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Cognitive phenotypes in Parkinson’s disease: A latent profile analysis.

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Manuscript Number:	NEU-2020-0362R2
Full Title:	Cognitive phenotypes in Parkinson’s disease: A latent profile analysis.
Article Type:	Data-Driven Article
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Keywords:	Parkinson's Disease; Cognition; latent profile analysis; neuropsychology
Corresponding Author:	Edoardo Barvas, Psy.D Universita degli Studi di Trento Rovereto (TN), ITALY
Corresponding Author E-Mail:	ebarvas@me.com
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universita degli Studi di Trento
Other Authors:	Giulia Mattavelli, PhD
	Francesca Zappini, MD
	Floriana Giardina, MD
	Donatella Ottaviani, MD
	Costanza Papagno, MD, PhD
Author Comments:	
Corresponding Author's Secondary Institution:	
First Author:	Edoardo Barvas, Psy.D
Order of Authors Secondary Information:	
Manuscript Region of Origin:	ITALY
Suggested Reviewers:	Gabriella Santangelo Second University of Naples, Caserta, Italy.

	gabriella.santangelo@unina2.it Expert in the field
	Maria Caterina Silveri Universita Cattolica del Sacro Cuore mariacaterina.silveri@unicatt.it Expert in the field
	Michel Panisset Centre Hospitalier de l'Université de Montreal michel.panisset@umontreal.ca Expert in the field
Opposed Reviewers:	
Response to Reviewers:	

Dear Dr. Wilde,

Thank you very much for giving us the opportunity to revise our paper “Cognitive phenotypes in Parkinson’s disease: A latent profile analysis”, NEU-2020-0362R1.
We would also like to thank once again the Reviewers for their insightful comments.
We made all the suggested changes in punctuation and wording with the exception of two sentences (page 5 line 4 and page 10 line 1) that were rephrased. These two sentences are highlighted in bold and in blue color in the main text.

Thank you very much.

Sincerely,
Edoardo Barvas

Thank you very much for your insightful comments.

We made all the suggested changes in punctuation and wording with the exception of two sentences (page 5 line 4 and page 10 line 1) that were rephrased. These two sentences are highlighted in bold and in blue color in the main text.

Cognitive phenotypes in Parkinson's disease: A latent profile analysis.

Edoardo Barvas[a,b,*], Giulia Mattavelli[c], Francesca Zappini[a], Floriana Giardina[d], Donatella Ottaviani[d], Costanza Papagno[a,e].

[a] CeRiN, Centro di Riabilitazione Neurocognitiva, CIMeC, Università di Trento, Via Matteo del Ben 5/b, 38068 Rovereto (TN), Italy.

[b] Unità Operativa di Neurologia, Ospedale di Stato della Repubblica di San Marino, Via Scialoja 20, 47893 Cailungo, Republic of San Marino.

[c] NETS, Scuola universitaria superiore IUSS, Piazza della Vittoria 15, 27100 Pavia, Italy.

[d] Unità Operativa di Neurologia, Ospedale Santa Maria del Carmine, Azienda Provinciale per i Servizi Sanitari, Corso Verona 4, 38068 Rovereto (TN), Italy.

[e] Dipartimento di Psicologia, Università degli studi di Milano-Bicocca, Piazza dell'Ateneo 1, 02100 Milan, Italy.

* Corresponding author:
Edoardo Barvas
Via Scialoja 20, 4789 - Republic of San Marino
(+378) 0549 994845
edoardo.barvas@iss.sm

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Cognitive phenotypes in Parkinson's disease: A latent profile analysis.

Abstract

Objectives: Neurocognitive disorders in Parkinson's disease (PD) are common and heterogeneous. The aim of this study was to use a data-driven method to describe different cognitive phenotypes in PD and to explore anxiety, depression, and motor disturbances across the different cognitive profiles.

Method: Latent profile analysis was applied to the neuropsychological performances of 65 patients with idiopathic PD assessed by means of a battery of tests that encompass measures of attention, memory, executive functions, social cognition, language, and visuo-spatial abilities.

Results: A three-clusters model produced the best solution: Cluster A (21.54%) included patients with intact cognition or with a relatively slight cognitive impairment in memory and executive functioning; Cluster B (53.85%) included patients with an intermediate level of cognitive impairment; Cluster C (24.61%) included patients with the most severe cognitive impairment, with greater deficit compared to Cluster B in executive functioning, and, notably, in tasks with a predominantly posterior cortical basis (naming and visuo-spatial abilities). The three subgroups did not differ in terms of age, gender, disease duration, motor symptom severity or side of onset, levodopa equivalent daily dose, level of anxiety, or depression; however, patients from Cluster C showed greater impairment than patients from Cluster A in measures of everyday functioning.

Conclusions: We presented a qualitative description of three distinct cognitive phenotypes emerging from a sample of 65 PD patients. The three clusters seem to be related to daily functioning, but are independent from stage of disease, motor functioning, anxiety, and depression.

Key words: Parkinson's disease; cognition; latent profile analysis; neuropsychology

Key Points:

Question: What are the profiles of cognitive symptoms in Parkinson's Disease?

Findings: We described three distinct cognitive profiles, which appear independent from stage of disease, motor functioning, anxiety, and depression, but related to daily functioning.

Importance: These findings support the presence of heterogeneity in the cognitive features of Parkinson's Disease and could inform tailored pharmacological and non-pharmacological intervention.

Next Steps: Future researchers should examine brain atrophy and investigate the risk of progression for different subgroups of patients.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that involves multiple neurotransmitter pathways and presents with a complex and heterogeneous clinical phenotype including motor and non-motor symptoms (Chaudhuri et al., 2006). The well-known nigro-striatal dopaminergic deficit and the consequent fronto-striatal dysfunction are believed to cause the hallmark motor features and the most common cognitive (dysexecutive) and behavioural changes; however, different brain systems are likely related to other cognitive (e.g., memory or visuo-spatial) and non-motor disturbances (Papagno & Trojano, 2018).

Neurocognitive disorders (NCD) are common in PD. The average prevalence of dementia in longitudinal studies ranges from 26% at baseline to an 8-year prevalence of 78.2% (Aarsland et al., 2003). Moreover, among patients without dementia, mild cognitive impairment (MCI) is common in early stages, with a prevalence of 25% (Aarsland et al., 2010). The prototypical pattern of cognitive impairment in PD is that of a dysexecutive disorder, although a variety of deficits affecting visuospatial, memory, and language functions are frequently observed (Papagno & Trojano, 2018). On the basis of this heterogeneity, it has been proposed that the cognitive deficits could result from two distinct, albeit partially overlapping, syndromes: an uneven dopaminergic loss across the basal ganglia circuitry leading to deficits in attention and executive functions, and an additional, more posterior, cortical degeneration associated with cholinergic loss and impairment in cognitive tasks with a predominantly posterior cortical basis (Kehagia et al., 2013). This profiling of cognitive symptoms is crucial in light of evidence suggesting that PD-MCI patients with deficits related to posterior cortical areas are at higher risk of developing PD dementia (Williams-Gray et al., 2013).

Data-driven statistical approaches, such as cluster analysis (CA), latent class analysis (LCA), and latent profile analysis (LPA), have been used to identify qualitatively different subgroups of patients and to understand heterogeneity in PD. These approaches have the advantage that phenotypical profiles arise from the data without *a priori* assumptions; patients can be classified into groups, which maximize between-groups differences, whereas within-group differences are minimized (Everitt et

al., 2001). CA and LCA have been widely used to identify overall clinical phenotypes in PD according to general dimensions such as tremor-dominant or non-tremor-dominant onset, early or late disease onset, and eventually, to compare cognitive and psychiatric symptoms between these clusters (e.g., Reijnders et al., 2009). Only a few studies used these methods to explore the heterogeneity within cognitive impairments in PD. To the best of our knowledge, six studies performed CA (Janvin et al., 2006; Weintraub et al., 2004; McKinlay et al., 2009; Dujardin et al., 2013), LCA (Brennan et al., 2017), or LPA (Alonso-Recio et al., 2018) in order to examine cognition in patients with PD as the primary outcome. Among these, Janvin et al. (2006) and Weintraub et al. (2004) employed CA using a single neuropsychological instrument, while the other 4 studies based their analyses on the performance of PD patients on a broad battery of neuropsychological tests. McKinlay et al. (2009) analyzed neuropsychological data of 40 patients with PD and identified a three-cluster solution with an unimpaired subgroup and two subgroups of patients with NCD, one with a variable or uncertain pattern of mild to severe cognitive impairment, and one with evidence of severe cognitive impairment across most cognitive domains. However, a five-cluster solution has been identified by analyzing neuropsychological data of 558 PD patients (Dujardin et al., 2013). The clusters were a cognitively unimpaired subgroup and 4 subgroups of patients with NCD: (a) patients with slight mental slowing, (b) patients with deficits in all cognitive domains except recognition memory, (c) patients with severe mental slowing and severe cognitive impairment in all cognitive domains including memory, and (d) patients with very severe impairment in all cognitive domains. Brennan et al. (2017) analyzed the data of 199 PD patients and identified a three-cluster solution with a cluster of cognitively unimpaired patients and 2 clusters of patients with NCD: an amnesic group (with impaired verbal recall and recognition, but intact performance on other measures) and a group with mixed impairments (with deficits on measures of verbal fluency, visuospatial abilities, and delayed free recall on a memory task, but intact recognition memory). Finally, Alonso-Recio et al. (2018)'s analysis on the neuropsychological data of 71 PD patients allowed for identification of a four-cluster solution with a cognitively unimpaired subgroup and three subgroups of patients with NCD: (a) executive

dysfunction, (b) memory dysfunction, and (c) mixed (memory and executive) dysfunction. This short review of the previous literature highlights large differences in cluster profiles, number of cognitive impairment profiles (from two to four subtypes), and relative prevalence of the different profiles. **These studies were conducted on different populations**, for example, McKinlay et al. (2009) excluded patients with dementia, while Dujardin et al. (2013) included them, and Janvin et al. (2006) limited their analyses to patients with PD and dementia only. Moreover, these studies assessed different cognitive domains and used different tests, making a comparison of results difficult. Crucially, none of the cited studies tested social cognition, which is impaired even in otherwise non-impaired PD patients (Mattavelli et al., 2020), and only two of the six studies assessed long-term visual memory. The present study aims to address these issues using a data-driven approach to explore the expression of NCD in idiopathic PD. We carried out LPA, which uses continuous variables and models membership probabilities estimated by maximum likelihood methods, without a priori selection of number of clusters as required by k-means CA methods (Magidson & Vermunt, 2002). Specifically, we applied LPA to neuropsychological data that were obtained with tests assessing different cognitive domains, including social cognition, with the aim to determine whether NCD related to idiopathic PD can be categorized as fitting different cognitive phenotypes and to explore anxiety, depression, and motor disturbances across the different cognitive profiles.

2. Method

2.1 Participants

Data were obtained from a database of patients with PD evaluated at the Center for Neurocognitive Rehabilitation (CeRiN) of the University of Trento from August 2017 to September 2019. All patients had previously received a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society brain bank criteria (Hughes et al., 1992) by a neurologist expert in movement disorders. Patients with history or evidence of other neurological disorders or potential different causes for NCD other than PD, including dementia with Lewy bodies, were excluded. Patients with incomplete

datasets were also excluded. The original database included 81 patients with idiopathic PD assessed for evaluating possible NCD. Following the screening of exclusion criteria, 65 patients entered the analysis (23 females, 42 males; mean age = 67.94 ± 7.49 years; mean educational level 10.75 ± 4.80 years; mean disease duration 88.46 ± 63.05 months). All patients were right-handed. The initial motor symptom profile was akinetic-rigid for 37 patients (22 right side onset, 12 left side onset, and 3 bilateral onset) and tremor-dominant for 28 patients (8 right side onset and 20 left side onset). Written informed consent was signed by participants. The study was conducted in accordance with ethical guidelines of the local ethics committee and the Declaration of Helsinki. All patients underwent a neurological examination and a battery of tests and questionnaires for neurocognitive and behavioral disorders. Assessments were carried out over 3-hour testing sessions with breaks as required. All patients were tested in the PD medication "on" state and none of them were receiving cholinesterase inhibitor drugs.

2.1.1 Clinical assessment

Median severity stage of the disease was 2 on the Hoehn and Yahr Scale (H&Y, Hoehn & Yahr, 2001), and the Unified Parkinson's Disease Rating Scale part III (UPDRS, Goetz et al., 2008) mean score was 17.8 ± 9.33. All patients were taking anti-Parkinsonian medication, and the mean levodopa equivalent daily dose (LEDD) was 751 ± 425 mg. Median Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores were 6/6 and 6/8, respectively.

2.1.2 Neuropsychological assessment

An extensive battery of standardized neuropsychological tests was used to assess cognitive functions. Each test was administered in Italian by a trained neuropsychologist. The following tests were selected for the analysis: Attentional Matrices (AM, Spinnler & Tognoni, 1987) as a measure of selective attention; Rey-Osterrieth Complex Figure – Delayed Recall (ROCF-DR, Caffarra et al., 2002a) and Rey Auditory Verbal Learning Test – Delayed Recall (RAVLT-DR, Carlesimo et al.,

1995) as measures of visual and verbal episodic memory, respectively; Ekman 60-Faces Test (EK-60F, Dodich et al., 2014) as a measure of social cognition; Stroop Color-Word Test time and error scores (SCWT-E and SCWT-T, Caffarra et al., 2002b) and Phonemic Verbal Fluency Test (PVFT, Costa et al., 2014) as a measures of executive functions; Semantic Verbal Fluency Test (SVFT, Costa et al., 2014), Action Verb picture Naming (AVN, Papagno et al., 2020), and Object picture Naming (ON, Catricalà et al., 2013) as measures of language; and Line Orientation Judgment (LOJ, Ferracuti et al., 2000) as a measure of visuo-spatial abilities. Indeed, these are the cognitive domains that are recommended in assessing potential neuropsychological deficits in PD (Dubois et al., 2007).

2.1.3 Depression and anxiety assessment

Depression and anxiety were assessed with the Geriatric Depression Scale (GDS, Massai et al., 2018) and the Parkinson Anxiety Scale (PAS, Santangelo et al., 2016), respectively. Of note, GDS and PAS were available only for a subset of patients (46/65) as some patients did not complete the assessment for time restrictions.

2.2 Statistical analyses

LPA was executed using "mclust" package (version 5.4.5, Scrucca et al., 2016) in R statistical software. This package performs model-based clustering, classification, and density estimation, based on finite normal mixture modelling. Expectation-maximization (EM) algorithm was used for maximum likelihood estimation and initialization was performed using results from hierarchical clustering. Bayesian Information Criteria (BIC) and Integrated Completed Likelihood (ICL) were used for model fitting, then Bootstrap Likelihood Ratio Test (BLRT) was performed to compare model fit between k-1 and k cluster models (Nylund et al., 2007). Eleven variables were introduced in the analysis corresponding to the standardized variables of corrected scores on the neuropsychological tests mentioned above. The PD groups resulting from LPA were then compared

for neuropsychological tests, demographics, and clinical data by means of between-groups univariate ANOVA.

3. Results

3.1 Latent profile analysis

Figure 1 represents boxplots with the distribution of the eleven cognitive variables in the sample. The three best models, resulting from BIC and ICL model fitting and their estimated likelihood, are reported in Table 1. BLRT for VVI model also suggested that the solutions with 3 clusters significantly outperformed other solutions (1 vs 2 clusters LRTS bootstrap = 337.43, p = .001; 2 vs 3 clusters LRTS bootstrap = 96.23, p = .001; 3 vs 4 LRTS bootstrap = 33.57, p = .71).

To control for the stability of our LPA results, we also performed K-means cluster analysis. Overall, the results of the two methods were similar. Furthermore, K-means cluster analysis also resulted in a three clusters solution. The profiles of the three clusters were similar and only 6 out 65 patients were classified differently with the two clustering methods (see table S1 and figures S1-S2 in online supplemental material).

[insert Figure 1 about here]

[insert Table 1 about here]

Cluster profiles are depicted in Figure 2 and descriptive statistics for the 11 variables included in the LPA are reported in Table 2.

- Cluster A (n=14, 21.54%) included patients with relatively higher scores in most cognitive tasks. Specifically, patients in Cluster A performed significantly better than patients in Cluster B and C in tests of attention (AM), visual (ROCF-DR) and verbal (RAVLT-DR) long-term memory, executive functions (PVFT), social cognition (EK-60F), language (SVFT), and visuo-spatial abilities (LOJ). In other measures of language (ON and AVN) and executive functions (SCWT-E and SCWT-T), patients from cluster A performed better than patients included in Cluster C, whereas they did not significantly

differ from patients in Cluster B. Thus, patients in Cluster A performed significantly better than patients in Cluster C in all cognitive measures.

- Cluster B (n=35, 53.85%) included patients with overall intermediate scores in most cognitive tests. Patients in this cluster did not significantly differ from patients in Cluster A in measures of executive functions (SCWT-E and SCWT-T) and language (ON and AVN), but showed greater impairment (as patients in Cluster C) in measures of attention (AM), episodic memory (ROCF-DR and RAVLT-DR), social cognition (EK-60F), and in other measures of language (SVFT) and executive functions (PVFT).
- Cluster C (n=16, 24.61%) included patients with the lower scores in cognitive tasks. Patients in Cluster C showed greater cognitive impairment than patients from Cluster A in all cognitive measures. Moreover, they performed significantly worse than patients from Cluster B in measures of language (ON and AVN), visuo-spatial abilities (LOJ), and executive functions (SCWT-E and SCWR-T).

[insert Figure 2 about here]

[insert Table 2 about here]

A contour plot of estimated mixture densities and uncertainty boundaries on the projection estimated subspace are depicted in Figure 3; these show that the clusters are well divided, with few patients falling in the uncertainty boundaries. Grubbs test for outliers was performed for each cognitive variable. When the whole sample was considered, 18 scores were classified as outliers, whereas only 6 scores resulted as outliers when the test was performed within the three clusters. This suggests that disproportional impairment in specific functions could be related to a different cognitive profile of PD.

[insert Figure 3 about here]

Table 3 reports the proportion of patients, for each of the three clusters and for each neuropsychological test, with a pathological score, according to published Italian normative data. Overall, 21.43% of patients from Cluster A, 71.43% of patients from Cluster B, and 100% of patients from Cluster C showed at least one pathological or borderline score (Equivalent score ≤1; see Capitani, 1997 for an extensive explanation) in the tests considered. Specifically, patients from Cluster A performed within normal limits on the majority of cognitive measures, with only sporadic (7.14%) impaired scores in visual memory (ROCF-DR) or executive functioning (SCWT-E and SCWT-T). For Cluster B, only the naming tests (ON and AVN) were not impaired in any patients; whereas for Cluster C, all tests were impaired in some patients with a prevalence ranging from 12.5% on AM to 93.75% on LOJ.

[insert Table 3 about here]

3.2 Differences on demographic and clinical variables.

Demographic and clinical characteristics of the three groups are reported in Table 4. There were no significant group differences in age and proportion of males and females; however, patients in Cluster B had received more years of formal education than patients from Cluster C. The three clusters did not significantly differ in disease duration, LEDD, and motor symptoms. However, patients from Cluster C had significantly lower ratings of ADL and IADL functioning than patients from Cluster A. The three clusters showed significantly different scores in the Montreal Cognitive Assessment (MoCA). No statistically significant differences emerged on anxiety or depression measures. Spearman's correlation analysis, performed in the whole sample, confirmed the lack of correlation between disease duration or motor symptoms and any cognitive measure, with the exception of weak negative correlations between UPDRS and object naming (r_S = -0.249, p = .049) and between UPDRS and PVFT (r_S = -0.266, p = .035). Age showed weak negative correlations with the performance in

SVFT (r_S = -0.283, p = .022) and SCWT-E (r_S = 0.270, p = .030); education showed a weak positive correlation with LOJ (r_S = 0.338, p = .001).

Previous studies evidenced different cognitive impairment related to the side of onset of motor symptoms (Katzen et al., 2006). Although our analyses did not reveal different distribution of patients with left- or right-side onset in the three clusters, we compared scores of neuropsychological tests and clinical variables between patients with different side of motor symptoms onset. Results showed higher levels of LEDD [$t_{(60)}$ = -2.3, p = .025] and higher motor symptoms measured by UPDRS [$t_{(58)}$ = -2.88, p = .006] in patients with right-sided symptoms when compared to left-sided symptoms, whereas t-tests on the neuropsychological and psychiatric assessment were not significant (see Table S3 in online supplemental material).

[insert Table 4 about here]

4. Discussion

The aim of this study was to use a data-driven method to explore the expression of NCD in idiopathic PD. For this purpose, we performed a LPA on the performances of 65 PD patients assessed with a battery of neuropsychological tests. These tests account for the recommended cognitive domains to evaluate in PD (Dubois et al., 2007), to which we added social cognition, due to findings in a previous study of possible early impairment in this disease (see Mattavelli et al., 2020). We presented a qualitative description of three distinct cognitive phenotypes: Cluster A (21.54%) included patients with intact cognition, or with a relatively slight cognitive impairment in memory and executive functions (Stroop test), but whose performance was better than in the other two groups in attention, long-term memory (both visual and verbal), executive functioning (Phonemic Verbal Fluency), social cognition, language, and visuo-spatial abilities; Cluster B (53.85%) included patients with an intermediate level of cognitive impairment and significantly lower scores than Cluster A in attention, episodic memory, social cognition, and verbal fluency, but non-significant different performances

from Cluster A in executive functions and naming; and Cluster C (24.61%) included patients with the most severe cognitive deficits, with impaired performance compared to Cluster A in all tests, and greater deficits compared to Cluster B in executive function and, notably, in tasks with a predominantly posterior cortical basis (naming and visuo-spatial abilities). In view of the dual syndrome hypothesis (Kehagia et al., 2013), we could speculate that Cluster A and Cluster B could reflect different degrees of cognitive symptoms associated with dopaminergic loss across the basal ganglia circuitry, and Cluster C could reflect cognitive symptoms associated with cortical degeneration and cholinergic loss. An alternative hypothesis is that Cluster B could reflect symptoms associated with dopaminergic loss and initial posterior cortical degeneration. Unfortunately, one limitation of our study is that neuroimaging confirmation and data on recognition memory to clarify whether the verbal and visual long-term memory dysfunction profile of patients belonging to Cluster B was a primary retrieval (and therefore attributable to frontal-executive dysfunction) or a primary encoding deficit (and therefore attributable to mesial temporal cortical degeneration) was not available. Comparisons of clinical and demographical variables across the three clusters revealed differences in the global cognitive functioning as measured by the MoCA (with a higher score for Cluster A than Cluster B and for Cluster B than Cluster C) and ADL-IADL functioning (with Cluster C reaching lower scores than Cluster A). Patients from Cluster B had received more years of formal education than patients from Cluster C, but the possibility that education affected group differences on neuropsychological scores is unlikely as all scores were adjusted for age, education, and, when indicated, gender according to normative Italian data. No other statistically significant between-groups differences emerged in demographic or clinical measures. Specifically, there was no difference in the three groups regarding age, motor impairment severity, LEDD, and level of anxiety and depression. In particular, the three clusters were not significantly different for disease duration (i.e., months from onset), ruling out the hypothesis that the three clusters could represent different stages of the disease. Moreover, we found no significant relationship between group membership and gender or motor symptoms subtype (akinetic-rigid vs tremor-dominant), or side of onset. Our data

are in line with previous studies that found that cognitive phenotype did not correlate with age (McKinlay et al., 2009; Brennan et al., 2017), gender (Dujardin et al., 2013), disease duration (McKinlay et al., 2009; Brennan et al., 2017; Alonso-Recio et al., 2018), LEDD (Brennan et al., 2017), depression (McKinlay et al., 2009; Brennan et al., 2017; Alonso-Recio et al., 2018), and motor impairment severity (McKinlay et al., 2009; Alonso-Recio et al., 2018). Furthermore, we found between-groups differences in measures of everyday functioning for basic and instrumental activities of daily living. Thus, our data suggest that the cognitive profile is related to daily functioning, but not to stage of disease and motor functioning. In contrast with our results, Brennan et al. (2017) found a significant association of group membership and motor symptoms subtype. However, as discussed in the introduction, major differences in inclusion-exclusion criteria, cognitive domains assessed, and neuropsychological tests adopted make results difficult to compare and account for the large variability among different studies.

Notably, patients with right-side onset had higher UPDRS score and LEDD than left-side onset patients, in line with previous evidence regarding the influence of the side of motor symptom onset in PD (Katzen et al., 2006). However, patients with right- and left-side onset symptoms did not differ in cognitive and psychiatric measures, and the three clusters did not show a different proportion of patients with right- or left-side onset.

The current study has some limitations that must be addressed. First, the small sample size reduces the statistical validity of the analysis; however, we performed K-means cluster analysis to confirm the stability of our LPA model. Indeed, the results of the two analyses are analogous in terms of cluster number and neuropsychological features and are similar in terms of patients' distribution across clusters. However, insufficient sample size did not allow for testing of the absolute stability of the model (e.g., with dataset split), thus, larger cohort studies would be needed to confirm the present findings. Secondly, GDS and PAS were available only for a subset of patients, which limits the interpretation of the absence of inter-cluster differences regarding anxiety and depression. Finally, the lack of data regarding premorbid IQ and cognitive reserve did not allow exclusion of the potential

influence of variables on the clustering. Specifically, since patients from Cluster C received less years of education than patients from Cluster B, less cognitive reserve or lower premorbid IQ could partially explain the presence of a more severe cognitive impairment, even in the absence of differences regarding age or disease durations (see Hindle et al., 2014 for a review). This is still a matter of debate as some previous studies found between-cluster differences for education and cognitive reserve (e.g., Dujardin et al., 2013; Alonso-Recio et al., 2018), and some did not (e.g., McKinlay et al., 2009; Brennan et al., 2017).

In summary, this study adds new evidence to the critical issue of cognitive impairments related to PD and to the definition of which tests are required to define these impairments. A better understanding of the different cognitive phenotypes characterizing PD is relevant to identifying the underlaying pathophysiological mechanism and could inform tailored pharmacological and non-pharmacological intervention. A follow up assessment could inform about different risk of progression to dementia for different subgroups of patients. Our data support the presence of heterogeneity in the clinical presentation of NCD in PD that seems independent from stage of the disease, motor functioning, anxiety, and depression, and that influences functioning in everyday life. These results highlight the importance of performing extensive neuropsychological assessment in these patients to identify strengths and weaknesses of cognitive profiles, which could represent markers for different outcomes of the disease.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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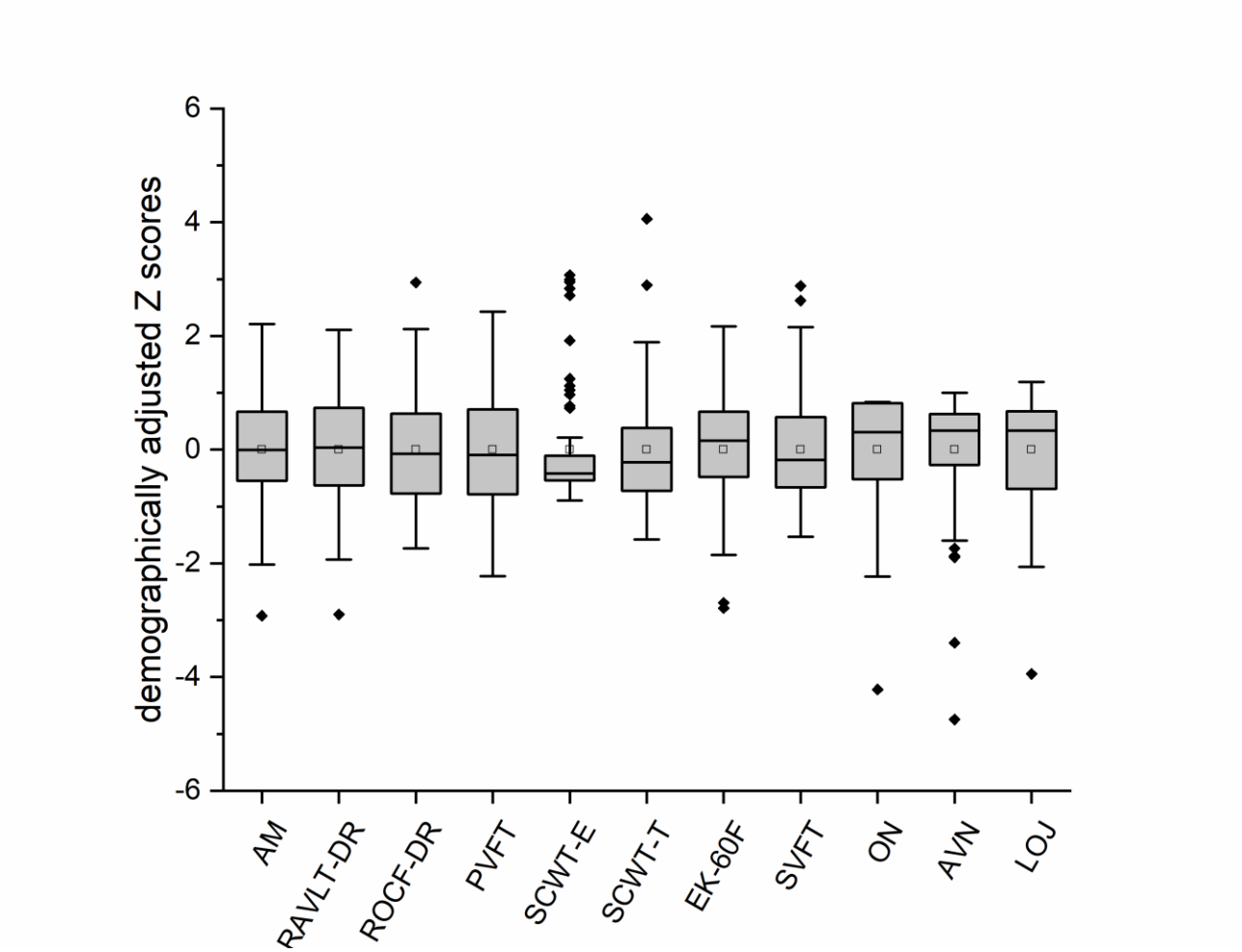

Figure 1. Boxplots of demographically adjusted Z scores of 65 PD patients at neuropsychological tests included as variables in the LPA.

Line inside the boxes = median; empty squared = mean; solid diamonds = potential outliers; boxes = distribution of scores between the first and third quartile; T-bars = range within 1.5 Interquartile range. Abbreviations: AM = Attentional Matrices; RAVLT-DR = Rey Auditory verbal Learning Test – Delayed Recall; ROCF-DR = Rey-Osterrieth Complex Figure – Delayed Recall; PVFT = Phonemic Verbal Fluency Test; SCWT-E = Stroop Color Word Test – Errors; SCWT-T = Stroop Color Word Test – Time; EK-60F = Ekman 60 Faces Test; SVFT = Semantic Verbal Fluency Test; ON = Object pictures Naming; AVN = Action Verb pictures Naming; LOJ = Line Orientation Judgment.

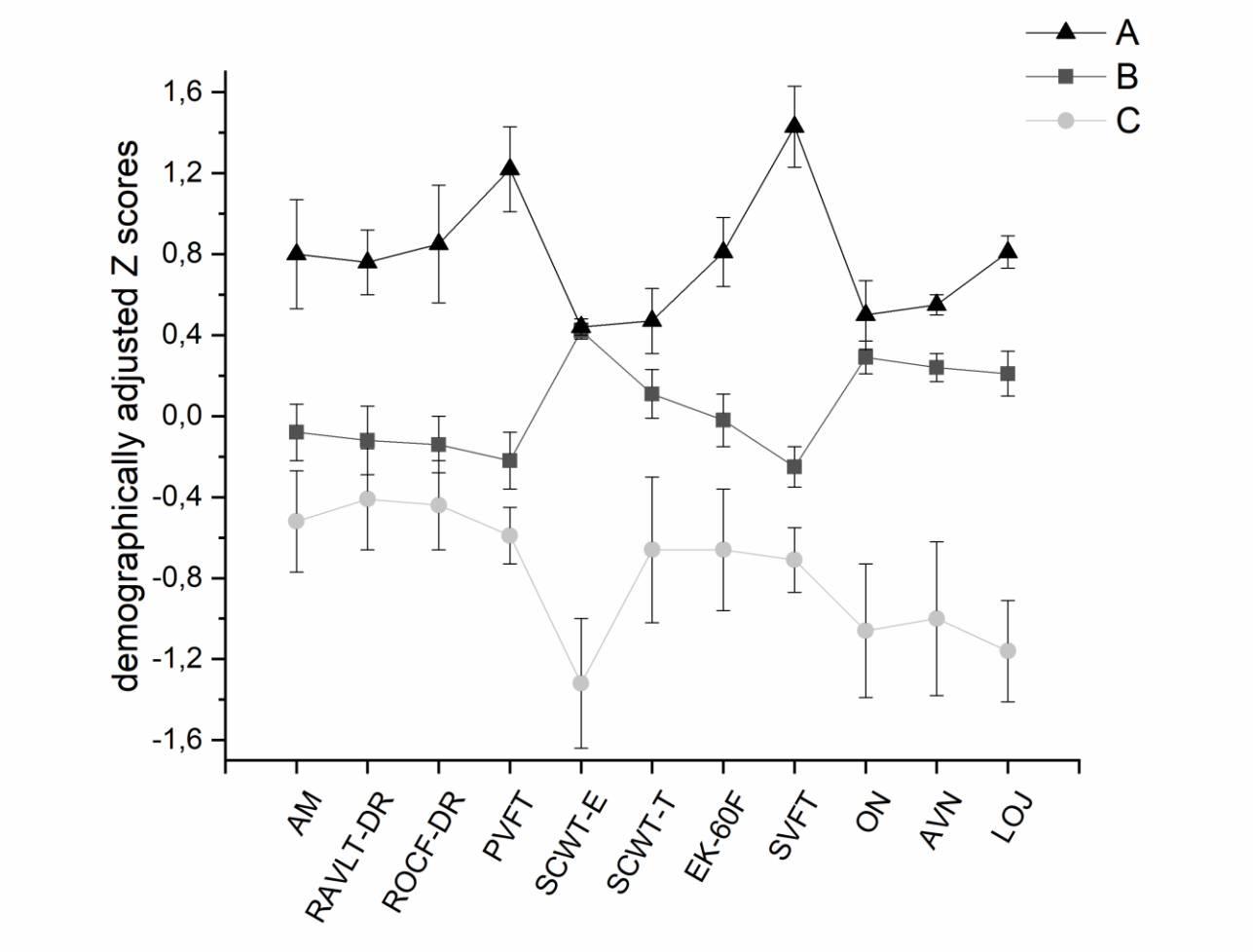

Figure 2. Latent class cluster profile scores on neuropsychological tests.

Bars represent standard errors of the means. Abbreviations: AM = Attentional Matrices; RAVLT-DR = Rey Auditory verbal Learning Test – Delayed Recall; ROCF-DR = Rey-Osterrieth Complex Figure – Delayed Recall; PVFT = Phonemic Verbal Fluency Test; SCWT-E = Stroop Color Word Test – Errors; SCWT-T = Stroop Color Word Test – Time; EK-60F = Ekman 60 Faces Test; SVFT = Semantic Verbal Fluency Test; ON = Object pictures Naming; AVN = Action Verb pictures Naming; LOJ = Line Orientation Judgment.

Note: Scores for Error and Time of Stroop Color Word test were inverted for graphical purpose (i.e. lower values indicate worse performance).

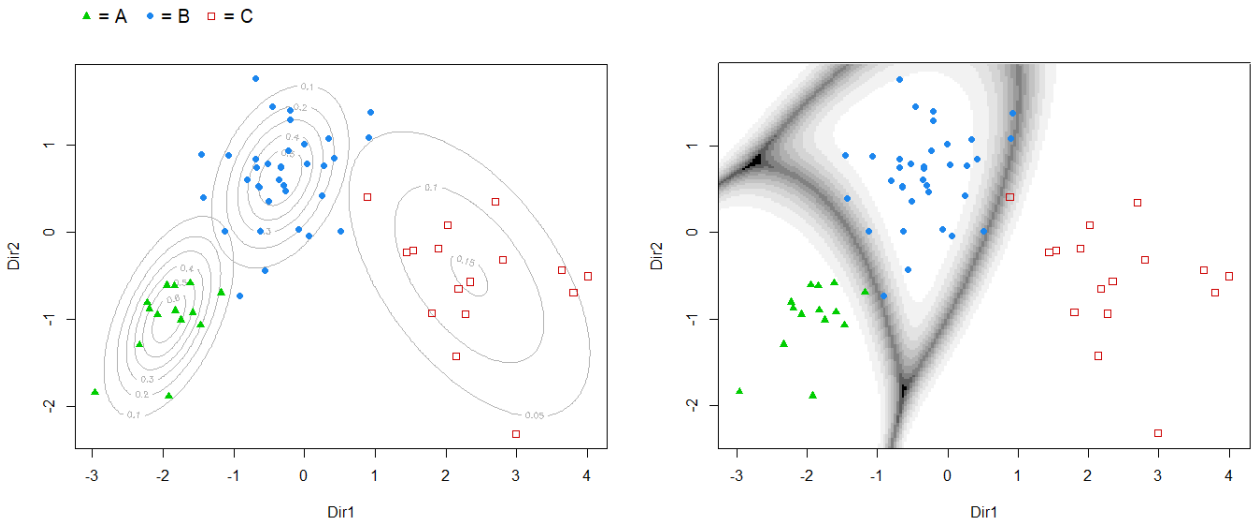

Figure 3. Contour plot of estimated mixture densities (left) and uncertainty boundaries (right) on the estimated projection in a two-dimensional space.

Table 1

Results of best BIC and ICL values for LPA

	VVI,3	VVI,2	VEI,3
BIC	-1868.196	-1868.417	-1907.440
BIC diff	0.000	-0.221	-39.245
ICL	-1871.591	-1871.832	-1910.313
ICL diff	0.000	-0.242	-38.722
log-likelihood	-792.169	-840.285	-853.535

Abbreviations: VVI,3 = diagonal, varying volume and shape model with 3 components; VVI,2 = diagonal, varying volume and shape model with 2 components; VEI,3 = (diagonal, equal shape) model with 3 components; BIC = Bayesian Information Criteria; ICL = Integrated Completed Likelihood.

Table 2

Descriptive statistics and between-groups comparisons for the 11 variables included in the latent profile analysis.

	Cluster A ***n* = 14**		**Cluster B** ***n* = 35**		**Cluster C** ***n* = 16**		***Between-groups comparisons***	
	Mea	***SD***	**Mean**	***SD***	**Mean**	***SD***	***p* ANOVA**	***post hoc***
Attention assessment								
Attentional Matrices (0-60)	53.55	7.78	46.62	6.31	43.23	7.83	$F_{(2, 62)} = 8.383$, $p < .01$	A > B, C
Memory assessment								
RAVLT – Delayed Recall (0-15)	10.98	1.84	8.35	2.96	7.45	2.95	$F_{(2, 62)} = 6.675$, $p < .01$	A > B, C
ROCF – Delayed Recall (0-36)	20.76	6.13	15.12	4.76	13.39	4.92	$F_{(2, 62)} = 8.644$, $p < .001$	A > B, C
Executive functioning assessment								
Phonemic Verbal Fluency Test	50.81	9.83	32.92	10.33	28.31	7.08	$F_{(2, 62)} = 23.878$, $p < .001$	A > B, C
Stroop Color-Word Test – Errors score	0.61	1.06	0.73	1.52	11.70	8.11	$F_{(2, 62)} = 41.919$, $p < .001$	A, B < C
Stroop Color-Word Test – Time score	16.28	10.12	22.38	12.00	35.41	24.65	$F_{(2, 62)} = 6.067$, $p < .01$	A, B < C
Social cognition assessment								
Ekman 60-Faces Test (0-60)	51.65	3.60	46.88	4.41	43.20	6.97	$F_{(2, 62)} = 10.628$, $p < .001$	A > B, C
Language assessment								
Semantic Verbal Fluency Test	58.61	8.63	39.75	6.59	34.51	7.21	$F_{(2, 62)} = 47.296$, $p < .001$	A > B, C
Object picture Naming (0-48)	47.31	1.42	46.83	1.10	43.85	2.89	$F_{(2, 62)} = 19.281$, $p < .001$	A, B > C
Action Verb picture Naming (0-50)	49.61	1.01	48.02	2.22	41.66	7.79	$F_{(2, 62)} = 14.296$, $p < .001$	A, B > C
Visuo-spatial abilities assessment								
Line Orientation Judgment (0-30)	27.79	1.76	24.26	3.94	16.25	5.84	$F_{(2, 62)} = 31.711$, $p < .001$	A > B > C

RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure.

Note. In the Stroop Color-Word Test higher (time and errors) scores indicate higher executive difficulties. Note. Bonferroni correction was applied to account for multiple comparisons.

Table 3

Proportion of patients with impaired scores for each neuropsychological measure in the three cluster.

Neuropsychological measure	Adjusted scores' cut-off	Cluster A *n* = 14		Cluster B *n* = 35		Cluster C *n* = 16	
		N	%	n	%	n	%
Attentional Matrices (0-60)	< 31 (Spinnler e Tognoni, 1987)	0	0%	4	11.43%	2	12.5%
RAVLT – Delayed Recall (0-15)	< 4.69 (Carlesimo et al., 1995)	0	0%	4	11.43%	5	31.25%
ROCF – Delayed Recall (0-36)	< 9.47 (Caffarra et al., 2002)	1	7.14%	8	22.86%	6	37.50%
Phonemic Verbal Fluency Test	< 17.35 (Costa et al., 2014)	0	0%	4	11.43%	3	18.75%
Stroop Color-Word Test – Errors score	≥ 4.24 (Caffarra et al., 2002b)	1	7.14%	4	11.43%	12	75%
Stroop Color-Word Test – Time score	≥ 36.92 (Caffarra et al., 2002b)	1	7.14%	6	17.14%	8	50%
Ekman 60-Faces Test (0-60)	< 37.46 (Dodich et al., 2014)	0	0%	3	8.57%	7	43.75%
Semantic Verbal Fluency Test	<23.59 (Costa et al., 2014)	0	0%	2	5.71%	5	31.25%
Object picture Naming (0-48)	≤ 41.48 (Catricalà et al., 2013)	0	0%	0	0%	6	37.5 %
Action Verb picture Naming (0-50)	≤ 36.86 (Papagno et al., 2020)	0	0%	0	0%	6	37.5 %
Line Orientation Judgment (0-30)	< 19 (Ferracuti et al., 2000)	0	0%	9	25.71	15	93.75%

RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure.

Note. Data refers to pathological (Equivalent score, ES = 0) or borderline (ES = 1) scores for each test according its published normative data and respective cut-off. ES correspond to a five-point interval scale from 0 to 4 defined on the basis of demographical adjusted scores and non-parametric tolerance limits (Capitani, 1997). An ES = 0 corresponds to performances below the fifth centile of the normal population, whereas an ES = 1 is between the outer and inner tolerance limits.

Table 4

Clusters' demographic and clinical features.

	Cluster A *n* = 14		Cluster B *n* = 35		Cluster C *n* = 16		*Between-groups comparisons*	
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	***p* ANOVA/Chi-Square**	***post hoc***
Demographic features								
Age (years)	64.93	6.02	67.71	6.13	71.06	10.18	$F_{(2, 62)} = 2.671$, $p = .077$	
Educational level (years)	11.64	5.85	11.63	4.48	8.06	3.57	$F_{(2, 62)} = 3.615$, $p < .05$	B > C
Gender (m/f)	8/6		24/11		10/6		$X^2_{(2)} = 0.613$, $p = .736$	
Clinical features								
Disease duration (months)	84.00	62.62	89.89	66.38	89.25	59.59	$F_{(2, 62)} = 0.044$, $p = .957$	
LEDD (mg)	796.62	529.81	800.71	408.49	600.72	343.47	$F_{(2, 62)} = 1.333$, $p = .271$	
H&Y	2.11	0.63	2.20	0.69	2.44	0.70	$F_{(2, 62)} = 0.987$, $p = .379$	
UPDRS	13.07	7.61	18.37	9.37	21.00	9.58	$F_{(2, 62)} = 2.846$, $p = .066$	
Initial motor symptom profile (AR/TD)	7/7		19/16		11/5		$X^2_{(2)} = 1.286$, $p = .526$	
Side of onset (LO/RO)	5/9		20/13		7/8		$X^2_{(2)} = 2.633$ $p = .268$	
ADL (0-6)	5.93	0.27	5.40	1.17	4.73	1.54	$F_{(2, 61)} = 5.236$, $p < .05$	A > C
IADL (0-8)	6.93	1.49	6.11	1.74	5.13	2.03	$F_{(2, 61)} = 3.776$, $p < .05$	A > C
MoCA (0-30)	24.60	1.89	21.99	2.92	18.67	3.64	$F_{(2, 62)} = 15.521$, $p < .001$	A > B > C
Psychiatric features								
GDS (0-30)	8.73	7.29	7.79	5.92	11.25	4.30	$F_{(2, 43)} = 0.912$, $p = .409$	
PAS (0-48)	13.55	8.513	13.85	8.29	17.13	5.74	$F_{(2, 43)} = 0.592$, $p = .558$	

LEDD = Levodopa equivalent daily dose; H&Y = Hoehn and Yahr scale; UPDRS = Unified Parkinson's Disease Rating Scale; AR = Akinetic-rigid; TD = Tremor dominant; LO = left onset; RO = right onset; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MoCA = Montreal Cognitive Assessment; GDS = Geriatric Depression Scale; PAS = Parkinson Anxiety Scale.

Note. Post hoc with Bonferroni correction for multiple comparisons are presented for statistically significant univariate ANOVAs.