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Neuropsychological subgroups in non-demented Parkinson's disease: A latent class analysis

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Abstract

Background—Methods to detect early cognitive decline and account for heterogeneity of deficits in Parkinson's disease (PD) are needed. Quantitative methods such as latent class analysis (LCA) offer an objective approach to delineate discrete phenotypes of impairment.

Objective—To identify discrete neurocognitive phenotypes in PD patients without dementia.

Methods—LCA was applied to a battery of 8 neuropsychological measures to identify cognitive subtypes in a cohort of 199 non-demented PD patients. Two measures were analyzed from each of four neurocognitive domains: executive functioning, memory, visuospatial abilities, and language. Additional analyses examined between-groups differences in demographic and clinical characteristics (Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory

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[ADCS-ADL]; UPDRS-III; PD subtype (i.e., tremor-dominant (TD) versus postural instability/gait disturbance-dominant(PIGD)); and cognitive diagnosis (i.e., intact cognition versus mild cognitive impairment; MCI).

Results—LCA identified 3 distinct groups of PD patients: an *intact* cognition group (n=109; 54.8%), an *amnestic* group (n=64[32.1%]; impaired recall and recognition on verbal memory tasks, but intact performance on other measures) and a *mixed impairment* group with dysexecutive, visuospatial and lexical retrieval deficits (n=26 [13.1%]; relative deficits on measures of verbal fluency, visuospatial abilities, and delayed free recall on a memory task, but intact recognition memory). The amnestic and mixed impairment groups had significantly lower ratings of IADL functioning and greater motor symptoms than the cognitively intact group. Additionally, patients with PIGD vs. TD PD subtype were more likely to be classified in either cognitively impaired group. Of those diagnosed as cognitively normal according to MDS criteria (n=151), LCA classified 35 patients as amnestic (23.2%), and 15 as mixed impairment (9.9%).

Conclusions—Non-demented PD patients exhibit distinct neuropsychological profiles. One-third of patients with LCA-determined impairment were diagnosed as cognitively intact by expert consensus, indicating that classification using a statistical algorithm may assist in detection of early and subtle cognitive decline. This study also demonstrates that memory impairment is common in non-demented PD even when cognitive impairment is not clinically apparent. This study has implications for earlier detection of cognitive difficulties in PD, predicting eventual emergence of significant cognitive decline, and treatment trials for cognitive dysfunction in PD.

Keywords

Parkinson's disease; cognition; latent class analysis; neuropsychology

Introduction

Cognitive impairment is common even in early Parkinson's disease (PD),[1] impacts daily function,[2] increases risk of developing PD dementia (PDD), increases mortality,[3] and contributes to caregiver burden.[4] Up to one-third of PD patients exhibit cognitive deficits in the early stages of the disease[5], and deficits in varied cognitive domains have been demonstrated even in drug-naïve PD patients.[6] A recent longitudinal cohort study[7] found that roughly half of a sample of 141 patients with established PD and normal cognition at baseline assessment developed cognitive impairment within 6 years, and incident cases of PD mild cognitive impairment (PD-MCI) universally converted to dementia within 5 years. Early detection of cognitive deficits in PD is necessary to optimize intervention, and due to heterogeneity of clinical presentations and underlying neural substrates, novel methods to aid early detection are needed.

Although cognitive dysfunction in non-demented PD is commonly viewed as a primarily dysexecutive syndrome, there is significant heterogeneity, with impairments in memory, visuospatial processes, and language also frequently observed.[8]–[14] Deficits in these domains have been demonstrated in PD patients deemed “cognitively normal” from a clinical diagnostic perspective as well as those who meet criteria for PD-MCI. Heterogeneity in cognitive presentations is also reflected in biomarker[15]–[21] and neuropathological

investigations[22], [23] in nondemented PD, which have revealed associations between cognitive impairments and diverse clinical and neuropathological biomarkers. Notably, these findings suggest comorbid disease processes, including both Lewy body and Alzheimer's disease pathology, in subgroups of PD patients.

The heterogeneity seen in cognitive, biomarker, and neuropathological investigations suggests the presence of shared or divergent neurodegenerative processes. Extant literature suggests that PD patients with primarily executive functioning deficits may be more likely to remain stable over time, while those with isolated or accompanying memory, language, or visuospatial deficits, more indicative of posterior dysfunction, may be at greater risk for future cognitive decline and dementia.[24], [25] Further understanding of cognitive heterogeneity early in the disease process has important implications regarding our ability to predict progression and better inform potential therapeutic targets. Utilizing statistical algorithms to examine neuropsychological test performance in non-demented PD patients has the potential to identify individuals at risk for decline before overt impairments are clinically apparent.

Cluster analysis and related statistical approaches have been utilized to examine heterogeneity regarding numerous clinical variables in PD, including cognition.[26]–[29] In addition to cluster analysis structural equation modeling methods, such as latent class analysis (LCA), have proven useful in detection of underlying homogenous groups. Like cluster analysis, LCA aims to classify individuals based on shared characteristics and to identify qualitatively different subgroups. The aim of the present study was to use LCA to further understanding of neuropsychological heterogeneity in non-demented PD. This is of particular importance for clinical trials, as drug development for cognitive decline has begun to emphasize intervention in preclinical stages.[30] Further, group differences were examined among LCA-derived classes to further characterize and validate the cognitive subgroups. Finally, LCA class differences in clinical cognitive diagnosis by expert consensus (i.e., intact versus PD-MCI) were assessed.

Methods

Participants

PD patients aged 50 or older were recruited from the University of Pennsylvania Udall Center of Excellence in Parkinson's Disease Research. PD patients with a consensus diagnosis of dementia were excluded from these analyses. The University of Pennsylvania Institutional Review Board approved the study, and informed consent was obtained from all participants.

Neuropsychological Assessment

All PD participants were administered a comprehensive neuropsychological battery by trained research staff. Global cognition was assessed with the Dementia Rating Scale-2 (DRS-2)[31] and the Montreal Cognitive Assessment (MoCA).[32] Eight core parameters from the neuropsychological battery were analyzed to derive statistically-determined cognitive subgroups. LCA was performed using 2 representative measures from each of 4

cognitive domains: 1) executive functioning (Letter-Number Sequencing[33], phonemic verbal fluency); 2) language (Boston Naming Test[34], semantic verbal fluency); and 3) verbal memory (Hopkins Verbal Learning Test-Revised (HVLT-R)[35] delayed free recall and recognition discriminability scores); 4) visuospatial (Judgement of Line Orientation[36], Clock Drawing command condition[37]). All assessments were performed in the PD medication “on” state.

Motor and Psychiatric Assessments

The Unified Parkinson's Disease Rating Scale (UPDRS) Part III[38] and Hoehn and Yahr staging[39] were performed by trained research staff to assess motor impairment and disease severity. Motor assessments were performed while participants were taking their regular regimen of PD medications. Subtype of motor impairment was also coded, i.e., tremor dominant (TD) versus postural-instability gait disturbance dominant (PIGD) for a subset of patients (91%). Subtype was determined based on Jankovic et al., and 12 subjects had an indeterminate subtype according to these criteria.[40] Levodopa equivalent daily dose (LEDD) was also recorded for each participant. Depression was assessed using the Geriatric Depression Scale-15 (GDS-15).[41]

Activities of Daily Living

A subset of patients (75%) had data regarding everyday functioning assessing basic and instrumental activities of daily living (IADLS) with the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL).[42] A knowledgeable informant (defined as a spouse, child, close relative, or friend seeing the patient a minimum of once per week) completed the ADCS-ADL for PD participants. The ADCS-ADL contains 23 items, with items 1-6 assessing basic ADLs and 7-17 assessing IADLs.

Cognitive Diagnosis

Assessment of cognitive status involved a consensus process performed by neurologists and psychiatrists with expertise in movement disorders and PD cognition at the University of Pennsylvania Udall Center, as previously described.[7] Multiple pairs of raters examined demographic and clinical data to reach a consensus cognitive diagnosis for each PD participant, based on Movement Disorders Society (MDS) level 1 criteria[43] (i.e., intact cognition versus MCI), using published demographically-corrected normative data for each neuropsychological assessment. For each neuropsychological test, standardized scores greater than or equal to 1.5 SD below the mean was deemed impaired, although discretion among raters was allowed.

Statistical Analyses

LCA—LCA was conducted in Mplus Version 7.1[44] using demographically-corrected normative scores obtained from the eight core neuropsychological variables. First, a one-class model was fit to the data. The number of classes was then increased one at a time until there was no additional model improvement.[45] The best-fitting model was selected based on a preponderance of evidence both quantitative (e.g., model fit statistics, class sizes) and qualitative (e.g., parsimoniousness, theoretical and clinical interpretability).[46]

Quantitative indicators of model fit included the following: Goodness-of-fit statistics included the *Akaike Information Criterion (AIC)*[47] and *Bayesian Information Criterion (BIC)*[48]; smaller values indicate better fit. The *Vuong-Lo-Mendel-Rubin (VLMR)*[49] likelihood ratio test was used to compare the model with *k* classes to the model with *k*-1 classes; a significant test indicates that the model with *k* classes better fits the data than the model with *k*-1 classes. *Posterior probabilities* (i.e., estimates of class probabilities for each individual) and *entropy*, both indices of classification quality [50], were also used to identify the best-fitting model; higher entropy values indicate better fit, with entropy values ≥.8 indicating adequate fit. Finally, *class size* was used as an indicator of model fit, as classes comprised of <10% of the total sample suggest possible over-fitting.

Class comparisons—Patients were assigned to groups based on their LCA-derived highest posterior probabilities. Differences among LCA-derived groups in demographics, global cognitive status, and clinical variables were assessed using ANOVA for continuous variables (age, years of education, Hoehn & Yahr, UPDRS-III, LEDD, GDS-15, DRS-2, and ADCS-ADL IADL Subscale) and Pearson's χ^2 test for categorical variables (sex and PD subtype, i.e., TD versus PIGD). When omnibus findings were significant, follow-up tests were performed using Tukey's t-tests for continuous variables or partitioned χ^2 test for categorical variables. Finally, LCA-derived classifications were compared with consensus cognitive diagnoses (i.e., intact cognition or MCI) based on Movement Disorders Society (MDS) criteria[43] using cross-tabulation, Pearson's χ^2 test, and Cohen's kappa.

Results

Cohort Characteristics

Demographics and clinical characteristics of the full sample (n=199) are presented in Table 1.

The sample was 66.8% male. Participants average age was 70.57 years old (SD=7.47) with a mean of 16.24 (SD=2.34 years of education, average disease duration of 6.85 years (SD=5.21), and average DRS-2 total score of 136.76 (SD=5.57).

Latent Class Analysis

The results of the LCA are found in Table 2. Several statistical fit indices supported the three-class model. The three-class model yielded the optimal values of entropy and BIC. AIC improved substantially through the three-class model but only minimally beyond the three-class model. The VLMR test indicated that the two-class model conferred a significant improvement in model fit over the one-class solution ($p < .01$), whereas the improvement in model fit conferred by the three-class model did not reach statistical significance ($p = .13$). Nonetheless, inspection of the two-class model suggested that one of the two classes exhibited a heterogeneous neuropsychological profile that was better differentiated by the three-class model. In addition, the smallest class yielded by the three-class model comprised 13% of the sample, which is within acceptable limits (i.e., ≥10% of the entire sample). Thus, we interpreted the three-class model as best.

Demographics and clinical characteristics for each of the three classes as determined by LCA are presented in Supplementary Table 1. Means and standard deviations of the eight core neuropsychological parameters for the three classes as determined by LCA are presented in Figure 1. These data provide evidence for an *amnestic* class (n = 64; 32%) with impairments on both HVLT-R free recall and recognition memory, but performance within the normal range across other measures; a *mixed impairment* class with lexical retrieval and visuospatial deficits (n = 26; 13%), reflected by impaired verbal fluency performance (semantic fluency more impaired than phonemic fluency), diminished HVLT-R recall but intact HVLT recognition, and visuoconstruction difficulties on the Clock Drawing task; and a *cognitively intact* class (n = 109; 55%) with no impairments across all eight core neuropsychological measures.

Between-Group Differences on Demographic and Clinical Variables

There were no group differences in age, education, or depression severity. There was a significant relationship between group membership and sex, $\chi^2(2) = 6.30$, $p < 0.05$. The overall sample was 67% male and 33% female. The greatest proportion of males was observed in the amnestic group (78%), followed by the mixed impairment (69%) and intact groups (60%). Follow-up tests revealed a significant difference in sex between the amnestic and intact groups ($p = 0.01$), whereas differences between the mixed impairment group and each of the other groups did not reach statistical significance.

Disease duration was significantly different among the groups, $F(2,196) = 3.63$, $p = 0.02$, with the mixed group having significantly longer disease duration than the intact group ($p = 0.02$). Disease duration did not significantly differ between the amnestic and intact or amnestic and mixed groups. Group differences in disease severity as measured by the Hoehn & Yahr were significant $F(2,192) = 7.47$, $p = 0.001$. The amnestic group ($p < 0.01$) and mixed impairment group ($p = 0.03$) exhibited greater disease severity than the intact group. Significant group differences were also revealed with regard to UPDRS-III motor symptom severity, $F(2,193) = 4.25$, $p = 0.02$. The amnestic group exhibited significantly greater motor symptoms than the intact group ($p = 0.01$) and there was a trend for the mixed impairment group exhibiting greater motor symptoms ($p = 0.06$). There were no differences between the amnestic and mixed impairment groups regarding Hoehn and Yahr or UPDRS-III scores. There were no group differences in LEDD.

Subtype of PD (i.e., TD versus PIGD) was significantly associated with group membership, $\chi^2(2) = 7.81$, $p = 0.02$, with the greatest proportion of PIGD observed in the mixed impairment group (88%), followed by the amnestic (66%) and intact groups (57%). Follow-up tests revealed a significant difference in subtype between the mixed impairment and intact groups ($p < 0.01$), and there was a trend regarding differences between the mixed impairment and amnestic groups ($p = 0.06$).

There were significant group differences regarding global cognition as assessed by the DRS-2 ($F(2,196) = 21.43$, $p < 0.001$). The amnestic and mixed impairment groups had lower total DRS-2 scores ($p < 0.001$) than the intact group. There were also significant group differences regarding the IADL subscale score of the ADCS-ADL ($F(2,144) = 6.40$, $p = 0.002$), in that the amnestic ($p = 0.03$) and mixed impairment groups ($p = 0.03$) exhibited

significantly more IADL impairment than the intact group, consistent with previous research.[51]

Classification Using Latent Class Analysis Versus Clinical Diagnosis

Table 3 compares clinical diagnoses (normal/intact cognition and PD-MCI using MDS consensus criteria) versus LCA-derived statistical classifications. Consensus clinical diagnosis of PD patients with normal cognition and PD-MCI was significantly associated with group membership, $\chi^2(2) = 37.17$, $p < 0.001$. When the two LCA-identified impaired groups were combined into a single LCA-impaired class for the purposes of assessing diagnostic agreement, Cohen's kappa indicated fair agreement between LCA and clinical diagnosis ($\kappa = 0.39$, SE = 0.06, 95% CI = 0.27 - 0.51). Agreement was present in 71% of the sample, with 101 patients classified as intact by both methods and 40 classified as impaired by both methods. A small number of patients (n = 8, 4% of the sample) were diagnosed with PD-MCI but were classified as intact by LCA.

Diagnostic disagreement was driven largely by patients who were classified as normal by consensus diagnosis but impaired by LCA. Of those PD patients diagnosed as “normal” according to consensus criteria (n = 151), 23% (n = 35) were classified as amnestic, and 10% (n = 15) were classified as mixed impairment in the present LCA. This indicates that one-third of the PD patients classified as normal/intact by clinical consensus criteria in this sample were statistically identified as having a distinct neuropsychological phenotype indicative of cognitive dysfunction using LCA.

Discussion

The present study reveals that person-centered statistical techniques such as LCA can identify distinct neuropsychological phenotypes even in clinical prediagnostic stages of cognitive decline in PD. One-third of patients in the two impaired LCA-derived groups were diagnosed as cognitively intact by expert consensus, indicating that classification using a statistical algorithm may assist in detection of early, subtle changes which may not lead to consensus diagnosis of PD-MCI. The two LCA-derived impairment groups had more severe motor symptoms and disease severity, lower ratings of IADL function, and were more likely to have PIGD- than TD-subtype PD.

Importantly, this study indicates that memory impairment is common even early in the course of PD when cognitive impairment is not clinically apparent to the treating physician. A larger proportion of the sample fell into the amnestic group (32%) than the mixed impairment group (13%). Research has suggested that executive-based deficits occur earlier in the disease course due to fronto-striatal dysfunction characteristic of PD, and memory deficits do not emerge until later in the disease course.[27] However, accumulating evidence suggests a subgroup of PD patients experience more posterior cortical dysfunction, which increases risk of dementia. In one longitudinal study examining predictors of dementia in PD, patients with deficits in measures of posterior cortical function were more predictive of dementia than measures of fronto-striatal function.[52] The presence of a primary amnestic group in the present study is in line with studies demonstrating Alzheimer's disease patterns of brain atrophy on structural imaging[19] and reduced cerebrospinal fluid levels of amyloid

β 1-42 in nondemented PD patients, both of which have been found to be predictors of cognitive decline at longitudinal follow-up.[18], [21]

The present findings support the presence of heterogeneity, which has been revealed in biomarker, neuropathological, and genetic investigations of cognition in PD. Imaging studies have revealed atrophy in frontostriatal regions and cholinergic structures such as the insular cortex and caudate nucleus[15], prefrontal cortical and hippocampal atrophy and caudate dopaminergic hypofunction[16], faster rates of cortical thinning[17] and greater amyloid burden[18] in PD patients with cognitive impairment. A structural imaging study found that an Alzheimer's disease pattern of brain atrophy (i.e., hippocampal and medial temporal lobe atrophy) predicted cognitive decline over a two-year period in non-demented PD patients.[19] Neuropathological studies of individuals with PD-MCI[22], [23] have revealed the presence of neocortical or limbic Lewy bodies, Alzheimer's disease pathology, and possible cerebrovascular disease. Studies examining genetic influences on cognition in PD have indicated that risk factors associated with the etiology of Alzheimer's disease confer additional risk for cognitive impairment and decline in a subset of PD patients, indicating more rapid decline and greater cognitive impairment in PD patients with the APOE ε4 allele.[53], [54] Studies examining other genes also reflect cognitive heterogeneity; the COMT genotype has been associated with performance on measures of frontostriatal and frontoparietal functioning[53], [55], GBA mutations linked to impaired executive and visuospatial functions[56], and MAPT H1/H1 genotype associated with impaired performance on measures of temporal lobe functioning[52], [53] and parietal functions [57], [58].

Importantly, LCA offers a number of advantages over cluster analysis, as it takes into account the uncertainty in allocating cases to groups, considers class size when assigning membership, and provides fit statistics for comparison of competing models.[59] Several studies have utilized LCA and a related approach, latent profile analysis (LPA), to examine subgroups of PD patients according to motor, psychiatric, or cognitive presentations.[60]–[65] Although two studies[64], [65] included examination of neuropsychological test performance, this was not the primary outcome variable of interest. This current study is the first to utilize LCA to examine cognition in PD as the primary outcome. In other studies examining cognition in patients without PD, (i.e., cognitively normal adults and dementia) person-centered statistical techniques such as LCA have also proven useful in detection of underlying homogenous groups.[66]–[68] The current study extends this methodology to non-demented PD patients.

Limitations of the current study include our inability to examine simple attention in addition to the four domains examined, a homogenous sample (primarily white and highly educated), and the absence of longitudinal follow-up data. Due to homogeneity of the sample, the present results need to be replicated in different PD cohorts. Follow-up studies on this cohort will examine the utility of LCA-derived groups in regards to risk and rate of progression to dementia, as well as associations with biomarkers. It is important to note that the mixed impairment group had significantly longer disease duration than the intact group, and both impairment groups had greater ratings of motor impairment than the intact group, raising the possibility that the presence of a group with intact cognition may reflect differences in

disease severity. Additionally, all measures were performed in the levodopa “on” state and results may differ if tested in the “off state” or in drug naïve patients. The use of these techniques requires validation in other PD cohorts as well as longitudinal studies to determine if they are useful in predicting future cognitive decline. LCA and related techniques examining longitudinal data can be implemented in other existing large cohorts of PD patients and in multi-center studies utilizing comprehensive neuropsychological test batteries. Validation in other PD cohorts using different neuropsychological assessments will also be informative, as the type of assessments used may impact results of the LCA. Finally, as we do not know the concordance between self-report of cognitive decline and cognitive assessment results, future research examining this relationship is warranted.

The use of a statistical algorithm offers a more objective approach to cognitive classification, extending our understanding of the cognitive profile beyond mean differences in performance to a more nuanced conceptualization of multiple, qualitatively distinct profiles of cognitive impairment. The presence of multiple cognitive phenotypes in early PD emphasizes the necessity of screening for impairment in a variety of cognitive domains (e.g., memory, language) in addition to those included in the conventional profile of PD-associated cognitive deficits (e.g., executive function). In addition, whereas conventional diagnostic strategies require prior assumptions about the degree of impairment, resulting in the use of potentially arbitrary cutoff scores, statistical approaches do not require such assumptions and instead may detect subtle weaknesses within an individual's neuropsychological profile. Importantly, early identification of patients at risk for cognitive decline improves ability to predict progression, better inform pharmacotherapy, and identify potential therapeutic targets for clinical trials based on these unique phenotypes of neuropsychological functioning. Accounting for heterogeneity may lead to a more personalized medicine approach to treatment of cognitive deficits in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Williams-Gray C, Foltynie T, Brayne CEG, Robbins W, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007; 130:1787–1798. [PubMed: 17535834]
2. Cahn D, Sullivan E, Shear P, Pfefferbaum A, Heit G, Silverberg G. Differential Contributions of Cognitive and Motor Component Processes to Physical and Instrumental Activities of Daily Living in Parkinson's Disease. Arch Clin Neuropsychol. Oct; 1998 13(7):575–583. [PubMed: 14590618]
3. Buter TC, van der Hour A, Matthews F, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease A 12-year population study. Neurology. 2008; 70:1017–1022. [PubMed: 18362281]
4. Aarsland D, Larsen JP, Karlsen K, Lim G, Tandberg E. Mental symptoms in Parkinson's disease and important contributors to caregiver distress. Int J Geriatr Psyciatry. 1999; 14:866–874.
5. Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004; 127(3):550–560. [PubMed: 14691062]
6. Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated parkinson disease: The Norwegian ParkWest study. Neurology. 2009; 72(13):1121–1126. [PubMed: 19020293]
7. Pigott K, et al. Longitudinal study of normal cognition in Parkinson disease. Neurology. 2015; 85:1276–1282. [PubMed: 26362285]
8. Watson G, Leverenz JB. Profile of Cognitive Impairment in Parkinson Disease. Brain Pathol. 2010; 20(3):640–645. [PubMed: 20522089]
9. Aarsland D, Bronnick K, Williams-Gray C. Mild cognitive impairment in Parkinson disease A multicenter pooled analysis. Neurology. 2010; 75(12):1062–1069. [PubMed: 20855849]
10. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of Mild Cognitive Impairment in Parkinson's Disease: Progression to Dementia. Mov Disord. 2006; 21(9):1343–1349. [PubMed: 16721732]
11. Muslimović D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinson's disease. Brain. 2007; 130(11):2887–2897. [PubMed: 17855374]

12. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol. 2010; 9(12):1200–1213. [PubMed: 20880750]
13. Yarnall AJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD study. Neurology. Jan; 2014 82(4):308–16. [PubMed: 24363137]
14. Cholerton, Ba, et al. Evaluation of mild cognitive impairment subtypes in Parkinson's disease. Mov Disord. May; 2014 29(6):756–64. [PubMed: 24710804]
15. Lee JE, et al. Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry. Jan; 2014 85(1):7–16. [PubMed: 23828835]
16. Jokinen P, Bru A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Park Relat Disord. 2009; 15:88–93.
17. Hanganu A, et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. Brain. Apr; 2014 137(Pt 4):1120–9. [PubMed: 24613932]
18. Gomperts SN, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology. 2013; 80:85–91. [PubMed: 23243071]
19. Weintraub D, et al. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain. Jan; 2012 135(Pt 1):170–80. [PubMed: 22108576]
20. Compta Y, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. Mov Disord. 2009; 24(15):2203–2210. [PubMed: 19795497]
21. Siderowf A, et al. CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease. Neurology. 2010; 75(12):1055–1061. [PubMed: 20720189]
22. Adler CH, et al. Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. Acta Neuropathol. Dec; 2010 120(6):827–8. [PubMed: 20838798]
23. Jellinger KA. Neuropathology in Parkinson's disease with mild cognitive impairment. Acta Neuropathol. 2010; 120:829–830. [PubMed: 20922398]
24. Garcia-Garcia D, et al. Posterior parietooccipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. Eur J Nucl Med Mol Imaging. 2012; 39(11): 1767–1777. [PubMed: 22872307]
25. Williams-Gray CH, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013; 84:1258–64. [PubMed: 23781007]
26. van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. Mov Disord. Jun; 2010 25(8):969–78. [PubMed: 20535823]
27. Dujardin K, et al. The spectrum of cognitive disorders in Parkinson's disease: a data-driven approach. Mov Disord. Feb; 2013 28(2):183–9. [PubMed: 23436633]
28. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. Cogn Behav Neurol. 2004; 17(4):195–200. [PubMed: 15622014]
29. Szeto JYY, et al. The relationships between mild cognitive impairment and phenotype in Parkinson's disease. npj Park Dis. 2015; 1:15015.
30. Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. N Engl J Med. 2013; 368(13):1169–1171. [PubMed: 23484795]
31. Mattis, S. Dementia Rating Scale. Odessa, FL: Psychological Assessment Resources; 1988.
32. Nasreddine ZS, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53(4):695–696. [PubMed: 15817019]
33. Wechsler, D. WAIS-III, Wechsler adult intelligence scale: Administration and scoring manual. Psychological Corporation; 1997.
34. Kaplan, E., Godglass, H., Weintraub, S. Boston naming test. Pro-ed; 2001.

35. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. Clin Neuropsychol. 1998; 12(1):43–55.
36. Benton, Arthur L., Sivan, Abigail B., Hamsher, Kerry deS, Varney, Nils R., Spreen, O. Contributions to Neuropsychological Assessment: A Clinical Manual. 1994
37. Hubbard EJ, et al. Clock drawing performance in cognitively normal elderly. Arch Clin Neuropsychol. 2008; 23(3):295–327. [PubMed: 18243644]
38. Fahn, S., Elton, R. Unified Parkinson's disease rating scale. In: Fahn, S.Marsden, C.Calne, D., Goldstein, M., editors. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan Health Care Information; 1987. p. 153-164.
39. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17(5):427–442. [PubMed: 6067254]
40. Jankovic J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology. 1990; 40(1):1529–34. [PubMed: 2215943]
41. Sheikh, JI., Yesavage, JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. In: Brink, T., editor. Clinical Gerontology: A Guide to Assessment and Intervention. New York: The Haworth Press; 1986. p. 165-173.
42. Galasko D, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. Alzheimer's Dis Assoc Disord. 1997; 11(Suppl. 2):S33–S29.
43. Litvan I, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement disorder society task force guidelines. Mov Disord. 2012; 27(3):349–356. [PubMed: 22275317]
44. Muthén L, Muthén B. Mplus user's guide (version 7.0). 2007
45. Nylund KL, Asparouhov T, Muthén BO. Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. Struct Equ Model A Multidiscip J. Oct; 2007 14(4):535–569.
46. Kline, RB. Principles and practice of structural equation modeling. New York: Guilford Press; 2005.
47. Akaike H. Factor analysis and AIC. Psychometrika. 1987; 52(3):317–332.
48. Schwarz G. Estimating the dimension of a model. Ann Stat. 1978; 6(2):461–464.
49. Lo Y, Mendell N, Rubin D. Testing the number of components in a normal mixture. Biometrika. 2001; 88(3):767–778.
50. Muthén, B. Latent variable mixture modeling. In: Marcoulides, G., Schumacker, R., editors. Advanced structural equation modeling: New developments and techniques. Mahwah, NJ: Erlbaum; 2000. p. 1-33.
51. Rosenthal E, et al. Association between cognition and function in patients with Parkinson disease with and without dementia. Mov Disord. Jul; 2010 25(9):1170–6. [PubMed: 20310053]
52. Williams-Gray CH, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009; 132:2958–2969. [PubMed: 19812213]
53. Morley JF, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord. 2012; 27(4):512–8. [PubMed: 22344634]
54. Mata IF, et al. APOE, MAPT, and SNCA genes and cognitive performnace in Parkinson disease. JAMA Neurol. 2014; 71(11):1405. [PubMed: 25178429]
55. Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker Ra. Catechol O-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci. 2007; 27(18):4832–4838. [PubMed: 17475791]
56. Mata IF, et al. GBA variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016; 31(1):95–102. [PubMed: 26296077]
57. Nombela C, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain. 2014; (i)
58. Robbins TW, Cools R. Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. Mov Disord. Apr; 2014 29(5):597–607. [PubMed: 24757109]
59. Eshghi A, Haughton D, Legrand P, Skaletsky M, Woolford S. Identifying Groups: A Comparison of Methodologies. J Data Sci. 2011; 9:271–291.

60. Paul SS, et al. Two-Year Trajectory of Fall Risk in People With Parkinson Disease: A Latent Class Analysis. Arch Phys Med Rehabil. 2016; 97(3):372–379.e1. [PubMed: 26606871]

61. Zahodne L, Marsiske M, Bowers D. A latent class analysis of psychological disturbance in Parkinson's disease. Int J Geriatr Psychiatry. 2013; 28(10):1054–1060. [PubMed: 23307695]

62. Burn D, et al. Parkinson's disease motor subtypes and mood. Mov Disord. 2011; 27(3):379–386. [PubMed: 22162098]

63. Starkstein SE, et al. Anxiety has specific syndromal profiles in parkinson disease: A data-driven approach. Am J Geriatr Psychiatry. 2014; 22(12):1410–1417. [PubMed: 24200594]

64. Flensborg Damholdt M, Shevlin M, Borghammer P, Larsen L, Ostergaard K. Clinical heterogeneity in Parkinson's disease revisited: a latent profile analysis. Acta Neurol Scand. May; 2012 125(5): 311–8. [PubMed: 21707551]

65. Mavandadi S, et al. Use of latent variable modeling to delineate psychiatric and cognitive profiles in Parkinson's disease. Am J Geriatr Psychiatry. 2010; 17(11):986–995.

66. Libon DJ, et al. Neuropsychological Syndromes Associated with Alzheimer's/Vascular Dementia: A Latent Class Analysis. J Alzheimers Dis. Jan; 2014 42(3):999–1014. [PubMed: 25024329]

67. Köhler S, et al. Progression to dementia in memory clinic patients without dementia: A latent profile analysis. Neurology. 2013; 81:1342–1349. [PubMed: 23997152]

68. Hayden KM, et al. Pre-clinical Cognitive Phenotypes for Alzheimer Disease: A Latent Profile Approach. Am J Geriatr Psychiatry. Sep.2013 :1–11. [PubMed: 23290197]

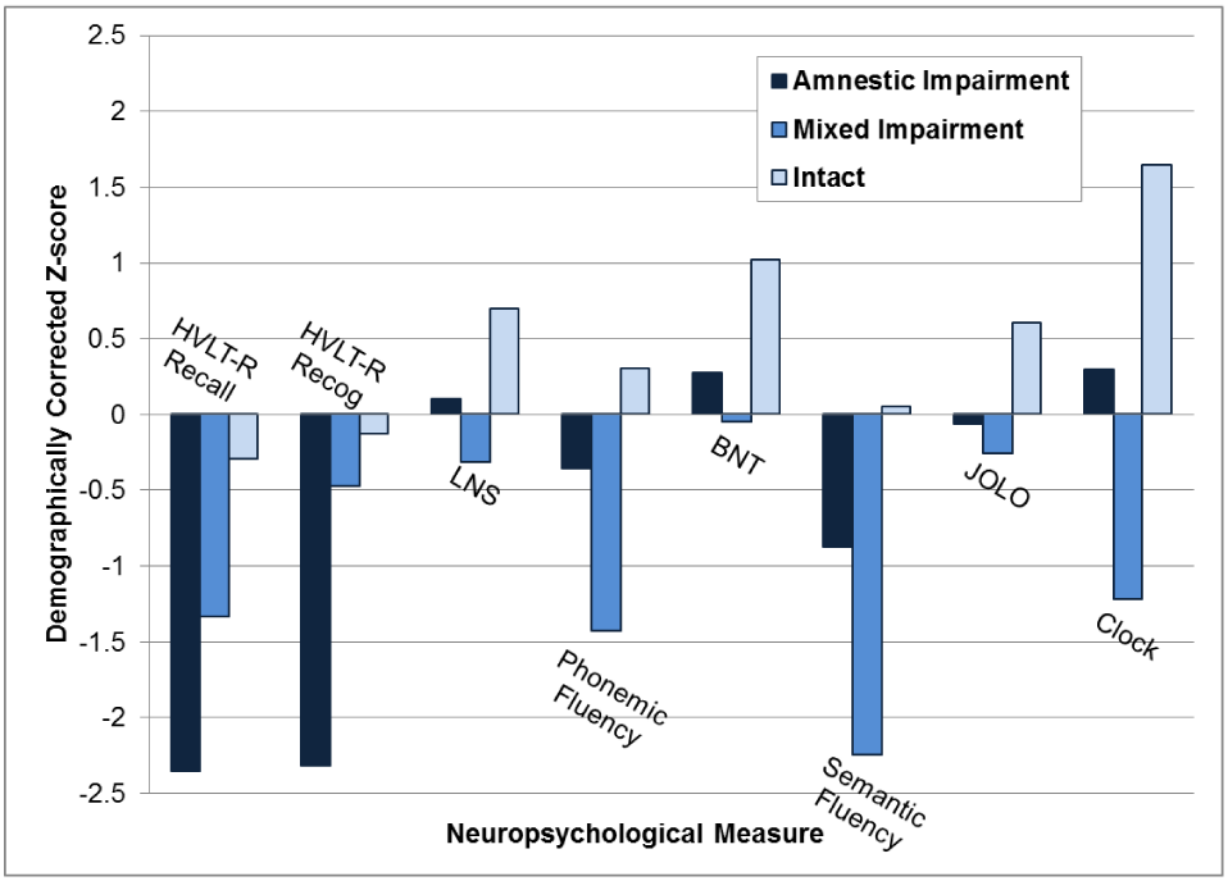

Figure 1. Neuropsychological Test Performance of LCA-Derived Classes

Memory: HVLT-R Recall = Hopkins Verbal Learning Test-Revised Delayed Recall, HVLT-R Recog = HVLT-R Recognition Discriminability

Executive Functioning: LNS = Letter-Number Sequencing, Phonemic Fluency = 'FAS' Phonemic Verbal Fluency

Language: BNT = Boston Naming Test, Semantic Fluency = Animal Verbal Fluency

Visuospatial: JOLO = Judgement of Line Orientation; Clock = Clock drawing to command

Table 1
Full Sample Demographic and Clinical Characteristics (n=199)

Age	70.57 (7.47)
Education	16.24 (2.34)
Sex (% male)	66.8%
Disease Duration	6.85 (5.21)
Hoehn & Yahr	2.36 (0.65)
UPDRS-III	22.95 (11.55)
PD subtype (% PIGD)	56.9%
LEDD	758.31 (481.25)
GDS-15	2.74 (2.78)
DRS-2	136.76 (5.57)
ADCS-ADL IADL Subscale	50.71 (6.83)

Results are presented as M (SD) except where noted (i.e., sex and PD subtype). UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; PIGD = postural instability/gait disturbance-dominant; LEDD = levodopa-equivalent daily dose; GDS-15 = Geriatric Depression Scale-15; DRS-2 = Dementia Rating Scale-2; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; IADL = Instrumental activities of daily living.

Table 2

Fit Indices for Latent Class Analysis Models with 1 - 4 Classes

Number of classes	Number of free parameters	AIC	BIC	Log likelihood	VLMR *p*	Entropy	Smallest class size (% of sample)
1	16	4944.642	4997.335	-2456.321	N/A	N/A	100%
2	25	4724.800	4807.133	-2337.400	.0006	0.82	45%
3	34	4648.771	4760.744	-2290.386	.1255	0.88	13%
4	43	4632.110	4773.722	-2273.055	.2048	0.81	11%

AIC = Akaike information criterion; BIC = Bayesian information criterion

Table 3

Cross-Tabulation of Latent Class Analysis versus Clinical Consensus Diagnostic Classification

		LCA classification		
		Intact (n=109)	**Mixed impairment (n=26)**	**Amnestic (n=64)**
Consensus diagnostic classification	**PD Patients with Normal Cognition (n=151)**	101	15	35
	PD-MCI (n=48)	8	11	29

LCA = latent class analysis; PD = Parkinson's disease; MCI = mild cognitive impairment.