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Predictors of Cognitive Change in Parkinson Disease
A 2-year Follow-up Study

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Background: Mild cognitive impairment is common in Parkinson disease (PD-MCI). However, instability in this clinical diagnosis and variability in rates of progression to dementia raises questions regarding its utility for longitudinal tracking and prediction of cognitive change in PD. We examined baseline neuropsychological test and cognitive diagnosis predictors of cognitive change in PD.

Methods: Persons with PD, without dementia PD (N = 138) underwent comprehensive neuropsychological assessment at baseline and were followed up to 2 years. Level II Movement Disorder Society criteria for PD-MCI and PD dementia (PDD) were applied annually. Composite global and domain cognitive *z*-scores were calculated based on a 10-test neuropsychological battery.

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Results: Baseline diagnosis of PD-MCI was not associated with a change in global cognitive *z*-scores. Lower baseline attention and higher executive domain *z*-scores were associated with greater global cognitive *z*-score worsening regardless of cognitive diagnosis. Worse baseline domain *z*-scores in the attention and language domains were associated with progression to MCI or PDD, whereas higher baseline scores in all cognitive domains except executive function were associated with clinical and psychometric reversion to "normal" cognition.

Conclusions: Lower scores on cognitive tests of attention were predictive of worse global cognition over 2 years of follow-up in PD, and lower baseline attention and language scores were associated with progression to MCI or PDD. However, PD-MCI diagnosis per se was not predictive of cognitive decline over 2 years. The association between higher executive domain *z*-scores and greater global cognitive worsening is probably a spurious result.

Key Words: cognitive dysfunction, dementia, Parkinson disease, neuropsychological tests, longitudinal studies

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Parkinson disease mild cognitive impairment (PD-MCI), the prodromal state between normal cognition and dementia,[1] identifies individuals at risk for cognitive decline and the development of dementia in PD (Fig. 1). Diagnostic criteria for PD-MCI were proposed by the Movement Disorder Society (MDS) PD-MCI Task Force,[2] which permits the diagnosis of PD-MCI on the basis of cognitive screening tests (level I criteria) or a more comprehensive neuropsychological battery (level II criteria).

Although PD-MCI is a useful concept in recognizing an intermediate cognitive state with predictive value for PD dementia, whether cognitive classifications (vs. cognitive test performance on a continuous scale) are the best cognitive outcomes, or predictors for longitudinal assessments in PD are uncertain. The rate with which patients with PD-MCI progress to dementia varies among studies and some patients with PD-MCI revert to a state of normal cognition, at least in the short term.[3–8] Diagnosing PD-MCI is fraught with uncertainties, including how to elicit cognitive complaints (and whether cognitive complaints are required) and operationalizing cognitive impairment. Prior work also has shown substantial differences in the categorization of MCI if one considers comparison to population-based norms versus estimated decline from the estimated prior level of functioning.[9] Furthermore, using global cognitive classifications such as MCI and dementia ignores subtypes of cognitive impairment within MCI (eg, amnestic, executive function-specific) or within dementia (from mild to moderate to severe) and may obscure prognostically relevant information contained in the cognitive profile. For example, visuospatial and semantic fluency cognitive domains have been suggested to be associated with the greater cognitive deterioration that relates to a posterior-cortical compromise associated with cholinergic depletion.[10–12] Thus, the purpose of the current study was to explore the association of change in cognitive classification with baseline cognitive test performance as well as to examine the predictive value of a diagnosis of PD-MCI and domain-specific cognitive test performance for future global cognitive test performance.

METHODS

Participants

We prospectively monitored a large, well-characterized PD cohort with 2 years of comprehensive clinical neurological and neuropsychological follow-up. Consecutive English-speaking persons with PD without dementia were enrolled at 6 North American movement disorders centers as part of an ongoing prospective longitudinal study of PD-MCI. All participants were enrolled with a consenting close contact, defined as a person in touch with the participant at least twice weekly. Recruitment started in December 2008 and continued through June 2011. Full details regarding inclusion and exclusion criteria were reported previously.[9] Enrolled participants received an annual clinical neurological evaluation followed 1 to 3 weeks later by formal neuropsychological testing performed blinded to clinical results. Each participating institution received local research ethics board approval before study enrollment. Written informed consent was obtained from all study participants and participating close contacts before formal screening and study visits.

Neuropsychological Assessment

At baseline and each follow-up assessment, participants underwent comprehensive neuropsychological testing

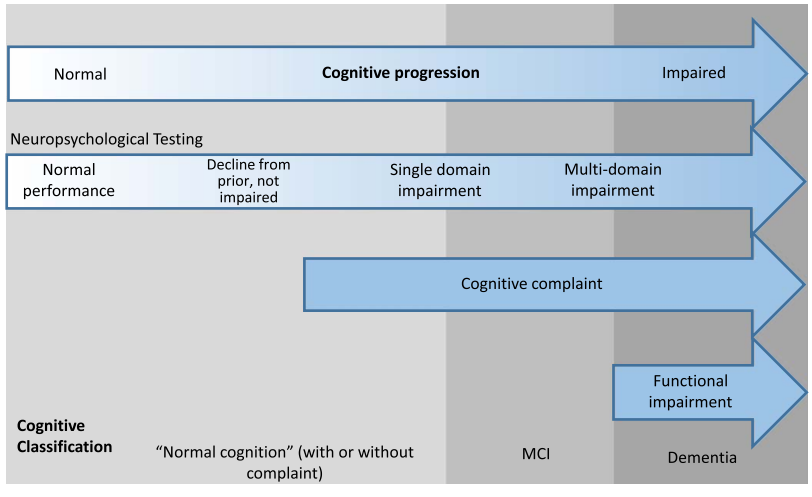

FIGURE 1. Conceptual model of cognitive impairment and dementia in PD. MCI indicates mild cognitive impairment. full color online

administered by a trained psychometrist. The neuropsychological battery included 2 tests within each of 5 different cognitive domains as recommended by the MDS Task Force Level II diagnosis of PD-MCI.[2] For each domain, the specific measures administered were Attention, Delis Kaplan Executive Function System (DKEFS) Color Word Interference Color Naming test[13] and the Wechsler Memory Scale-III Letter Number Sequencing test[14]; Language, DKEFS Verbal Fluency Category Fluency test[13] and the 30-item Boston Naming Test[15]. Visuospatial, Benton Judgment of Line Orientation test (JLO)[16] and the Copy Trial of the Rey Complex Figure Test and Recognition Trial (RCFT)[17]; Memory, Delayed Recall of the RCFT[16] and California Verbal Learning Test-II (CVLT-II) Long Delay Free Recall trial[18]; Executive, Trail Making Test B minus A[19]; and the Visual Verbal Test abbreviated 10-item version.[20] Clinical and neuropsychological evaluations were performed at a similar time of day, and participants were evaluated in the Ontario state as judged by the patient's self-report of the effectiveness of their PD medication at the time of testing. To reduce practice effects, alternative versions of DKEFS, category fluency, Boston naming test, JLO, CVLT-II, and Trail Making Test were administered at follow-up assessments.

Consensus Cognitive Diagnosis

Clinical diagnoses of normal cognition, PD-MCI, or PDD were assigned annually by consensus conference, including 2 movement disorder neurologists (C.M. and M.J. A.) and a clinical neuropsychologist (S.D.C.). PD-MCI diagnosis was based on Level II MDS Task Force criteria[2]: presence of a subjective cognitive complaint (participant or close contact) as assessed by a modified Neurobehavioral Inventory, cognitive score of at least 1.5 SDs or more below normative values on at least 2 cognitive measures and absence of functional decline in basic and instrumental activities of daily living due to cognitive impairment as assessed by a modified Disability Assessment for Dementia (for details see Marras et al[9]). Evaluators confirmed PD diagnosis at each annual visit. PDD diagnosis was based on consensus criteria[21] using neuropsychological test scores and an indication of impaired functional activities of daily living based on the modified Disability Assessment for Dementia. Participants who did not meet the criteria for PD-MCI or PDD were deemed cognitively normal (PD-CN). In addition, as a secondary analysis, we used an additional method for PD-MCI diagnosis according to the distribution of abnormal cognitive scores that has been previously proposed[9,22] as a more stringent criterion with greater prognostic value. Specifically, scores of at least 1.5 SDs or more below normative values were required on at least 2 cognitive measures within a single domain (domain-specific MCI classification).

Cognitive Outcome

Cognitive outcomes were examined in 2 ways: (1) change in clinical diagnostic category and (2) change in neuropsychological test scores since baseline.

Five cognitive classifications were defined by a change in diagnosis: PD-CN progressor: participants diagnosed as cognitively normal at baseline who progressed to MCI or PDD at year 1 or year 2. PD-CN stable: participants diagnosed as cognitively normal at baseline and who remained cognitively normal until the end of follow-up. PD-MCI stable: participants diagnosed as MCI at baseline and annually until the end of follow-up. PD-MCI reverter: participants diagnosed as MCI at baseline who reverted to a clinical state of cognitively normal at year 1 or year 2. PD-MCI progressor: Participants diagnosed as MCI at baseline who were diagnosed as PDD at year 1 or 2. Individuals changing cognitive classification at year 1 who were then lost to follow-up or who withdrew from the study were classified according to their cognitive diagnosis at year 1. Individuals progressing to a worse cognitive classification at year 1 and then reverting to a better classification at year 2 were classified as progressors.

Cognitive change in neuropsychological test performance was determined using composite z-scores. z-scores for each neuropsychological test were calculated based on published normative data where available[13,14,17,18,20,23,24] cf. JLO (P. Eslinger, personal communication, 2009) and VVT-shifts (N Johnson, personal communication, 2009). In addition to age correction, the JLO and CVLT-2 were corrected for sex and TMT for education. Composite z-scores were calculated by summing and averaging z-scores across the 10 cognitive measures in the neuropsychological battery (Global Cognitive z-score) and by summing and averaging the z-scores of the 2 tests within each cognitive domain (Cognitive Domain z-score). The global cognitive change was defined as the difference in the Global Cognitive z-scores obtained at each of year 1 and year 2 assessments relative to baseline (ie, year 1 minus Baseline; year 2 minus Baseline).

Statistical Analysis

Descriptive statistics were calculated as mean and SD or median and interquartile range for continuous variables and proportions for categorical variables. The χ^2 or Fisher exact test was used to test for the association between categorical variables. For continuous variables, comparisons between 2 groups were performed using the 2-sample t test or Wilcoxon rank sum test, and comparisons of more than 2 groups were performed with ANOVA or the Kruskal-Wallis test, as appropriate. Pairwise group comparisons were based on the Bonferroni adjustment (after Kruskal-Wallis test) or Tukey-Kramer test (after ANOVA). Repeated measures analyses with a compound symmetry variance structure adjusted for year of study, age, Geriatric Depression Scale score, premorbid intelligence quotient (IQ), disease duration from symptom onset, and motor unified Parkinson's disease Rating scale score were performed to examine baseline predictors of global cognitive change since baseline over the 2-year follow-up. Separate models were generated including either baseline cognitive classification or baseline cognitive domain z-scores. All statistical tests were 2-sided, and statistical significance was defined if the P-value was <0.05. All analyses were conducted using SAS 9.4.[25]

RESULTS

Of a total sample of 138 participants, 92 (67%) participants were identified as PD-CN and 46 (33%) were diagnosed with PD-MCI at baseline. According to the domain-specific classification, 26 (19%) participants were diagnosed with PD-MCI at baseline. One hundred eighteen participants (85%) were followed for 1 year, and 103 (75%) participants were followed for 2 years (Fig. 2). Demographic, clinical, and cognitive characteristics of participants at baseline, and each follow-up are shown in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A446. More details are available in Marras et al.[9]

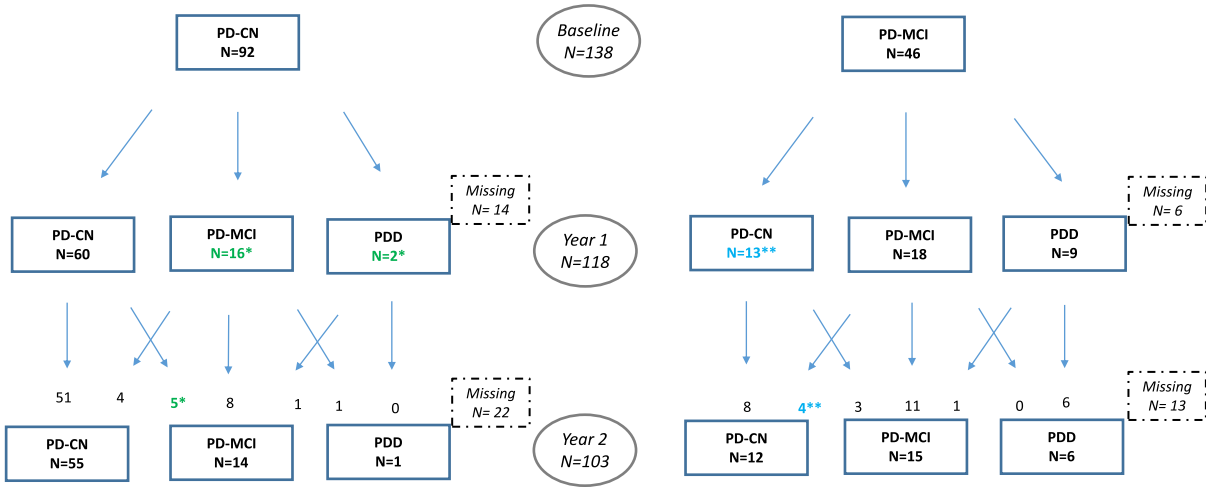

FIGURE 2. Cognitive evolution of total cohort across baseline, year 1 and year 2. *Patients classified as converters (green); **Patients classified as reverters (blue). CN indicates cognitively normal; MCI, mild cognitive impairment; PDD, Parkinson disease with dementia. full color online

Retained Participants Versus Drop-outs

By year 1, 5 participants were lost to follow-up, 14 declined continued study participation, and 1 died. By year 2, 7 additional participants were lost to follow-up; 6 declined further study participation, and 1 died. The proportion of participants who dropped out by year 2 was similar for PD-CN (22/92, 24%) and PD-MCI (13/46, 28%) ($P = 0.48$). Participants who dropped out by year 2 compared with those who did not drop-out had lower estimated premorbid IQ [mean (SD) = 109.7 (10.0) vs. 114.4 (8.4)], montreal cognitive assessment score [mean (SD) = 23.9 (3.1) vs. 25.7 (2.7)]. There were no other clinical differences between those participants who were retained and those who dropped out (see Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/WAD/A447).

Evolution of Cognitive Classification

The evolution of cognitive classification within the sample over 2 years of follow-up is depicted in Figure 2. Thirty-two of 138 (23.2%) participants progressed to a more advanced cognitive classification at either year 1 or year 2. Of the 103 patients completing the 2 years follow-up, 21 (20%) progressed to a more advanced cognitive classification by year 2. This included 15 PD-CN at baseline advancing to MCI (n = 14) or PDD (n = 1) and 6 MCI converting to PDD. Seventeen percent of participants classified as PD-MCI at baseline went on to develop PDD at 1-year follow-up in contrast to only 2% of participants classified as cognitively normal at baseline.

Of the participants classified as PD-MCI at baseline, 17 (37%) reverted to cognitively normal at year 1 or year 2. Of the 17 PD-MCI reverters, 2 changed cognitive classification due to an absence of cognitive complaint. In addition, some PD-MCI reverters showed improvements on some of the neuropsychological tests such that they no longer met the −1.5 SD cutoff for a diagnosis of PD-MCI at 1 year of follow-up. The most frequent tests for which participants no longer met the cutoff criterion included the Visual Verbal Test (6/13) and Rey Complex Figure Test Copy (6/13). Participants in the 5 cognitive classifications (PD-CN stable, PD-CN converter, PD-MCI stable, PD-MCI converter, and PD-MCI reverter) at year 1 of follow-up showed statistically significant differences in estimated premorbid IQ but did not differ with respect to other baseline demographic nor motor characteristics (Table 1).

When using the domain-specific classification for PD-MCI requiring 2 abnormal cognitive tests within a domain, 23 (22.12%) patients progressed from CN to PD-MCI or PD-MCI to PDD, and 8 (7.6%) patients reverted to normal cognition over the 2-year follow-up period.

Baseline Neuropsychological Predictors of Cognitive Diagnostic Category Over 2 Years

Reverters to cognitively normal had a significantly higher baseline z-score in all cognitive domains compared with nonreverters except executive function, where the difference was not statistically significant ($P = 0.069$). The memory domain showed the greatest difference (mean z-score 0.27 vs. −1.11) (Table 2). According to the domain-specific classification for PD-MCI, the differences in baseline z-scores between reverters and nonreverters were similar in magnitude to that seen then using the current classification, but only attention and executive function reached statistical significance (Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/WAD/A448). This may have been due to low power, given only 8 reverters.

In comparison with PD patients with a stable cognitive diagnosis, PD progressors to PD-MCI or PDD showed significantly worse performance in the attention and language domains at baseline and worse performance in the memory domain that approached significance ($P = 0.07$) (Table 3). On the other hand, when the domain-specific classification was used, PD progressors had poorer scores in all cognitive domains except visuospatial function (Supplementary Table 4, Supplemental Digital Content 4, http://links.lww.com/WAD/A449).

Evolution of Global Cognitive Scores

At year 1, 74 of 118 (62.7%) experienced cognitive decline (global cognitive change <0), and 36.8% improved (global cognitive change >0) relative to baseline. Global Cognition z-scores were significantly worse compared with baseline [beta (SE) = −0.15 (0.04), $P < .001$] At year 2, 45 of 103 (43.2%) experienced cognitive decline relative to

TABLE 1. Baseline Demographics, Clinical Characteristics, Cognitive Domain and Global Cognitive *z*-scores of PD-CN Stable, PD-CN converters, PD-MCI Stable, PD-MCI Converters, and PD-MCI Reverters at year 1 and 2*

	PD-CN stable N = 69	PD-CN converter N = 23	PD-MCI stable N = 20	PD-MCI converter N = 9	PD-MCI reverter N = 17	*P*
Age, y	70.5 (5.7)	72.5 (5.6)	71.5 (4.6)	69.7 (3.7)	71.9 (5.7)	0.50
Sex, % male	46 (66.7)	17 (73.9)	13 (65.0)	7 (77.8)	9 (52.9)	0.64
Education, y	16 (15, 18)	16 (16, 18)	15.5 (12, 18)	16 (12, 18)	16 (14, 17)	0.63
Estimated premorbid IQ	114.8 (7.9)	115.2 (9.0)	108.1 (10.8)	109.7 (8.8)	112.2 (9.1)	0.0353
Time since diagnosis, y	4 (2, 7)	5 (2, 8.5)	3 (2, 10)	5 (1, 6)	2 (2, 7)	0.87
Total MDS-UPDRS	41.2 (16.8)	45.9 (16.7)	46.1 (16.6)	54.6 (13.1)	36.4 (15.3)	0.07
MDS-UPDRS-III	26.2 (11.3)	27.3 (13.0)	28.3 (9.5)	29.8 (4.8)	24.2 (12.8)	0.57
Total LEU, mg	400 (267, 800)	600 (380, 925)	455 (300, 737.5)	540 (375, 750)	450 (300, 600)	0.29
MoCA total score	26.2 (2.5)	25.1 (2.2)	23.2 (3.5)	23.0 (3.2)	25.2 (2.9)	0.0003
Geriatric Depression scale	1 (0, 2)	1 (0, 2)	2 (0, 3)	2 (1, 2)	1 (0, 1)	0.17

*Individuals changing cognitive classification by year 1 then lost to follow-up or withdrawn from the study were classified according to their cognitive diagnosis at year 1 Individuals changing cognitive classification at year 1 then reverting back to the original classification at year 2 are classified according to their cognitive classification at year 1.

IQ, intelligence quotient; LEU, levodopa equivalent units; MDS-UPDRS, movement disorder society unified Parkinson disease rating scale; MOCA, montreal cognitive assessment; PD-CN, Parkinson disease cognitively normal; PD-MCI, Parkinson disease mild cognitive impairment.

baseline, and 56.3% improved. Year 1 and year 2 scores did not differ from baseline [beta (SE) = 0.04 (0.04), $P = 0.37$].

Baseline Diagnostic and Neuropsychological Predictors of Cognitive Change Over 2-year Follow-up

Baseline diagnosis of PD-MCI was not associated with global cognitive change (*z*-score) over 2 years of follow-up whether using the original ($\beta = 0.038$ (SE = 0.08), $P = 0.66$) or domain-specific classification ($\beta = -0.16$ (SE = 0.10), $P = 0.11$]. There was a positive association between baseline attention scores and global cognitive change [$\beta = 0.194$ (SE = 0.065), $P = 0.0035$] and a negative association between baseline executive function scores and cognitive change over follow-up [$\beta = -0.082$ (SE = 0.025), $P = 0.0012$, see Supplementary Table 5, Supplemental Digital Content 5, http://links.lww.com/WAD/A450] regardless of cognitive diagnosis. For every one point decrease in baseline attention domain *z*-score, change in Global Cognitive *z*-score since baseline decreased by 0.20 points over 2-year follow-up. For every 1 point decrease in baseline executive domain *z*-score, change in Global Cognitive *z*-score since baseline increased by 0.08 points over 2-year follow-up (ie, poorer baseline executive domain scores predicted improvement in Global Cognitive *z*-score over time).

TABLE 2. Baseline Domain Cognitive *z*-scores Among Reverters to Cognitively Normal and Nonreverters Over 2 Years of Follow-up

Domain at baseline	Reverter (n = 17)	Nonreverter (n = 29)	*P*
Attention			
Mean (SD)	0.36 (0.68)	−0.32 (0.88)	0.0132
Language			
Mean (SD)	0.55 (0.71)	−0.04 (0.80)	0.0061
Visuospatial			
Mean (SD)	−0.78 (0.83)	−1.74 (1.02)	0.0041
Memory			
Mean (SD)	0.27 (0.66)	−1.11 (0.92)	< 0.0001
Executive			
Mean (SD)	−1.44 (0.91)	−2.55 (1.91)	0.0685

DISCUSSION

In this prospective study of individuals with PD, we found that a baseline diagnosis of PD-MCI was not associated with global cognitive decline over 2 years of follow-up as measured by a summative score on a comprehensive neuropsychological battery. In contrast, baseline neuropsychological domain scores for attention and executive function were associated with global cognitive change to follow-up. Finally, lower baseline attention and language scores were associated with progression to MCI or PDD, and higher baseline scores in all cognitive domains except executive function were associated with reversion to normal cognition.

The absence of a relationship between a baseline diagnosis of PD-MCI and cognitive decline appears counterintuitive. This is particularly remarkable given the lower premorbid IQ at baseline in the PD-MCI group, which would be predicted to increase the likelihood of cognitive deterioration, potentially due to less cognitive reserve.[26] However, this finding is consistent with other longitudinal studies showing that cognition in PD can remain stable for long periods[4,27] or even fluctuate over time.[4,6,28] For example, in 2 clinic-based patient populations with early PD (disease duration of 3 y) and long disease duration (12 y) applying level I and II diagnostic criteria for PD-MCI, respectively, > 60% of PD-MCI participants remained cognitively stable based on cognitive classification at 5-year follow-up.[3,27] In addition, several recent studies have demonstrated that a sizable proportion of PD-MCI may revert to "normal cognition."[3,4,28] In our sample, 37% of PD-MCI patients at baseline reverted to normal cognition over the 2-year follow-up. Previous studies showed a reversion rate from 9% to 29% of PD patients,[23,28–31] and a recent meta-analysis investigating this issue estimated that 28% of PD-MCI patients revert to PD-CN for follow-up periods under 3 years.[6] Factors associated with reversion have been reported to include younger age at onset,[27,32] shorter disease duration and less severe motor dysfunction,[26] better visuoconstructional skills,[32] and better attention, semantic fluency, and

TABLE 3. Baseline Domain Cognitive *z*-scores Among Converters to Parkinson Disease Mild Cognitive Impairment or Parkinson Disease Dementia and Nonconverters Over 2-year Follow-up

Domain at baseline	Converter (n = 32)	Nonconverter (n = 106)	*P*
Attention			
Mean (SD)	−0.14 (0.70)	0.25 (0.69)	0.007
Language			
Mean (SD)	0.24 (0.70)	0.55 (0.80)	0.042
Visuospatial			
Mean (SD)	−0.62 (0.99)	−0.61 (1.09)	0.91
Memory			
Mean (SD)	−0.24 (0.99)	0.15 (1.09)	0.07
Executive			
Mean (SD)	−1.54 (1.92)	−1.07 (1.68)	0.17

memory.[26] Interestingly, these domains were more preserved in our PD-MCI reverter population. As mentioned above, this reversion can also be explained by fluctuation in PD cognition over time and changes in dopaminergic replacement medication.[33,34] Taken together with the results of other studies, the high reversion rates highlight the need for more prognostically meaningful criteria for PD-MCI, at least in the short term. In this regard, next steps for research could include carefully examining prognostic value of PD-MCI according to different cutoffs (−1 to −2 SDs) for pathologic test scores, educational level, the neuropsychological battery, or the absence/presence of subjective cognitive complaints. In our study, we examined the effect of requiring at least 2 impaired cognitive tests within a single domain to meet the neuropsychological test criteria for PD-MCI. Using this alternative classification method, only 8 (17%) of individuals with PD-MCI at baseline were classified as reverters at follow-up, suggesting a more stable classification.

The prognostic implications of reversion to a cognitively normal classification in PD are unclear due to conflicting findings in prior studies. Two studies[3,30] have reported an increased risk of dementia associated with PD-MCI even in those who experienced episodes of reversion, suggesting that, regardless of the stability of the PD-MCI diagnosis, it is still of prognostic value in identifying at-risk patients. Nevertheless, a subsequent study did not corroborate this finding that individuals who revert to a classification of normal cognition have a favorable cognitive prognosis with a similar risk of cognitive decline as those classified as cognitively normal at baseline, as well as greater cortical thickness in the parahippocampal gyrus (involved in episodic memory and visuospatial processing) and more preserved functional integrity relative to nonreverters.[31] Some of the reversions in our study were associated with the loss of a cognitive complaint. We have previously shown in the same cohort that in PD with normal cognition, the presence of a subjective cognitive complaint does not predict cognitive decline over time. This raises concern about the value of relying on a cognitive complaint for diagnosis of PD-MCI.[35,36] Further research is warranted to understand the nature and factors associated with cognitive complaints and the impact on reversion in PD-MCI. Future studies of the evolution of PD-MCI should examine closely the underlying factors associated with "reversion" and the impact of varying the criteria for PD-MCI on the predictive value of reversion for further cognitive outcome.

Lower baseline neuropsychological scores on attention tests predicted worse global cognition over 2 years of follow-up in PD. Attention/working memory impairment is common in PD[37,38] and is linked to dysfunction in frontostriatal dopaminergic systems[39,40] as well as nondopaminergic systems.[41,42] Poor baseline attentional function has been shown to be associated with more rapid cognitive decline in PD patients based on MMSE and CAMCOG performances at 3-year follow-up.[43] In addition, we previously found that PD-MCI patients' subjective complaints related to inattention may predict progression to dementia.[44] On the other hand, we found that better baseline executive domain function was associated with an overall decrease in global cognitive scores over time. This finding is counterintuitive and may be accounted for by differential attrition of lower functioning participants over the course of the study, given the relative improvement in neuropsychological scores on average in our sample across the 2 follow-up time points. Nevertheless, this inverse association could be a spurious finding and must also be tested by further longitudinal studies. Executive function scores at baseline were worse in individuals not completing 2 years of follow-up, and this pattern was also seen in other domains.

We also found that lower baseline language scores were associated with progression to MCI or PDD in PD-CN, this is in line with previous data showing lower performance in naming and verbal fluency as independent predictors of progression.[45] Individuals with PD-MCI converting to PDD in our study exhibited lower baseline performances on the cognitive tasks compared with those with stable or reverting classifications; however, there was no particular cognitive pattern associated with development of PD-MCI or PDD. It is possible that low power may have contributed to this finding, given the small number of conversions to PDD in our sample. However, Wood et al[22] reported a similar result to ours in a study with 4 years of follow-up. They interpreted the finding as reflecting the heterogeneous nature of the neuropsychological deficits in PD-MCI. To be classified as multidomain PD-MCI, a participant requires 2 or more impaired neuropsychological test scores distributed across any domains, whereas to be classified as single-domain PD-MCI a participant must exhibit 2 or more impairments in a single domain. The less stringent criteria for multidomain PD-MCI results in this being the most frequent subtype reported in PD-MCI studies and with many more domains involved in the diagnostic category no one particular cognitive pattern emerges for prediction to PDD.[4,5,9,32]

The strengths of our study include its prospective, longitudinal design with a well-characterized cohort using Level II MDS Task Force criteria for PD-MCI. Study limitations are similar to other longitudinal studies; over the 2 years of follow-up, there was a 25% attrition rate, which may impact inferences regarding cognitive change over time. There were small sample sizes in our diagnostic subgroups, which reduced power and the ability to detect potential associations. In addition, a practice effect cannot be excluded since the battery was the same at baseline and follow-up visits. We did not adjust for multiple testing; therefore, findings are hypothesis generating and require replication in independent cohorts. We demonstrate the instability of cognitive classification over the short term; however, what proportion of "reverters" and "converters" maintain their new classifications and for how long was not evaluated. The length of follow-up of only 2 years is relatively short, and this could have facilitated practice effects due to repeated testing; however, this effect was reduced by applying and alternative version in the follow-up assessment in 6 out of the 10

neuropsychological tests. In addition, practice effects have previously showed to be small in this population.[46]

Finally, the cohort was highly educated, limiting generalizability to the broader population.

In summary, a baseline diagnosis of PD-MCI is not necessarily predictive of cognitive decline over 2-year follow-up; however, baseline performance in the attentional domain is associated with cognitive decline, suggesting that careful monitoring of those participants with attentional deficits might be worthy. From a clinical standpoint, the presence of particular cognitive strengths or weaknesses at initial assessment may be more valuable than the PD-MCI diagnosis *per se* in terms of cognitive prognosis. We believe that our juxtaposition of the prognostic value of a diagnosis of PD-MCI compared with domain-specific test performance is instructive, and prompts a critical appraisal of the value of a categorization of PD-MCI per se. The nature and meaning of "reversion to normal cognition" is worthy of further study in studies with longer follow-up and larger sample sizes, taking into account the challenges presented by the operationalization of the PD-MCI diagnosis and exploring domain-specific PD-MCI criteria. Future studies pairing domain-specific cognitive performance with other motor and nonmotor manifestations, and eventually biomarker changes such as brain hypometabolism, genetics, or Alzheimer disease changes[47] will provide a more comprehensive understanding of the factors that predict cognitive decline in PD.

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REFERENCES

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256:183–194.
2. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord*. 2012;27:349–356.
3. Pedersen KF, Larsen JP, Tysnes OB, et al. Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study. *Neurology*. 2017;88:767–774.
4. Lawson RA, Yarnall AJ, Duncan GW, et al. ICICLE-PD study group. Stability of mild cognitive impairment in newly diagnosed Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2017;88:648–652.
5. Galtier I, Nieto A, Lorenzo JN, et al. Mild cognitive impairment in Parkinson's disease: diagnosis and progression to dementia. *J Clin Exp Neuropsychol*. 2016;38:40–50.
6. Saredakis D, Collins-Praino LE, Gutteridge DS, et al. Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord*. 2019;65:20–31.
7. Hoogland J, Boel JA, de Bie RMA, et al. Mild cognitive impairment as a risk factor for Parkinson's disease dementia. *Mov Disord*. 2017;32:1056–1065.
8. Hoogland J, Boel JA, de Bie RMA, et al. Risk of Parkinson's disease dementia related to level I MDS PD-MCI. *Mov Disord*. 2019;34:430–435.
9. Marras C, Armstrong MJ, Meaney CA, et al. Measuring mild cognitive impairment in patients with Parkinson's disease. *Mov Disord*. 2013;28:626–633.
10. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132:2958–2969.
11. Hobson P, Meara J. Mild cognitive impairment in Parkinson's disease and its progression onto dementia: a 16-year outcome evaluation of the Denbighshire cohort. *Int J Geriatr Psychiatry*. 2015;30:1048–1055.
12. Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol Dis*. 2012;46:590–596.
13. Delis DC, Kaplan E, Kramer JH. *Delis–Kaplan Executive Function System (D-KEFS): Examiner's Manual*. The Psychological Corporation; 2001.
14. Wechsler D. *Wechsler Memory Scale*. The Psychological Corporation; 1997.
15. Williams BW, Mack W, Henderson VW. Boston naming test in Alzheimer's disease. *Neuropsychologia*. 1989;27:1073–1079.
16. Benton AL, Sivan AB, Hamsher K, et al. *Contributions to Neuropsychological Assessment: A Clinical Manual*. Oxford; 1994.
17. Meyers JE, Meyers KR. *Rey Complex Figure Test and Recognition Trial—Professional Manual*. Psychological Assessment Resources; 1995.
18. Delis D, Kramer JH, Kaplan E. *The California Verbal Learning Test*. The Psychological Corporation; 2000.
19. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. Oxford University Press; 2006.
20. Wicklund AH, Johnson N, Weintraub S. Preservation of reasoning in primary progressive aphasia: further differentiation from Alzheimer's disease and the behavioral presentation of frontotemporal dementia. *J Clin Exp Neuropsychol*. 2004;26:347–355.
21. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689–1707.
22. Wood KL, Myall DJ, Livingston L, et al. Different PD-MCI criteria and risk of dementia in Parkinson's disease: 4-year longitudinal study. *NPJ Parkinsons Dis*. 2016;2:15027.
23. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19:203–214.
24. Lansing AE, Ivnik RJ, Callum CM, et al. An empirically derived short form of the boston naming test. *Arch Clin Neuropsychol*. 1999;14:481–487.
25. SAS Institute Inc. *SAS® 94 Procedures Guide: Reference*. SAS Institute Inc; 2013.
26. Armstrong MJ, Naglie G, Duff-Canning S, et al. Roles of education and IQ in cognitive reserve in Parkinson's disease-mild cognitive impairment. *Dement Geriatr Cogn Dis Extra*. 2012;2:343–352.
27. Di Battista ME, Rubino A, Valente M, et al. Is cognitive stability in Parkinson's disease a predictable phenomenon? A 5-year follow-up study. *J Neural Transm (Vienna)*. 2015;122:1703–1706.
28. Pedersen KF, Larsen JP, Tysnes OB, et al. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. *JAMA Neurol*. 2013;70:580–586.
29. Broeders M, de Bie RM, Velseboer DC, et al. Evolution of mild cognitive impairment in Parkinson disease. *Neurology*. 2013;81:346–352.
30. Jones JD, Kuhn TP, Szymkowicz SM. Reverters from PD-MCI to cognitively intact are at risk for future cognitive impairment: analysis of the PPMI cohort. *Parkinsonism Relat Disord*. 2018;47:3–7.
31. Chung SJ, Park YH, Yoo HS, et al. Mild cognitive impairment reverters have a favorable cognitive prognosis and cortical integrity in Parkinson's disease. *Neurobiol Aging*. 2019;78:168–177.
32. Santangelo G, Vitale C, Picillo M, et al. Mild Cognitive Impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. *Parkinsonism Relat Disord*. 2015;21:1219–1226.
33. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*. 2006;30:1–23.

34. Pascual-Sedano B, Kulisevsky J, Barbanoj M, et al. Levodopa and executive performance in Parkinson's disease: a randomized study. *J Int Neuropsychol Soc*. 2008;14:832–841.
35. AlDakheel A, Gasca-Salas C, Armstrong MJ, et al. Cognitive complaints in nondemented Parkinson's disease patients and their close contacts do not predict worse cognitive outcome. *Alzheimer Dis Assoc Disord*. 2019;33:147–153.
36. Gasca-Salas C, Duff-Canning S, Armstrong MJ, et al. Parkinson disease with mild cognitive impairment: domain-specific cognitive complaints predict dementia. *Acta Neurol Scand*. 2020;142:585–596.
37. Gasca-Salas C, Estanga A, Clavero P, et al. Longitudinal assessment of the pattern of cognitive decline in non-demented patients with advanced Parkinson's disease. *J Parkinsons Dis*. 2014;4:677–686.
38. Muslimovic D, Post B, Speelman JD, et al. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005;65:1239–1245.
39. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. *Neurodegener Dis*. 2013;11:79–92.
40. Lewis SJ, Slabosz A, Robbins TW, et al. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia*. 2005;43:823–832.
41. Bohnen NI, Kaufer DI, Hendrickson R, et al. Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. *J Neurol*. 2006;253:242–247.
42. Zgaljardic DJ, Foldi NS, Borod JC. Cognitive and behavioral dysfunction in Parkinson's disease: neurochemical and clinicopathological contributions. *J Neural Transm (Vienna)*. 2004;111:1287–1301.
43. Taylor JP, Rowan EN, Lett D, et al. Poor attentional function predicts cognitive decline in patients with non-demented Parkinson's disease independent of motor phenotype. *J Neurol Neurosurg Psychiatry*. 2008;79:1318–1323.
44. Gasca-Salas C, Duff-Canning S, Armstrong MJ, et al. Parkinson disease with mild cognitive impairment: domain-specific cognitive complaints predict dementia. *Acta Neurol Scand*. 2020;142:585–596.
45. Pigott K, Rick J, Xie SX, et al. Longitudinal study of normal cognition in Parkinson disease. *Neurology*. 2015;85:1276–1282.
46. Tröster AI, Woods SP, Morgan EE. Assessing cognitive change in Parkinson's disease: development of practice effect-corrected reliable change indices. *Arch Clin Neuropsychol*. 2007;22:711–718.
47. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. 2021;7:47.