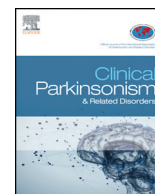




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## Clinical Parkinsonism &amp; Related Disorders

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# Characterization of cognition in mild cognitive impairment with and without Parkinson's disease

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## Introduction

### Background

Cognitive decline is one of the major non-motor complications of Parkinson's disease (PD). In 2012, a Movement Disorders Society (MDS) taskforce published consensus recommendations for the diagnosis of Mild Cognitive Impairment (MCI) in PD [1]. The recommendations describe two levels of diagnostic certainty and clinical characterization. PD-MCI level I diagnosis provides less diagnostic certainty and does not allow MCI subtyping into relevant categories (e.g., amnesic vs. non-amnesic MCI; single vs. multi-domain MCI) [2,3]. To receive a level I PD-MCI diagnosis, a patient must score below the recommended cut-off score on a global cognition screening test or have an impaired performance on at least two tests of a short neuropsychological battery. Impairment is defined as performance that is at least 1 to 2 standard deviations below the norm. PD-MCI level II diagnosis is associated with higher diagnostic certainty and allows MCI subtyping. It requires a comprehensive neuropsychological battery covering five cognitive domains (executive functions, attention, memory, language and visuo-spatial processing) with at least two tests for each domain. To receive a level II PD-MCI diagnosis, a patient must have an impairment on at least two tests, either within one cognitive domain or across all domains.

Although level II criteria are preferable from a clinical and research point of view, they may not always be applicable in practice [1]. Test administration and scoring time, and availability of qualified professional resources impose major constraints on cognitive assessment in the clinic. Global cognition screening tests such as the Montreal Cognitive Assessment (MOCA) [4] have been validated for use in PD and are now widely used [5,6].

As acknowledged by the MDS taskforce, defining the cut-off for a significant impairment and grouping tests according to cognitive domains involve a certain degree of arbitrariness [1]. The definition of an optimal cut-off for the presence of a significant impairment is still a matter of debate [7–9]. A recent review and meta-analysis found considerable variability between studies, and even within single studies for different cognitive domains [9]. Similarly, there is no consensus on the division of tests into cognitive domains [10]. In fact, differences can be noted between the consensus recommendations for the diagnosis of PD-MCI [1] and the most recent recommendations for the diagnosis of MCI due to Alzheimer's disease [11]. However, these differences may be justified by the specificities of the cognitive profiles associated with MCI of different etiologies. The specific characteristics of PD-MCI and its differences from MCI of other etiologies still need to be clarified [12,13].

### Objectives

This study's main objective was to characterize the cognitive profile of people with and without PD diagnosed with MCI based on their MOCA score. Characterization was done by conducting group comparison analyses of cognitive composite scores, and MCI level II diagnosis and subtyping using different impairment cut-offs. Cognitive profiles obtained using composite scores based on a traditional division of tests into cognitive domains vs. a data-driven division using factor analysis were compared.

## Methods

### Participants

Sixty-six control participants (71.19 [7.08] years old; 15.8 [2.8] years of education; 31 males) and sixty-six participants with PD (71.3 [6.44] years old; 15.27 [2.86] years of education; 49 males) participated in this study. All participants were non-demented men and women aged 60 years and older. Exclusion criteria included current presence or history of alcohol

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abuse, major psychiatric disorder, neurological disorder (other than PD for the PD group), stroke or cerebrovascular disorder, and general anesthesia in the past six months. PD patients were diagnosed by movement disorder neurologists and met the UK brain bank criteria for idiopathic PD [14]. They were recruited at the Movement Disorders Clinic (Foothills Medical Centre, University of Calgary), were at stage II or III on the Hoehn & Yahr scale and did not present severe medication-induced dyskinesia. They took their usual dose of anti-parkinsonian medication during all visits. Control participants were recruited in the community. The project was approved by the Research Ethics Board of the University of Calgary and all participants provided written informed consent to participate in this study.

## Material

All tests were administered and scored by a single person who is trained as a psychometrist (MK). As per the recommended cut-off [4], a score below 26 on the MOCA (corrected for education when appropriate) was used to detect the presence of MCI. The MOCA was used to identify participants with MCI in order to ensure the independence of the MCI diagnosis from the measures used to further characterize cognitive profiles. The MOCA also served as a common point of comparison for the characterization of cognitive profiles using a traditional vs. a data-driven approach. Participants completed a comprehensive neuropsychological battery that included 14 tests and covered five domains of cognition. In total, 24 measures were extracted from the neuropsychological battery. All raw scores were converted into z-scores (corrected for age, sex and education, when appropriate) before being used in the analysis. Five participants had one missing value each which was replaced by the sample's z-score average for these measures.

For the traditional division of tests, three measures were selected for each of the five cognitive domains. The selection of measures was based on suggestions included in the MDS task force recommendations [1], standard description of neuropsychological tests and measures [15] and studies of cognition in PD [16–18]. All 24 measures were entered into the initial factor analysis. A table giving the tests, measures, and their division into cognitive domains is provided as Supplementary Material online.

## Analysis

### MCI subtyping

The presence of MCI based on MDS taskforce level II criteria was determined for all participants. Impaired performance on at least two measures across all five cognitive domains was used to diagnose MCI. Discrepancy between the diagnosis made using the MOCA score vs. level II criteria was noted. Each participant's profile was subtyped based on the presence of at least one impaired measure in the memory domain (amnestic MCI) and the presence of impaired measures in at least two different domains (multi-domain MCI). MCI identification and subtyping was done using an impairment cut-off of 1, 1.5 and 2 standard deviations below the norm. The proportion of participants with a discrepant diagnosis, amnestic profile, and multi-domain profile was compared between groups with normal cognition and groups with MCI using Fisher's Exact Test, two-tailed,  $\alpha = 0.05$ .

### Factor analysis

Initial screening of data was performed on the complete sample of 132 participants to ensure its suitability for factor analysis. All 24 measures were normally distributed (all skewness and kurtosis values comprised between  $-2$  and  $2$ ). An exploratory regression analysis was done to screen for multicollinearity and multivariate outliers. Collinearity statistics indicated the absence of multicollinearity (Tolerance  $> 0.1$ ; VIF  $< 10$ ). The Mahalanobis distance ( $\alpha = 0.001$ ; 24 degrees of freedom) did not reveal any multivariate outliers.

The factorability of the 24 measures was examined. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy showed that the relationships among variables was high (KMO = 0.803). The Bartlett's Test of Sphericity

was significant ( $\chi^2(276) = 1116.89, p < .05$ ) and the communalities were all above 0.3. Factor analysis was deemed appropriate with those measures.

Principal component analysis (PCA) with orthogonal (Varimax) rotation was used to summarize performance on the comprehensive neuropsychological battery. Components with a minimum eigenvalue of 1 were retained. The initial solution included seven factors that explained 63.67% of the variance. Nine measures had cross-loadings of 0.3 or more and were excluded from the analysis (see Supplementary Material). The final analysis was done on the remaining 15 measures with PCA extraction and Varimax rotation.

### Group comparisons

For the traditional division of tests, composite scores were computed by averaging the z-scores of measures included in each cognitive domain. For the data-driven approach, composite scores were computed by averaging the z-scores of measures which had their primary loadings on each component. Composite scores were entered as dependent variables in separate analyses of variance (ANOVA) to test the difference between groups of participants with and without PD and presenting with MCI or not based on their MOCA score. Post-hoc comparisons were examined using Bonferroni correction. When the homogeneity of variance was not assumed, Welch's test with Dunnett's C post-hoc comparison was used.

## Results

### Participant characteristics

Of the 66 participants with PD, 23 were identified as having MCI based on their MOCA score. Twenty-five of the 66 participants without PD were identified as having MCI. The four groups (PD with normal cognition (PD-NC), PD-MCI, controls with normal cognition (NC) and MCI) showed differences in age but not education. The proportion of men and women was significantly different across groups. The average MOCA score was not different between the groups with normal cognition (PD-NC, NC) and the groups with MCI (PD-MCI, MCI), but all pairwise comparisons of normal cognition vs. MCI groups were significant. The severity of motor symptoms (UPDRS-III) and duration of the disease was not significantly different between the PD groups. PD-MCI patients reported more depressive symptoms (Beck Depression Inventory-II) than NC. However, depressive symptoms were not different between PD-NC and PD-MCI, nor between PD-MCI and MCI. Participant characteristics and group comparisons are reported in Table 1.

### MCI subtyping

Using a cut-off of 1 standard deviation below the norm to determine the presence of a significant impairment, 17.07% of participants categorized as NC and 48.84% of participants categorized as PD-NC based on the MOCA score met level II criteria for MCI. The difference in the proportion of participants with a discrepant diagnosis between the NC and the PD-NC group was significant (Fisher's Exact Test, two-tailed,  $p = .003$ ). This proportion dropped to 9.76% for NC and 20.93% for PD-NC using a cut-off of  $-1.5$ , and to 2.43% for NC and 13.95% for PD-NC using a cut-off of  $-2$ . Those differences were not significant.

The proportion of participants who were identified as MCI based on the MOCA and level II criteria was similar for the PD-MCI and MCI groups at all impairment cut-offs. The proportion of coherent diagnosis was around 70% at the  $-1$  cut-off (PD-MCI: 73.91%; MCI: 72%), 50% at the  $-1.5$  cut-off (PD-MCI: 56.52%; MCI: 52%) and 40% at the  $-2$  cut-off (PD-MCI: 39.13%; MCI: 40%). The differences in the proportion of discrepant diagnoses were not significant. There was no significant difference in the proportion of participants presenting an amnestic profile and a multi-domain profile between the PD-MCI and the MCI group at any cut-off. The proportion of amnestic profiles in the PD-MCI group was 64.71%, 53.85% and 33.33% at the  $-1$ ,  $-1.5$  and  $-2$  cut-offs, respectively. In the MCI group, the proportion of amnestic profiles was 66.67%, 46.15% and 60%,

**Table 1**  
Participant characteristics.

	NC n = 41	PD-NC n = 43	PD-MCI n = 23	MCI n = 25	Overall Group Difference	Pairwise Comparisons
Age	70.2 (6.8)	69.69 (6.14)	74.32 (6)	72.82 (7.36)	$p = .022^1$	d <sup>1</sup>
Sex (W:M)	24: 17	12: 31	5: 18	11: 14	$p = .008^2$	a, b <sup>2</sup>
Education	16.37 (2.9)	15.3 (2.27)	15.22 (3.79)	14.88 (2.42)	$p = .142^1$	NA
MOCA	27.8 (1.44)	27.72 (1.4)	23.09 (2.8)	23.28 (2.44)	$p < .001^1$	b, c, d, e <sup>1</sup>
UPDRS-III	NA	16.63 (7.92)	17 (8.15)	NA	$p = .858^1$	NA
Disease Duration (years)	NA	5.77 (4.17)	6.07 (5.05)	NA	$p = .798^1$	NA
BDI-II	3.59 (4.3)	5.35 (4.19)	7.57 (5.31)	5.84 (6.2)	$p = .018^1$	b <sup>1</sup>

1. ANOVA, alpha = 0.05.

2. Pearson Chi Square, alpha = 0.05.

a. NC different from PD.

b. NC different from PD-MCI.

c. NC different from MCI.

d. PD-NC different from PD-MCI.

e. PD-NC different from MCI.

f. PD-MCI different from MCI.

respectively. Multi-domain profiles constituted the majority in the PD-MCI group (−1: 94.12%; −1.5: 92.31%; −2: 88.89%). All MCI participants had multi-domain profiles at all three cut-offs. Results are reported in Table 2.

### Factor analysis

The final factor solution had five components and explained 63.61% of the variance. The components were named based on the characteristics of tests having their primary loading on each component. Factor loadings, communalities and percentage of explained variance for each component are reported in Supplementary Material online.

### Group comparisons

Groups defined based on the MOCA score were compared on their average composite scores computed based on a traditional and a data-driven approach. Table 3. reports the average composite score for the two approaches in each group, as well as the overall group differences and pair-wise comparisons. Briefly, all composite scores from both approaches distinguished PD-MCI from NC. All composite scores except the Visual Construction Skills score distinguished MCI from NC. Composite scores from both approaches identified differences between NC and PD-NC. More composite scores from the traditional approach identified differences between

PD-NC and the two MCI groups. None of the composite scores distinguished between PD-MCI and MCI.

For the traditional division of tests, the overall difference between groups survived correction for age, sex and education for all composite scores. For the data-driven approach, all overall differences survived correction except for the difference on the Visual Construction Skills score ( $p = .109$ ).

Internal consistency of composite scores was examined using Cronbach's alpha. For the traditional approach, internal consistency was poor overall ( $< 0.6$ ). For the data-driven approach, internal consistency ranged from good ( $> 0.8$ ) to poor ( $< 0.6$ ). Cronbach's alpha for each composite score is reported in Table 3.

### Discussion

As expected, the MOCA differentiated groups with normal cognition from groups with MCI in participants with and without PD. However, MCI diagnosis using MDS level II criteria suggested a potential lack of sensitivity to mild cognitive decline that was specific to PD. Using 1 standard deviation below the norm as the cut-off for a significant impairment, almost half of the PD-NC participants who had been classified as having normal cognition based on their MOCA score fit level II criteria for MCI. The proportion of NC participants with a discrepant diagnosis was significantly lower. This cut-off was used (at least for some measures or domains) in several studies of cognition in PD-MCI [9]. The results are coherent with those reported in previous studies and may contribute to explain the variability in the prevalence of PD-MCI [7–9]. They may also account for some of the variability in the association between cognitive decline and different disease characteristics, such as the duration of the disease and the severity of motor symptoms. These characteristics were not different between the PD-NC and the PD-MCI group in the present study, but increased disease duration and severity of motor symptoms have been associated with PD-MCI in other studies [19]. Results are also coherent with the presence of an overall greater vulnerability to cognitive decline in individuals with PD compared to adults without neurological disorders [20,21]. Both sets of composite scores revealed differences between PD-NC and NC participants. Inherent to the definition of MCI [1,11], these mild cognitive difficulties may not all lead to impacts on activities of daily living.

The dual syndrome hypothesis was based on the longitudinal follow-up of a cohort of incipient cases of PD [16]. According to this hypothesis, the pathological mechanisms responsible for the diminution of prefrontal dopaminergic activity and executive deficits are different from the pathological mechanisms responsible for posteriorly based cognitive deficits (i.e., visual construction and semantic deficits) [16]. In that study, only posteriorly based cognitive deficits were predictive of the progression to dementia. Therefore, measures that are sensitive to deficits in frontal-based aspects

**Table 2**  
MCI level II criteria identification and MCI subtyping.

	NC n = 41	PD-NC n = 43	PD-MCI n = 23	MCI n = 25	NC vs. PD-NC <sup>1</sup>	PD-MCI vs. MCI <sup>1</sup>
Level II criteria: −1 std. dev.						
MCI (n)	7	21	17	18	0.003	1
Amnesic (n)	4	10	11	12	1	1
Multi-domain (n)	7	20	16	18	1	0.486
Level II criteria: −1.5 std. dev.						
MCI (n)	4	9	13	13	0.229	0.78
Amnesic (n)	1	5	7	6	0.559	1
Multi-domain (n)	4	8	12	13	1	1
Level II criteria: −2 std. dev.						
MCI (n)	1	6	9	10	0.11	1
Amnesic (n)	0	5	3	6	0.286	0.37
Multi-domain (n)	1	6	8	10	NA	0.474

<sup>1</sup> Fisher's Exact Test, two-tailed,  $p < .05$ .

**Table 3**

Average Composite Score and Group Differences for the Division of Tests into Cognitive Domains and the Composite Scores Computed Based on Factor Analysis.

		Cronbach's alpha	NC	PD-NC	PD-MCI	MCI	Overall group difference	Pairwise comparisons
Cognitive Domains	Executive Functions	0.495	0.38 (0.45)	−0.04 (0.62)	−0.75 (0.72)	−0.45 (0.78)	$p < .001$	a, b, c, d
	Attention	0.390	0.34 (0.46)	0.02 (0.48)	−0.53 (0.5)	−0.4 (0.65)	$p < .001$	a, b, c, d, e
	Language	0.541	0.46 (0.66)	0.16 (0.5)	−0.18 (0.57)	−0.47 (0.71)	$p < .001$	b, c, d, e
	Memory	0.434	0.51 (0.55)	0.36 (0.78)	−0.35 (0.81)	−0.3 (0.83)	$p < .001$	b, c, d, e
	Visuo-spatial Processing	0.457	0.48 (0.52)	0.29 (0.66)	−0.2 (0.75)	−0.21 (0.8)	$p < .001$	b, c, d, e
Components	Attention and Processing Speed	0.801	−0.26 (0.64)	−0.48 (0.74)	−1.12 (0.68)	−1.01 (0.67)	$p < .001$	b, c, d, e
	Visual Learning and Memory	0.676	0.36 (0.59)	0.3 (0.89)	−0.36 (0.95)	−0.41 (0.97)	$p < .001$	b, c, d, e
	Verbal Memory and Lexical Access	0.559	0.34 (0.53)	0.01 (0.53)	−0.44 (0.79)	−0.37 (0.83)	$p < .001$	a, b, c
	Short-Term and Working Memory	0.663	0.56 (0.83)	0.33 (0.74)	−0.16 (0.74)	−0.13 (0.79)	$p < .001$	b, c
	Visual Construction Skills	0.631	0.57 (0.91)	0.3 (1.02)	−0.3 (1.28)	0.04 (1.19)	$p = .016$	b

a. NC different from PD.

b. NC different from PD-MCI.

c. NC different from MCI.

d. PD-NC different from PD-MCI.

e. PD-NC different from MCI.

f. PD-MCI different from MCI.

of cognition, such as executive functions, may not necessarily predict the progression to dementia. Although many aspects of the clinical profile in PD are related to changes in fronto-striatal activity, cognitive evaluation should also consider changes that affect posterior brain areas. Broeders et al. applied the MDS criteria for MCI diagnosis in a five-year longitudinal study of 145 consecutive patients with newly diagnosed PD [22]. The authors did not characterize the participants' cognitive profile beyond identifying participants who had single vs. multi-domain MCI. Due to limited power, they did not assess the predictive value of the criteria. Although they discussed the discrepancies that can be induced by the use of different cut-offs for impairment in different studies, they did not proceed to a systematic comparison of MCI prevalence at different cut-offs. Longitudinal studies of PD patients that combine a detailed analysis of cognitive profiles and a systematic comparison of cut-offs at different time points would be useful to clarify remaining issues around the diagnosis of MCI in PD.

The results reported in this study are consistent in showing the similarity between PD-MCI and MCI of other etiologies. MCI subtyping revealed comparable proportions of amnesic profiles in PD-MCI and MCI. This was coherent with the differences observed at the group level between participants with PD-MCI and MCI vs. NC on memory composite scores. The majority of participants from both MCI groups had a multi-domain profile. Similarly, PD-MCI participants had lower scores than NC for all composite scores, and MCI had lower scores than NC for all composite scores except the data-driven Visual Construction Skills score. Results support those from previous studies [3,7,8,23,24] and highlight the need to cover all aspects of cognition, including those that had been neglected in the past, such as language [10].

Several large-scale studies have reported a higher prevalence of PD in males [25]. In the present study, there was a higher proportion of male participants among the PD group than the control group. Some studies have identified differences between men and women with PD in cognition, more specifically in the verbal domain (women performing better than men) and in the visuo-spatial domain (men performing better than women) [26,27]. These differences are similar to the ones reported in healthy older adults [28]. More studies are needed to confirm the existence of these differences [29], and if warranted, to clarify their origin and their impact on cognition and cognitive decline [25]. In this study, standardized scores entered in the analyses were corrected for sex whenever possible. Furthermore, except for the difference on the data-driven Visual Construction Skills score, all overall differences survived correction for age, sex and education.

The two approaches used to derive composite scores led to similar results, especially when considering the difference between NC and the two MCI groups. Composite scores computed based on the factorial approach had better internal consistency, although most still fell in the moderate

and poor range. Neuropsychological batteries used to study cognition in PD have been criticized for their lack of consistency and comparability, and imbalance in the number of measures included in each domain [8,10]. More than the number of measures used to assess a domain, the internal consistency of those sets of measures should be considered carefully [30]. Measures with good internal consistency can be used to derive useful composite scores that can help prevent problems such as counting two largely overlapping measures as two different impairments. The use of composite scores to replace individual measures for MCI diagnosis and subtyping seems premature at this time. Further refinement of neuropsychological batteries and a more systematic approach to defining cut-offs are needed.

## Funding

N.A.O. is supported by a FRQS Research Scholars – Junior 1 Salary Award [number 266718]. This work was supported by a Canadian Institutes of Health Research (CIHR) Fellowship [FAH-381468] (N.A.O.), and by a CIHR operating grant [MOP-126017], the Canada Research Chair in non-motor deficits of Parkinson's disease, and the Tourmaline Oil Chair in Parkinson's Disease (O.M.).

## Declaration of competing interest

None to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2020.100034>.

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