Smith, C. R., Cullen, B., Sheridan, M. P., Cavanagh, J., Grosset, K. and Grosset, D. G. (2020) Cognitive impairment in Parkinson's disease is multifactorial: a neuropsychological study. *Acta Neurologica Scandinavica*, 141(6), pp. 500-508. (doi: [10.1111/ane.13226](https://doi.org/10.1111/ane.13226)).

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

This is the peer reviewed version of the following article:

Smith, C. R., Cullen, B., Sheridan, M. P., Cavanagh, J., Grosset, K. and Grosset, D. G. (2020) Cognitive impairment in Parkinson's disease is multifactorial: a neuropsychological study. *Acta Neurologica Scandinavica*, 141(6), pp. 500-508, which has been published in final form at [10.1111/ane.13226](https://doi.org/10.1111/ane.13226). This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/209014/>

Deposited on: 29 January 2020

Title: Cognitive impairment in Parkinson's disease is multifactorial: a neuropsychological study.

Running title: Variation in Parkinson's disease cognition.

Authors: Callum R. Smith^a, Breda Cullen^b, Matthew P. Sheridan^c, Jonathan Cavanagh^b, Katherine A. Grosset^a, and Donald G. Grosset^a.

Affiliations: ^aDepartment of Neurology, NHS Greater Glasgow and Clyde, G51 4TF, Glasgow, UK. ^bInstitute of Health and Wellbeing, University of Glasgow, G51 4TF, Glasgow, UK. ^cDivision of Old Age Psychiatry, NHS Greater Glasgow & Clyde, G15 6PX, Glasgow, UK.

Acknowledgements

The work was supported by the Neurosciences Foundation (project number 173503). The funder had no role in the study design, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Conflicts of Interest Statement

DGG has received honoraria for meetings attendance from Bial Pharma and Merz Pharma. BC has received research funding from the Scottish Executive Chief Scientist Office (ref: TCS/18/09). JC acknowledges the support of the Sackler Trust and is part of the Wellcome Trust funded Neuroimmunology of Mood and Alzheimer's Consortium (104025/Z/14/Z) that includes collaboration with GSK, Lundbeck, Pfizer, and Janssen & Janssen. KAG and CRS have no declarations.

Data Availability Statement

Due to the sensitive nature of the information collected in this study, participants were informed that raw data would remain confidential and would not be shared.

Abstract

Background. In Parkinson's disease, mild cognitive impairment and dementia are associated with α -synuclein deposition and spread. However, coexistent Alzheimer's disease and cerebrovascular disease are common at autopsy, and may affect cognition. Our objective was to map cognitive impairment in Parkinson's disease to these different causes using clinical assessment.

Methods. Neuropsychological testing was performed in a cross-sectional sample of cognitively impaired patients with Parkinson's disease. The pattern of deficits in varying cognitive domains was mapped to the presentations that typify different diseases. Data were analyzed by an expert multidisciplinary panel, referencing diagnostic criteria, to reach a consensus diagnosis for the cognitive dysfunction.

Results. There were 45 participants with Parkinson's disease and cognitive impairment, 73.3% male, mean age 69.1 years (standard deviation 8.3). Twenty-seven (60.0%) had mild cognitive impairment, and 18 had dementia (40.0%). Cognitive impairment was primarily attributable to Lewy body disease alone in 19/45 patients (42.2%), to Lewy body disease plus Alzheimer's in 14/45 (31.1%), to Lewy body plus cerebrovascular disease in 6/45 (13.3%), and to Lewy body plus Alzheimer's and cerebrovascular disease in 1/45 (2.2%). The cognitive decline was not primarily Lewy-related in 5/45 patients (11.1%); in 4/45 (8.9%), it was primarily attributable to Alzheimer's disease, and 1/45 (2.2%) had behavioural-variant frontotemporal dementia.

Conclusion. Neuropsychological testing identifies distinct patterns of cognitive impairment in Parkinson's disease that provide clear pointers to comorbid disease processes, the most common being Alzheimer's disease. This approach may prove useful in clinical practice, and has implications for clinical trials that target α -synuclein.

Keywords: Parkinson's disease, mild cognitive impairment, dementia, neuropsychology.

Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by progressive bradykinesia, rigidity, and tremor resulting from nigrostriatal dopamine loss and propagation of α -synuclein in Lewy bodies¹. Cognitive decline, including mild cognitive impairment (PD-MCI) and PD dementia (PDD), is a common and debilitating feature². Better characterization of cognitive decline in PD is needed to improve our understanding of the effects of cognitive enhancement therapy, and to inform clinical trials testing potentially disease modifying therapies that target specific disease processes.

Dementia disorders are characterized by distinct cognitive profiles that result from differences in the nature and distribution of the underlying disease process. In Lewy body disorders, including PDD and dementia with Lewy bodies (DLB), frontostriatal dysfunction results in predominantly executive and attentional deficits. Fluctuating cognition, visual hallucinations, and rapid eye movement sleep behaviour disorder (RBD) are closely associated^{3, 4}. Alzheimer's disease (AD) typically has an episodic memory deficit, reflecting degeneration of medial temporal lobe structures⁵. Vascular cognitive disorder (VCD) is associated with impairments in complex attention, processing speed, and executive function in the context of a relevant cerebrovascular event or disease⁶. Finally, frontotemporal dementia (FTD) is characterized by linguistic or behavioural abnormalities^{7, 8}. These different patterns of cognitive dysfunction are captured in the diagnostic criteria for each disease, and are applied in conjunction with other distinguishing clinical features³⁻⁸.

The diagnostic criteria for each disorder demand exclusivity, in order to increase diagnostic specificity. However, there is increasing evidence that a substantial proportion of PD patients with cognitive impairment have more than one underlying disease process. Pathological signs of AD are present in between one-fifth and one-third of PD cases at autopsy, and these are significantly more frequent in cases with dementia compared to those without. A synergistic interaction of Lewy and AD pathologies accelerates cognitive decline in PD⁹. Additionally, cerebrovascular disease is present in around one-fifth of autopsied PD cases⁹, and vascular comorbidity correlates with the severity of cognitive impairment¹⁰.

The coexistence of other neurodegenerative diseases in PD has clinical and research implications. Cholinesterase inhibitors are approved for AD, PDD, and DLB, though not for FTD, in which the cholinergic system is relatively intact¹¹. In PDD and DLB, there is considerable variation in the response to cholinesterase therapy¹¹; this may reflect variation in the nature of the cholinergic deficit, which may be due to PD or to comorbidities¹². Preventive therapy for cerebrovascular disease may be overlooked if cognitive impairment is assumed to be due to PD¹³. Finally, the assessment of novel treatments targeting α -synuclein¹⁴ may be confounded by coexistent AD changes.

A clinical approach may help to identify the likely presence of common comorbid disease processes in PD patients, and form part of an assessment algorithm. The viability of this approach depends on whether the differing patterns of cognitive impairment, which map to these differing diseases, can be identified in cognitively impaired PD patients. The objective of the present study was to identify the proportion of cognitively impaired PD patients whose clinical and neuropsychological profile mapped to diagnostic criteria for different cognitive disorders.

Materials and Methods

The study was cross-sectional and observational, and it was approved by the local UK National Health Service (NHS) research ethics committee (reference code 17/NS/0049). Informed consent was obtained in writing. Recruitment was between October 2017 and February 2019. Reporting followed STROBE guidelines¹⁵.

Participants

Participants had PD diagnosed by a specialist neurologist in movement disorder clinics, and had self-reported and/or documented cognitive problems. Adults up to 90 years old were recruited, gave written informed consent, and were assessed for cognitive impairment on screening, defined by a) a score <27 on the Montreal Cognitive Assessment (MoCA)¹⁶ and b) a score >3.3 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)¹⁷, and/or c) functional impairment

resulting from cognitive problems reported on the Unified Parkinson's Disease Rating Scale (UPDRS) item 1.1¹⁸.

Each participant nominated one adult who knew them for at least 10 years, and who consented to complete informant-rated questionnaires.

Materials

After screening, a multi-domain neuropsychological assessment was performed, lasting around 90 minutes. This included at least two tests per cognitive domain, following consensus guidelines¹⁹; selected subtests suitable for people with PD were used from various batteries. Additional questionnaires captured relevant clinical features including mood, hallucinations (visual, auditory, tactile, gustatory, and olfactory), delusions, RBD, and excessive daytime fatigue (Table 1).

Urinary incontinence, falls, syncope, body mass index, and smoking history were recorded. Constipation was defined as fewer than one bowel movement per day or laxative use. Medication, medical history, motor scores, and neuroimaging results were noted. Antiparkinson medications were converted to levodopa equivalent daily dose using an established formula³¹. Motor severity was quantified with the MDS UPDRS 3, if this was available from review of recent medical notes.

Informants completed 3 questionnaires. The PD Cognitive Functional Rating Scale identified functional impairment due to cognitive decline; a score of 3-8 indicated mild impairment, and >8 indicated marked impairment³². The Dementia Cognitive Fluctuation Scale³³ identified cognitive fluctuations by a positive answer to 3 of 4 discriminating items. The Cambridge Behavioural Inventory³⁴ evaluated behavioural changes (disinhibition, apathy, loss of empathy, stereotypy, and hyperorality); total scores for each variable were ranked (0-25% normal, 26-50% mild, 51-75% moderate, 76-100% severe).

Procedure

Results of the assessments were anonymized and reviewed by the expert panel, consisting of specialists in movement disorders neurology (DGG), psychiatry (MPS and JC), and clinical neuropsychology (BC). The panel issued a heuristic diagnosis for each patient describing the disease process (or processes) underlying the cognitive profile. The diagnosis was based on the pattern of performance across all neuropsychological tests, and the presence or absence of characteristic psychiatric and behavioural symptoms. Reference was made to the clinical diagnostic criteria for different dementia disorders^{3-8, 19}. Multiple diagnoses (conferred as probable or possible) were permitted in a single case. Final diagnoses were by consensus.

MCI was defined when functional impairment resulting from cognitive problems was absent or mild, and dementia was defined by marked functional impairment. Participants reporting cognitive decline prior to or within one year of motor onset were classified as PD (DLB subtype)¹. In the absence of criteria for the MCI stage of DLB, “MCI-LB” was defined analogously to PD-MCI, except that cognitive onset emerged prior to, or around the time of, motor onset.

The panel’s performance was assessed by randomly and blindly including 3 pathologically confirmed published cases that included neuropsychological findings in different dementias³⁵⁻³⁷.

Data analysis

Results are reported as descriptive statistics and proportions with 95% confidence intervals (CI).

Results

Table 2 provides descriptive statistics for the 45 participants in the study. All had a diagnosis of idiopathic PD by a movement disorder neurologist. Thirty-nine (86.7%) had clinically established PD by MDS diagnostic criteria¹, and the remaining six (13.3%) had probable PD. The recruitment, screening, and eligibility assessment process is in Supplementary Figure 1.

Core DLB features⁴ were common: cognitive fluctuations in 27 patients (60.0%), RBD in 24 (53.3%), and visual hallucinations in 14 (31.1%). Other non-motor features were hyposmia in 28 patients (62.2%), constipation in 25 (55.6%), excessive daytime fatigue in 23 (51.1%), one or more falls in the previous 3 months in 19 (42.2%), hallucinations in a non-visual modality in 14 (31.1%), clinically significant anxiety in 12 (26.7%), depression in 9 (20.0%), and urinary incontinence in 7 (15.6%). Two (4.4%) were current smokers, and 7 (15.6%) were ex-smokers.

In 16 participants (35.6%), the clinical diagnosis of PD was supported by functional imaging of the presynaptic dopamine system; in the remaining 29 (64.4%), no functional scans had been performed. Eleven participants (24.4%) had documented structural brain imaging: computed tomography only (n=2), magnetic resonance imaging only (n=7), or both (n=2).

Consensus panel diagnoses

The consensus panel diagnosed MCI in 26 (57.7%), and dementia in 19 (42.2%). Cognitive status, clinical diagnosis, and other key findings are in Table 3. Normative scores for every participant in each cognitive test are provided in Supplementary Tables 1 and 2.

For all patients, Lewy body disease was either a probable or a possible cause of cognitive deficits. Forty of the 45 participants (88.9%, [95% CI: 79.7, 98.1]) had probable Lewy-related cognitive decline, which developed within established PD in 37, and before or around the time of motor onset in 3 (Figure 1).

19/45 (42.2% [27.7, 56.6]) participants had probable Lewy-related cognitive decline without comorbid disease. There were impairments of visuospatial abilities in 9, executive function in 8, memory in 7, and attention in 7. Three showed language deficits, and 3 had possible ideomotor apraxia. RBD, cognitive fluctuations, and hallucinations affected 11 participants each; the hallucinations were primarily visual in 8. Behavioural symptoms were mild or absent, except for moderate apathy and/or loss of empathy in 3 participants.

In the remaining 21/45 participants (46.7% [32.1, 61.3]) with a probable Lewy-related cognitive pattern, there were additional features indicating other disease processes. AD was the most common, being present in 15 (33.3% [19.5, 47.1]), of whom 7 had MCI and 8 had dementia. The primary deficits were in memory, language, and executive function. Semantic fluency was universally worse than phonemic fluency. Four had RBD, 4 were moderately depressed, 3 had cognitive fluctuations, and 2 had prominent psychosis. Core DLB features (RBD, fluctuations, hallucinations) were more common in probable AD than possible AD.

In the 7 participants with comorbid probable AD, cognitive deficits were typically global, and there was also a substantial non-cognitive burden. Memory was universally affected, and none benefited significantly from cueing, indicating a hippocampal encoding deficit rather than an information retrieval problem³⁸. Posterior cortical deficits were common: 6 had impaired object naming, and 3 showed ideomotor apraxia. Semantic fluency was consistently poor. Five had cognitive fluctuations, 4 had hallucinations, and one had delusions. Five reported excessive daytime fatigue, though only one had RBD. Behavioural symptoms were also common: 3 had moderate or severe apathy and loss of empathy, and 2 had disinhibition, stereotypy, and/or hyperorality. Five reported multiple recent falls, and all had autonomic dysfunction (constipation in 6, urinary incontinence in 2, and orthostatic hypotension in one).

In 5/45 participants (11.1% [1.9, 20.3]), the cognitive profile was primarily related to an alternative disease process. In 4 of these, cognitive deficits were primarily attributable to coexistent AD: all had a clear amnesic profile, with limited or no benefit from cueing; semantic fluency was considerably worse than phonemic fluency; and 3 of the 4 had impaired language. PDD features were infrequent in this group: 2 had RBD, one had cognitive fluctuations, and none had hallucinations.

Cerebrovascular disease contributed to cognitive impairment in 8/45 participants (17.8% [6.6, 29.0]), of whom 7 had probable Lewy-related cognitive decline, and one had an AD pattern. All had characteristic deficits of executive function and attention, including processing speed, cognitive flexibility, and response inhibition. Vascular risk factors were frequent, including one or more vascular event in 5, hypertension in 5, diabetes in 3, obesity in 2, long-term cigarette smoking in 2, and hypercholesterolaemia in one. Neuroimaging data were available for 2; both showed evidence of small vessel disease. In all 8 cases, cerebrovascular disease was not considered to be the primary cause of cognitive symptoms.

Probable behavioural-variant frontotemporal dementia was identified in one participant (2.2%) who had dramatic behavioural changes, including severe disinhibition, apathy, loss of empathy, stereotypy, and hyperorality.

Neuropsychological scores were generally in the average to high average range, consistent with education and work history. However, executive tests, processing speed, and the line orientation task were low average.

The proportion of cases fulfilling criteria for each cognitive disorder is in Figure 2.

Consensus clinical diagnosis was correct for each of the 3 pathologically-confirmed test cases.

Discussion

We found that a neuropsychological assessment of people with PD and cognitive impairment identifies distinct patterns of deficit, which map to different disease

processes. Most participants had a Lewy-related clinical and cognitive profile, but more than half of patients had features fulfilling the clinical criteria for other cognitive disorders. Almost 45% of participants had pointers to coexistent AD, graded probable in around 30%, and possible in around 15%. A coexistent cerebrovascular pattern was present in just under one-fifth of participants. These proportions are comparable to autopsy findings of comorbid AD in between one-fifth and one-third of PD cases, and established cerebrovascular disease in approximately 20%⁹. The more severe comorbidity at autopsy, relative to our sample, is likely to be due to their older age and longer disease duration³⁹. Our study, in conjunction with those pathological reports, indicates that cognitive impairment in PD is frequently multifactorial. Other disorders contribute in approximately half of patients, and in around 10%, another disorder may be the primary explanation for cognitive impairment in PD.

We found that the cognitive pattern that is typical of AD was readily identifiable in PD. The profile includes the presence of worse semantic than phonemic fluency, and free recall deficits that do not improve with cueing, both of which indicate the temporal lobe dysfunction that is characteristic of AD⁵. Language deficit, generally manifesting as impaired object naming, was also frequent, and is typical of early AD⁴⁰. The findings are consistent with a recent autopsy study, in which there was significantly worse object naming in dementia cases with comorbid α -synucleinopathy and AD changes⁴¹. We also found worse semantic fluency and object naming in MCI, suggesting utility of these tests in earlier stages. In our dementia cases, comorbid AD was linked to a higher frequency of falls, behavioural disturbances, and ideomotor apraxia. Considering the clinicopathological evidence that coexistent tau and (particularly) amyloid- β induce a more rapid cognitive decline and earlier mortality in PD⁹, the markers of coexistent AD identified in our study are likely to be associated with a worse prognosis.

These findings may usefully inform the design and interpretation of clinical trials of treatments that target α -synuclein. Domain-focused neuropsychological assessment and selected clinical questionnaires would help to either exclude or stratify participants according to the likelihood of comorbid AD. Therapies targeting α -synuclein have the greatest chance of showing efficacy if they are applied in a relatively homogeneous group of patients, without significant comorbidity.

Our finding that cerebrovascular disease was contributory, rather than a primary cause of cognitive impairment, is also consistent with autopsy studies, which report that cerebrovascular pathology does not correlate with dementia in PD⁹. In apparent contrast, a large prospective study found that cardiovascular disease and increasing vascular risk were associated with lower cognitive scores in early PD¹⁰. It is possible that cerebrovascular factors influence cognition in early PD, but that this relationship is obscured by the later burden of extensive Lewy and/or Alzheimer lesions.

The study had some limitations. We did not perform biomarker assessment for AD, and are therefore likely to have underestimated the proportion of patients with coexistent AD changes, given that biomarkers increase diagnostic sensitivity. However, the clinical criteria have shown very good specificity against autopsy: 0.81 for AD⁴², 0.93 for DLB⁴³, and 0.95 for behavioural-variant FTD⁴⁴.

In conclusion, different cognitive profiles, which are attributable to several disease processes, are common in cognitively impaired PD patients. AD is the most common, and this shows a distinctive pattern, which can be identified by a clinical approach including neuropsychological testing.

References

1. Postuma, R.B., et al., *MDS clinical diagnostic criteria for Parkinson's disease*. Movement Disorders, 2015. **30**(12): p. 1591-1601.
2. Aarsland, D., J. Zaccai, and C. Brayne, *A systematic review of prevalence studies of dementia in Parkinson's disease*. Mov Disord, 2005. **20**(10): p. 1255-63.
3. Emre, M., et al., *Clinical diagnostic criteria for dementia associated with Parkinson's disease*. Movement disorders, 2007. **22**(12): p. 1689-1707.
4. McKeith, I.G., et al., *Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium*. Neurology, 2017. **89**(1): p. 88-100.
5. Dubois, B., et al., *Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria*. The Lancet Neurology, 2014. **13**(6): p. 614-629.
6. Sachdev, P., et al., *Diagnostic criteria for vascular cognitive disorders: a VASCOG statement*. Alzheimer disease and associated disorders, 2014. **28**(3): p. 206.
7. Rascovsky, K., et al., *Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia*. Brain, 2011. **134**(Pt 9): p. 2456-77.
8. Gorno-Tempini, M.L., et al., *Classification of primary progressive aphasia and its variants*. Neurology, 2011. **76**(11): p. 1006-14.
9. Smith, C., et al., *Neuropathology of dementia in patients with Parkinson's disease: a systematic review of autopsy studies*. J Neurol Neurosurg Psychiatry, 2019.
10. Malek, N., et al., *Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease*. Mov Disord, 2016. **31**(10): p. 1518-1526.
11. O'Brien, J.T., et al., *Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology*. J Psychopharmacol, 2017. **31**(2): p. 147-168.
12. Müller, M.L., et al., *Clinical markers for identifying cholinergic deficits in Parkinson's disease*. Mov Disord, 2015. **30**(2): p. 269-73.
13. Swallow, D.M., et al., *Statins are underused in recent-onset Parkinson's disease with increased vascular risk: findings from the UK Tracking Parkinson's and Oxford Parkinson's Disease Centre (OPDC) discovery cohorts*. J Neurol Neurosurg Psychiatry, 2016. **87**(11): p. 1183-1190.
14. Brundin, P., K.D. Dave, and J.H. Kordower, *Therapeutic approaches to target alpha-synuclein pathology*. Exp Neurol, 2017. **298**(Pt B): p. 225-235.
15. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies*. Lancet, 2007. **370**(9596): p. 1453-7.
16. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment*. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
17. Jorm, A.F., *A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation*. Psychol Med, 1994. **24**(1): p. 145-53.

18. Goetz, C.G., et al., *Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results*. *Mov Disord*, 2008. **23**(15): p. 2129-70.
19. 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): p. 349-56.
20. Millar Vernetti, P., et al., *Validation of a new scale to assess olfactory dysfunction in patients with Parkinson's disease*. *Parkinsonism Relat Disord*, 2012. **18**(4): p. 358-61.
21. Stern, A.F., *The hospital anxiety and depression scale*. *Occup Med (Lond)*, 2014. **64**(5): p. 393-4.
22. Shine, J.M., et al., *Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease*. *Mov Disord Clin Pract*, 2015. **2**(2): p. 175-181.
23. Stiasny-Kolster, K., et al., *The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument*. *Mov Disord*, 2007. **22**(16): p. 2386-93.
24. Johns, M.W., *A new method for measuring daytime sleepiness: the Epworth sleepiness scale*. *Sleep*, 1991. **14**(6): p. 540-5.
25. Delis, D.C., E. Kaplan, and J.H. Kramer, *Delis-Kaplan Executive Function System: Technical Manual*. 2001, San Antonio, TX: Harcourt Assessment Company.
26. Leach, L., et al., *The Kaplan-Baycrest Neurocognitive Assessment (KBNA): Test Manual*. 2000, San Antonio, TX: Harcourt Assessment Company.
27. Randolph, C., et al., *The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*. 1998, San Antonio, TX: The Psychological Corporation.
28. Smith, A., *Symbol digit modalities test: Manual*. 1982, Los Angeles, CA: Western Psychological Services.
29. Warrington, E.K. and M. James, *The Visual Object and Space Perception Battery*. 1991, Bury St. Edmunds, England: Thames Valley Test Company.
30. Wechsler, D., *Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV)*. 2008, San Antonio, TX: Pearson.
31. Tomlinson, C.L., et al., *Systematic review of levodopa dose equivalency reporting in Parkinson's disease*. *Mov Disord*, 2010. **25**(15): p. 2649-53.
32. Ruzafa-Valiente, E., et al., *Parkinson's Disease--Cognitive Functional Rating Scale across different conditions and degrees of cognitive impairment*. *J Neurol Sci*, 2016. **361**: p. 66-71.
33. Lee, D.R., et al., *The dementia cognitive fluctuation scale, a new psychometric test for clinicians to identify cognitive fluctuations in people with dementia*. *Am J Geriatr Psychiatry*, 2014. **22**(9): p. 926-35.
34. Wear, H.J., et al., *The Cambridge Behavioural Inventory revised*. *Dement Neuropsychol*, 2008. **2**(2): p. 102-107.
35. Gurd, J.M., et al., *Dementia with Lewy bodies: a pure case*. *Brain Cogn*, 2000. **44**(3): p. 307-23.
36. Eratne, D., et al., *Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis*. *Australas Psychiatry*, 2018. **26**(4): p. 347-357.
37. Price, B.H., et al., *Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease*. *Arch Neurol*, 1993. **50**(9): p. 931-7.

38. Economou, A., C. Routsis, and S.G. Papageorgiou, *Episodic Memory in Alzheimer Disease, Frontotemporal Dementia, and Dementia With Lewy Bodies/Parkinson Disease Dementia: Disentangling Retrieval From Consolidation*. Alzheimer Dis Assoc Disord, 2016. **30**(1): p. 47-52.
39. Jellinger, K.A. and J. Attems, *Prevalence of dementia disorders in the oldest-old: an autopsy study*. Acta Neuropathol, 2010. **119**(4): p. 421-33.
40. Verma, M. and R.J. Howard, *Semantic memory and language dysfunction in early Alzheimer's disease: a review*. Int J Geriatr Psychiatry, 2012. **27**(12): p. 1209-17.
41. Coughlin, D., et al., *Cognitive and Pathological Influences of Tau Pathology in Lewy Body Disorders*. Ann Neurol, 2019. **85**(2): p. 259-271.
42. de Jager, C.A., et al., *Retrospective evaluation of revised criteria for the diagnosis of Alzheimer's disease using a cohort with post-mortem diagnosis*. Int J Geriatr Psychiatry, 2010. **25**(10): p. 988-97.
43. Skogseth, R., et al., *Accuracy of Clinical Diagnosis of Dementia with Lewy Bodies versus Neuropathology*. J Alzheimers Dis, 2017. **59**(4): p. 1139-1152.
44. Harris, J.M., et al., *Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia*. Neurology, 2013. **80**(20): p. 1881-7.

Table 1. List of neuropsychological tests and questionnaires.

A. Cognitive domains	Test
Memory	KBNA word lists (free recall, delayed recall, and recognition); KBNA picture recognition
Executive function	KBNA phonemic and semantic fluency; KBNA practical problem-solving and conceptual shifting; DKEFS color-word interference
Attention and speed	WAIS-IV digit span forwards and backwards; SDMT (spoken)
Visuospatial skills	RBANS line orientation; VOSP incomplete letters; VOSP object decision; interlocking pentagons
Language	KBNA picture naming; KBNA auditory comprehension
Praxis	KBNA praxis test
B. Non-cognitive features	Questionnaire
Hyposmia	Hyposmia Rating Scale <23 ²⁰
Anxiety	HADS >10 ²¹
Depression	HADS >10 ²¹
Hallucinations	PsychH-Q, yes to any ²²
Delusions	PsychH-Q, yes to any ²²
RBD	RBD Screening Questionnaire, >5 ²³
Excessive daytime fatigue	Epworth Sleep Scale, >9 ²⁴

DKEFS = Delis-Kaplan Executive Function System²⁵, HADS = Hospital Anxiety and Depression Scale, KBNA = Kaplan-Baycrest Neurocognitive Assessment²⁶, PsychH-Q = Psychosis and Hallucinations Questionnaire, PD = Parkinson's disease, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status²⁷, RBD = rapid eye movement sleep behaviour disorder, SDMT = Symbol Digit Modalities Test²⁸, VOSP = Visual Object and Space Perception Battery²⁹, WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition³⁰.

Table 2. Descriptive statistics for 45 study participants.

Variable	Value
Sample size	45
Male sex (n, %)	33 (73.3%)
Age in years	69.1 (8.3)
Disease duration in years	8.9 (6.0)
Education in years	13.2 (2.9)
LEDD	567 (318)
MoCA	21.9 (3.6)
IQCODE	3.5 (0.7)
MDS UPDRS 1.1	1.9 (0.9)
PD-CFRS	2.4 (1.7)

Data are mean (standard deviation) unless otherwise specified. The IQCODE was missing for 9 participants, and PD-CFRS for 7. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, LEDD = levodopa equivalent daily dose, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, PD-CFRS = Parkinson's Disease Cognitive Functional Rating Scale, UPDRS = Unified Parkinson's Disease Rating Scale.

Table 3. Clinical features and diagnoses for individual participants.

Diagnosis	Status	Case	PD duration (years)	MDS UPDRS 3	MoCA	Memory	Attention	Executive	Visuospatial	Language	Praxis	Behaviour	Vascular	DLB features
Probable Lewy-related pattern														
No coexistent diagnosis	MCI	1	20+	NA	21	+	-	-	+	-	-	+	1	
		2	4	26	22	+	-	-	-	-	-	-	1	
		3	20+	15	23	-	-	-	+	-	-	++	++	2
		4	11	32	23	-	+	-	-	-	NA	+	1	
		5	2	NA	23	-	-	-	-	-	NA	-	NA	
		6	4	20	24	-	-	-	-	-	-	-	1	
		7	8	36	24	-	-	+	-	-	-	++	+	3
		8	11	28	25	-	-	-	-	-	+	-	-	1
		9	9	NA	25	-	++	+	+	+	-	+	+	3
		10	1	NA	26	-	-	-	-	-	-	+	2	
		11	10	30	27	-	-	-	-	-	-	-	2	
		12	2	NA	27	-	-	+	-	-	-	-	1	
	Dementia	13	7	19	13	++	++	+	++	-	-	NA	-	1
		14	14	25	18	-	+	+	-	-	-	-	3	
		15	9	33	19	+	++	-	++	-	-	-	1	
		16	17	30	20	++	+	+	+	+	-	NA	2	
		17	18	NA	22	-	-	+	++	+	+	-	2	
		18	15	NA	23	+	-	-	++	-	-	+	3	
		19	4	45	23	+	++	++	+	-	-	+	1	
Coexistent AD	MCI	20	4	19	21	+	-	++	-	-	-	-	2	
		21	11	37	23	-	-	-	-	+	-	+	2	
		22	2	44	23	-	+	+	-	+	-	+	2	
		23	6	29	23	++	-	++	-	+	-	++	2	
		24	10	31	24	+	-	+	-	-	-	+	1	
		25	10	39	24	-	-	+	-	-	-	NA	1	
	Dementia	26	7	NA	13	++	-	-	-	+	-	++	+	3
		27	9	48	13	++	-	+	++	+	+	++	++	2
		28	15	NA	14	+	-	++	+	+	+	NA	+	NA
		29	6	NA	18	+	+	++	++	++	-	-	1	
		30	4	NA	20	++	++	-	+	-	-	NA	0	
		31	10	44	20	-	+	+	++	++	+	-	3	
		32	15	33	21	+	-	++	-	+	+	++	1	
		33	12	25	23	+	-	+	-	++	-	-	1	
Coexistent vascular	MCI	34	17	26	22	-	-	-	-	-	-	+	0	
		35	1	36	23	+	-	-	-	-	-	+	++	2
		36	2	NA	23	-	-	++	+	+	-	++	2	
		37	20+	NA	23	-	++	+	+	-	-	NA	++	NA
		38	8	25	26	-	-	-	-	-	-	+	++	1
		39	6	NA	26	-	-	+	+	-	-	++	++	3
Coexistent AD + vascular	MCI	40	8	29	22	+	-	++	+	++	-	++	1	
Possible Lewy-related pattern														
AD	MCI	41	8	19	25	+	-	-	-	+	-	+	-	0
		42	1	22	27	-	-	-	-	-	-	-	+	0
	Dementia	43	6	28	19	-	-	+	-	++	-	-	+	2
AD + vascular	Dementia	44	5	29	19	++	++	++	-	+	-	-	++	1
FTD	Dementia	45	4	16	22	-	-	-	-	-	-	++	-	2

All patients had either probable or possible Lewy-related cognitive decline. Behavioural features are disinhibition, apathy, loss of empathy, stereotypy, and hyperorality. Vascular burden is derived from vascular risk factors and medical history. The three core DLB features are cognitive fluctuations, visual hallucinations, and RBD. For cognitive features: – no impairment, + mild impairment (1-2 SDs below the mean), ++ marked impairment (2+ SDs below the mean). AD = Alzheimer's disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MCI = mild cognitive impairment, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, NA = not available, PD = Parkinson's disease, RBD = rapid eye movement sleep behaviour disorder, SD = standard deviation, UPDRS = Unified Parkinson's Disease Rating Scale.

Figure 1. Consensus clinical diagnoses in each disease category.

Lewy body disease was a probable cause of cognitive decline in 40 patients. Nineteen of these cases had no comorbidity; 15 had coexistent AD; and 7 had coexistent VCD. Lewy body disease was a possible cause of cognitive decline in 5 patients; in 4 the cognitive profile was primarily attributable to AD, and one patient had behavioural variant FTD.

*One patient had PD-MCI plus possible AD and possible VCD. AD = Alzheimer's disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MCI = mild cognitive impairment, PD = Parkinson's disease, PDD = Parkinson's disease dementia, VCD = vascular cognitive disorder.

Figure 2. Pattern of cognitive impairment based on neuropsychological and clinical profile in 45 Parkinson's disease patients.

In almost 90% of patients, Lewy body disease was the probable cause of cognitive decline. In the remainder, Lewy body disease was a possible cause of cognitive decline. Probable Alzheimer's disease was diagnosed in around one quarter, mainly coexisting with Lewy body disease. Just under one-fifth had possible cerebrovascular disease, and one patient had behavioural-variant frontotemporal dementia. Categories are not exclusive; participants were often in more than one. Error bars indicate 95% confidence intervals.

Supplementary Table 1. Normative scores for every participant in each cognitive test (KBNA).

Case	Word List 1	Word List 2 Recall	Word List 2 Recognition	Picture Recognition	Picture Naming	Auditory Comprehension	Phonemic Fluency	Semantic Fluency	Practical Problem-Solving / Conceptual Shifting	Praxis
1	14	13	11	<2	>16	>16	12	11	8	>16
2	4	10	11	>16	>16	>16	15	8	13	>16
3	9	12	7	>16	>16	>16	10	13	6	>16
4	8	9	12	>16	>16	>16	12	8	8	>16
5	7	9	12	>16	>16	>16	8	8	11	>16
6	11	11	13	>16	>16	>16	9	12	12	>16
7	6	8	14	>16	>16	>16	6	6	10	>16
8	7	10	12	>16	>16	>16	12	10	6	<2
9	8	10	11	>16	2-16	>16	14	9	4	>16
10	10	10	11	>16	>16	>16	14	12	7	>16
11	7	9	13	>16	>16	>16	13	8	8	>16
12	10	10	12	>16	>16	>16	7	11	12	>16
13	5	5	2	<2	>16	>16	7	6	5	>16
14	11	7	6	>16	>16	>16	15	11	12	>16
15	5	9	11	>16	>16	>16	13	7	6	>16
16	4	4	6	2-16	>16	2-16	5	6	6	>16
17	10	15	13	2-16	>16	2-16	7	8	6	2-16
18	4	7	6	>16	>16	>16	12	6	6	>16
19	8	7	5	>16	>16	>16	5	3	3	NA
20	5	10	12	>16	>16	>16	11	4	11	>16
21	10	10	9	>16	>16	2-16	10	7	9	>16
22	7	8	13	>16	<2	>16	10	7	5	>16
23	7	4	6	<2	2-16	>16	4	3	7	>16

Supplementary Table 1 (continued).

Case	Word List 1	Word List 2 Recall	Word List 2 Recognition	Picture Recognition	Picture Naming	Auditory Comprehension	Phonemic Fluency	Semantic Fluency	Practical Problem-Solving / Conceptual Shifting	Praxis
24	5	7	12	>16	>16	>16	5	4	14	>16
25	7	6	6	>16	>16	>16	15	5	7	>16
26	5	4	7	2-16	2-16	>16	8	7	7	>16
27	5	5	5	<2	<2	>16	5	1	4	<2
28	6	5	4	>16	<2	>16	9	5	8	2-16
29	3	6	10	>16	<2	2-16	5	1	6	>16
30	10	5	12	>16	>16	>16	11	7	7	>16
31	6	9	7	>16	<2	2-16	8	11	3	2-16
32	4	7	3	>16	2-16	>16	4	2	5	2-16
33	5	8	8	>16	<2	2-16	7	8	13	>16
34	9	11	12	>16	>16	>16	7	8	9	>16
35	4	11	12	>16	>16	>16	11	9	6	>16
36	7	14	10	>16	>16	2-16	9	8	6	>16
37	9	10	9	>16	>16	>16	14	10	5	>16
38	7	10	13	>16	>16	>16	9	6	9	>16
39	8	10	11	>16	>16	>16	9	10	8	>16
40	7	9	4	>16	<2	2-16	4	4	4	>16
41	5	8	12	>16	<2	>16	12	8	9	>16
42	6	8	11	>16	>16	>16	14	9	11	>16
43	8	8	12	>16	<2	2-16	5	3	9	>16
44	3	3	9	<2	>16	2-16	8	2	5	>16
45	10	12	11	>16	>16	>16	11	8	9	>16

Data are age-adjusted scaled scores (Word List 1, Word List 2 Recall, Word List 2 Recognition, Phonemic Fluency, Semantic Fluency, Practical Problem-Solving / Conceptual Shifting) or percentiles (Picture Recognition, Picture Naming, Auditory Comprehension, Praxis). KBNA = Kaplan-Baycrest Neurocognitive Assessment; NA = data not available.

Supplementary Table 2. Normative scores for every participant in each cognitive test (other assessment batteries).

Case	Color Words 3	Color Words 4	SDMT	Line Orientation	Incomplete Letters	Object Decision	Interlocking Pentagons	Digit Span Forwards	Digit Span Backwards
1	9	9	-1.99	-0.21	Pass	Fail	Pass	11	8
2	10	10	-1.69	-0.86	Pass	Pass	Pass	13	10
3	12	7	-0.63	-1.80	Pass	Fail	Pass	11	9
4	9	6	-2.95	-1.42	Pass	Pass	NA	9	10
5	11	11	-0.16	-0.14	Pass	Pass	Pass	8	11
6	15	12	0.40	-0.90	Pass	Pass	Pass	10	9
7	8	3	-1.40	0.55	Pass	Pass	Pass	14	11
8	10	8	-1.07	0.21	Pass	Pass	Pass	12	10
9	9	7	-1.51	-1.57	Pass	Fail	Pass	12	1
10	12	8	0.40	1.17	Pass	Pass	Pass	10	11
11	10	10	0.17	-1.24	Pass	Pass	Pass	7	10
12	8	4	0.01	0.14	Pass	Pass	Pass	8	11
13	7	NA	NA	-2.76	Pass	Fail	Pass	8	2
14	7	1	-2.21	-0.21	Pass	Pass	Pass	13	16
15	8	6	-3.24	-4.07	Fail	Fail	Fail	8	5
16	4	9	-3.30	-0.90	Pass	Fail	Pass	8	11
17	11	2	-1.03	-2.62	Pass	Fail	Fail	11	12
18	7	8	-2.33	-0.55	Fail	Fail	Pass	13	10
19	11	9	-1.55	-1.24	Pass	Fail	Pass	2	6
20	3	1	-1.91	0.57	Pass	Pass	Pass	8	8
21	13	11	-0.11	-0.21	Pass	Pass	Pass	8	7
22	9	10	-0.63	-0.55	Pass	Pass	Pass	9	5
23	11	5	-1.25	-1.57	Pass	Pass	Pass	12	9

Supplementary Table 2 (continued).

Case	Color Words 3	Color Words 4	SDMT	Line Orientation	Incomplete Letters	Object Decision	Interlocking Pentagons	Digit Span Forwards	Digit Span Backwards
24	9	8	0.22	-0.14	Pass	Pass	Pass	12	10
25	11	11	-0.73	-0.14	Pass	Pass	NA	8	10
26	8	NA	-1.87	-0.27	Pass	Pass	Pass	8	8
27	NA	NA	NA	NA	Fail	Fail	Fail	9	6
28	11	NA	-1.25	-1.04	Fail	Fail	NA	8	11
29	7	1	-3.24	-0.86	Fail	Fail	Fail	12	9
30	10	10	-1.91	1.65	Pass	Fail	Pass	4	8
31	8	8	-3.38	-1.93	Pass	Fail	Fail	9	8
32	9	1	-1.16	-0.86	Pass	Pass	Pass	13	8
33	9	1	-1.61	0.57	Pass	Pass	Pass	12	10
34	9	6	-0.66	-0.14	Pass	Pass	Pass	10	11
35	11	7	-0.71	-1.21	Pass	Pass	Pass	10	8
36	3	1	-0.80	-1.59	Pass	Fail	Pass	9	10
37	7	3	-3.10	-3.31	Pass	Pass	NA	12	8
38	10	10	-0.67	-0.20	Pass	Pass	Pass	9	7
39	5	4	-1.96	0.48	Pass	Pass	Pass	8	11
40	11	10	-1.32	0.57	Pass	Fail	Pass	8	6
41	12	10	-0.84	1.17	Pass	Pass	Pass	11	12
42	12	12	0.44	-0.14	Pass	Pass	Pass	13	11
43	9	13	-1.77	0.55	Pass	Pass	Pass	7	7
44	NA	NA	-3.02	-1.24	Pass	Pass	Fail	7	8
45	11	8	-1.17	-0.90	Pass	Pass	Pass	14	9

Data are age-adjusted scaled scores (Color Words 3, Color Words 4, Digit Span Forwards, Digit Span Backwards), z-scores (SDMT, Line Orientation), or pass/fail (Incomplete Letters, Object Decision, Interlocking Pentagons). SDMT is also adjusted for education. The Color Words tests are taken from the Delis-Kaplan Executive Function System; the Digit Span tests are taken from the Wechsler Adult Intelligence Scale (Fourth Edition); and the Line Orientation, Incomplete Letters, and Object Decision tests are taken from the Visual Object and Space Perception battery. NA = data not available, SDMT = Symbol Digit Modalities Test.

Supplementary Figure. Flow diagram showing the recruitment process.