Cognitive Characteristics Associated with Mild Cognitive Impairment in Parkinson’s Disease

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Introduction

Patients with Parkinson’s disease (PD) frequently experience cognitive problems which for some will progress to dementia (PDD) [1]. However, research indicates that subgroups of patients may exist that differ in terms of the severity of cognitive deficits, with particular subgroups being more vulnerable to later dementia [2]. Early identification of those patients at the preclinical stage of dementia, or ‘mild cognitive impairment’ (MCI) [3] would provide an opportunity for interventions to slow the progression of dementia [4]. The concept of MCI has only recently been studied in relation to PD [5, 6], but it is reasonable to expect that it might be useful for identifying those patients that are more likely to progress to dementia [7].

The present study used a data-driven approach to identify subgroups of patients based on cognitive ability across multiple domains. Methods such as cluster analysis have the advantages of avoiding arbitrary cut-offs and predetermined classification systems, and enabling discrete subgroups to be identified so that all within a given group are maximally similar. Compared to previous studies [2, 6], we focused on cognitive functioning and used a broader range of neuropsychological tests (26 variables). We did this because we were interested in establishing not only that these subgroups exist but the pattern of strengths and weakness associated with each.

Key Words
Parkinson’s disease with dementia • Assessment of cognitive disorders/dementia • Mild cognitive impairment

Abstract

Background: Cognitive deficits are common in Parkinson’s disease (PD), but the range of deficits is variable. The aim of this study was to identify different cognitive subgroups associated with PD. Methods: A broad range of neuropsychological measures and cognitive domains were used in a cluster analysis to identify subgroups of patients. Results: Three subgroups of patients were identified. Compared to controls, one PD subgroup showed no or minimal cognitive impairment (PD-NCI), a second group showed a variable or uncertain pattern of mild to severe cognitive impairments (PD-UCI), and a third group had evidence of severe cognitive impairment across most cognitive domains (mild cognitive impairment; PD-MCI). The subgroups did not differ with regard to age, motor impairment, or disease duration. Conclusions: Patients with PD are heterogeneous with regard to cognitive presentation and it may be possible to identify patients in the preclinical stage of dementia. The identification of preclinical dementia in PD patients (PD-MCI) provides an opportunity to understand cognitive decline in PD and its progression to dementia.
We hypothesised that if PD-MCI represents a distinct subtype, then a cluster analysis should reveal those patients comprising the PD-MCI subgroup and the tests that best characterise this subgroup. Thus, we repeated the cluster analysis using a subset of 13 variables which had previously been found to differentiate the PD patients from a healthy matched comparison group. If there is an identifiable PC-MCI subgroup, then the variables associated with cognitive heterogeneity in PD patients should be those for which cognitive deficits are apparent, and so the cluster analysis should yield the same results with the restricted subset of variables.

**Methods**

Approval was granted by the Upper South Regional Ethics Committee, with informed consent obtained from the patients and comparison group.

**Subjects**

All patients with a diagnosis of idiopathic PD in the Canterbury region of New Zealand, who could be identified via consecutive admissions and hospital records and had not been diagnosed with dementia, were invited to participate. The diagnosis of PD was confirmed by a neurologist specialising in movement disorders according the UK Brain Bank [8] criteria. Inclusion criteria were: Hoehn and Yahr (H&Y) stage I–IV, aged between 50 and 80 years, adequate or corrected hearing, stable on PD medication, and English as the primary spoken language. Exclusion criteria were: currently involved in a therapeutic trial; history of moderate or severe head injury, stroke or other neurological impairment, major medical illness, significant psychiatric illness, suspicion of dementia symptoms (Mini-Mental State Examination [MMSE] <25, Dementia Rating Scale <130 and evaluation by a registered clinical psychologist using the DSM-IV-TR criteria), major depressive episode in the previous 6 months, or neurological intervention; premorbid intelligence quotient (IQ) estimated at <85 using National Adult Reading Test (NART); currently taking non-PD medications known to have a significant effect on cognition (checked by neurologist); Beck Depression Inventory-II (BDI-II) score of >17 [9].

Of the 115 letters that were mailed to potential participants, 6/115 (5.2%) of individuals with PD could not participate due to illness, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined, 34/115 (29.6%) did not respond, and 21/115 (18.3%) did not meet the inclusion/exclusion criteria, leaving 40 PD participants who were included in the analyses. Forty healthy individuals without PD were recruited from a previously established database and through advertisements at local clubs, to form a comparison group that was similar in terms of premorbid intelligence and age.

The similarity between the PD and comparison group was confirmed by t tests (IQ: t = 0.94, d.f. = 78, p > 0.30; and age: t = 0.31 d.f. = 78, p > 0.75). Comparisons with healthy elderly of similar IQ and age enable us to be more certain that the cognitive profiles we identify are due to decline associated with PD and not other premorbid factors.

**Procedure**

Assessments were carried out at the University of Canterbury over three 3-hour testing sessions. Tests were presented in a fixed order with breaks as required. Information pertinent to the inclusion/exclusion criteria and current social and occupational functioning was elicited from all participants using a semi-structured interview, and separately with a person who knew the patient well. All patients were tested while optimally medicated (patient report).

**Clinical Assessment**

Two motor impairment scales were used: (1) the Unified Parkinson’s Disease Rating Scale (UPDRS) [10], generating 3 scores – severity of motor symptoms using the motor section, tremor score and non-tremor score [11], and (2) the H&Y scale to rate disease stage [12].

**Cognitive Tests Used in the Cluster Analysis**

Cluster analysis included tests from 6 cognitive domains: executive function/planning, problem solving, working memory/attention, speed of processing, memory/learning and visuospatial ability.

All tests were scored according to standard procedures. The Wechsler Abbreviated Scale of Intelligence (WASI) (mean 50, SD 10) [13], Delis-Kaplan Executive Function System (D-KEFS) [14] and the Wechsler Memory Scale-III (WMS-III) [13] (both mean 10, SD 3) were scored with age-adjusted norms. Norms were not available for tests from the Behavioral Assessment of the Dysexecutive Syndrome (BADS) (scores range from 0–4) [15], Cambridge Neuropsychological Test Automated Battery (CANTAB) [16], the Reading Span task, and the visuospatial functioning tests.

Executive function/planning skills were evaluated using tests from the D-KEFS: Verbal Fluency (with subtests for letter fluency, category fluency and category fluency switching) and Color-Word Interference (with subtests for inhibition and inhibition switching). Also included were the Key Search and Zoo Map from the BADS, the Intradimensional/Extradimensional Shift (ID/ED) from the CANTAB [16] (number of stages completed, scores vary from 0–9) and the clock drawing task CLOX-I (scores range from 0–15, with higher scores indicating better performance) [17].

Problem solving was assessed using the Card Sorting subtest sorting recognition, and the Tower Task (number of towers completed in the minimum number of moves, maximum score possible 9), both from the D-KEFS, Matrix Reasoning subtest from the WASI, and the Stockings of Cambridge (SOC) from the CANTAB [16] (number of towers completed in the minimum number of moves, maximum score possible 12).

Working memory/attention was assessed using letter number sequencing and Digits forward and reversed from the WMS-III, Spatial Span (maximum sequences correctly recalled 0–9) from the CANTAB, and the Daneman and Carpenter Reading Span test (scores range from 1–6) [18].

Speed of processing was evaluated using word naming and color naming from the D-KEFS Color-Word interference test.

Memory/learning was assessed with the WMS-III, Paired Associates immediate and delayed, Logical Memory immediate and delayed and the Auditory Recall Index. The Rey Osterrieth Figure (ROF) recall after 3 (ROF-I) and 30 min (ROF-II) was also used as a measure of memory ability.
Visuospatial/constructive skills were assessed using the Judgment of Line Orientation; scores are number of correct line-pairs, with possible scores ranging from 0–30 [19]. Also included in this domain were the ROF copy task [20] and the CLOX part 2. All 3 parts of the ROF are rated the same, scores range from 0–36, with higher scores indicating more accurate performance [20].

Statistical Analysis
Non-hierarchical (k-means) cluster analyses were performed with 2-, 3- and 4-cluster solutions. Analyses were conducted using the 26 tests covering all 6 cognitive domains (26 tests were completed by all patients1) and again using 13 cognitive tests that had previously been found to differentiate PD patients significantly from the comparison group (p < 0.01) [21]. Differences in demographic and clinical characteristics for the resulting subgroups were examined using analysis of variance (ANOVA). Measures were then transformed to z-scores, using the comparison group mean and standard deviations, so that comparisons could be made across tests. Because of the number of comparisons, a 0.01 significance level was used to provide more stringent protection against Type 1 error without unduly compromising power.

Results
Figure 1 shows the results of the cluster analyses for 2-, 3- and 4-cluster solutions using 26 and 13 variables. Analysis of the 2-, 3- and 4-cluster solutions for the 26 variables shows that groupings were consistent (fig. 1a). Because the fourth group in the 4-cluster solution comprised only 2 patients, a final 3-cluster solution was forced by combining the yellow and red groups which were most closely related in terms of their cognitive performance. We re-ran the analysis using only the 13 variables previously found to differentiate the PD patients and a healthy comparison group [21]. This analysis yielded essentially the same clusters with 90% of cases remaining in their respective groups (fig. 1b). Three subgroups of patients were identified. Compared to controls, one PD subgroup showed no or minimal cognitive impairment (PD-NCI), a second group showed a variable or uncertain pattern of mild to severe cognitive impairments (PD-UCI), and a third group had evidence of severe cognitive impairment across most cognitive domains (mild cognitive impairment; PD-MCI).

Table 1 displays the results of the ANOVAs for the resulting 3 groups for the full set of 29 variables. Numbers 1–13 on table 1 indicate tests that we have previously found to be significant for PD patients versus the comparison group at p < 0.01 [21]. ANOVAs found significant differences (p < 0.01) across the PD subgroups for 10 of the 13 measures (77%). Of the remaining 16 variables which were not differentiated between PD patients and the comparison group, significant ANOVA results were obtained in just 3 cases (18.8%). This confirms that the variables which were most indicative of cognitive heterogeneity in cognitive functioning among PD patients were largely the same variables that differentiated PD patients from the comparison group [21]. This finding, combined with the stability of the cluster groupings whether 26 or 13 variables were used, suggests that there is a subgroup of PD patients with cognitive impairment.

In terms of impairments found for specific cognitive domains over the 29 tests, significant differences among the PD subgroups were found for 5 out of 9 measures of executive function, 3 of 4 measures of problem solving, 1

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1 Due to motor impairments, 2 patients were not able to complete the Key Search, ROF or the CLOX tasks.
of 4 working memory measures, and all measures used to test speed of processing and visual-spatial ability (all \( p < 0.01 \)). None of the measures used to assess memory/learning or attention showed evidence of a group effect (see table 1).

ANOVA was used to examine the clinical and demographic characteristics for the 3 PD groups (table 2). The groups showed significant differences in terms of current mental status as measured by the MMSE. The only other significant differences between the groups were obtained...
for one measure of premorbid ability. Patients in the PD-UCI and PD-MCI subgroups had lower premorbid intelligence as measured by the NART (F = 17.45, d.f. = 37, p < 0.001).

As shown in figure 2a, for the PD-NCI group, significant differences (p < 0.01) with their comparison group were found for 2 out of 29 measures, Reading Span (t = 3.62, d.f. = 36) and Paired Associates I (t = 2.85, d.f. = 36) in 2 separate domains: Working Memory and Memory/Learning. The PD-UCI group, (fig. 2b) had deficits over 4 domains, Working Memory, Executive Function, Speed of Processing and Visuospatial skills (specific deficits included: CLOX-I (t = 4.81, d.f. = 16), Color Naming (t = 3.10, d.f. = 16), ROF-I (t = 4.98, d.f. = 16), and CLOX-II (t = 6.83, d.f. = 16)).

By contrast, the PD-MCI group (fig. 2c) showed deficits across 5 of the 6 domains versus their comparison group (the exception being Memory/Learning). Specific measures that showed a significant difference (p < 0.01) included: Letter Fluency (t = 5.27, d.f. = 22), Category Switching (t = 5.08, d.f. = 22), Inhibition (t = 4.18, d.f. = 22), Inhibition Switching (t = 3.77, d.f. = 22), Matrix Reasoning (t = 4.00, d.f. = 22), SOC (t = 2.97, d.f. = 22), Reading Span (t = 4.80, d.f. = 22), Word Reading (t = 3.18, d.f. = 22), Color Naming (t = 4.16, d.f. = 22), ROF-I (t = 3.82, d.f. = 22) and Line Orientation (t = 3.08, d.f. = 22).

Using a previously used criterion, cognitive impairment was defined as ≥1.5 SD below the comparison group norm [6]. Across the PD-NCI, PD-UCI, and PD-MCI subgroups, there was a trend for an increasing number of patients to exhibit deficits on at least one cognitive domain (table 3).

### Table 2. Comparison between the 3 PD groups identified by the cluster analysis for clinical and demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>PD-NCI (n = 19)</th>
<th>PD-UCI (n = 9)</th>
<th>PD-MCI (n = 12)</th>
<th>F</th>
<th>p level</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>29.32 ± 0.8</td>
<td>28.77 ± 1.8</td>
<td>27.50 ± 1.8</td>
<td>8.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DRS-IIa</td>
<td>10.52 ± 2.1</td>
<td>10.29 ± 1.6</td>
<td>9.16 ± 3.7</td>
<td>1.03</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.13 ± 0.1</td>
<td>12.89 ± 1.8</td>
<td>12.83 ± 1.0</td>
<td>4.67</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>NARTb</td>
<td>116.37 ± 7.3</td>
<td>103.33 ± 7.9</td>
<td>101.75 ± 7.4</td>
<td>17.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>64.37 ± 6.6</td>
<td>66.00 ± 7.4</td>
<td>69.08 ± 5.5</td>
<td>1.94</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>UPDRS totalc</td>
<td>26.68 ± 6.0</td>
<td>28.11 ± 11.1</td>
<td>31.82 ± 12.6</td>
<td>1.03</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>UPDRS tremor</td>
<td>0.57 ± 0.3</td>
<td>0.42 ± 0.3</td>
<td>0.66 ± 0.6</td>
<td>0.96</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>UPDRS non-tremor</td>
<td>1.07 ± 0.3</td>
<td>1.21 ± 0.5</td>
<td>1.32 ± 0.5</td>
<td>1.46</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>PD onsetd</td>
<td>5.79 ± 3.0</td>
<td>6.33 ± 2.9</td>
<td>7.84 ± 6.1</td>
<td>0.77</td>
<td>&gt;0.47</td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>2.03 ± 0.7</td>
<td>2.05 ± 0.8</td>
<td>2.33 ± 1.0</td>
<td>0.54</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>BDI-II</td>
<td>7.68 ± 4.5</td>
<td>8.22 ± 5.2</td>
<td>6.92 ± 3.5</td>
<td>0.24</td>
<td>&lt;0.79</td>
</tr>
</tbody>
</table>

*a* Mattis Dementia Rating Scale adjusted for age and education. *b* Premorbid intelligence estimate using the NART. *c* Unified Parkinson’s disease rating scale motor score. *d* Number of years since PD was first diagnosed.

### Discussion

This study used a data-driven method to identify different sub-categories of cognitive impairment for patients with PD. We found that the same variables that differentiated the PD patients from the healthy comparison group were those that were associated with cognitive heterogeneity among PD subgroups [21]. Use of a broad range of tests enabled us to identify a pattern of impaired and unimpaired functioning. This result suggests that a particular subgroup of PD patients with MCI can be identified.

Differences among the PD subgroups were found for measures of executive function, problem solving, working memory, speed of processing, and visual spatial ability. There was no difference between the groups in terms of memory/learning or attention. While different areas of cognitive impairment have previously been reported, our study is novel in that it establishes a comprehensive pattern of cognitive performance for different subgroups of patients (both strengths and weaknesses).

Comparisons of the subgroups indicated that the groups represented a continuum of cognitive impairment (see fig. 1 and 2) ranging from none/minimal (PD-NCI) to PD patients with a more varied pattern of cognitive...
Fig. 2. Comparison between PD patients and matched controls on measures of cognitive functioning. **a** PD-NCI group. **b** PD-UCI group. **c** PD-MCI group. *p < 0.05; **p < 0.01; ***p < 0.001. The 29 tests performed in this study: 1 = Letter Fluency; 2 = category Fluency; 3 = Category Switching; 4 = CLOX-I; 5 = Key Search; 6 = Zoo Map; 7 = Inhibition; 8 = Inhibition Switching; 9 = ID/ED; 10 = Card Sorting description; 11 = Matrix Reasoning; 12 = SOC; 13 = Tower Test; 14 = Digits forward; 15 = Digits reversed; 16 = letter number sequencing; 17 = Reading Span; 18 = Spatial Span; 19 = Word Reading; 20 = Color Naming; 21 = Logical Memory-I; 22 = Logical Memory-II; 23 = Paired Associates-I; 24 = Paired Associates-II; 25 = Auditory recall; 26 = ROF-II and -III; 27 = ROF-I; 28 = Line Orientation; 29 = CLOX-2.
impairment (PD-UCI), through to PD patients showing evidence of multiple domains with cognitive impairments but did not yet meet the criteria of dementia (PD-MCI). Taken together with the consistency of the tests which differentiated the PD patients from the comparison group and were associated with cognitive heterogeneity across the PD subgroups, this suggests that MCI is an identifiable syndrome that affects a subset of PD patients.

The heterogeneity of cognitive deficits reported here is not surprising given the diverse pattern of neuronal degeneration associated with PD [22, 23]. Neuropathologically, PD is characterised by loss of cells in the substantia nigra and the presence of Lewy bodies [24]. Alpha-synuclein is a major constituent of Lewy bodies, and is implicated in dopaminergic neuronal death associated with PD [24]. Evidence of abnormalities in other subcortical structures including the loss of noradrenergic neurons in locus coeruleus, serotonergic neurons in the dorsal raphé nucleus, and cholinergic neurons in the nucleus basalis of Meynert, are evident from the early stages of the disease process [23, 25–27]. Furthermore, there is strong evidence that the mesocortical dopaminergic system also contributes to deficits in cognitive and behav-ioral functioning [28]. The mesocortical dopaminergic system arises from the ventral tegmental area with direct projections to the frontal cortex.

Consistent with previous research, our study found evidence for different subgroups of PD patients based on cognitive functioning [2]. The importance of accurately defining different subgroups is amplified by the suggestion that some PD patients may be more at risk of progressing to PDD [3]. Prevalence rates of dementia among people with PD are much higher than in the general population; approximately 4 to 5 times that of elderly individuals without PD [29]. However, the cognitive symptoms associated with PD-MCI have yet to be fully established [30]. Previous studies have found evidence for a range of different cognitive deficits that may best predict PDD, including attention [31], inhibition [32], mental flexibility [33], memory [34], language [35], and visuospatial impairment [36]. While the range of measures previously suggested as predictive of PDD may seem diverse, the majority of them reflect what would generally be considered as executive functions, and have previously been suggested as the most common deficit in PD-MCI [6].

In our study, all patients in the PD-UCI and PD-MCI subgroup had deficits (1.5 SD below control mean) of visuospatial ability, and all but 1 patient in the PD-MCI group had deficits in other areas of cognitive functioning. The only area that appeared to be relatively spared was general memory/learning. Consistent with our findings, executive dysfunction has previously been reported as the most prevalent abnormal domain for PD-MCI [6]. However, there is some inconsistency regarding the significance of memory impairments in PD-MCI [3, 6, 37]. Moreover, some studies have failed to find memory impairments in PDD patients [31], suggesting that memory impairments may emerge later and are not reliably impaired in the preclinical stages of PDD. We also found consistent evidence of visuospatial deficits, which has not been reported by other researchers examining the cognitive characteristics of PD-MCI [3, 6]. However, this inconsistency is likely to be due to methodological differences between the studies. For example, while some research has examined heterogeneity of cognitive profiles for patients in the early clinical stages [2, 38], others have examined patients in the late stages of disease progression [31]. Other researchers have used different exclusion criteria, for example a BDI-II cutoff of 10 [39], different criteria for poor performance and different test batteries to assess cognitive performance.

<table>
<thead>
<tr>
<th>Table 3. Number and percentage of patients versus matched controls who exhibited deficits (&lt;1.5 SD below the control mean) separately for each of the 6 domains</th>
</tr>
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<tbody>
<tr>
<td>Mild deficits &gt;1.5 SD, n (%)</td>
</tr>
<tr>
<td>(n = 19)   (n = 9)   (n = 12)</td>
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<tr>
<td><strong>Executive function</strong></td>
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<tr>
<td>PD patients</td>
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<td>Matched controls</td>
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<tr>
<td>Problem solving</td>
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<td>PD patients</td>
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<td>Matched controls</td>
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<td>Working memory</td>
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<td>PD patients</td>
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<td>Matched controls</td>
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<td>Speed of processing</td>
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<td>PD patients</td>
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<td>Matched controls</td>
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<tr>
<td>Memory/learning</td>
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<td>PD patients</td>
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<tr>
<td>Matched controls</td>
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<tr>
<td>Vисuospatial ability</td>
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<tr>
<td>PD patients</td>
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<td>Matched controls</td>
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Preclinical Dementia in PD

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127

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Progression to dementia has been reported by some as being more likely in patients with longer disease duration [34], older age and more severe motor symptoms. However, in our study the subgroups were comparable on most of the demographic, clinical, and motor characteristics assessed. Other research suggests that clinical and motor characteristics by themselves are not sufficient to identify patients in the preclinical stages of PDD [40]. More recent research examining the characteristics of PD-MCI has also reported comparable clinical and demographic characteristics for this group compared with other PD subgroups [3]. However, the association between motor symptoms and PD-MCI appears to be variable [40]. This inconsistency appears to be related to the different subgroups that may exist within the PD-MCI grouping [3, 6].

This study had a number of strengths as it used a wide range of tests across a broad range of possible domains to determine cognitive deficits for the different groups. Also, we used a data-driven approach in examining the data to avoid the difficulties of predetermined cutoffs. However, a limitation of the study was the use of a cross-sectional design. The groups identified here would have to be followed longitudinally to confirm whether the patients in the PD-MCI group were indeed more likely to progress to dementia. Furthermore, the number of patients available for inclusion in the study and in the subgroups identified by the cluster analysis was relatively small. In addition, a number of patients did not respond to the invitation to participate which may have caused a bias in the composition of those who participated.

It is clear from these findings that patients with PD are heterogeneous with regard to their cognitive presentation. Longitudinal assessment of patients in this study is underway and will be essential to confirm the initial findings. The identification of diagnostic criteria associated with PD-MCI would present an opportunity to understand cognitive decline in PD and its progression to dementia.

Acknowledgements

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