Subjective Cognitive Complaint in Parkinson’s Disease Patients With Normal Cognition: Canary in the Coal Mine?

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ABSTRACT: Objective: The objective of this study was to determine the frequency and impact of subjective cognitive complaint (SCC) in Parkinson’s disease (PD) patients with normal cognition.

Methods: Patients with PD with expert consensus-determined normal cognition at baseline were asked a single question regarding the presence of SCC. Baseline (N = 153) and longitudinal (up to 4 follow-up visits during a 5-year period; N = 121) between-group differences in patients with PD with (+SCC) and without (−SCC) cognitive complaint were examined, including cognitive test performance and self-rated and informant-rated functional abilities.

Results: A total of 81 (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, F1,431 = 5.71, P = 0.02), processing speed (Symbol Digit Modalities Test, F1,425 = 7.52, P = 0.006), and executive function (Trail Making Test Part B, F1,419 = 4.48, P = 0.04), although the results were not significant after correction for multiple testing. In addition, the +SCC group was more likely to progress to a diagnosis of cognitive impairment over time (hazard ratio = 2.61, P = 0.02). The +SCC group also demonstrated significantly lower self-reported and knowledgeable informant–reported cognition-related functional abilities at baseline, and declined more on an assessment of global functional abilities longitudinally.

Conclusions: Patients with PD with normal cognition, but with SCC, report poorer cognition-specific functional abilities, and are more likely to be diagnosed with cognitive impairment and experience global functional ability decline long term. These findings suggest that SCC and worse cognition-related functional abilities may be sensitive indicators of initial cognitive decline in PD. © 2020 International Parkinson and Movement Disorder Society

Key Words: cognition; cognitive complaints; Parkinson disease

Patients with Parkinson’s disease (PD) frequently exhibit nonmotor symptoms such as cognitive impairment, even early in the course of the disease.1 Up to 80% of patients with PD develop dementia in the long term,2 and up to 30% of patients without dementia meet the criteria for mild cognitive impairment (PD-MCI).3 Examining patients prior to the onset of cognitive decline, one study of established patients with PD with normal cognition at baseline found that within 6 years nearly 50% had developed PD-MCI, and all of
the 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 patients with PD without dementia is not well understood. Some studies, with sample sizes ranging from 70 to 250 participants, have shown that patients with PD with SCC perform significantly worse on objective cognitive measures than those without SCC,7-13 whereas others have not.14,15 Only 4 of the studies reported longitudinal follow-up data to examine the conversion of nondemented patients with PD to PD-MCI or PD with dementia; 2 of these studies found higher rates of conversion from normal cognition to PD-MCI during a 2 to 2.5-year period in patients with PD with SCCs.8,11 One study found higher conversion to dementia in patients with PD with SCC compared with those without SCC during a 7.5-year period,12 and one study found no change in neuropsychological assessments between nondemented patients with PD with and without SCCs at the 1-year and 2-year follow-up.15

SCCs, such as problems with attention, processing speed, and word finding, are commonly reported among cognitively normal patients with PD, but their significance remains unclear. The goal of the present study was to assess the utility of a single question in cognitively normal patients with PD 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. A total of 153 patients with idiopathic PD and normal cognition at baseline were administered cognitive assessments and ratings of functional abilities performed by trained research staff. Of the 153 patients, 121 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 the Movement Disorders Society criteria (see Cognitive Consensus).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 the following 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 the responses, the participants were then divided into 2 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 Part III,18 and disease severity was measured using the Hoehn and Yahr Scale.19 Depression was assessed using the 15-item Geriatric Depression Scale (GDS-15).20 Rapid eye movement sleep behavior disorder was assessed with a single item (range 0–4) from the Parkinson’s Disease Sleep Scale.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 KI version of the PDAQ-15. Patients with PD completed the PDAQ-15 patient version.

Neuropsychological Assessments

A battery of neuropsychological tests was administered by trained research personnel. The measures were part of the recommended standard battery of cognitive tests for patients with PD enrolled in cognitive research studies at the Morris K. Udall Center.24 Global cognition was assessed using the Mattis Dementia Rating Scale–25 and the Montreal Cognitive Assessment.26 Measures of attention-processing speed were Trail Making Test Part A27 and the Symbol Digit Modalities Test.28 Measures of executive functioning were Letter-Number Sequencing,29 phonemic verbal fluency (FAS),30 and the Trail Making Test Part B.27 Memory was assessed using the Hopkins Verbal Learning Test–Revised.31 Visuospatial measures were the Benton Judgment of Line Orientation32 and the
Clock Drawing Test (command condition). Language was assessed using the Boston Naming Test and semantic verbal fluency (animals). Because of the timing of assessment introduction into the battery, the number of participants who completed each assessment varied (see Table 1). All assessments were performed in the PD medication on state.

**Cognitive Consensus**

An 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 Morris K. Udall Center. The consensus process involved multiple (5 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 Movement Disorders Society Task Force for MCI (level 1 criteria) and dementia. For a given test, a standardized score $\geq 1.5$ 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. Interrater agreement among the pairs was high ($\kappa = 0.80$; 95% confidence interval, 0.70–0.90).

**Statistical Analyses**

To compare demographic and clinical characteristics in the +SCC and −SCC groups, a 2-sample $t$ test was used.
used to examine the mean differences for continuous variables and a 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 covariate in 1-way analysis of covariance to examine the 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, and 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. The 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 the Cox regression model was used to examine the association between cognitive complaint status and risk of conversion to MCI or PD with dementia. The 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 and with correction for multiple testing using the Bonferroni method. All statistical tests were 2-sided. Statistical analyses were performed using SPSS (version 23, IBM Corp., Armonk, NY).

Data Availability Statement

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

TABLE 2. Baseline demographics and clinical characteristics

| Variable                         | N−SCC| +SCC | t Test; P Value* |
|----------------------------------|------|------|-----------------|
| Age, y, mean (SD)                | 72   | 81   | 68.2 (8.3)      |
| Sex, % male                      | 72   | 81   | 54              |
| PD duration, y, mean (SD)        | 72   | 81   | 5.8 (4.0)       |
| Education, y, mean (SD)          | 72   | 81   | 16.7 (2.1)      |
| GDS-15 total score, mean (SD)    | 72   | 81   | 16.4 (2.2)      |
| Hoehn and Yahr stage, median (IQR)| 72  | 81   | 2.0 (2–3)       |
| UPDRS motor score, mean (SD)     | 72   | 81   | 19.7 (11.3)     |
| REM sleep behavior disorder item score, mean (SD) | 58   | 70   | 0.5 (0.6)       |

*Bonferroni-corrected significance set at P < 0.006.
Abbreviations: SCC, subjective cognitive complaint; PD, Parkinson’s disease; GDS-15, 15-item Geriatric Depression Scale; IQR, interquartile range; UPDRS, Unified Parkinson’s Disease Rating Scale; REM, rapid eye movement.

Results

Participant Demographics

Demographic and clinical features are detailed in Table 2. There were a total of 153 patients with PD with consensus process–determined normal cognition at baseline, including 81 (52.9%) who reported cognitive complaint. The 2 groups did not differ significantly in age, sex, disease duration (ie, time since diagnosis), education, Hoehn and Yahr stage, rapid eye movement sleep behavior disorder item score, or Unified Parkinson’s Disease Rating Scale motor score. The +SCC group had significantly higher GDS-15 scores (t152 = −2.94, P = 0.003). Therefore, the GDS-15 score was included as a covariate in all subsequent between-group comparisons, including the Cox regression model.

Baseline Neuropsychological and Functional Assessments

The results of the baseline cognitive and functional assessments are presented in Table 1. The entire sample had Mattis Dementia Rating Scale–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 KI total (F1,113 = 7.00, P = 0.009) and patient total (F1,128 = 13.91, P < 0.001)
than the −SCC group. Scores on the ADCS-ADL did not significantly differ between the 2 groups.

Longitudinal Neuropsychological and Functional Assessments

A total of 121 patients completed at least 2 follow-up visits, and up to 4 annually scheduled, post-baseline visits, with the last visit occurring 5 years post-baseline in some participants because of 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, whereas 57 (47.1%) did not, mirroring the baseline sample. A total of 68 patients had 2 follow-up visits (+SCC = 56%), 30 patients had 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 Mattis Dementia Rating Scale–2 total score ($F_{1,431} = 5.71, P = 0.02$), Symbol Digit Modalities Test ($F_{1,425} = 7.52, P = 0.006$), and Trail Making Test Part B ($F_{1,419} = 4.48, P = 0.04$) over time, but this did not withstand correction for multiple testing (Table 3).

A total of 33 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), $\chi^2(1) = 4.36, P = 0.04$ (Fig. 1). On the Cox regression model and controlling for GDS-15 score, +SCC patients

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**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                                                |
| HVLT-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                                                |
| Trail Making Test Part A, time  | 2.04 (0.64)                       | 3.54 (0.61)                      | 0.09                                                |
| Trail Making Test Part 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 $P < 0.02$ for 3 functional measures.

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

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**FIG. 1.** Kaplan-Meier survival curve for the progression from normal cognition to any cognitive impairment between groups. The presence of SCC at baseline predicted earlier onset of cognitive impairment (mild cognitive impairment or dementia) as determined by consensus. SCC, subjective cognitive complaint. [Color figure can be viewed at wileyonlinelibrary.com]
were 2.61 times more likely to convert to MCI or dementia than were −SCC patients (hazard ratio = 2.61, \( P = 0.02 \)). As the clock drawing test scores were 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 clock drawing test scores 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 SCC and objective decline in a cohort of patients with PD comprised exclusively of consensus process–determined cognitively normal patients at baseline. The results of the present study show that about half of the established patients with PD with normal cognition report cognitive complaints, even when their global and detailed cognitive performance is not clearly distinguishable from patients without such complaints. In addition, such patients either 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 patients with PD, we examined global cognitive complaint as opposed to just memory complaint; included a larger number of patients with SCC;8,11,12 followed some patients for a longer period of time for some,8,15 but not all,12 studies; and included important covariates in our models.12,15

The 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 preclinical Alzheimer’s disease 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 nondemented patients with PD.39,40 Executive functioning and attention in particular are reliant on fronto-striatal functioning, which is disrupted initially during the course of PD.41,42 The findings of the present study suggest that a simple, single clinical question focused on the 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, patients with PD 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, patients with PD 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 the groups regarding the ADCS-ADL, a functional questionnaire that was developed for use in Alzheimer’s disease and assesses both basic and instrumental activities of daily living. 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 patients with PD because although 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 shows the 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), whereas 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 in the +SCC group. A previous study examined the relationship between subthreshold depression and subjective cognitive complaint in patients with PD and found that patients with subthreshold depression reported more subjective cognitive complaint than non-depressed patients.45 As SCC predicted cognitive decline even when controlling for the 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. Although 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 homogeneous sample with a high level of education. Thus, the results may not be applicable to the general PD population and should be replicated in a multisite study with heterogeneous cohorts. In addition, 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, although we examined depression in relation to cognitive complaint, we did not explore other psychiatric symptoms (eg, apathy or anxiety) or possible confounding variables (eg, family history of dementia) as potential contributing factors to subjective decline. Research has demonstrated that apathy and anxiety are associated with cognition in PD, and future research should explore the potential relationship of these factors with SCC.

This study demonstrates that the presence of SCC as determined by a single question predicts future cognitive decline in patients with normal cognition by detailed testing and consensus diagnosis. In addition, it may serve as a useful indicator for patient and KI perceptions 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 during the next several years. As observational studies and clinical trials in PD shift their focus to preclinical and prodromal patients and the testing of possible disease-modifying therapies, the 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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