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## Similar association between objective and subjective symptoms in functional and organic tremor

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## ABSTRACT

**Background:** A previous study reported a dramatic mismatch in objectively detected and self-reported tremor duration in patients with functional tremor. As these findings have an important and widespread impact in both clinical care and research, we conducted a validation study with a longer study duration and a larger sample of patients.

**Methods:** Fourteen patients with functional tremor and 19 with organic tremor completed a 30 day study period. Objective tremor duration was recorded using a wrist-worn accelerometer. Simultaneously, participants completed a web-based diary five times a day, each time rating their symptom burden since the previous diary entry.

**Results:** Patients with functional tremor had shorter objective tremor duration compared to patients with organic tremor (21.6% vs 30.7%,  $P = 0.034$ ). A post-hoc analysis revealed the difference in objective duration was mainly due to patients with essential tremor (37.2%). Subjective symptom burden was not significantly different between functional and organic tremors (38.7 vs 28.7 on a 0–100 VAS scale,  $P = 0.138$ ). Finally, a mixed model analysis did not reveal significant differences in the association between subjective and objective tremor symptoms ( $P = 0.168$ ).

**Conclusions:** patients with functional tremor do have an objectively detectable, persistent tremor during daily life activities. Furthermore, they have a similar symptom burden and a similar association between subjective and objective tremor symptoms as patients with organic tremor.

### 1. Introduction

Functional tremor (FT) is the most common functional movement disorder. Functional movement disorders account for 1.5% of all patients seen in neurology clinics [1]. Clinically, FT is defined as a mixed resting, postural and action tremor incongruent with typical organic neurological tremors. It is suppressed by distraction [1].

The pathophysiology is only partly understood, with an important role attributed to altered attention, as well as abnormal predictions and expectations related to the symptoms, and an abnormal sense of agency [2,3]. These pathophysiological features might lead to altered symptom perception in patients with FT, and therefore, the self-reported symptom level might differ from objective recordings.

As far as we know, only one study has assessed objective and subjective symptom levels in patients with FT [4]. In this study, patients with FT dramatically overestimated their tremor duration: they

indicated they had tremor, on average, 83.5% of their waking day, while actigraphy only recorded tremor for 3.9% of the time. Patients with organic tremor (OrgT) overestimated their tremor duration to a much lesser extent (58.0% vs 24.8%). As the tremor duration in patients with FT fell within the same range as tremulous movements in healthy controls [5], these results support a widely held belief that patients with FT have almost no objectively detectable tremor when they feel not being observed [6].

However, the study by Pareés and colleagues had significant limitations that make the generalizability of the results questionable. First, only eight patients with FT completed the study. Second, patients with FT had significantly higher levels of self-reported psychopathology and lower scores on quality of life compared to the patients with OrgT [4], while previous studies reported comparable levels for both groups [7,8]. Third, the short study duration of 5 days might also be insufficient, since functional movement disorders are a heterogeneous

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group with marked inter- and intra-individual variability [1].

Thus, the aim of the current study was to compare accelerometry-based objective tremor duration and diary-based subjective symptom burden in patients with FT or OrgT. To overcome the limitations of the previous study, we included a larger sample of patients with FT or OrgT. To address the problem of heterogeneity, we studied patients on a group level and on an individual level by applying a repeated measures design, which correlated subjective and objective symptoms in individual patients. Finally, we adopted a longer study period of 30 days to account for intra-individual symptom variability.

## 2. Materials and methods

### 2.1. Patients

Patients were recruited from the outpatient clinics of the University Medical Center Groningen and the Ommelander Ziekenhuis Groep, the Netherlands, from September 2015 to December 2017. Inclusion criteria were age greater than 18 years and capable of completing an electronic diary five times a day for 30 days. To obtain a reliable and stable symptom estimate, we included only patients with a symptom duration of longer than one year, and those with a stable medication regimen (e.g. excluding those with current medical treatment with botulinum toxin as this is given every three months). We excluded patients with psychological treatment in the previous six months as this might influence symptom report [9]. In addition, patients with FT were required to meet the Fahn criteria for probable functional movement disorder [10], while patients with OrgT were required to meet the criteria for that specific tremor type as judged by a movement disorder specialist.

The study was approved by the Medical Ethical Committee (METC, no. 2015/579) of the University Medical Center Groningen. All patients received written information and provided written consent according to the declaration of Helsinki (2013).

### 2.2. Study procedure

During the inclusion visit, patients were video-recorded using a standardized video protocol, and rated according to the simplified functional movement disorder rating scale [11] and the Fahn-Tolosa-Marin scale [12]. Each video was rated by two clinicians with experience in the field of movement disorders. Ratings were averaged to provide a single rating per patient; the intra-class coefficients between raters were 0.81 (simplified functional movement disorder rating scale) and 0.68 (Fahn-Tolosa-Marin scale).

After the video-recording, participants completed questionnaires on self-efficacy [13], quality of life (EQ5D) and their global impression of the severity of the disease (patient-rated CGI [14]). They were also screened for depression, dysthymia, anxiety disorders, somatisation disorders and undifferentiated somatoform disorders using the Mini International Neuropsychiatric Interview [15,16].

### 2.3. Web-based diary

Participants completed web-based diaries five times a day for 30 days. Each participant could choose the first time in the day, after which he or she would receive diaries at 3-h intervals followed by a 12-h night interval without a diary. At each assessment point, patients received a notification by SMS with a personal link to a secure website to complete their diary. In this diary, patients were requested to indicate on a 0–100 visual analogue scale how much they had been bothered by their tremor since the last diary entry.

### 2.4. Accelerometry

The percentage of time with tremor was determined using

accelerometry. A detailed description of this method is provided as supplementary material (**supplementary file**). In short, participants wore the Shimmer3<sup>®</sup> (Shimmer Sensing, Dublin, Ireland) for 30 days on their most affected arm. The participants attached the shimmer to the dorsal side of their wrist upon awakening and recharged the device during the night, thereby creating a day specific accelerometer data file. Participants were instructed to perform their activities as usual, apart from removing the device during showering and swimming.

Accelerometer data were analysed in MATLAB (MathWorks, version R2016b). Each day-specific file was divided into segments covering the same 3-h intervals as in-between the diary entries. Subsequently, each segment was divided into windows of 4 s [17]. The dominant frequency of each 4-s window was analysed using the periodogram method, which allows discrimination between tremor and non-tremor windows [17]. If the dominant frequency was between 3 and 8 Hz, the window was regarded as a tremor window. To calculate the percentage of time with tremor, the number of tremor windows was divided by the total number of windows and multiplied by 100. This percentage of time with tremor was used in the subsequent analysis.

### 2.5. Statistical analysis

Data analysis was performed in the free-to-use statistical program R [18]. Missing data were imputed by multiple imputation using the *Amelia* package [19]. If a participant had more than 25% missing values in the diary or accelerometer, this participant was excluded from further statistical analysis, as multiple imputation only works well up to 25% missing values [20].

Differences in baseline characteristics between patients with FT or OrgT were calculated for those who completed the study sufficiently. Categorical data were analysed using Fisher's exact test, and ordinal data were analysed using the Kruskal-Wallis test.

A linear mixed-effects analysis was performed using the *lme4* package [21] to test for differences between objective or subjective symptom levels between patients with OrgT or FT. The average objective or subjective symptom level during the 30 days was used as the outcome measure. Diagnosis (FT or OrgT) was entered as the fixed effect; participant number as random effect. To test whether patients had a higher level of objective or subjective symptoms at the beginning of the study, the diary entry number (1–150) was added as a random effect, along with an interaction term between diagnosis and diary entry number to check for any differences between patients with FT or OrgT.

To test for differences between patients with FT or OrgT with respect to an association between subjective and objective tremor symptoms, we extended the linear mixed-effects analysis by adding an interaction term between diagnosis and objective symptom duration. Visual inspection of residual plots was performed to check the assumptions of homoscedasticity and normality. In the case of doubt, a sensitivity analysis, with the exclusion of outliers > 3 SD, was performed. P-values were obtained by likelihood ratio tests. All statistical tests were two-sided, unless otherwise specified. A P-value < 0.05 was considered significant.

### 2.6. Data availability

The authors can provide the raw data related to this manuscript upon request.

## 3. Results

### 3.1. Patient characteristics

In total, 176 patients received an invitation: 101 patients with OrgT and 75 with FT. Of the patients with OrgT, 27 agreed to participate, 45 declined as they considered the study would require too much effort, seven did not respond, and the remaining 22 eventually did not meet

**Table 1**  
Baseline characteristics.

	Functional tremor (n = 14)	Organic tremor (n = 19)
Age (years), mean (SD)	60.4 (12.9)	65.9 (8.9) - PT: 68.5 (6.6) - ET: 70.3 (8.1) - Others: 58.3 (7.9)
Sex, n males (%)	8 (57.1%)	- 14 (73.7%)PT: 3 (50%) - ET: 6 (85.7%) - Other: 5 (83.3%)
<b>Disease duration (years), median (IQR)</b>	<b>2.5 (1.5–5.0)</b>	<b>10.0 (5.0–33.5)</b> - PT: 6.5 (5.5–10.0) - ET: 12.0 (4.0–44.0) - Others: 18.5 (1.75–49.25)
Simplified Functional Movement Disorder Rating Scale	10.0 (7.2)	7.4 (2.3)
Fahn-Tolosa-Marin scale	5.5 (2.4)	5.7 (2.4)
General self-efficacy	31.9 (6.5)	35.1 (4.0)
<b>Patient-rated CGI</b>	<b>3.6 (1.0)</b>	<b>2.6 (1.8)</b>
Psychiatric disorders, n (%)		
- Major depressive disorder	1 (7)	0 (0)
- Dysthymia	1 (7)	1 (5)
- Anxiety disorder	2 (14)	1 (5)
- Somatisation disorder	0 (0)	0 (0)
- Undifferentiated somatoform disorder	0 (0)	0 (0)
Previous treatment		
- Tremor-specific <sup>a</sup>	10	14
- Psychologist	4	6
- Psychiatrist	3	2
EQ5D <sup>b</sup>		
Mobility	9	10
Self-care	5	1
<b>Usual activities</b>	<b>12</b>	<b>6</b>
Pain	8	8
Anxiety/depression	1	2
EQ5D (visual analogue scale)	71.6 (13.4)	74.0 (14.7)

**Table 1.** Patient characteristics of the functional and organic tremor groups at baseline for those who completed the study. Significant differences are indicated in bold ( $P < 0.05$ ).

CGI Clinical global impression.

PT Parkinsonian tremor.

ET Essential tremor.

Others: other (rare) tremor types, including enhanced physiological tremor, dystonic tremor, Holmes tremor, and medication-induced tremor.

<sup>a</sup> Tremor-specific treatment indicates whether a participant received treatment for his/her tremor.<sup>b</sup> Number of patients reporting some/severe problems.

the inclusion criteria. Of the patients with FT, 17 agreed to participate, 30 declined as they considered the study would require too much effort, 15 did not respond, and the remaining 13 eventually did not meet the inclusion criteria.

In total, 17 patients with FT and 27 patients with OrgT started the study. Of these patients, 14 with FT and 19 with OrgT completed the study with sufficient data for statistical analysis. The completion rate was not significantly different between the FT and OrgT group (82% vs 70%,  $P = 0.486$ ). The reasons for not completing the study were: insufficient use of the accelerometer (five patients with OrgT and one with FT) insufficient diary completions (one with OrgT and one with FT); device failure due to water activities (one patient with OrgT); leaving the study due to time constraints (one patient with OrgT); and loss to follow-up (one patient with FT).

**Table 1** shows the baseline characteristics of the 33 patients on whom the analyses were based. The group with OrgT patients consisted of seven patients with essential tremor, six with Parkinsonian tremor, and six with a rare tremor type. This latter category consisted of one patient with enhanced physiological tremor, two with Holmes tremor,

two with dystonic tremor, and one with medication-induced tremor. Patients with FT had a shorter disease duration, higher global impression of severity and reported more problems with daily activities.

### 3.2. Comparison between level of objective and subjective tremor symptoms

**Fig. 1** shows the results of both objective and subjective symptom registration for the FT and OrgT groups. Linear mixed-effects analysis revealed that patients with FT had a statistically significant lower level of objective tremor duration (estimate 9.03, standard error 4.06,  $P = 0.034$ ).

A post-hoc analysis revealed that essential tremor patients were the main reason for this difference (estimate 15.64, standard error 5.19,  $P = 0.005$ ). The objective tremor duration of patients with FT was comparable to that in patients with Parkinsonian tremor (estimate 5.14, standard error 5.47,  $P = 0.354$ ) and the remaining rare tremor types (estimate 5.20, standard error 5.47,  $P = 0.349$ ). The intercept of this model was 21.64, meaning that patients with FT had tremor, on average, 21.6% of the time; patients with essential tremor, 37.3% of the time; patients with Parkinsonian tremor, 26.8% of the time; and patients with a rare tremor type, 26.8% of the time. A time-varying coefficient was significantly associated with objective tremor duration (estimate  $-0.012$ , standard error 0.005,  $P = 0.013$ ), meaning that, on average, participants had an absolute decrease in percentage of time with tremor of 1.87 at the end of the study. An interaction term to account for any differences between patients with FT or OrgT was not significant (estimate 0.007, standard error 0.007  $P = 0.250$ ).

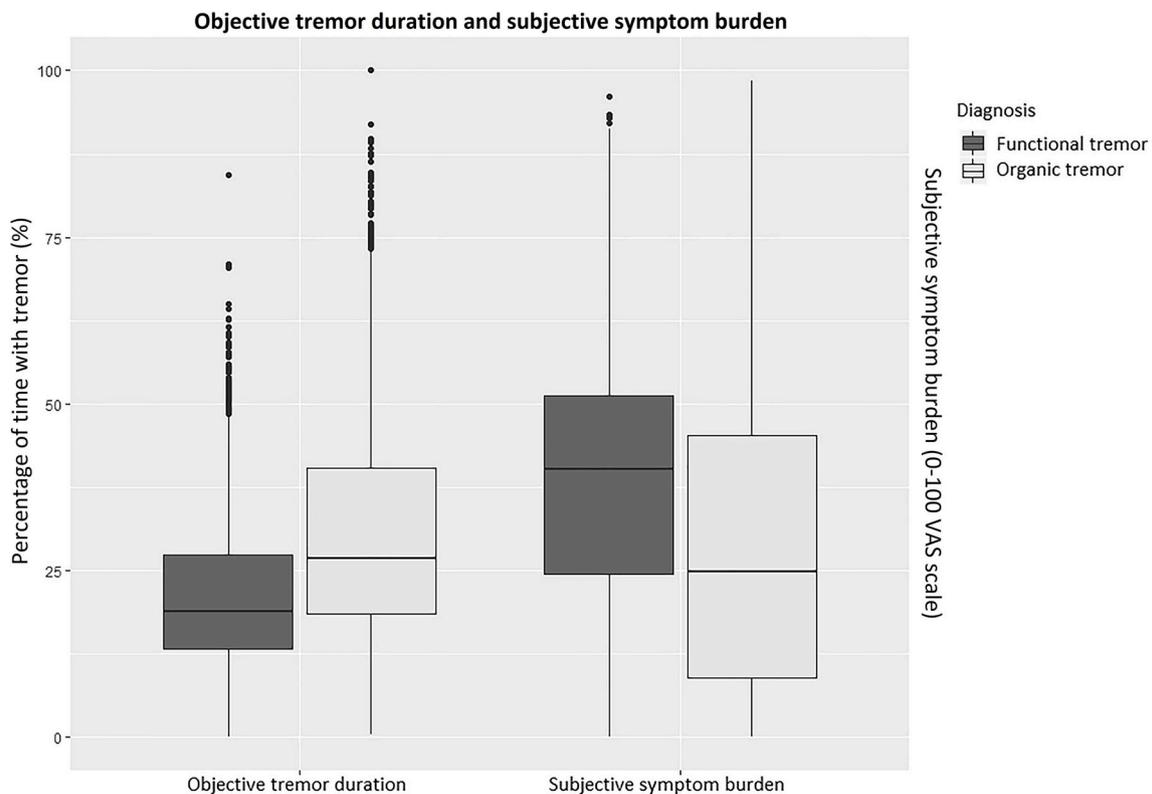
Subjective symptom burden was not significantly different in patients with a FT or OrgT (estimate  $-10.00$ , standard error 6.56,  $P = 0.138$ ). The intercept of this model was 38.72, meaning that patients with a FT and OrgT, on average, reported a subjective symptom burden of 38.72 and 28.72, respectively (on a 0–100 VAS scale). A time-varying coefficient was not significantly associated with subjective symptom burden (estimate  $-0.009$ , standard error 0.007,  $P = 0.230$ ), while an interaction term between this time-varying coefficient and diagnosis was significant (estimate 0.021, standard error 0.009,  $P = 0.023$ ), meaning that patients with OrgT had slightly higher symptom burden at the end of the study.

Objective tremor duration was significantly associated with subjective symptom burden (estimate 0.086, standard error 0.035,  $P = 0.014$ ), while diagnosis was not a significant factor (estimate  $-8.95$ , standard error 6.60,  $P = 0.171$ ), nor was the interaction term ‘diagnosis\*objective symptoms’ (estimate  $-0.060$ , standard error 0.043,  $P = 0.168$ ).

## 4. Discussion

We measured objective tremor duration and subjective symptom burden in patients with FT or OrgT for 30 days in their home environment. In contrast to previous findings, we detected a considerable level of objective tremor duration in patients with FT, equivalent to 21.6% of the time. Patients with OrgT had a statistically significant higher level of objective tremor duration (30.7% of the time): this was mainly due to patients with essential tremor. Furthermore, subjective symptom burden was not statistically different between patients with FT or OrgT. Finally, we did not find a difference between the FT and OrgT groups with respect to the association between subjective and objective symptoms.

In patients with FT, we found an objective time with tremor of 21.6%, while a previous study only found 3.9% [4]. One possible explanation for this difference is the use of a different tremor algorithm. In our current study, we used a peak-frequency detection method in 4-s windows, which was validated in both patients with FT and OrgT [17]. In contrast, the study by Pareés and colleagues used a variety of parameters (e.g. number of zero crossings) in 2-s windows, which differed between healthy controls and Parkinson's disease patients in a previous



**Fig. 1.** This box-and-whisker plot contains the median, interquartile range, and data range of objective and subjective tremor symptoms in the functional and organic tremor groups. Objective tremor symptoms is assessed by accelerometry and expressed as percentage of time with tremor; subjective tremor symptoms is expressed as subjective symptom burden on a 0–100 VAS scale.

study [4,5]. As the latter method used a fixed set of parameters [5], it might detect tremor appropriately in diseases with a stable tremor generator, such as Parkinson's disease [22], but not in FT, which is characterized by considerable frequency variation [23]. Therefore, our method might detect tremor in patients with FT more accurately due to its frequency-adaptive nature.

Another explanation might be the longer study duration of 30 days, as far as we know, the longest study period of objective and subjective tremor recordings. A long period might be necessary to obtain reliable symptom estimates in FT, which is known for its spontaneous variability [23,24]. Furthermore, we cannot exclude the possibility that we underestimated objective tremor duration in both the functional and organic tremor groups, as our tremor algorithm had high specificity (0.96) but only reasonable sensitivity (0.70) compared to the clinical assessment by two neurophysiologists [17]. Also, the tremor algorithm selected time windows with a dominant signal frequency between 3 and 8 Hz. Although the tremor types in our study usually have a dominant frequency in this bandwidth [25,26], we cannot exclude the possibility that some patients did have time periods with a higher tremor frequency than 8 Hz, thereby underestimating the objective tremor symptoms in those participants.

Patients with OrgT, as a group, had a higher level of objective tremor duration compared to patients with FT (30.7% vs 21.6%), a finding similar to the study by Pareés et al., although with a much smaller difference between the FT and OrgT group (24.8% vs 3.9%) [4]. In a subgroup analysis, the difference between FT and OrgT was mainly explained by patients with essential tremor, which accords with a previous study in which patients with essential tremor reported more time with tremor than patients with Parkinson's disease [27]. We cannot exclude the possibility that a study with a larger sample size might have detected significant differences between patients with functional tremor, Parkinsonian tremor, and rare tremor types. However, if the effect size estimates of the previous study [4] were accurate,

even a smaller sample should have been sufficient to detect significant differences between functional tremor and any organic tremor type.

We detected a similar level of subjective symptom burden in patients with FT or OrgT. In our study, we asked participants to rate their subjective symptom burden since the previous diary entry, which is slightly different from the previous study, which requested participants to rate the percentage of time they had tremor [4]. We felt that asking patients to indicate their symptom burden more accurately reflects clinical practice. Another explanation is the comparable level of psychopathology and quality of life between patients with FT or OrgT in our study, which accords with previous literature that describes a similar loss of quality of life [8]. In the study by Pareés et al., the patients with FT had a much higher level of psychopathology and a lower quality of life compared to their organic tremor counterparts [4]. As mood affects symptom report [28], it is possible that the higher subjective symptom levels in the previous study may be explained, at least partly, by the higher level of psychopathology in the patients with FT compared to the patients with OrgT. Furthermore, this comparable level of psychopathology cannot simply be attributed to the exclusion of participants with psychological treatment in the previous six months, as this was only relevant in very few potential participants.

In contrast to the previous study, we did not find a difference in the association between subjective and objective symptoms in patients with FT compared to patients with OrgT [4]. One of the reasons for this is the higher level of objective tremor duration in patients with FT, a second reason is the slightly different scale for detecting subjective symptom levels, while a third reason is the similar levels of psychopathology in patients with FT or OrgT. These results have implications for the suggested pathophysiology in FT, especially regarding the hypothesis of abnormal prior beliefs and attention [2,3]. As we found a similar association between subjective and objective tremor symptoms in both groups, it seems likely that the prior beliefs and attention to tremor symptoms in patients with FT are still connected to real world data.

We acknowledge that our study has its own limitations. First, we had relatively low participation and completion rates (26.5% and 70.5% respectively). This was probably due to the long study duration of 30 days and, therefore, our study included motivated participants. However, the baseline characteristics of patients with FT or OrgT were mostly similar and, therefore, we have no indication that the relatively high drop-out affected the study outcome. Second, the percentage of time with tremor might not be the only parameter contributing to symptom burden. For example, tremor amplitude and tremor frequency might be just as relevant, and therefore, should be included in future studies. Third, as participants wore an accelerometer and received frequent diary prompts, they might have felt they were under heightened observation, and therefore, had more attention towards their tremor symptoms, and this might have affected outcome. We hypothesized if this were true, participants might show a decrease in tremor symptoms during the study period as they would get more used to the study design. As this decrease (in objective tremor symptoms) was similar in the OrgT and FT groups, we consider it unlikely that this affected study outcome.

As we mainly detected similarities between patients with FT or OrgT, our findings have important implications for clinical practice and the design of future studies. First, patients with FT do have tremor for a considerable percentage of the time and have no substantial mismatch between objective and subjective symptom burden, therefore, they cannot be regarded as ‘merely having a perception problem’ or ‘stop trembling as soon as they leave the hospital’. Therefore, in clinical practice, it is important to accept that the tremor is real and not imagined or ‘all in the mind’ [29]. Second, this similar association between objective/subjective tremor symptoms and the similar level of psychopathology in patients with FT or OrgT reinforces the need to diagnose FT using positive criteria like entrainment or distraction, thereby omitting the need for “psychogenic” criteria [30]. Third, the finding of a considerable level of objective tremor duration in patients with FT provides a unique opportunity to study functional movement disorders and, perhaps by inference, other functional neurological disorders. For example, as long-term recordings of both objective and subjective symptom levels are achievable, it might be possible to study factors influencing objective and subjective symptom levels on a daily basis at an individual level, thereby gaining valuable knowledge about the mechanisms underlying functional neurological symptoms.

## 5. Contributors

GK: Study design, acquisition and analysis of data, manuscript drafting, study coordination. ZTDV, HSAL, RB, MS, AMMS: Acquisition and analysis of data, reviewing the manuscript. JWJE, NMM: reviewing the manuscript, reviewing statistical methods. JGMR, MAJT: study design, study coordination, article drafting, reviewing of the manuscript.

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## Competing interest

None declared.

## Patient consent for publication

Obtained.

## Ethics approval

Ethics committee of the University Medical Center Groningen.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.05.026>.

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