ARTICLE

Dopamine-responsive and dopamine-resistant resting tremor in Parkinson disease

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Abstract

Objective

We tested the hypothesis that there are 2 distinct phenotypes of Parkinson tremor, based on interindividual differences in the response of resting tremor to dopaminergic medication. We also investigated whether this pattern is specific to tremor by comparing interindividual differences in the dopamine response of tremor to that of bradykinesia.

Methods

In this exploratory study, we performed a levodopa challenge in 76 tremulous patients with Parkinson tremor. Clinical scores (Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale part III) were collected "off" and "on" a standardized dopaminergic challenge (200/50 mg dispersible levodopa-benserazide). In both sessions, resting tremor intensity was quantified using accelerometry, both during rest and during cognitive coactivation. Bradykinesia was quantified using a speeded keyboard test. We calculated the distribution of dopamine-responsiveness for resting tremor and bradykinesia. In 41 patients, a double-blinded, placebo-controlled dopaminergic challenge was repeated after approximately 6 months.

Results

The dopamine response of resting tremor, but not bradykinesia, significantly departed from a normal distribution. A cluster analysis on 3 clinical and electrophysiologic markers of tremor dopamine-responsiveness revealed 3 clusters: dopamine-responsive, intermediate, and dopamine-resistant tremor. A repeated levodopa challenge after 6 months confirmed this classification. Patients with dopamine-responsive tremor had greater disease severity and tended to have a higher prevalence of dyskinesia.

Conclusion

Parkinson resting tremor can be divided into 3 partially overlapping phenotypes, based on the dopamine response. These tremor phenotypes may be associated with different underlying pathophysiologic mechanisms, requiring a different therapeutic approach.

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Glossary

ANOVA = analysis of variance; **BIC** = Bayesian Information Criterion; **CI** = confidence interval; **COCO** = cognitive coactivation; **LED** = levodopa equivalent dose; **MDS-UPDRS** = Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale; **MDS-UPDRS-Trem** = resting tremor subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale; **PD** = Parkinson disease; **S-W** = Shapiro-Wilk test; **VAS** = visual analogue scale.

Parkinson disease (PD) is characterized by dopamine depletion in the basal ganglia, leading to the cardinal motor signs resting tremor, bradykinesia, and rigidity.[1] Resting tremor occurs in approximately 75% of patients with PD.[2] The pathophysiology of tremor has been linked to the combined actions of both the basal ganglia and the cerebello-thalamo-cortical circuit.[3,4] Furthermore, patients with tremor-dominant PD have a different pattern of brain atrophy than do patients with PD without tremor.[5] However, the neurochemical alterations that lead to tremulous activity in this circuit are under debate.[6] Specifically, it remains unclear whether and how dopaminergic dysfunction of the basal ganglia leads to the expression of Parkinson resting tremor,[7] and to what extent other neurotransmitters (such as noradrenaline or serotonin) play a role.[2,8–10] For instance, contrary to bradykinesia and rigidity, tremor severity does not correlate with the degree of nigrostriatal dopamine depletion.[11,12] Previous findings in PD have shown that levodopa reduces tremor-related activity in the ventrolateral thalamus, particularly in patients with a clinical dopamine response,[7] and it reduced thalamo-cortical connectivity.[13] These findings underscore that the dopaminergic system plays a key role in PD resting tremor, although not to the same extent in all patients. An important clinical argument against the role of the dopaminergic system in PD resting tremor is the observation that, in many patients, resting tremor does not respond to dopaminergic medication, even in high doses.[14–17] This raises the question whether there are different resting tremor phenotypes (dopamine-responsive and dopamine-resistant), perhaps with different underlying pathophysiologic mechanisms. The fact that some patients respond selectively to anticholinergic drugs, while others respond only to dopaminergic medication, supports this idea.[15] Alternative explanations for the lack of a dopamine response in some tremulous patients with PD are also possible. For instance, patients with a dopamine-responsive and dopamine-resistant tremor may form 2 ends of a normal distribution, which would point to a single phenotype. Furthermore, tremor may have a generally lower dopamine response than bradykinesia (across all patients), or tremor may need higher doses of levodopa to achieve a similar clinical effect as bradykinesia.[18] Here we distinguished among these different alternatives, by comparing for the first time the distribution of the dopamine response between resting tremor and bradykinesia, using a supramaximal dose of levodopa in a standardized dopaminergic challenge. To this end, we used clinical and electrophysiologic measurements to quantify accurately the dopamine response of PD rest tremor across different contexts.

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the local ethics committee and was performed according to the standards of the 1964 Declaration of Helsinki. All participants gave written informed consent prior to their inclusion. The trial was registered at the Netherlands National Trial Register (NTR5042).

Study population

We enrolled 83 patients with PD, diagnosed according to the UK Brain Bank criteria.[19,20] Patients participated in a combined electrophysiologic and neuroimaging study at the Parkinson Center, Radboud University Medical Center, in Nijmegen, the Netherlands. Only patients with a resting tremor score of ≥1 points in at least one arm on item 17 of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were included. Two independent movement disorders specialists recruited all patients from our outpatient clinic and performed the examination. Exclusion criteria were neurologic comorbidity, signs of psychogenic tremor (e.g., entrainment or distractibility), known allergy against levodopa–benserazide or domperidone, and significant cognitive impairment (Mini-Mental State Examination score <24 or frontal assessment battery <12).[21,22] To avoid inclusion of patients with general dopamine resistance due to atypical parkinsonism or gastric absorption problems, we excluded patients with general dopamine resistance reflected by less than 20% clinical levodopa response for bradykinesia/rigidity in the MDS-UPDRS.[23,24] Out of 76 included patients, 69 patients used dopaminergic medication: 48 patients used only levodopa, 3 patients used anticholinergic drugs, 5 patients used only dopamine agonists, and 20 patients used both.

Design

We measured patients twice on one day, both before ("off" medication) and after ("on" medication) a levodopa challenge. Specifically, we evaluated patients after overnight fasting in a practically defined "off"-state.[8,25] For the "on"-state assessment, patients first received 10 mg domperidone to reduce possible side effects and to improve gastrointestinal absorption. This was followed by a standard dose of 200/50 mg dispersible levodopa–benserazide (on average 70% higher than the patients' own morning levodopa equivalent dose; "morning LED") 1 hour later.[23] The first tremor assessment in the "on" state started on average 52 minutes (range 35–58 minutes) after taking levodopa.

After 46–394 days, we selected a subgroup of 41 patients based on their dopamine response (either a clear or absent response) and reevaluated them to test whether the levodopa response was stable within subjects. This time, patients came for 2 separate sessions, both "off"-medication. During one session, they received 200/50 mg dispersible levodopa–benserazide plus 10 mg domperidone and during the other session they received a placebo (cellulose dispersed in water) plus 10 mg domperidone (order counterbalanced). Both patients and clinical raters were blinded to the intervention. In a recent article, we reported differences in tremor-related activity (using functional MRI) between dopamine-responsive and dopamine-resistant patients within this subgroup of 41 patients with PD.[26] Given that this subgroup of 41 patients was selected based on an absent or present clinical dopamine response (in order to compare cerebral activity), we used this sample only to test whether dopamine effects were stable over time. In contrast, we used the entire (unselected) sample of 76 to test our primary hypothesis that there are different tremor phenotypes (dopamine-resistant vs responsive).

Clinical ratings

We clinically assessed patients using the MDS-UPDRS part III and the Hoehn & Yahr scale.[27] Subscores of the MDS-UPDRS part III were used to calculate the dopamine response for each of the 3 cardinal motor symptoms of the limbs separately: resting tremor (MDS-UPDRS-Trem; 5 scores on items 17 and 18); bradykinesia (14 scores on items 4–11 and 14), and rigidity (5 scores on item 3). More specifically, for each sign, we divided the total MDS-UPDRS subscore by the number of items for that sign. Thus the total tremor and rigidity subscores were both divided by 5 and the total bradykinesia subscore was divided by 14. This resulted in a value ranging from 0 to 4 for each sign. We calculated the percentage change of the signs using the following formula (briefly, Elble calculation), where $\alpha = 0.5$[28]:

$$\%\text{change} = 100 \times \left[10^{\alpha(\text{Rating ON} - \text{Rating OFF})} - 1\right] \quad (1)$$

Thus we corrected for the nonlinear relationship between changes in clinical symptom scores and for tremor, the actual change in tremor amplitude (as measured with accelerometry). Based on combined accelerometry and clinical tremor studies, the α has been estimated to be 0.5 for tremor.[28] We used the same α level for bradykinesia and rigidity in this study.

We also measured the patients' own impression regarding the dopamine response of their tremor. A subgroup of 51 patients indicated the subjective improvement of tremor on a visual analogue scale (VAS) by marking a 10-cm line ranging from "no improvement" (0%) to "optimal improvement" (100%).[25]

To objectively quantify bradykinesia in a continuous manner, a subgroup of 22 patients performed keyboard finger tapping (alternating between the "M/N" keys for 30 seconds and the "P/Q" 20 times as fast as possible, with each hand separately). The composite score is an average of keys typed per second. Higher scores indicate less bradykinesia.[29]

Electrophysiologic tremor assessments

We followed the same steps as in our previous study.[25] Mean resting tremor power during each condition was quantified by accelerometry using a lightweight biaxial piezoelectric accelerometer (Medifactory International; Heerlen, Netherlands; sensitivity: 128 Hz) attached to the dorsum of the most affected hand. Patients lied down comfortably on a bed to achieve complete resting state; hands and fingers were unsupported. Resting tremor was recorded in 2 different contexts: during rest and during cognitive coactivation (COCO; loud backwards counting in steps of 3 or 7 as fast as possible[30]). For each context, we collected three 1-minute trials.

Data were stored on a computer for offline analysis using FieldTrip.[31] We applied a bandpass filter (1–40 Hz) and calculated time-frequency representations (TFR) between 1 and 20 Hz in steps of 0.1 seconds using a 2-second Hanning taper, resulting in a 0.5 Hz resolution. By averaging over all time points, we obtained an average power spectrum across segments. We calculated mean tremor intensity (for each patient, context, and trial) by taking the power at each patient's individual peak tremor frequency. To test the effect of levodopa on log tremor power, we calculated the natural log of the ratio of "off" tremor power to "on" tremor power [ln("off"/"on"), which is equivalent to ln("off") – ln("on")]. Here, higher values indicate a better dopamine response of tremor.[32–36]

Statistical analysis

First, we calculated the dopamine response (% improvement "on" vs "off") among motor signs (resting tremor, bradykinesia, and rigidity). We also calculated objective assessments of dopamine response of resting tremor (accelerometry, ln ["off"/"on"]) and for bradykinesia (tapping speed, "on" minus "off").

Second, we calculated the distribution of the dopamine response for tremor and bradykinesia (both clinical and objective assessments) to test for differences between signs of PD using the Shapiro-Wilk (S-W) test for normality (i.e., a specific form of unimodal distributions). We omitted rigidity from this analysis, because these scores were very low in our sample (on average 70% lower than bradykinesia scores), which may lead to flooring effects. This may be explained by the fact that we included patients with tremor-dominant PD, who have relatively low rigidity scores.[37] Furthermore, in tremulous PD, rigidity is not required for the diagnosis (so it can be absent).

Third, we performed a data-driven 2-step cluster analysis to test our primary hypothesis that there are different tremor phenotypes ("clusters") with a different dopamine response, as previously done for postural tremor in PD.[38] Specifically, we included 3 relevant variables (clinical tremor dopamine

responsiveness, accelerometry-based tremor dopamine responsiveness during rest and during COCO). We calculated the log-likelihood of each model using the Bayesian Information Criterion (BIC) and compared the statistical evidence for different solutions (i.e., 1 to n clusters) using the delta BIC. Post hoc we tested whether these 3 variables (clinical tremor dopamine responsiveness, accelerometry-based tremor dopamine responsiveness during rest and during COCO) differed between the resulting clusters using one-way analysis of variance (ANOVA). Finally, we explored whether clinical characteristics (disease severity, disease duration, levodopa equivalent dose, dyskinesia occurrence, sex, levodopa response for bradykinesia and rigidity, subjective ratings of the dopamine response [VAS], levodopa response on the keyboard test) differed between the resulting clusters using ANOVA and χ^2 test (for ordinal variables). Given the exploratory nature of this analysis, we corrected for multiple (n = 9) comparisons using a conservative Bonferroni correction (i.e., $p < 0.0056$ was considered significant). We also calculated correlations between the dopamine responses of all cardinal signs using Spearman rho (one-tailed).

Fourth, we calculated the extent to which individual patients were underdosed (or overdosed) with our standard levodopa dose. Thus we calculated the relative morning dose: the patient's own morning dose, expressed as the levodopa equivalent dose (LED), divided by our standard levodopa dose (200 mg).

Finally, we tested whether our findings were reproducible in a follow-up group of 41 patients. Statistical analyses were performed using SPSS 25.0.

Data availability

Individual data underlying the findings published in the article are available by reasonable request from the corresponding author.

Results

Out of 83 recruited patients, 2 were excluded due to signs of psychogenic and atypical tremor and 5 were excluded due to dopamine resistance of bradykinesia/rigidity. All analyses were performed on the remaining 76 patients (table 1). A significant levodopa effect across the whole group was present for clinical and quantitative assessments of all 3 motor signs, and these changes were comparable among bradykinesia, rigidity, and tremor (table 2). Clinical tremor improvement correlated with reduced tremor power, as measured with accelerometry during rest (ρ = 0.48, 95% confidence interval [CI] 0.29–0.64; Spearman) and during COCO (ρ = 0.62, 95% CI 0.46–0.74). See also figure 1.

Distributions of levodopa response

The dopamine response of bradykinesia in the clinical assessment and the keyboard test showed a relevant correlation (Spearman ρ = 0.37, 95% CI 0.16–0.55) and was normally distributed according to S-W, both for the clinical assessment and for the keyboard test (figure 2). This was not the case for the dopamine response of resting tremor, where the distribution across patients significantly departed from a normal distribution, both for the clinical and the accelerometry assessments (MDS-UPDRS-Trem improvement $p < 0.001$, S-W; accelerometry-based tremor improvement during rest and during COCO both $p < 0.01$, S-W) (figure 1).

Table 1 Clinical characteristics (n = 76)

	Values
Age, y	62 (38–81)
Sex, F/M	24/52
H&Y stage, median	2.0 (1.0–3.0)
Disease duration, y	4.1 (0.12–26)
MMSE	29 (24–30)
FAB	17 (13–18)
LED at home, mg/d	458.6 (0–1,500)
Morning LED at home, mg	126.1 (0–400)

Abbreviations: FAB = frontal assessment battery (score 0–18); H&Y stage = Hoehn and Yahr stage (score 0–5); LED = levodopa equivalent dose during the entire day; morning LED = levodopa equivalent dose in the morning; MMSE = Mini-Mental State Examination (score 0–30).
For H&Y stage, higher scores indicate worse functioning. For both FAB and MMSE, lower scores indicate worse functioning. The scores were evaluated "off" medication. Data are mean (range) across 76 Parkinson patients unless indicated otherwise.

Cluster analysis

A 2-step cluster analysis showed that a 2- or 3-cluster solution was statistically much more likely (Δ BIC >10, i.e., >99% more likely)[39] than a 1-cluster or any other n-cluster solution. There was no significant difference between a 2- and 3-cluster solution (Δ BIC = 0.19). The 3 groups showed a significant difference in the clinical and electrophysiologic dopamine response of tremor (table 3). More specifically, there was a main effect of group for the clinical dopamine response of tremor ($F_{2,75} = 119.2$, $p < 0.001$), for the effect of levodopa on tremor power at rest ($F_{2,75} = 72.6$, $p < 0.001$), and for the effect of levodopa on tremor power during cognitive coactivation ($F_{2,75} = 49.9$, $p < 0.001$). Thus, patients could be classified as having a dopamine-responsive (n = 21), intermediate (n = 25), or dopamine-resistant (n = 30) tremor (figure 1). Besides tremor, the 3 groups also showed non-significant differences in dopamine responsiveness of rigidity and bradykinesia, which were much smaller than for tremor (table 3).

Across all participants, the clinical response to dopamine, reflected in the MDS-UPDRS ratings, was significantly correlated among the 3 signs of PD. When exploring other clinical differences among the 3 groups, we found that levodopa responsiveness was associated with a higher MDS-

Table 2 Levodopa effect (n = 76)

Clinical ratings and quantified measurements	"Off" state	"On" state	% Change	"Off"–"On" difference (95% CI)
MDS-UPDRS part III	44.0 ± 1.8	25.5 ± 1.3	42.2	18.5 (16.6–20.6)
MDS-UPDRS-Brad	19.3 ± 0.9	11.6 ± 0.7	43.4	7.7 (6.6–8.7)
MDS-UPDRS-Rig	5.89 ± 0.4	2.84 ± 0.3	45.4	3.1 (2.6–3.5)
MDS-UPDRS-Trem	10.5 ± 0.4	6.1 ± 0.5	50.4	4.4 (3.6–5.2)
Tremor power, rest, μV^2	5.74 ± 0.4	2.7 ± 0.4	NA	3.0 (2.2–3.8)
Tremor power, COCO, μV^2	8.4 ± 0.4	6.02 ± 0.4	NA	2.4 (1.6–3.2)
Keyboard finger tapping test, keys/second	2.86 ± 0.2	3.2 ± 0.2	14	0.4 (0.1–0.6)

Abbreviations: CI = confidence interval; COCO = cognitive coactivation; MDS-UPDRS = Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (score ranges from 0 to 132); MDS-UPDRS-Brad = bradykinesia subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (items 4–11 and 14; score ranges from 0 to 56); MDS-UPDRS-Rig = rigidity subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (item 3; score ranges from 0 to 16); MDS-UPDRS-Trem = resting tremor subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (items 17 and 18; score ranges from 0 to 20). Data are mean ± SEM across 76 Parkinsonian patients. MDS-UPDRS-Brad reflects the total score of limb bradykinesia items of the MDS-UPDRS, MDS-UPDRS-Rig reflects the total score of limb rigidity items of the MDS-UPDRS, and MDS-UPDRS-Trem reflects the total score of limb rest tremor items of the MDS-UPDRS; the percentages of levodopa response on the cardinal signs (MDS-UPDRS-Brad, MDS-UPDRS-Rig, MDS-UPDRS-Trem) were calculated using the Elble calculation.[28] Tremor power during the relaxed condition (accelerometry at rest) and cognitive activation (accelerometry during COCO) reflect the log-transformed tremor power (i.e., in ln[μV^2]) for the most-affected hand. Keyboard finger tapping test is a quantified bilateral measurement for bradykinesia in a subgroup of 22 patients. The scores indicate the average number of keys typed per second; higher scores indicate less bradykinesia. Higher relative change (% change) indicates better levodopa response.

UPDRS score in the "off" state ($F_{2,73} = 6.94$, $p = 0.002$; table 3). Furthermore, the objective categorization was consistent with the patients' own impression regarding the dopamine response of their tremor: the VAS score significantly differed among the 3 groups ($F_{2,48} = 9.72$, $p < 0.001$; table 3). Other group differences did not survive correction for multiple comparisons (table 3). Similar results were obtained when considering the 2-cluster solution. When comparing the standard dose (200mg levodopa) to each patient's usual morning dose, 13 out of 21 (62%) responsive patients, 15 out of 25 (60%) intermediate responsive, and 17 out of 30 (57%) resistant patients received at least twice their usual morning dose. Only 4 (out of 76) patients had a morning LED at home above 200 mg: 1 was in the responsive group, 1 was in the resistant group, and 2 were in the intermediate group.

Follow-up

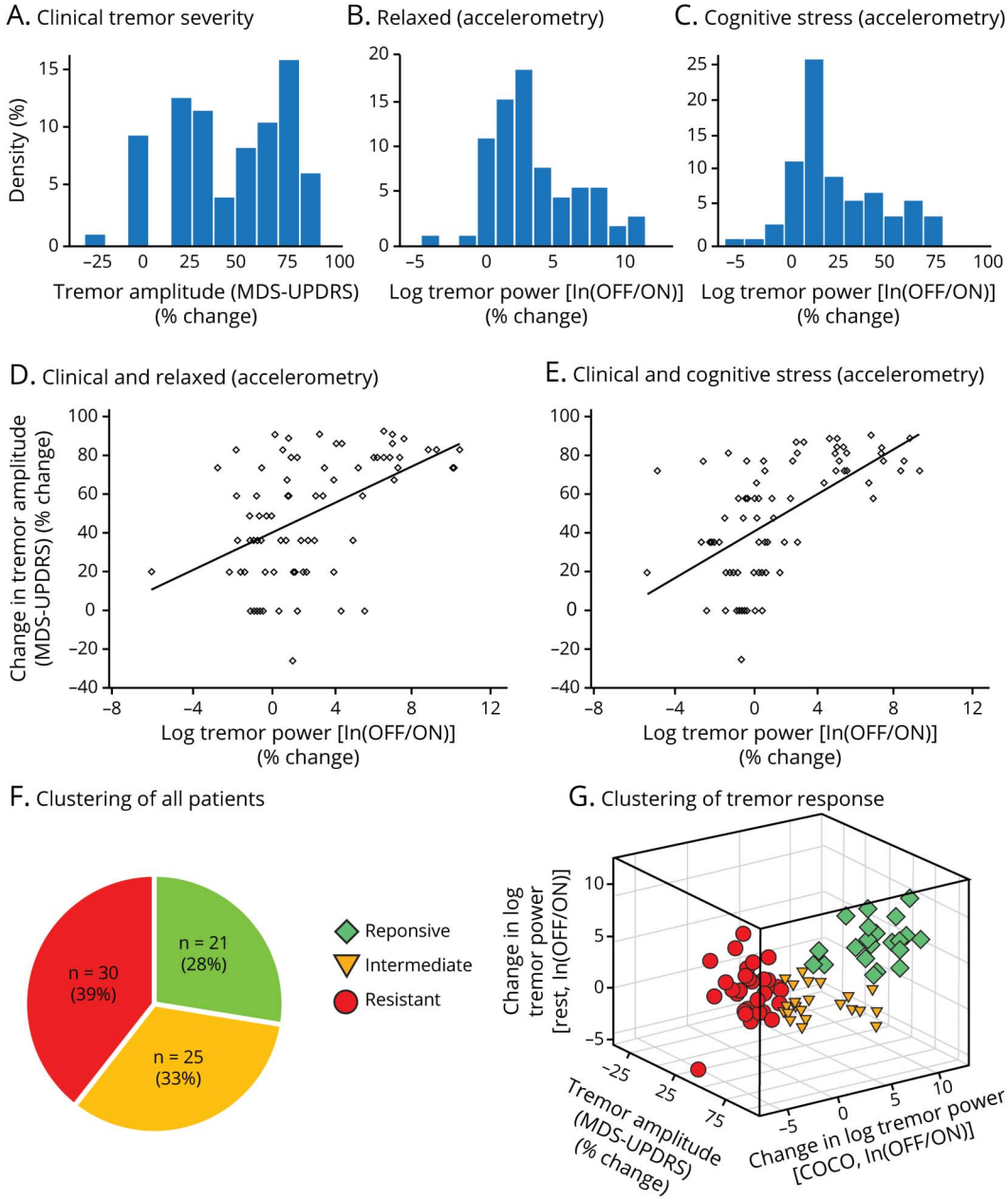
In a subgroup of 41 patients (n = 13 originally classified as dopamine-responsive, n = 9 intermediate, n = 19 dopamine-resistant), a second levodopa challenge (double-blind, placebo-controlled) was performed 6–394 days (average 6 months) later to test whether the dopamine response was stable over time. The dopamine response during clinical ratings at the follow-up significantly differed between groups for resting tremor (55% [95% CI 38.6–70.9] vs 46% [95% CI 28.5–63.4] vs 9% [95% CI −2.4 to 20.7] improvement; effect of group: $F_{2,38} = 15.2$, $p < 0.001$), but not bradykinesia (49% [95% CI 37.3–60.7] vs 49% [95% CI 35.7–61.2] vs 39% [95% CI 29.5–47.6] improvement; effect of group: $F_{2,38} = 1.58$, $p = 0.22$). More specifically, the dopamine response for tremor (reflected by lower scores in the MDS-UPDRS) significantly differed between the responsive vs resistant group (mean difference 45.6%, 95% CI 27.1–64.0), the intermediate vs the resistant group (mean difference 36.8%, 95% CI 17.2–56.4), and differed nonsignificantly between the responsive vs the intermediate group (mean difference 8.7%, 95% CI −14 to 31.5).

Discussion

We investigated whether Parkinson resting tremor can be divided into different phenotypes, based on its dopamine response. Furthermore, we tested whether this distinction is unique to tremor, or whether a similar pattern can be seen for bradykinesia. We found evidence for the presence of 3 subgroups of patients with PD with dopamine-resistant, intermediate, and dopamine-responsive resting tremor. Instead, the dopamine response of bradykinesia followed a normal distribution. This classification was consistent with the patients' subjective perception of the dopamine response of their tremor and reproducible when measuring the same patients approximately 6 months later. Higher disease severity (MDS-UPDRS), longer disease duration, and the presence of dyskinesia were associated with a relatively dopamine-responsive tremor. Our findings argue against the idea that dopamine-responsive and dopamine-resistant tremor are 2 ends of a normal distribution. However, due to the considerable amount of overlap between the groups, no strict black and white distinction can be made.

We scrutinized several possible factors that may have influenced the dopamine response of resting tremor. First, our findings do not support the idea that dopamine-resistant tremor requires higher doses of levodopa than other motor signs, and is therefore pseudoresistant[11]: 57% of dopamine-

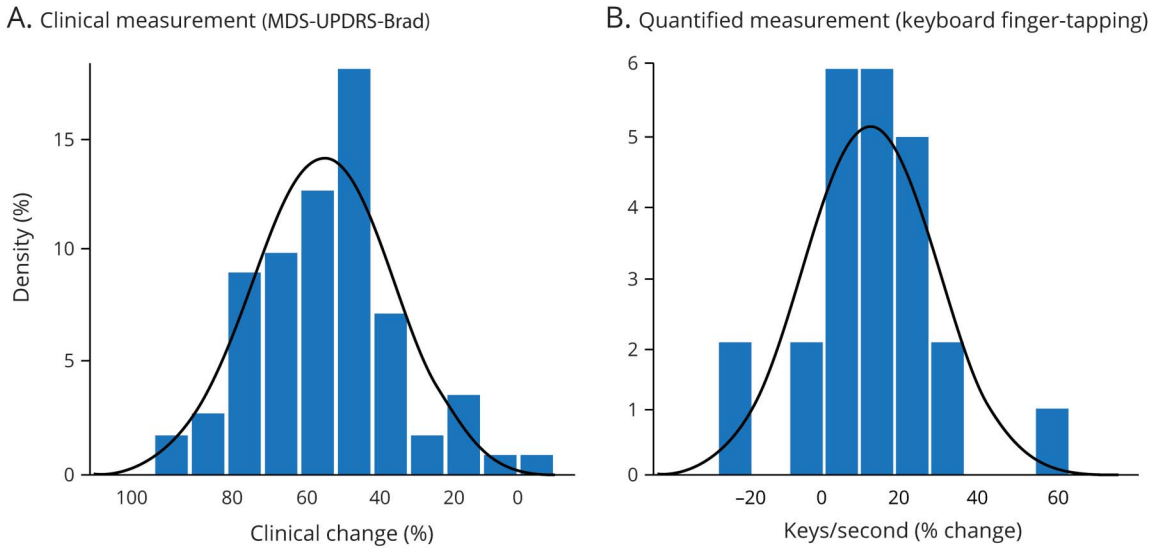
Figure 1 Distribution of levodopa effect on tremor and patient classification



(A) Distribution of the clinical tremor response during the levodopa challenge across all 76 patients (percentage change in resting tremor subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS] [items 17 + 18], "on" vs "off," as measured with the Elble calculation[28]). The distribution significantly departed from normal ($p < 0.001$, Shapiro-Wilk test [S-W]). (B, C) Distribution of the tremor response as measured with accelerometry (tremor power, ln["off"/"on"]) in relaxed condition (B) and during cognitive stress (mental arithmetic, C). Both distributions significantly departed from normal ($p < 0.01$, S-W). (D, E) Correlation of clinical tremor response (as in A) with the tremor response measured with accelerometry (as in B and C) in relaxed condition (D) and during cognitive stress (E). (F, G) Results of the cluster analysis (3-cluster solution). COCO = cognitive coactivation.

resistant patients received at least their double morning dose during the levodopa challenge, and this number was comparable to that in dopamine-responsive tremor (62%). Second, trivial factors such as reduced levodopa absorption (e.g., due to delayed gastric emptying) cannot explain dopamine-resistant resting tremor: we excluded patients with an overall dopamine response <20%. The levodopa response of bradykinesia and rigidity was also higher in patients with a dopamine-responsive vs dopamine-resistant tremor, but this difference was smaller than that for tremor. This finding suggests that the dopamine response of tremor is not entirely independent from that of other motor signs, and that it might be influenced by general patient characteristics (such as the gastrointestinal environment or levodopa metabolism). Third, it is unlikely that dopamine-resistant tremor is caused by a placebo response,[40] since our (placebo-controlled, blinded)

Figure 2 Distribution of levodopa effect on bradykinesia



(A) Distribution of clinically measured bradykinesia in all 76 patients (percentage change of bradykinesia subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS-Brad] [items 4–11 & 14], "on" vs "off," as measured with the Elble calculation[28]). The distribution was not significantly different from normal (p = 0.2, Shapiro-Wilk test [S-W]). (B) Distribution of bradykinesia as measured with the keyboard finger tapping test in a subgroup of 22 patients (% change of keys typed/second). The distribution was not significantly different from normal (p = 0.3, S-W).

follow-up measurements confirmed our initial (unblinded) observations. We have ruled out that the placebo effect caused the differences in tremor responsiveness between subgroups, by adding the (controlled) measurements performed in a subsample (i.e., the 41/76 patients described in our previous article[26]). The disadvantage of using an uncontrolled levodopa challenge should be weighed against the advantage of using a procedure that is commonly applied in the clinic. Therefore, the findings we report here are clinically more relevant than when using a controlled procedure. Also, the findings are larger for resting tremor (i.e., not present for bradykinesia), and it is unlikely that the placebo effect should be symptom-specific. Nevertheless, given that our cluster analysis is based on data that were not placebo-controlled, it is possible that we underestimated the prevalence of dopamine-resistant tremor.

In search for clinical predictors of a dopamine-responsive tremor, we classified patients as having a dopamine-responsive or dopamine-resistant tremor, based on a data-driven cluster analysis. This revealed significantly higher symptom severity, longer disease duration, and the presence of dyskinesias in the dopamine-responsive group. Although Kipfer et al.[41] have shown that rest tremor as an initial disease manifestation is a negative predictor for the development of dyskinesias, no distinction between levodopa-resistant and responsive tremor has been made; therefore these findings are not fully comparable with our study. The positive correlation between disease severity and tremor dopamine-responsiveness might be explained by the fact that less affected patients had a lower tremor amplitude, which could have led to a flooring effect (i.e., a smaller possible range for levodopa to further reduce a low-amplitude tremor). On the other hand, this same effect should be expected to occur in a similar way for bradykinesia and rigidity, but this was not the case. Also, electrophysiologic measurements are less susceptible to flooring effects, and we observed the same effects there. The correlation with disease severity suggests that patients may move from one subgroup to another with disease progression, although this is speculative. A similar phenomenon has been described for tremor-dominant and nontremor phenotypes, where it was observed that patients often change from a tremor-dominant phenotype to a postural instability and gait difficulties phenotype during disease progression.[42,43] Longitudinal studies may test whether the tremor dopamine-responsiveness changes with disease progression, and what the underlying mechanisms could be. Here, we assessed tremor severity in an acute levodopa challenge. Prospective studies may test whether long-term treatment with levodopa could lead to plastic changes, thereby changing acute responsiveness.[44] A limitation of this study is that we used only levodopa to test the dopamine response in our sample. It is possible that some levodopa-resistant patients may respond favorably to one or more dopamine agonists, as has been reported for several cases in the literature.[17] Furthermore, given that we only recruited patients with clear tremor (independent of their reported dopamine response), our findings may not apply to patients with very little tremor or to patients without tremor.

Pathophysiologic implications

The clinical observation that resting tremor has an unpredictable response to levodopa, and the lack of a correlation between striatal dopamine depletion and tremor severity,[4,11,12] has cast some doubt on the role of the

Table 3 Comparison of clinical characteristics (based on 3-cluster solution)

Groups	Responsive (n = 21)	Intermediate (n = 25)	Resistant (n = 30)
MDS-UPDRS "off"	52.57 (46.7–58.5)	44.8 (39.4–50.2)	37.2 (31.0–43.4)
Disease duration, y	6.24 (4.43–8.04)	4.65 (1.99–7.11)	2.62 (1.62–3.62)
LED, mg/day	510.0 ± 364.2–655.8	478.9 ± 332.6–625.2	405.7 ± 301.8–509.6
Dyskinesia occurrence	11 (52)	3 (12)	3 (10)
F/M	8/13	8/17	8/22
Clinical evaluation			
MDS-UPDRS-Trem "off"	2.45 (2.14–2.75)	1.96 (1.72–1.20)	1.73 (1.44–2.01)
MDS-UPDRS-Trem "on"	0.94 (0.66–1.23)	0.93 (0.64–1.28)	1.54 (1.21–1.87)
MDS-UPDRS-Brad "off"	1.57 (1.37–1.78)	1.45 (1.21–1.69)	1.17 (9.58–1.39)
MDS-UPDRS-Brad "on"	0.89 (0.71–1.07)	0.89 (0.69–1.09)	0.72 (0.58–0.86)
MDS-UPDRS-Rig "off"	1.57 (1.23–1.91)	1.07 (0.85–1.30)	0.99 (0.71–1.27)
MDS-UPDRS-Rig "on"	0.73 (0.46–1.01)	0.47 (0.31–0.64)	0.53 (0.33–0.74)
Quantified tremor assessment (accelerometry)			
Tremor power at rest, "off," μV^2	8.35 (7.13–9.56)	3.53 (2.42–4.65)	5.78 (4.03–7.25)
Tremor power at rest, "on," μV^2	0.74 (−0.24 to 1.71)	2.06 (0.91–3.20)	4.68 (3.44–5.91)
Tremor power during COCO, "off," μV^2	10.36 (9.33–11.39)	6.99 (5.57–8.41)	8.31 (6.82–9.80)
Tremor power during COCO, "on," μV^2	4.02 (2.41–5.62)	4.96 (3.63–6.30)	8.31 (7.06–9.56)
Relative clinical levodopa response			
Tremor (MDS-UPDRS-Trem), % change	80.6 (77.0–84.3)	64.3 (57.0–71.6)	17.6 (11.3–24.0)
Bradykinesia (MDS-UPDRS-Brad), % change	51.6 (44.0–59.3)	44.4 (36.6–52.2)	36.7 (29.3–44.1)
Rigidity (MDS-UPDRS-Rig), % change	56.9 (48.3–65.6)	47.5 (41.0–54.1)	35.6 (27.1–44.2)
Quantified levodopa response (accelerometry)			
Tremor power at rest, ln("off"/"on")	7.60 (6.65–8.56)	1.50 (0.79–2.14)	1.10 (0.24–1.96)
Tremor power during COCO, ln("off"/"on")	6.35 (5.07–7.62)	2.03 (1.01–3.05)	0.002 (−0.55 to 0.55)
	n = 5	n = 8	n = 9
Keyboard test, % change	16.20 (0.66–31.75)	21.44 (4.84–38.1)	7.25 (−8.47 to 22.97)
Subjective rating of dopamine response	n = 15	n = 18	n = 18
VAS–tremor, perceived % change	74.7 (64.7–84.6)	56.1 (41.0–71.2)	34.7 (21.3–48.1)
Follow-up group	n = 13	n = 9	n = 19
MDS-UPDRS "off"	48.7 (39.2–58.3)	46.1 (32.0–60.3)	40.1 (32.3–47.7)
MDS-UPDRS "on"	33.2 (25.2–41.3)	32.7 (21.3–44.2)	33.0 (25.1–40.9)

Abbreviations: CI = confidence interval; COCO = cognitive coactivation; LED = levodopa equivalent dose during the entire day; MDS-UPDRS = Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (score ranges from 0 to 132); MDS-UPDRS-Brad = bradykinesia subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (items 4–11 and 14; score ranges from 0 to 56); MDS-UPDRS-Rig = rigidity subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (item 3; score ranges from 0 to 16); MDS-UPDRS-Trem = resting tremor subscore of the Movement Disorders Society–sponsored version of the Unified Parkinson's Disease Rating Scale (items 17 and 18; score ranges from 0 to 20); VAS = visual analogue scale.
Data are mean (95% CI), or n (%), unless indicated otherwise. Clinical evaluation reflects the absolute values of the MDS-UPDRS-Trem "off" and "on" (items 17 and 18, divided by 5, i.e., the number of limb tremor items), the absolute values of the MDS-UPDRS-Brad "off" and "on" (items 4–11 and 14, divided by 14, i.e., the number of bradykinesia items), and the absolute values of the MDS-UPDRS-Rig "off" and "on" (item 3, divided by 5, i.e., the number of rigidity items). Quantified tremor assessment reflects the absolute tremor power for the most-affected hand during the relaxed condition (rest) and cognitive activation (COCO) using accelerometry (i.e., in ln[μV^2], separately for "off" and "on" sessions). Relative clinical levodopa responses are calculated using the Elble calculation.[28] Quantified levodopa response reflects the effect of levodopa on tremor power (ln["off"/"on"]) for the most-affected hand. Keyboard test is a quantified measurement for bradykinesia in a subgroup of 22 patients; the levodopa response indicates the relative levodopa response regarding the average number of keys typed per second. VAS-tremor is a visual analogue scale that indicates the change in tremor intensity after the dopaminergic challenge, perceived by the patients themselves, in a subgroup of 51 patients.

dopaminergic system in the pathophysiology of PD resting tremor and could also be a hint towards the role of cortical impairment in the genesis of tremor.[5] It has also sparked interest in the role of other neurotransmitters in resting tremor, for example serotonin[9,10] and noradrenaline,[45] which have both been associated with a tremor-dominant phenotype. On the other hand, we and others have found evidence for a role of dopamine in the pathophysiology of Parkinson resting tremor as well: dopaminergic medication increased thalamic inhibition—and more so in patients with a better clinical response[7]—and reduced thalamocortical connectivity.[13] This finding was replicated in part of the cohort described here. In 41 out of 76 patients, we compared patients with a dopamine-resistant vs a dopamine-responsive tremor, and showed that patients with a responsive tremor had increased inhibitory effects of levodopa onto the ventrolateral thalamus and reduced tremor-related activity in the cerebellum.[26] This finding indicates that the tremor subtypes we describe here are associated with pathophysiologic differences, reinforcing the idea that they are distinct. Other studies have also shown that dopamine transporter binding in the globus pallidus was reduced in tremor-dominant patients (compared to akinetic-rigid patients with PD), and that it was correlated with tremor severity,[46] although subsequent studies have failed to replicate this finding.[45,47] The current findings suggest that both dopaminergic and nondopaminergic mechanisms may play a role, but that their relative contribution may differ between patients. This fits with recent findings from Pasquini et al.,[10] who found that patients with PD with a relatively dopamine-resistant tremor had more serotonergic denervation in the raphe (relative to dopamine depletion in the putamen) than patients with a relatively dopamine-responsive tremor. Differences between included patients (i.e., the mix between dopamine-responsive or resistant patients) may thus explain some discrepancies in the literature, e.g., regarding the role of the serotonergic system in resting tremor (which was found in some studies[9,48] but not others[49]) and the role of dopamine depletion in the pallidum (which was found by some[46] but not others[45]).

Our results suggest that there are distinct subgroups of patients with PD with a dopamine-responsive and a dopamine-resistant tremor, although there is partial overlap (intermediate group). This pattern is unique for tremor and differs from bradykinesia, where dopamine-responsiveness was normally distributed. These interindividual differences suggest that precision medicine is required for optimal treatment of Parkinson resting tremor. Pathophysiologic studies into the mechanisms underlying dopamine-resistant tremor may help develop treatments for this debilitating sign of PD.

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Michiel F. Dirkx, MD	Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands	Design, organization, and conception of the study, execution, parts of data analysis, manuscript writing
Dominik Roth, MD, PhD	Department of Emergency Medicine, Medical University Vienna, Austria	Execution, data analysis, and manuscript writing
Jaco W. Pasman, MD	Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands	Substantial input to all versions of this manuscript, review and critique of the last version
Bastiaan R. Bloem, MD, PhD	Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands	Design, organization, and conception of the study, substantial input to all versions of this manuscript (review and critique of the last version)
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