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Cognitive Function in 1736 Participants in NINDS Exploratory Trials in PD Long-term Study-1

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Abstract

Introduction—Clinical cohort studies suggest that mild cognitive impairment (MCI) is common in early Parkinson's disease (PD). The objectives of this paper were to describe cognitive function in a large clinical trial of early treated PD patients at baseline and over time using two brief cognitive screening tests.

Methods—In total 1,741 participants were enrolled in the NINDS Exploratory Trials in Parkinson's disease (NET-PD) Long-term Study-1 (LS-1). The Symbol Digit Modalities Test (SDMT) was collected annually. The SCales for Outcomes in PArkinson's disease-COGnition (SCOPA-COG) was collected at baseline and at year 5. The trial was stopped early based on a planned interim analysis after half the cohort completed 5 years of follow-up. The median length of follow-up was 4 years (range 3 to 6 years). Predictors of cognitive change were examined using cross sectional (baseline) and longitudinal multivariable linear regression.

Results—The mean (SD) change from baseline to 5 years was −1.9 (5.1) for the SCOPA-COG and −2.1 (11.1) for the SDMT. Age and baseline UPDRS motor scores were associated with a more rapid decline in SDMT scores and 5 year SCOPA-COG scores. Male gender was associated with more rapid decline in SDMT. Self-reported income was a novel predictor of baseline cognitive function, even adjusted for educational status, although not significantly associated with change over time.

Conclusion—This large prospective cohort study demonstrated mild cognitive decline in early treated Parkinson's disease. The study identified income level as a novel predictor of cognitive function.

Keywords

Cognitive Impairment; Parkinson's Disease; SCOPA-COG; SDMT; MCI

Introduction

Cognitive dysfunction is an important non-motor manifestation of Parkinson's disease (PD) [1] and contributes more to health-related Quality of Life than motor symptoms or motor complications [2, 3]. Cognitive impairment (in 3 or more cognitive domains) has been

reported in as many as 18–24% of early PD patients in clinic-based cohorts using comprehensive neuropsychological testing [4–7], but is less frequently documented in clinical trial cohorts of early PD.

Several clinical trials in PD have measured cognitive function as a secondary outcome, the largest of which to date has been the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study (DATATOP) study. In DATATOP less than 1% of subjects had cognitive impairment at baseline (as assessed using the Mini Mental State Exam) and only 5.8% met criteria for cognitive impairment after 5 years [8]. This may have been due to the higher educational and performance status of the trial participants, as well as the insensitivity of the MMSE, a non-specific dementia screening instrument, to detect mild cognitive impairment in PD [9–11]. Despite these limitations, Uc et al. found that predominantly affected side, tremor score, dopaminergic therapy type, total daily levodopa equivalent dose, time since diagnosis, and years between symptom onset and diagnosis were all significant predictors of cognitive decline on the MMSE in the DATATOP cohort [8].

Schneider et al. studied 413 early de novo PD patients from the NET-PD FS1 and FS-TOO studies using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Frontal Assessment Battery (FAB), and Letter-Number Sequencing [12–14]. They found that none of the cognitive measures declined significantly over the 12–18 months of the trials.

The recently reported MODERATO trial of rasagiline for cognitive function in 170 participants with PD-MCI utilized the SCales for Outcomes in PArkinson's disease-COGnition (SCOPA-COG) and the Montreal Cognitive Assessment (MoCA). Neither the treatment nor placebo groups experienced a decline in these outcome measures during the 24 month study[15]. This outcome may have been due to the sample size of the study and/or to the short duration of the trial. The recently completed NIH Exploratory Trials in Parkinson's Disease Long-term Study-1 (NET-PD LS-1) used two screening measures: the SCOPA-COG and the Symbol Digit Modalities Test (SDMT). The SCOPA-COG was selected because it assesses multiple domains including memory, attention, executive function and visuospatial function [16–18]. The SCOPA-COG has been validated in small samples of PD dementia and PD-MCI [18, 19] but has not been shown to have high sensitivity or specificity for PD-MCI [20]. van Rooden et al examined the change in SCOPA-COG over time in the PROfiling PARKinson's disease (PROPARK) study and found a more rapid decline in patients who were older at the time of enrollment[21]. Using the same cohort, Zhu et al. found age at enrollment, education, total daily levodopa dose and daytime sleepiness to be most predictive of incident dementia, as defined by a score of 22 or less on the SCOPA-COG [22].

The SDMT was also administered annually during the NET-PD LS1 study. It is a brief cognitive test of short-term memory and attention switching that can be administered written or orally. While this brief screening test has not been validated as a screening instrument for PD cognitive impairment, it can differentiate non-demented and demented PD from healthy controls [23–25]. As the SDMT is a timed test, it has been criticized for being confounded by PD motor impairment when completed by hand [26]. In the NET-PD LS-1 study, the

SDMT was administered orally to try to reduce motor effects on performance. The Parkinson's Progression Markers Initiative (PPMI) recently examined the performance of the SDMT over 3 years and found that participants with possible REM behavior disorder experienced a more rapid annual decline of −0.69 points/year [27].

The objective of this paper is to describe the cognitive profile of the NET-PD LS-1 study participants using the two screening measures (SCOPA-COG and SDMT), and to examine demographic and disease-related predictors of cognitive decline in this cohort. We hypothesized that the size and duration of this clinical trial cohort would permit us to detect small changes in cognitive function over time which had not been identified in previous trial cohorts.

Methods

Participants

The NINDS Exploratory Trials in Parkinson's Disease Long-term Study-1 (NET-PD LS-1) was a large, randomized, multicenter, placebo-controlled trial of creatine as a potential disease modifying agent for PD. A total of 1741 participants were enrolled with early, treated PD. The institutional review boards of the 45 participating sites approved the study, the study protocol, and the informed consent process and documentation. All patients provided written informed consent. The primary study findings have been published [28]. Parkinson's disease patients could be enrolled if they were within 5 years of diagnosis and 2 years of starting dopaminergic therapy. While there were no specific cognitive screening tests for enrollment, participants were excluded if they had "any unstable or clinically significant condition that would impair the subjects' ability to comply with long-term study follow-up" and if they had "any significant features suggestive of a diagnosis of atypical parkinsonism." Because the study terminated early, patients were followed for a minimum of 3 years and a maximum of 6 years, with annual in-person assessments. This analysis is based on the final database lock on May 5, 2014.

Assessments

The SCOPA-COG was measured twice (baseline and year 5) and the SDMT was administered annually orally to try to reduce motor effects on performance. SDMT scores of zero (29 events) were treated as missing.

Statistical Methods

The SCOPA-COG and SDMT were analyzed both at baseline and as change over time in separate multivariable linear regression models. Baseline models used baseline measures of either SCOPA-COG or SDMT as continuous dependent variables. The models included the predictor variables measured at baseline listed below:

- Demographic variables: age, gender, income level (defined as the self-reported "average income for someone in your profession"), level of education, side of onset of symptoms, years since diagnosis, years since PD symptom onset.

- Disease severity: UPDRS II (activities of daily living), UPDRS III (motor symptoms). Bulbar symptoms were defined as the sum of UPDRS questions 5,6,7, 18 & 19 [8], postural instability defined as the average of 5 UPDRS items 13, 14, 15, 29, 30, total tremor score defined as the average of 8 tremor items from the UPDRS questions 16, 20–21[29], orthostatic blood pressure[30], and depression as measured by the Beck Depression Inventory –II (BDI-II) score.
- Type of dopaminergic therapy used at baseline (levodopa, levodopa and dopamine agonist, or dopamine agonist), total daily levodopa-equivalent dose (LED), and the ratio of levodopa to total LED (including levodopa and DA agonist).

Baseline Models—An automated selection approach was used to screen the predictor variables for the multiple linear regression models of SCOPA-COG and SDMT at baseline. A stepwise selection procedure was used allowing variables to enter and leave the model based on significance level (alpha of 0.20 to enter and alpha of 0.10 to stay in the model). The criterion for selecting among models was adjusted R-squared (PROC GLMSELECT / selection=stepwise (select=SL SLE=0.2 SLS=0.1 choose=ADJRSQ)). The following variables were forced into each model due to their *a priori* presumed importance: side predominantly affected, tremor score, dopaminergic therapy type, total daily levodopa equivalent dose, time since diagnosis, and years between symptom onset and diagnosis [8, 30]. Once the variables were selected, a mixed effect linear model was fit with clinical site as a random effect and the predictor variables obtained from the automated selection step as fixed effects. The final mixed effect linear models included those variables with a p-value less than 0.01 in either model. However, only variables with a Bonferroni-corrected p-value less than 0.0015 were considered statistically significant, due to the large number of hypotheses being tested. As a sensitivity analysis to the automated approach, backward and forward selection methods were also applied using the change from baseline to 5 years. Graphical and formal model diagnostic procedures indicated that no outliers were present. Variance inflation factor (VIF) was used to assess multicollinearity.

Change from Baseline Models—The following methods were used for change in SCOPA-COG at 5 years and for change in SDMT over 1–6 years. For SCOPA-COG a linear regression model of change from baseline to 5 years included only those participants who had 5 year data collected (completers only); missing data was not imputed. For the SDMT model of change from baseline, repeated measures on the same patient were included in a linear mixed model with years from baseline as a continuous predictor variable in the model. The model included all participants who had at least 1 post baseline assessment. The model assumed a first order autoregressive covariance structure between years 1–6 (via the repeated statement of SAS Proc Mixed). Firstly a model was fit for each predictor variable and for its interaction with time, adjusting for age, gender, site (random effect), treatment group (creatine or placebo). Variance inflation factor (VIF) was used to assess multicollinearity. Variables, with a p-value less than 0.2 in a simpler model of either SCOPA-COG or SDMT, were included in a multivariable model. Next, variables with a p-value less than 0.1 were retained in the final model along with treatment group, education

level, gender and site, but only variables with a significance level of <0.0015 were considered statistically significant given the large number of hypotheses being tested.

Subjects missing SDMT and SCOPA-COG at 5 years (N=284) were on average older and had lower (worse) cognitive scores at baseline compared to those participants with 5 year data (N=722) and compared to participants who were not expected to have 5 year data due to early termination of the study (n=735), (see Table e1). We assumed that given age and the baseline cognitive score, the probability of having a missing cognitive assessment does not further depend on the cognitive status. Thus, missing at random (MAR) was assumed, and maximum likelihood estimation was used to handle missing SDMT assessments. Specifically in this method, the SDMT assessments collected in earlier years were used to "borrow" information for missing observations in later years while "account[ing] for the uncertainty of this projection in the calculation of the standard errors and test statistics."[31]

Results

The SCOPA-COG was completed by 1731 participants at baseline and by 676 participants at year 5 (70% of the participants who completed their Year 5 visit). The SDMT was completed by 1736 participants at baseline and by 715 participants at year 5 (75% of the participants who completed year 5). Figure 2 shows the number of participants who completed the SDMT at each year of the study. Reasons for missing cognitive data at year 5 included 284 participants (30% of expected) who were missing (not at random) either due to withdrawal of consent, loss to follow-up, death, or some other reason. There were 737 participants (42% of the total enrolled) who were considered missing at random because of premature termination of the study. Supplementary Table 1 shows the baseline data for participants who completed the 5 year data compared to those who did not complete the study either because of early termination or other reasons. Participants who were missing not at random (missing for the reasons above) were older and had more severe UPDRS total, SDMT, and SCOPA-COG scores at baseline.

Among completers, the mean (SD) SCOPA-COG score decreased from 30.3 (5.4) at baseline to 28.6 (7.1) at Year 5 (for a mean change of −1.9 (5.1) points over 5 years). The mean (SD) SDMT score decreased from 44.4 (11.7) at baseline to 42.4 (14.8) at Year 5 (mean change of −2.1 (11.1) points over 5 years). As shown in Figure 1, the distribution of both the SCOPA-COG and SDMT became more highly skewed to the left at year 5, suggesting either that there was a subset of participants who experienced a more rapid decline, or that the subjects with missing data were more likely to have a lower score at baseline. As shown in Figure 2, there was an initial increase in SDMT scores at Year 1, consistent with a practice effect, which then declined in a curvilinear manner over time.

First we examined predictors of cognitive function measured at baseline. Table 1 shows the parameter estimates from the multivariable linear regression models of SCOPA-COG and SDMT at baseline. The results of the two separate models were similar and confirmed previous reports of predictors of cognitive function in early PD [8, 30]. Age, gender, education, UPDRS part III and the BDI-II depression score were all significantly associated with both the baseline SCOPA-COG total score and the baseline SDMT score, consistent

with prior reports. On average, women scored 3.49 points on the SDMT (S.E. 0.52, p<0.0001) and 1.76 points on the SCOPA-COG (S.E. 0.24 p<0.0001) higher than men at baseline. Unexpectedly, disease duration, time since diagnosis, and side of onset were not significant in our multivariable model. Finally lower self-reported income was associated with lower (worse) cognitive scores in both models, even after adjusting for years of education.

We then examined predictors of change over time using longitudinal regression models for the SDMT and linear regression models for the change from baseline to year 5 in the SCOPA-COG. Table 2 shows parameter estimates of the final, longitudinal regression models of the change from baseline over 1–6 years for the SDMT and the change from baseline to year 5 for the SCOPA-COG. The results of the two multivariable models were fairly similar. The predicted annual rate of decline was −0.63 points per year for SDMT and the adjusted mean change for SCOPA-COG over 5 years was −1.82 when adjusting for the mean value of each covariate in the final model. On the SDMT, on average, the difference in the change from baseline between males and females was −1.27 at any given year (males scored lower at every time point). The adjusted mean change in SDMT from baseline to 5 years was −1.0 for females and −2.3 for males. Gender was not a significant predictor of change in SCOPA-COG although the trend was in the same direction as in the SDMT model. Older age at baseline was associated with worse change (more rapid decline) on the SCOPA-COG. On average, the change from baseline to 5 years in SCOPA-COG was 1.08 points greater for each 10 year increase in baseline age. Similarly, older age was associated with faster decline on the SDMT; the adjusted mean change in SDMT from baseline to 5 years was −1.38 for patients enrolled at age 60 vs. −4.36 for patients enrolled at age 70 (See figure 2). As expected, higher (worse) UPDRS part III scores were associated with a greater (worse) change in SDMT and SCOPA-COG. Symmetric symptom onset and depression as measured using the BDI-II were marginally associated with lower SDMT over time however neither was statistically significant (p=0.003 for both) and neither variable entered into the SCOPA-COG model. Participants who started the study on levodopa containing regimens appeared to have a more rapid rate of decline over time on SDMT than participants on dopaminergic agonists alone, however this did not reach our Bonferroni-adjusted level of significance (p=0.006). Finally, neither education nor income level were statistically significant in these models, although there was a trend towards lower SCOPA-COG scores at 5 years in participants earning <45K (−1.007, p=0.09).

Discussion

This study presents longitudinal cognitive data from a large well-characterized early cohort of treated PD study participants. The main strength of our study was the large number of participants enrolled, allowing us to detect weak determinants of cognitive function. Overall participants exhibited very little change on the SCOPA-COG and SDMT over time, however this is likely to be an under-estimate of the true cognitive decline in PD patients related to: 1) recruitment bias into this randomized controlled trial excluding PD patients with early cognitive symptoms; 2) early dropout of subjects due to cognitive impairment (as evidenced by the lower cognitive function at baseline in those with missing follow-up visits); 3) the limitations of these brief cognitive screening instruments [32].

Limitations of our study include the fact that the SCOPA-COG was administered only twice during the study, unlike the SDMT, and that there was a high degree of missing SDMT and SCOPA-COG data at year 5. Nearly half of the total enrolled cohort was followed for less than 5 years due to the fact that the study was terminated prematurely. However, 30% of the expected 5 year data was missing due to drop out for various reasons including death. The longitudinal SDMT model considered the relationship of missingness to baseline cognitive function and adjusted for missingness accordingly. However, it is possible that the baseline characteristics included in the model do not fully explain the reasons for missing SDMT cognition scores; in other words, those with missing follow-up assessments may have not only been worse at baseline, but had faster rates of decline. The SCOPA-COG model of change from baseline included completers only. Since there was only one post-baseline SCOPA-COG assessment performed, it was not possible to use the same approach to implicitly impute missing data. Hence this analysis may be more likely to be biased towards patients who are declining more slowly and the predictors of cognitive decline identified in our analysis may not be the same predictors for more severe patients.

Another limitation of the study is that although the SDMT was administered orally, it is still possible that bradyphrenia, slow visual saccades and bradyphemia could have confounded the SDMT results [33–35]. Indeed, improved performance on the manual version of the SDMT after treatment with levodopa has previously been published [26]. We note that in the NET-PD LS-1 study, participants on levodopa (only) at baseline had lower cognitive screening scores and lower scores over time, however this may have been due to reverse causation (i.e. participants with lower baseline cognition were more likely to be prescribed levodopa only).

In our multivariable analysis, we were able to confirm previously reported predictors of cognitive decline including male gender, age and motor severity [8] [21]. One novel predictor of baseline cognitive performance in our study was income level, even adjusted for educational status. Baseline self-reported income was significantly associated with cognitive performance and marginally associated with cognition over time. This may have been due to reverse causation (lower pre-morbid cognitive status leading to lower income) although interestingly this was adjusted for highest education level achieved. Income has been reported to predict cognitive decline in other cohorts [36–38], however it has not been previously examined in studies of cognition in Parkinson’s disease.

In summary, this study provides a description of cognitive function over time in a large cohort of early treated PD patients, and explores demographic and clinical predictors of cognitive function in PD. These data support prior studies showing that PD patients experience mild cognitive decline early in their disease course. The study identified income level (even adjusted for educational status) as a novel predictor of cognitive function, suggesting that this variable should be collected in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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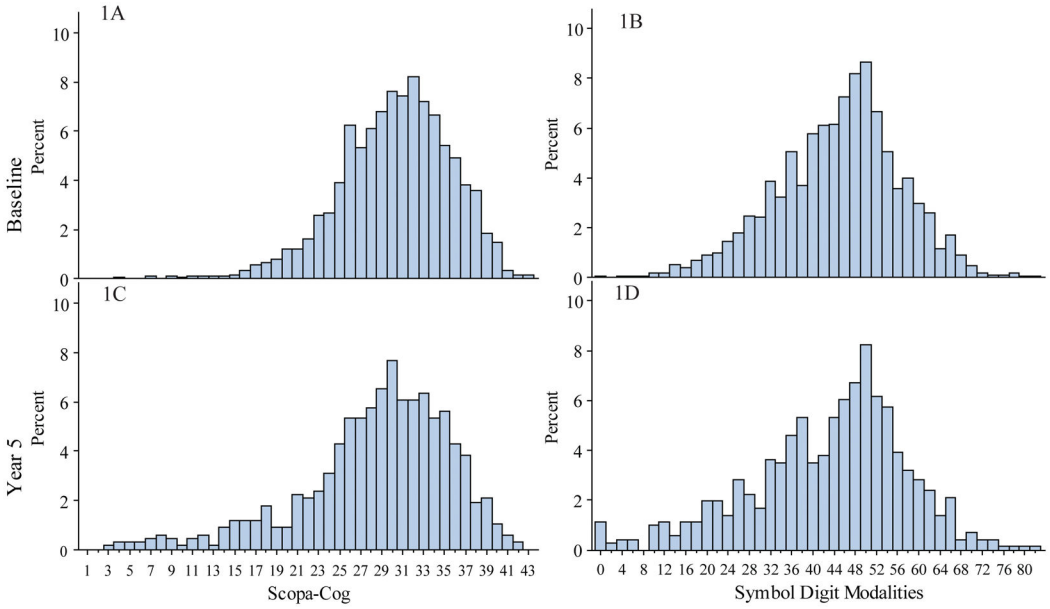
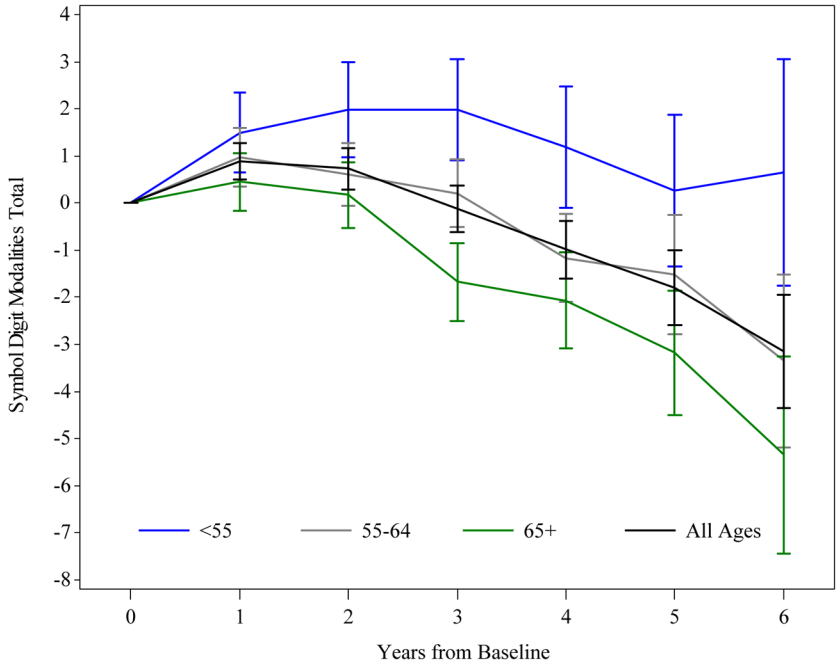


Figure 1.

Distribution of SCOPA-COG (N=1731) and Symbol Digit Modalities (N=1736) total scores in participants at baseline and Year 5 in the NET-PD LS-1 study. For both scales higher scores are “better”. At baseline the SCOPA-COG distribution (1A) shows a slight left skew, while the SDMT distribution (1B) lacks significant skew or kurtosis. At Year 5, the SCOPA-COG (1C, N=676) and SDMT (1D, N=715) distributions show a stronger left skew compared to baseline possibly due to missing data for those patients with worse baseline scores, or due to more rapid decline in participants with lower baseline scores.



Expected	1741	1741	1741	1741	1365	955	369
Observed	1735	1601	1502	1397	1075	704	316
Mean SDMT (SD)	44.5 (11.7)	45.5 (12.3)	45.5 (12.6)	45.1 (13.1)	44.3 (13.9)	42.8 (14.1)	42.0 (14.3)

Figure 2. Mean Change (95% CI) from Baseline in SDMT by Age Group

Plot of change from baseline in SDMT scores over 5 years by baseline age. At baseline n=378 (22%) were less than 55 years old, n=663 (38%) were 55–64 years, and n=694 (40%) were 65 or older. The number of participants at each time point is shown below the graph in tabular form. Expected= the number of subjects expected to have the annual visit based on the subject's enrollment and date of study termination. Observed= the actual number of participants with SDMT data at each time point. SD= Standard Deviation.

Table 1

Parameter estimates of the regression models of SCOPA-COG and SDMT at Baseline

Parameter estimates of the final linear regression models for total SCOPA-COG and SDMT at baseline adjusted for age and education level. PD=Parkinson's disease; UPDRS ADL= Unified Parkinson's Disease Rating Scale Part II; UPDRS Motor= Unified Parkinson's Disease Rating Scale Part III; BDI-II= Beck Depression Inventory-II; LED= Levodopa equivalent daily dose; DA=dopamine agonist (including pramipexole, ropinirole, rotigotine, and bromocriptine (one subject))

		Baseline SDMT (N=1714)			**Baseline SCOPA-COG (n=1707)**		
Baseline Characteristics		**Estimate**	**S.E.**	**Pr > |t|**	**Estimate**	**S.E.**	**Pr > |t|**
Gender (Male reference)		3.49	0.52	**<.0001**	1.76	0.24	**<.0001**
Age		−0.44	0.03	**<.0001**	−0.12	0.01	**<.0001**
Education (High school is reference)	Graduate	4.60	0.74	**<.0001**	3.40	0.34	**<.0001**
	Bachelors	3.35	0.74	**<.0001**	2.60	0.34	**<.0001**
	Associate	3.75	1.01	**0.0002**	1.30	0.47	0.005
	Some college	1.38	0.81	0.08	1.23	0.37	**0.001**
Income level (>85K reference)	Refused to disclose	−1.98	0.78	0.011	−1.39	0.36	**0.0001**
	≤45k	−1.17	0.72	0.11	−1.08	0.34	**0.0013**
	45k–85K	−1.07	0.62	0.085	−0.73	0.29	0.011
Duration since diagnosis		−0.44	0.22	0.049	−0.06	0.10	0.54
Dominant Side (Right is reference)	Symmetric	−3.17	2.24	0.16	−0.40	1.03	0.70
	Left	−0.24	0.47	0.60	0.52	0.22	0.02
BDI-II total		−0.15	0.05	**0.0014**	−0.08	0.02	**0.0001**
UPDRS ADL part II		0.05	0.08	0.51	0.17	0.04	**<.0001**
UPDRS motor part III		−0.28	0.04	**<.0001**	−0.12	0.02	**<.0001**
Average Tremor Score		1.18	0.81	0.14	1.04	0.37	0.006
Type of Dopaminergic Therapy (compared to DA only)	levodopa only	−1.22	0.57	0.03	−0.83	0.27	0.002
	levodopa + DA	−0.51	0.66	0.44	−0.30	0.31	0.33

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Table 2

Parameter estimates of the regression models for Change in SDMT and SCOPA-COG

Parameter estimates of the regression models for change in SCOPA-COG over 5-years and change in SDMT scores over 1–6 years. Values <0.0015 are bold. BDI-II= Beck Depression Inventory-II; UPDRS Motor= Unified Parkinson's Disease Rating Scale Part III; DA=dopamine agonist (including pramipexole, ropinirole, rotigotine, and bromocriptine). Parameter estimates provided are adjusted for all variables listed in the table and for treatment (not significant) and clinical site (random effect). The SDMT model assumes a first-order autoregressive covariance structure for repeated measurements within subject.

		Longitudinal Model of Change in SDMT over 1–6 years N=1592			**Model of 5-year Change in Scopa-Cog N=668**		
Effect		**Estimate**	**SE**	**two sided p-value**	**Estimate**	**SE**	**two sided p-value**
Intercept		25.913	2.288	**<.0001**	13.145	2.244	**<.0001**
Baseline Cognition Score (SDMT or SCOPA-COG)		−0.286	0.017	**<.0001**	−0.206	0.042	**<.0001**
Age (years)		−0.153	0.031	**<.0001**	−0.108	0.024	**<.0001**
Year		1.151	0.546	0.03			
Age*Year		−0.029	0.009	0.002			
Gender (male is reference)		1.274	0.338	**0.0002**	0.625	0.432	0.15
Education (high school is reference)	Graduate	0.772	0.493	0.12	0.559	0.611	0.36
	Bachelors	0.259	0.503	0.61	0.054	0.611	0.93
	Associate	−0.503	0.692	0.47	0.604	0.888	0.50
	Some college	−0.250	0.554	0.65	−0.814	0.667	0.22
Income level (>85K reference)	Refused to disclose				−0.454	0.644	0.48
	≤ 45k				−1.007	0.598	0.09
	45k–85K				−0.628	0.499	0.21
Dominant Side (right is reference)	Symmetric	−4.917	1.630	0.003	−3.012	1.772	0.09
	Left	−0.536	0.314	0.09	0.137	0.382	0.72

		Longitudinal Model of Change in SDMT over 1–6 years N=1592			Model of 5-year Change in Scopa-Cog N=668		
Effect		**Estimate**	**SE**	**two sided p-value**	**Estimate**	**SE**	**two sided p-value**
Baseline BDI-II total		−0.092	0.031	0.003			
Baseline UPDRS motor		−0.161	0.023	**<.0001**	−0.089	0.027	**0.001**
Baseline Average Tremor Score		3.084	0.540	**<.0001**			
Baseline Type of Dopaminergic Therapy (DA alone is reference)	levodopa only	0.550	0.639	0.39	−0.821	0.476	0.08
	levodopa+DA	0.185	0.741	0.80	0.080	0.536	0.88
Baseline Type of Dopaminergic Therapy *Year (DA alone is reference)	levodopa only	−0.521	0.189	0.006			
	levodopa+DA	−0.513	0.218	0.019			