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Daily fluctuations of negative affect are only weakly associated with tremor symptoms in functional and organic tremor patients

Gerrit Kramer, Elisabeth H. Bos, Mark J. Edwards, Marina A.J. Tijssen, Judith G. M. Rosmalen

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ABSTRACT

Background: There is a long-standing research history on the presumed psychological origin of functional movement disorders. Most studies do not address the heterogeneity in functional movement disorders and do not distinguish between risk factors, causes and consequences. We studied the associations between negative affect and objective as well as subjective symptom levels in patients with functional and organic tremor.

Methods: Thirty-three patients with a functional (14) or organic tremor (19) completed a web-based diary on subjective symptom burden and negative affect, five times a day for 30 days (total number of observations = 4759). During the same period, the participants wore an accelerometer to objectively record tremor. Vector autoregressive modelling was used to determine the time-lagged and contemporaneous associations between negative affect and objective/subjective tremor symptoms, both on an individual and a group level.

Results: In contrast to previous literature, patients with a functional or organic tremor showed a weak contemporaneous association between negative affect and objective/subjective tremor symptoms (on average r = 0.038 and 0.174 respectively). Time-lagged associations between negative affect and objective/subjective tremor symptoms were mixed in effect and direction and only present in a subset of patients, with no differences between patients with functional or organic tremor.

Conclusions: Negative affect is only weakly associated with objective/subjective tremor symptoms, both on the contemporaneous and time-lagged associations, and these associations were mainly similar between patients with functional or organic tremor. These results argue against a strong influence of daily stress on tremor symptoms in patients with a functional or organic tremor.

1. Introduction

About 30% of the patients attending tertiary movement disorder clinics have a functional movement disorder (FMD) [1]. While the diagnosis relies on the presence of specific clinical signs such as distractibility of tremor, historically significant emphasis has been placed on psychological origins of the presence and severity of symptoms. Some studies found that patients with FMD have a higher rate of anxiety and depression [2]. In addition, affective disorders have been suggested to be both risk factors and perpetuating factors in FMD [3].

Studying the assumed contribution of negative affect to symptoms in FMDs is not straightforward. First, FMDs are known for their significant heterogeneity in symptomatology and treatment response [4]. Second, most of the current studies do not distinguish between cause and consequence, as they are mostly cross-sectional. These studies typically provide between-person information and no within-person information [5] and in heterogenous sample, this can yield a result that is true on a group level, but can be incorrect on an individual level. Third, most studies focus on risk factors for the onset of the disorder [3], however, it is more likely that negative affect influences day to day fluctuations in the occurrence and severity of symptoms [6], especially since symptom variability over time and during examination is a diagnostic feature of...
FMD [4]. Fourth, the association between negative affect and is not likely to be specific to functional movement disorders, but most likely plays a role in organic movement disorders as well [7].

Ecological momentary assessment (EMA) can address some of these issues. It accounts for heterogeneity by allowing data analysis on an individual level, by virtue of the multitude of repeated observations within individuals. EMA can also help to unravel the temporal dynamics between variables, thereby providing information regarding cause and consequence. Participants report on symptoms and affect, many times over the course of a study [8]. Such data can be used to study both contemporaneous and time-lagged associations.

In this study, we used EMA to study the temporal dynamics between negative affect and movement disorder symptoms in both functional (FT) and organic tremor (OrgT) patients. We chose to use people with tremor as tremor can be studied both subjectively, using a diary, and objectively, using an accelerometry-based device [9,10]. Previously, we described in this patient group a similar association between subjective and objective tremor symptoms in patients with FT or OrgT, while the FT had a slightly lower (but still considerable) level of objective tremor symptoms [11]. The current study focused on the influence of negative affect on these objective and subjective tremor symptoms, while simultaneously accounting for potential reverse causation, i.e. the influence of tremor symptoms on negative affect. Given the presumed psychogenic origin, we hypothesized a stronger relationship between negative affect and tremor symptoms in patients with FT than in patients with OrgT.

2. Methods

Patients were recruited from the neurology outpatient clinic from the University Medical Center Groningen or Ommelander Ziekenhuis Groep between September 2015 and December 2017. This study was part of a larger study, which also focused on the association between subjective and objective tremor symptoms. Inclusion criteria were: age above 18 years, symptom duration of at least one year, capable of completing a web-based diary, and a tremor affecting an upper limb. Patients with a FT had to have a probable or definite FMD [12] and tremor was their main type of movement disorder; patients with an OrgT had to meet the diagnostic criteria for that specific tremor type as was judged by clinical chart review. Exclusion criteria were treatment with botulinum toxin or psychological treatment in the previous six months (see also [11]).

All participants provided written informed consent according to the declaration of Helsinki (2013). Study approval was obtained from the Medical Ethical Committee of the UMCG (nr. 2015/579).

2.1. Study protocol

Before the assessment period of 30 days, participants were video-taped using a standardized video protocol and completed a number of questionnaires. Videos were rated by two experienced movement disorder clinicians using the Fahn-Tolosa-Marin scale [13] and Simplified Functional Movement Disorder Rating scale (S-FMDRS) [14]. Intra-class coefficients between raters were 0.68 (Fahn-Tolosa-Marin scale) and 0.81 (S-FMDRS).

Psychiatric assessment included the Mini International Neuropsychiatric Interview [15,16] for depression, dysthymia, anxiety disorders, somatization disorders and undifferentiated somatoform disorders. Also, participants completed questionnaires on self-efficacy [17], quality of life (EQSD), their global impression of the severity of the disease (patient-rated CGI [18]), disease duration, and demographic variables.

The assessment period was 30 days during which participants completed a web-based diary five times a day and wore an accelerometer until after the final diary assessment, followed by a 12-h night period without assessment. Assistance by telephone was available during this period.

As there is very little literature on the study length to reliably assess tremor characteristics and, as far as we know, no evidence on the influence of daily changes in affect on these tremor characteristics, the required study duration was difficult to determine. Furthermore, the effect sizes of the studied variables are unknown. Previous studies indicated that 60 time points provided enough power to obtain a stable model for two endogenous variables [19], however higher numbers (>100) give more reliable results, especially if more variables are being studied [20]. As we studied more than two variables, we estimated that 150 time points would be sufficient for vector autoregressive modelling.

2.2. Web-based diary

Participants could choose the starting time of the first diary assessment, after which each subsequent assessment was provided after a three-hour interval. During the five assessments, participants indicated the severity of subjective tremor symptoms and negative affect on a 0–100 visual analogue scale (VAS), using eight items. Regarding the first item, participants indicated how much they were bothered by their tremor since the last diary entry. Regarding negative affect, we used the Positive And Negative Affect Schedule, a brief reliable and valid mood scale [21]. Participants were asked to indicate to what extent they felt distressed, upset, afraid, irritable, hostile, jittery, or nervous at the time of assessment. Negative affect (NA) was calculated as the mean of these seven emotions.

2.3. Accelerometry

Participants wore an accelerometry-based device (Consensys®, Shimmer Sensing, Dublin, Ireland) on the wrist of their most tremulous arm. Participants attached this device upon awakening and put the shimer in the charging dock before sleeping, upon which a day-specific data file was created. To ensure synchronicity at the first diary assessment, participants were asked to report the time they started to wear the accelerometer.

Data were transferred from the Shimmer to a personal computer using software provided by the manufacturer. Data were analysed in MATLAB (MathWorks, version R2016b). To calculate the subjective tremor symptoms during the period covered by the corresponding diary entry, the following procedure was followed. First, the segment length between two diary entries was determined by subtracting the diary assessment starting time from the previous diary assessment starting time. In case of the first segment of the day, the accelerometer starting time was subtracted from the first diary assessment starting time. Second, this time length was multiplied by 51.2 (the sampling frequency) to determine the segment length in samples. Third, the day-specific accelerometer file was cut into the aforementioned segments. Fourth, each segment was divided into four-second windows [22] and each four-second window was analysed using the periodogram method to determine its dominant tremor frequency [22]. If the dominant frequency was between three and eight Hertz, the window was regarded as tremor window. To calculate the tremor duration, expressed as percentage of time with tremor, we divided the number of tremor windows by the total number of windows and multiplied it by 100.

2.4. Statistical analysis

Statistical analyses were performed in R [23] unless otherwise specified. Only participants who completed at least 75% of the diary assessments were included in the data analysis to improve reliability of the VAR models [24]. Missing values of the time-series of the remaining patients were imputed using the Amelia package [25]. Imputations were performed for each patient separately, including all diary variables and polynomials of time.
2.5. Vector autoregressive modelling (individual level)

Vector autoregressive modelling (VAR) was applied to determine the temporal dynamics between negative affect and subjective/objective symptom level. For an extensive explanation of this method, see [19]. Using VAR, it is possible to determine whether a change in one variable precedes a change in another variable (lagged relationship) or whether high levels of both variables co-occur (contemporaneous relationships).

This method enabled us to determine whether an increase in negative affect preceded, followed, or was concurrent with an increase in subjective/objective tremor symptoms in the following three hours. An advantage of this method is that all three equations are estimated simultaneously, thereby accounting for reverse causation.

In formula:

\[
\begin{align*}
\text{Objective tremor symptomst} &= \text{Objective tremor symptomst} - 1 + \text{Subjective tremor symptomst} - 1 + \text{Negative affectt} - 1 + \varepsilon \\
\text{Subjective tremor symptomst} &= \text{Subjective tremor symptomst} - 1 + \text{Objective tremor symptomst} - 1 + \text{Negative affectt} - 1 + \varepsilon \\
\text{Negative affectt} &= \text{Objective tremor symptomst} - 1 + \text{Subjective tremor symptomst} - 1 + \text{Negative affectt} - 1 + \varepsilon
\end{align*}
\]

The lagged predictors (t-1) in these equations provide the time-lagged relationships among the variables. The correlations among the error terms provide the contemporaneous relationships among the variables.

In this study, we used the autovar package in R to determine the best VAR model [26]. This package uses an automated approach which closely resembles an expert’s approach [27]. Several diagnostic tests were performed to check model assumptions of stability, normality, homoscedasticity, and independence. If necessary to create a valid model, outliers were handled by including dummy variables in the model and log transform was applied against non-normality or heteroscedasticity. The best-fitting model was selected using the Bayesian Information Criterion (BIC).

We included one lag in the VAR-model, that is, the values of the previous three-hour interval. Furthermore, we included a squared trend and dummy variables for the time of the day. We standardized the data before analysing them in autovar. Standardized regression coefficients were retrieved for both the contemporaneous and lagged associations. Differences between groups in the number of patients with significant associations were compared using Fisher’s exact test.

2.6. Multilevel autoregressive modelling

We also analysed the data on the group level, using a multilevel variant of VAR [28] in SPSS (IBM corporation, version 25.0). We used multilevel versions of the same three equations as described above, but analysed these equations separately. Variables were detrended and person-mean centred before analysis [29]. To examine whether lagged associations differed by diagnosis, we added diagnosis (FT or OrgT) to the model, along with interaction terms between diagnosis and each of the time-lagged variables. We also added a random intercept and random effects for the time-lagged variables, to take individual differences in within-person associations into account [28,30]. We evaluated different (co)variance structures and selected the best fitting model using the BIC. Interaction terms were removed from the model in a stepwise fashion if nonsignificant. Residuals of the best model were saved and analysed using Pearson correlation test to determine the contemporaneous correlation among variables. This was done for the FT and OrgT group separately. Differences between correlation coefficients between groups were analysed using a Fisher r-to-z transformation.

3. Results

Forty-four participants started the 30-day study period: 17 patients with FT and 27 patients with OrgT. Of these 44 participants, 14 patients with FT and 19 with OrgT completed the study period to such an extent that data analysis was possible, which was not significantly different between groups (82% vs 70% respectively, \( P = 0.49 \)). Reasons for not completing the study period were various: insufficient wearing of the device (5 patients with OrgT, one with FT), insufficient diary entries (one with OrgT, one with FT), loss to follow-up (one with FT), device failure due to water activities (one with OrgT), and leaving the study due to time constraints (one with OrgT).

The average percentage of valid observations for those who completed the study period sufficiently was high: 90.9% for the FT group (IQR: 86.4–95.0%) and 92.5% for the OrgT group (IQR: 89.5–98.0%). In total, we collected 4759 observations from 33 participants.

Table 1 shows the demographic and clinical characteristics of those who completed the study. Patients with FT and OrgT only differed in disease duration; this was longer for OrgT patients. In all patients with FT, tremor was the predominant movement disorder type and the body part with tremor was the most affected body part. In 9 out of 14 participants with FT, there were some minor functional symptoms in other

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FT (n = 14)</th>
<th>OrgT (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) in years</td>
<td>60.4 (12.9)</td>
<td>65.9 (8.9)</td>
</tr>
<tr>
<td>Sex, n males (%)</td>
<td>8 (57%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>Educational level (0–3), mean (SD)</td>
<td>1.9 (0.9)</td>
<td>2.3 (0.8)</td>
</tr>
<tr>
<td>Employed, yes (%) (yes/no)</td>
<td>5 (35%)</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>Disease duration in years, mean (SD)*</td>
<td>7.3 (12.2)</td>
<td>18.4 (19.5)</td>
</tr>
<tr>
<td>Fahn-Tolosa-Marlin scale, mean (SD)</td>
<td>5.5 (2.4)</td>
<td>5.7 (2.4)</td>
</tr>
<tr>
<td>S-FMDRS, mean (SD)</td>
<td>10.0 (7.2)</td>
<td>7.4 (2.3)</td>
</tr>
<tr>
<td>MINI, n (%)</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1 (7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>2 (14)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Somatisation disorder</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Undifferentiated somatoform disorder</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>EQ5D (VAS 0–100)</td>
<td>71.6 (13.4)</td>
<td>74.0 (14.7)</td>
</tr>
<tr>
<td>Objective tremor symptoms, percentage of time with tremor (SD)**</td>
<td>21.6 (7.9)</td>
<td>30.7 (13.1)</td>
</tr>
<tr>
<td>Subjective symptom burden VAS 0–100 (SD)</td>
<td>38.7 (18.2)</td>
<td>28.7 (18.0)</td>
</tr>
<tr>
<td>Negative affect, VAS 0–100 (SD)</td>
<td>9.3 (7.7)</td>
<td>6.8 (7.1)</td>
</tr>
</tbody>
</table>

Educational level was classified as an ordinal variable with 0 the lowest (only primary school) and 3 the highest (University) level of education.

S-FMDRS simplified movement disorder rating scale.

MINI mini international neuropsychiatric interview. EQ5D EuroQol group 5 dimensions of health-related quality of life.

* \( P < 0.05 \) (Mann Whitney U test; *linear mixed model analysis).

FT functional tremor.

OrgT organic tremor.

VAS visual analogue scale.

SD standard deviation.
body parts as well.

The group of patients with OrgT included the following diagnoses: essential tremor (n = 7), Parkinsonian tremor (n = 6), dystonic tremor (n = 2), Holmes tremor (n = 2), enhanced physiological tremor (n = 1), and medication-induced tremor (n = 1). Patients with a Parkinsonian tremor were treated with levodopa during the assessment period, the patient with a medication-induced tremor (due to tacrolimus) did also use this medication during the assessment period. The remaining participants (including those with FT) did not receive a pharmacological treatment for their tremor.

3.1. Individual-level VAR models – Time-lagged relationships

A valid model could be created in 19 participants: six participants with FT and 13 with OrgT. In the other 14 participants, no model could be created, mainly due to violation of the assumption of a normal distribution of the residuals. The number of invalid models was not statistically different between groups (p = 0.17). Below, only the outcomes of the valid models are shown.

The time-lagged relationships between negative affect and subjective/objective tremor symptoms that were significant are shown in Fig. 1. In the majority of participants, no significant time-lagged effects were observed (12 out of 19). In participants with a significant relationship between negative affect and subjective/objective tremor symptoms, the results were mixed in both direction and size and varied considerably between participants.

3.2. Individual-level VAR models – Contemporaneous relationships

The contemporaneous relationships between negative affect and subjective/objective tremor symptom level are shown in Fig. 2 (only significant correlations shown). Most participants did not show a significant contemporaneous relationship between negative affect and objective tremor symptoms. Three FT participants and one OrgT participant showed a positive contemporaneous relationship between negative affect and objective tremor symptoms, meaning that high levels of objective tremor symptoms and high levels of negative affect co-occurred. The number of patients with a significant association between objective tremor symptoms and negative affect was not significantly different between patients with a FT and OrgT (p = 0.06).

Twelve participants showed a significant contemporaneous relationship between negative affect and subjective symptom level. This number was also not significantly different between the two groups (3 in the FT, 9 in OrgT group, p = 1.0). In 11 participants, this effect was positive, meaning that high levels of subjective symptoms co-occurred with higher levels of negative affect. In one participant (with a FT), this effect was negative, meaning that more negative affect was associated with lower subjective symptom levels in this participant. Pooled over the two groups, the number of statistically significant associations between negative affect and subjective symptom level was higher than that between negative affect and objective symptom level (12 vs 4, p = 0.02).

3.3. Multilevel autoregressive modelling

In the group-level multilevel analysis, data of all participants who completed the study could be used (14 FT, 19 OrgT). The outcomes of the three models are shown in Table 2. The multilevel autoregressive models yielded similar outcomes as the individual level VAR regarding the time-lagged effects, with some differences regarding the
contemporaneous associations. In the first model with objective tremor duration as outcome, no significant cross-lagged effects were found: previous values of subjective tremor symptoms and negative affect did not predict current objective tremor symptoms. The autoregressive effect was significant: previous values of objective tremor symptoms predicted current values of objective tremor. Also a significant main effect of diagnosis was found with objective tremor levels being higher in patients with OrgT. Interaction terms between diagnosis and lagged objective/subjective tremor symptoms or negative affect were not significant, implying that the time-lagged effects did not differ between the groups. In the other two models, with subjective tremor symptoms and negative affect as outcome, also no significant cross-lagged effects were found. Interaction terms were not significant, and there was also no significant effect of diagnosis group (FT or OrgT). Also in these models, significant autoregressive effects were found.

Table 2 also shows the results of the multilevel analysis for the random effects. In each of the three models, significant random effects were found, implying significant heterogeneity within groups. This corresponds with the heterogeneity found in the individual analysis.

Table 2. Shown are the outcomes of the multilevel models with the following dependent variables: objective tremor symptoms, subjective tremor symptoms and negative affect. For each dependent variable, the fixed and random effects are shown in terms of estimates with their standard error and P-value. Significant random effects imply significant heterogeneity within groups. Interaction terms were removed from the model if non-significant.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Objective tremor symptoms</th>
<th>Subjective tremor symptoms</th>
<th>Negative affect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>P-value</td>
<td>B (SE)</td>
</tr>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective tremor symptoms (t-1)</td>
<td>0.116 (0.022)</td>
<td>&lt;0.0005</td>
<td>-0.0061 (0.037)</td>
</tr>
<tr>
<td>Subjective tremor symptoms (t-1)</td>
<td>0.020 (0.012)</td>
<td>0.129</td>
<td>0.231 (0.028)</td>
</tr>
<tr>
<td>Negative affect (t-1)</td>
<td>0.017 (0.026)</td>
<td>0.529</td>
<td>0.059 (0.047)</td>
</tr>
<tr>
<td>Diagnosis (functional or organic)</td>
<td>9.07 (3.94)</td>
<td>0.028</td>
<td>-9.911 (6.37)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective tremor symptoms (t-1)</td>
<td>0.0075 (0.0033)</td>
<td>0.236</td>
<td>0.028 (0.010)</td>
</tr>
<tr>
<td>Subjective tremor symptoms (t-1)</td>
<td>0.0013 (0.0013)</td>
<td>0.339</td>
<td>0.017 (0.0060)</td>
</tr>
<tr>
<td>Negative affect (t-1)</td>
<td>0.0017 (0.0032)</td>
<td>0.590</td>
<td>0.020 (0.021)</td>
</tr>
</tbody>
</table>

4. Discussion

This is the first study to analyse the relationship between negative affect and subjective tremor symptoms on a day-to-day basis in individual tremor patients. Time-lagged associations were mixed and only occurred in a subset of patients with FT and OrgT. Contemporaneous associations between negative affect and subjective tremor symptoms were weak, both on the individual, as well as on the group level. These findings argue against a stronger influence of negative affect on tremor symptoms in patients with FT compared to patients with OrgT.

Time-lagged associations between negative affect and objective/subjective tremor symptoms were mixed in direction and were only present in a subset of both FT and OrgT patients. Also, multilevel autoregressive modelling showed no cross-lagged effects; only significant autocorrelation was found, i.e. previous values of a variable predicted current values. The cross-lagged effects did not differ between the
groups, but significant random effects indicated substantial heterogeneity within groups. Thus, negative affect did not seem to predict tremor symptoms any differently in patients with FT or OrgT during this 30-day study period.

Remarkably, patients with an FT presented a weaker association between negative affect and subjective tremor duration than patients with OrgT. A positive association between negative affect and subjective tremor symptoms was expected, as mood may affect symptom report [7]. One explanation might be a higher prevalence of alexithymia, the inability of individuals to identify and describe their emotions, in patients with FT [31]. The association between objective and subjective tremor symptoms is discussed extensively in another article [11].

Our study has several strengths. First, the study duration of 30 days, as far as we know the longest period of continuous symptom assessment in FMD. Second, we measured negative affect repeatedly and simultaneously with objective and subjective tremor symptoms, providing a unique opportunity to study differences between FT and OrgT in the dynamic associations between negative affect and objective/subjective tremor symptoms. Third, we were able to study patients on an individual level, thereby clearly illustrating between-person differences, which might not have been discovered using the classic group-based approach. Fourth, the analysis of the temporal dynamics between negative affect and tremor symptoms provides more information regarding the causal direction (temporal order) of the effects than traditional cross-sectional studies. Fifth, the EMA approach enables to analyse the relative strengths of various predictors or contributing factors to fluctuations in FMD symptoms. This approach might also be relevant to study other possible predictors such as autonomic imbalance [32]. Sixth, the most obvious relationship between the studied variables - the contemporaneous association between negative affect and objective/subjective tremor symptoms - was almost consistently positive, strengthening the validity of our data.

Our study has limitations as well. First, the high drop-out of (potential) participants during various stages of the study should be mentioned, which seemed to be mainly caused by the expected high study burden. However, baseline characteristics did not differ between completers and dropouts and baseline characteristics of completers did not differ between the FT and OrgT group. Second, in 14 out of 33 participants, it was not possible to create a valid individual VAR model, mainly due to a skewed distribution of negative affect. The multilevel autoregressive modelling applied to all data of the 33 participants yielded similar results as the individual VAR models with regard to the cross-lagged effects, but showed some group differences in the contemporaneous effects; the latter may suggest that the absence of group differences in the individual-level analysis was due to a power problem. Third, the group of patients with OrgT were heterogeneous in terms of aetiology. Comparison with a single type of OrgT might have shown differences between functional and non-functional tremor. The presence of patients with essential tremor and enhanced physiological tremor also explains the relative long duration of illness and relatively low FTMS score. Fourth, patients with a Parkinsonian tremor and or medication-induced tremor did use their medication (levodopa and tacrolimus respectively) during the assessment period which might have influenced their tremor severity and therefore, might have influenced the results. Fifth, patients with FT could have other minor functional movement symptoms as well and we could not exclude a correlation between negative affect and these other minor functional movement symptoms. However, no other patient with FT had tremor as their predominant movement disorder symptom, we consider this unlikely.

Future studies should investigate whether patients with a significant lagged effect of negative affect on objective and subjective symptoms could particularly benefit from psychotherapy. Furthermore, other potential contributing factors to objective/subjective tremor symptoms could be studied as well.

In summary, this study on the temporal dynamics of negative affect and objective/subjective symptoms in functional and organic movement disorders showed that the associations between negative affect and subjective/objective tremor symptoms were mostly similar in patients with FT and OrgT, thereby providing evidence against the conceptualization of tremor presence and severity as a simple reflection of affect in patients with a FT.

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Declaration of Competing Interest

Dr. Kramer, Bos, and Rosmalen have nothing to disclose.

Dr. Edwards reports that he is a medical adviser to two patient charities who support people with functional neurological disorders: FNDHope and FNDAction.

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References


