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RESEARCH ARTICLE

The Clinical Profile of Tremor in Parkinson's Disease

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Abstract: Background: Tremor is one of the most troublesome manifestations of Parkinson's Disease (PD) and its response to dopaminergic medication is variable; an evidence-based framework of PD tremor is lacking yet needed to inform future investigations.

Objective: To perform a comprehensive longitudinal analysis on the clinical characteristics, course and response to dopaminergic medication of tremor in de-novo PD.

Methods: Three hundred ninety-seven participants were recruited in the Parkinson Progressive Markers Initiative, a prospective observational cohort study in early de-novo PD. Rest, postural and kinetic tremor scores were extracted from the Movement Disorders Society—Unified Parkinson's Disease Rating Scale. Progression from baseline to 7-year follow-up of rest, postural and kinetic tremor scores, and their response to in-clinic dopaminergic medication were analyzed through linear mixed-effects models adjusted for age, sex and disease duration at enrollment. A sensitivity analysis was conducted through subgroup and imputation analyses.

Results: 382 (96.2%) participants showed tremor and 346 (87.2%) showed rest tremor in at least one assessment over 7 years. *Off*-state rest, postural and kinetic tremor scores increased significantly over time, coupled with a significant effect of dopaminergic medication in reducing tremor scores. However, at each assessment, tremor was unresponsive to in-clinic dopaminergic medication in at least 20% of participants for rest, 30% for postural and 38% for kinetic tremor.

Conclusions: PD tremor is a troublesome manifestation, with increasing severity and variable response to medications. This analysis details the current clinical natural history of tremor in early-to-mid stage PD, outlining an evidence-based framework for future pathophysiological and interventional studies.

Tremor is an involuntary, rhythmic, oscillatory movement of a body part, and is a cardinal sign of Parkinson's Disease (PD).[1] Tremor is detrimental on quality of life, and at least one third of patients are unable to perform simple activities without its occurrence.[2–5] In a recent survey, tremor was the most frequently reported manifestation patients wished to see improved over the first 10 years after diagnosis.[6] Indeed, currently available PD medications may not have optimal efficacy on tremor.[7] Nonetheless, studies that systematically and comprehensively investigate the course and clinical characteristics of tremor in PD are lacking. Early clinical and pathological studies showed a high prevalence of tremor in PD, indicating that almost all patients experience tremor during the disease.[8–10] One retrospective study showed a unilateral-to-bilateral spread of tremor over 10 years of disease, hinting increasing severity.[11] Two longitudinal studies over an average of 3 and 5 years hypothesized either a stability or slower progression compared to other cardinal signs.[12,13] However, in these studies tremor characteristics in the *off*- and *on*-state were not systematically assessed, as well as the longitudinal responsiveness to dopaminergic therapy. Furthermore, a less refined, qualitative scale for tremor[14] was used,

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compared to the current Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

The aim of this study is to provide a 7-year longitudinal evaluation of the clinical characteristics of rest, postural and kinetic tremors and their response to dopaminergic therapy in *de-novo* PD patients treated according to current standards. By outlining an evidence-based framework of tremor in PD, we also aim to show current clinical needs to inform interventional studies.

Methods

Study Design

A seven-year longitudinal analysis was conducted in a *de-novo* PD cohort recruited in the Parkinson's Progressive Markers Initiative (PPMI), a multicenter, longitudinal study aiming to identify biomarkers of PD progression.

The analysis is based on the PPMI "analytic dataset," the latest published database update by the PPMI consensus committee, created to reflect the most accurate current participant cohort. The PPMI database was accessed on February 1, 2022. At baseline 397 patients were retrieved.

All patients had a clinical diagnosis of PD for 2 years or less and evidence of dopaminergic deficit on molecular imaging investigations, and were untreated.[15] As per study protocol (https://www.ppmi-info.org/sites/default/files/docs/archives/Amendment-12.pdf), the PPMI was designed to be an 8 year natural history study (with a minimum of 5-year involvement) of de novo idiopathic PD participants. All PD subjects were planned to have an annual assessment of the motor exam in a practically defined *off*-state and a repeat *on*-state assessment 1 hour after receiving their usual PD medication in clinic.

Briefly, this study is based on both *off* and *on* tremor scores from baseline to the 7-year follow-up, analyzed through linear-mixed effects models to account for the longitudinal data design. Clinical characteristics and progression of rest, postural and kinetic tremor scores are analyzed based on *off*-state tremor scores. Furthermore, the response of rest, postural and kinetic tremor scores to dopaminergic medication is analyzed based on both *off*- and *on*-state tremor scores.

Clinical Data

Tremor scores were extracted from the MDS-UPDRS part III. Rest tremor amplitude was scored for each limb and jaw/lip (item 3.17; score range: 0–20); postural and kinetic tremors were evaluated in each upper limb (items 3.15 and 3.16; score range for each item: 0–8).

Off-State Tremor Scores Analyses

At each yearly assessment, rest, postural and kinetic tremor amplitude *off*-state scores were recorded. All analyses involving *off*-state tremor scores excluded participants: (1) that did not observe the 12-h overnight dopaminergic medication withdrawal; (2) with active Deep Brain Stimulation (DBS) during MDS-UPDRS evaluation.

Descriptive data regarding the pattern (combinations of the tremor types), symmetry and severity of tremors were collected and reported. Symmetry of rest tremor (unilateral or bilateral) was defined according to upper and lower limbs scores, and according to upper limbs only for postural and kinetic tremors. Participants with MDS-UPDRS rest and/or postural and/or kinetic tremor score >2 in a single upper limb (eg, a patient with a rest tremor amplitude score 3 in the upper left limb; items 3.15, 3.16, 3.17) were identified as having severe tremor.

Furthermore, the burden of tremor on the total motor performance was calculated as:

$$\frac{\text{sum of subitems of MDS} - \text{UPDRS items } 3.15, 3.16, 3.17, 3.18}{\text{total MDS} - \text{UPDRS III score}} * 100$$

MDS-UPDRS item 2.10, "Tremor," was used to score participants' perception of tremor ("Over the past week have you usually had shaking or tremor?"; score range: 0–4).

Off- and on-State Tremor Scores Analyses

To examine the response of tremor to in-clinic administration of dopaminergic medication, rest, postural and kinetic tremor scores were also collected in the *on-state* when available. *On-state* scores were collected approximately 1 hour after receiving the usual PD medication and clinical *on-state* was confirmed for all included participants. In this analysis, all participants with the following characteristics were included: (1) availability of both *off*- and *on*-state assessments at the same yearly visit, (2) treatment with at least one dopaminergic medication (levodopa and/or dopamine agonist); (3) without DBS.

Statistical Analysis

Descriptive data for demographic and clinical variables were reported for all included participants at each follow-up. Due to the analysis exclusion criteria and missing data in the dataset, at each assessment only a subgroup of the baseline cohort was available (Table 1). To preserve available data and to avoid a selection bias, no participant was excluded from the analysis based on the presence of missing data at follow-ups. As conceivable in a longitudinal observational study in PD, it is possible that younger, less severe participants were more likely to attend the frequent follow-ups of the PPMI schedule. Therefore, demographic (age, sex) and clinical characteristics (disease duration at enrollment, MDS-UPDRS III, postural/kinetic/rest tremor subscores) of the *baseline cohort* were compared at each follow- up between participants with and without missing data (Tables S1–S3). Comparisons were carried out through Mann–Whitney *U* test for continuous variables and χ^2 test for categorical variables.

Then, linear mixed-effects (LME) models (lme4 package in *R*) fit by Restricted Maximum Likelihood (REML) with random intercept were separately fit to *off* and *off* + *on* tremor scores to analyze their progression over time. LME models offer the

TABLE 1 *Table showing the inclusion process and the total number of participants included in the* off *analysis and the* off + on *analysis*

	Total *N.* of participants	*N.* missing	*N.* with *off* < 12 hours	*N.* with DBS (DBS on)	*N.* eligible for *off* analysis	*N.* eligible for *off* + *on* analysis
Baseline	397	0	0	0	397	0
1 year	325	72	69	0	256	67
2 years	314	83	92	0	222	111
3 years	314	83	115	3 (2)	197	127
4 years	293	104	104	4 (2)	187	146
5 years	282	115	117	11 (10)	155	130
6 years	252	145	106	12 (9)	137	123
7 years	210	187	84	12 (8)	118	105

Note: N. eligible for off analysis: participants with an available off-state evaluation, with >12 h since the last dopaminergic medication dose and without DBS (or DBS switched off). N. eligible for off + on analysis: participants with both off-state and on-state evaluation at the same yearly visit.
Abbreviations: DBS: deep brain stimulation; N.: number.

flexibility to analyze longitudinal design data, without a case-wise data removal in the presence of missing data, while addressing for continuous and categorical covariates. Thus, rest, postural and kinetic tremor scores were each used as outcome variables, and time (as a continuous variable), sex, age and disease duration at enrollment were used as predictors. The significance ($P < 0.05$, two-tailed) of the models' predictors were calculated using bootstrap resampling with 1000 replicates.

In *off*-state tremor scores models, a binary covariate coded the presence or absence of missing data to account for such potential effect (equation 1).

$$\text{OFF postural/kinetic/rest tremor scores} \sim \text{time} + \text{sex} + \text{age at diagnosis} + \text{disease duration at enrollment} + \text{missing data} + (1|\text{id}) \quad (1)$$

The same models were also run including a binary covariate coding the use of specific non-dopaminergic anti-tremor medication (propranolol, primidone, clozapine, and trihexyphenidyl, as listed in the PPMI database); no significant effects were found, therefore this covariate was not included in the final models.

Then, *off* models were also computed after imputation with five different methods (mean, median, k-nearest neighbor with the mean of 20 nearest observations, k-nearest neighbor with the median of 20 nearest observations, classification and regression trees [CART]) to verify the findings of the original models.

In the analysis of tremor response to dopaminergic medication, rest, postural and kinetic tremor *off*- and *on*-state scores were used. A treatment covariate modeling *off*- and *on*-state scores, and a time*treatment interaction term were also included (equation 2). Dopaminergic medication dose was not used as a covariate since all patients enrolled in the PPMI were treated according to current standards.

$$\text{postural/kinetic/rest tremor scores} \sim \text{time} + \text{sex} + \text{age at diagnosis} + \text{disease duration at enrollment} + \text{treatment} + \text{time} * \text{treatment} + (1|\text{id}) \quad (2)$$

The models with the time * treatment interaction term were compared to the corresponding models without the interaction term after being refitted through a maximum likelihood approach (ML); a likelihood ratio test (LRT) was carried out to assess differences in models' goodness-of-fit.

Finally, a LME model adjusted for the effects of age, sex and disease duration at enrollment was also applied to MDS-UPDRS item 2.10 ("Tremor") scores to investigate whether participants' tremor perception changed over time.

To assess the dispersion of tremor scores distribution in the cohort at each assessment, the coefficient of variation, ie, standard deviation to mean ratio of a measure, was calculated. This is a non-dimensional relative index of the dispersion of the values of a variable; greater coefficients indicate greater dispersion of the standard deviation compared to the mean.

Statistical analyses were conducted in IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA) and R-Studio version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and clinical characteristics are reported in Table 2. Comparisons between participants included and excluded or missing from the analyses are shown in Tables S1–S3. *Off-state* summary descriptive statistics for available participants over the entire follow-up for tremor patterns, scores, symmetry, severe tremors and patients' perception of tremor (MDS-UPDRS item 2.10) are reported in Tables S4 to S7, respectively. Notably, the proportion of participants showing all three types of tremor (rest, postural and kinetic) was greatest at the last follow-up (41.5%, Table S4). Participants with action tremor (either postural or kinetic tremor, or both) were 18.9% at baseline and 12.7% at the last follow up. Participants with both rest and action tremor were 47.6% at baseline and 66.9% at the last follow up. Furthermore, for all three types of tremor the proportion of participants showing bilateral tremor was greatest at the last follow up, while the

TABLE 2 *Demographic and clinical characteristics of patients included in the analyses at each follow up. All scores refer to the* off-*state*

	Baseline	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Number of eligible participants	397	256	222	197	187	155	137	118
Number not included[1]	0	141	175	200	210	234	260	279
Males/Females	261/136 (66%/34%)	170/86 (66%/34%)	211/115 (68%/32%)	132/65 (67%/33%)	128/59 (68%/32%)	110/45 (71%/29%)	99/38 (72%/28%)	82/36 (70%/30%)
Age at diagnosis (years), mean (SD), range	61.91 (9.59), 34–85	60.85 (9.77), 34–85	61.89 (9.95), 34–85	61.61 (9.67), 34–85	60.75 (9.46), 35–85	60.92 (9.91), 34–85	61.05 (9.39), 35–82	60.92 (9.38), 37–85
Disease duration at enrollment (months), mean (SD), range	6.76 (4.07), 0–37	6.92 (6.96), 0–37	6.98 (6.73), 1–32	6.60 (6.42), 1–37	6.35 (5.85), 1–37	6.07 (5.63), 1–29	6.17 (5.81), 1–35	6.56 (6.26), 1–36
MDS-UPDRS III, mean (SD), range	21.00 (8.88), 4–51	24.64 (10.65), 6–60	27.77 (11.50), 3–62	28.89 (12.04), 4–80	30.99 (12.11), 6–80	31.43 (11.26), 7–59	33.88 (12.39), 10–73	35.36 (12.57), 9–68
Bradykinesia score[2], mean (SD)	8.32 (4.90)	9.59 (5.55)	10.89 (5.79)	11.34 (6.10)	11.80 (6.13)	11.96 (5.97)	12.58 (6.30)	13.42 (6.68)
Rigidity score[3], mean (SD)	3.82 (2.66)	4.59 (2.95)	5.54 (3.29)	5.57 (3.15)	6.15 (3.37)	6.10 (3.41)	6.66 (3.44)	6.67 (3.44)
Hoehn&Yahr, median (range)	2 (1–2)	1 (0–4)	2 (0–4)	2 (1–5)	2 (1–5)	2 (1–4)	2 (0–3)	2 (0–4)
Tremor burden[4] on MDS-UPDRS III, mean (SD), range	15% (11%), 0%–73%	15% (11%), 0%–67%	14% (10%), 0%–53%	14% (11%), 0%–46%	15% (11%), 0%–57%	14% (11%), 0%–52%	14% (11%), 0%–53%	16% (11%), 0–45%

Abbreviations: MDS-UPDRS III = Movement Disorders Society–Unified Parkinson Disease Rating Scale part III; SD = standard deviation.
[1]Partipants with either missing scores, time since last dopaminergic medication <12 h, or on active deep brain stimulation during the motor evaluation;
[2]Sum of MDS-UPDRS of subitems of items 3.4, 3.5, 3.6, 3.7, 3.8;
[3]Sum of subitems of item 3.3;
[4]Tremor burden on MDS-UPDRS III: [(sum of subitems of items 3.15, 3.16, 3.17, 3.18) / MDS-UPDRS III total score] * 100.

TABLE 3 *Results of the linear mixed models to test the effect of time, sex, age at diagnosis, disease duration at enrollment, and the presence of missing follow-ups on postural, kinetic and rest tremor scores over the 7-year follow-up*

	Postural tremor	Kinetic tremor	Rest tremor	MDS-UPDRS III
Intercept, estimate (SE)	0.691 (0.283)	0.306 (0.266)	−0.361 (0.537)	8.227 (3.061)
Time, estimate (SE)	0.084 (0.010)***	0.034 (0.010)**	0.193 (0.015)***	2.242 (0.083)***
Sex, estimate (SE)	0.195 (0.091)*	0.300 (0.086)**	−0.00008 (0.172)	1.911 (0.980)*
Age, estimate (SE)	−0.002 (0.004)	0.003 (0.004)	0.026 (0.008)**	0.181 (0.048)***
Disease duration at enrollment, estimate (SE)	0.008 (0.006)	0.007 (0.006)	0.040 (0.012)***	0.179 (0.069)**
Missing follow-ups, estimate (SE)	0.092 (0.14)	0.157 (0.139)	0.302 (0.289)	0.029 (1.656)

Note: The variable "Time" refers to follow-ups, once every year after baseline. The variable "Sex" was coded as 0 for females and 1 for males. The variable "missing follow-ups" was coded as 0 for the presence of missing data at follow-ups and 1 for the absence of missing data at follow-ups. *P*-values are represented as follows below.
Abbreviations: MDS-UPDRS III, Movement Disorders Society—Unified Parkinson's Disease Rating Scale; SE, standard error.
***$P < 0.001$;
**$0.01 < P \leq 0.001$;
*$0.05 < P \leq 0.01$.

TABLE 4 *Results of the linear mixed-effects models to test the effect of time, sex, age at diagnosis, disease duration at enrollment, treatment and interaction time * treatment on postural, kinetic and rest tremor* off *and* on *scores over the 7-year follow-up*

	Postural tremor	Kinetic tremor	Rest tremor	MDS-UPDRS III
Intercept, estimate (SE)	0.847 (0.357)	0.326 (0.320)	−0.0793 (0.681)	3.450 (4.192)
Time, estimate (SE)	0.081 (0.016)***	0.053 (0.016)**	0.149 (0.026)***	2.178 (0.141)***
Sex, estimate (SE)	0.244 (0.115)*	0.199 (0.101)*	0.347 (0.220)	2.769 (1.361)
Age, estimate (SE)	−0.005 (0.006)	0.004 (0.005)	0.018 (0.011)	0.238 (0.066)***
Disease duration at enrollment, estimate (SE)	0.010 (0.008)	0.004 (0.007)	0.048 (0.016)	0.320 (0.099)***
Treatment, estimate (SE)	−0.171 (0.092)	−0.160 (0.092)	−0.337 (0.153)*	−4.961 (0.818)**
Time * Treatment, estimate (SE)	−0.068 (0.020)*	−0.043 (0.020)*	−0.164 (0.034)**	−0.904 (0.180)**

Note: The variable time refers to follow-ups, once every year after baseline. The variable "Sex" was coded as 0 for females and 1 for males. The variable treatment was coded as 1 for *off-state* scores and as 2 for *on-state* scores. P-values are represented as follows below.
Abbreviations: MDS-UPDRS III, Movement Disorders Society—Unified Parkinson's Disease Rating Scale; SE, standard error.
***$P < 0.001$;
**$0.01 < P \leq 0.001$;
*$0.05 < P \leq 0.01$.

proportion of those without tremor was lowest at the last follow up (Table S5).

Over the 7 years observation, in at least one assessment 382 of 397 (96.2%) participants showed one type of tremor, 346 (87.2%) showed rest tremor, 338 (85.1%) showed postural tremor and 315 (79.3%) showed kinetic tremor. Off-state rest tremor scores showed high dispersion with a mean coefficient of variation (standard deviation/mean) over 7 years of 93%, compared to the composite scores of bradykinesia, rigidity and total MDS-UPDRS-III of 53%, 58% and 39%, respectively.

Tremor Severity

Off-state rest, postural and kinetic tremor scores showed a significant increase over time in the LME models adjusted for age, disease duration at enrollment and sex (Table 3). The presence of missing values was not a significant predictor. Male sex was associated with greater postural and kinetic tremor scores. Older age and longer disease duration at enrollment were associated with greater rest tremor scores. For comparison, a model was also fit to MDS-UPDRS III scores. The models computed after imputation overlapped with previous findings (Table S8), although the association between male sex and greater postural tremor scores was not confirmed in all imputation scenarios.

A total of 123 participants had a severe hand tremor (amplitude score >2 in one upper limb) in at least one assessment over the 7-year follow-up. At baseline 6.3% of the cohort showed a severe hand tremor; this proportion was 26.3% in the subgroup that completed the 7-year follow-up (Table S6). Notably, nearly all patients with a severe tremor had a severe rest tremor (118 of 123).

Participants' subjective perception of tremor (MDS-UPDRS item 2.10, "Tremor") showed a significant increase over time (estimate = 0.012, 95% CI 0.000–0.0024, $P = 0.046$). Age, sex and disease duration at enrollment did not show significant effects.

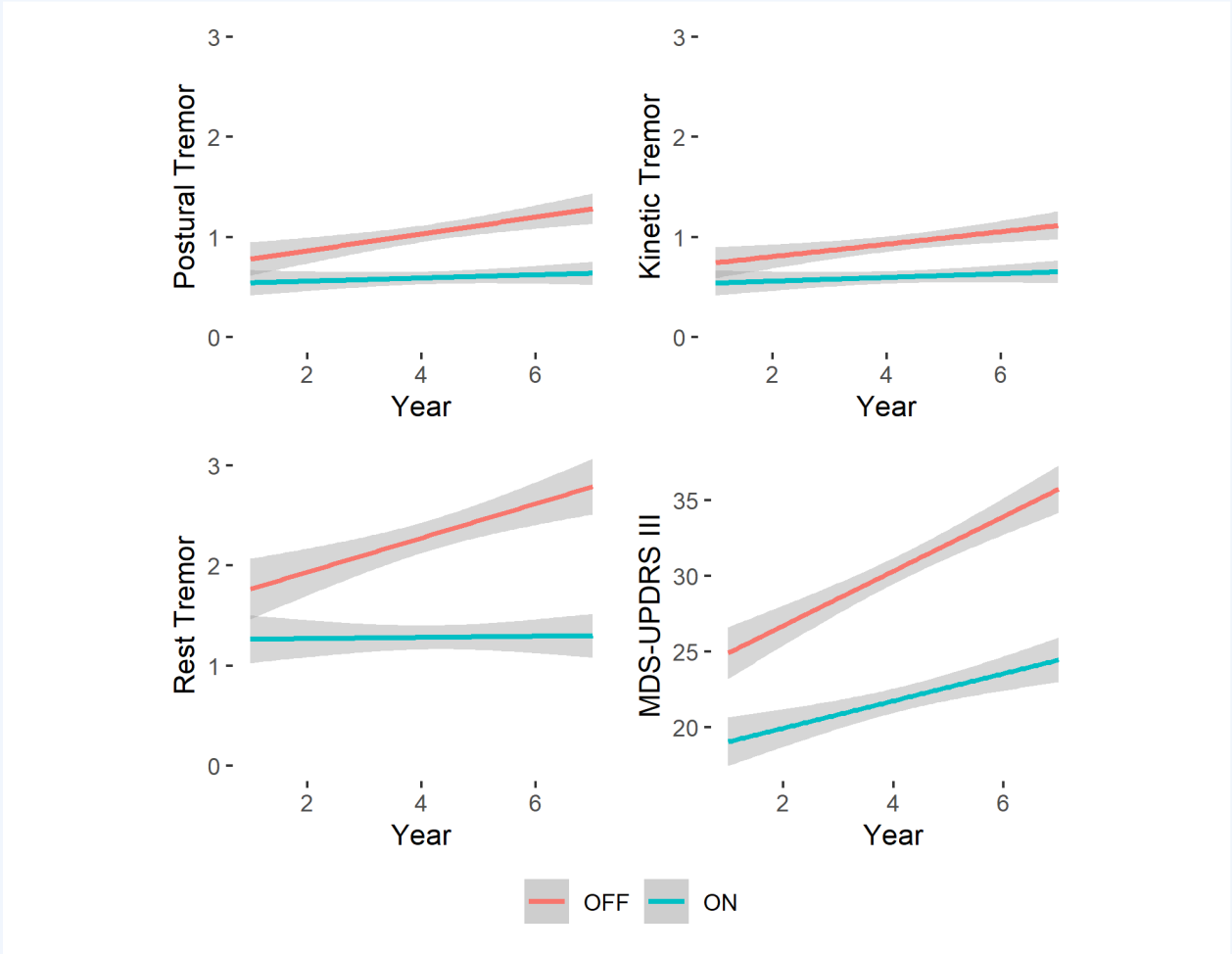

Figure 1. Tremor and total Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) scores change over time. For each type of tremor and for MDS-UPDRS III, a linear regression line with 95% confidence interval shows scores' change over time. The data source for these graphs is the same used for the analysis of tremor response to dopaminergic treatment, ie, it includes data from participants with both *off-state* and *on-state* assessment at each yearly follow up. Rest, postural and kinetic tremor graphs depict upper limbs scores only.

Tremor Response to Dopaminergic Therapy

Participants included in this analysis and their medications are reported in Table S9. The comparison between patients included and excluded is reported in Table S3.

In LME models adjusted for sex, age and disease duration at enrollment, the interaction term time * treatment was significant for all types of tremor (Table 4, Fig. 1). This implies that the effect of these two variables on tremor cannot be disentangled in the sole effects of the two parent variables. Thus, while tremor scores increase over time, the effect of treatment in reducing tremor scores also remains statistically significant. For all three types of tremor, the model with the interaction fitted significantly better than the model without the interaction term (all P-values<0.05).

To give a clinical picture of tremor scores improvement after dopaminergic medication administration at each assessment, a categorical classification (no improvement, partial improvement, full improvement) is also shown in Fig. 2 and Table S10. This showed that across the observation period, at each assessment dopaminergic medication resulted in no improvement in at least 20% of participants for rest tremor, 30% for postural tremor and 38% for kinetic tremor. There was an overlap between rest tremor non-responders and postural and/or kinetic tremor non-responders: among participants with rest tremor and another type of tremor, between 38% and 63% of rest tremor non-responders across the 7-year follow up were also non-responders in the other types of tremor.

Discussion

In this study, we conducted a comprehensive, 7-year longitudinal analysis on the clinical characteristics of tremor and its response to dopaminergic therapy in a large cohort of *de-novo*

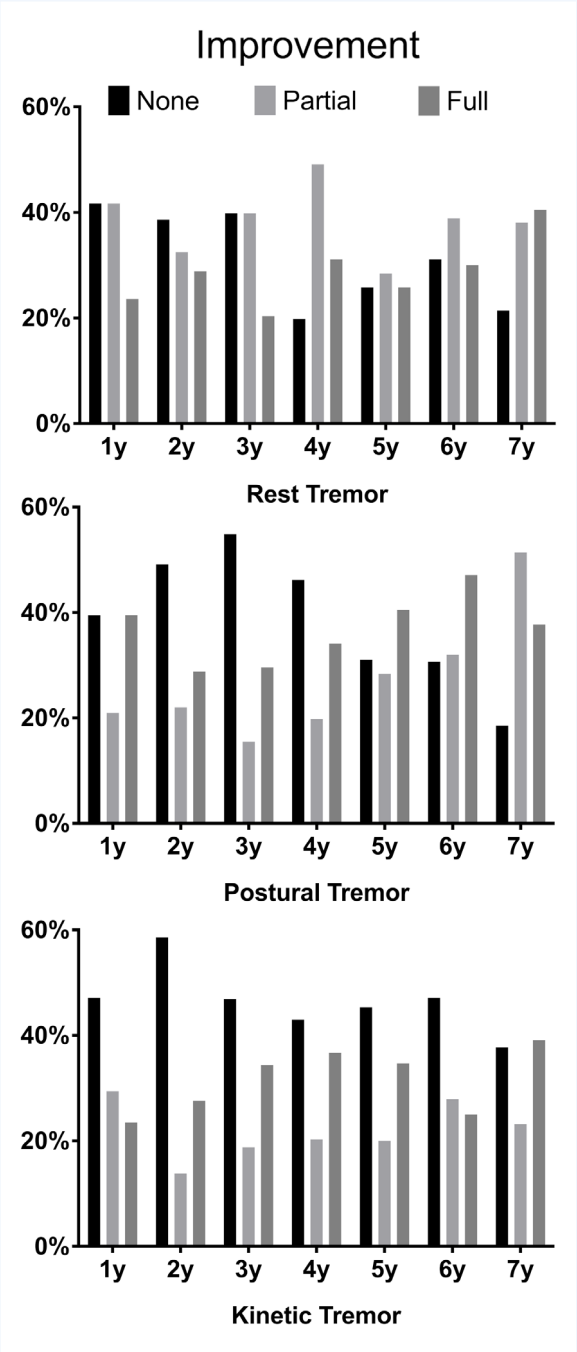

Figure 2. Figure showing the percentage of participants with no improvement, partial improvement or full improvement (resolution) of tremor after in-clinic dopaminergic medication administration. For each tremor type, at each assessment the total percentage adds to 100%.

PD patients. Compared to previous studies,[11–13] several characteristics are unique to this analysis: the long follow-up in a large cohort of idiopathic, well-characterized *de-novo* PD participants; the semi quantitative scoring system for rest, postural and kinetic tremor amplitude introduced with the latest MDS-UPDRS[16]; the *off*- and *on*-state in clinic assessment that allowed for the examination of both *off*-state tremor scores progression and the response to dopaminergic medication.

The main findings may be summarized as follows: (1) *off-state* tremor scores increase over time along with MDS-UPDRS III total score; (2) there is a significant effect of acute dopaminergic treatment in reducing tremor scores from *off-state* to *on-state*; (3) at each follow-up, in-clinic dopaminergic medication administration resulted in no improvement in at least 20% of participants for rest tremor, 30% for postural tremor and 38% for kinetic tremor; (4) tremor patterns (ie, the combinations of tremor types) and tremor scores are highly variable in the cohort and over time.

Nearly all patients (96.2%) exhibited one tremor type in at least one assessment over 7 years, with 87.2% showing rest tremor. Rest tremor was the most common tremor type, present in about 65–75% of participants at each follow-up. These findings are in agreement with a clinico-pathological study in 30 PD patients that showed that all participants experienced rest tremor when observed over a sufficient timespan.[8] Of note, the descriptive data provided in this study add details on the clinical characteristics, such as severity, symmetry and combinations of tremors, that were not present in the literature[9–13] and that may facilitate future investigations.

Off-state rest, postural and kinetic tremor scores in this cohort showed significant increases in the first 7 years after diagnosis. To the best of the authors' knowledge, a very limited number of studies have systematically addressed this subject, with conflicting findings and in different study settings. A study by Louis and colleagues found no annual rate increase in tremor over a mean observation of 3.3 years.[13] However, as pointed out by those authors, such study involved many participants with advanced disease (mean disease duration 6.8 years, 26.6% demented at baseline), so the findings may not apply to early PD cohorts.[13] Furthermore, that study was based on a community-based registry and tremor was recorded only in the medicated *on*-state. Another study by Goetz and colleagues found no increase in tremor and rigidity scores over 4 years in treated, *on*-state PD participants in HY stages II and III[17]; however, this study also enrolled mid-to-late stage PD patients (mean disease duration of 8.8 years). One study based on the DATATOP cohort,[12] a clinical trial that enrolled early treatment-naïve PD participants to initially receive tocopherol or selegiline followed by conventional treatment,[18] described an increase in tremor scores over time that was slower (half-time 3.9 years) compared to bradykinesia and rigidity (half-time 2 years); this finding does not seem to imply a stability of tremor scores, although a more detailed analysis was not carried out and tremor response to dopaminergic medication was not analyzed. It should also be noted that an exclusion criterion of DATATOP was "resting tremor of severe intensity as determined by tremor score ≥3", which might have excluded PD participants with more severe tremulous PD. Finally, in all these studies the original UPDRS version was employed. Such scale included a qualitative 0–4 rating (none, slight, mild, moderate, marked) for rest and action (ie, postural and kinetic) tremor that also included the evaluation of tremor constancy. Conversely, the latest MDS-UPDRS rates

rest, postural and kinetic tremor amplitudes through a semi quantitative scoring system (absent, <1 cm, 0–3 cm, 3–10, >10 cm etc.), and rest tremor constancy is scored separately.[19] Noteworthy, one previous study in early untreated PD participants that employed a clinical quantitative tremor rating during cognitive stress found a worsening of tremor scores after a 14 month follow-up.[20] Overall, the results of the current study indicate an increase in *off*-state tremor scores in the early years after PD diagnosis. It is likely, as indicated in the above-mentioned studies, that a stability or an overall decrease of tremor scores will follow with PD progression, although the evidence to support this statement is limited.[21] Additionally, an overall reduction of patients manifesting tremor may occur in more advanced stages, as shown by Hughes and colleagues in a neuropathological study.[10]

The effect of in-clinic dopaminergic treatment administration was also assessed and a significant effect in reducing all tremor types was found. Interestingly, these models showed the statistical significance of the time * treatment interaction term. Statistically, this finding may be attributable to increasing *off-state* tremor scores over time combined with substantially stable *on-state* tremor scores. Instead, the pathophysiological interpretation of this finding may not be straightforward. It is possible that increasing doses of dopaminergic medications achieve better results over time. Also, tremor ratings in the early stages may show a floor effect, so that greater improvements may become evident only when participants show higher *off-state* scores.[22] It should be noted that in the PPMI, dopaminergic medication was administered according to current clinical standards, and therefore it should be assumed that all study participants received the best medical therapy. Thus, it is unlikely that the effects shown in the models are due to different medications regimens across the cohort. The pathophysiology of tremor could also be involved. PD tremor, particularly rest tremor, has a neural substrate in a basal ganglia-cerebellum-thalamo-cortical circuitry,[23] and is also influenced by serotonergic[24–26] and noradrenergic projections;[27,28] these interactions may evolve as disease progresses.

Although the statistical effect in reducing tremor scores is significant, at each follow-up a proportion of the included subgroup of participants showed a partial or no response (20% of participants for rest tremor, 30% for postural tremor and 38% for kinetic tremor). This finding adds to a clinical report focused on rest tremor that highlighted how tremulous PD individuals may be divided in approximately equal proportions in responsive, intermediate and resistant based on the response to levodopa.[29]

Current treatments for levodopa-resistant tremor (eg, dopamine agonists and/or anticholinergics) are mostly based on clinical experience and only small studies.[30] Novel treatments for PD tremor, such as serotonergic or noradrenergic medications, deserve further investigation. It has previously been suggested that selective modulation of serotonin postsynaptic receptors may improve tremor;[31] also, beneficial effects of low dose clozapine, an atypical neuroleptic with serotonin receptors modulation properties, has been demonstrated in the past,[32–34] but side effects limit its clinical use. The current role of DBS in PD tremor has been recently assessed in societies' guidelines, indicating its appropriateness in advanced PD if tremor cannot be controlled with medication.[35] However, the use of early invasive interventions or non-invasive lesional techniques is still under investigation.

In light of our findings, it is not surprising that previous surveys showed that tremor is reported as the most troublesome motor manifestation by people with early PD.[2,3,18,36] In this regard, we found a significant increase over time in scores of patient's subjective experience of tremor. It should be noted that the effect identified in statistical modeling is rather small and therefore its clinical significance should be interpreted with caution.

Great variability of tremor scores and patterns was also observed. This implies an inherent difficulty in quantifying tremor amplitude and tremor types in the clinic. Therefore, in the clinical research setting, the use of instrumental recordings (eg, surface electromyography and/or accelerometers) could be beneficial to better classify tremor characteristics and response to medication. Indeed, the lack of detailed information about the type and amplitude of tremor is likely to result in the under recognition of any positive or negative effect of medications. Instrumental measurements would also allow a better characterization of re-emergent tremor, which is currently not separately assessed by MDS-UPDRS III and may also be more troublesome than rest tremor itself.[37,38]

Limitations

Several limitations should be addressed. There was a reduction in the number of available participants over time. Furthermore, although the PPMI applied a strict protocol to ensure uniformity in data collection, some participants were unable to attend the yearly assessment after an overnight withdrawal of at least 12 hours. To account for these issues, LME models adjusted for age, disease duration at enrollment, sex and the presence of missing data were implemented. Then, a sensitivity analysis with imputation strategies was performed to support the validity of the original models.

Tremor scores used in this study were derived from the MDS-UPDRS III evaluation, which includes a single rating for postural and re-emergent tremor. Therefore, we were unable to evaluate this specific aspect, which should be assessed in future studies. Indeed, re-emergent tremor is thought as a continuation of rest tremor and may have an overlapping network pathophysiology. Furthermore, the use of the MDS-UPDRS III evaluation did not allow to classify tremor according to proposed classifications which include the evaluation of tremor frequency.[39]

The baseline cohort included 70% of Tremor Dominant patients, usually less severe than akinetic-rigid patients and more ready to enter a longitudinal study in which medication is withheld for 6 months.[40] Although participants evaluated in the *off*-state observed a 12 h overnight medication withdrawal, dopamine agonists and even levodopa can have long-lasting antiparkinsonian effects.[41] Nonetheless, significant reductions of rest, postural and kinetic tremors scores after in-clinic dopaminergic medication administration were shown. Finally, we did not

consider rest tremor constancy scores to maintain homogeneity across upper limbs scores of postural, kinetic and rest tremor.

Conclusion

In this study, we examined the clinical characteristics, longitudinal progression, and response to dopaminergic medication of rest, postural, and kinetic tremors in the large, de novo PD PPMI cohort over a 7-year follow-up. The main findings of this analysis show that tremor is present in nearly all patients in early PD. *Off*-state tremor severity increases over time and a response to dopaminergic medication was found at the cohort level for all tremor types. However, great interindividual variability was shown, with no improvement in at least 20% of participants for rest, 30% for postural and 38% for kinetic tremor. Since tremor is the most troublesome manifestation during the first 10 years of the disease,[2,3,6] studies that address the pathophysiology and treatments for PD tremor are needed. Overall, this study details the current clinical landscape of PD tremor and highlight critical issues for interventional studies.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

J.P.: 1A, 1B, 1C, 3A, 3B.
G.D.: 1A, 1B, 1C, 3A, 3B.
A.P.: 1C, 2A, 2B, 2C, 3B.
S.S.: 1C, 2A, 2B, 2C, 3B.
R.C.: 1A, 1B, 1C, 3B.
N.P.: 1A, 1B, 1C, 3A, 3B.

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Ethical Compliance Statement: All participating PPMI sites received approval from an ethical standards committee prior to study initiation and written informed consent for research was obtained from all participants in the study. An additional specific IRB approval was not required to carry out the analysis presented in this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Data Availability

Data used in the preparation of this article was obtained from the Parkinson's Progressive Markers Initiative database (https://www.ppmi-info.org). Source data used for analyses presented in this study are available from the authors upon request. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Table showing *baseline values* for participants with and without missing data at each follow-up. The purpose of this table is to compare included and excluded groups at each follow-up, according to their *baseline values*, with the aim to show the baseline clinical characteristics of the participants who attended/missed subsequent follow-ups. All scores refer to the *off-state*.

Table S2. Table showing p-values of statistical tests performed to investigate differences in *baseline* characteristics and scores between participants included and excluded at each follow-up in the *off* analysis. Differences in MDS-UPDRS III, postural, kinetic and rest tremor, age and disease duration were tested through Mann–Whitney *U* test. Differences in sex proportions were tested through Pearson's Chi-Square test.

Table S3. Table showing *baseline values* of the subgroups included and missing in the analysis of tremor response to dopaminergic treatment. The purpose of this table is to compare included and excluded groups at each follow-up, according to their *baseline values*, with the aim to show the baseline clinical characteristics of the participants who attended/missed subsequent follow-ups.

The subgroups in the "Included" column are those with both an *off-state* and an *on-state* assessment at the same visit: these participants were included in the linear mixed model used to characterize the response of tremor to dopaminergic treatment over the follow-up period.

Table S4. Distribution of tremor patterns, defined according to MDS-UDPRS items 3.15, 3.16, 3.17, in the *off-state* across the cohort at each yearly assessment from baseline to 7-year follow-up.

Table S5. Mean scores and characteristics of laterality of rest, postural and kinetic tremor, defined according to MDS-UDPRS items 3.15, 3.16, 3.17 in the *off-state* from baseline to 7-year follow-up.

Table S6. Severe hand tremors and severe hand rest tremor in the cohort over the 7-year follow-up. Severe hand tremor was defined as a MDS-UPDRS III tremor score >2 in at least one upper limb (MDS-UPDRS III items 3.15, 3.16, 3.17, upper limbs only, in the *off-state*).

Table S7. Distribution of MDS-UPDRS item 2.10 ("Tremor") scores in the cohort over the 7-year follow-up.

Table S8. Results of the linear mixed models with different imputation methods to test the effect of time, sex, age at diagnosis, disease duration at enrollment, and the presence of missing follow-ups on postural, kinetic and rest tremor scores over the 7-year follow-up.

Table S9. Parkinson's disease medication in patients with both *off* and *on* assessments over the 7-year follow-up. In the *off* + *on* linear mixed-effects models, only patients with the following characteristics were included: (1) both *off* and *on* assessment at the same yearly follow-up; (2) taking at least one dopaminergic agent; (3) without deep brain stimulators.

Table S10. Table showing the number and percentage of participants with no improvement, partial improvement or full improvement (resolution) of tremor after in-clinic dopaminergic medication administration.