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Subjective cognitive complaint in Parkinson disease patients with normal cognition: Canary in the coal mine?

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Abstract

Objective: To determine the frequency and impact of subjective cognitive complaint (SCC) in Parkinson disease (PD) patients with normal cognition (NC).

Methods: PD patients with expert consensus-determined NC at baseline were asked a single question regarding presence of SCC. Baseline (N=153) and longitudinal (up to 4 follow-up visits over a 5-year period; N=121) between-group differences in PD patients with (+SCC) and without

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(-SCC) cognitive complaint were examined, including cognitive test performance and self- and informant-rated functional abilities.

Results: Eighty-one (53%) participants reported a cognitive complaint. There were no between-group differences in global cognition at baseline. Longitudinally the +SCC group declined more than the -SCC group on global cognition (Mattis Dementia Rating Scale-2 total score (F=(1, 431)=5.71; p=0.02), processing speed (Symbol Digit Modalities Test (F=(1, 425)=7.52; p=0.006) and executive function (Trails B (F=(1, 419)=4.48; p=0.04)), although results were not significant after correction for multiple testing. In addition, the +SCC group was more likely to progress to a diagnosis cognitive impairment over time (hazard ratio=2.61, p=0.02). The +SCC group also demonstrated significantly lower self- and knowledgeable informant-reported cognition-related functional abilities at baseline, and declined more on an assessment of global functional abilities longitudinally.

Conclusions: PD patients diagnosed with normal cognition, but with SCC, report poorer cognition-specific functional abilities, and long-term are more likely to be diagnosed with cognitive impairment and experience global functional ability decline. These findings suggest that SCC and worse cognition-related functional abilities may be sensitive indicators of initial cognitive decline in PD.

Keywords

Parkinson disease; cognition; cognitive complaint

INTRODUCTION

Parkinson disease (PD) patients frequently exhibit non-motor symptoms such as cognitive impairment, even early in the course of the disease[1]. Up to 80% of PD patients develop dementia (PDD) in the long-term[2], and up to 30% of patients without dementia meet criteria for mild cognitive impairment (PD-MCI)[3]. Examining patients prior to onset of cognitive decline, one study of established PD patients with normal cognition at baseline found that within 6 years nearly 50% had developed PD-MCI, and all patients with incident PD-MCI subsequently progressed to dementia within 5 years[4].

Research in healthy older adults suggests that subjectively-identified cognitive decline may indicate early changes in cognitive functioning not detected on neuropsychological tests[5, 6]. The value of subjective cognitive complaint (SCC) and its relationship to objective cognitive decline in PD patients without dementia is not well understood. Some studies, with sample sizes ranging from 70 to 250 participants, have shown that PD patients with SCC perform significantly worse on objective cognitive measures than those without SCC[7–13] while others have not[14, 15]. Only four of the studies reported longitudinal follow-up data to examine conversion of non-demented PD patients to PD-MCI or PDD; two of these studies found higher rates of conversion from normal cognition to PD-MCI over a 2-2.5-year-period in PD patients with SCCs[8, 11], one study found higher conversion to dementia in PD patients with SCC compared to those without SCC over a 7.5-year-period[12], and one study found no change in neuropsychological assessments between non-demented PD patients with and without SCCs at 1 and 2 year follow-up[15].

Subjective cognitive complaints, such as problems with attention, processing speed and word finding, are commonly reported among cognitively-normal PD patients, but their significance remains unclear. The goal of the present study was to assess the utility of a single question in cognitively-normal PD patients to identify those with and without cognitive complaint, and compare them cross-sectionally and longitudinally on cognitive and functional measures.

METHODS

Participants

Participants were enrolled through the National Institute of Neurological Disorders and Stroke- funded Morris K. Udall Center for Parkinson's Disease Research at the University of Pennsylvania. One hundred fifty-three patients with idiopathic PD and normal cognition at baseline were administered cognitive assessments and ratings of functional abilities performed by trained research staff. One hundred twenty-one of the 153 patients were then followed for a minimum of 3 years (corresponding to at least 2 follow-up visits), and up to 5 years, either annually or biennially based on their length of time in the study. The remaining 37 participants did not have at least 2 follow-up visits at the time of analyses and therefore were not included in our longitudinal data. PD diagnosis was made according to UK Brain Bank criteria[16]. All participants had an expert consensus determination of normal cognition based on Movement Disorders Society (MDS) criteria (see below)[3, 17]. Patients with a diagnosis of PD-MCI or dementia at baseline were excluded.

Standard protocol, approvals, registrations, and patient consents

Approval from the institutional ethical standards committee on human experimentation was obtained before study initiation, and written informed consent was obtained from all study participants.

Assessments

Clinical assessments—The presence of a cognitive complaint was assessed with a single yes/no question: "Do you feel that your memory and thinking have gotten worse?" If the rater was asked to elaborate on the question, the timeframe of noticeable change in cognition since PD diagnosis was given. Based on response, participants were then divided into two groups: those with cognitive complaint (+SCC) and those without cognitive complaint (-SCC). "Subjective cognitive complaint" is used in the present study as it is a well-known term, however we technically are assessing self-reported cognitive decline. Motor symptom severity was measured with the Unified Parkinson's Disease Rating Scale (UPDRS) Part III[18], and disease severity was measured using the Hoehn & Yahr (H&Y) Scale[19]. Depression was assessed using the 15-item Geriatric Depression Scale (GDS-15)[20]. REM sleep behavior disorder (RBD) was assessed with a single item (range 0-4) from the Parkinson's Disease Sleep Scale (PDSS-2)[21]. General functional abilities were assessed with the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)[22], and cognition-specific function was assessed with the Penn Parkinson's Disease Activities Questionnaire-15 (PDAQ-15)[23]. Knowledgeable Informants (KIs) completed the

ADCS-ADL and Knowledgeable Informant version of the PDAQ-15. PD patients completed the PDAQ-15 Patient version.

Neuropsychological assessment—A battery of neuropsychological tests was administered by trained research personnel. The measures were part of the recommended standard battery of cognitive tests for PD patients enrolled in cognitive research studies at Udall Centers[24]. Global cognition was assessed using the Mattis Dementia Rating Scale-2 (MDRS-2)[25] and Montreal Cognitive Assessment (MoCA)[26]. Measures of attention/ processing speed were Trail Making Test Part A[27] and the Symbol Digit Modalities Test (SDMT)[28]. Measures of executive functioning were Letter-Number Sequencing (LNS)[29], phonemic verbal fluency (FAS)[30], and Trail Making Test Part B[27]. Memory was assessed using the Hopkins Verbal Learning Test– Revised (HVLT-R)[31]. Visuospatial measures were the Benton Judgment of Line Orientation (JOLO)[32] and the Clock Drawing Test (CDT; command condition)[33]. Language was assessed using Boston Naming Test (BNT)[34] and semantic verbal fluency (animals)[30]. Due to the timing of assessment introduction into the battery, the number of subjects that completed each assessment varied (see Table 2). All assessments were performed in the PD medication “on” state.

Cognitive consensus—Assignment of cognitive status was made for each patient during an annual consensus conference held for each patient by movement disorders specialists and a geriatric psychiatrist affiliated with the Penn Udall Center. The consensus process involved multiple (five on average) pairs of experienced physician raters reviewing demographic and available clinical data, including the clinician or patient impression of cognitive decline compared with premorbid state, the ADCS-ADL, and all raw and standardized cognitive test scores. The physician raters assigned patients a determination of normal cognition, MCI, or dementia based on the available data following the diagnostic criteria proposed by the MDS Task Forces for MCI (level 1 criteria)[3] and dementia[17]. For a given test, a standardized score ≥1.5 SD below the mean was considered impaired, although consensus rater discretion was allowed. The raters within a pair reached agreement on all cases assigned to them. For cases with a between-pair discrepancy in determination, an independent physician rater adjudicated. Inter-rater agreement among pairs was high (kappa=0.80, 95% confidence interval=0.70-0.90)[4].

Statistical analyses

To compare demographic and clinical characteristics in the +SCC and -SCC groups, two sample t-test was utilized to examine mean differences for continuous variables and chi-square test for categorical variables. If any significant differences were revealed regarding relevant demographic or clinical characteristics, the significant variable was included as a co-variate in one-way ANCOVA analyses to examine group differences in cognitive and functional performance. To assess group differences in long-term cognitive functioning, linear mixed-effects model analyses were performed. Fixed effects in the mixed-effects model include SCC group status, follow-up time, interaction between SCC group status and follow-up time, along with appropriate covariates. A random intercept was included to account for correlations among repeated measures of cognitive functioning. Kaplan-Meier method was used to estimate the incident impairment probability (rate) from normal

cognition to any cognitive impairment between the +SCC and -SCC groups, and Cox regression model was used to examine the association between cognitive complaint status and risk of conversion to MCI or PDD. Kaplan-Meier method was also used to estimate the sensitivity and specificity of SCC by year 4. Although our study was exploratory rather than confirmatory, we present results both without[35] and with correction for multiple testing using the Bonferroni method. All statistical tests were two-sided. Statistical analyses were performed using SPSS (version 23).

Data availability statement

Data will be shared at the request of other investigators for purposes of replicating procedures and results.

RESULTS

Participant demographics

Demographic and clinical features are detailed in Table 1. There were a total of 153 PD patients with consensus process-determined normal cognition at baseline, including 81 (52.9%) who reported cognitive complaint. The two groups did not differ significantly in age, sex, disease duration (i.e., time since diagnosis), education, Hoehn & Yahr stage, RBD item score, or UPDRS motor score. The +SCC group had significantly higher GDS-15 scores ($t(152)=-2.94$; $p=.003$). Therefore, GDS-15 score was included as a covariate in all subsequent between-group comparisons, including the Cox regression model.

Baseline neuropsychological and functional assessments

Results of baseline cognitive and functional assessments are presented in Table 2. The entire sample had MDRS-2 data, and the majority had data for the entire neuropsychological battery. A subset of the sample had data regarding functional measures. At baseline, consistent with having been classified as having normal cognition by expert consensus, the +SCC group did not perform significantly worse than the -SCC group on any of the 14 cognitive tests after correction for multiple comparisons. The +SCC group demonstrated significantly lower scores on the PDAQ-15 Knowledgeable Informant Total ($F(1, 113)=7.00$, $p=0.009$) and Patient Total ($F(1, 128)=13.91$, $p<0.001$) than the -SCC group. Scores on the ADCS-ADL did not significantly differ between the two groups.

Longitudinal neuropsychological and functional assessments

One hundred twenty-one patients completed at least two follow-up visits, and up to 4 annually-scheduled, post-baseline visits, with the last visit occurring 5 years post-baseline in some participants due to a missed visit. Of the 121 patients, 5 (-SCC=3; +SCC=2) were deemed to have developed cognitive impairment by consensus at some point during follow-up, and then reverted to normal cognition at a subsequent visit. The average duration of follow-up for the entire sample was 2.9 years. For the -SCC group the average duration of follow-up was 2.88 years, and was 2.83 years for the +SCC group. At baseline, 64 (52.9%) of these patients had a cognitive complaint while 57 (47.1%) did not, mirroring the baseline sample. Sixty-eight patients had 2 follow-up visits (+SCC=56%), 30 patients 3 follow-up visits (+SCC=40%), and 23 patients had 4 follow-up visits (+SCC=48%).

On our follow-up analyses, controlling for baseline GDS-15 score and baseline cognitive test score, the +SCC group declined at a significantly faster rate than the -SCC group on the ADCS-ADL (F=(1,404)=12.98; p<0.001). The +SCC group also declined more on the MDRS-2 Total score (F=(1, 431)=5.71; p=0.02), SDMT (F=(1, 425)=7.52; p=0.006) and Trails B (F=(1, 419)=4.48; p=0.04) over time, but this did not withstand correction for multiple testing (Table 3).

Thirty-three patients (28.4%) developed cognitive impairment by consensus determination (either MCI [N=29] or dementia [N=4]) over time. On Kaplan-Meier analysis of these patients, the +SCC group (N=24) had a higher conversion rate to MCI and dementia than did the -SCC group (N=9) ($\chi^2(1)=4.36$, p=0.04) (Figure 1). On Cox regression model and controlling for GDS-15 score, +SCC patients were 2.61 times more likely to convert to MCI or dementia than were -SCC patients (hazard ratio=2.61, p=0.02). As CDT was significantly different between groups at baseline before adjustment for multiple comparisons, we ran an additional Cox regression model in the subset of patients with this score available (-SCC N=33; +SCC N=41), and baseline CDT did not predict long-term cognitive decline (p=0.10).

We also examined the sensitivity and specificity of baseline SCC for predicting future cognitive impairment by year 4 using the Kaplan-Meier method. The sensitivity of SCC was 69% and the specificity of SCC was 51%.

DISCUSSION

To our knowledge, this is the largest study examining the relationship between subjective cognitive complaint and objective decline in a cohort of PD patients comprised exclusively of consensus process-determined cognitively normal patients at baseline. The results of the present study show that about half of established PD patients with normal cognition report cognitive complaint, even when their global and detailed cognitive performance is not clearly distinguishable from patients without such complaint. Additionally, such patients reported or were deemed to have worse function both cross-sectionally and longitudinally. Finally, these patients also performed worse long-term on several cognitive measures, and were more likely to be diagnosed with an incident cognitive disorder over time.

In comparison to some previous longitudinal research examining the impact of SCC on cognitive performance over time in PD patients, we examined global cognitive complaint as opposed to just memory complaint[8], included a larger number of patients with SCC[8, 11, 12], followed patients over a longer period of time for some[8, 15], but not all[12], studies, and included important co-variates in our models[12, 15].

Presence of cognitive complaints in an overall intact patient might denote a stage of cognitive decline in PD between normal cognition and MCI, as has been reported in the general population[5, 6, 36], and SCC in pre-clinical Alzheimer's disease (AD) is associated with an increased risk for conversion to dementia[37, 38]. However, in PD it is important to emphasize cognitive complaints broadly, rather than a memory complaint specifically, given the range of cognitive deficits that occurs in non-demented PD patients[39, 40]. Executive functioning and attention in particular are reliant on fronto-striatal functioning, which is

disrupted initially in the course of PD[41, 42]. The findings of the present study suggest a simple, single clinical question focused on self-perception of general cognitive changes compared with one's premorbid state may predict future decline in these cognitive domains. A report of subjective cognitive decline is simple to administer and may be meaningful in a clinical setting, alerting clinicians to closely monitor cognition over time and to consider earlier referral for a comprehensive neuropsychological evaluation to establish a clear baseline.

Interestingly, PD patients with cognitive complaint and their KIs both reported functional decline at baseline as assessed by the PDAQ-15. Functional decline has been demonstrated in studies of PD-MCI using performance-based functional assessments[43], the PDAQ-15[23] and the Parkinson's Disease-Cognitive Functional Rating Scale[44]. These results illustrate that even prior to the development of MCI, PD patients with cognitive complaints and their KIs may perceive a subtle decline in everyday cognitive functional abilities. Notably, there was no significant difference at baseline between groups regarding the ADCS-ADL, a functional questionnaire which was developed for use in AD and assesses both basic and instrumental activities of daily living (ADLs). However, on follow-up, the rate of change between groups was significantly different, with the +SCC group declining more quickly on this global functional measure compared with the -SCC group. This highlights the utility of cognition-related functional rating scales developed specifically for PD patients, because while the ADCS-ADL detected functional decline over time, only the PDAQ-15 detected functional differences at baseline. One possible explanation for this is that the PDAQ-15 may be more sensitive to initial functional impairment and therefore show greatest changes early on in the cognitive decline process (+SCC patients on average scored 81-86% of maximum available points on the PDAQ-15 at baseline), while the ADCS-ADL may only start to decline in parallel with more significant changes in cognition (+SCC patients on average scored 94% of maximum available points on the ADCS-ADL at baseline).

The mean baseline GDS-15 scores were 2.7 (SD=2.8) and 1.5 (SD=1.9) in the +SCC and -SCC groups, indicating a higher likelihood of subthreshold depression (SubD) in the +SCC group. A previous study examined the relationship between SubD and subjective cognitive complaint in PD patients and found that SubD patients reported more subjective cognitive complaint than non-depressed patients[45]. As SCC predicted cognitive decline even when controlling for baseline depression score, the finding suggests that minor depressive symptoms occur secondary to or independent of cognitive complaints.

The sensitivity for baseline SCC to predict future cognitive impairment was acceptable, but the specificity was low. So while approximately 70% of participants who developed cognitive impairment over time had a cognitive complaint while intact, many participants who did not develop cognitive impairment also had subjective complaints at baseline.

Limitations of the current study include a racially and ethnically homogenous sample with a high level of education. Thus, results may not be applicable to the general PD population and should be replicated in a multi-site study with heterogeneous cohorts. Additionally, we used a single, unvalidated question that queried only about "memory" and "thinking" to assess cognitive complaints, and the question was answered only by the patient. Finally,

while we examined depression in relation to cognitive complaint, we did not explore other psychiatric symptoms (e.g., apathy or anxiety) or possible confounding variables (e.g., family history of dementia) as potential contributing factors to subjective decline. Research has demonstrated that apathy[46, 47] and anxiety[48, 49] are associated with cognition in PD, and future research should explore the potential relationship of these factors with subjective cognitive complaint.

This study demonstrates that the presence of subjective cognitive complaint, as determined by a single question, predicts future cognitive decline in PD patients with normal cognition by detailed testing and consensus diagnosis. Additionally, it may serve as a useful indicator for patient and KI perception of mild difficulties performing cognitive activities of daily living. Asking a simple yes/no question to a patient who appears cognitively normal, and who may not spontaneously report cognitive concern, may help clinicians identify those patients at risk for cognitive decline over the next several years. As observational studies and clinical trials in PD shift their focus to preclinical and prodromal patients and testing of possible disease-modifying therapies, identification of cognitively-intact patients with cognitive complaint will allow the study of cognitive decline in PD from its earliest clinical manifestation.

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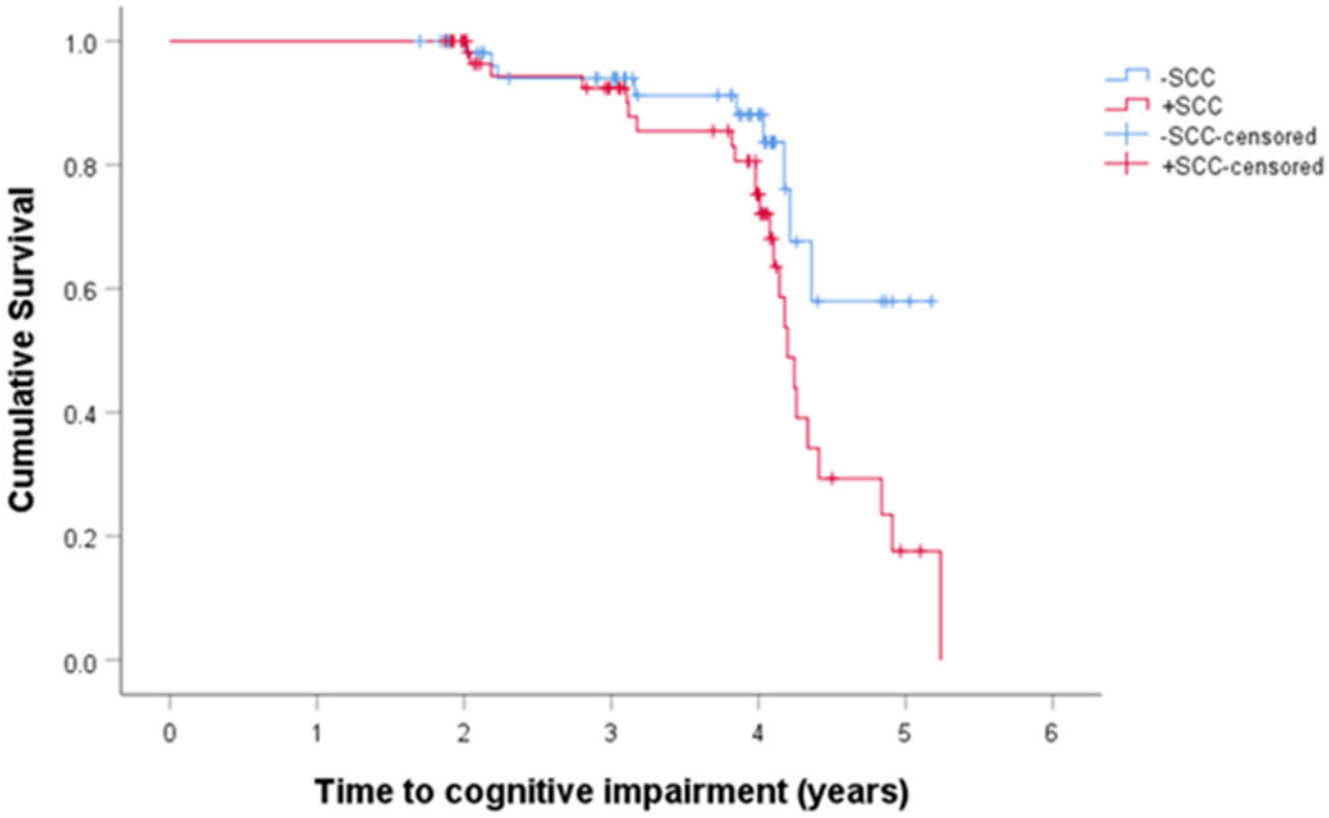

Figure 1.
Cognitive Complaint in PD Patients

Table 1.

Baseline demographics and clinical characteristics

Variables	N (-SCC) (+SCC)	Mean -SCC (SD)	Mean +SCC (SD)	t-test; p-value*
Age (years)	72 81	68.2 (8.3)	68.3 (7.9)	0.92
Sex (% male)	72 81	54%	59%	0.62
PD duration (years)	72 81	5.8 (4.0)	7.0 (5.0)	0.12
Education (years)	72 81	16.7 (2.1)	16.4 (2.2)	0.34
GDS-15 total score	72 81	1.6 (2.0)	2.7 (2.8)	0.003
Hoehn & Yahr stage (median (IQR))	72 81	2.0 (IQR=2-3)	2.5 (IQR=2-3)	0.11
UPDRS motor score	72 81	19.7 (11.3)	23.0 (11.0)	0.07
REM sleep behavior disorder item score	58 70	0.5 (0.6)	0.7 (1.1)	0.18

*Bonferroni corrected significance set at $p<0.006$.

Abbreviations: GDS-15 = 15-item Geriatric Depression Scale; UPDRS = Unified Parkinson's Disease Rating Scale; IQR = interquartile range

Table 2.

Baseline neuropsychological and functional assessments

Assessment*	N (-SCC) (+SCC)	-SCC mean (SD)	+SCC mean (SD)	F statistic; p-value**
MoCA	72 81	27.21 (2.09)	27.05 (2.04)	$F(1, 150)=0.18$, p=0.67
MDRS-2 total score	72 81	141.00 (2.31)	140.56 (2.51)	$F(1, 150)=2.81$, p=0.10
HVLT-R immediate recall	72 79	23.88 (5.44)	22.80 (4.36)	$F(1, 148)=2.81$, p=0.10
HVLT-R delayed recall	72 79	7.63 (3.20)	7.51 (3.11)	$F(1, 148)=0.03$, p=0.87
HVLT-R recognition discrimination	72 79	9.67 (2.44)	9.38 (2.60)	$F(1, 148)=0.27$, p=0.61
LNS	72 80	10.5 (2.54)	10.63 (2.40)	$F(1, 149)=0.04$, p=0.85
Phonemic verbal fluency (FAS)	71 80	47.63 (12.98)	46.96 (12.94)	$F(1, 148)=0.05$, p=0.82
Animal fluency	71 80	21.30 (5.19)	20.16 (4.40)	$F(1, 148)=1.50$, p=0.22
Trails A (time)	72 80	38.26 (12.07)	42.48 (15.08)	$F(1, 149)=2.23$, p=0.14
Trails B (time)	72 80	87.79 (46.16)	92.30 (43.49)	$F(1, 149)=0.21$, p=0.65
SDMT	71 79	41.34 (8.89)	38.51 (9.19)	$F(1, 147)=3.90$, p=0.05
JOLO	72 80	24.25 (5.1)	24.55 (4.15)	$F(1, 149)=0.61$, p=0.44
Clock Drawing	41 53	6.34 (0.79)	5.87 (1.11)	$F(1, 91)=4.18$, p=0.04
BNT	70 79	69.20 (99.32)	57.57 (3.07)	$F(1, 146)=1.32$, p=0.25
ADCS-ADL total	61 69	75.48 (3.23)	73.30 (8.81)	$F(1, 127)=1.47$, p=0.23
PDAQ-15 KI total	54 62	56.00 (4.86)	51.63 (9.41)	$F(1, 113)=7.00$,p=0.009
PDAQ-15 patient total	64 67	54.95 (5.88)	48.67 (9.03)	$F(1, 128)=13.91$, p<0.001

*All scores presented are raw scores.

**Bonferroni corrected significance set at p<0.004 for 14 cognitive tests and at p<.02 for 3 functional measures.

Abbreviations: MoCA = Montreal Cognitive Assessment; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; BNT = Boston Naming Test; MDRS-2 = Mattis Dementia Rating Scale-2; HVLT-R = Hopkins Verbal Learning Test-Revised; SDMT = Symbol Digit Modalities Test; JOLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; PDAQ-15 = 15-item Penn Parkinson's Disease Activities Questionnaire.

Table 3.

Longitudinal neuropsychological and functional assessments

Assessment*	Annual change (SE) in -SCC group	Annual change (SE) in +SCC group	p-value** (between-group difference in annual change)
MoCA	−0.31 (0.10)	−0.45 (0.09)	0.28
MDRS-2 total score	−0.45 (0.15)	−0.94 (0.14)	0.02
HVLT-R immediate recall	0.10 (0.20)	−0.03 (0.18)	0.62
HLVT-R delayed recall	0.04 (0.13)	0.07 (0.12)	0.87
HVLT-R recognition discrimination	0.06 (0.08)	0.15 (0.08)	0.48
LNS	−0.22 (0.09)	−0.38 (0.08)	0.18
Phonemic verbal fluency (FAS)	−1.01 (0.35)	−1.34 (0.33)	0.48
Animal fluency	−0.77 (0.17)	−0.88 (0.16)	0.65
Trails A (time)	2.04 (0.64)	3.54 (0.61)	0.09
Trails B (time)	6.10 (1.79)	11.31 (1.70)	0.04
SDMT	−1.32 (0.29)	−2.40 (0.27)	0.006
JOLO	−0.26 (0.18)	−0.47 (0.17)	0.41
Clock Drawing	−0.06 (0.05)	−0.01 (0.05)	0.46
BNT	−0.23 (0.08)	−0.18 (0.08)	0.64
ADCS-ADL total	−0.51 (0.33)	−2.16 (0.31)	<0.001
PDAQ KI total	−1.11 (0.32)	−1.50 (0.30)	0.38
PDAQ patient total	−0.62 (0.30)	−0.36 (0.30)	0.54

*All scores presented are raw scores.

**Bonferroni corrected significance set at p<0.004 for 14 cognitive tests and at p<.02 for 3 functional measures.

Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; BNT = Boston Naming Test; MDRS-2 = Mattis Dementia Rating Scale-2; MoCA= Montreal Cognitive Assessment; HVLT-R = Hopkins Verbal Learning Test-Revised; SDMT= Symbol Digit Modalities Test; JOLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; PDAQ-15 = 15-item Penn Parkinson's Disease Activities Questionnaire.