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PII: S1353-8020(22)00381-9
DOI: https://doi.org/10.1016/j.parkreldis.2022.11.013
Reference: PRD 5221

To appear in: Parkinsonism and Related Disorders

Received Date: 12 August 2022
Revised Date: 8 November 2022
Accepted Date: 11 November 2022

Please cite this article as: Jones JD, Rivas R, Luna K, Ryczek CA, Thomas KR, Subjective cognitive complaints are important in PD-MCI criteria: Associations with CSF markers and cognitive decline, Parkinsonism and Related Disorders (2022), doi: https://doi.org/10.1016/j.parkreldis.2022.11.013.

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Subjective Cognitive Complaints Are Important in PD-MCI Criteria: Associations with CSF Markers and Cognitive Decline

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Acknowledgements/ Study Funding

Jacob Jones was supported by NIH SC3 NS124906.

Kelsey Thomas was supported by the U.S. Department of Veterans Affairs Clinical Sciences Research and Development Service (Career Development Award-2 1IK2CX001865) and the NIH (R03 AG070435).

Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson’s Research funding partners 4D Pharma, Abbvie, Acurex Therapeutics, Allergan, Amathus Therapeutics, ASAP, Avid Radiopharmaceuticals, Bial Biotech, Biogen, BioLegend, Bristol-Myers Squibb, Calico,
Celgene, Dacapo Brain Science, Denali, The Edmond J. Safra Foundation, GE Healthcare, Genentech,
GlaxoSmithKline, Golub Capital, Handl Therapeutics, Insitro, Janssen Neuroscience, Lilly, Lundbeck,
Merck, Meso Scale Discovery, Neurocrine Biosciences, Pfizer, Piramal, Prevail, Roche, Sanofi Genzyme,
Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics.
Abstract

**Introduction:** According to the Movement Disorder Society (MDS), subjective cognitive complaints (SCC) are a diagnostic criterion for PD-mild cognitive impairment (PD-MCI); however, studies often do not incorporate SCC when classifying PD-MCI. This inconsistent use may reflect mixed findings regarding the association between SCC and objective measures of cognitive impairment. Our study aimed to describe the extent that inclusion/exclusion of SCC affects the occurrence of PD-MCI, and if the inclusion of SCC is associated with faster cognitive decline and cerebrospinal fluid markers (CSF) of alpha-synuclein, amyloid beta, total tau, and phosphorylated-tau.

**Methods:** Individuals with PD (N=358) from the PPMI cohort whom completed measures of neuropsychological performance, subjective cognitive complaints, motor severity, and CSF markers were included. Participants were classified as cognitively normal (CN), PD-MCI with subjective cognitive complaints (PD-MCI+SCC) and PD-MCI without subjective cognitive complaints (PD-MCI-SCC).

**Results:** PD-MCI rates were consistently higher (16.5-19.1%) across the 5 years when SCC was not included in the diagnostic criteria as opposed to when SCC was included (4.4-11.0%). PD-MCI+SCC experienced greater cognitive decline and had significantly higher levels of tau/ab and p-tau/ab relative to both the CN and PD-MCI-SCC groups.

**Conclusions:** Inconsistent implementation of an SCC requirement in PD-MCI classifications may have important implications in terms of the occurrence of PD-MCI and its prognostic value. Classifying PD-MCI only using neuropsychological cut-off criterion, without regard to SCC, may lead to higher rates of PD-MCI. Inclusions of SCC in PD-MCI criteria in newly diagnosed PD participants may strengthen the ability to detect individuals at risk for future cognitive decline, though it is possible that this decline is related to Alzheimer’s disease changes rather than worse PD pathology.
Introduction

Parkinson’s Disease (PD) is a neurodegenerative disorder occurring mostly in the older adult population and is characterized by both motor and non-motor symptoms. One common non-motor symptom is cognitive impairment. Some symptoms of cognitive impairment in PD patients include deficits in attention, executive functioning, and memory [1]. Development of severe cognitive impairments in the form of Parkinson’s disease dementia (PDD) is seen in 83% of PD patients within 20 years of disease duration [2]. The time of onset from the initial PD diagnosis is varied, with a mean of 10.9 years [2]. Once PDD has onset, patients have a median survival rate of 54 months [2].

Parkinson’s Disease Mild Cognitive Impairment (PD-MCI) is defined as cognitive decline that is greater than average for the individual’s age, but not severe enough to interfere with independence in daily functioning [3, 4]. Among PD cohort studies, 19-55% of PD patients met the diagnostic criteria for PD-MCI [4,5]. PD-MCI has become a topic of interest because PD-MCI predicts a shorter time to development of PDD compared to cognitively normal PD patients [6]. From a systematic review of 39 articles, approximately 20% of those with PD-MCI converted to PDD within 3 years [7].

PD-MCI diagnostic criteria from the Movement Disorder Society (MDS) requires both a subjective cognitive complaint (SCC) and objective cognitive deficits on neuropsychological tests [8]. SCC are commonly defined as a patient, caregiver/study partner, or clinician observation of declines in cognitive abilities [8]. Prior to the publication of the MDS PD-MCI criteria, a critical review of eight studies on PD-MCI found that only one study used SCC as a diagnostic criterion for PD-MCI [4,9]. A more recent review found 207 studies that used the MDS PD-MCI criteria but did not mention or use SCC in their criteria [10]. In contrast, only 112 studies did utilize the SCC criterion; albeit only 26 of the 112 studies operationally defined SCC [10]. Clearly, there is inconsistent utilization of SCC in PD-MCI classifications despite clearly published criteria.
One potential reason for the inconsistent use of SCC in PD-MCI criteria is that studies demonstrating an association between SCC and cognitive impairment are mixed. One study found no association between SCC and PD-MCI nor cognitive decline over time [11]. However, other studies have reported an association between SCC and objective measures of cognitive impairment. The Vienna Mild Cognitive Impairment and Cognitive Decline in Parkinson’s Disease Study included 248 healthy controls and 104 PD patients [12]. They found that only 7% of controls reported SCC compared to 16% of PD patients [12]. This percentage increased to 31% reporting SCC in PD patients who also showed memory deficits on neuropsychological testing. Another study found that the severity of SCC was correlated with objective cognitive performance as measured by the Korean versions of the Mini Mental State Examination and the Montreal Cognitive Assessment (MOCA) [13]. Similarly, Purri et al., found PD patients with SCC displayed worse global cognition than PD patients without SCC, suggesting SCC may be prognostically useful in identifying cognitive impairment [14].

Cerebrospinal fluid (CSF) biomarkers such as tau and amyloid beta (ab) are associated with cognitive dysfunction in PD. Higher amounts of CSF total (t-tau) and phosphorylated tau (p-tau) were associated with poorer global cognition performance as measured by the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [15,16]. The Norwegian ParkWest Study found CSF markers of amyloid burden were associated with memory impairment among individuals newly diagnosed with PD.[17] Post-mortem findings revealed that 75% of individuals with PD-MCI had significant amount of Alzheimer’s pathology in the hippocampus and limbic regions (i.e. Braak stage III & IV).[18] Additionally, cortical amyloid or tau pathology (i.e. Braak stage V & VI) are present in 94% of individuals with PDD.[19] These post-mortem findings are consistent with a meta-analysis finding that CSF markers of amyloid beta (pooled standard mean difference [Std.MD] = -0.60, 95% CI = -0.75 to -0.45), total tau (pooled Std.MD = 0.21, 95% CI = 0.06 to 0.35), and phosphorylated tau (pooled Std.MD = 0.36, 95% CI = 0.02 to 0.69) were aberrant among individuals with PDD relative to cognitively intact PD.
patients.[20] Findings suggest that cognitive impairment in PD may be multifaceted and at least partially associated with Alzheimer’s pathology.

Although past studies are inconsistent regarding whether or not SCC is associated with objective measures of cognitive impairment, and few studies have examined how the inclusion/exclusion of SCC affects the rate of PD-MCI classification and prognostic utility of PD-MCI. Therefore, we will first describe the extent that inclusion/exclusion of SCC in PD-MCI criteria affects the frequency of PD-MCI. Second, we will investigate whether inclusion/exclusion of SCC in PD-MCI criteria is associated with cognitive decline and CSF markers of amyloid, tau, and alpha synuclein. Specifically, we will compare three groups: 1) individuals with PD-MCI and SCC (PD-MCI+SCC); 2) individuals with PD-MCI without SCC (PD-MCI-SCC); 3) cognitive normal individuals with PD (CN). The rationale for comparing these groups is not because we are suggesting that PD-MCI-SCC should be considered as a future diagnostic group (e.g. SCC should not be an exclusion for PD-MCI). Rather, if SCC is an important criterion for classifying PD-MCI, then we would expect group differences among the PD-MCI groups with and without SCC (e.g. the PD-MCI+SCC groups with have worse outcomes relative to the PD-MCI-SCC group). Conversely, if SCC is not an important criteria for classifying PD-MCI (as is commonly practiced in the literature) then we would not expect group differences between the PD-MCI groups with and without SCC.

Methods

Study Design & Participants

This study utilized data taken from the Parkinson’s Markers Initiative (PPMI) database (http://www.ppmi-info.org/data). The PPMI is an international longitudinal observational study conducted at multiple sites and designed to identify various biomarkers in PD. The data was downloaded from the PPMI database in February 2019. At enrollment, participants were newly diagnosed and followed for up to 5 years (baseline and 5 annual follow-ups); however, data on SCC was not routinely collected until the 1st annual follow-up; therefore this secondary analysis only utilizes data...
from the first through fifth annual follow up. From the 487 individuals with PD enrolled, 127 participants were excluded for missing SCC data and two participants were excluded due to the presence of PDD (based on 1.5 SD below the mean on two neuropsychological tests and reported functional impairment) at the first available assessment. This resulted in a total of 358 participants. Additionally, all participants provided informed consent and approval from the Institutional Review Board (IRB) was obtained at each site.

Cognitive Measures

Participants completed a series of neurocognitive tests at each annual visit. These tests included Hopkins Verbal Learning Test (HVLT-II; trials 1-3 and delayed free recall) assessing verbal learning and verbal delayed recall, Letter-Number Sequencing (LNS) assessing attention/working memory, Judgment of Line Orientation (JOLO) measuring visuospatial function, Animal Fluency measuring verbal fluency, and Symbol Digit Modalities Test (SDMT) assessing processing speed. The Montreal Cognitive Assessment (MOCA) assessed global cognitive functioning.

SCC Criteria

Participants and/or study partners were asked a simple yes or no question indicating whether they have observed a decline in cognitive function in the participant. MCI participants were categorized as having a cognitive complaint if either the participant, study partner, or both individuals endorsed decline.

PD-MCI Criteria

Participants were classified into the following groups: cognitively normal (CN), PD-MCI with subjective cognitive complaints (PD-MCI +SCC) or PD-MCI without subjective cognitive complaints (PD-MCI -SCC) at each time point. PD-MCI criteria was consistent with MDS Level 1 (abbreviated assessment) [8]. Individuals were classified as PD-MCI +SCC if two or more neuropsychological scores fell greater than 1.5 SD below the normative mean score and the participant and/or study partner endorsed that
the participant had experienced cognitive decline. Conversely, participants were classified as PD-MCI - SCC if two or more neuropsychological scores fell greater than 1.5 SD below the mean score but both the participant and the study partner subjectively denied the presence of cognitive decline. The MOCA was not used for classifying PD-MCI because it was used as a separate outcome/measure of cognitive functioning.

Motor Severity

The clinician rated MDS Unified Parkinson’s Disease Rating Scale- part III motor scale (UPDRS-III) was used to assess the severity of motor symptoms with higher scores representing more severity.

CSF Markers

For details on collection, shipment, storage and standard operating procedures at each site, see the biologics manual ppmi.info.org. Briefly, a lumbar puncture was performed to collect 15-20 mL of CSF from participants during 1st, 2nd and 3rd annual follow-ups. Samples were analyzed using an enzyme-linked immunosorbent assay (ELISA) to detect tau (total tau), phosphorylated tau (p-tau), amyloid beta (ab), and alpha-synuclein (asyn). The Elecsys electrochemiluminescence immunoassays on cobas e 601 platform were used. Tau and ab markers were examined as ratios: tau/ab, p-tau/ab and p-tau/tau. Ratios were log transformed to reduce problematic skewness and kurtosis. Asyn was not transformed (skewness and kurtosis values were less than 2). The tau/ab and p-tau/ab ratios are markers of Alzheimer’s disease pathologies, while Asyn was included as a marker of PD/Lewy body pathology.

Statistical Analyses

Aim 1 examined the occurrence of PD-MCI as a function of inclusion/exclusion of SCC in the PD-MCI classification criteria. The frequency of each group (CN, PD-MCI +SCC, PD-MCI -SCC) was examined over the 5 years of the study.

Aim 2 examined if inclusion of SCC in PD-MCI criteria was associated with cognitive performance and CSF markers. First, multilevel modeling (MLM) was used to examine group differences (CN, PD-MCI -
SCC, and PD-MCI +SCC) in trajectories of global cognition (MOCA). MOCA scores were entered as the dependent variable and group was entered as an independent variable. Additional independent variables included age at baseline, motor severity, gender, education, occasion (1st, 2nd, 3rd, 4th, and 5th annual follow-up visits) and a group X occasion interaction term. Random intercept and slope effects were modeled for all time-varying parameters (e.g. motor severity, occasion, group X occasion interaction).

Similar analyses were repeated with CSF biomarkers entered as the dependent variable. Separate analyses were conducted for each marker ratio: tau/ab, p-tau/ab, and p-tau/tau, and asyn. Independent variables included: group (CN, PD-MCI -SCC, and PD-MCI +SCC), occasion, age, motor severity, gender, and education. Statistical significance was evaluated at the alpha = 0.05 level.

**Results**

Participants included 358 individuals diagnosed with PD. Baseline sample information can be found in Table 1. Sample size at each occasion is available in Supplemental Table 1. Regarding the source of SCC, the patient was the sole source of data for 88.1% of cases, a study partner for 0.4% of cases, and both the patient and a study partner for 11.4% of cases. In the final year (year 5) 13 individuals met criteria for PDD based on criteria of 1.5 SD below the mean on two cognitive tests and reported functional impairment. Of these 13 individuals, at the first available assessment 3 were CN, 2 were PD-MCI -SCC and 8 were PD-MCI +SCC.

**Aim 1. SCC Criteria and PD-MCI Frequency**

The frequencies of PD-MCI status over the 5 years of the study were examined among the three groups (CN, PD-MCI, PD+MCI; Figure 1). When SCC was included in diagnostic criteria, rates of PD-MCI ranged from 4.4%-11%. When SCC was not required as diagnostic criteria (i.e. combining both the PD-MCI-SCC and PD-MCI+SCC groups) the rates of PD-MCI ranged from 16.5%-19.1%.

**Aim 2. SCC Criteria, Cognitive Decline and CSF Markers**
Multilevel modeling examined if inclusion of SCC, relative to exclusion of SCC, in PD-MCI criteria was associated with performance on a separate measure of global cognition (MOCA; Table 2). Analyses revealed a significant group X time interaction (Figure 2). Specifically, the PD-MCI +SCC group experienced greater decline in global cognition relative to the other two groups. The CN and PD-MCI - SCC groups did not significantly differ. Worse performance on global cognition was also associated with older age, male gender, fewer years of education and more severe motor symptoms.

Multilevel modeling also examined if inclusion of SCC, relative to exclusion of SCC, in PD-MCI criteria was associated with Alzheimer’s disease and PD CSF markers. Analyses revealed the PD-MCI +SCC group had significantly higher levels of tau/ab and p-tau/ab relative to both the CN and PD-MCI - SCC group (Figure 3; Table 3). There were no significant group differences in p-tau/tau and asyn (Supplemental Table 2).

Discussion

The 2012 Movement Disorder Society (MDS) published criteria for PD-MCI had minimal discussion on the SCC criterion [8]. The rationale provided was that a report of SCC from the patient, informant, or clinician would increase the likelihood of capturing a change in cognitive functioning. Due to the lack of a strong rationale, and inconsistent findings for the associations between SCC and cognitive impairment, it is not surprising that the majority of studies on PD-MCI do not utilize the SCC criterion proposed by the MDS taskforce.

Findings from this paper suggest that inclusion/exclusion of SCC may have important implications for PD-MCI criteria among relatively newly diagnosed PD patients. Specifically, the percentage of patients classified as PD-MCI was larger when SCC was not a diagnostic requirement (16.5%-19.1%) compared to when it was a requirement (4.4%-11.0%). Researchers generally do not utilize SCC in PD-MCI criteria and typically report the rates of PD-MCI to be ranging from 18.9-55%
Past studies incorporating SCC in PD-MCI criteria report PD-MCI to be present in 21-24% of participants [21-23]. Consistent with our results, the presence of PD-MCI in past studies is considerably higher when SCC is excluded from criteria. This raises the possibility of inflated rates when SCC is not a requirement for PD-MCI classification, or potentially an underestimate when SCC is utilized in PD-MCI classifications.

A review article of PD-MCI suggests that varied prevalence in the literature may be a result of differing methods of criteria, including a SCC requirement [24]. Another review by Kjeldsen and Damholdt suggests the lack of a SCC requirement has to do with inconsistency in scale of measurement, though standardized measures of SCC do exist [10]. Furthermore, evidence suggests standardized measures have reasonable reproducibility, and certain measures may have the added benefit of assessing complaints across cognitive domains as opposed to a single construct [25]. Continued work to establish a widely-recognized standard approach for assessing SCC may lead to improved uniformity in the rates of PD-MCI reported in the literature.

Results from the current study demonstrate that the rate of cognitive decline was fastest among the PD-MCI +SCC group, relative to CN and PD-MCI -SCC groups. This suggests that failure to utilize the SCC criterion in PD-MCI classifications (i.e. combining the PD-MCI +SCC and the PD-MCI -SCC groups) may dilute or weaken group differences between PD-MCI and CN on important outcomes. The importance is highlighted by the fact that a majority of studies do not require SCC when classifying PD-MCI [4, 5, 10, 22].

The inconsistent use of SCC in PD-MCI criteria likely reflects contradicting results on whether SCC is a valid marker of objective cognitive impairment. Some studies have reported associations between SCC and objective measures of cognitive functioning [12, 14]. However, this has not been consistent in the literature [11]. One study examined the relationship between SCC and measures of psychological and cognitive impairment [26]. They found that SCC provided by participants correlated
more with depression, anxiety and neuroticism than objective cognitive performance. Although SCC may be associated with psychiatric complications, the conclusion ‘SCC holds minimal value’ may be an overgeneralization. Researchers likely have two concerns regarding the SCC criterion in PD-MCI: 1) patients may exaggerate/hyperfocus on benign cognitive complaints; 2) patients may lack insight/awareness or concern about the severity of the cognitive impairment. Although these concerns may be reasonable in some patients, the other MDS PD-MCI criteria may reduce these concerns. Most obviously, PD-MCI criteria requires objective evidence of cognitive impairment in the form of neuropsychological testing. Although individuals with PD-MCI may still have a subjective complaint that is out of proportion to the objective deficits, by definition all complaints from individuals with PD-MCI will have at least some validity. Second, the fact that the MDS PD-MCI criteria allows the cognitive complaint to come from either the patient, informant or clinician may reduce concerns of lack of insight from a single source.

The rationale for requiring SCC in PD-MCI criteria is that it may increase the likelihood of capturing a change in cognitive functioning, in contrast to longstanding cognitive weaknesses that may be relatively common and non-pathological. A review of neuropsychological testing in healthy normative adults revealed that impaired scores are common when participants are presented with a battery of multiple tests [27]. Approximately 72-75% of healthy individuals score 1 SD below the mean at least two tests when more than 20 scores are administered [28, 29]. Although this number drops if fewer tests are administered (35% of healthy individuals have ≥2 scores in the impaired range when 10 tests are administered) it suggests non-pathological low scores are quite common in the normative population. Indeed, results from the current study found individuals with objective impairments but without SCC (i.e. the PD-MCI -SCC group) in general did not experience declines over the five annual assessments. Inclusion of SCC in addition to objective neuropsychological testing may be an efficient means to
increase confidence that PD-MCI is reflective of pathological declines in cognitive functioning rather than long standing and non-pathological weaknesses.

While SCC may contribute greater prognostic certainty for predicting early cognitive decline, the PD-MCI +SCC group displayed significantly higher levels of biomarkers indicative of Alzheimer’s disease pathology compared to the CN and PD-MCI -SCC groups, but not alpha-synuclein. These findings suggest that individuals classified as PD-MCI +SCC may be experiencing comorbid Alzheimer’s disease pathology, which could be related to their faster cognitive declines. Another cohort study of individuals newly diagnosed with PD found tau (MAPT H1/H1) genotype and a “posterior cognitive profile” were associated with PDD within the first 5 and 10 years of diagnosis [30]. Indeed, pathological studies have confirmed that comorbid AD is present in approximately 20%-33% of PD cases and that amyloid pathology is associated with a more rapid cognitive decline [31]. In the AD literature, SCC is a common requirement in amnestic mild cognitive impairment (a-MCI) diagnostic criteria set by [32]. However, studies examining the association between SCC and amyloid burden have been inconsistent among individuals with MCI/AD [33, 34]. The inclusion of SCC in PD-MCI, particularly in relatively newly diagnosed PD, may be detecting individuals experiencing comorbid PD and AD pathology who are at increased risk for more rapid cognitive decline.

There are limitations worth noting within this study. The sample consisted of relatively newly diagnosed PD patients, who may display lower rates of PD-MCI compared to patients who have had a longer diagnosis. The frequency of PD-MCI has been shown to increase with age, disease duration, and severity [7]. Additionally, the cognitive battery was relatively limited and PD-MCI classification was based on only 6 cognitive scores across 5 tests. Although the battery assesses aspects of cognition that are commonly subsumed under the domain of executive functioning (e.g. verbal fluency, working memory), other common aspects of executive functioning were not assessed (e.g. inhibition, set-shifting, novel problem solving). Indeed the sample characteristics (newly onset PD patients) and limited
number of neuropsychological tests may at least partially explain why the reported rates of PD-MCI are relatively lower than other past studies. The current study used a single-item yes or no question to determine presence of SCC. While no standardized measure/method is widely accepted, it is possible that standardized and more psychometrically sound measures of SCC may provide meaningful information above and beyond a single item. Given the possibility that apathy may also play a role in endorsement of SCC, future studies may wish to examine whether self- or study partner-report differentially impacts the prognostic value of SCC. Additionally, SCC was determined from the report of the patient and/or study partner only. MDS PD-MCI criteria state that clinicians can also be a possible source of SCC. PD-MCI classification was based on neuropsychological cut-offs; variations in approaches (i.e. actuarial approaches, consensus clinician diagnosis procedures) could lead to variations in PD-MCI rates across studies.

Overall, inconsistent implementation of an SCC requirement in PD-MCI classifications may have important implications in terms of the occurrence of PD-MCI and its prognostic value. This study provides initial evidence to support the inclusion of SCC in PD-MCI diagnostic criteria. Failure to incorporate SCC may lead to inflated rates of PD-MCI. Additionally, incorporation of SCC in PD-MCI criteria may improve detection of future cognitive decline. Continued research in the area of SCC in PD is needed, though the current work highlights the potential value of utilizing SCC in PD-MCI criteria if the goal is specificity to determine individuals a risk for future decline regardless of etiology.
References


severity of cognitive complaints in individuals with subjective cognitive decline: the SCIENCe project.

Table 1. Demographic and Clinical Information at the First Available Assessment

<table>
<thead>
<tr>
<th></th>
<th>CN (n=299)</th>
<th>PD-MCI -SCC (n=26)</th>
<th>PD-MCI +SCC (n=33)</th>
<th>p</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.1</td>
<td>61.3</td>
<td>65.5</td>
<td>0.047</td>
<td>CN &lt; MCI+SCC</td>
</tr>
<tr>
<td>% Male</td>
<td>65.6%</td>
<td>73.1%</td>
<td>63.6%</td>
<td>0.710</td>
<td>--</td>
</tr>
<tr>
<td>% White</td>
<td>93.3%</td>
<td>92.3%</td>
<td>81.8%</td>
<td>0.076</td>
<td>--</td>
</tr>
<tr>
<td>Education</td>
<td>15.7</td>
<td>15.0</td>
<td>15.00</td>
<td>0.292</td>
<td>--</td>
</tr>
<tr>
<td>MDS-UPDRS III</td>
<td>26.4</td>
<td>31.4</td>
<td>30.8</td>
<td>0.047</td>
<td>CN &lt; MCI-SCC, CN &lt; MCI+SCC</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr Stage</td>
<td>1.7</td>
<td>1.8</td>
<td>1.9</td>
<td>0.364</td>
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<tr>
<td>LEDD</td>
<td>305</td>
<td>296</td>
<td>338</td>
<td>0.881</td>
<td>--</td>
</tr>
<tr>
<td>MOCA</td>
<td>26.9</td>
<td>24.0</td>
<td>22.0</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC &gt; MCI+SCC</td>
</tr>
<tr>
<td>Immediate Verbal Recall</td>
<td>24.8</td>
<td>18.8</td>
<td>16.8</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC &gt; MCI+SCC</td>
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<td>Delayed Verbal Recall</td>
<td>8.8</td>
<td>6.4</td>
<td>4.5</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC &gt; MCI+SCC</td>
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<td>Working Memory</td>
<td>10.8</td>
<td>8.7</td>
<td>6.9</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC &gt; MCI+SCC</td>
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<tr>
<td>Animal Fluency</td>
<td>21.9</td>
<td>15.9</td>
<td>15.6</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC, CN &gt; MCI+SCC</td>
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<tr>
<td>Processing Speed</td>
<td>42.5</td>
<td>30.7</td>
<td>23.1</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC &gt; MCI+SCC</td>
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<tr>
<td>Line Orientation</td>
<td>13.2</td>
<td>11.4</td>
<td>10.4</td>
<td>&lt;0.001</td>
<td>CN &gt; MCI-SCC, CN &gt; MCI+SCC</td>
</tr>
</tbody>
</table>

CN = cognitively normal, MCI- SCC = mild cognitive impairment without subjective cognitive complaints, MCI + SCC = mild cognitive impairment with subjective cognitive complaints, MDS-UPDRS III = Movement Disorder Society Unified Parkinson’s Disease Rating Scale- Part III; LEDD = levodopa equivalent daily dose MOCA = Montreal Cognitive Assessment.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardized Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN vs. PD-MCI+SCC X Time</td>
<td>-0.18</td>
<td>-0.31 to -0.04</td>
<td>0.009</td>
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<tr>
<td>PD-MCI-SCC vs. PD-MCI+SCC X Time</td>
<td>-0.14</td>
<td>-0.24 to -0.02</td>
<td>0.018</td>
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<td>CN vs. PD-MCI+SCC</td>
<td>-0.88</td>
<td>-1.0 to -0.70</td>
<td>&lt; 0.001</td>
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<td>PD-MCI-SCC vs. PD-MCI+SCC.</td>
<td>-0.41</td>
<td>-0.55 to -0.26</td>
<td>&lt; 0.001</td>
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<tr>
<td>Male Sex/Gender</td>
<td>0.08</td>
<td>0.01 to 0.15</td>
<td>0.036</td>
</tr>
<tr>
<td>Age at Baseline</td>
<td>-0.34</td>
<td>-0.42 to -0.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MDS-UPDRS III</td>
<td>-0.13</td>
<td>-0.19 to -0.06</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Education</td>
<td>0.15</td>
<td>0.07 to 0.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Occasion</td>
<td>0.07</td>
<td>0.04 to 0.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Between-Person Pseudo R²</td>
<td>0.602</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within-Person Pseudo R²</td>
<td>0.279</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dependent Variable = Montreal Cognitive Assessment. CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints; MDS-UPDRS III = Movement Disorder Society Unified Parkinson’s Disease Rating Scale- Part III.
Table 3. Subjective Cognitive Complaint and CSF Markers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN vs. PD-MCI+SCC</td>
<td>-0.31</td>
<td>-0.55 to -0.05</td>
<td><strong>0.007</strong></td>
<td>-0.26</td>
<td>-0.47 to -0.05</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>PD-MCI-SCC vs PD-MCI+SCC</td>
<td>-0.30</td>
<td>-0.52 to -0.08</td>
<td><strong>0.018</strong></td>
<td>-0.26</td>
<td>-0.51 to -0.02</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>Male Sex/Gender</td>
<td>-0.05</td>
<td>-0.25 to 0.15</td>
<td>0.633</td>
<td>-0.04</td>
<td>-0.23 to 0.16</td>
<td>0.713</td>
</tr>
<tr>
<td>Age</td>
<td>0.25</td>
<td>0.15 to 0.35</td>
<td><strong>&lt;0.001</strong></td>
<td>0.25</td>
<td>0.15 to 0.35</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>MDS-UPDRS III</td>
<td>-0.04</td>
<td>-0.12 to 0.03</td>
<td>0.249</td>
<td>-0.05</td>
<td>-0.12 to 0.02</td>
<td>0.198</td>
</tr>
<tr>
<td>Occasion</td>
<td>0.06</td>
<td>-0.01 to 0.13</td>
<td>0.069</td>
<td>0.03</td>
<td>-0.04 to 0.10</td>
<td>0.353</td>
</tr>
<tr>
<td>Education</td>
<td>0.09</td>
<td>-0.02 to 0.19</td>
<td>0.098</td>
<td>0.11</td>
<td>0.01 to 0.21</td>
<td><strong>0.037</strong></td>
</tr>
</tbody>
</table>

Between-Person Pseudo R^2          | 0.171    |             |         |          | 0.130       |         |

Within-Person Pseudo R^2           | 0.076    |             |         |          | 0.191       |         |

CI = confidence interval; AB = amyloid beta; CN = cognitively normal, MCI-SCC = mild cognitive impairment without subjective cognitive complaints, MCI+SCC = mild cognitive impairment with subjective cognitive complaints; MDS-UPDRS III = Movement Disorder Society Unified Parkinson’s Disease Rating Scale- Part III.
Figure 1. Relative Frequency of PD-MCI With and Without a SCC Criterion. CN = cognitively normal, PD-MCI = mild cognitive impairment, PD-MCI +SCC = mild cognitive impairment with subjective cognitive complaints.
Figure 2. Group Differences in Cognition. Cognition is depicted as the standardized predicted value. CN = cognitively normal, MCI- SCC = mild cognitive impairment without subjective cognitive complaints, MCI + SCC = mild cognitive impairment with subjective cognitive complaints.
Figure 3. Group Differences in CSF Markers. CSF markers were log transformed and the predicted values are depicted. AB = amyloid beta; CN = cognitively normal, MCI- SCC = mild cognitive impairment without subjective cognitive complaints, MCI + SCC = mild cognitive impairment with subjective cognitive complaints.
Highlights

- Mild cognitive impairment (PD-MCI) criteria require cognitive complaints (SCC)
- A majority of studies do not utilize SCC when classifying PD-MCI
- Inclusion/exclusion of SCC affects the occurrence of PD-MCI
- Inclusion of SCC improves prediction of Alzheimer’s pathology from CSF ratios
- Failure to utilize the SCC criterion may dilute important associations