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Identifying Subtypes of Mild Cognitive Impairment in Parkinson’s disease using
Cluster Analysis

Dana Pourzinali1,2, Ji Hyun J Yang1, Gerard J. Byrne1,3, John D. O’Sullivan1,4, Leander Mitchell2, Katie L McMahon5, David A. Copland1,6, Nadeeka N. Dissanayaka1,2,4*

1UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Royal Brisbane & Women’s Hospital, Herston QLD 4029, Brisbane, Australia.
2School of Psychology, The University of Queensland, St Lucia, QLD 4067, Brisbane, Australia
3Mental Health Service, Royal Brisbane & Women’s Hospital, Herston, QLD 4029, Brisbane, Australia
4Department of Neurology, Royal Brisbane & Women’s Hospital, Herston QLD 4029, Brisbane, Australia
5School of Clinical Sciences and Institute of Health and Biomedical Innovation, Queensland University of Technology, QLD, 4000, Brisbane, Australia
6School of Health & Rehabilitation Sciences, The University of Queensland, St Lucia, QLD 4067, Brisbane, Australia

*Corresponding Author
Nadeeka Dissanayaka
Phone: +617 33465577, +61 405715622
Email: n.dissanayaka@uq.edu.au
Postal address:
University of Queensland, UQ Centre for Clinical Research,
Building 71/918 Royal Brisbane & Women’s Hospital,
Herston QLD4029, Brisbane, Australia

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Declarations

Author Contributions:

*D.P.* - conceptualization, design of study, data analysis, writing of the first draft & revision of subsequent drafts

*J.J.Y.* - conceptualization, design of the test battery, data collection, critical revision

*G.J.B.* - design of the test battery, supervision, financial support, critical revision

*J.D.O.* - recruitment of participants, critical revision

*L.M.* - design of the test battery

*K.L.M* - design of the test battery, student supervision, critical revision

*D.A.C.* - design of the test battery, student supervision, critical revision

*N.N.D.* - conceptualization, design of study, design of the test battery, student supervision, critical revision of subsequent drafts

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Abstract

Introduction: The concept of Mild Cognitive Impairment (MCI) in Parkinson’s disease (PD) has shown potential for identifying at-risk dementia patients. Identifying subtypes of MCI is likely to assist therapeutic discoveries and better clinical management of patients with PD (PWP). Recent cluster-based approaches have demonstrated dominance in memory and executive impairment in PD. The present study will further explore the role memory and executive impairment and associated clinical features in non-demented PWP.

Method: A K-means cluster analysis was performed on 10 “frontal” and “posterior” cognitive variables derived from a dataset of 85 non-demented PWP. The resulting cluster structure was chosen based on quantitative, qualitative, theoretical, and clinical validity. Cluster profiles were then created through statistical analysis of cognitive and clinical/demographic variables. Descriptive analysis of each cluster’s performance on a comprehensive PD-MCI diagnostic battery was also explored.

Results: The resulting cluster structure revealed four distinct cognitive phenotypes: (i) Frontal-dominant impairment; (ii) Posterior-cortical-dominant impairment; (iii) Global impairment, and (iv) Cognitively intact. Demographic profiling revealed significant differences in the age, gender split, global cognitive ability, and motor symptoms between these clusters. However, there were no significant differences between the clusters on measures of depression, apathy and anxiety.

Conclusion: These results validate the existence of distinct cognitive phenotypes within PD-MCI and encourage future research into their clinical trajectory and neuroimaging correlates.

1. Introduction

The concept of Mild Cognitive Impairment in PD (PD-MCI) aims to identify a potential prodromal phase of PD Dementia (PDD) [1]. However, a consistent heterogeneity in the diagnosis, symptomatology, and trajectory of PD-MCI has been acknowledged in recent literature [2,3].

The Dual Syndrome Hypothesis proposes that there are two anatomically-based cognitive sub-phenotypes of PD-MCI: the frontal syndrome, associated with executive and attentional dysfunction, and the posterior-cortical syndrome, associated with visuospatial and memory dysfunction [4]. Multidisciplinary evidence suggests that the frontal syndrome may be unrelated to severe cognitive decline whereas the posterior-cortical syndrome may be prone to rapid progression toward PDD [4], potentially leading to more refined targets for dementia therapies and research. A more profound PD-MCI phenotype presenting with both frontal and posterior-cortical deficits has also been identified in the literature [5,6]. This globally impaired phenotype may reflect an overlap of the dual syndromes, alluding to the fronto-temporo-parietal dysfunction characteristic of PDD with pervasive cognitive impairments [2].

Data-driven cluster analysis has been adopted to model cognitive phenotypes within PD. An exemplar cluster model produced by Dujardin and colleagues [7,8] using K-means analysis revealed a progressive gradient of five clusters; two cognitively intact, a primarily executive-impaired (reminiscent of the frontal syndrome), and two severely impaired groups. Interestingly, while there were no significant differences between the two severely
impaired clusters across all domains, one demonstrated a trend of lower memory ability and higher executive function than the other on certain measures [8]. It is likely that their small sample sizes (\(N=5\) and \(N=11\)) account for the lack of concrete statistical differences between the two severely impaired groups. However, the overall results reaffirm the relevance of the dual syndrome framework, with the memory and executive domains contributing the most to cluster classifications.

Additionally, the inclusion of global cognitive measures as cluster variables may have hindered the ability to unmask the dual syndromes. This is because, in the context of the dual syndrome framework, these variables are non-informative as they do not provide information pertaining to the relevant frontal/posterior domains. For example, participants with low memory but high executive performance and vice versa may spuriously produce the same global cognitive score as it is a sum of performance across all domains. Non-informative variables increase dimensionality and noise within the analysis [9], thereby interfering with the appraisal of each clusters’ ability within specific domains.

Narrowing the focus to only frontal- and posterior-type domains may therefore produce more detailed results. This was recently demonstrated by Alonso-Recio and colleagues [10], who performed a Latent Profile Analysis on a cognitive dataset contributed to by 71 non-demented PWP. Ten variables within two memory and executive domains were included in the analysis, which resulted in four clusters defined by the most affected domain within each: cognitively intact, executive-impaired, memory-impaired, and memory- and executive-impaired. In line with the Dual Syndrome Hypothesis, distinct executive-impaired and memory-impaired phenotypes were revealed that reflected the frontal and posterior-cortical syndromes, respectively.

Because the interpretation of the overall model is dependent on the domain structure that is employed, the two-domain paradigm appears to have been more amenable to revealing the dual syndromes. Thus, the efficacy and parsimony of this paradigm motivated the exploration of PD-MCI through the dual syndrome framework in the present study. We aimed to apply the two-domain clustering approach to characterize distinct cognitive phenotypes within PD and further explore their cognitive and clinical features, with the intention of grounding future exploration into their anatomical foundations and prognoses.

2. Method

2.1. Participants and Ethics

Eighty-eight patients who met the UK Brain Bank criteria for idiopathic PD were recruited from movement disorders out-patient neurology clinics [11]. Patients with a diagnosis of dementia or other neurological disease were excluded and 85 patients were eligible for analysis. Of these, 49 (57.6%) were male, 77 (90.6%) were taking levodopa-based medications and 8 (9.4%) were drug-naïve. Demographic information for the overall sample is summarised in Table 1.

2.2. Data Collection Procedure

Participants completed a self-report questionnaire and attended two 90-120-minute interviews assessing their cognitive, psychological, and Parkinsonian symptoms. Written informed consent was collected from each patient prior to their participation. All participants were interviewed in their “on-state”. Human Research Ethics Committees of the University of Queensland and Royal Brisbane & Women’s Hospital provided ethical clearance for this study.
2.3. Measures

2.3.1. Clinical measures.

The following scales were administered: Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [12]; Hamilton Depression Rating Scale (HDRS) [13]; Starkstein Apathy Scale (SAS) [14]; and Parkinson’s Anxiety Scale (PAS) [15]. Levodopa Equivalent Daily Dose (LEDD) was calculated following Tomlinson and colleagues’ guidelines [16].

2.3.2. Cognitive measures.

Global cognitive ability was assessed with the Montreal Cognitive Assessment (MoCA) [17]. A neurocognitive battery at level II of the MDS guidelines for PD-MCI diagnosis was administered to patients, consisting of ten tests covering five cognitive domains [18]. Executive function was measured using the Delis-Kaplan Executive Function System (D-KEFS) Card-sorting and phonemic, switching fluency tasks [19]. Memory was measured with the Hopkin’s Verbal Learning Test-Revised (HVLT-R) [20] and Brief Visual Memory Test-Revised (BVMT-R) [20]. Attention was measured using the interference index of the STROOP [21] and scales A and B of the Trail-Making (TMT) [22]. Visuospatial ability was measured using Benton’s Judgement of Line Orientation [23] and CLOX clock drawing test [24]. Language was measured using the D-KEFS semantic fluency task [19] and Boston Naming Test (BNT) [25].

2.3.3. MCI diagnosis.

In accordance with the MDS guidelines [18], PD-MCI was diagnosed by evaluating patients’ z-scores for each measure in the above neurocognitive battery of 10 tests against normative data. In alignment with the level II criteria, scores 1.5 SD below the norms were considered a “failed” test, and MCI was attributed to participants who failed two or more tests from the same or separate domains.

2.4. Analysis

2.4.1. Power analysis

There is no consensus in the literature on parameters for cluster analyses. For exploratory analyses, it is recommended to critically evaluate the number of variables to ensure adequate dimensionality for the sample size [26]. Thus, the current study has limited the exploration to 10 variables within two cognitive domains.

2.4.2. Cluster variables

From the series of previously mentioned cognitive measures, ten variables were selected for the cluster analysis such that each of the five cognitive domains (executive function, memory, attention, language, visuospatial) were represented. The variables were recategorized into either “posterior” or “frontal” domains based on whether they were stronger measures of memory/visuospatial ability or executive function/attention, respectively, as well as previously published norms [6]. Previous research has linked measures of verbal, visuospatial, and semantic memory to posterior and temporal regions of the brain in PD [27]. Thus, posterior cluster variables included the immediate and delayed scores from both HVLT-R (verbal memory) and BVMT-R (visual memory), category fluency (semantic memory), and Boston naming test (BNT) (semantic memory). Frontal cluster variables included
measures which have been linked to frontal brain regions; phonemic fluency (executive function),[28] and the Trail-Making scores (task A, task B-A; processing speed, alternating attention).[29] Due to the association between digit-based working memory measures and frontal regions of the brain,[30] we decided to employ the Working Memory subscale from the Parkinson’s Disease Cognitive Rating Scale (WM-PDCRS), which was administered to participants as part of our broader research program. The WM-PDCRS is a validated measure of working memory, attention, and cognitive flexibility and has demonstrated concurrent validity with the Backward Digit Span scale[31].

2.4.3. Cluster analysis
The 10 cluster variables were standardized using range weights and imputed in multiple K-means cluster analyses using the Euclidian distance. Several models were generated and contrasted to determine the most appropriate structure for the dataset. Clusters were evaluated using two graphical methods; a Within-Sum-of-Squares (WSS) plot and a Silhouette plot. They were also quantitatively evaluated on 21 cluster validity criteria within the “NbClust” R package[32]. The graphical methods, validity criteria, relevant theory, and clinical significance of each model were compared and contrasted to determine the final cluster structure. All cluster analyses and data visualizations were performed using R software (v3.5.1; R Core Team, 2018) with the “cluster”[33] package.

2.4.4. Cluster profiling
To create the cognitive and demographic/affective profiles for the final cluster model, data were analyzed in the following manner: one-way between-groups ANOVA with Tukey comparisons (α = .05) where data was normally-distributed; Welch test with Tamhane T2 comparisons (α = .05) where homogeneity of variance was violated; and Kruskal-Wallis test with Šidák-corrected Mann-Whitney U follow-ups where data was non-normal. Categorical variables were assessed using a Fisher’s exact test as cell frequencies were less than 5. SPSS v.25 was used for all profiling analyses.

3. Results
3.1. Data Checks
No cluster variables had missing scores. Three scores on the full neurocognitive battery were missing due to inability to complete the tasks, preventing three participants from receiving a PD-MCI classification. Of the demographic/affective data, the maximum number of missing scores for any given variable (8%) or participant (18%) was well below the conventional 50% response rate threshold. The variable with the most missing data, SAS, was treated with an Expectation-Maximization algorithm using SPSS v.25.

3.2. Cluster Analysis
Taking into consideration the graphical methods, quantitative criteria, and the theoretical relevance of each model, the four-cluster model appeared to be the most appropriate. This structure accounted for 56.3% of the total variability in the model. Tables 2A and 2B summarize the means, standard deviations and statistical results for each of the four clusters on the cognitive variables and the demographic/affective measures, respectively. The results of the exact Fisher’s tests also showed that sex, \( \chi^2 (3, 85) = 13.37, p = .003, \varphi = .397 \), and PD-MCI, \( \chi^2 (3, 82) = 27.79, p < .001, \varphi = .566 \), were not equally distributed throughout the clusters.
Cluster one comprised 36 participants who, on average, performed below the grand mean on posterior variables and above on frontal variables. The second cluster of 18 participants embodied a more impaired group, performing consistently below the grand mean across all cognitive variables. The 24 participants of cluster three produced the best overall scores on all cognitive variables, indicating relatively higher cognitive ability compared to the other three clusters. The fourth cluster consisted of seven participants who, on average, performed below the grand mean on frontal variables and relatively strongly on posterior variables. To assist the interpretation of results, a heat-map of the cognitive profiles is provided in Figure 1.

3.3. Descriptive MCI Analysis

Cognitive performance in terms of the MDS PD-MCI neurocognitive battery was also explored to scrutinize the nature of each cluster’s impairments. The distribution of MDS-diagnosed PD-MCI within each cluster is also provided in Figure 2. From these charts, it becomes clear that clusters two and three reflected the relatively impaired and relatively intact ends of the cognitive spectrum, respectively. Clusters one and four, however, did not clearly conform to either the MCI or non-MCI diagnoses.

To investigate this further the number of failed tests within each domain of the full PD-MCI neurocognitive battery were also calculated and are provided in Table 3. These values restate a similar pattern to the statistical results, revealing failed tests mostly within the posterior and frontal domains for clusters one and four, respectively. The percent of failed tests per cluster also indicate the level of impairment experienced by each group, with clusters two and three again reflecting each end of the cognitive spectrum and clusters one and four demonstrating a milder level of impairment. Notably, however, only clusters one and two produced failed tests within the visuospatial domain, which consisted of two measures (CLOX, Benton’s Judgement of Line Orientation) that were not included in the cluster analysis. This additional information further supports the notion that clusters one and two reflect patients with posterior-type impairments.

4. Discussion

The present study used an exploratory data-driven approach to identify cognitive phenotypes based on the Dual Syndrome Hypothesis within a sample of PWP. The results yielded four clusters of patients with varying degrees of cognitive impairment:

**Globally Impaired MCI.** Cluster two demonstrated global impairment across all cluster variables, the lowest mean MoCA score, and a high rate of PD-MCI (82%) as displayed in Figure 2. This older, majority-male cohort with low education and severe motor symptoms fits the demographic profile of a cognitively impaired group, as higher age, lower education, greater motor symptom severity, and male gender have all been associated with PD-MCI [34].

**Posterior-cortical-dominant MCI.** Cluster one – an older, majority-male group – demonstrated stronger deficits in the posterior cluster variables compared to the frontal. This cluster performed particularly poorly on the BVMT measure of visual memory. Additional failures in the extraneous visuospatial measures within the full neurocognitive battery further highlights the posterior-cortical nature of this cluster’s deficits. The mean MoCA score below 26 (indicative of abnormal cognition) suggested this group reflects a PD-MCI subtype, however, 63% of patients were classified as non-MCI according to the MDS criteria.
Frontal-dominant MCI. Cluster four – Frontal impairments were characteristic of cluster four while the posterior-cortical domain remained relatively intact. Performance on the WM-PDCRS working memory measure was particularly compromised. This group did not fail any tests within the memory or visuospatial domains of the full neurocognitive battery. The mean MoCA score below 26 indicated another PD-MCI subtype, yet there was a low proportion of patients meeting the MDS PD-MCI criteria (33%). This phenotype was characterized by a younger cohort with a high level of education.

Cognitively Intact Non-MCI. Cluster three demonstrated strong performance across all cluster variables. A mean MoCA score above 26 and low rate of PD-MCI (4%) indicated normal cognitive ability for this group. This younger, majority-female cohort with high education and less severe motor symptoms also matched the demographic profile of a cognitively intact group [34].

It is evident that the Globally Impaired and the Cognitively Intact clusters reflect either end of the PD cognitive spectrum; they are clinically distinct groups which embody the characteristics of typical MCI and non-MCI groups, respectively. However, the other two clusters presented with impairments specific to either the posterior or frontal domains. The results suggest that, apart from the distinct MCI and non-MCI phenotypes, subtypes of impairment also exist in PD. These results confirm the patterns of impairment uncovered by Alonso-Recio and colleagues [10], and also align with the predictions of Kehagia and colleagues’ Dual Syndrome Hypothesis [7,8]. In line with this theory, Frontal-dominant and Posterior-cortical-dominant phenotypes were revealed, corresponding to the frontal and posterior-cortical syndromes, respectively. The Globally Impaired pattern of impairment may correspond to the severe PD-MCI phenotype uncovered in the literature [6,3], presenting with advanced, pervasive cognitive impairments reminiscent of PDD. Interestingly, no differences were found between any cluster on any measure of affect (depression, apathy, anxiety). Overall, this contrasts with previous literature as it may suggest a lack of association between cognitive subtypes and affect in PD.

4.1. Implications

Based on MoCA scores, demographic (e.g. age) and clinical characteristics (e.g. severity of PD), the four cognitive subtypes reflect a gradient of severity levels thus contributing to the cognitive staging of PD. The results also suggest that the future diagnostic criteria for PD-MCI may benefit from accounting for specific Frontal-dominant and Posterior-cortical-dominant phenotypes. Standardizing the diagnosis of these subtypes would also open opportunities to tailor the clinical management of patients to their specific cognitive needs.

The results also show that global cognitive assessments (e.g. MoCA) are inadequate at distinguishing PD-MCI subtypes, and thus should not substitute full neurocognitive assessments in contexts where cognition is a clinical priority for the patient. Furthermore, these findings suggest that limiting the number of cognitive domains may simplify the PD-MCI subtyping process. While assigning measures to cognitive domains is somewhat arbitrary [22], current DSM-5 [35] and MDS [18] standards recommend assessing multiple cognitive domains for MCI diagnosis. The results of the present study suggest that streamlining measures into frontal/posterior domains could generate more clinically and theoretically relevant PD-MCI diagnoses. Similarly, the results indicate that distinct cognitive subtypes can be identified using a limited neurocognitive battery. This has positive implications for the administration of diagnostic batteries, with potential for improving future PD-MCI diagnoses.

Lastly, the Dual Syndrome Hypothesis predicts a more rapid cognitive decline for the Posterior-cortical-dominant phenotype compared to the Frontal-dominant phenotype [4]. If those susceptible to dementia can be
more efficiently defined and identified, this produces a vast array of opportunities for more person-centered care and targeted interventions which meet specific patient needs. While the present study cannot make any conclusions about their cognitive progression, it validates the existence of cognitive phenotypes within a PD sample and outlines a refined, novel method to uncover them.

4.2. Limitations

While there is no consensus in the literature for sample size to variable ratio in cluster analyses, a general rule of thumb is 10 subjects per variable. Thus, the present sample size of 85 limits the study to an exploratory cluster analysis. However, the classification of patients based on behavioral cognitive trends produced results purely from data, reducing the number of a-priori assumptions and strengthening the findings. This sets an important precedent for exploring the neural mechanisms behind the behavioral symptoms of the clusters in an objective, data-driven manner.

The small sample size of cluster four (N=7) also potentially compromised the statistical power of the profiling analyses to prevent the reveal of significant cognitive and demographic differences. Although the results still resonated strongly with previous literature, replication in a larger sample with higher frequency of this phenotype is recommended. Similarly, a ceiling effect within the BNT may have masked meaningful differences between clusters. Although this scale was not entirely redundant, employing a more difficult measure of semantic memory could address this limitation.

The results are further limited by the lack of visuospatial measures in the cluster analysis owing to a restricted number of variables due to limited sample size. However, the BVMT has an inextricable visuospatial component from which we are able to make inferences about visuospatial ability. The clusters which performed most poorly on the BVMT also exhibited more test failures in the visuospatial domain of the full neurocognitive battery than the other clusters. While this suggests that the cluster analysis somewhat accounted for visuospatial ability, future research should consider direct measures of visuospatial ability in identifying the dual syndromes given that it is a major aspect of the posterior-cortical syndrome.

Another limitation was the poor ability of the category and phonemic fluency tasks to discriminate between the phenotypes, potentially attributable to the multidimensionality of the tasks. Category and phonemic fluency have consistently been associated with the memory and executive domains, respectively [22]. However, both tasks are thought to require a diverse range of cognitive functions such as planning, working memory, memory storage, and memory retrieval [36]. This complexity may explain their sensitivity to cognitive impairment within PD, but also their insensitivity to the more nuanced subtypes. Specifically, it may be that the tasks are too responsive to impairments within both domains to be able to differentiate the Frontal-dominant and Posterior-cortical-dominant phenotypes. Further research into the relationship between verbal fluency tasks and PD-MCI subtypes is required for a better understanding of this phenomenon.

Finally, the resulting structure was limited by the fact that symptoms and neural networks may overlap between clusters, which is to be expected due to the inherent overlap of cognitive domains. While this inherent overlap also complicates the categorization of measures into distinct domains, we carefully selected frontal and posterior tests based on current consensus in the cognitive neuroscience literature.
4.3. Suggestions for Future Research

The most important finding for future research to establish would be whether the *Posterior-cortical-dominant* phenotype truly embodies a faster rate of cognitive decline, as predicted by the Dual Syndrome Hypothesis [4]. It is also important to confirm the neural, anatomic and pathological foundations of each phenotype. Although these require the efforts of longitudinal and neuroimaging studies, the results could be revolutionary for therapeutic innovations. A final suggestion would be to optimize the PD-MCI diagnosis by empirically evaluating different diagnostic methods for the cognitive phenotypes. Once a sufficient method has been established, further research into medical and therapeutic interventions for dementia prevention can be better targeted to the appropriate at-risk groups.

5. Conclusions

Through the use of data-driven techniques, the present study delineated four distinct groups of PWP: Cognitively Intact, *Frontal-dominant*, *Posterior-cortical-dominant*, and Globally Impaired phenotypes. Confirming the existence of these distinct cognitive phenotypes within PD highlighted the limitations of the current diagnostic methods for PD-MCI. Future research should focus on establishing the cognitive trajectory and neural foundations of these phenotypes, with the intention of improving diagnostic and prognostic outcomes for PWP.
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Figure captions

**Fig 1.** Four-cluster heat-map: Performance of clusters 1-4 on the cognitive measures, with redder shades indicating stronger impairment relative to the rest of the sample and lighter shades indicating less impairment.

Note. HVLT = Hopkin’s Verbal Learning Test – Revised; BVMT = Brief Visual Memory Test – Revised; WM-PDCRS = Working Memory scale from the Parkinson’s Disease Cognitive Rating Scale.

**Fig 2.** Pie charts indicating proportion of MCI and non-MCI patients per cluster, as identified according to the standardized criteria for PD-MCI (N, %).