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Prediction of cognitive progression in Parkinson's disease using three cognitive screening measures

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ABSTRACT

Introduction: Cognitive impairment is a common complication of Parkinson's disease (PD) and identifying risk factors for progression to Parkinson's disease dementia (PDD) is important. However, little research has been done comparing the utility of commonly used cognitive screening tests in predicting cognitive progression in PD.

Methods: We retrospectively reviewed data from patients with PD enrolled in the Pacific Udall Center who had baseline and longitudinal neuropsychological and global cognitive screening tests. The diagnostic accuracies of 3 common screening tests were compared: Montreal Cognitive Assessment (MoCA), Mattis Dementia Rating Scale (DRS-2), and Mini Mental Status Examination (MMSE). Cognitive diagnoses of PD with mild cognitive impairment (PD-MCI) and PDD were based on full neuropsychological testing and established Movement Disorder Society criteria. Logistic regression and Cox proportional hazards regression models were used to examine predictors of cognitive decline.

Results: Four hundred seventy patients for whom scores on all 3 screening tests were available from the same assessment were included in a cross-sectional analysis. The MoCA demonstrated the best overall diagnostic accuracy for PD-MCI (AUC = 0.79, sensitivity = 76.4%) and for PDD (AUC = 0.89, sensitivity = 81.0%) compared to the DRS-2 and MMSE.

A longitudinal analysis was performed on the subset of patients (316/470; 67.2%) who were nondemented at baseline and had undergone two or more assessments. After controlling for covariates, the MoCA was the only test associated with progression to PDD (OR = 1.27 95% CI 1.1–1.5, p = 0.001) and faster time to dementia (HR = 1.3, 95% CI 1.1–1.4, p < 0.0001).

Conclusions: This study provides additional support for the use of the MoCA as a primary screening tool for cognitive impairment in PD and is the first to show that the MoCA is a predictor of conversion to PDD.

Introduction

Cognitive impairment in Parkinson's disease (PD-CI) is an important nonmotor complication with an estimated 20–30% of newly diagnosed Parkinson's disease (PD) patients affected with mild cognitive impairment (PD-MCI) [1] and ~80% of those who live longer than 20 years diagnosed with dementia (PDD) [2]. PD-MCI is a known risk factor for progression to PDD [3] and in a recent study, PD-MCI was identified as a significant risk factor for increased mortality [4]. Identification of cognitive impairment through neuropsychological testing [5–7] has advantages over other biomarkers due to its ease of availability in clinic or referral to a neuropsychiatrist, low cost, and lack of experimental protocols.

The Movement Disorder Society (MDS) Task Force established recommended diagnostic criteria for both PD-MCI [8] and PDD [9]: Level I for abbreviated testing and level II for more comprehensive neuropsychological evaluation. Although level II testing is ideal in fully characterizing PD-CI, it can be time-consuming, burdensome for the patient, and the clinician may lack timely access to such services. The MDS recently proposed guidelines on screening global cognitive tests for PD-CI [10]. Included in the

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guidelines are three commonly used tests: Montreal Cognitive Assessment (MoCA), Mattis Dementia Rating Scale Edition 2 (DRS-2) and Mini Mental Status Examination (MMSE).

The MoCA has been shown to be sensitive for detecting and predicting progression to PD-MCI and PDD [5–7,11–13] though its low specificity reduces its utility as a diagnostic test [11,12]. The DRS-2 is a recommended test for PD-CI [10] that assesses multiple cognitive domains. However, prior studies have shown varied results regarding the most sensitive cut-off score for identifying PD-MCI and PDD [14–17]. Furthermore, the long time needed for its administration may limit its use as an efficient cognitive screen in clinical practice. The MMSE is still a widely used cognitive screen that was included in the 2007 MDS Task Force PDD diagnostic criteria [9]. However, due to its limited executive function testing and poor sensitivity for detecting PD-MCI [6,16], the MMSE is currently recommended as a "suggested" test for PD-CI [10].

Given the heterogenous, multidomain presentation of PD-CI [11], it is not clear which cognitive screen has the best accuracy in predicting progression of cognitive impairment. To our knowledge, the ability of these three cognitive screening tests to predict PD-CI has not been compared directly. Our study sought to assess the accuracy of the MoCA, DRS-2, and MMSE in detecting PD-MCI and PDD in a large, well characterized cohort and to evaluate these patients longitudinally to determine the utility of these measures in predicting the progression of PD-CI.

Methods

Study design and participants

The Pacific Udall Center (PUC) was established in 2010 with a multisite clinical core to characterize and longitudinally follow patients with United Kingdom Brain Bank (UKBB) confirmed PD by collecting clinical, neuropsychological, and biomarker data, as described previously [18]. For baseline analyses in the current study, 470 patients who were administered all three global cognitive screening tests (MoCA, DRS-2, MMSE) and had clinical and neuropsychological data at two sites (University of Washington/Veterans Affairs Puget Sound Health Care System and Oregon Health and Sciences University/Veterans Affairs Portland Health Care System) were enrolled. Nondemented PUC patients who had at least one follow-up visit with clinical and neuropsychological data were included in the longitudinal cohort to determine the ability of the global cognitive tests to predict development of PD-CI (n = 316). The study was approved by the institutional review boards at all participating institutions, and written consent was provided by all patients or their legal surrogates to participate in the study.

Neuropsychological and clinical assessment

Patients were administered three global cognitive measures: MoCA [19], DRS-2 [20], and MMSE [21]. The remainder of the neuropsychological battery included tests of the following cognitive domains: memory (Hopkins Verbal Learning Test-Revised, Logical Memory I & II, Brief Visual Memory Test-Revised [Total and Delayed Recall]), visuospatial (Judgement of Line Orientation, Clock Copy, Brief Visual Memory Test-Revised [Copy Trial]), language (Boston Naming Test, Shipley Vocabulary, semantic verbal fluency), executive (Clock Drawing Test, phonemic verbal fluency), and attention/working memory (Trail making test, parts A & B, Letter-Number Sequencing, Digit Symbol, Digit Span, Stroop-Golden Version). See Supplemental Table 1 for further details. Motor severity was assessed using the Movement Disorders Society- sponsored Unified Parkinson's Disease Rating Scale revision (MDS-UPDRS) Part III. Levodopa equivalent daily dose (LEDD) was calculated [22] and depression symptoms were evaluated using the 15-item Geriatric Depression Scale (GDS) [23]. The glucocerebrosidase gene (*GBA*) was sequenced and apolipoprotein E (*APOE*) genotype determined as previously described [24,25].

Consensus diagnosis

Motor and cognitive diagnoses were assigned during regular diagnostic consensus conferences. Conferences were attended by at least two movement disorders specialists, a neuropsychologist, and study support personnel. Cognitive diagnoses were based on data collected from detailed neuropsychological testing (Supplemental Table 1), clinical history, and data obtained via interview of the patients and informant (if available) as described previously [18]; PDD and PD-MCI diagnoses were made according to published criteria [8,26].

Statistical analysis

Cognitive diagnostic group differences were calculated using one-way analysis of variance for continuous variables, Kruskal-Wallis for ordinal variables, or chi-square for categorical variables. Post-hoc testing was calculated using Scheffe's test for continuous variables, Dunn's for ordinal variables, and Bonferroni correction for categorical variables. To determine the diagnostic accuracy profile for each screening test, separate logistic regression analyses were run using cognitive diagnostic status (PD-not cognitively impaired [PD-NCI] vs. PD-MCI, nondemented vs. PDD) as the dependent variable and MoCA, DRS-2, or MMSE scores as the independent variable. The resulting receiver operating characteristic (ROC) curves were analyzed to determine the diagnostic accuracy of each measure using the following scale [27]: Area under the curves (AUC) 0.9–1.0 excellent, 0.8–0.9 very good, 0.7–0.8 good, 0.6–0.7 sufficient, 0.5–0.6 bad, <0.5 not useful. Youden's index [28] was calculated to determine the optimal cutoff score for each test for the PUC cohort. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each test to correctly classify PDD and PD-MCI are reported. Separate logistic regression analyses controlling for age, education, sex, disease duration, LEDD, MDS-UPDRS part III, GDS, and site were run to determine the association of each screening measure with cognitive diagnostic status after controlling for potentially confounding factors.

To determine whether screening tests at baseline predicted subsequent progression from PD-NCI to PD-CI, or from PD-MCI to PDD during study follow-up, separate logistic regression models were run for the MoCA, DRS-2, or MMSE with conversion to PD-MCI or PDD (Yes, No) as the dependent variable, controlling for age, sex, education, disease duration, site, LEDD, MDS-UPDRS part III, GDS, and length of follow up. Predicted probabilities as a function of screening test scores if all covariates were held at the population mean and their 95% confidence intervals were estimated based on the fitted logistic regression models. To determine whether screening tests predicted time to PDD conversion, separate survival analyses were performed using Cox proportional hazards regression models, entering the continuous values for the MoCA, DRS-2, or MMSE, again controlling for all covariates. We included inheritance of an *APOE* ε4 allele and *GBA* variants (pathogenic mutations and the E326K polymorphism) as covariates in our sensitivity analyses given our prior findings of an effect with cognition. All analyses were performed using Stata 14.2. (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.)

Results

Cross-sectional cohort

Baseline demographic variables, clinical characteristics, and cognitive test scores for the 470 patients with baseline data are presented in Table 1. Cognitively impaired patients were older, more likely male, had more severe motor symptoms, and had worse cognitive global screening scores than cognitively normal patients.

ROC curves for each of the three screening measures are provided for each level of impairment. AUCs for the MoCA (0.89), DRS-2 (0.87), and MMSE (0.86) indicated very good diagnostic accuracy for PDD (Fig. 1A–C). Conversely, only the AUC for the MoCA (0.79) indicated good diagnostic accuracy for PD-MCI (Fig. 1D–F). To determine the best cutoff score(s) for

Table 1
Baseline characteristics of the PUC cohort, by cognitive diagnosis.

	PD-NCI (n = 106)	PD-MCI (n = 280)	PDD (n = 84)	Overall p-value*	Pairwise[a]
Age, years					
Mean (SD)	63.6 (8.4)	67.8 (8.7)	71.2 (10.5)	<0.0001	PD-NCI < PD-MCI < PDD
Range	43.0–83.9	41.2–90.1	35.1–91.6		
Education, years					
Mean (SD)	16.2 (2.6)	15.8 (2.5)	15.3 (2.7)	<0.02	PD-NCI > PDD
Range	12–20	8–20	8–20		
Sex					
n (%) male	49 (46.2)	201 (71.8)	76 (90.5)	<0.001	PD-NCI < PD-MCI < PDD
Disease duration, years					
Mean (SD)	7.7 (5.2)	7.9 (5.7)	10.4 (6.9)	0.001	PD-NCI < PDD, PD-MCI < PDD
Range	0–26	0–25	0–29		
LEDD, mg/d					
Mean (SD)	553.5 (500.3)	619.0 (522.5)	695.1 (502.9)	0.170	
Range	0–2792	0–3375	0–3058		
Geriatric Depression Scale					
Mean (SD)	5.6 (1.3)	5.8 (1.7)	6.5 (1.8)	0.0003	PD-NCI < PDD, PD-MCI < PDD
Range	3–10	2–13	4–11		
MDS-UPDRS-III					
Mean (SD)	21.5 (10.5)	26.4 (11.8)	35.1 (13.3)	<0.0001	PD-NCI < PD-MCI < PDD
Range	3–56	0–66	5–68		
Modified Hoehn & Yahr					
Median	2	2	2.5	0.0001	PD-NCI < PDMCI < PDD
Range	1–4	1–5	1.5–5		
APOE ε4 allele					
n (%)	21 (20.0)	62 (22.7)	16 (19.8)	0.771	
GBA variant					
n (%)	9 (8.5)	24 (8.7)	15 (18.1)	0.037	PD-NCI < PDD, PD-MCI < PDD
MoCA					
Mean (SD)	27.4 (2.0)	24.7 (2.4)	19.5 (4.3)	0.0001	PD-NCI > PD-MCI > PDD
Range	22–30	17–30	7–29		
DRS-2					
Mean (SD)	139.9 (2.9)	136.6 (5.5)	123.5 (14.3)	0.0001	PD-NCI > PD-MCI > PDD
Range	131–144	103–144	59–141		
MMSE					
Mean (SD)	28.9 (1.2)	28.1 (1.6)	24.9 (3.6)	0.0001	PD-NCI > PD-MCI > PDD
Range	25–30	22–30	6–30		

Abbrev: *APOE*, apolipoprotein; DRS-2, Mattis Dementia Rating Scale-2; *GBA*, glucocerebrosidase gene; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society- sponsored Unified Parkinson's Disease Rating Scale revision; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease-mild cognitive impairment; PD-NCI, Parkinson's disease-not cognitively impaired; PUC, Pacific Udall Center; SD, standard deviation.

* Groups compared using one-way ANOVA for continuous variables (age, education, disease duration, LEDD, Geriatric Depression Scale, MDS-UPDRS, MMSE, MoCA, DRS-2), chi-square for categorical variables (sex), and Kruskal-Wallis one-way analysis of variance for ordinal data (Modified Hoehn and Yahr).

[a] Post-hoc testing: Scheffe (age, education, disease duration, MDS-UPDRS, MMSE, MoCA, DRS-2), Dunn's test (Modified Hoehn & Yahr), and Bonferroni (sex, APOE, GBA).

the PUC cohort, maximum Youden index derived from ROC analyses indicated that for dementia classification, a score of ≤23 on the MoCA (sensitivity = 81.0, specificity = 83.7, PPV = 51.9, NPV = 95.3), ≤134 on the DRS-2 (sensitivity = 78.6, specificity = 78.5, PPV = 44.3, NPV = 94.4), and ≤27 on the MMSE (sensitivity = 84.5, specificity = 72.0, PPV = 39.7, NPV = 95.5) provided the best overall sensitivity/specificity profile for each test. For PD-MCI, ≤26 on the MoCA (sensitivity = 76.4, specificity = 65.1, PPV = 85.3, NPV = 51.1), ≤139 on the DRS-2 (sensitivity = 61.1, specificity = 65.1, PPV = 82.2, NPV = 38.8), and ≤28 on the MMSE (sensitivity = 52.1, specificity = 68.5, PPV = 81.6, NPV = 35.3) were determined to have the best sensitivity/specificity profile.

After controlling for all primary covariates, lower scores on each screening measure were significantly associated with PDD (MoCA: OR = 1.8 95% CI 1.5–2.0, p < 0.001; DRS-2: OR = 1.2 95% CI 1.1–1.3, p < 0.001; MMSE: OR = 1.9 95% CI 1.6–2.3, p < 0.001), and PD-MCI (MoCA: OR = 1.6 95% CI 1.4–1.8, p < 0.001; DRS-2: OR = 1.2 95% CI 1.1–1.3, p < 0.001; MMSE: OR = 1.2 95% CI 1.0–1.5, p = 0.027). These results did not change when genetic variables (*APOE* ε4 and *GBA* variants) were included.

Longitudinal cohort

Baseline clinical and demographic characteristics for the 316 patients who were nondemented at baseline and had longitudinal data (82% of the nondemented sample; average 3.8 years of follow up) are shown in Table 2. Among the 91 patients with PD-NCI at baseline, 33 developed PD-MCI and 4 developed PDD over the course of follow up. Of the 225 patients with PD-MCI at baseline, 62 developed PDD during follow-up. None of the cognitive screening tests were associated with conversion from PD-NCI to PD-MCI, thus comparisons were made between those who were nondemented at baseline (PD-NCI or PD-MCI) and those who converted to PDD. Patients that converted to dementia were older, more likely to be male, had worse motor severity, higher depression scores, and lower cognitive scores at baseline.

After controlling for age, education, sex, disease duration, GDS score, MDS-UPDRS part III, LEDD, follow-up time, and site, lower baseline MoCA score was associated with progression to dementia during follow-up (OR = 1.27 95% CI 1.1–1.5, p = 0.001), while the DRS-2 and MMSE scores were not (DRS-2: OR = 1.0 95% CI 1.0–1.1, p = 0.556; MMSE: OR = 1.0 95% CI 0.9–1.3, p = 0.628) (Fig. 2). Similarly, Cox regression analyses indicated that lower baseline MoCA scores were associated with faster time to dementia (HR = 1.3, 95% CI 1.1–1.4, p < 0.0001), while the DRS-2 and MMSE baseline scores were not associated with time to dementia (DRS-2: HR =1.0 95% CI = 0.9–1.1, p = 0.498; MMSE: HR = 1.1 95% CI 0.9–1.3, p = 0.256). When the tests scores were analyzed using a median split, cox regression analyses showed that MoCA scores <25 were a significant risk factor for time to dementia (HR = 3.1 95% CI 1.8–5.4 p < 0.001, Supplemental Fig. 1A) whereas DRS-2 scores <139 (HR = 1.6 95% CI 0.9–2.7 p = 0.095, Supplemental Fig. 1B) and

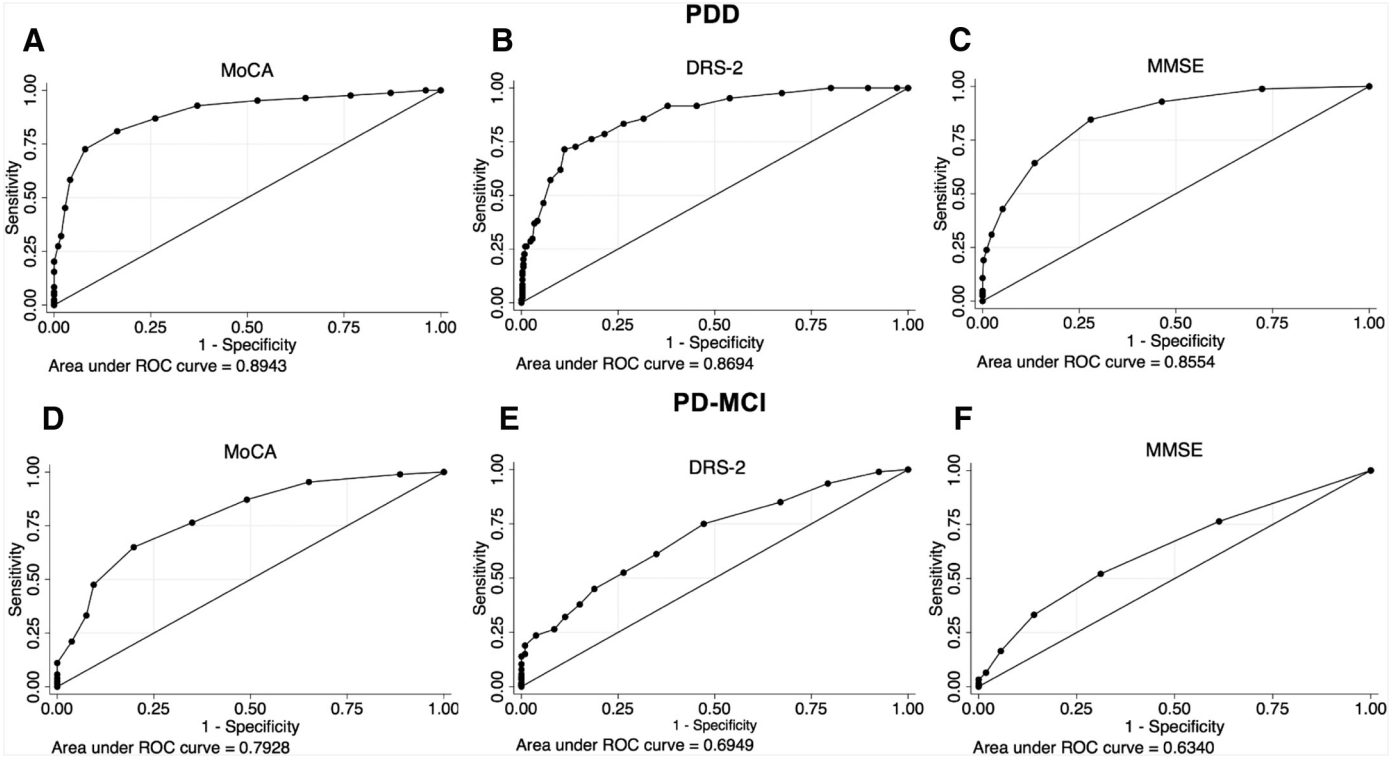

Fig. 1. ROC curves displaying sensitivity and specificity for the MoCA, DRS-2, and MMSE for prediction of PD-MCI and PDD.

MMSE scores <29 (HR = 1.3 95% CI 0.7–2.2 p = 0.399, Supplemental Fig. 1C) did not confer a risk for subsequent PDD. In all analyses, the results were not significantly changed by the inclusion of genetic variables (*APOE* ε4 and *GBA* variants).

Discussion

The results of this study show that the MoCA is the global cognitive test that provided the highest measure of overall diagnostic accuracy for both PD-MCI and PDD whereas the DRS-2 and MMSE had very good accuracy for screening for PDD only. This study also found that none of the cognitive tests were associated with prediction of progression from PD-NCI to PD-MCI. When controlling for covariates, the MoCA was the only test in which a lower baseline score was associated with an increased risk of and faster progression to PDD.

Our finding from the cross-sectional study supports previous reports that the MoCA has the best overall discriminative accuracy when assessing for PD-CI as compared to other cognitive tests as well as the best diagnostic consistency across different cohorts [6,11–13,16,29]. Our results also affirm previously reported findings of a ceiling effect for both the MMSE and DRS-2 [12,13,17,29]. In our study, while all three cognitive tests reached above or close to 80.0% sensitivity for PDD, the cutoff scores needed to achieve this were ≤134/144 for the DRS-2 (93% correct of raw score) and ≤27/30 on the MMSE (90% correct of raw score). In comparison, the cutoff score for the MoCA was ≤23/30 (77% correct of raw score). This is even more apparent for PD-MCI, with cutoff scores needed to achieve the determined sensitivities for DRS-2 and MMSE of ≤139/144 (97% correct of raw score) and ≤28/30 (93% correct of raw score) respectively. This ceiling effect could explain the observed finding of the limited sensitivities of the DRS-2 and MMSE for detecting earlier cognitive impairment such as PD-MCI. For example, one study showed that 51.9% patients that were classified as cognitively normal by MMSE had MoCA scores <26 [30].

The main finding of our study stems from the longitudinal portion showing that only lower performance on the MoCA was associated with conversion from a nondemented state to PDD and with faster progression to PDD when controlling for all covariates. A previous prospective study of 95 patients followed for over 2 years found that a lower baseline MoCA score was associated with an increased risk for conversion to any PD-CI [10]. Another study assessing clinical predictors for conversion to PD-CI using the DRS-2 as the global cognitive screen found that lower DRS-2 scores were predictive of future PD-CI [12].

There are several possible explanations for the observed differences. One reason for this discrepancy is the difference in the cohorts and baseline cognitive status. In the study by Pigott, et al., all patients at baseline were cognitively normal due to the prospective study design targeting incident PD-MCI and PDD cases. The baseline cohort characteristics in the study by Kandiah et al. were also similar in that many of the patients (55/64, 85.9%) were classified as PD-NCI. This contrasts with our study in which most of the patients at baseline (225/316, 71.2%) were classified as PD-MCI. Additionally, the progression characteristics also differed between the studies. In the Kandiah, et al., study, 13/64 (20.3%) progressed from PD-NCI to PD-MCI and in the Pigott et al. study, a similar rate of progression from PD-NCI to PD-MCI was estimated at 18.5%. In our cohort, a smaller number converted from PD-NCI to PD-MCI (33/316, 10.4%). These combined factors could explain why none of the cognitive tests predicted conversion to PD-MCI in our cohort.

The early identification of individuals at risk of conversion to PDD is important for prevention and management of cognitive impairment related complications. There are several established clinical risk factors associated with an increased hazard of PDD including age, higher motor scores, and PD-MCI. Hoogland et al. showed that when applying level II MDS PD-MCI criteria, levels of impairments >1.5 SD were significantly associated with an increased hazard of PDD [31]. Understanding that level II criteria may not be practical in every situation, a more recent study found that fulfilling level I PD-MCI criteria defined as abbreviated neuropsychological testing also significantly increased hazard of PDD [32].

Fulfilling level I MDS PD-MCI criteria also can be achieved by impairment in global cognitive screening tests [8] and with the recent recommendations for global cognitive tests for PD-CI [10], our study takes this one step further by assessing if these tests can be used to predict the risk of future PD-CI. There are a number of advantages of this including the ease of administration in clinic, little training needed, cost, and ability to

Table 2
Baseline characteristics of PUC cohort, PDD converters vs. nonconverters.

	Converted to dementia (n = 66)	Did not convert (n = 250)	p-value*
Age, years			
Mean (SD)	70.7 (8.4)	65.4 (8.5)	<0.0001
Range	50.1–90.1	43.04–89.2	
Education, years			
Mean (SD)	16.0 (2.6)	16.0 (2.5)	0.906
Range	12–20	8–20	
Sex			
n (%) male	51 (77.3)	159 (63.6)	0.036
Follow-up time, years			
Mean (SD)	3.5 (1.8)	3.8 (1.8)	0.278
Range	1.0–7.0	0.8–8.0	
Number of visits			
Mean (SD)	2.8 (1.0)	3.0 (1.1)	0.190
Range	2–6	2–6	
Disease duration, years			
Mean (SD)	8.5 (5.7)	7.6 (5.7)	0.275
Range	1–24	0–24	
LEDD, mg/d			
Mean (SD)	678.5 (507.0)	559.2 (472.9)	0.074
Range	0–2876	0–2972	
Geriatric Depression Scale			
Mean (SD)	6.0 (1.6)	5.6 (1.5)	0.019
Range	4–12	2–12	
MDS-UPDRS-III			
Mean (SD)	26.5 (10.6)	23.5 (11.3)	0.052
Range	10–57	3–60	
Modified Hoehn & Yahr			
Median	2.25	2	0.004
Range	1–4	1–5	
APOE ε4 allele			
n (%)	14 (21.9)	54 (22.0)	0.990
GBA variant			
n (%)	6 (9.1)	21 (8.4)	0.865
MoCA			
Mean (SD)	23.7 (2.4)	25.7 (2.5)	<0.0001
Range	17–30	18–30	
DRS-2			
Mean (SD)	136.4 (4.6)	138.2 (5.1)	0.012
Range	125–144	103–144	
MMSE			
Mean (SD)	27.9 (1.5)	28.4 (1.6)	0.031
Range	24–30	23–30	

Abbrev: *APOE*, apolipoprotein; DRS-2, Mattis Dementia Rating Scale; *GBA*, glucocerebrosidase gene; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society- sponsored Unified Parkinson's Disease Rating Scale revision; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; PDD, Parkinson's disease dementia; PUC, Pacific Udall Center; SD, standard deviation.

* Groups compared using *t*-tests for continuous variables (age, education, disease duration, LEDD, Geriatric Depression Scale, MDS-UPDRS, MMSE, MoCA, DRS-2), chi-square for categorical variables (sex), and Kruskal-Wallis one-way analysis of variance for ordinal data (Modified Hoehn and Yahr).

perform longitudinally to track progression of impairment. Our finding that a lower MoCA score can predict future PDD conversion has several interesting considerations.

While PD-MCI is a risk factor for PDD, not all PD-MCI progresses to PDD, with some remaining PD-MCI at follow-up and others reverting back to PD-NCI [1,3]. Identifying those at most risk of converting from PD-MCI to PDD is needed and performance on the MoCA can provide an initial screen to identify these individuals. Incorporating the performance on the MoCA into a predictive clinical model can also provide more meaningful risk stratification. In one example, the Montreal Parkinson Risk of Dementia Scale (MoPaRDS) includes a clinical item screening for PD-MCI, defined either by MDS Task Force guidelines or a MoCA score < 26 [33]. Although a score of <26 is accepted as the cutoff for PD-MCI, lowering the MoCA cutoff score may provide improved predictive accuracy for PDD risk. For example, using a MoCA cutoff value of <25 resulted in a significantly higher hazard of PDD (HR = 3.1 CI 1.8–5.4 p < 0.001). These results are similar to the reported finding of progressively increased PDD risk with worse neuropsychological performance [32].

There are several limitations of our study. First the design of our study was retrospective which by its nature, can be affected by a variety of confounding factors including selection bias and variable data collection. For example, all three global cognitive screening tests were initially administered but subsequently the DRS-2 and MMSE were removed from the protocol. Although this reduced the number of eligible patients, we were still able to include 470 patients, which represent one of the largest cross-sectional PD cohorts. Second, we cannot rule out the potential effects of anti-cholinergic medications on cognitive performance since this information was not captured. Third, while our results are consistent with prior studies demonstrating male sex as a risk factor for PDD [34,35], the proportion of males in the PDD group at baseline (90.5%) was larger than that reported in other studies [14,36]. This might be due, in part, to the high proportion of males in the overall baseline cohort (69.4%). However, patients diagnosed with PDD at the initial assessment were not included in subsequent longitudinal analyses. Finally, the PUC cohort is not a de novo cohort, and patients were enrolled at all levels of cognitive impairment and disease duration. However, we separated the group according to baseline cognitive diagnosis which permitted looking at cognitive change over a shorter period and included disease duration as an additional control.

In summary, our study largely supports the 2018 MDS recommendations for global cognitive tests for PD-CI [10]. Our results affirm that the MoCA is the best suited global cognitive screening test for both PD-MCI and PDD. However, although the MDS guidelines list the DRS-2 as a "recommended" test for PD-CI, including PD-MCI, we found that the DRS-2 lacks the sensitivity to accurately screen for PD-MCI and should be reserved for screening for PDD instead. To the best of our knowledge, our data also provide the first evidence that performance on the MoCA is predictive of risk for subsequent conversion to PDD. We hope that a similar designed study could be applied to prospective cohorts comparing the MoCA to other cognitive tests such as the Parkinson's Disease Cognitive Rating Scale and abbreviated neuropsychological level I PD-MCI testing.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2019.08.006.

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Authors' roles

All authors participated in the research and/or manuscript preparation. This article is of original work and is not published elsewhere or considered for publication at another journal. All authors have approved the final submitted article. Please see below for the respected roles for each author.

1.A. Conception and design, B. Acquisition of Data, C. Analysis/interpretation of data; 2. Drafting the article; 3. Revising the article; 4. Final approval of the submitted version

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Dr. Edwards: 1B, 1C, 3, 4
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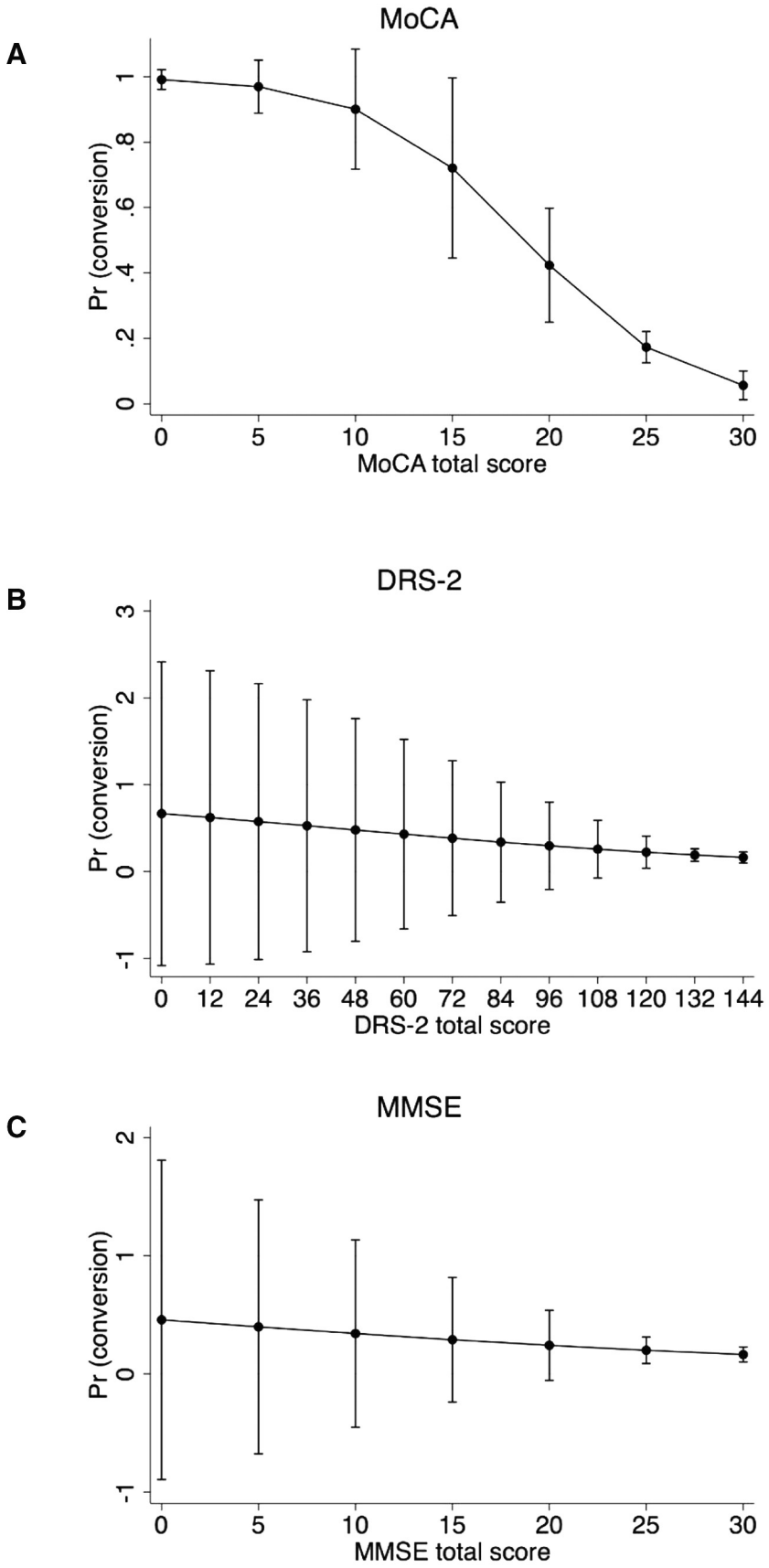

Fig. 2. Predicted probabilities of conversion from nondemented to PDD as a function of MoCA, DRS-2, and MMSE scores if all covariates are held at the population mean and their 95% confidence intervals, estimated based on the fitted logistic regression models.

Declaration of competing interest

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