

The occurrence of significant coherence (in a binary fashion) was analyzed for each muscle pair and compared between groups using Fisher's exact tests in SPSS.

Actual coherence values were Fisher-Z transformed prior to statistical analysis. We analyzed intermuscular coherence by means

of a linear mixed effects model with muscle pair and tremor group as factors, instead of using a repeated-measures ANOVA, because mixed-effects models are more robust to missing data (23). Analysis was performed with the lmer and pvals.fnc functions in the lme4 library, as well as the pamer.fnc function in the LMERConvenienceFunction library for the statistical software R (www.r-project.org, version 3.0.1).

Statistical analysis of the cumulant density classifications was done by means of Fisher's exact tests.

RESULTS

PATIENT CHARACTERISTICS

No difference in gender distribution was detected between groups (Table 3.2). There was a difference in age across groups (p=0.003); ET patients were older than PD (p=0.01), EPT (p=0.008) and FT patients (p=0.005).

CLASSIC EMG TREMOR CHARACTERISTICS

Mean tremor frequency was 5.54 Hz in ET patients, 5.54 Hz in PD patients, 7.84 Hz in EPT patients and 5.42 Hz in FT patients (Table 3.2). There was a difference between patient groups (p=0.001): tremor frequency was higher in the EPT group (p=0.000). Frequency variability, defined as maximal tremor frequency – minimal tremor frequency throughout the polymyography, was on average 1.0 Hz in ET patients, 0.8 Hz in PD

patients, 2.3 Hz in EPT patients and 2.1 Hz in FT patients. There was a significant difference between groups (p=0.000); post-hoc analyses revealed that frequency variability was higher in EPT and FT than in ET and PD patients (p=0.000). We found no difference in tremor amplitude on EMG (defined as mean absolute EMG of the lower extensor in μV) between groups (p=0.104).

ADVANCED EMG MEASURES: COHERENCE & CUMULANT

Overall, significant intermuscular coherence was found in 98% of PD measurements, 97% of FT measurements, 80% of ET measurements, and 72% of EPT measurements. Statistically, a significant difference between groups was found in the occurrence of significant coherence for muscle pair 3: wrist + elbow extensors. For this muscle pair, intermuscular coherence occurred in all PD patients, 94% of FT patients, 70% of ET patients, and only in 50% of EPT patients (p=0.001).

Median intermuscular coherence was 0.58 (IQR 0.37) in the PD group, 0.43 (0.34) in the FT group, 0.40 (0.32) in the ET group, and 0.16 (0.14) in the EPT group (Figure 3.3). Coherence differed between groups (p=0.002). Coherence was higher in PD patients than in ET patients (p=0.049), as well as in EPT patients (p<0.001). Moreover, coherence was higher in ET patients compared to EPT patients (p=0.041). Finally, coher-

TABLE 3.2. PATIENT CHARACTERISTICS.

	M/F	Age	Mean freq.	Freq. var.	Amplitude
ET	11/9	69 (10)*†	5.54 (0.93)	1.0 (0.7)*	33.4 (34.2)*
PD	9/10	54 (10)*	5.54 (0.70)	0.8 (0.9)*	32.3 (38.1)*
EPT	13/6	43 (36)*	7.84 (1.36)†	2.3 (2.4)*†	25.2 (47.8)*
FT	11/10	57 (18)*	5.42 (0.56)	2.1 (2.0)*†	49.1 (59.1)*

ET: essential tremor, PD: parkinsonian tremor, EPT: enhanced physiological tremor, FT: functional tremor. M/F: male/female. Mean frequency in Hz, frequency variability in Hz, amplitude in μV. Mean (standard deviation). *Median (interquartile range). †Significant difference at $p<0.05$.

ence was larger in FT patients than in EPT patients (p=0.004). To summarize: the relationship between groups for intermuscular coherence was PD > ET > EPT, FT > EPT.

As coherence was highest in PD patients, and lowest in EPT patients, we investigated cut-off values for coherence measures in these tremor types, using ROC-curves. Unfortunately, we did not find useful (i.e. with a sensitivity and specificity > 80%) cut-off values for PD. For EPT, we were able to establish two useful cut-off values. First, in the muscle pair wrist flexor + extensor, a coherence value below 0.35 distinguishes EPT from the other tremors with a sensitivity of 89% and a specificity of 80% (positive predictive value 0.53, negative predictive value 0.97, odds ratio 40). Secondly, in the muscle pair wrist + elbow extensors, a coherence value below 0.18 differentiates EPT with a sensitivity of 86% and a specificity of 84% (positive predictive value 0.60, negative predictive value 0.96, odds ratio 32).

Moreover, we directly compared ET versus EPT, as this is a clinically relevant comparison; distinction is frequently asked for in polymyography requests and can be difficult. Cut-off values were useful in the same two muscle pairs. In the muscle pair wrist flexor + extensor, a coherence value above 0.27 indicates ET with a sensitivity of 91% and a specificity of 78% (positive predictive value 0.88, negative predictive value 0.83, odds ratio 35), and in the muscle pair wrist + elbow extensors a coherence value above 0.18 differentiates ET from EPT with a sensitivity of 71% and a specificity of 86% (positive predictive value 0.71, negative predictive value 0.86, odds ratio 45).

In the cumulant analysis, results differed between groups for muscle pair 3: wrist + elbow extensors. In ET patients, the cumulant for this muscle pair showed more broad negative peaks, indicating more alternating activity. Contrarily, PD, FT and EPT showed more broad positive peaks, signifying more synchronous activity (p=0.008, test sensitivity: 91%, specificity 64%, positive predictive value 0.5, negative predictive value 0.95, odds ratio 6). Moreover, results trended towards significance in muscle pair 4: wrist + elbow flexors in all PD patients showed broad positive peaks, whereas a broad negative peak was found in about half of the other tremors (p=0.059, test sensitivity: 100%, specificity 43%, positive predictive value 0.41, negative predictive value 1.0; odds ratio incalculable). There were no differences between groups for muscles pairs 1 (p=0.379), or 2 (p=0.327).

DISCUSSION

In this study, our aim was to examine the potential value of intermuscular coherence and cumulant analysis as additional diagnostic measures in the polymyographic assessment of postural tremor.

Firstly, differences in coherence were found between patient groups. PD patients scored highest (median coherence 0.58), EPT patients lowest (0.16) and FT and ET patients scored intermediate (0.43 and 0.40 respectively). We determined cut-off values that may be diagnostically useful for the comparison of EPT versus other tremors, and EPT versus ET specifically. Moreover, absence of significant coherence was also found significantly more often in EPT patients. These features may be of additional clinical value, most of all for diagnosis of EPT.

With regard to what is known about tremor pathophysiology, our coherence results are in broad agreement with expectations. As high coherence between different muscles at the tremor frequency indicates a common drive and generator mechanism (10) we expected high coherence in PD, which we indeed found. ET is also considered to be of cen-

tral origin (11) and our results also support this. In FT, coherence has only been studied between limbs so far: coherence between two tremulous limbs seems to be a sign of functional origin as it occurs in about half of FT patients but rarely in tremor of organic origin (9, 11, 12). The strong intermuscular, intralimb coherence we found in the current study is a new finding, and points towards a highly organized common drive most likely of central origin in FT.

The strong coherence in PD, ET and FT is in contrast with the weak coherence found in EPT. EPT is regarded as a composite of 1) a peripheral mechanical reflex oscillation, which is dependent of the hand's resonant frequency and therefore changes with increased inertial loading, and 2) a centrally driven component in the 7-14 Hz range (10). Under normal circumstances, coherence does not occur as a result of mechanical reflex oscillation; this only happens under high load conditions (24). The low coherence in our EPT patients corresponds well with a relatively strong role for the peripheral mechanism in EPT, compared to other types of tremor.

Cumulant analysis, the second advanced EMG measure we investigated, resulted in typical characteristics for ET and for PD. First, EMG activity in the wrist and elbow extensors was almost exclusively predominantly alternating in ET patients, whereas a more synchronous, co-contracting pattern was predominant in other tremors. This feature of ET has not been reported previously; it is informative on the phenomenology of ET, regarding the muscular expression of this movement disorder. The high sensitivity of this measure (91%) means that the finding of a synchronous instead of an alternating pattern of muscle activity between wrist and elbow extensors in a patient decreases the likelihood of a postural tremor being ET. Secondly, a trend was found regarding the

relation between muscle activity in the wrist and elbow flexors: EMG burst activity was more synchronous between these muscle groups in all PD patients, but a more alternating burst activity pattern was found in about half of the other tremors (sensitivity 100%, specificity 43%). This feature was described before in a group of PD patients that showed synchronous muscle activity patterns for the wrist and elbow flexors, and wrist and elbow extensors, as well (11). Those patients were performing a slightly different postural task, where they sat with the hand out-stretched and the arm supported by an armrest. Our findings are in accord with this previous study, and additionally the present study extends these results by comparing muscle activity patterns between tremor groups.

A limitation of this study is that the population studied was a carefully selected cohort. Diagnosis in all patients was maximally reliable. This is ideal for an initial study, but sensitivity and specificity should ultimately be tested prospectively in an unselected group of patients with postural tremor, before the definite diagnostic value of the advanced EMG measures can be determined. A second limitation is that we used EMG power as an approximation for tremor amplitude: the optimal approach would be to derive tremor amplitude from accelerometry. However, in this paper, the focus lies on EMG analysis.

For those who are interested in implementing coherence and cumulant analysis in their neurophysiology clinic the Matlab script that we used is provided as supplementary material on the journal's website. It can be used freely, together with the NeuroSpec library (open source, www.neurospec.org, (17))

In this carefully selected cohort, we investigated whether intermuscular coherence and cumulant analysis might be of help as

additional diagnostic measures in polymyographic assessment of postural tremor. We have shown that intermuscular coherence differs between tremor groups, and were able to identify EPT patients with high specificity and sensitivity by low coherence in our study population. Cumulant analysis helped to distinguish ET or PD from other tremors. We conclude that coherence and cumulant analysis may be of additional value in the diagnostic work-up of postural tremor.

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