RESEARCH ARTICLE

Characterizing Mild Cognitive Impairment in Parkinson's Disease

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ABSTRACT: There is growing interest in identifying Parkinson's disease (PD) patients with mild cognitive impairment (PD-MCI), but widely disparate criteria have been used. We assessed 143 PD patients and 50 matched controls on 20 measures across 4 cognitive domains (executive function, attention and working memory, learning and memory, visuoperception). Twenty-four patients met criteria for dementia (PD-D); nondementia patients were classified as either with normal cognition or MCI for 12 neuropsychological criteria. We compared the influence of these criteria on the distribution of global cognitive performance in the resulting PD-MCI groups relative to the control and PD-D groups. Different criteria produced substantial variation in the proportion of PD-MCI cases identified. Fourteen percent PD-MCI was found when using 2 scores in 1 domain at 2 standard deviations (SD) below normative scores, with no controls identified as MCI, through to 89% PD-MCI with 1 score in 1 domain at 1 SD below normative scores, when 70% of controls were identified as MCI. The balance of cases with impaired cognition but not those with generally intact cognition was better served by using criteria that required 2 specific deficit scores or deficits across 2 domains. As comparisons with external normative data may have greater applicability across centers, we suggest that 2 scores at −1.5 SD within any single domain (30% PD-MCI) or 1 score at −1.5 SD in each of 2 domains (37% PD-MCI) provide suitable criteria to minimize the inclusion of cognitively well patients. Clinical dementia rating did not improve the relative identification of cognitively impaired and unimpaired nondementia PD patients. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; mild cognitive impairment; dementia; cognition; criteria

Recent studies have shown that Parkinson's disease (PD) produces a 75%–90% cumulative prevalence of dementia (PD-D).[1] Consequently, there is interest in a potential transition stage, PD with mild cognitive impairment (PD-MCI), to identify those at increased risk for PD-D and to facilitate intervention studies.[2,3] Most researchers emphasize psychometric criteria for PD-MCI and sample impairments in multiple cognitive domains because several deficits are implicated as predictors of progression to PD-D.[3–7] The difficulty facing clinicians, however, is that markedly heterogenous criteria have been applied.[2] This study directly compared the influence of different MCI criteria in a large sample of PD patients.

The predominant strategy in PD follows that used in the wider MCI literature,[8,9] which is to identify patients with minimally impaired everyday function whose cognitive test scores fall 1.5 standard deviations (SD) or more below the mean of age-adjusted normative data or a control group (ie, below the seventh

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

This study was funded by the Neurological Foundation of New Zealand (to T.J.A., J.C.D.-A., M.R.M., R.P., and J.K.), the Canterbury Medical Research Foundation (to T.J.A., J.C.D.-A., M.R.M., R.W., and R.K.), and the Neurology Trust (to L.L.).

Received: 20 July 2010; **Revised:** 26 October 2010; **Accepted:** 22 November 2010

Published online 1 February 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23592

TABLE 1. Group characteristics (mean ± SD)

	Controls	PD (nondementia)	PD-D (with dementia)	Analysis (adjacent comparisons)*
Number	50	119	24	
Age	67.1 ± 9.0	66.7 ± 8.3	72.9 ± 7.1	$F_{2,190} = 5.6$, $P < .01$ (Con = PD < PD-D)
Sex, M/F	33/17	80/39	19/5	
Education (y)	13.6 ± 3.0	12.9 ± 2.9	12.75 ± 3.0	$F_{2,190} = 1.5$, ns
Premorbid IQ (WTAR)	111.9 ± 9.4	110.9 ± 8.5	107.5 ± 10.7	$F_{2,190} = 1.9$, ns
Symptom duration (y)	N/A	5.2 ± 4.0	12.2 ± 7.8	M/W $Z = 4.27$, $P < .0001$
Hoehn and Yahr stage	N/A	2.05 ± 0.8	3.35 ± 0.7	M/W $Z = 5.64$, $P < .0001$
UPDRS (motor)		25.3 ± 13.6	49.9 ± 17.5	M/W $Z = 5.55$, $P < .0001$
MMSE	28.5 ± 1.6	27.5 ± 2.2	22.9 ± 2.8	$H_2 = 53.0$, $P < .0001$ (Con > PD > PD-D)
MoCA	27.1 ± 2.0	25.8 ± 2.7	17.3 ± 4.0	$H_2 = 63.4$, $P < .0001$ (Con > PD > PD-D)

MMSE, Mini–Mental State Examination; MoCA, Montreal Cognitive Assessment; WTAR, Wechsler Test of Adult Reading; *F*, ANOVA; *H*, Kruskall–Wallis; M/W, Mann–Whitney;
*post hoc $P < .05$ for each adjacent pair.

percentile). The uncertainty is that some groups identified PD-MCI if a patient obtained at least 1 test score within a cognitive domain that was −1.5 SD or worse (1.5SD:1 score),[10–15] whereas others required either 2 measures (1.5SD:2 scores),[16–18] a consistent impairment,[19] or an average score that fell 1.5 SD below that obtained by controls in 1 domain (1.5SD:Ave).[20,21] We interpret *consistent impairment* as 1 score meeting 1 SD and a second meeting 1.5 SD below the norm (1SD:1&1.5SD:1). Another complication is that 1 group employed a score of −1 SD or worse within a domain (1SD:1).[22,23] Conversely, others have characterized deficits in nondementia patients at −2 SD, again with either 1 measure (2SD:1)[24,25] or 2 measures (2SD:2)[26] in 1 domain. An additional layer of uncertainty arises from the use of a clinical dementia rating (CDR)[27] of 0.5 or clinical judgment as alternatives to psychometric classification.[28–31]

The frequent use of a small number of tests or a restricted range of cognitive domains presents further challenges. In particular, an isolated deficit in only 1 cognitive domain may encourage false positives because of an existing but unrepresentative weakness.[8,9,32,33] In contrast, PD patients experiencing the transition to dementia are expected to show poor cognitive performance overall.[34] Impaired activities of daily living associated with deficits across at least 2 cognitive domains are required for a PD-D diagnosis. Heterogeneity of impairments and multisystem brain changes are associated with progression to PD-D.[3,35] We therefore assessed multiple cognitive tests across the 4 domains specified as relevant for PD-D by the Movement Disorders Society (MDS) Task Force.[36] These domains may be pertinent to PD-MCI cases at increased risk of dementia.

We compared PD-MCI criteria that relied on poor performance in either 1 or 2 of the 4 domains to evaluate their impact on the composition of the PD-MCI group. External normative data were used to express cognitive performance, and a global neuropsychological score was derived from the 4 cognitive domains. This global psychometric measure illustrated the relative distribution of MCI cases identified by the different criteria. Comparison with a normal control group and with a group of PD-D patients facilitated the assessment of whether individual criteria are unnecessarily liberal or relatively strict.

Patients and Methods

A convenience sample of 156 PD patients (UK Parkinson's Society criteria)[37] > 1 year since symptom onset were recruited (beginning in March 2007) through the Van der Veer Institute for Parkinson's and Brain Research (Table 1). Atypical parkinsonian disorder, other neurological or major medical conditions (eg, head injury, stroke, early-life learning disability), current psychiatric problems, or poor English (precluding testing) provided a general exclusion. The 52 age- and education-matched controls were volunteers responding to community advertisements who reported no subjective cognitive decline or problems on interview. A clinical report (R. Keenan, Hagley Radiology, Christchurch, New Zealand) on 3T MRI structural brain scans (controls, 75%; patients, 73%; limited by funding) resulted in the exclusion of 5 patients and 2 controls for 1 or more of: moderate to severe white matter disease (5 cases), atrophy and ventriculomegaly (4 cases), thalamic lesion (1 case), and cerebellar infarcts (1 case). The proportion of MRI exclusions suggests that only 2 more would be expected in nonscanned participants.

The study was approved by the local Ethics Committee, New Zealand Ministry of Health, with informed consent provided by all participants (and significant other when required).

Participants completed neuropsychological assessments over 2 sessions using 20 measures (Table 2) across the 4 cognitive domains proposed by the MDS Task Force. Mental status tests (Tables 1 and 3) were not included in these evaluations. As shown in Table 2,

TABLE 2. Individual neuropsychological tests and domains (mean ± SD) with PD-MCI classified by the 1.5SD:2 criterion

Tests and domains	Controls (n = 50)	PD-N (n = 83)	PD-MCI (n = 36)	PD-D (n = 24)	Controls vs PD-N: AUC (95% CI)	PD-N vs PD-MCI: AUC (95% CI)	PD-MCI vs PD-D: AUC (95% CI)
Executive function							
Action (verb) fluency	0.66 ± 1.0	0.13 ± 1.2[a]	−0.81 ± 0.9	−1.80 ± 0.6	0.65[f] (0.56–0.73)	0.75[g] (0.66–0.82)	0.82[g] (0.69–0.90)
Letter fluency (D-KEFS)	0.80 ± 1.2	0.74 ± 1.2	0.07 ± 1.3	−1.24 ± 1.1	0.50 ns (0.41–0.58)	0.65[g] (0.56–0.74)	0.77[g] (0.64–0.87)
Category fluency (D-KEFS)	1.31 ± 0.9	0.76 ± 1.1	−0.08 ± 1.0	−1.46 ± 0.9	0.65[f] (0.56–0.73)	0.71[g] (0.62–0.79)	0.85[g] (0.73–0.93)
Category switch (D-KEFS)	0.86 ± 1.2	0.16 ± 1.0	−0.63 ± 1.0	−2.09 ± 0.9	0.70[g] (0.62–0.78)	0.71[g] (0.62–0.79)	0.85[g] (0.73–0.93)
Stroop interference (D-KEFS)	0.52 ± 0.5	0.38 ± 0.7[b]	−0.94 ± 1.3	−2.54 ± 0.7	0.56 ns (0.47–0.65)	0.81[g] (0.73–0.88)	0.85[g] (0.74–0.93)
Trails B	0.69 ± 0.5	0.17 ± 0.8	−1.07 ± 1.1[a]	−2.74 ± 0.6	0.68[g] (0.59–0.76)	0.81[g] (0.73–0.89)	0.91[g] (0.81–0.97)
Executive domain	0.81 ± 0.5	0.39 ± 0.6	−0.58 ± 0.7	−1.98 ± 0.5	0.69[g] (0.61–0.77)	0.86[g] (0.78–0.92)	0.96[g] (0.87–0.99)
Attention[d]							
Stroop word reading	0.28 ± 0.8	0.20 ± 0.6[b]	−0.37 ± 0.8	−1.65 ± 1.1	0.56 ns (0.48–0.65)	0.70[g] (0.61–0.79)	0.83[g] (0.71–0.91)
Stroop color naming	0.14 ± 0.8	0.04 ± 0.8[b]	−0.49 ± 0.8	−2.04 ± 0.9	0.54 ns (0.45–0.63)	0.68[g] (0.59–0.76)	0.89[g] (0.79–0.96)
Digits forward plus backward	0.85 ± 1.1	0.43 ± 0.8	0.07 ± 0.8	−0.60 ± 1.0	0.61 ns (0.52–0.69)	0.65[f] (0.55–0.73)	0.68[g] (0.55–0.80)
Digit ordering	−0.59 ± 0.9	−0.59 ± 0.9	−1.63 ± 0.8	−2.20 ± 0.6	0.52 ns (0.43–0.61)	0.81[g] (0.73–0.88)	0.75[g] (0.62–0.85)
Map search	0.81 ± 0.9	−0.24 ± 0.9[c]	−1.48 ± 0.9[a]	−2.27 ± 0.7[a]	0.80[g] (0.71–0.86)	0.82[g] (0.74–0.89)	0.75[g] (0.62–0.86)
Trails A	0.35 ± 0.7	0.05 ± 0.7	−0.93 ± 0.9[a]	−2.57 ± 0.7	0.62 ns (0.53–0.70)	0.80[g] (0.71–0.87)	0.92[g] (0.82–0.97)
Attention domain	0.31 ± 0.5	−0.01 ± 0.4	−0.81 ± 0.4	−1.89 ± 0.5	0.68[g] (0.60–0.76)	0.89[g] (0.82–0.94)	0.94[g] (0.84–0.98)
Learning and memory							
CVLT-II SF							
Acquisition	0.95 ± 0.9	0.32 ± 0.9	−0.78 ± 0.9	−2.02 ± 1.0	0.69[g] (0.61–0.77)	0.81[g] (0.73–0.87)	0.82[g] (0.70–0.91)
Short delay (30 s)	0.92 ± 1.2	0.25 ± 1.1	−0.79 ± 1.0	−1.81 ± 0.7	0.66[f] (0.57–0.74)	0.75[g] (0.66–0.82)	0.79[g] (0.66–0.88)
Long delay (10 min)	0.72 ± 0.8	0.31 ± 0.8	−0.50 ± 0.9	−1.15 ± 0.7	0.66[f] (0.57–0.74)	0.75[g] (0.66–0.82)	0.70[g] (0.57–0.81)
Rey Complex Figure							
Short delay (3 min)	1.08 ± 1.2	0.24 ± 1.4[a]	−0.76 ± 1.4	−1.81 ± 0.9[a]	0.66[f] (0.57–0.74)	0.62 ns (0.53–0.71)	0.79[g] (0.66–0.88)
Long delay (30 min)[e]	0.84 ± 1.4	0.1 ± 1.5	−0.85 ± 1.2	−1.95 ± 1.0[a]	0.62 ns (0.50–0.73)	0.70[g] (0.57–0.80)	0.75[g] (0.61–0.86)
Memory domain	0.91 ± 0.8	0.29 ± 0.8	−0.67 ± 0.7	−1.77 ± 0.6	0.72[g] (0.64–0.80)	0.82[g] (0.74–0.89)	0.87[g] (0.76–0.94)
Visuospatial/visuoperceptual							
Rey Complex Figure—Copy	0.24 ± 0.8	0.11 ± 0.8	−0.85 ± 1.3	−2.08 ± 1.3	0.57 ns (0.48–0.65)	0.73[g] (0.64–0.81)	0.75[g] (0.62–0.86)
Judgment of line orientation	0.68 ± 0.6	0.53 ± 0.6	0.03 ± 0.9	−0.74 ± 1.0	0.57 ns (0.48–0.65)	0.67[g] (0.58–0.75)	0.73[g] (0.60–0.84)
Fragmented letters	0.60 ± 0.7[a]	0.54 ± 0.6	0.15 ± 0.9	−0.88 ± 1.1	0.47 ns (0.38–0.55)	0.62 ns (0.53–0.71)	0.75[g] (0.62–0.85)
Visual domain	0.50 ± 0.5	0.39 ± 0.4	−0.22 ± 0.7	−1.23 ± 0.8	0.61 ns (0.52–0.69)	0.77[g] (0.68–0.84)	0.82[g] (0.70–0.91)
Global neuropsychological Z score	0.63 ± 0.4	0.26 ± 0.4	−0.57 ± 0.4	−1.72 ± 0.5	0.76[g] (0.68–0.83)	0.94[g] (0.88–0.97)	0.97[g] (0.89–1.0)

Neuropsychological test values are *Z* scores (mean ± SD) based on age- and education-adjusted norms. Controls, age- and education-matched controls; PD-N, Parkinson's disease patients with normal cognition; PD-MCI, PD meeting the 1.5SD:2 single-domain criterion; PD-D, with dementia; AUC, area under the receiver operating characteristics curve (chance = 0.5; perfect separation = 1.0). Either, but not both, delay measure was allowed to contribute to a single impairment at 1.5 SD for each of the CVLT-SF and Rey Complex Figure tests. Not all cases tested on every measure, as follows: [a]sample size = n − 1; [b]sample size = n − 2; [c]sample size = n − 6; [d]attention, working memory, and processing speed; [e]assessment made on a subset of control (n = 34), PD-N (n = 41), and PD-MCI (n = 27) cases; CVLT-SF, California Verbal Learning Test–II Short Form; D-KEFS, Delis–Kaplan executive function system; [f]$P < .01$; [g]$P < .001$; ns, nonsignificant at 0.01, adjusted for multiple comparisons.

all age- and education-adjusted normative scores but 2 (Rey-short delay, fragmented letters) discriminated the PD-MCI group meeting our institute's current MCI criterion (1.5SD:2, single domain) from the remainder classified as having normal cognition (PD-N).[18] There were substantial differences on all measures between this PD-MCI group and PD-D patients. The PD-D diagnosis required a clear decline in everyday functional activities not attributed to motor impairment, with a significant deficit in at least 2 cognitive domains (in practice, all met the criterion at 2 SD below normative data).[36] The Reisberg instrumental activities of daily living[38] and CDR were obtained through interview with a significant other for all PD-D patients, 64% of nondementia patients, and 72% of controls (Table 3). To avoid confusion between MCI and dementia, 8 PD cases missing functional assessments and with cognitive test scores of −2 SD in 2 domains were excluded from analysis. Incomplete assessments resulted from the lack of a significant other or insufficient time.

Data Analysis

The externally derived standardized scores were used to classify each nondementia PD patient on each psychometric criterion, and then the global neuropsychological performance was used to illustrate the resulting

TABLE 3. Dementia assessments (mean ± SD) with PD-MCI classified by the 1.5SD:2 criterion

	Controls (n = 34)	PD-N (n = 44)	PD-MCI (n = 32)	PD-D (n = 24)	Controls vs PD-N: AUC (95% CI)	PD-N vs PD-MCI: AUC (95% CI)	PD-MCI vs PD-D: AUC (95% CI)
Clinical Dementia Rating (CDR)	0.00 ± 0.0	0.11 ± 0.2	0.38 ± 0.2	−1.29 ± 0.5	0.60 ns (0.49–0.71)	0.76[b] (0.65–0.85)	1.00[b] (0.94–1.0)
CDR sum of boxes	0.03 ± 0.1	0.47 ± 1.1	1.42 ± 1.1	7.27 ± 2.5	0.65 ns (0.53–0.75)	0.79[b] (0.68–0.87)	1.00[b] (0.93–1.0)
Reisberg IADL	0.19 ± 0.2	0.43 ± 0.5	0.67 ± 0.5	2.00 ± 0.4	0.61 ns (0.50–0.72)	0.66 ns (0.54–0.77)	0.98[b] (0.90–1.0)
DRS-2 (AESS)	12.9 ± 2.3[a]	12.5 ± 1.9	9.9 ± 1.9	5.0 ± 2.7	0.56 ns (0.45–0.67)	0.83[b] (0.72–0.90)	0.93[b] (0.83–0.98)

Controls, age- and education-matched controls; PD-N, Parkinson's disease patients with normal cognition; PD-MCI, PD meeting the 1.5SD:2 single-domain criterion; PD-D, with dementia. [a]Control (n = 38). AUC, area under the receiver operating characteristics curve (chance = 0.5; perfect separation = 1.0); CDR, Clinical Dementia Rating; DRS-2 (AESS), Dementia Rating Scale–2 age- and education-adjusted standard score; IADL, instrumental activities of daily living; [b]$P < .001$; ns, nonsignificant at 0.01, adjusted for multiple comparisons.

PD-MCI groups by comparison with the control and PD-D groups (Fig. 1). Global performance was expressed by an aggregate *Z* score for each individual by first averaging their standardized scores within each cognitive domain and then taking the mean of these 4 scores. This *Z* score provides a common indicator across all participants. As the whole nondementia sample was used to classify MCI versus relatively normal cognition for each criterion, nondementia PD cases feature in 1 or more dot-plots. All controls were included because variation due to the criteria was the primary interest. For example, a control scoring 1 SD below normative data might be considered MCI on 1 criterion but intact on another. Only 1 control showed poor overall performance, although unimpaired memory, but he had low education and no history of declining cognition. The 2 broken lines in Figure 1 show the 1.5 SD (+0.05) and 2 SD (−0.14) values below the mean global *Z* score (+0.63) for the control group. For consistency, the primary analyses provide proportions relative to all nondementia patients (95% confidence interval [CI], http://faculty.vassar.edu/lowry/VassarStats.html). The cognitive profile analyses examined proportions within a given criterion.

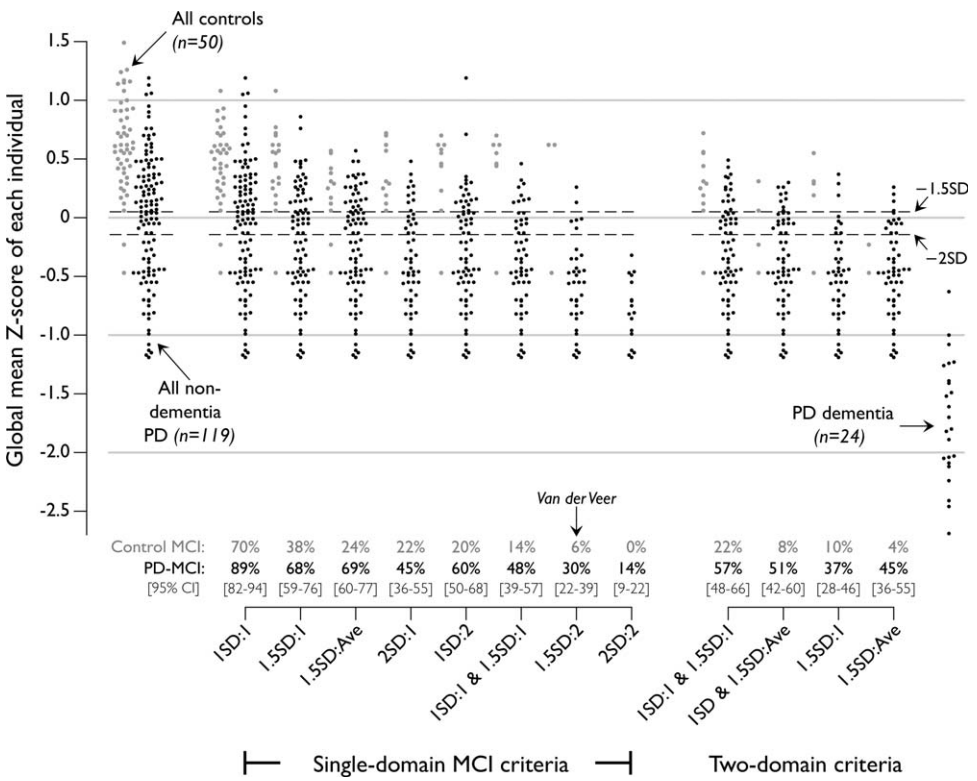

FIG. 1. Global *Z* scores for all participants derived from performance across 4 cognitive domains. All controls and nondementia PD patients are shown on the far left, and the PD-D patients are shown on the far right. The main body of the figure plots controls and nondementia patients classified as MCI using 12 neuropsychological criteria. For example, (1) "1.5SD:2" classifies a person as MCI if they have at least 2 test scores at or worse than 1.5 standard deviations (SD) below normative data within any domain, and (2) "1.5SD:Ave" refers to an average domain score that falls 1.5 SD below the domain scores for the control group in either 1 (left side) or 2 (right side) domains. Percentages indicate the proportions classified as MCI by each criterion (with 95% confidence interval [CI] for PD-MCI). For reference, the dashed lines indicate −1.5 and −2.0 SD below the control group mean.

Results

The 2 dot-plots on the far left of Figure 1 show the distribution of global cognitive scores for the 50 controls and 119 nondementia PD patients. The *Z* scores of the 24 PD-D patients are provided on the far right of Figure 1. Relative to an aggregate *Z* score at 1.5 SD below the average for the control group, 61 (51%, CI 42%–60%) of the nondementia patients could be regarded as showing relatively poor cognition and 58 (49%, CI 40%–58%) as showing intact cognition. Clearly, the proportion of cases identified as MCI varied markedly across different criteria.

When a single-domain criterion was used (left side of Fig. 1), the criteria 1SD:1, 1.5SD:1 (single score relative to normative data), and 1.5SD:Ave (average of domain normative scores below 1.5 SD of the controls' average score) identified all or nearly all patients whose global cognitive score fell below −1.5 SD of the control group's mean (ie, 51%, CI 42%–60%, of all nondementia patients; 49%, CI 40%–58%; 50%, CI 41%–60%, respectively). This high sensitivity was, however, at the probable expense of too many false positives because these criteria captured a high proportion of nondementia patients showing intact cognition by comparison with the −1.5 SD global value of the controls (39%, CI 30%–48%; 21%, CI 14%–30%; 20%, CI 14%–29%, respectively). In addition, 70%, 38%, and 24% of the controls were also classified as MCI on these 3 criteria despite all but 2 of the controls achieving an aggregate *Z* score above zero. The single-domain 1SD:2 criterion was similar to these first 3 criteria, identifying 60% of nondementia cases as PD-MCI, including 14% (CI 9%–22%) of the sample who had relatively intact global cognition and omitting 5% (CI 2%–11%) who showed impaired cognition.

As shown on Figure 1, the remaining 4 single-domain criteria (2SD:1, 1SD:1 & 1.5SD:1, 1.5SD:2, 2SD:2) identified fewer PD-MCI cases. These criteria included few patients with relatively intact cognition (8%, CI 5%–15%; 7%, CI 3%–13%; 2%, CI 0%–7%; and 0%, respectively) but at the expense of omitting patients with relatively poor overall cognition (13%, CI 7%–20%; 8%, CI 4%–15%; 21%, CI 14%–30%; 36%, CI 28%–36%, respectively). They classified between 0% and 20% of controls as MCI.

MCI criteria requiring impairments in 2 domains (right side of Fig. 1) may identify patients who are starting to show more diverse changes in cognition expected of those at risk of dementia. The 1SD:1 & 1.5SD:1 2-domain criterion (1 of either value below normative data in each of 2 domains) identified a high proportion of PD-MCI cases, many with relatively intact cognition (11%, CI 6%–18%) and omitted few cases with low cognitive scores (3%, CI 1%–9%). Twenty-two percent of controls were identified. As shown in Figure 1, moderate proportions of PD-MCI cases were found using the criteria 1SD & 1.5SD:Ave (1 of each in separate domains, based on the individual's domain average relative to the control group's average domain score), 1.5SD:1 (1 score below normative data in each of 2 domains), and 1.5SD:Ave. These 2-domain criteria included low proportions of PD-MCI cases with relatively intact global cognition (8%, CI 4%–14%; 3%, CI 1%–8%; 3%, CI 1%–9%, respectively) and omitted a low to moderate number of low cognitive scores (5%, CI 2%–11%; 15%, CI 9%–23%; 8%, CI 4%–15%, respectively). They also identified control cases with global scores in the lower range.

Logistic regression revealed that all average cognitive domain scores (attention, beta coefficient = −2.98, $P < .01$; executive function, −1.64, $P < .02$; memory, −1.48, $P < .01$; visuoperception, −1.91, $P < .05$) were significant predictors of MCI status in the nondementia sample when using a relatively lenient criterion (1.5SD:Ave, 1 domain). However, only attention (−3.82, $P < .0001$) and memory (−1.81, $P < .01$), not executive function (−0.49, $P = .43$) or visuoperception (−0.42, $P = .55$), were predictors of MCI status using the relatively strict criterion of 1.5SD:2 in 1 domain.

In terms of cognitive profile, 22% of PD-MCI cases (7% of the whole sample) who were classified using the Van der Veer 1.5SD:2 criterion[18] showed "multidomain excluding memory" deficits, and 25% showed "multidomain amnesic" deficits (Fig. 2). Patients showing multiple-domain deficits using this criterion had worse global performance than those with only single-domain deficits. "Attention, working memory, and processing speed" was the most frequent single-domain impairment, and no cases showed single-domain "visuoperception" deficits. More lenient criteria (ie, 1.5SD:1 and 2SD:1) tended to identify patients with single-domain deficits whose global cognition was relatively good. Use of 1.5SD:1 normative scores in 2 domains resulted in a close split across the 2 multiple-domain categories, but the multidomain amnesic subgroup exhibited more domain deficits (medians, 3 vs 2; $Z = 4.26$, $P < .0001$) and worse global cognition (Fig. 2).

Of the 76 nondementia patients assessed on the CDR, 59% had global cognitive scores that suggested impaired cognition relative to control values (nonassessment was more common in early PD cases). The CDR and CDR sum of boxes were significantly higher for patients with impaired cognitive scores (median: 0 vs 0.5, $Z = 2.85$, $P < .01$; 0 vs 0.78, $Z = 3.78$, $P < 0.001$), but 40% of these impaired patients received a CDR of 0.0. Conversely, a CDR of 0.5 was made in 19% of assessed patients achieving relatively intact

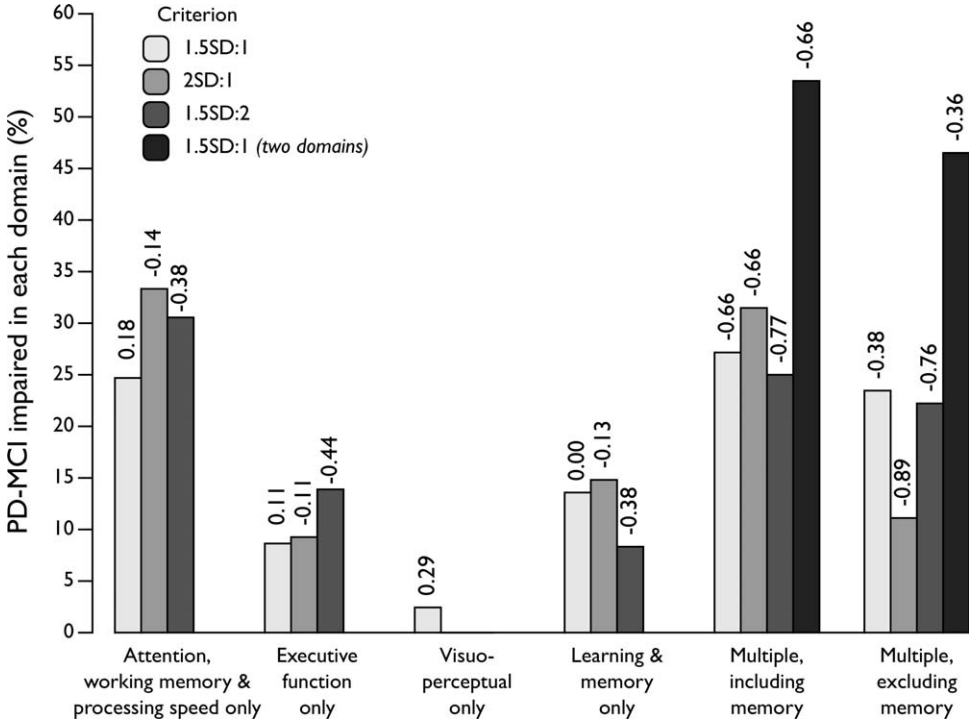

FIG. 2. Proportion of single and/or multidomain deficits in PD-MCI cases identified using 4 of the criteria. Numerical values represent the mean global *Z* score for those patients in that category. Three criteria were based on scores within a single domain: 1.5SD:1 includes those with at least 1 test score at 1.5 standard deviations (SD) or worse below the mean of normative data; 2SD:1, those with at least 1 test score that was −2 SD or worse; 1.5SD:2, those with at least 2 test scores −1.5 SD or worse. One criterion was based on 1.5SD:1 but for 2 domains.

cognitive scores. For both the 1.5SD:2 and 1.5SD:1 single-domain MCI criteria, a zero CDR sum-of-boxes score produced approximately 80% sensitivity but only approximately 67% specificity, whereas a 0.5 CDR sum of boxes produced approximately 64% sensitivity and approximately 86% specificity.

Discussion

The concept of PD-MCI has become highly relevant in PD,[2,3,34] and an MDS Task Force is currently addressing this issue. The array of different MCI criteria used across different PD studies is a source of potential confusion and may hamper targeted intervention to minimize progression to dementia. This problem was illustrated in our study because markedly different proportions of PD-MCI were found when different criteria were implemented. These differences were evident by comparing global neuropsychological status and the performance of controls and PD-D patients. The number of tests used and the addition of PD-D and healthy control groups provided a sound perspective on the relative impairments shown by various PD-MCI groups.

The global psychometric performance of the matched control group confirmed the expectation that many cognitively normal individuals may be classified as MCI when criteria rely on a single impaired measure.[8,9,32,33] In general, poor performance on multiple tests is more likely to detect worsening impairments over time.[8,9] This observation may be more relevant in PD, so criteria such as 1.5SD:2 and 2SD:2 are more likely to identify cases at greater risk of dementia. These 2 criteria also minimized the overlap of global scores in PD-MCI cases with those obtained by the control group

The 1.5SD:2 and 2SD:2 criteria are conservative, as they omitted several cases whose cognition was poor. Detailed neuropsychological assessment and exclusion criteria made it unlikely that they included misdiagnosed PD-D patients. The 2SD:2 criterion, in particular, may classify cases who could be considered advanced MCI or with prodromal dementia. This question is relevant to intervention studies because disease-modifying treatments may need to be tailored to different patients and different pathological processes at different times in the course of PD. Our findings suggest that single-deficit measures, but in 2 domains, may provide a suitable, less stringent alternative. Of the 2-domain criteria investigated, the criterion 1.5SD:1 *against normative data* produced an effective balance of identifying cases who showed poor cognition while avoiding those with relatively good cognition. Our preference is to use external normative data, which are more applicable across centers.

A recent study pooled data from 8 centers and analyzed 1346 patients with the 1.5SD:Ave criterion, using a combination of normative data and control data.[21] The proportion of MCI was 26%, although significantly variable rates were evident across centers (range, 20%–39%). The proportion identified by this criterion

was 69% in the current study. Sample characteristics may explain this difference, but neither age nor duration of PD appears to be markedly different. Aarsland et al[21] found in their study that dopamine agonists did not influence their findings, but UPDRS motor scores and Hoehn and Yahr stage were important factors, with low scores evident in their unimpaired group. Motor severity in our nondementia sample was similar to that of their MCI group, so this could explain the higher MCI rate in our study. Nonetheless, many of our MCI patients using 1.5SD:1 or 1.5SD:Ave within a single domain showed relatively intact cognition. We used a more extensive battery of tests and more domains compared to the 8 research centers described by Aarsland et al,[21] so isolated deficits would be more likely in our study. We could not discern any particular measures that were more likely to identify deficits, and all measures appeared sensitive to impairment. Regression analyses suggested that all 4 domains were sensitive to PD-MCI with the 1.5 SD:Ave criterion, whereas attention and memory deficits became more discriminating with a more strict criterion (1.5SD:2).

The cognitive profile shown by PD-MCI cases meeting the 1.5SD:2 criterion revealed frequent multiple cognitive deficits when weaker criteria were employed in these cases (data not shown). Single deficits in visuoperception were rare in the absence of other deficits. This evidence supports the use of multiple measures, as deficits that reflect both frontal and posterior brain networks are expected to predict a decline to PD-D.[3–7] A larger sample could in the future test a deficit model of both general and specific factors for PD, similar to that described for Alzheimer's disease, where a general factor maximizes the detection of dementia.[39]

Although the sample size was limited, a functional criterion based on the CDR produced many misclassifications judging by their cognitive performance. Recent evidence on predictors of future dementia in large community samples supports the value of using neuropsychological criteria.[40]

Longitudinal follow-up is needed to confirm the predictive value of different PD-MCI criteria. Many of the MCI criteria produced too many false positives, at low risk of dementia judging by their performance relative to normative data and healthy controls. We propose that using 1.5 SD below normative data for 2 measures either within a single domain (1.5SD:2) or across 2 domains (1.5SD:1) provides suitably balanced criteria for PD-MCI. The criterion 1.5SD:2 could be especially useful for a PD-MCI sample at more immediate risk of future dementia. ■

Acknowledgments: We are grateful to the Neurological Foundation of New Zealand (T.J.A., J.C.D.-A., M.R.M., and R.P.), the Canterbury Medical Research Foundation (T.J.A., J.C.D.-A., and M.R.M., R.W.), and the Neurology Trust (L.L.) for financial support and to the participants for their time and effort.

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