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Diagnosing PD-MCI by MDS Task Force criteria: how many and which neuropsychological tests?

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Abstract

Background—The optimal properties of a comprehensive (Level II) neuropsychological battery for determining Parkinson's disease mild cognitive impairment (PD-MCI) by Movement Disorder Society (MDS) Task Force criteria remain unresolved.

Methods—Seventy-six non-demented PD patients underwent PD-MCI classification using a consensus diagnosis and Level II criteria. We examined the optimal number of tests in each of the five designated cognitive domains, identified the best tests within each domain, and determined the best overall battery for PD-MCI Level II diagnosis.

Results—A battery with two tests per domain provided a highly practical, robust diagnostic assessment. Level II testing with the two best tests and impairment defined as 2 standard deviations below norms was highly sensitive and specific for PD-MCI diagnosis.

Conclusions—Our findings strongly support the MDS Task Force Level II testing recommendations, provide a framework for creating an optimal, efficient neuropsychological test battery for PD-MCI diagnosis, and offer specific test recommendations.

Keywords

Cognitive tests; Dementia; Mild cognitive impairment; Parkinson's disease

Introduction

Mild cognitive impairment occurs in 20–50% of Parkinson's disease patients (PD-MCI)[1] and frequently progresses to dementia.[2, 3] The Movement Disorder Society (MDS) PD-MCI Task Force diagnostic criteria for PD-MCI have two levels: an abbreviated assessment (Level I) or a comprehensive assessment (Level II) requiring formal neuropsychological testing with at least two tests in each of the five cognitive domains (Attention/Working memory, Executive function, Language, Memory, Visuospatial function).[4] The MDS Task Force proposed these test recommendations to enhance diagnostic validity,[5] but acknowledged the need for additional research on the optimal number and type of tests per cognitive domain.[4] While the MDS PD-MCI guidelines provide examples of neuropsychological tests, there is no consensus regarding an optimal battery. Studies

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exploring which neuropsychological tests differentiate PD-MCI from PD with normal

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cognition (PD-NC) or from PD with dementia are essential to define an optimal diagnostic Level II battery.[6, 7]

Validation of the MDS PD-MCI criteria are underway, with the MDS PD-MCI Study Group examining pooled datasets.[8] Other studies, including our work, applied Level II criteria to non-demented PD cohorts, reporting PD-MCI in 20–62%[2, 7, 9–11] depending on the inclusion of cognitive complaints,[10] reported decline from premorbid levels,[10] and different cutoff scores to define impairment.[11] Against the gold standard of a consensus clinical diagnosis, we previously demonstrated that a Level II battery with 19 tests, including at least two tests per domain and impaired performance defined by a cutoff score of 2 SD below norms, provided the best classification for diagnosing PD-MCI (sensitivity 85.4%, specificity 78.6%, accuracy 82.9%).[11] Because comprehensive neuropsychological test batteries (e.g., our 19 test battery) can be time-consuming and burdensome for patients and test administrators, having an efficient, robust test battery would benefit clinicians and researchers in diagnosing PD-MCI. Thus, our study goal was to determine whether accurate Level II diagnostic classification, compared to our gold standard, could be optimized with a reduced battery. We aimed to establish the optimal number of neuropsychological tests needed in each cognitive domain and identify which specific tests provide the best fit to diagnose PD-MCI by Level II criteria.

Methods

Subjects and evaluations

Seventy-six non-demented PD subjects were included in the current study. We previously described this PD cohort, recruited from the Rush University Movement Disorders clinic as part of a prospective study of clinical and neuroimaging markers of PD cognitive impairment,[11, 12] in our paper demonstrating optimal properties of a 2 SD cutoff score in classifying subjects as PD-MCI.[11] The study was approved by the Rush University Institutional Review Board, Chicago, IL; participants provided written informed consent.

Subjects underwent detailed clinical evaluations and neuropsychological assessments [11, 13–17] including the MiniMental State Examination (MMSE)[18] and 19 MDS-recommended tests representing five cognitive domains[4]: (a) Attention/Working memory (Digit Span Forwards,[19] Letter Number Sequencing,[19] Symbol Digit Modalities Test [SDMT],[20] Trail Making Test-A [TMT-A][21]), (b) Executive function (Clock Drawing Test,[22] Controlled Oral Word Association Test,[23] Digit Span Backwards,[19] Progressive Matrices,[24] Trail Making Test-B [TMT-B][21]) (c) Language (Boston Naming Test,[25] animal naming in 1 minute,[25] Similarities[19]), (d) Memory (3 trials of word list learning, delayed recall, and recognition from the Consortium to Establish a Registry for AD [CERAD],[25] total free recall and delayed recall from Free and Cued Selective Reminding Test (FCSRT),[26] figure learning and delayed recall for Figural Memory,[27] Logical Memory I and II prose passages[28]), and (e) Visuospatial function (Clock Copying Test,[22] Judgment of Line Orientation [JLO]),[29] Intersecting pentagons from the MMSE[18, 30]). Raw scores were transformed to z-scores based upon normative data.[31, 32] Composite scores for each memory test (e.g., CERAD, FCSRT, Figural Memory, Logical Memory) were computed by averaging individual subcomponent z-scores (e.g., list learning, delayed recall). Cognitive

domain scores were calculated by averaging z-scores for neuropsychological tests within each domain.

Cognitive classification

Subjects were classified as PD-MCI or PD-NC by two methods. The first method was based on review of clinical and neuropsychological data for each subject in a consensus conference (J.G.G, G.T.S., B.B.) with determinations of PD-MCI or PD-NC using a systematized, uniform process for discussing each case.[11, 33] The consensus diagnosis was used as the gold standard for comparison of the second method.[11] This method involved applying MDS PD-MCI diagnostic criteria and Level II guidelines, including impairment present on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains.[4] Non-demented PD subjects who did not fulfill MDS PD-MCI criteria were classified as PD-NC.

Since the Level II criteria do not specify an exact cutoff for impairment on neuropsychological tests and we previously demonstrated that a 2 SD cutoff below norms provided the best sensitivity and specificity for detecting impairment, we utilized the 2 SD cutoff to define impairment in this study.[11] We also conducted an exploratory analysis using the 1.5 SD cutoff (Supporting table).

Neuropsychological test number and combinations in classifying PD-MCI

To examine the effect of test number, we calculated the probability of determining impaired cognition based on the number of tests used per domain, which ranged from one to five tests per domain. Then, we assessed the contributions of the tests to PD-MCI diagnosis and identified the best performing tests within each domain using a least absolute shrinkage and selection operator (LASSO) logistic regression analysis.[34] We determined PD-MCI classification using the Level II criteria of two tests per domain with the “best” two tests selected by LASSO ranking. We tested this ten-test model for classifying PD-MCI by Level II criteria at 2 SD below norms versus consensus diagnosis, calculating sensitivity, specificity, positive and negative predictive, and kappa values. Finally, we examined PD-MCI subtype classification, according to Level II criteria and using the ten-test model described above, to determine single and multiple domain impairment subtypes. Statistical analyses were performed using SAS 9.1 (Institute Inc., Cary, NC) and R 2.15.2 (R development core team, 2013) with *glmnet* package.[35]

Results

Clinical characteristics

Table 1 depicts the clinical features of the PD cohort as defined by consensus diagnosis. Forty-eight of 76 subjects (63.2%) were classified as PD-MCI by consensus diagnosis as detailed in our previous study.[11]

Probability of detecting impairment based on number of tests per domain

Overall, the probability of detecting impairment on a test increased when more tests were included per domain (Table 2). However, the upper limit of this range (maximum

probability) for detecting impairment on a test stabilized at two tests in the Attention/Working memory and Executive function domains (36.8% and 57.9%, respectively), and did not increase with 3 or 4 tests in the domain. The other domains (Language, Memory, Visuospatial function) demonstrated less than a 5% increase in the maximum probability of having at least one impaired test when more than two tests were used. Therefore, we pursued a battery with two tests in each of the domains in further analyses.

Selection of best performing tests

Within each domain, we identified the two best tests by the LASSO method and ranked them based on their LASSO regression coefficient, where larger coefficients reflects higher rank (Table 2). The resultant ten-test battery included: (i) TMT-A, SDMT (Attention/Working memory); ii) TMT-B, Clock Drawing Test (Executive function); iii) Boston Naming Test, Animal naming (Language); iv) FCSRT, Figural Memory (Memory); and v) JLO, Intersecting pentagons (Visuospatial function).

Classifying PD-MCI with an optimized two test per cognitive domain battery

Using the above ten-test battery (two tests per domain) provided a sensitivity of 81.3% and specificity of 85.7% for diagnosing PD-MCI by Level II criteria (Supporting Table). Positive and negative predictive values were 90.7% and 72.7%, respectively. This battery demonstrated good agreement with PD-MCI classification by consensus diagnosis (kappa=0.65 [95th CI=0.47–0.82]). Overall accuracy for classifying subjects as PD-MCI and PD-NC was 82.9%, compared to consensus classification.

PD-MCI subtype classification

With the ten-test battery, multiple domain impairment was more frequent than single domain impairment, occurring in 40/43 subjects (93.0%) and 3/43 subjects (7.0%), respectively. The number of multiple domains impaired ranged from two to five (27.9% of subjects had two domains impaired, 18.6% three domains, 34.9% four domains, and 11.6% five domains). Impaired single domains included executive function (n=1) and visuospatial function (n=2). The proportion of PD-MCI subtypes was similar to our consensus classification.[11]

Discussion

To our knowledge, our study is the first to examine the MDS PD-MCI Task Force Level II criteria for the number and specific tests proposed within each domain and thereby contributes several key findings regarding operationalizing the MDS PD-MCI diagnostic criteria.[11] Although the probability of detecting impairment with an increased number of tests in a domain is commonly espoused clinically, this issue has not been well-studied in the MCI literature.[5] In fact, increased probability of detecting impairment did not hold true when there were more than two tests in the Attention/Working memory and Executive function domains, and in the other domains, including more than two tests added very little to the final assessment. We established that a neuropsychological battery with two tests per domain provides a practical, efficient, and robust approach to diagnosing PD-MCI. From 19 neuropsychological tests, we identified the ten best performing tests to use in a Level II battery with two tests per domain. This model yielded a high sensitivity and specificity for

classifying subjects as PD-MCI. Indeed, specificity improved and sensitivity was comparable to the battery of all 19 neuropsychological tests. Thus, extensive, time-consuming batteries are not necessarily superior. These findings strongly support the MDS PD-MCI Level II criteria that neuropsychological testing includes two tests within each of the five cognitive domains.

Our study provides a first step for selecting tests for a PD-MCI-specific Level II battery. Based on our findings, we propose a core, Level II battery including the ten LASSO-selected tests which efficiently and effectively diagnosed PD-MCI: TMT-A, SDMT, TMT-B, Clock Drawing Test, Boston Naming Test, Animal naming, FCSRT, Figural Memory, JLO, and Intersecting pentagons. Buindo and colleagues reported that impairment on the TMT-B, along with other tests, discriminated PD-MCI from PD-NC subjects, thereby overlapping with our study but employing a different test battery in a different PD population (younger, shorter disease duration, fewer years of education).[7]

Multiple domain impairment was more common than the single domain PD-MCI subtype using the ten best test model, though the proportion of subtypes was similar to prior studies using MDS PD-MCI criteria.[9, 10] These findings support the heterogeneity of PD-MCI but suggest potential challenges in detecting sufficient numbers of individual domain-specific PD-MCI subtypes as currently defined.

Strengths include our well-defined, expert-diagnosed PD cohort and comprehensive testing using the suggested MDS PD-MCI tests. Limitations include a relatively small sample, high education level, and university setting. Studies with larger and more diverse PD-MCI cohorts and varied neuropsychological tests, as in MDS PD-MCI Study Group efforts, provide the opportunity to validate our observations. Additional studies are needed to identify which tests and batteries are most sensitive to change, both over time and with intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical features of the PD cohort

	PD-NC, n=28	PD-MCI, n=48	p value
Demographics			
Age, y	72 ± 6.5	73.2 ± 5.8	0.41
Male, n (%)	20 (71.4)	39 (81.3)	0.32
Education, y	15.5 ± 2.8	15.1 ± 3.4	0.55
PD duration, y	8.7 ± 2.9	9.7 ± 4.4	0.24
Motor features			
MDS-UPDRS Part III Motor score	31 ± 8.9	36.8 ± 11.3	0.02
Hoehn and Yahr stage, median (range)	2.0 (2–3)	2.0 (2–5)	0.03
Medications			
LEDD, mg/d	821.6 ± 492.1	736.8 ± 395.5	0.41
Dopamine agonist, n (%)	16 (57.1)	18 (37.5)	0.10
Sleep medication, n (%)	5 (17.9)	15 (31.2)	0.20
Antidepressant, n (%)	5 (17.9)	10 (20.8)	0.75
Cognitive enhancing medications, n (%)	2 (7.1)	4 (8.3)	1
Antipsychotic, n (%)	1 (3.6)	2 (4.2)	1
Cognitive and neuropsychological features			
Cognitive decline by patient, informant, or clinician, n (%)	21 (75)	48 (100)	0.001
CDR Global score, median (range)	0 (0–0.5)	0.5 (0–0.5)	<0.0001
Functional Assessment Questionnaire, median (range)	0 (0–5)	2 (0–11)	0.001
MMSE scores	28.6 ± 1.1	27.7 ± 1.7	0.005
Attention/working memory domain	−0.32 ± 0.58	−1.3 ± 0.85	<0.0001
Executive function domain	−0.33 ± 0.62	−1.52 ± 0.97	<0.0001
Language domain	−0.15 ± 0.72	−0.81 ± 0.65	<0.0001
Memory domain	−0.23 ± 0.51	−1.33 ± 0.70	<0.0001
Visuospatial domain	−0.21 ± 0.77	−1.48 ± 1.77	<0.0001
Hamilton depression rating scale	5.1 ± 3.1	6.1 ± 3.9	0.27
Beck anxiety inventory	8.4 ± 6.3	7.3 ± 7.8	0.56

Results are expressed as mean (SD), unless otherwise noted. Abbreviations: CDR = Clinical Dementia Rating Scale, LEDD = levodopa equivalent daily doses, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination

Table 2

Properties of an optimal neuropsychological test battery: number and type of tests

A. Test number: probability of detecting impairment based on number of tests per domain					
Number of Tests Used	**Attention/Working Memory**	**Executive Function**	**Language**	**Memory**	**Visuospatial**
1	15.1% (0–27.6%)	19.0% (0–46.4%)	14.0% (7.9–18.4%)	16.8% (6.6–35.5%)	26.7% (19.7–38.2%)
2	25.7% (6.6–36.8%)	32.4% (5.3–57.9%)	25.4% (22.4–31.6%)	28.5% (17.1–39.5%)	40.8% (35.5–44.5%)
3	32.6% (27.6–36.8%)	43.3% (13.2–57.9%)	34.2% (34.2%)	36.8% (23.7–42.1%)	48.7% (48.7%)
4	36.8% (36.8%)	50% (36.5–57.9%)	-	43.4% (43.4%)	-
5	-	57.9% (57.9)	-	-	-

B. Test type: selection of best performing neuropsychological tests by LASSO method			
Domain	**Test**	**LASSO coefficient**	**Ranking of test**
Attention/Working Memory	Digit Span Forward	-	-
	Letter Number Sequencing	-	-
	Symbol Digit Modalities Test	1.50	2
	Trail Making Test-A	2.97	1
Executive Function	Clock Drawing	0.56	2
	Controlled Oral Word Association	-	-
	Digit Span Backwards	-	-
	Progressive Matrices	-	-
	Trail Making Test-B	1.25	1
Language	Boston Naming Test	0.39	2
	Category fluency: animal Naming	0.60	1
	Similarities	-	-
Memory	CERAD trials, delayed recall, recognition	-	-
	Free and Cued Selective Reminding Test	3.12	1
	Figural Memory learning and delayed recall	0.7	2
	Logical Memory I and II	-	-
Visuospatial	Clock Copying	-	-
	Judgment of Line Orientation	0.03	2

B. Test type: selection of best performing neuropsychological tests by LASSO method			
Domain	**Test**	**LASSO coefficient**	**Ranking of test**
	Intersecting Pentagons	0.84	1

Results are expressed as percent mean (range) of the probability distribution

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation

Shaded tests did not meet LASSO criteria for inclusion in the battery.

Abbreviations: CERAD, Consortium to Establish a Registry for AD.