ARTICLE

The nature of postural tremor in Parkinson disease

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Abstract

Objective

To disentangle the different forms of postural tremors in Parkinson disease (PD).

Methods

In this combined observational and intervention study, we measured resting and postural tremor characteristics in 73 patients with tremulous PD by using EMG of forearm muscles. Patients were measured both "off" medication (overnight withdrawal) and after dispersible levodopa-benserazide 200/50 mg. We performed an automated 2-step cluster analysis on 3 postural tremor characteristics: the frequency difference with resting tremor, the degree of tremor suppression after posturing, and the dopamine response.

Results

The cluster analysis revealed 2 distinct postural tremor phenotypes: 81% had re-emergent tremor (amplitude suppression, frequency difference with resting tremor 0.4 Hz, clear dopamine response) and 19% had pure postural tremor (no amplitude suppression, frequency difference with resting tremor 3.5 Hz, no dopamine response). This finding was manually validated (accuracy of 93%). Pure postural tremor was not associated with clinical signs of essential tremor or dystonia, and it was not influenced by weighing.

Conclusion

There are 2 distinct postural tremor phenotypes in PD, which have a different pathophysiology and require different treatment. Re-emergent tremor is a continuation of resting tremor during stable posturing, and it has a dopaminergic basis. Pure postural tremor is a less common type of tremor that is inherent to PD, but has a largely nondopaminergic basis.

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Glossary

BIC = Bayesian Information Criterion; **EDC** = extensor digitorum communis; **ET** = essential tremor; **FCR** = flexor carpi radialis; **MDS-UPDRS** = Movement Disorders Society Unified Parkinson's Disease Rating Scale; **PD** = Parkinson disease; **TFR** = time frequency representations.

Parkinsonian tremor classically occurs at rest, but many patients (46%–93%)[1–3] also have postural tremor. The exact phenomenology and etiology remain unclear.[4] This is largely because postural tremor in Parkinson disease (PD) is highly heterogeneous in appearance and origin.[5] We aim to disentangle the different postural tremors in PD, using a combination of clinical, electrophysiologic, and pharmacologic tremor features.

The most common postural tremor in PD is re-emergent tremor, which occurs in approximately two-thirds of patients,[3,6] and has been suggested to be an "extension of the resting tremor that has reset itself after a brief latency."[7] However, other postural tremors also occur in PD.[5] First, given the high prevalence of dystonic symptoms in PD[8] and the clear link between idiopathic dystonia and tremor,[9] some postural tremors in PD may have a dystonic origin. Second, given the increased co-occurrence of essential tremor (ET) and PD,[10] it is conceivable that patients with PD with a bilateral postural arm tremor also have ET. Finally, since 8% of healthy elderly people have an enhanced physiologic tremor that is electrophysiologically similar to mild ET,[11] a comparable proportion of patients with PD may also have this type of tremor.

The correct classification of postural tremors in PD is important for 2 reasons. First, similar to ET—which has been called a "family of tremors"—pooling of different postural tremors may lead to inconsistent findings across studies.[12] Second, the correct postural tremor classification has clinical relevance, since different postural tremors may respond differently to pharmacologic treatments.[4] Specifically, while re-emergent tremor likely responds to dopaminergic medication, other postural tremors may rather respond to β-blockers or primidone, given its phenomenologic resemblance to ET.[13–15]

We investigated the clinical phenomenology and dopaminergic basis of PD postural tremor by considering 3 important tremor characteristics: (1) the frequency difference with resting tremor (which is larger when 2 tremors have a different origin)[16]; (2) the onset of tremor after posturing (which is typically delayed in re-emergent tremor)[6,17]; (3) the response of tremor to levodopa. We used an automated cluster analysis, which was clinically validated, to dissect postural tremor in 2 phenotypes: re-emergent tremor and "pure postural tremor." Furthermore, we compared clinical characteristics between both tremor phenotypes.

Methods

Study population

We included 77 patients (55 men; mean age 63 years; range 38–81 years) with idiopathic PD and a history of resting tremor, diagnosed according to the UK Brain Bank criteria by an experienced movement disorders specialist. Patients with neurologic comorbidity, signs of psychogenic tremor, or substantial cognitive impairment (Mini-Mental State Examination score <24 or Frontal Assessment Battery <12) were excluded. In total, 4 patients were excluded: 1 patient due to signs of psychogenic tremor and 3 due to noisy data recordings. This resulted in 73 patients for our main analyses (table 1).

Standard protocol approvals, registrations, and patient consents

The study was conducted according to the standards of the 1964 Declaration of Helsinki and was approved by the local ethics committee. Before inclusion, all patients provided their written consent.

Design

Patients were measured twice on one day at the Radboud University Medical Center: first in a practically defined "off" state (after overnight fasting; >12 hours after the last dose of dopaminergic medication; >24 hours after anticholinergics or β-blockers)[18] and then "on" levodopa (after 200/50 mg dispersible levodopa-benserazide[19]; on average 44 minutes after intake [range 32–59], when patients experience the maximal benefit of the levodopa treatment). In addition, 10 mg domperidone was given (to reduce side effects and enhance gastrointestinal absorption). Measurements took place from July 2014 until February 2016.

Clinical tremor assessment

Patients were clinically assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Hoehn & Yahr Scale, and Fahn-Tolosa-Marin Tremor Rating Scale.[20] We used item 15 of the MDS-UPDRS part III for postural tremor and part 17 for resting tremor.

Electrophysiologic tremor assessment

Patients lay on a bed during all electrophysiologic measurements, while their forearms rested on a pillow, thereby leaving the hands hanging unsupported to measure maximum tremor amplitude. Four conditions were used: rest tremor (rest) and 3 postural tremor measures (posh, post, and weight). For the postural conditions, patients received a verbal start signal, after which they (1) extended their wrists/fingers into a horizontal plane (posh), (2) lifted and stretched out both arms at the shoulder level into the horizontal plane with extension of the wrists/fingers (post), and (3) same as post but while wearing

Table 1 Clinical characteristics

Characteristic	Average (n = 73 patients)
Disease duration, y	3.0 (4.1)
H&Y	2 (1–3)
FAB	17 (13–18)
MMSE	29 (24–30)
LEDD	502 (0–1,500)

MDS-UPDRS	Off	On	*p* Value
Total	44.4 (15.9)	26.3 (12.2)	<0.001
Non-tremor (B + R)	22.6 (9.1)	13.3 (7.3)	<0.001
Axial	4.1 (2.5)	2.7 (2.2)	<0.001
Rest tremor			
Most	4.5 (1.6)	2.7 (1.8)	<0.001
Least	2.1 (1.9)	1.2 (1.5)	<0.001
Postural tremor			
Most	1.9 (1.0)	1.0 (1.0)	<0.001
Least	0.9 (0.8)	0.5 (0.7)	<0.001
Kinetic tremor			
Most	1.0 (1.0)	0.6 (0.7)	<0.001
Least	0.6 (0.7)	0.4 (0.5)	0.001
TRS			
Part AB	25.8 (12.2)	15.1 (8.8)	<0.001
Part C	6.4 (5.2)	NA	NA

Abbreviations: B + R = limb bradykinesia and rigidity (sum of MDS-UPDRS items 3–8); FAB = Frontal Assessment Battery; H&Y = Hoehn & Yahr; LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; TRS = tremor rating scale.
Disease characteristics of all patients are shown (H&Y: median [minimum and maximum scores]; LEDD: mean [range]; other measures: mean [SD]). Disease severity of each patient was measured using H&Y stages (maximum 5) and the MDS-UPDRS part III (maximum score is 132). MDS-UPDRS scores are compared between sessions (paired *t* test, 2-tailed). Axial referrers to axial symptoms (sum of MDS-UPDRS items 9–14). Rest tremor refers to MDS-UPDRS item 17 and postural/kinetic tremor to items 15 and 16 (most and least affected hand). In addition, the Fahn-Tolosa-Marin TRS[20] was used to compare tremor characteristics between sessions. The FAB was used as a measure of cognitive function (maximum is 18). Duration was defined as the time since subjective symptom onset (in years). Use of dopaminergic medication was objectified by calculating the LEDD. Seven patients did not use any Parkinson disease medication. The others used dopaminergic medication (levodopa and dopamine agonists) and 2 patients used anticholinergics. Furthermore, 5 patients used β-blockers for hypertension or tremor.

a 0.5-kg wristband (weight). Each condition lasted 1 minute and was repeated 3 times for rest, 2 times for posh/post, and once for weight. Trials were averaged per condition.

Tremor characteristics were quantified using EMG. We placed surface electrodes (sampling rate 512 Hz) on the tendons (reference) and belly (signal) of the extensor digitorum communis (EDC) and flexor carpi radialis (FCR) muscles. Preprocessing included (1) detrending to remove temporal drifts; (2) bandpass filtering between 20 and 200 Hz to only include muscle signal; (3) rectification to capture the frequency of muscle bursts; (4) high-pass filtering using a threshold of 2 Hz to remove slow frequency drifts; (5) averaging across EDC and FCR to obtain 1 EMG signal (after confirming that tremor characteristics were highly correlated between both muscles; appendix e-1 and e-2, links.lww.com/WNL/A294; figure e-1, links.lww.com/WNL/A295).

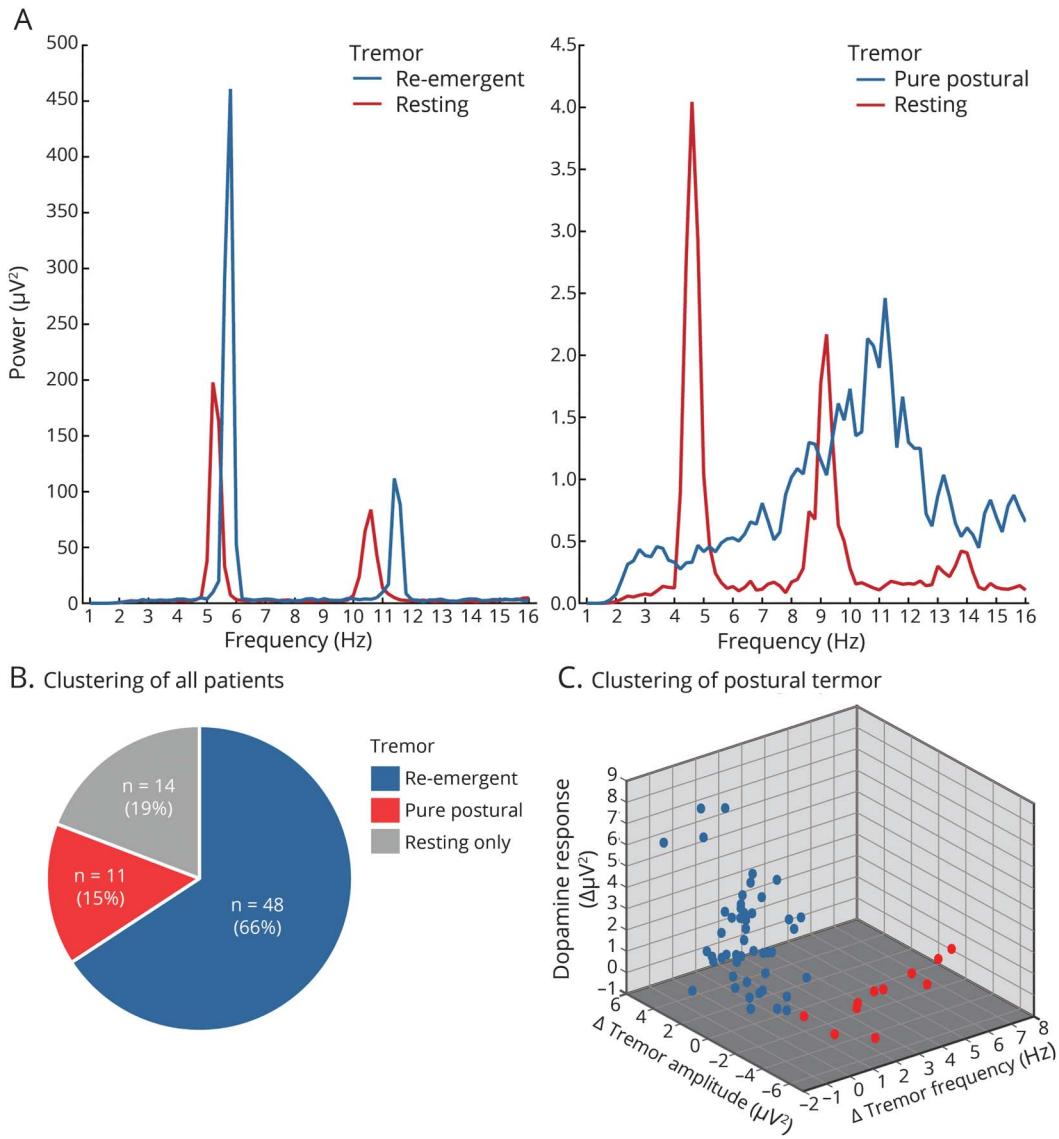
Using FieldTrip,[21] we calculated time frequency representations (TFR) between 1 and 16 Hz in steps of 0.1 seconds using a Hanning taper with a duration (time interval) of 5 seconds, resulting in a 0.2-Hz spectral resolution. Thus, we determined tremor frequency in rest and postural conditions (figure 1A). Subsequently, we repeated our TFR analyses using a Hanning taper with a duration of 2 seconds, resulting in a 0.5-Hz spectral resolution and a higher temporal resolution. This allowed us to test the effect of wrist extension on tremor power. We applied a log-transformation, given the log-linear relationship between tremor power and clinical rating scales.[22,23]

Classification of tremor

To classify postural tremor, we selected 3 continuous variables derived from our electrophysiologic measurements. First, we calculated the difference in frequency between postural and rest tremor (Δ frequency, posh − rest). This criterion is based on the 1998 Consensus Statement of the Movement Disorders Society, which considers postural tremor separate from resting tremor if their frequencies differ more than 1.5 Hz.[16] Second, we calculated the effect of wrist extension on tremor amplitude (Δ amplitude [mean power −3 until −1 second before onset posture] − [mean power 1 until 3 seconds after onset posture]). This criterion is based on the finding that PD resting tremor is suppressed by a voluntary action, and often emerges shortly afterwards during stable posturing.[6,17] Third, we calculated the dopamine response of the postural tremor, i.e., the difference between the power at each participant's individual peak tremor frequency in the "off" minus "on" state. This criterion is based on reports that, on average, re-emergent tremor responds to dopamine, while some action tremors do not.[15,24]

Next, we used a 2-step clustering analysis (IBM [Armonk, NY] SPSS Statistics 22) to distinguish between different types of postural tremor, based on these 3 variables. This analysis identifies clusters using nonhierarchical preclustering and subsequently traditional hierarchical methods for definitive clustering. We calculated the log-likelihood of each model using the Bayesian Information Criterion (BIC) with no constraint on the number of clusters possible. Finally, we manually validated the outcome of the cluster analysis by characterizing the postural

Figure 1 Example power spectra and participant classification



Power spectrum example of a patient with a re-emergent tremor (left panel in A) and an example of a patient with pure postural tremor (right panel in A; downscaled with factor 3 for illustration purposes). (B) Overview of all patients demonstrating the number of patients without a postural tremor (gray piece) and division of patients with a postural tremor according to the 2-step clustering (blue and red pieces). (C) Values of the variables used for clustering. Blue data points indicate patients from the re-emergent tremor cluster, whereas red indicates patients from the pure postural tremor cluster.

tremor in each patient, using the 3 measures above in a blinded fashion (appendix e-3, links.lww.com/WNL/A294; table e-1, links.lww.com/WNL/A296).

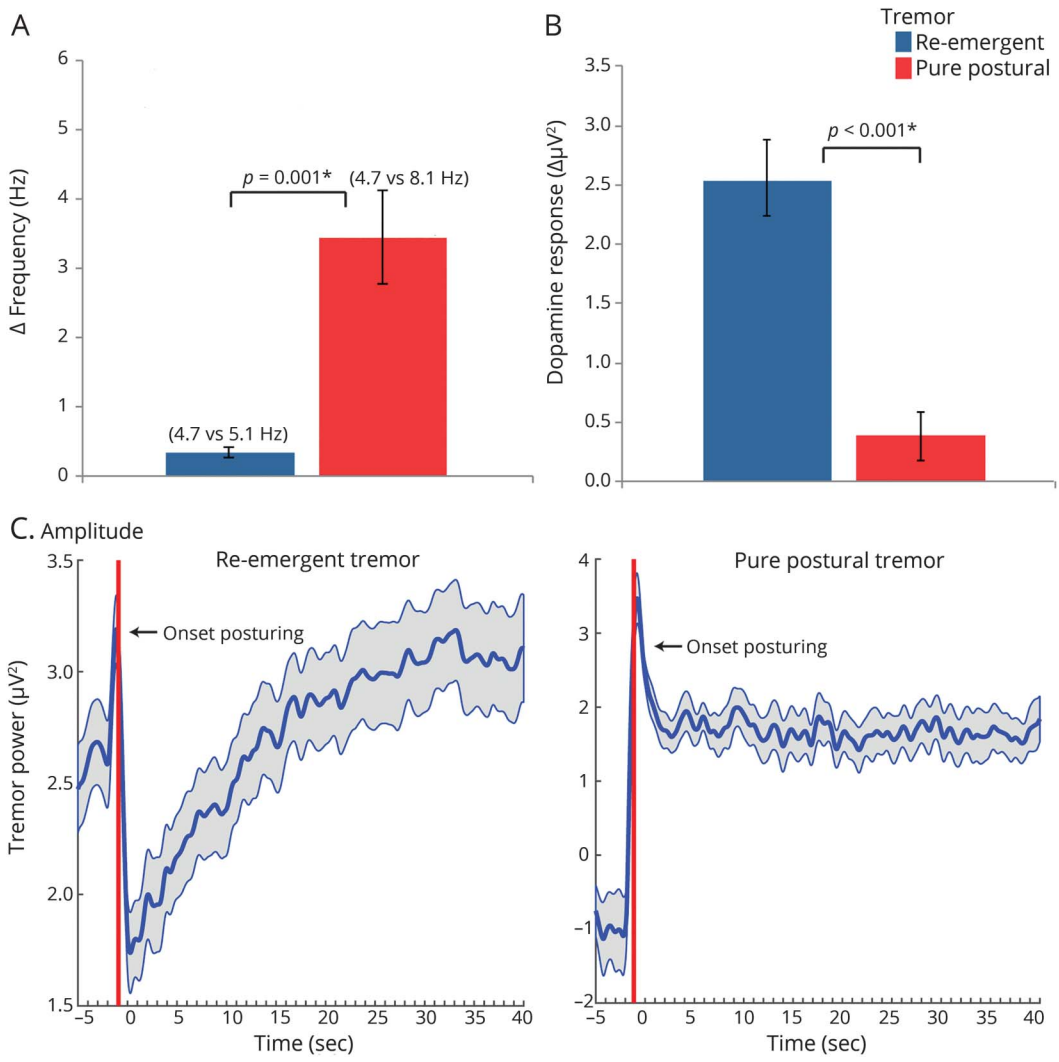
Statistical comparisons

First, we compared the tremor measures outlined above between the 2 subgroups resulting from the cluster analysis, i.e., the difference between the power at each participant's individual peak tremor frequency in the "off" minus "on" state. Thus, we compared Δ frequency, Δ amplitude, and the dopamine response between subgroups using 2-sample *t* tests (figure 2, A and B). The transition from resting tremor to postural tremor (from −5 to +40 seconds relative to wrist extension) is shown in figure 2C.

Second, we tested the hypothesis that in group 1 resting tremor and postural tremor share the same pathophysiology. Thus, in these patients we correlated the (log-transformed) power and dopamine response of rest tremor vs postural tremor (figure 3, B and C), while controlling for "off"-state tremor power (partial correlation). We also tested for differences in the dopamine response between postural and rest tremor, using repeated-measures analysis of variance.

Third, we tested several hypotheses regarding the pathophysiology underlying postural tremor in group 2. We first tested whether weighing (post vs weight condition, paired *t* test) decreased tremor frequency, since this would point towards a peripheral rather than a central origin.[11] Next, we tested whether

Figure 2 Tremor subgroup comparison



The difference between re-emergent and pure postural tremor for Δ frequency (A; postural minus rest tremor frequency), dopamine response (B; mean tremor power in "off" minus "on"), and the effect of wrist extension on tremor amplitude (C; log-transformed tremor power at individual tremor frequency ± 1.5 Hz to accommodate slight changes in tremor frequency).

the occurrence of specific clinical characteristics (i.e., dystonia, history of ET, disease severity) differed between both subgroups.

Results

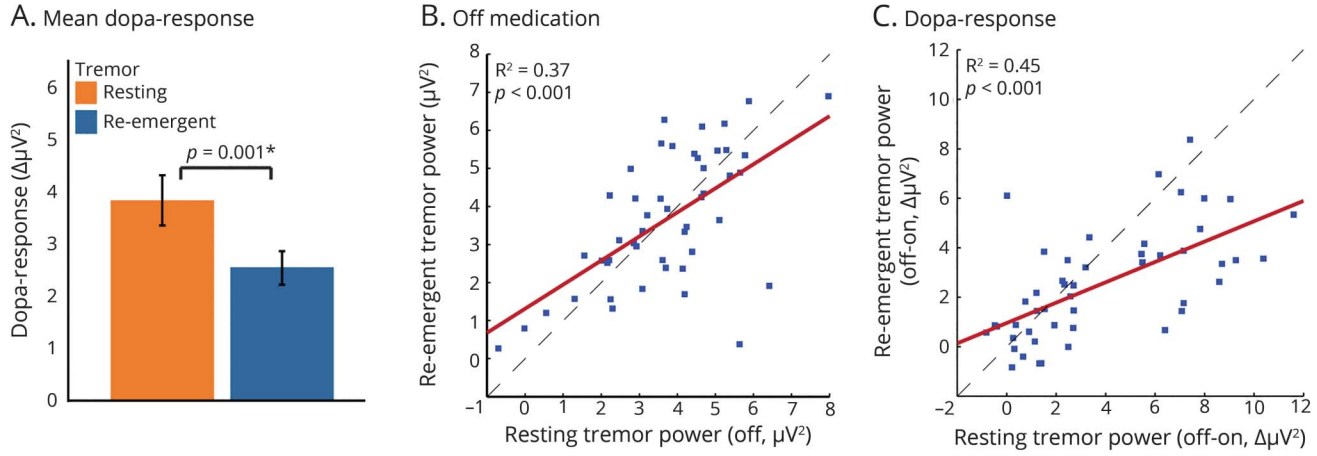
Prevalence and classification of postural tremor

Out of the 73 included patients, 60 patients (82%) had a postural tremor (indicated by a peak in the power spectrum). One of the 60 patients had a very subtle rest tremor of the thumb and not the EDC/FCR muscle, so we excluded him from further analyses.

The cluster analysis revealed 2 separate groups of patients with very distinct postural tremors. The 2 clusters significantly differed on each of the 3 tremor characteristics (table 2). In cluster 1 (n = 48; 81%), there was a small but significant difference between the frequency of resting tremor and postural tremor (figure 3A); tremor amplitude significantly decreased after posturing (average duration from posture onset to time point where postural tremor power exceeded resting tremor power[6]: ±15 seconds, figure 2C), and levodopa significantly reduced tremor power (figure 2B). In cluster 2 (n = 11; 19%), there was a much larger difference between the frequency of resting tremor and postural tremor (figure 2A); there was no amplitude reduction upon posturing (figure 2C), and no dopamine response (figure 2B). Based on these findings, cluster 1 can be classified as re-emergent tremor[6] and cluster 2 as pure postural tremor.[16] It should be noted that patients with re-emergent tremor had a variable dopamine response (figure 1C). Thus, re-emergent tremor was not dopamine-responsive in all patients.

The evidence for a 2-cluster model was very strong: the Δ BIC was >10 for a 2-cluster model compared to

Figure 3 Rest vs re-emergent tremor



(A) Dopamine response (on the y-axis, tremor power "off" minus "on," ± SEM) for resting and re-emergent tremor, with a larger dopamine response for rest tremor than for re-emergent tremor (same patient group). (B, C) Correlation of (log-transformed) tremor power (B) and dopamine response (log-transformed tremor power "off" minus "on" corrected for absolute "off" state tremor power, C) between resting tremor (x-axis) and re-emergent tremor (y-axis). The dashed lines indicate a reference line when x = y.

a one-cluster model, and compared to any n-cluster model (with n > 3). This means that our model was >99% more likely than any other model.[25] The Δ BIC for a 2-cluster model compared to a 3-cluster model was 5.0, meaning that our model was 75%–95% more likely.[25] Exploration of the 3-cluster model revealed that this procedure divided cluster 1 (re-emergent tremor) into 2 subgroups: a dopamine-resistant group (n = 25; dopamine response 0.71 ± 0.17) and a dopamine-responsive group (n = 24; dopamine response 4.35 ± 0.35; 2-sample *t* test: $p < 0.001$) (see appendices e-1–e-3, links.lww.com/WNL/A294). This fits with the idea that the classical PD tremor is sometimes dopamine-resistant.[26]

The automated clustering was manually validated: 46 patients were classified as re-emergent and 13 as pure postural tremor (93% accordance with 2-cluster model; statistical comparisons described above were replicated). Differences could be explained by the strict cutoff values used for manual classification (see appendices e-1–e-3).

Comparison between re-emergent tremor and rest tremor

Within group 1, we compared resting tremor and re-emergent tremor characteristics. The power and dopamine response were highly correlated (power: $R^2 = 0.37$; $p < 0.001$, figure 3B; dopamine response: $R^2 = 0.45$; $p < 0.001$, figure 3C), which may suggest a common mechanism underlying both tremor types. However, there were also important differences: the dopamine response of resting tremor was significantly higher than that of re-emergent tremor (interaction between tremor type and levodopa; $F_{1,47} = 11.7$, $p = 0.001$; figure 3A). Furthermore, re-emergent tremor frequency was slightly (but significantly) higher than resting tremor frequency (4.7 vs 5.1 Hz, $p < 0.001$).

The nature of pure postural tremor in PD

First, we tested whether pure postural tremor may have a peripheral origin. Postural tremor frequency was stable across conditions (wrist extension [posh; frequency 8.1 ± 0.6 Hz] vs lifting of the arms [post; frequency 8.5 ± 0.7 Hz]; paired *t* test: t[10] = 1.4, $p = 0.19$). Importantly, weighing did not significantly alter tremor frequency (weight: 8.1 ± 0.5 Hz; difference between post vs weight: t[10] = 1.2, $p = 0.27$). This suggests that pure postural tremor has a central rather than a peripheral origin.[11]

Second, we tested whether pure postural tremor was related to specific clinical symptoms. There were no significant differences in the occurrence of dystonic posturing or a (family) history of ET (table 2). This indicates that pure postural tremor is not ET co-occurring in PD, or a form of dystonic tremor. The total MDS-UPDRS score and disease duration were significantly lower in the pure postural group (table 2). This suggests that pure postural tremor is a feature of early PD, or that a more severe tremor (such as re-emergent tremor) can "swamp" subtler postural tremors. Accordingly, the MDS-UPDRS postural and rest tremor scores were lower in the pure postural group (table 2).

Discussion

We investigated the nature of postural tremor in PD. The data show 2 distinct postural tremor phenotypes: re-emergent tremor (81%) and pure postural tremor (19%). Re-emergent tremor had a slightly higher frequency than resting tremor, a delayed onset after posturing, and on average a clear dopamine response (although individual responses varied considerably). Pure postural tremor had a higher frequency than resting tremor, occurred immediately after posturing, and did

Table 2 Clinical and electrophysiologic features per tremor subgroup

Clinical features	Group 1 (re-emergent, n = 48)	Group 2 (pure postural, n = 11)	Two-sample *t* Test
Dystonia	17 (35%)	3 (27%)	NS
Preexisting tremor	1 (2%)	2 (18%)	NS
Family history	12 (25%)	5 (45%)	NS
Male sex	35 (72%)	10 (91%)	NS
Age, y	62.1 (38–81)	58.4 (43–67)	NS
Hoehn & Yahr	2.0 (1–3)	2.0 (1–3)	NS
Duration, y	4.2 (0–26)	1.2 (0–5)	t(57) = 2.1, $p = 0.04$
Patients with dyskinesias	12 (25%)	1 (9%)	NS
MDS-UPDRS total "off"	48.1 (20–84)	29.5 (18–54)	t(57) = 3.84, $p < 0.001$
MDS-UPDRS total "on"	28.4 (10–57)	17.6 (4–34)	t(57) = 2.7, $p = 0.008$
MDS-UPDRS rest tremor both arms "off"	4.8 (1–8)	2.9 (1–5)	t(57) = 3.28, $p = 0.002$
MDS-UPDRS rest tremor both arms "on"	6.8 (0–15)	4.1 (0–9)	t(57) = 2.1, $p = 0.04$
MDS-UPDRS postural tremor both arms "off"	3.4 (1–6)	2.0 (0–5)	t(57) = 2.79, $p = 0.007$
MDS-UPDRS postural tremor both arms "on"	1.77 (0–7)	0.6 (0–2)	t(57) = 2.4, $p = 0.02$

Electrophysiologic features	Group 1 (re-emergent)	One-sample *t* test	Group 2 (pure postural)	One-sample *t* test	Two-sample *t* test
Δ Frequency	0.4 ± 0.07	t(47) = 4.9, $p < 0.001$	3.5 ± 0.7	t(10) = 5.0, $p < 0.001$	t(10) = 4.5, $p = 0.001$
Δ Amplitude	1.2 ± 0.3	t(47) = 4.8, $p < 0.001$	-3.6 ± 0.4	t(10) = −8.2, $p < 0.001$	t(17) = 9.5, $p < 0.001$
Dopamine response	2.5 ± 0.3	t(47) = 8.0, $p < 0.001$	0.4 ± 0.2	NS	t(52) = 5.7, $p < 0.001$

Abbreviation: MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale.
For the clinical features, mean values plus their range or percentage are displayed. The electrophysiologic features are displayed as mean ± standard error of the mean. The dopamine response is calculated as the mean power in "off" minus the mean power in "on." This means a positive value indicates a decrease in tremor after dopaminergic medication. Dystonia refers to observed dystonic symptoms during "off" (n = 11) or "on" (n = 8), as well as clinical reports of dystonic symptoms in the patient's history or during previous evaluations (n = 10).

not respond to levodopa. Furthermore, pure postural tremor was not associated with dystonic symptoms or a history of ET. Taken together, we propose that both postural tremor types are inherent to PD, have distinct but central origins, and require different treatment.

The prevalence of re-emergent tremor (81% of patients with postural tremor) is similar to estimates from previous electrophysiologic studies (67%–75%),[6,27] although one study reported a much lower prevalence (38%).[28] It is, however, higher than estimates from clinical studies (30%–34%)[3,29]—which report a higher prevalence of non-re-emergent tremor (58%–59%).[28,29] This discrepancy may be explained by reduced ability to clinically detect subtle tremor suppression and frequency changes, by differences in patient selection (previous studies included all PD phenotypes rather than tremor-dominant patients),[3,29] and medication status (most previous studies were performed "on" dopaminergic medication).[3,29]

Re-emergent tremor intensity, and its response to levodopa, was highly correlated with that of resting tremor. This suggests that both tremor types are manifestations of a single underlying tremor mechanism. Accordingly, it has been suggested to label both tremors as tremor of stability,[4] as both tremors occur in motorically stable contexts (at rest or during stable posturing) and are only transiently interrupted by voluntary movements.[17] The reason why voluntary movements interrupt resting tremor remains a topic for future research.

There were also 2 relevant differences between both tremor types: re-emergent tremor had a slightly higher frequency and was less responsive to levodopa than resting tremor. Previous studies in smaller samples have shown nonsignificant trends in the same direction.[6,28] Speculatively, these findings may be explained by the fact that a voluntary movement increases neural excitability within the cerebello-thalamo-cortical motor circuit, resulting in faster synaptic transmission (higher frequency). Also, the increased somatosensory input during posturing may produce reverberations within the cerebello-thalamo-cortical tremor circuit,[30] making it less dependent from dopaminergic influences from the basal ganglia[4,31] (reduced dopamine response).

Pure postural tremor had a much higher frequency than resting tremor and no dopamine response. This indicates that (partly) distinct neural mechanisms are involved in both tremors. The frequency difference fits with previous work, which described similar frequencies for PD resting tremor (5 Hz) and action tremor (9 Hz) as shown here.[32] The absent dopamine response also fits with previous findings, which showed that the cerebellar pathway,[33] and possibly serotonin depletion in the raphe,[34] has a specific role in postural tremor—although these studies did not differentiate between postural tremor types.

We systematically tested several possible hypotheses regarding the nature of pure postural tremor in PD.[5] First, postural tremor frequency was not lowered by weighing, making it unlikely that is has a peripheral (non-neuronal) origin. This fits previous observations that high-frequency action tremor in PD continued at the same frequency after anesthesia of the limb, suggestive of a central origin.[32] However, 8% of healthy patients have enhanced physiologic tremor of central origin, with a frequency of 9–12 Hz (young patients) or 5–7 Hz (elderly). The prevalence of pure postural tremor in our sample was considerably higher (19% vs 8%), and the frequency was higher than in healthy elderly (8.1 vs 5–7 Hz). Thus, it is unlikely that pure postural tremor in PD reflects enhanced physiologic tremor of central origin. Second, the onset of pure postural tremor preceded the onset of PD symptoms in only 2 patients with pure postural tremor (18%), and in one patient with re-emergent tremor (2%), without a significant group difference. This makes it unlikely that pure postural tremor in our sample reflects co-occurring ET—which has been suggested to occur more often in PD than expected.[10] Future research may test whether the tremor stability index, which differentiates ET from PD resting tremor,[35] can also distinguish pure postural tremor from re-emergent tremor. Third, dystonic symptoms were as frequent in patients with pure postural tremor as in patients with re-emergent tremor. Taken together, we propose that pure postural tremor is inherent to PD, that (like rest and re-emergent tremor) it has a central origin, and that nondopaminergic systems may be involved in its pathophysiology.

Our findings show that levodopa is effective for treating a good portion of patients with re-emergent tremor, but not pure postural tremor. Besides dopaminergic medication, other pharmacologic treatments are sometimes used for treating PD tremor, including β-blockers, anticholinergics, and atypical neuroleptics (e.g., clozapine).[36] Although a positive effect of these drugs on PD tremor has been described, most studies did not distinguish between rest and postural tremor,[37–39] and even if they did,[40] no distinction between pure postural and re-emergent tremor was made. As nondopaminergic systems may be involved in pure postural tremor, it may respond better to nondopaminergic treatments such as β-blockers. Future studies may focus on alternative treatment strategies for postural tremor, considering the distinct phenotypes described here.

We propose that PD harbors 2 distinct postural tremor phenotypes. Re-emergent tremor is a continuation of resting tremor during stable posturing, and it has a dopaminergic basis. Pure postural tremor is a second, less common tremor that is inherent to PD, but has a largely nondopaminergic basis.

Author contributions

M.F. Dirkx collected and analyzed the data and wrote a substantial part of the paper. Dr. Zach collected the data, analyzed a part of the data, and wrote a part of the paper. Dr. Hallett contributed to the construction of study design. Dr. Bloem contributed to construction of the study design. Dr. Helmich contributed to the construction of the study design and wrote a substantial part of the paper.

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Disclosure

M. Dirkx and H. Zach report no disclosures relevant to the manuscript. B. Bloem reports personal fees from Nutricia, personal fees from Glaxo-Smith-Kline, personal fees from UCB, personal fees from Adamas, personal fees from TEVA, personal fees from Zambon, personal fees from AbbVie, grants from National Parkinson Foundation, grants from The Netherlands Organisation for Scientific Research, grants from Hersenstichting, grants from Michael J Fox foundation, and grants from Stichting Internationaal Parkinson Fonds, all outside the submitted work. M. Hallett and R. Helmich report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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FULL-LENGTH ARTICLE NPub.org/1kalr1

The nature of postural tremor in Parkinson disease

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Study question

How many distinct postural tremor phenotypes occur in Parkinson disease (PD)?

Summary answer

There are 2 distinct postural tremor phenotypes in PD: re-emergent tremor and pure postural tremor.

What is known and what this paper adds

Postural tremor in PD is common and highly heterogeneous. This study provides insights into appropriate classifications for postural tremor in PD, which may aid research and clinical practice.

Participants and setting

This study examined 73 patients with tremulous PD at the Radboud University Medical Center between July 2014 and February 2016.

Design, size, and duration

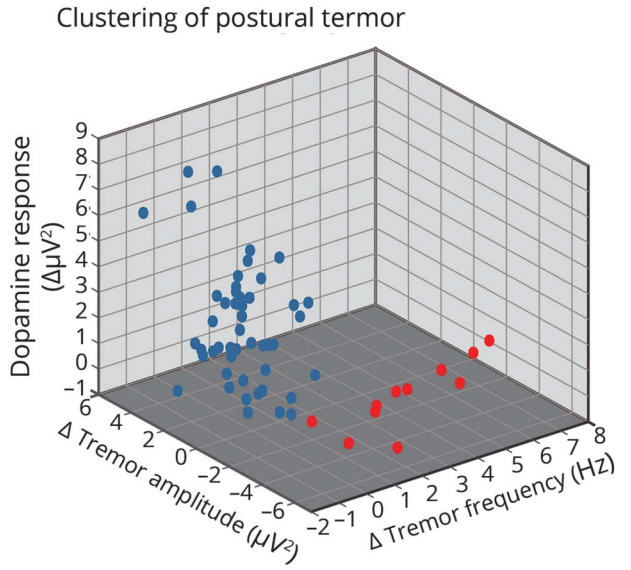
The participants' resting and postural tremor characteristics were assessed with EMG measurements from forearm muscles. Measurements were conducted in both the "off" and "on" states with regard to dopaminergic medications.

Primary outcomes

The primary outcome was the result of a two-step cluster analysis based on 3 postural tremor characteristics: the frequency difference relative to resting tremor (Δfrequency), the effect of wrist flexion on tremor amplitude, and the dopamine response observed when comparing tremor power at individual peak tremor frequencies in the "off" and "on" states.

Main results and the role of chance

Of the 73 patients, 59 (81%) had a postural tremor suitable for clustering. The cluster analysis sorted these 59 patients into one cluster with re-emergent tremor (n = 48; 81%) and another with pure postural tremor (n = 11; 19%). The Δfrequency value was greater in the pure postural tremor group than in the re-emergent tremor group ($p = 0.001$). The re-emergent tremor group exhibited amplitude suppression after posturing ($p < 0.001$), whereas the pure postural tremor group did not. The dopamine response was greater in the re-emergent group than in the pure postural tremor group ($p < 0.001$).



Bias, confounding, and other reasons for caution

This study reports a much higher prevalence of re-emergent tremor than clinical studies do.

Generalizability to other populations

This study was performed in patients with tremor-dominant PD. This may limit the generalizability of the results to such persons.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.