

UNIVERSIDADE DE LISBOA
Faculdade de Medicina de Lisboa



COGNITIVE DISORDERS IN LATE-STAGE PARKINSON'S DISEASE

Catarina Filipa Severiano e Sousa

Orientador: Prof. Doutor Joaquim José Coutinho Ferreira

**Coorientador: Prof. Doutora Maria Isabel Segurado Pavão Martins Catarino
Petiz**

**Tese especialmente elaborada para obtenção do grau de Doutor em
Ciências Biomédicas, Especialidade de Neurociências**

2023

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Instituição financiadora: Bolsa de doutoramento da Fundação para a Ciência e a
Tecnologia (SFRH/BD/139853/2018)

2023

A impressão desta tese foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 15 de novembro de 2022.

As opiniões expressas nesta dissertação são da exclusiva responsabilidade do seu autor.

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ABSTRACT

Introduction: Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting more than 1% of the population with more than 65 years of age and with a prevalence set to double by 2030.

In addition to the defining motor symptoms of PD, multiple non-motor symptoms occur. Among them, cognitive impairment is common and can potentially occur at any disease stage. Cognitive decline is usually slow and insidious, but rapid in some cases.

Although it is estimated that the prevalence of Parkinson's disease dementia (PDD) is around 24-31%, several studies have reported a considerable variation in their results, ranging from 8% to 83%, thus making it difficult to accurately estimate dementia frequency in this population.

Methodological characteristics of the studies and clinical and demographic characteristics of PD patients have been associated with this variability. Important methodological features include the analytical design used (cross-sectional versus longitudinal), tests to assess cognition (screening scales versus comprehensive neuropsychological assessment), definitions of dementia, and the criteria for diagnosing PDD and selecting patients. Most of the previous studies on PDD also included patients at varying disease stages.

The phenotype of PD changes considerably in later stage, and the symptoms that contribute most to disability differ from those in early and advanced stages.

The term "late-stage" was proposed to describe PD patients who progressed in severity of treatment-resistant motor and NMS, are highly dependent on caregivers for activities of daily life (ADL), and require specialist medical care.

Late-stage PD (LSPD) is a poorly studied population due to these typically severe motor and non-motor symptoms that often complicate cognitive assessment. Most studies including this population are neuropathological studies (4), assess cognition using cognitive screening tests (5), or do not make a detailed description of cognitive performance (6). It is common to observe the inclusion of this population in heterogeneous groups regarding the motor dysfunction/severity associated with PD, without providing a particular description of this population.

LSPD is a good clinical model to identify the symptoms that cause most disability and mortality, highlighting the symptoms that should be targeted at an earlier stage of disease.

Previous studies have shown that patients with PD had a short life expectancy compared with the general population. Dementia, old age, late age of onset, male gender, and more severe motor impairment have been identified as risks factors for mortality.

In this sense, the identification of the specific features that may predict the progression of cognitive impairment could have important implications for the treatment planning and clinical management of PD patients.

It is of the utmost importance the use of a comprehensive neuropsychological assessment that takes into account the special characteristics of LSPD population (often in an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL), with cognitive instruments validated for PD, preferably brief in their utilization, and that require as little as possible the use of paper and pencil. This is determinant to better understand the pattern of their cognitive impairment, and for improving our understanding of the therapeutic and supportive strategies that must be implemented at an earlier stage of disease, when they are more likely to be effective.

Aim: The present thesis aims: (1) To evaluate the frequency of PDD reported in published observational studies and to examine the impact of methodological, clinical, and demographic characteristics of the studies and PD patients in dementia frequency; (2) To examine the most used instruments to assess cognition in LSPD and to recommend a neuropsychological battery adapted to the special characteristics of this population; (3) To assess the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD; (4) To characterize the cognitive profile of LSPD patients by using a selection of neuropsychological tests proposed by MDS task force on PDD diagnostic procedures, and to examine clinical, demographic, and cognitive variables that are associated with PDD diagnosis.

Methods: To achieve the aims purposed, four research projects were planned.

Research project 1: Systematic review and meta-analysis of observational studies available in EMBASE and MEDLINE databases, from inception to May 2019. The outcome of interest was the number of PDD among a population of PD patients. Pooled estimates of

dementia frequency and 95% confidence intervals (CI) were derived by random effects meta-analysis. We proceeded to a subgroup analysis of the dementia frequency according to the methodological, clinical, and demographic characteristics of the included studies. Meta-regression was used to determine whether a significant difference was present between subgroups. The study protocol was registered at PROSPERO: CRD42020140044.

Research project 2: Systematic review of observational studies available in EMBASE and MEDLINE databases, from inception to May 2019. The outcome of interest was the cognitive tests used in a population of LSPD patients. We grouped them according to the respective cognitive demands described in the studies. We selected the four most used cognitive tests in each cognitive domain and we verified their global characteristics in order to recommend a battery of cognitive instruments, brief in their utilization but covering all relevant cognitive domains, that require as little as possible the use of paper and pencil and preferably not timed (minimized motor demands), and possible to be used in the patient's home.

Research project 3: Cross-sectional study designed to evaluate the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD. The primary objective was to evaluate the frequency of dementia by using MDS clinical criteria for "probable" and "possible" PDD, operationalized according to the Level II procedures which were based on neuropsychological tests, functional autonomy as well as clinical interview. The secondary objective was to evaluate the frequency of dementia by using different diagnostic criteria (MDS PDD Level I, DSM-IV, and DSM-5 criteria).

Research project 4: Cross-sectional study designed to examine the cognitive functioning of the same LSPD study population. The primary objective was to examine the cognitive performance of LSPD patients by using MDS Level II criteria and the suggested neuropsychological tests to diagnose MCI and PDD. The secondary objectives were to examine the cognitive profiles according to the pattern of cognitive impairment and to investigate the associated clinical, demographic, and cognitive variables with PDD diagnosis.

Results: Aim 1: We included 295 studies. The global pooled dementia frequency was 26.3%. These estimations varied according to methodological (14%-55%), clinical (18%-46%), and demographic (21%-43%) variables. The declared primary objective of the studies

(to study PDD), the follow-up length (≥ 7 years), the age of the participants (≥ 75 years), Parkinson's disease (PD) duration (> 10 years), and the Hoehn & Yahr (H&Y) stage (> 3) were important factors affecting reported dementia frequency.

Aim 2: We included 60 studies which reported 53 different neuropsychological instruments used with LSPD patients. Montreal Cognitive Assessment, Digit Span, Trail Making Test, Semantic Fluency, Rey's Auditory Verbal Learning Test, Brief Visuospatial Memory Test-Revised, Boston Naming Test, Judgment of Line Orientation, and Clock Drawing Test were the cognitive instruments that globally best corresponded to the requirements considered important for the selection of the instruments.

Aim 3: 93 participants with a mean age of 75.8 years (SD 6.8) and 16.5 years (SD 7.5) of disease duration were included. 64.3% were classified as demented using the International Parkinson and Movement Disorders Society (MDS) (Level II) clinical diagnostic criteria. We observed a high discrepancy on the frequency of dementia depending on the criteria applied (6.2% with MDS (Level I), 58.8% with DSM-IV, and 72.0% with DSM-5 criteria).

Aim 4: Eighty-four LSPD patients were included (age 75.4 ± 6.9 ; disease duration 16.9 ± 7.5). 54 (64.3%) were classified as demented and presented a global impairment cognitive profile. In the non-demented group (N=30), 25 (83.3%) LSPD patients met the diagnostic criteria for mild cognitive impairment, mostly with multiple domain impairment (96.0%) and a heterogeneous profile. Memory was the most frequent and severely impaired cognitive domain in both groups. Disease disability, orientation, complex order comprehension, verbal learning and visuoconstructive abilities were significantly associated with dementia diagnosis ($p < 0.05$).

Conclusions: The best evidence available in observational studies showed that approximately one-quarter of the PD patients were diagnosed with PDD. Dementia frequency varied according to methodological, clinical and demographic variables. We cannot examine PDD frequency without considering all these variables that have an impact on it.

Based on global characteristics and psychometric properties of the more frequently used cognitive instruments in the studies that reported a neuropsychological assessment, we recommended a battery taking into account the special characteristics of LSPD population.

We found a frequency of dementia below what was observed in similar populations. The particular characteristics of our sample may have contributed as protective factors for late-stage dementia. Dementia frequency varied depending on the criteria used mainly due to the presence of major depression.

Cognitive impairment in multiple domains was common in LSPD patients. The most frequent and prominent deficits were in the memory domain, with a strong interference from attention impairment. Disease disability, orientation, complex order comprehension, verbal learning and visuoconstructive abilities proved to be important determinants for dementia diagnosis.

Key words: Parkinson's disease, late-stage, dementia, diagnostic criteria, cognitive impairment, cognitive assessment, cognitive tests, systematic review.

RESUMO

Introdução: A doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum. Afeta mais de 1% da população com mais de 65 anos de idade e prevê-se que a sua prevalência duplique até 2030.

Para além dos sintomas motores que a definem, ocorrem na DP múltiplos sintomas não-motores. Entre eles, são comuns os défices cognitivos que podem surgir em qualquer fase da doença. O declínio cognitivo geralmente é lento e insidioso mas, nalguns casos, pode evoluir rapidamente.

Embora se estime que a prevalência de demência na DP é de cerca de 24-31%, vários estudos têm relatado uma variação considerável nos seus resultados, variando de 8% a 83%, tornando difícil estimar com precisão a frequência de demência nesta população.

As características metodológicas dos estudos e as características clínicas e demográficas dos doentes com DP têm sido associadas a esta variabilidade. Entre as características metodológicas estão incluídos o desenho analítico utilizado (transversal versus longitudinal), os testes para avaliar a cognição (escalas de rastreio versus avaliação neuropsicológica completa), definições de demência, e os critérios para diagnosticar demência e seleccionar os doentes. A maioria dos estudos anteriores acerca da demência na DP incluíram também doentes em diferentes fases da doença.

O fenótipo da DP altera-se consideravelmente nas fases tardias da doença, e os sintomas que mais contribuem para a incapacidade diferem dos sintomas que surgem nas fases precoces e avançadas.

O termo "fase tardia" foi proposto para descrever os DP que progrediram na gravidade dos sintomas motores e não-motores resistentes ao tratamento, altamente dependentes dos cuidadores para atividades de vida diária, e que requerem cuidados médicos especializados.

Os doentes de Parkinson em fase tardia de doença (LSPD) são uma população mal estudada devido à gravidade destes sintomas motores e não-motores que muitas vezes dificultam a avaliação cognitiva. Grande parte dos estudos que incluem esta população são estudos neuropatológicos, avaliam cognição utilizando testes de rastreio cognitivo, ou não fazem uma descrição detalhada do seu desempenho cognitivo. É comum observar a inclusão desta

população em grupos heterogêneos no que diz respeito à disfunção/gravidade motora associada à DP, sem disponibilizarem uma descrição específica desta população.

A fase tardia da DP é um bom modelo clínico para identificar os sintomas que causam maior disfuncionalidade e mortalidade, destacando assim os sintomas que devem ser alvo de intervenção em fases mais precoce da doença.

Estudos anteriores revelaram que os DP têm uma esperança de vida curta em comparação com a população em geral. Demência, idade avançada, idade tardia no início da DP, sexo masculino e disfuncionalidade motora mais grave foram identificados como fatores de risco para a mortalidade.

Neste sentido, a identificação das características específicas que podem prever a progressão do declínio cognitivo pode ter implicações importantes para o planejamento do tratamento e gestão clínica dos doentes com DP.

É de extrema importância a realização de uma avaliação neuropsicológica completa que tenha em consideração as características especiais dos DP em fase tardia (muitas vezes com idade avançada, com sintomas motores e não-motores resistentes ao tratamento, e altamente dependentes dos cuidadores nas atividades de vida diária), com testes cognitivos validados para a DP, preferencialmente breves na sua utilização, e que exijam o mínimo possível a utilização de papel e lápis. Este procedimento é determinante para compreendermos melhor o padrão das alterações cognitivas dos DP, e para melhorar a nossa compreensão acerca das estratégias terapêuticas e de apoio que devem ser implementadas em fases mais precoces da doença, quando são mais propensas a serem eficazes.

Objetivos: A presente tese visa: (1) Avaliar a frequência de demência da DP relatada nos estudos observacionais publicados e examinar o impacto das características metodológicas, clínicas e demográficas dos estudos e dos doentes com DP na frequência de demência; (2) Averiguar quais os instrumentos mais utilizados para avaliar cognição na fase tardia da DP e recomendar uma bateria de avaliação neuropsicológica adaptada às características especiais desta população; (3) Avaliar a frequência da demência e determinar a aplicabilidade e o impacto da utilização de diferentes critérios de diagnóstico na LSPD; (4) Caracterizar o perfil cognitivo dos DP em fase tardia, utilizando uma seleção de testes neuropsicológicos efetuada a partir da proposta do grupo de trabalho da *Movement Disorder*

Society (MDS) que desenvolveu os procedimentos a adotar para o diagnóstico de demência; e examinar as variáveis clínicas, demográficas e cognitivas associadas ao diagnóstico de demência;

Métodos: Para alcançar os objetivos, foram planeados quatro projetos de investigação.

Projeto de investigação 1: Revisão sistemática e meta-análise de estudos observacionais disponíveis nas bases de dados EMBASE e MEDLINE, desde o início até maio de 2019. O *outcome* primário foi o número de doentes com demência numa população com DP. A estimativa da frequência de demência e os intervalos de confiança de 95% (CI) foram calculados através de uma meta-análise de efeitos aleatórios. Procedemos a uma análise de subgrupos da frequência da demência de acordo com as características metodológicas, clínicas e demográficas dos estudos e dos DP incluídos. Efetuámos uma meta-regressão para averiguar se existiam diferenças significativas entre os subgrupos. O protocolo de estudo foi registado na PROSPERO: CRD42020140044.

Projeto de investigação 2: Revisão sistemática dos estudos observacionais disponíveis nas bases de dados EMBASE e MEDLINE, desde o início até maio de 2019. O *outcome* primário foram os testes cognitivos utilizados para avaliar a população de DP em fase tardia. Agrupámo-los de acordo com as respetivas atribuições para avaliar os diferentes domínios cognitivos, descritas nos estudos. Seleccionámos os quatro testes cognitivos mais utilizados para cada domínio cognitivo e verificámos as suas características globais com o intuito de recomendarmos uma bateria de avaliação cognitiva breve na sua utilização, mas abrangendo todos os domínios cognitivos relevantes, que requeiram o mínimo possível a utilização de papel e lápis e, preferencialmente, não cronometrados (exigências motoras minimizadas), e possível de serem utilizados no domicílio dos DP.

Projeto de investigação 3: Estudo transversal, concebido para avaliar a frequência de demência e determinar a aplicabilidade e o impacto da utilização de diferentes critérios de diagnóstico nos DP em fase tardia. O objetivo primário foi avaliar a frequência da demência utilizando os critérios clínicos propostos pela MDS para demência "provável" e "possível", operacionalizados de acordo com os procedimentos de nível II que se basearam em testes neuropsicológicos, autonomia funcional e entrevista clínica. O objetivo secundário foi avaliar a frequência da demência utilizando diferentes critérios de diagnóstico (critérios de diagnóstico de demência nível I propostos pela MDS, DSM-IV e DSM-5).

Projeto de investigação 4: Estudo transversal, concebido para examinar o funcionamento cognitivo da mesma população de DP em fase tardia. O objetivo primário foi avaliar o desempenho cognitivo dos DP em fase tardia, utilizando os critérios e os testes neuropsicológicos sugeridos pela MDS (Nível II) para diagnosticar defeito cognitivo ligeiro e demência. Os objetivos secundários foram examinar os perfis cognitivos de acordo com o padrão das alterações cognitivas e investigar as variáveis clínicas, demográficas e cognitivas associadas com o diagnóstico de demência.

Resultados: Objetivo 1: Incluímos 295 estudos. A estimativa global da frequência de demência foi 26,3%. Esta estimativa variou de acordo com variáveis metodológicas (14%-55%), clínicas (18%-46%) e variáveis demográficas (21%-43%). O objetivo primário dos estudos (avaliar demência), a duração do *follow-up* (≥ 7 anos), a idade dos participantes (≥ 75 anos), a duração da doença de Parkinson (> 10 anos) e o estadió Hoehn & Yahr (H&Y) (> 3) foram fatores importantes que afetaram a frequência da demência reportada.

Objetivo 2: Incluímos 60 estudos que reportaram 53 testes neuropsicológicos utilizados para avaliar cognição na DP em fase tardia. O *Montreal Cognitive Assessment*, *Digit Span*, *Trail Making Test*, *Semantic Fluency*, *Rey's Auditory Verbal Learning Test*, *Brief Visuospatial Memory Test-Revised*, *Boston Naming Test*, *Judgment of Line Orientation*, e o *Clock Drawing Test* foram os testes cognitivos que globalmente melhor corresponderam aos requisitos considerados importantes para avaliar cognição na DP em fase tardia.

Objetivo 3: Foram incluídos 93 DP com uma idade média de 75,8 anos (SD 6,8) e 16,5 anos (SD 7,5) de duração da doença. Utilizando os critérios de diagnóstico propostos pela MDS (Nível II), foram diagnosticados 64,3% DP com demência. Observámos uma elevada discrepância na frequência da demência em função dos critérios aplicados (6,2% de acordo com os critérios de diagnóstico propostos pela MDS (Nível I), 58,8% com critérios de diagnóstico do DSM-IV e 72,0% com critérios de diagnóstico do DSM-5).

Objetivo 4: Foram incluídos 84 DP em fase tardia (idade $75,4 \pm 6,9$; duração da doença $16,9 \pm 7,5$). 54 (64,3%) DP foram diagnosticados com demência e apresentaram um perfil cognitivo com alterações globais. No grupo de DP sem demência (N=30), 25 (83,3%) reuniram critérios para diagnóstico de defeito cognitivo ligeiro, com alterações em múltiplos domínios (96,0%) e um perfil de alterações heterogéneo. A memória foi o domínio cognitivo mais frequente e severamente alterado em ambos os grupos. A disfuncionalidade motora

associada à DP, a orientação, a compreensão de ordens complexas, a aprendizagem e o desempenho visuoespacial surgiram significativamente associados ao diagnóstico de demência ($p < 0.05$).

Conclusões: A evidência científica disponibilizada pelos estudos observacionais revelou que aproximadamente um quarto dos doentes com DP reúnem critérios para diagnóstico de demência. A frequência da demência variou de acordo com variáveis metodológicas, clínicas e demográficas. Não podemos analisar a frequência de demência sem considerarmos todas as variáveis que nela têm impacto.

Com base nas características globais e nas propriedades psicométricas dos instrumentos cognitivos mais utilizados nos estudos que relataram uma avaliação neuropsicológica, propusemos uma bateria de avaliação cognitiva que contempla as características especiais desta população.

Observamos uma frequência de demência abaixo do que foi observado em estudos efetuados com populações semelhantes. As características particulares da nossa amostra de DP podem ter contribuído como fatores de proteção para a demência nas etapas tardias da DP. A frequência de demência variou de acordo com os critérios de diagnóstico utilizados, sobretudo devido à presença de depressão maior.

As alterações cognitivas em múltiplos domínios foi frequente nos DP em fase tardia. Os défices mais frequentes e proeminentes foram ao nível da memória, mas com uma significativa interferência da atenção. A disfuncionalidade motora associada à DP, a orientação, a compreensão de ordens complexas, a aprendizagem e o desempenho visuoespacial revelaram-se importantes para o diagnóstico da demência.

Palavras-chave: Doença de Parkinson, fase tardia, demência, critérios de diagnóstico, alterações cognitivas, avaliação cognitiva, testes cognitivos, revisão sistemática.

ABBREVIATION

AChE Acetylcholinesterase

AD Alzheimer's disease

ADL Activities of daily living

APOE ε4 Apolipoprotein E allele 4

ARM Associative reinstatement memory

BDNF Brain-derived neurotrophic factor

CBF Cerebral blood flow

CNS Central nervous system

CSF Cerebrospinal fluid

DAT Dopamine transporter

DBS Deep brain stimulation

DLB Dementia with Lewy bodies

DTI Diffusion tensor imaging

EGF Epidermal growth factor

fMRI Functional magnetic resonance imaging

GBA Glucocerebrosidase gene

H&Y Hoehn and Yahr

IADL Instrumental activities of daily living

LB Lewy body

LRRK2 Leucine-rich repeat kinase 2 gene

LSPD Late-stage Parkinson's disease

MCI Mild cognitive impairment

MDS Movement disorder society

MIBG Scintigraphy using metaiodobenzylguanidine labeled to iodine-123 or iodine-131

MMSE MiniMental state examination

MoCA Montreal cognitive assessment

MRI Magnetic resonance imaging

MTL Medial temporal lobe

NCD Neurocognitive disorder

NFT Neurofibrillary tangles

NMS Non-motor symptoms

NPA Neuropsychological assessment

p-tau Phosphorylated tau
PD Parkinson's disease
PD-CN Parkinson's disease without cognitive impairment
PD-MCI Parkinson's disease mild cognitive impairment
PDD Parkinson's disease dementia
PET Positron emission tomography
PINK1 PTEN-induced kinase 1
RBD REM sleep behavioral disorder
ROI Region of interest
S&E Schwab and England
SCD Subjective cognitive decline
SCOPA-COG Scales for outcome in Parkinson's disease-cognition
SD Standard deviation
SN Substantia nigra
SNc Substantia nigra pars compacta
SNCA α -synuclein gene
SPECT Single-proton emission computed tomography
t-tau Total tau
TFAM Transcription factor A, mitochondrial
TNF Tumor necrosis factor
UPDRS Unified Parkinson disease rating scale
VACHT Vesicular acetylcholine transporter
VBM Voxel-based morphometry
VMAT2 Vesicular monoamine transporter
VPS35 Vacuolar protein sorting ortholog 35
VTA Ventral tegmental area
WMS Wechsler memory scale

Chapter I: Introduction

1. Parkinson's Disease

Idiopathic Parkinson's disease (PD) is the most common movement disorder and the second most common age-related neurodegenerative disorder after Alzheimer's disease. The Global Burden of Disease Study estimates that 6.2 million individuals currently have PD and this prevalence is expected to increase up to 12.9 million by 2040¹.

Population-based prevalence and incidence studies show a strong correlation between PD and age², with approximately 1% of people older than 60 years being affected³. At the age of 80 years, the prevalence rises to 3%. To date, aging represents the most significant risk factor for developing PD⁴. This increasing prevalence with age is higher in men than women, and men also present an increased risk of developing PD, leading to a higher prevalence of PD in men (1.4 to 2:1.0 male-female ratio)⁵.

Ethnicity and geographic variation play a role in many characteristics of Parkinson's disease, including its epidemiology⁶. In Portugal the adjusted prevalence of PD above 50 years is 0.24% with the total number of cases in Portuguese population being 180/100 000 inhabitants and higher prevalence in men was reported (0.45% vs 0.12%)⁷.

Most cases of PD are idiopathic, however there are known genetic and environmental factors that have been associated with the development of PD⁵. For instances, high prevalence of leucine-rich repeat kinase 2 (LRRK2) mutation in familial (16.1%) and sporadic (3.7%) PD patients have been reported in Portugal⁸.

Parkinson's disease diagnosis is still grounded in clinical criteria. It is based on the presence of bradykinesia and at least one of the other features – tremor, rigidity and postural instability⁹. However, neuroimaging studies focusing on loss of neuromelanin in substantia nigra present a growing evidence helping clinicians to differentiate atypical parkinsonism and/or essential tremor from Parkinson's Disease¹⁰. Additionally, the good response to treatment is also a key element that supports clinical criteria-based diagnose⁹.

The neuropathological hallmarks of PD are neuronal loss in the substantia nigra, which causes striatal dopaminergic deficiency, and alpha-synuclein accumulation in intraneuronal inclusions, referred to as Lewy bodies. However, multiple mechanisms and pathway

dysfunctions play a role in the pathogenesis of PD, including oxidative stress, dysfunctional mitochondria, cellular calcium imbalance, neuroinflammation, and other neurotransmitter system deficits¹¹.

The etiopathology of sporadic PD is still unknown. However, studies suggest that the interaction of extrinsic and intrinsic factors, such as exposure to environmental toxins and specific immune responses, may trigger disease onset¹². According to Braak's hypothesis, the idiopathic incidence of PD may originate outside the central nervous system (CNS) while "the stereotypic topographic expansion pattern of the lesions may resemble that of a falling row of dominos"¹³.

Thus, PD is now viewed as a slowly progressive neurodegenerative disorder that begins years before diagnosis can be made, implicates multiple neuroanatomical areas, results from a combination of genetic and environmental factors, and manifests with a broad range of symptoms¹⁴.

As PD progresses, the loss of substantia nigra dopaminergic neurons results in the typical motor symptoms (resting tremor, rigidity, bradykinesia, and postural instability), initially described in 1817 by James Parkinson in his "Essay on the shaking palsy". However, non-motor features such as cognitive impairment have a significant role in this progressive, multisystem condition, and often precede the onset of motor symptoms¹⁵.

Motor features in patients with PD are heterogeneous, which has prompted attempts to classify subtypes of the disease with distinct aetiologies and pathogenesis¹⁶. According to Kalia & Lang (2015)¹⁴, a consensus on the classification of PD subtypes has not yet been established, but empirical clinical observations suggest two major subtypes: tremor-dominant PD (with a relative absence of other motor symptoms) and non-tremor-dominant PD (which includes phenotypes described as akinetic-rigid syndrome and postural instability gait disorder). An additional subgroup has a mixed or indeterminate phenotype with several disabling motor symptoms. Jankovic et al. (1990)¹⁷ referred that the course and prognosis of PD differ between these subtypes, being tremor-dominant slower in its progression and less disabling than non-tremor-dominant subtype.

Non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue. These symptoms are common in early PD¹⁸ and are associated with reduced health-related quality of life¹⁹.

Non-motor features are also frequently present in PD before the onset of the classical motor symptoms²⁰. This premotor or prodromal phase of the disease can be characterized by impaired olfaction, constipation, depression, excessive daytime sleepiness, and REM sleep behavioral disorder (RBD). This premotor phase can be prolonged. The average latency between onset of RBD and occurrence of parkinsonian motor symptoms is 12-14 years²⁰.

Progression of PD is characterized by worsening of motor features, appearance of patients' physical dependence and motor complications, whose severity classically define the beginning of the advanced PD stage^{21,22}. This motor progression is non-linear, with a more rapid decline in motor function in earlier stages compared with later stages²³. As the disease advances, there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia, psychosis²⁴, postural instability, freezing of gait, falls, and dysphagia^{14,22}. These treatment-related complications are substantial challenges in the clinical management of the advanced stage of PD. However, in later stages, disability from motor complications seemed to decline relative to disability associated with symptoms that are resistant to levodopa treatment²⁴⁻²⁶.

For several decades, attempts have been made to stage the clinical evolution of PD²⁷. In the pre-levodopa era, Hoehn & Yahr (H&Y) developed a staging system to describe clinical function at different stages of disease, including the concepts of disability (functional deficits) and impairment (objective signs)^{27,28}. The H&Y scale was based on the concept that severity of parkinsonism depended mainly on the presence of bilateral symptoms and compromise of gait and balance, and that physical independence was ultimately lost owing to postural instability, gait disorder and severe bilateral parkinsonism^{27,28}. This scale has been the most widely used tool to stage the severity of parkinsonism²⁹, and available data show significant correlations between later H&Y stages and worse scores for motor impairment^{30,31}. In addition to physical signs, the H&Y scale can capture other important features of PD: when patients reach stage 3, risk of dementia is increased and survival decreases, and total in the Unified Parkinson Disease Rating Scale (UPDRS) scores increase despite drug adjustment^{28,32}. Advanced PD is commonly defined as stages higher than 3 on the H&Y scale, which corresponds with loss of physical independence²⁸ (Figure 1).

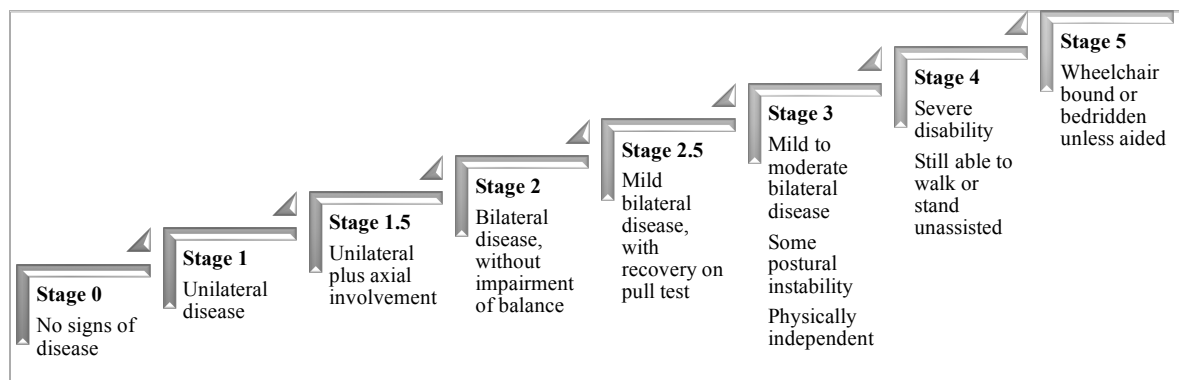


Figure 1. The modified Hoehn & Yahr Parkinson's disease severity staging scale

1.1 The Late-Stage Parkinson's Disease: Concept and Clinical Features

In the last two decades, it has been observed that a small subset of advanced PD patients progress to a later phase of the disease, clinically discernible from the previous one³³.

The clinical progression of PD in later stages is dominated by the emergence or aggravation of symptoms that are nonresponsive to levodopa^{24,25,33}. These include non-motor symptoms (NMS) such as dementia, psychosis or dysautonomia, and axial motor symptoms such as falls, postural instability or dysphagia³³. These symptoms are the main determinants of quality of life, and are a major source of disability, as well as being risk factors for institutionalization and death^{24-26,33-39}. As such, according to Coelho & Ferreira 2012³³, NMS and axial motor symptoms that are resistant to levodopa dominate the clinical picture of late stages of PD and should be incorporated into the classic model of PD progression (Figure 2).

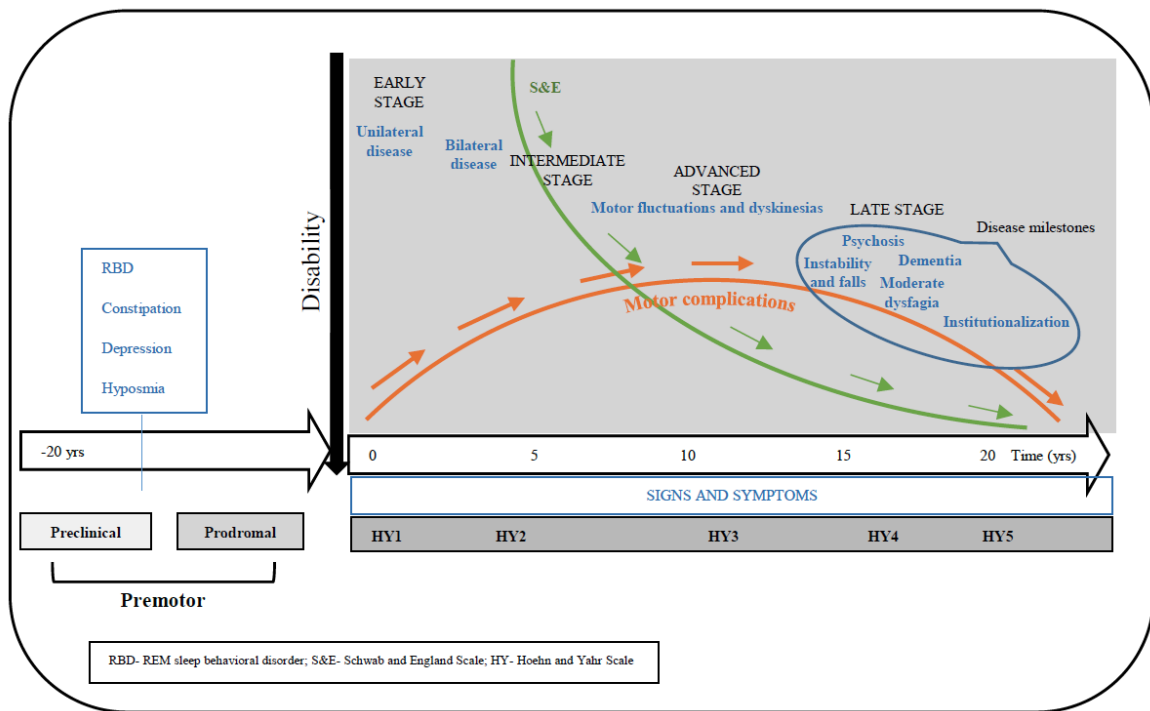


Figure 2. Parkinson's disease progression and staging

In this latter stage, late-stage Parkinson's disease (LSPD) patients usually present a severe bradykinesia with reduced or absent appendicular rigidity^{26,40}. Disability from motor complications is reduced, because these complications attenuate naturally, either due to levodopa treatment reduction or in response to device-aided therapies^{41,42}. Conversely, disability is related to a cluster of variables that consists of NMS, as cognitive impairment, psychosis, depression, daytime sleepiness, autonomic dysfunction, and axial symptoms poorly responsive to levodopa^{26,40}.

Taken as a whole, we have a "late" phenotype³³. Some patients who enter late-stage PD will have had longer disease duration than other patients at the same disease stage, with earlier disease onset and motor complications that may, at some point, justify device-aided therapies like deep brain stimulation (DBS) because of severe disability. Another group of patients will have had a shorter disease course, with older age at onset and few or no motor complications, and this group will eventually enter late-stage PD without prior DBS³³.

Four principal disability milestones, i.e., symptoms of disease progression that should draw additional medical attention, have been identified to precede death by around 5 years, independently from disease duration and age of onset: visual hallucinations (5.1 years), falls (4.1 years), dementia (3.3 years), and institutionalization (3.3 years)⁴³ (Figure 3). Other

recognized red flags for a poor outcome are the need for a formal caregiver and the presence of swallowing problems⁴⁴.

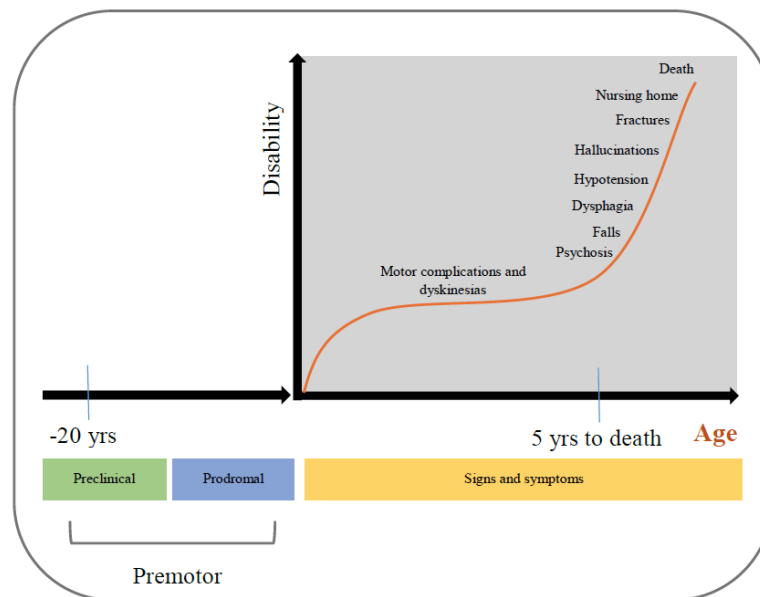


Figure 3. Late-stage Parkinson's disease milestones

Coelho & Ferreira (2012)³³ proposed the term “late-stage” to describe patients who are highly dependent on caregivers for activities of daily living (ADL), owing to treatment-resistant motor symptoms or NMS, who require specialist medical care, although they are usually excluded from clinical trials and even from observational studies.

For this definition, the authors proposed behind a H&Y motor severity scale score higher than 3, the Schwab and England (S&E) ADL Scale⁴⁵, which is a questionnaire that measures patients' perceived functional independence. Scoring ranges from 0% (denoting a bedridden or vegetative state) to 100% (denoting normal ability with complete independence). The authors proposed an operational definition of late-stage PD that includes a score on the S&E scale of less than 50% during periods of adequate symptom control. A score of 50% corresponds with the patient requiring help with half of their chores and experiencing difficulty with all activities. A score of 40% corresponds with the patient being highly dependent on support from carers, able to assist with all chores, but unable to complete most tasks alone⁴⁵ (Figure 4).

100%	Completely independent. Able to do all chores without slowness, difficulty, or impairment.
90%	Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.
80%	Independent in most chores. Takes twice as long. Conscious of impairment.
70%	Not completely independent. More difficult with chores. Three to 4 times as long on chores for some. May take large part of day for chores.
60%	Some dependency. Can do most chores, but very slowly and with much effort. Errors, some chores impossible.
50%	More dependent. Help with half of chores. Difficulty with everything.
40%	Very dependent. Can assist with all chores but accomplish few alone.
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.
20%	Nothing alone. Can occasionally provide slight help with chores.
10%	Totally dependent, helpless.
0%	Vegetative. Functions such as swallowing, bladder and bowel are not functioning. Bedridden.

Figure 4. Schwab & England scale score

The prevalence of late-stage PD is likely to increase in the future owing to better general health care, increased longevity, and better clinical management of PD⁴⁶. According to Coelho & Ferreira (2012)³³, clinical assessment and therapeutic management of LSPD patients should focus on such problems as falls and postural instability, urinary dysfunction, freezing, bradykinesia, dysarthria and choking, dementia, psychosis, excessive daytime sleepiness, apathy, depression, and anxiety. Treatment for motor complications should be less of a priority.

These particular changes observed in LSPD patients probably reflect the dynamics of neurodegeneration over time, together with the effects of antiparkinsonian drugs^{47,48}. In this sense, late-stage PD is a good clinical model to identify the symptoms that cause most disability, and even mortality, in patients who are severely disabled, highlighting the symptoms that should be targeted at an earlier stage of disease³³. On the other hand, pathogenesis and neuropathology of late-stage levodopa-unresponsive symptoms are key areas for future PD research³³. Loss of dopaminergic neurons in the substantia nigra pars compacta is considered to be the key biological substrate for the classic motor features of PD⁴⁹. However, extranigral involvement has been extensively documented in PD, and has been implicated in the pathogenesis of levodopa-unresponsive motor symptoms and NMS⁵⁰⁻⁵², like cognitive impairment.

2. *Parkinson disease-associated cognitive impairment*

Cognitive decline is among the most common non-motor symptoms. It is up to six times more common in individuals with PD than in the healthy population⁵³ and is one of the most important non-motor manifestations of PD, integral to the natural history of the disease¹¹.

As one of the most severe and disabling non-motor symptoms of PD, cognitive impairment, particularly dementia, has been statistically associated with mortality⁵⁴. In addition, cognitive impairment can severely affect quality of life, impairs social function, intensifies caregiver burden and the costs of disease-related medical care, even at the early stages of PD⁵⁵⁻⁵⁸, thereby representing a high priority for both patients and care partners.

Despite increased research over the past two decades, the knowledge and treatment of cognitive difficulties in PD lag far behind the knowledge and treatment of its motor features¹¹. As there is no treatment to prevent or delay cognitive decline in PD, no effective treatments for Parkinson's disease with mild cognitive impairment (PD-MCI), and only one treatment (cholinesterase inhibitors) approved for PDD, continued efforts for a better comprehension of this complex feature of PD are required^{11,59,60}.

Cognitive decline can occur prior to or at the time of a diagnosis of PD or a few years or decades after diagnosis and has high variability in its clinical severity, the cognitive domains involved and the rate of progression^{11,61}.

Aarsland (2001)⁵³ and Perez (2012)⁶², in their longitudinal cohort studies have found that people with PD have a 2.5–6-times higher risk of developing dementia than people without PD of similar age. However, the epidemiology of cognitive impairment in PD is not entirely clear, as population-based studies of PD rarely include PDD or PD-MCI and most studies assess the prevalence and incidence of cognitive impairment in established PD cohorts¹¹.

The reported prevalence of PD-MCI varies widely, which has been attributed to the use of different methodologies in the studies. Recently, Baiano et al (2020)⁶³ in their meta-analysis reported pooled PD-MCI prevalence to be 40%. Broeders et al (2013)⁶⁴ and Hoogland et al (2017)⁶⁵, in their studies, by using the Movement Disorder Society Task Force Level II criteria, enrolling early stage and *de novo* PD, reported prevalence varying from 20% to 41%. Pedersen et al (2017)⁶⁶, by following a population-based cohort of early-stage PD found that in those with normal cognition at baseline, the cumulative incidence of PD-MCI

was 9.9% after 1 year and 28.9% after five years of follow-up. The estimated prevalence of MCI in the general older population (aged 60–90 years) ranges between 16% and 20%⁶⁷.

As for type of PD-MCI, prevalence of multiple-domain was estimated in 31%⁶³. Interestingly, only disease progression and lower education levels significantly moderated the prevalence rate of PD-MCI.

Patients with PD-MCI are also more likely to eventually develop dementia²⁵ and to develop it earlier^{68,69} than PD patients without cognitive impairment.

The cross-sectional proportion of patients with PD who have dementia is 24–31%⁷⁰. Although findings vary among studies, the cumulative prevalence of PDD in patients with a mean age at diagnosis from 54 to 70.2 years is 17% at 5 years after diagnosis⁷¹, 46% at 10 years after diagnosis⁷² and 83% at 20 years after diagnosis^{25,37} (Table 1), compared with a global prevalence of 5–7% of dementia in the general population with more than 60 years of age⁷³.

Although several risk factors for cognitive impairment in individuals with PD have been identified, further understanding of the mechanisms driving this difference and identifying those with a high risk of early dementia to allow for closer monitoring and management is crucial¹¹.

	Criteria	Disease duration (yrs)	Dementia frequency
Taylor 1985 ⁷⁴	Neuropsychological tests	NS	8%
Williams-Gray 2009 ⁷¹	MMSE, DSM-IV	5	17%
Katzenschlager 2008 ⁷⁵	MMSE, DSM-IV	19	18%-29%
Williams-Gray 2013 ⁷²	MMSE, DSM-IV	10	46%
Hely 2005 ²⁴	Neuropsychological tests	15	48.5%
Coelho 2010 ²⁶	DSM-IV	18	50%
Papapetropoulos 2005 ⁷⁶	Medical records	12	50.7%
Kempster 2007 ⁷⁷	Medical records	10-18	55.6%
Aarsland 2003 ⁷⁸	DSM-III-R	8	78.2%
Hely 2008 ²⁵	Neuropsychological tests	20	83%

Table 1. Dementia frequency reported by different cohort studies

NS- not specified

A better understanding of the contribution of different pathological substrates to the development of dementia in PD would be useful for the planning and analysis of the efficacy of these new treatments⁷⁹.

To date, it is still an ongoing debate as to the pathogenesis of cognitive dysfunction in PD. Some authors believe that not only neurochemical alterations in dopaminergic, cholinergic, and other systems but also neuropathological contributions of limbic and cortical Lewy bodies, neurites, amyloid deposition, neurofibrillary tangles, cerebrovascular disease, mitochondrial dysfunction, inflammation, and neurotrophic factors have frequently given rise to cognitive deficits in PD⁷⁸.

In healthy individuals, cortical dopamine modulation can boost working memory as well as visuospatial and attentional processing, and promotes cognitive effort^{80,81}, suggesting a key role for dopamine in cognitive function¹¹.

By definition, all patients with PD have a moderate-to severe loss of dopaminergic neurons in the nigrostriatal projection pathway¹¹.

In patients with PD-MCI occurs more widespread degeneration of dopaminergic terminals in the striatum, particularly denervation of dopaminergic terminals in the associative dorsal caudate nucleus, when compared with those with PD without cognitive impairment¹⁵ (Figure 5). However, in patients with PD-MCI, there is relative preservation of other dopaminergic systems in the brain, whilst those with PDD have a considerable loss of the lateral dopaminergic system to frontal, parietal and temporal cortical regions¹⁵.

Extensive literature has been discussing the relationships among executive function and dopamine.

A research with functional magnetic resonance imaging (fMRI) showed that the neural activity of prefrontal cortex, striatum, and thalamus in frontal- striatum regions decreases when executive dysfunction of PD patients is tested with task-switching and working memory tests⁸².

The frontal cortex and the hippocampus, two areas of dense noradrenergic innervation originating in the locus coeruleus, are particularly important for cognitive behaviours⁸³.

The locus coeruleus contains noradrenaline-synthesizing neurons⁸⁴. These neurons promote waking and arousal and are involved in sensory signal detection and modulation of various aspects of cognition but particularly in attention, behavioral flexibility, working and long-term memory⁸³.

The evaluation of dopaminergic, noradrenergic and serotonergic markers in cerebrospinal fluid (CSF) and serum of patients with PD shows increasing alterations in noradrenergic markers that differentiate controls from PD and PD from PDD cases⁸⁵, with only noradrenergic markers significantly reduced in all brain tissue regions from patients with PDD⁸⁶.

The basal forebrain cholinergic neurons are the major source of cholinergic innervation to the neocortex, hippocampus and amygdala^{87,88}. These neurons provide important control over circuit dynamics underlying cognitive processing, in particular attention and executive and memory functions⁸⁹.

Pereira et al (2020)⁹⁰, in their longitudinal study observed that a reduction in the volume and density of the basal forebrain cholinergic region and their projections to the neocortex, hippocampus and amygdala is associated with cognitive decline over a 4-year period⁹⁰.

It is assumed that the disrupted ascending cholinergic pathway is of great importance to progress to dementia of PD, which is supported by neuroimaging findings that patients with PD and PDD both have cholinergic neuron deficits with vesicular acetylcholine transporter (VACHT) and acetylcholinesterase (AChE)^{91,92}.

The loss of basal forebrain cholinergic projections to the hippocampus correlates with memory deficits and conversion to PDD⁹³. Loss of hippocampal cholinergic fibres and activity occurs in patients with PD-MCI, whereas those with PDD have a subsequent increase in α -synuclein deposition and dysfunction in both the basal forebrain and hippocampal systems⁹⁴.

The loss of brainstem serotonergic neurons occurs preclinically and prior to the loss of dopamine neurons in PD¹¹. However, there is no clear relationship between the degeneration of serotonergic neurons and cognitive decline⁹⁵, with both disease progression and older age affecting the severity of degeneration in serotonergic neurons⁹⁶.

In PD, the loss of brain serotonergic structures relates to the deposition of β -amyloid, and medications that increase serotonin neurotransmission reduce β -amyloid peptide generation and reduce the risk of cognitive decline⁹⁷.

The degeneration of serotonergic neurons in PD is linked to motor and other nonmotor features such as sleep dysfunction, depression and anxiety^{98,99}.

Autopsy studies are the definitive approach to identify the pathological basis of dementia in PD. They also ensure that the clinical diagnosis of PD is accurate, which is important given known diagnostic error rates in vivo^{100,101}.

Propagation of α -synuclein aggregates to the neocortical regions is the main substrate of cognitive decline in PDD and dementia with Lewy bodies (DLB)⁷⁹.

In addition to the deposition of α -synuclein in Lewy pathologies, other prevalent age-related pathologies can coexist with PD and DLB to affect cognition¹⁰². The most common neuropathology in PDD is limbic and/or neocortical Lewy pathology, with few documented cases without this pathology¹⁰³.

The most common age-related pathologies in individuals with PD and cognitive impairment are those associated with AD, extracellular β -amyloid and intracellular tau deposition¹¹.

One of the earliest age-related pathological markers is the deposition of extracellular β -amyloid in association cortices¹¹.

However, some authors observed that the prevalence of positive β -amyloid scanned by PET in PD-MCI (5–11%) is similar to that found in aged-matched controls¹⁰⁴⁻¹⁰⁶, suggesting that the initiation of cognitive decline in PD is not due to significant β -amyloid deposition¹¹.

Smith et al (2019)¹⁰³ in their meta-analysis of more sensitive histological analyses on post-mortem brain tissue found moderate-to-severe extracellular β -amyloid in cortical and subcortical regions in about half of samples with PDD and severe tau pathology in hippocampal and neocortical regions in around one-third of samples with PDD.

In patients with PDD who have coexisting AD pathology, amyloid angiopathy and neuroinflammation are common and cognitive decline is more rapid with earlier mortality than in PDD without pathological AD¹⁰³. Patients with PDD and AD pathology are older at PD onset¹⁰⁷ and have more impaired language, with the severity of language dysfunction correlating with increased measures of tau and not of β -amyloid deposition¹⁰⁸.

Finally, previous in vitro and animal studies indicate that α -synuclein, amyloid- β and tau may promote one another's aggregation to accelerate neurodegeneration and dementia¹⁰⁹⁻¹¹². Multiple studies found correlations that support this theory in PD cases¹¹³⁻¹¹⁶.

This suggests that disease-modifying therapies targeted against one pathology may inhibit the proliferation of another, increasing the overall benefit¹⁰³. This effect has been observed in a murine model, in which mice over-expressing α -synuclein were protected from both cognitive and motor impairment after treatment with an antibody for tau¹¹⁷. How this would translate to clinical research involving humans remains to be evaluated.

Most cases of PD are sporadic, although a significant minority have strong genetic determinants (termed 'monogenic PD') and a proportion of individuals carry one or more genetic variants known to increase PD risk¹¹⁸.

Clinically, there are differences between the sporadic and monogenic forms of PD, and this includes the risk of cognitive decline¹¹⁸. Genetic risk variants may have an influence on the incidence and rate of progression of cognitive impairment in sporadic PD¹¹⁸.

Some of the most studied genes include α -synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), as well as the glucocerebrosidase (GBA) gene¹¹⁸.

According to Gonzalez-Latapi et al (2021)¹¹⁸, SNCA mutations cause autosomal-dominant PD and are associated with severe effects on cognition.

Mutations in the GBA gene are reported to be associated with faster rates of motor and cognitive progression compared with sporadic PD¹¹⁸ and with a 3.2-fold increased risk of dementia or cognitive impairment¹¹⁹.

Further work in longitudinal cohorts of genetic PD in both pre-symptomatic and symptomatic individuals is needed to better elucidate the nature of the observed associations¹¹⁸. There are no available studies that specifically examine the association between neural network dysfunction, neuropathological findings and domain impairment in genetic PD¹¹⁸.

Many of the pathologies associated with cognitive impairment can be identified in vivo using a variety of biomarkers¹¹.

These biomarkers can be used to provide an increased understanding of the mechanisms underlying cognitive impairment in PD and, from a clinical perspective, can identify patients with an increased risk of early and rapid cognitive decline¹²⁰.

Some authors that used structural MRI in their investigations have shown that cognitive decline in PD is related to cortical structural changes and that specific cognitive dysfunctions can be attributed to atrophy in specific brain regions¹²¹.

Region of interest (ROI) imaging studies have shown reduced hippocampal and amygdala volumes in patients with PDD and a lesser extent of reduction in patients with PD-MCI. Atrophy in these structures has been related to overall cognitive declines in PD¹²².

Voxel-based morphometry (VBM) studies have demonstrated that patients with PDD exhibit atrophy in limbic/paralimbic areas, including the hippocampus¹²³⁻¹²⁵, amygdala¹²⁵, and entorhinal cortex¹²⁶, and widespread neocortical gray matter loss¹²¹. In contrast, patients with PD without dementia mainly exhibit atrophy in frontal and temporal areas¹²².

White-matter integrity was measured in detail with diffusion tensor imaging (DTI), based on the assumption that DTI reflects microstructural alterations in white matter¹²¹.

Studies using DTI tract-based spatial statistics showed that white-matter integrity in certain areas, particularly the bilateral parietal area, was significantly correlated with MiniMental State Examination (MMSE) scores in patients with PD¹²¹.

Biofluid markers, particularly analytes in CSF, can be useful in predicting cognitive impairment in PD¹²¹.

There is growing evidence of a synergistic role between Alzheimer's-type brain lesions, that contain A β proteins and neurofibrillary tangles (NFT), and cortical Lewy aggregates in PDD. Therefore, biomarkers for assessing α -synuclein, amyloid, and tau levels may be considered diagnostic and possibly predictive markers for PDD¹²¹.

CSF analytes are among the most promising biomarker candidates for cognitive impairment in PD¹²¹.

Mollenhauer et al (2006)¹²⁷ with their study found that patients with PDD have lower CSF levels of amyloid β 1-42 ($A\beta$ 1-42) and higher or normal levels of total tau (t-tau) and phosphorylated tau (p-tau) compared to patients with PD without cognitive impairment or age-matched control subjects.

Another prospective study with an 18-month follow-up also showed that low CSF $A\beta$ 1-42 was associated with posterior-cortical neuropsychological decline in PD patients¹²⁸.

Since no single above-mentioned biomarkers, including neuroimaging, biofluids and common genetic variants, could provide all the necessary information for the risk and progression of cognitive impairment in PD, some authors believe the combined biomarker approaches will enable early diagnosis and provide indicators of cognitive progression in PD patients¹²¹.

Compta et al (2012)¹²⁹ combined CSF biofluid markers and MRI images. They concluded that elevated total tau protein and decreased $A\beta$ 1-42 level were correlated with reduced grey matter volume using the VBM approach in PDD patients compared to PD-normal cognitive subjects.

In addition to $A\beta$ 1-42 protein and in another study, Compta et al (2015)¹³⁰ combined CSF levels of α -synuclein and MRI images. They observed that high CSF level of total α -synuclein correlated to posterior cortical thinning in PDD patients. On the contrary, there was a correlation between low CSF level of total α -synuclein and frontal-cortical thinning in non-demented PD cases.

Given the wide variation in the time to and rate of cognitive decline in PD, a key research priority is to identify predictors of the future cognitive course for patients with PD¹³¹, in order to assist the clinician in identifying patients who have a high risk of early dementia.

According to Liu et al (2017)¹³², several clinical features are associated with an increased risk of cognitive decline and, thus, it is possible to predict the risk for future cognitive impairment or dementia using various algorithms that combine demographic, clinical and genetic features.

Marinus et al (2018)¹³³ studied the risk factors for non-motor symptoms in Parkinson's disease. They concluded that some predictors were independently associated with the

development of cognitive impairment or dementia. Ranked in a descending order of weight, they identified the following predictors: presence of hallucinations, older age, overall severity of motor symptoms, presence of speech impairment, older age at PD onset, bradykinesia severity, higher Hoehn and Yahr stage, axial impairment (for example, postural instability and gait difficulty features), a low level of education, presence of depression and male sex.

Mayeux and colleagues¹³⁴ in a longitudinal study showed that age-specific incidence rates for dementia in a clinic-based sample of PD increased with age. The cumulative incidence of dementia reached 65% by age 85 years. In a population-based sample, the same investigators found that the age-specific prevalence of dementia in PD ranged from 12.4% in the group 50 to 59 years old to 68.7% in the group older than 80 years old¹³⁵.

Szewczyk-Krolkowski et al (2014)¹³⁶, in their Oxford Parkinson Disease Centre cohort study included PD patients within 3 years of diagnosis. They observed that most indices of cognitive performance, including Montreal cognitive assessment (MoCA) indices and phonemic and semantic fluency, were significantly worse in males compared to females. Males also had a greater rate of RBD and orthostatic hypotension.

Liu et al (2015)¹³⁷ also observed domain-specific sex difference patterns, with males with PD showing worse performance on verbal memory tests and better visuospatial abilities, compared to females with PD.

The mechanism linking male sex and cognitive performance has not been elucidated. RBD and orthostatic hypotension have been associated with worse cognitive performance and these symptoms are also more frequent in males. Thus, they may be contributing to worse cognitive performance¹¹⁸.

There are also indications that, in addition to MCI being a risk for dementia, deficits in different cognitive domains may have different predictive power¹¹. However, the conclusions are discrepant probably due to different genetic or ethnic backgrounds of PD patients¹¹.

Williams-Gray et al (2007)¹³⁸, in the CamPaIGN study found that posterior cortical deficits were closely related to incident dementia in PD. On the other hand, other authors showed

that frontal atrophy and frontal/executive dysfunction were associated with a higher risk for dementia conversion^{139,140}.

Some authors suggest that individuals with prodromal features of PD, such as hyposmia (loss of smell), RBD and reduced dopamine transporter binding, may present with worse cognitive performance compared with people without any or with only one of these features¹⁴¹⁻¹⁴³. Interestingly, prodromal PD and DLB¹⁴⁴ may overlap and it is not yet known how to distinguish between those who will develop PD versus those who will develop DLB¹¹. Cognitive deficit has been recently defined as a new prodromal marker and has been included in the last update of the research criteria for prodromal PD¹⁴⁵.

Cognitive reserve has been proposed to explain the mismatch between the degree of brain damage or pathological changes and clinical manifestations¹⁴⁶ including the variation in the rate of cognitive decline and the development of dementias such as AD¹⁴⁷. However, it is not clear whether cognitive reserve affects the development of cognitive impairment and dementia in PD.

Exercise is an important lifestyle consideration. The general health benefits of exercise are well-known and there is reliable evidence for significant benefits on cognition in healthy older adults, especially for executive control processes¹⁴⁸.

Since executive dysfunction is a key finding in PD-MCI and PDD, exercise may be a relevant factor preventing or modifying cognitive impairment in PD¹¹⁸.

Resistance exercise may benefit cognition in PD¹¹⁸. In a study made by David et al (2015)¹⁴⁹, the authors observed that after 24 months of twice-weekly progressive resistance exercise, adults with PD improved on working memory, inhibition, and attention.

Of note, some studies suggest that high intensity exercise may lead to an increase in reactive oxygen species, which theoretically could lead to increased brain oxidative stress. However, this effect has not been observed with moderate intensity exercise¹⁵⁰⁻¹⁵².

Overall, the results of these studies appeal for the importance of determining the type, frequency, and intensity of exercise that may be most effective in PD.

Foods and other dietary components have received significant attention as potentially important environmental factors related to the pathogenesis of and protection against PD¹¹⁸. There is also interest in describing which nutrients and food may impact the development of cognitive changes in PD, but the body of literature in this area is small¹¹⁸.

The Mediterranean diet has been of interest given its reported association with cognitive health in the general population and in other neurodegenerative disorders, such as AD¹⁵³.

Paknahad et al (2020)¹⁵⁴ recently studied the effect of the Mediterranean diet on cognitive function in patients with Parkinson's disease. Patients with PD were randomly assigned to either an individually designed Mediterranean diet or usual dietary intake. After 10 weeks, those in the intervention group had significantly improved MoCA scores in the executive function, language, attention, concentration and active memory tasks, while they were unchanged in the control group. There was no significant change in visual-spatial ability, memory learning or navigation tasks.

The potential mechanisms regarding these effects have been studied. Caprara (2021)¹⁵⁵ referred that the reduction in vascular risk factors, particularly hypertension and dyslipidemia, the beneficial effect on oxidative stress and the anti-inflammatory effect may play a role.

Several longitudinal studies support an inverse association between caffeine consumption and decreased memory impairment associated with aging, as well as reduced risk of dementia and AD^{156,157}. Coffee has been inversely associated with PD risk¹⁵⁸. A cross-sectional study involving treatment-naïve PD patients showed that coffee drinking was significantly associated with a reduced severity in the cognitive domain of the non-motor symptom assessment scale¹⁵⁹.

2.1 Cognitive profile in Parkinson Disease

The cognitive profile in PD can range from normal cognition to MCI and eventually dementia¹¹⁸.

PD patients can have normal scores on neuropsychological testing with and without subjective complaints (normal), impairments on neuropsychological testing without (MCI) or with a substantial impact on daily instrumental life activities (dementia)¹¹⁸.

Clinical diagnosis of PD is primarily based on the presence of motor symptoms⁹. Nevertheless, according to Postuma & Berg (2019)¹⁶⁰, the neurodegenerative process underlying PD starts long before the onset of the motor symptoms, and cognitive changes can occur during these earlier phases of neurodegeneration.

Several reports have shown increased PD risk in people with cognitive changes, and cognitive deficits are included in the prodromal PD criteria^{145,161}.

Fereshtehnejad et al (2019)¹⁶², in their longitudinal study including individuals without PD at baseline who later developed PD during the follow-up period, observed that subtle cognitive changes occurred within 7 to 9 years before the diagnosis of PD.

According to Erro et al (2014)¹⁶³, after the diagnosis of PD patients can present with subjective complaints which may or may not be accompanied by objective changes.

In terms of the cognitive profile in early PD, the majority of patients have a non-amnesic single-domain cognitive decline with impairments in visuospatial functioning, attention, or executive functioning¹⁶⁴. However, patients do not always have single-domain cognitive decline, and decline can be present across multiple and/or all those cognitive domains¹⁶⁵.

According to Williams-Gray & Mason (2012)¹⁶⁶, this heterogeneity may be due to methodological factors. The prevalence of early cognitive impairment depends on a number of factors, including whether the cohort is incident (i.e. only includes newly diagnosed patients) or prevalent (includes all patients with the diagnosis, no matter when diagnosed), hospital or community based, the selection of neuropsychological tests employed, and the criteria used to define cognitive impairment.

The number of impaired tests required and the cut-off levels for impairment also have a major impact on cognitive impairment estimated prevalence, as demonstrated by Dalrymple-Alford et al (2011)¹⁶⁷ in a study which assessed 20 neuropsychological measures across 4 cognitive domains in 119 non-demented PD patients. This study reported that prevalence figures varied from 14% when using 2 scores in 1 domain at 2 standard deviations below normal, to 89% of patients (and 70% of healthy controls) when using 1 score from 1 domain at 1 standard deviation below normal.

Kehagia et al (2013)¹⁶⁸ proposed another explanation for this heterogeneity in the affected cognitive domains in PD: the “dual syndrome hypothesis”.

This hypothesis suggests that in PD patients with more fronto-striatal network dysfunction, modulated by dopamine, attention/working memory and executive functions are predominantly affected, whereas in patients with more posterior cortical degeneration, memory, language, and visuospatial functioning are predominantly affected related to greater cholinergic loss.

Comprehensive evaluation of individual cognitive domains is crucial for estimating the underlying pathophysiology and subsequently lead to development of effective treatments¹¹⁸.

The cognitive profile can be hard to discern if the patient’s cognitive decline is too advanced with severe impairment across all domains at the time of testing¹¹⁸.

Although dementia may seem frequent in PD²⁵, the rate of progression to dementia is highly variable.

The additional high variability for the affected cognitive domains and the severity of the cognitive decline in PD makes it challenging to make predictions about the progression and underlying pathologies¹¹⁸.

Although there are currently no pharmacological treatments to delay or prevent cognitive decline in PD, from a research perspective it is important to be able to detect the patients at risk before the onset of severe cognitive decline and to monitor the progression to determine the rate of decline¹¹⁸.

Detecting such patients and progression rates will enable the development of effective strategies to prevent or delay progression to dementia in PD¹¹⁸.

In the human brain, the prefrontal cortex occupies a large portion of the cortical mantle and has extensive connections to most brain regions¹⁶⁹. It is responsible for the regulation of the flow of information that determines how an individual will behave¹⁶⁹.

The prefrontal cortex allows an individual to pay attention to one event or phenomenon to the exclusion of others, as well as switch among them. It allows one to act automatically or

even override automatic actions, and act in a fashion counter to biological or environmental programming. Furthermore, the prefrontal cortex facilitates reasoning. Together, these cognitive abilities are frequently grouped together as “frontal- executive” functions¹⁶⁹.

According to Mesulam (2002)¹⁷⁰, damage to the prefrontal cortex can substantially disrupt everyday functioning, while leaving many cognitive functions intact.

Dirnberger & Jahanshahi (2013)¹⁷¹ referred that in PD, different facets of executive functions have been found impaired, including set shifting, planning, inhibition, conflict resolution, impairment in dual task performance, and decision making.

Fallon et al (2016)¹⁷² observed that PD patients are relatively unable to shift attention away from previously relevant information (leading to perseveration errors) and to shift attention towards previously irrelevant information (learned irrelevance). However, they perform as well as control in attending to, or ignoring, novel information.

Similarly, Trojano & Papagno (2018)¹⁷³ in their update on cognitive and behavioral disorders in Parkinson's disease referred that severe executive defects are also related to psychological/behavioral disorders such as depression, apathy, and hallucinations.

Working memory impairment is another characteristic defect in PD patients¹⁷⁴.

Uitvlugt et al (2016)¹⁷⁴ studied the nature of working memory gating in Parkinson's disease. They assessed PD patients in on and off dopaminergic medication on verbal and visuospatial working memory tasks with low or high cognitive load and in presence or lack of distractors. They concluded that in off medication, patients tended to show many false negative responses across all conditions and domains, in line with the hypothesis that a fronto-striatal dysfunction prevents updating of working memory. When they tested PD patients in on medication, failures were found particularly in the presence of distractors, likely because of an overdosing of the ventral striatum.

These findings are consistent with the idea that fronto-striatal mechanisms of working memory can act as a domain-general gate filter for cognitive computations¹⁷⁴.

Evens et al (2016)¹⁷⁵ referred that working memory, together with attentional set shifting, is considered to be strongly dependent on dopamine depletion in the striatum, whereas decision-making would be less dopamine-dependent.

“Memory” is not a unitary construct. There are multiple memory systems subserved by multiple brain structures¹⁶⁹.

Evaluation of memory in PD patients has largely focused on explicit memory and implicit memory¹⁶⁹.

Wang et al (2009)¹⁷⁶ compared PD patients without dementia and healthy controls on measures of explicit (Wechsler memory scale - WMS), implicit (stem completion and degraded picture identification) and procedural memory (choice reaction time). They observed that PD patients and controls were equivalent on the WMS battery, stem completion and picture identification, but only the controls decreased reaction time over sequential learning trials.

Van Asselen et al (2009)¹⁷⁷ examined the role of spatial context cuing and found that controls, but not patients, responded faster on a visual search task when the visual context was repeated, concluding that certain types of implicit memory may decline early in mild PD.

Implicit learning may be impaired in PD without dementia¹⁷⁶.

Massman et al (1990)¹⁷⁸ traditionally believed that impaired learning in non-demented PD was largely due to inefficient use of strategies during encoding because of fronto-striatal dysfunction, even if cholinergic depletion and Lewy body pathology affecting temporal regions can contribute to memory impairment.

However, this issue is controversial. Pirogovsky-Turk et al (2015)¹⁷⁹ investigated different facets of memory functioning in PD patients without MCI and correlated scores with regional volumes in the medial temporal lobe (MTL) and fronto-striatal system. They found that memory was impaired only for verbal learning, which was not associated with executive, attention/working memory, or visuospatial functioning. Despite absence of cortical atrophy, smaller right MTL volumes in patients were associated with poorer verbal learning, long delayed free and cued recall, and recognition memory hits and false positives.

On the other hand, inferior frontal volumes, namely of the right pars triangularis, were associated only with poorer long delayed cued recall and recognition memory hits. The authors concluded that MTL volumes were sensitive to subtle changes in almost all aspects of memory, whereas frontal volumes were sensitive only to memory performances in cued-testing formats.

Cohn et al. (2016)¹⁸⁰, to disentangle the role of executive functions and hippocampal damage in episodic memory impairment in PD, have developed a new experimental memory task, the associative reinstatement memory (ARM). In this task, participants were instructed to identify word pairs containing two studied words (intact or rearranged pairs) and those containing at least one new word (new or half new pairs).

ARM, as assessed by the differences in hit rates between intact and rearranged pairs, was poorer in PD relative to controls and was correlated with verbal memory measures, but not with attention or executive functioning in the PD group.

Moreover, fMRI data showed that hippocampal activation covaried with ARM scores in both PD and healthy controls, but was reduced in PD patients compared with controls.

Similarly, memory for nonverbal information can be impaired in PD patients without dementia¹⁶⁹.

Deficits have been reported on measures of facial recognition, figure copy and visual retention¹⁸¹.

Taken together, the deficits in verbal and nonverbal memory suggest that PD patients without dementia have an increased risk for memory impairments¹⁶⁹.

According to Tröster (2008)¹⁸², PD patients with dementia may have impaired remote memory. However, these changes are not prominent in PD patients without dementia.

Visuospatial skills include cognitive abilities tied to the processing of visual information. This includes pattern recognition (facial recognition), constructional ability (figure drawing), color recognition (color naming) and spatial analysis (ability to perceive multiple objects in a visual field)¹⁶⁹.

Posterior cortical areas have been associated with deficits in visual processing including the occipital, parietal and temporal lobes¹⁶⁹. Neuroimaging suggests that visuospatial impairment in PD without dementia is associated with posterior cortical dysfunction¹⁸³.

Numerous reports have confirmed that PD patients without dementia perform more poorly than healthy controls on visuoperceptual/visuospatial tasks with and without motor components¹⁶⁹.

Deficits have been reported on judgement of line orientation¹⁸¹, facial recognition¹⁸⁴, form discrimination¹⁸⁴, reasoning¹⁸¹, block construction¹⁸⁵ and figure copy¹⁸⁶.

According to Troster (2008)¹⁸², the predominance of visuospatial dysfunction in PD is further emphasized in PDD. These patients have more severe impairments on visuoperceptual measures such as drawing figures, identifying television personalities, form discrimination and visual counting than observed in Alzheimer's disease¹⁸².

The same author also referred that although motor dysfunction may contribute to impairments on some visuospatial tasks (e.g. copying figures or constructing designs with blocks), patients with PDD have an enhanced risk for visuospatial impairments that reflect disrupted praxis and visuoperception over and above the contributions of motor dysfunction.

Dubois & Pillon (1997)¹⁸⁷, in their review on cognitive defects in PD, favored the idea that visuospatial disorders in PD result more from a decrease in central processing resources than from specific visuospatial defects, as most visuospatial tasks are characterized by high cognitive demand, and visuospatial impairments often result strongly correlated to frontal defects.

According to Papagno & Trojano (2018)¹⁸⁸, one instance of visuospatial disturbances related to attentional/executive dysfunction is the tendency to overlap the copy to the model, i.e., the so-called closing-in phenomenon, in figure copying tasks. Trojano & Gainotti (2016)¹⁸⁹ demonstrated that closing-in is correlated to executive dysfunctions in several neurodegenerative diseases. This must be the reason why closing-in has been searched for and detected in PD patients with and without dementia^{190,191}.

Nevertheless, the assessment of visuospatial cognition still important in the diagnostic work-up. It has been reported that Judgement line orientation test (JLOT) or visuoconstructional

(copying) tests can be useful to characterize clinical phenotypes¹⁹², or GBA mutations¹⁹³. Visuospatial defects are among the main correlates of subjective cognitive impairment¹⁹⁴ and are possible cognitive predictors of cognitive decline in PD¹⁹⁵.

These findings suggest that visuospatial defects are multidetermined in PD. Pereira et al (2009)¹⁸⁴ investigated the neuroanatomical substrate of visuospatial and visuoperceptual impairment in PD and they concluded that both frontal/executive and posterior/non-executive defects concur to impair visuospatial cognition.

Complex pathogenic mechanisms likely underlay also impairments in spatial learning and spatial navigation in PD, pointing to the role of dopamine in hippocampal functioning¹⁹⁶.

PD patients' speech is less intelligible than that of non-PD individuals, due to reduction of intensity, increase of pauses, phonetic alterations, and difficulty in emotional conveyance¹⁹⁷. However, other aspects of language are particularly relevant in PD¹⁸⁸.

While there is a general acknowledgment that persons with PD may experience declines in attention/executive functions, memory and visuospatial skills, there is less agreement concerning language impairments¹⁸⁸.

Among recent reviews of cognitive deficits and PD, some have identified language as a specific area of concern^{198,199}. Others have not specified language as a separate area of concern, although they may have identified impairments in specific language functions (e.g. verbal fluency)²⁰⁰. One explanation for this discrepancy is that language changes are a relatively minor aspect of cognitive impairment in PD. More likely, language functions known to become impaired have been assigned to other domains. For example, verbal fluency (especially phonemic verbal fluency) has been classified both as a language function and an index of executive functioning¹⁸⁸.

Language impairments have been reported on measures of phonemic verbal fluency²⁰¹, semantic verbal fluency²⁰² and visual confrontation naming²⁰³. It appears that semantic verbal fluency is more affected in AD, whereas the converse is thought to be true for PDD¹⁹⁹.

In addition to traditional scoring methods, error analyses may further elucidate PD- related changes in language¹⁶⁹.

2.2 Neuropsychiatric profile in Parkinson Disease

Neuropsychiatric symptoms are common already at the time of diagnosis of PD²⁰⁴. In more advanced stages their impact is often greater than that of motor symptoms²⁰⁵.

According to Aarsland et al (1999)²⁰⁶, the most frequent symptoms are depression, hallucinations, and apathy.

Many patients have more than one symptom, adding to the complexity and challenge both for patients and for their caregivers²⁰⁵.

Mueller et al (2018)²⁰⁵, in their review discussed the assessment and management of neuropsychiatric symptoms in PD. They concluded that neuropsychiatric symptoms are strong predictors of poor quality of life and key drivers for nursing home admission and thus are costly for society.

Although the prevalence rates vary considerably according to sample definitions and assessment criteria, according to Reijnders et al (2008)²⁰⁷ about one-third of patients with PD are considered to experience clinically relevant depressive symptoms.

Depression in PD is associated with increased caregiver burden and mortality, as well as decreased patient functioning, quality of life, and possibly cognitive decline^{208,209}.

Ehgoetz Martens & Lewis (2017)²¹⁰ in their overview referred that some neurobiological factors might play a role like the degeneration in the serotonergic raphe nucleus and noradrenergic locus coeruleus as well as the dysregulation of the dopaminergic circuits in the frontostriatal and mesolimbic regions.

Anxiety disorders are more common in patients with PD than in the general population or those with other chronic conditions²¹¹. According to Leentjens et al (2011)²¹², about one-third of PD patients experiences a diagnosable anxiety disorder.

Dissanayaka et al (2017)²¹³ referred that the most common are generalized anxiety disorder, with the typical symptoms of persistent tension, irrational worrying and physical arousal, and phobias, especially social phobias and panic disorders.

Robert et al (2009)²¹⁴ proposed diagnostic criteria for apathy in AD and other neuropsychiatric disorders. They defined apathy, loss or diminished motivation as a multidimensional syndrome that includes reduced emotions, goal-directed behaviors and cognitive activity. These proposed diagnostic criteria for apathy have been validated in people with PD²¹⁵.

According to Bostrom et al (2007)²¹⁶, up to one-third of people with PD without depression or dementia have apathy, which is associated with high levels of disability, accelerated cognitive and functional decline, weight loss, and poor quality of life.

Further, apathy may impair the ability to engage with treatment and care of other motor, cognitive and behavioral symptoms²⁰⁵.

Santangelo et al (2013)²¹⁷ reviewed structural and functional neuroimaging studies investigating apathy in PD and they observed that these studies have reported changes in the right frontal lobe, orbitofrontal cortex, fusiform gyrus, insula, postcentral gyrus, inferior frontal gyrus, left middle frontal gyrus, bilateral cingulate gyrus, bilateral inferior parietal gyrus and right precuneus.

Parkinson's disease psychosis is a term used to describe the range of illusions, hallucinations and delusions occurring in PD and related disorders²¹⁸.

The prevalence of PD psychosis increases with disease duration, with most patients eventually developing such symptoms. However, estimates vary depending on whether minor symptoms are included²⁰⁵.

In cross-sectional studies, typical rates of complex visual hallucinations range from 22 to 38% and auditory hallucinations around half this value (0–22%)²¹⁹.

Visual hallucinations are associated with the move from living independently into a care setting, irrespective of motor impairment or cognitive ability²²⁰.

According to Ffytche et al (2017)²¹⁸, patients who present with PD psychosis early in the disease have accelerated cognitive decline and worse longer term outcomes.

The underlying cause of PD psychosis is currently unclear²⁰⁵.

Early theories linked PD psychosis to the use of dopamine therapy and it remains the case that PD psychosis often starts after the onset of dopamine therapy and may improve with dose reduction²⁰⁵.

However, evidence that PD psychosis can occur without the use of dopamine medication and a lack of a relationship between medication dose and symptom severity shows the relationship is complex²⁰⁵.

Ravina et al (2007)²²¹ referred that PD psychosis may be integral to PD itself but triggered or modified by the use of dopamine medication. Jaakkola et al (2017)²²² studied the ventral striatal dopaminergic defects and their association with hallucinations in PD and observed a reduction in striatal dopamine binding in PD prior to the onset of PD psychosis, a fact that supports this view.

There is evidence for a specific profile of cognitive deficits in PD psychosis, including deficits in memory, executive function, visuospatial function and attention²¹⁸. The cognitive changes are consistent with the distribution of cortical and hippocampal atrophy^{218,223}.

2.3 Diagnostic criteria

The accurate diagnosis of cognitive impairment in individuals with PD is important for clinical management, patient information and counselling, and research, including trial selection¹¹.

The diagnosis can be made based on the evaluation of global cognitive function or on a more detailed neuropsychological assessment¹¹.

A full medical examination is mandatory and biomarkers can be useful to identify the causes and predict the risk of cognitive decline, although their use in clinical practice is yet to be validated¹¹.

To promote uniformity amongst those who work on cognition in PD, clinical criteria for stages of cognitive decline (MCI and PDD) have been previously defined by the Movement Disorder Society (MDS) expert panels for use in clinical and research settings^{224,225}. These stages are based on a combination of patient and caregiver reports, clinician observations, and neuropsychological assessments of the patients.

2.3.1 Subjective and mild cognitive impairment diagnostic criteria

Research in healthy older adults has suggested that SCD may indicate early changes in cognitive functioning that are not detected on neuropsychological tests. SCD can be reported by the patient, family members or friends, or clinicians¹¹.

According to Aarsland et al (2021)¹¹, there are no validated instruments to determine the presence of SCD in PD. However, some tools developed for the assessment of non-motor symptoms include questions on the cognitive status as perceived by the patient. Nevertheless, the value of subjective cognitive complaints in patients with PD without objective impairment in formal neuropsychological testing is not well understood¹¹.

Diagnostic criteria for PD-MCI from the MDS²²⁵ are based on (1) the individual having a diagnosis of PD, (2) a gradual cognitive decline reported by the patient, informant, or the clinician, (3) cognitive decline on comprehensive neuropsychological testing or a scale of global cognitive abilities validated in PD and (4) cognitive decline not sufficient to interfere significantly with functional independence (Table 2).

PD-MCI represents the prodromal stage of PDD and can provide a window to prevent or delay the progression to PDD¹¹⁸.

The PD-MCI diagnostic criteria have two levels. Level I implies brief assessment and Level II implies a more comprehensive assessment with at least two tests for each of the five cognitive domains (attention, executive function, visuospatial functioning, language, memory)²²⁵ (Table 2).

If Level II testing can be performed, the patient needs to show impairments on two tests in one cognitive domain or one impaired test in two different cognitive domains. Impairment is defined by performance 1-2 standard deviations (SDs) below appropriate norms, decline from prior neuropsychological testing, and decline from estimated premorbid levels²²⁵.

Some authors concluded that both Level I and II criteria are valid predictors of PDD^{65,226}. However, according to Galtier et al (2016)²²⁷, detailed neuropsychological evaluations can be more sensitive to detect cognitive decline.

Given the heterogeneous nature of the cognitive decline in PD, detailed neuropsychological evaluations assessing various cognitive domains can provide a more comprehensive view of the cognitive state¹¹⁸.

Criteria for the Diagnosis of PD-MCI
I. Inclusion criteria • Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria • Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, <i>or</i> observed by the clinician • Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III) • Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present II. Exclusion criteria • Diagnosis of PD dementia based on MDS Task Force proposed criteria • Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma) • Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing III. Specific guidelines for PD-MCI level I and level II categories Level I (abbreviated assessment) • Impairment on a scale of global cognitive abilities validated for use in PD <i>or</i> • Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed) Level II (comprehensive assessment) • Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial) • Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains • Impairment on neuropsychological tests may be demonstrated by: - Performance approximately 1 to 2 SDs below appropriate norms <i>or</i> - Significant decline demonstrated on serial cognitive testing <i>or</i> - Significant decline from estimated premorbid levels IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes) • PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired <i>or</i> • PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

Table 2. Criteria for the diagnosis of Parkinson's disease with mild cognitive impairment (PD-MCI)²²⁵

2.3.2 Parkinson disease dementia diagnostic criteria

Establishing the diagnosis of PDD is important for the management of patients and their caregivers, including personalized care packages, forward planning and use of medication¹¹.

Diagnostic criteria for PDD from the MDS²²⁴ is based on (1) the individual having a diagnosis of PD, (2) a slowly progressive cognitive decline that developed after an established PD diagnosis, and (3) impairment in more than one cognitive domain, which represents a decline from premorbid level and is severe enough to impair instrumental daily life activities (Table 3 and 4).

Behavioral symptoms including hallucinations, delusions, apathy, depression, anxiety, personality changes, and excessive daytime sleepiness frequently co-occur with PDD but are not required for the diagnosis of PDD²²⁴. Nevertheless, according to Szeto & Lewis (2016)²²⁸, these behavioral symptoms impact the quality of life of both the patient and the caregiver and need to be addressed by the clinician.

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
 - Impairment in more than one cognitive domain
 - Representing a decline from premorbid level
 - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
 - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
 - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
 - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
 - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
 - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
 2. Behavioral features:
 - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
 - Changes in personality and mood including depressive features and anxiety
 - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
 - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
 - Excessive daytime sleepiness
-

III. Features which do not exclude PDD, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
Acute confusion due to
 - a. Systemic diseases or abnormalities
 - b. Drug intoxicationMajor Depression according to DSM-IV
 - Features compatible with “Probable Vascular dementia” criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits).
-

Table 3. Features of dementia associated with Parkinson’s disease²²⁴

Criteria for the diagnosis of probable and possible PDD

Probable PDD

- A. Core features: Both must be present
- B. Associated clinical features:
 - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing)
 - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PDD, lack of behavioral symptoms, however, does not exclude the diagnosis
- C. None of the group III features present
- D. None of the group IV features present

Possible PDD

- A. Core features: Both must be present
 - B. Associated clinical features:
 - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
 - Behavioral symptoms may or may not be present
 - OR
 - C. One or more of the group III features present
 - D. None of the group IV features present
-

Table 4. Criteria for the diagnosis of probable and possible Parkinson’s disease with dementia (PDD)²²⁴

Similar to the PD-MCI criteria, the PDD criteria contain a two-level operational scheme depending on the comprehensiveness of the clinical assessment²²⁹ (Table 5).

Diagnostic procedure Movement Disorder Society PDD criteria
Level I — Parkinson disease dementia (PDD) • A diagnosis of Parkinson disease (PD) based on the UK Brain Bank criteria for PD • PD developed prior to the onset of dementia • Mini-Mental State Examination (MMSE) below 26 • Cognitive deficits severe enough to impact daily living (caregiver interview or Pill Questionnaire) independent of motor symptoms • Impairment in more than one cognitive domain, that is, at least two of the following aspects: - Months Reversed or Seven Backward - Lexical Fluency or Clock Drawing - MMSE Pentagons - Three-Word Recall • Absence of major depression • Absence of delirium • Absence of other abnormalities that obscure diagnosis
Level II — Comprehensive assessment for characterizing PDD The level II evaluation assesses four domains: • Decreased global cognitive efficiency • Subcorticofrontal features of PDD • Instrumental (cortically mediated) functions: - Language - Visuoconstructive - Visuospatial - Visuoceptive • Neuropsychiatric features: - Apathy - Depression - Visual hallucination - Psychosis

Table 5. Diagnostic procedure Movement Disorder Society Parkinson’s disease with dementia (PDD) criteria²²⁹

For both PD-MCI and PDD, the presence of other conditions which may explain the cognitive impairment (e.g., delirium, stroke, trauma, metabolic abnormalities) and other PD-related comorbidities (e.g., motor impairment, severe depression, anxiety, excessive daytime sleepiness, psychosis) that may significantly influence neuropsychological testing need to be taken into account¹¹⁸.

In addition to physical examination and history, basic blood tests (for example, thyroid function tests, vitamin B12 level and relevant tests for metabolic, infectious, autoimmune

and other aetiologies)²³⁰ and structural brain imaging with MRI should be performed to rule out other causes such as severe cerebrovascular disease¹¹.

2.3.3 Differential diagnosis

The differential diagnosis of PDD can be difficult.

When symptoms of dementia occur, it is essential to exclude reversible and potentially treatable acute causes of dementia or other situations that can simulate it.

Similarly, it will have to be verified whether cognitive impairment is due to PD or other diseases such as AD or DLB.

Traditionally, the 1-year rule has been used to distinguish DLB from PDD: if dementia occurs more than 1 year after the diagnosis of PD, the diagnosis is PDD, whereas parkinsonism occurring after or simultaneously with dementia is classified as DLB^{224,231}.

Despite DLB and PDD share many pathological and clinical features, they show locally and quantitatively divergent neuropathological lesions and they are considered as two clinical entities on a spectrum of Lewy body disease²²⁴.

	Overlap	Dissimilarities
Clinical	- Rigidity - Akinesia - REM sleep behavior disorder (RBD) - Cognitive impairments (frontal executive dysfunction, visual-constructive impairment, mild language impairment) - Mood disturbances (depression, anxiety) - Neuroleptic sensitivity	- Relative timing of dementia and parkinsonism (one year rule) - Tremor less frequent in DLB - Motor performance: slower walk and poorer balance in DLB - Orthostatic hypotension more frequent in DLB - Cognitive decline is faster in DLB/DLB+AD - Attentional fluctuation more frequent in DLB - Greater attention impairment and episodic verbal memory tasks lower in DLB - Frontal/temporal-associated cognitive subsets more severe in DLB - Hallucinations (visual) and delusions more frequent in DLB

		- Visual hallucinations: spontaneous in DLB; after L-dopa therapy in PDD, but also in drug-naïve cases
Laboratory	- Decreased DAT binding in putamen - Reduced cardiac MIBG binding - Medial temporal lobe relative preservation - Similar metabolic decrease in cerebral cortex - Occipital hypoperfusion - Similar EEG abnormalities - GBA mutations	- Decreased DAT binding in caudate related to functional impairment in DLB, not in PDD - Grey matter cortical atrophy more frequent and more severe in DLB - White matter hyperintensities in temporal lobe more severe and more frequent in DLB - Different functional connectivity, corticostriatal disruption: PDD: frontal cortical disruption; DLB: parietal and occipital disruption - Greater amyloid binding in DLB - Tau-PET imaging more severe in DLB - SN sonography (size, asymmetry) - CSF AD profile more common in DLB - CSF αSyn oligomers increased in PDD - Several genetic differences (APOE ϵ4, TFAM))

Morphological	- Variable mixture of cortical and subcortical LB/αSyn pathology and AD-related pathology - Similar Braak LB stages (4-6) and neuritic stages (5 or 6) - Relationship between pαSyn and tau aggregation to Aβ deposition in frontal and temporal cortex - Initial αSyn aggregation in pre-synapses inducing neurodegeneration via interference with axonal transport - Postsynaptic protein downregulation	- Higher Aβ load in cortex and striatum in DLB - Neuritic plaque scores higher in DLB - Higher cortical LB load in temporal and parietal cortex in DLB - Increased tau loads in cortex and striatum in DLB - More frequent and severe αSyn load in hippocampal subareas C2(3) in DLB - Minor deviations in lesion pattern in SNc - Pedunculopontine cholinergic cell loss in hallucinating PDD, but not in DLB - Higher 5-HT1A receptor binding in cerebral cortex in DLB - More frequent cerebral microbleeds in DLB
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Table 6. Clinical, laboratory and morphological overlap and dissimilarities between dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD)²³².

AD Alzheimer disease, DAT dopamine transporter, MIBG scintigraphy using metaiodobenzylguanidine labeled to Iodine-123 or Iodine-131, SN substantia nigra, CSF cerebrospinal fluid, LB Lewy body, SNc substantia nigra pars compacta.

Type of lesion	DLB	PDD
- LB / αSyn pathology	- Both subtypes are characteristic by a combination of progressed LB pathology (LB Braak stage 5–6) and AD pathology of variable severity and extent	
- Aβ load	- More severe and extended in cortex and striatum	- Less severe and less extended
- Tau load	- Higher tau load, particularly in medial temporal cortex	- Comparatively low tau load in cortex and striatum
- αSyn load (hippocampus)	- CA 1/2 more severely involved	- CA 2/3 more frequently involved
- SN neuronal cell loss	- Preferentially involving dorsolateral substantia nigra pars compacta	- More severe, preferentially involving medioventral SNc
- Pedunculopontine cholinergic cell loss	- Negative	- Positive in hallucinating PDD
- 5-HT1A receptor binding density in cortex	- Higher	- Lower
- Cortical LB load	- Higher in temporal & parietal cortex, hippocampus	- Diffuse or focal

Table 7. Neuropathological features of dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD)²³²

LB Lewy body, AD Alzheimer disease, SN substantia nigra

Smirnov et al (2020)²³³ examined the cognitive profiles in PDD and in DLB. They observed that PDD and DLB may have different cognitive profiles, such as the presence of a more severe impairment in executive functions in PDD patients and in memory in DLB patients. They also observed different trajectories of cognitive decline, which appear to be more rapid for DLB in the language domain.

Nevertheless, Petrova et al (2015)²³⁴ compared clinical and neuropsychological features of the earliest stages of dementia and they observed worse performance on tests of attention and executive functions and constructive abilities in DLB than in PDD.

Cognitive domains	PDD	DLB	AD
Attention and executive function	• Prominent and early deficits; • Impairment in planning, set shifting, abstract reasoning, mental flexibility, focused and complex attention (e.g. choice reaction time, internally cued behavior), and working memory; • Fluctuating attention.	• Prominent and early deficits; • Impairment in planning, set shifting, abstract reasoning, mental flexibility and working memory more severe than in PDD.	• Impairment is later and less severe than in PDD/DLB.
Memory	• Impairment in episodic memory; • Free recall impaired, may improve with cueing, recognition usually better.	• Impairment in episodic memory is less severe than in PDD.	• Early memory complaints are common; • Both encoding and retrieval affected; • Inability to form new memories is common; • Remote memories are preserved.
Visuospatial function	• Both perceptual and constructional deficits; • Usually early and disproportionate to the level of overall cognitive impairment.	• Both perceptual and constructional deficits.	• Deficits present but less pronounced than in PDD/DLB.
Language	• Usually preserved except for word-finding difficulties and understanding complex sentences.	• Usually preserved.	• Language problems including paraphasic errors are common; • Poor verbal fluency, better for letters than categories; • Moderate disturbances of discourse with word-finding problems; • Poor comprehension; • Spared repetition; • Poor naming.
Neuropsychiatric features	• Depression, anxiety, apathy, visual hallucinations.	• Depression, anxiety, and apathy; • More frequent visual hallucinations than in PDD.	• Visual hallucinations unusual; • Suspiciousness, paranoia, and disinhibition more common.

Table 8. Distinctive features of cognitive impairment in Parkinson disease with dementia (PDD), dementia with Lewy bodies (DLB) and Alzheimer's dementia (AD)

2.4 Neuropsychological assessment

Neuropsychology involves the scientific study of brain-behavior relationships and the clinical application of this knowledge to the assessment and remediation of cognitive, emotional, and behavioral changes in persons with known or suspected central nervous system dysfunction²³⁵

Cognitive function in PD can be measured in different settings²³⁵:

- 1) in the course of an evaluation by a physician, occupational or speech therapist;
- 2) by a neuropsychologist performing a dedicated clinical cognitive evaluation; or
- 3) in a research study.

Depending on these settings and their goals, cognitive assessment requires different tools that can be a relatively short global cognitive scale (screening scales) or multiple tests each emphasizing a specific cognitive domain to provide a detailed assessment of the pattern of cognitive dysfunction (comprehensive neuropsychological assessment)²³⁵.

2.4.1 Screening

Screening of cognitive function in patients with PD is not performed regularly but should be part of routine clinical care¹¹.

According to Aarsland et al (2021)¹¹, this screening requires less time, fewer resources, is more available and is less burdensome for patients compared with detailed neuropsychological assessments.

Disadvantages of screening include limited information about the cognitive profile and reduced reliability compared with neuropsychological assessment¹¹.

The Movement Disorder Society published a paper with critique and recommendations on global scales for cognitive screening in PD²³⁶. Based on their clinimetric properties, three scales were recommended and two scales were classified as recommended with caveats (Table 9).

Although the MMSE is frequently used, it is not suitable for cognitive screening in the early stage of PD owing to a ceiling effect and the lack of sensitivity in detecting MCI²³⁷.

The MoCA is the most frequently used screening instrument in PD research and clinical practice¹¹.

Based on the individual MoCA score or course of successive MoCA scores, a detailed neuropsychological assessment can be indicated¹¹.

Scale	Reliability	Validity	Sensitive to change	Used beyond original developers	Recommendation Level	Major caveats and clinimetric limitations of the scales
DRS-2	Good	Good	Yes	Yes	Recommended	
MoCA	Good	Good	Yes	Yes	Recommended	
PD-CRS	Good	Good	Yes	Yes	Recommended	
MMP	Good	Good	Limited data	Yes	Recommended with caveats	Limited coverage of executive abilities and visuospatial and constructional praxis, limited information on sensitivity to change
SCOPA-COG	Good	Good	Limited information	Yes	Recommended with caveats	Limited information on sensitivity to change
ADAS-COG	Good ^a	Good	Yes	Yes	Suggested	Reliability not fully assessed in PD, limited coverage of executive abilities
CAMCOG-R	Good ^a	Good ^a	Yes	Yes	Suggested	Reliability not assessed in PD, sensitivity to change not assessed in PD
MMSE	Good	Mixed - not good/Acceptable	Yes, but mixed results	Yes	Suggested	Mixed results for validity, documented lower sensitivity to change compared with other cognition scales, multiple cognitive scales shown superior in PD
PANDA	Mixed - some aspects not assessed	Mixed	Not assessed	Yes	Suggested	Some aspects of reliability not assessed, no information on sensitivity to change
PDD-SS	Good	Good	Not assessed	No	Suggested	Sensitivity to change not assessed, limited coverage of executive abilities, not used beyond developers
RBANS	Good ^a	Good ^a but no data for PDD or PD-MCI	Yes	Yes	Suggested	Limited coverage of executive abilities, reliability and validity not fully assessed in PD, needs to be validated for MDS PDD and PD-MCI criteria
SPSMQ	Good ^a	Mixed	Not assessed	Yes	Listed	Minimal use in PD, clinimetric data insufficient or not available in PD

Table 9. Summary of “use recommendations” of cognition rating scales used in Parkinson’s disease²³⁶

ADAS-COG, Alzheimer’s Disease Assessment Scale – Cognition; CAMCOG-R, Cambridge Cognitive Assessment (Revised); DRS-2, Mattis Dementia Rating Scale Second Edition; MMP, Mini-Mental Parkinson; MMSE, Mini-Mental State Examination; MDS, International Parkinson and Movement Disorder Society; MoCA, Montreal Cognitive Assessment; PANDA, Parkinson Neuropsychiatric Dementia Assessment; PD, Parkinson’s disease; PD-CRS, Parkinson’s Disease Cognitive Rating Scale; PDD, Parkinson’s disease-related dementia; PD-MCI, Parkinson’s disease-related mild cognitive impairment; PDD-SS, Parkinson’s Disease Dementia-Short Screen; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCOPA-COG, Scales for Outcomes in Parkinson’s Disease-Cognition; SPSMQ, Short Portable Mental Status Questionnaire.

aClinimetric data not fully available from studies in PD.²³⁶

The Movement Disorder Society Task Force²²⁵ recommended specific guidelines and a simple and short algorithm for the diagnosis of PD-MCI²²⁵ and PDD²²⁹ based on an abbreviated cognitive assessment (Level I). This level is best considered as a screening tool for the diagnosis of PD-MCI and PDD.

Level I (PD-MCI Abbreviated Assessment)²²⁵

The requirements for level I are:

- impairment on a scale of global cognitive abilities validated for use in PD or
- impairment on a limited battery of neuropsychological tests (e.g., including only one test per cognitive domain or those assessing fewer than five cognitive domains).

The relevant cognitive domains are attention and working memory, executive, language, memory, and visuospatial functions.

When a limited battery of neuropsychological tests is performed, impairment must be present on at least two tests to diagnose PD-MCI by level I criteria (Table 10).

Level I criteria do not allow complete subtyping of PD-MCI.

Cognitive Domain	Neuropsychological Tests	Estimated Time of Test, min
Attention and working memory	- WAIS-IV (or earlier version) Letter Number Sequencing	5
	- WAIS-IV Coding (or earlier version) or other substitution task, written or oral	5
	- Trail Making Test	5 to 10
	- Digit span backward or digit ordering	5
	- Stroop color-word test	5 to 10
Executive function	- Wisconsin Card Sorting Test (CST), or modified CST (Nelson's modification)	15
	- Tower of London test–Drexel version, or Stockings of Cambridge (CANTAB)	10 to 15
	- Verbal fluency test, such as letter fluency (COWAT or similar tests), category fluency (animals, supermarket, or similar), or alternating fluency tasks (if a well-standardized version is used). Not more than one verbal fluency test abnormality should be used to satisfy the MCI criterion of two abnormal test performances because of the strong relationship among these tests; 10 points Clock Drawing Test	5
Language	- WAIS-IV (or earlier version) Similarities	10 to 15
	- Confrontation naming task, such as Boston Naming Test (or short-form validated in PD) or Graded Naming Test	5 to 15
Memory	- Word list learning test with delayed recall and recognition conditions, such as Rey's Auditory Verbal Learning Test, California Verbal	10 to 20

	Learning Test, Hopkins Verbal Learning Test, and Selective Reminding Test	10 to 15
	- Prose recall ³ test with a delayed recall condition, such as Wechsler Memory Scale-IV Logical Memory subtest (or earlier version) or Rivermead Behavioural Memory Test paragraph recall subtest	10 to 15
	- Brief Visuospatial Memory Test–Revised (BVM-T-R)	
Visuospatial function	- Benton’s Judgment of Line Orientation	5 to 10
	- Hooper Visual Organization Test	10
	- Clock copying (e.g., Royall’s CLOX)	5

Table 10. Examples of tests for cognitive domains and estimated time²²⁵

Level I (PDD Abbreviated Assessment)²²⁹

Recommended Algorithm for Level I PDD Diagnosis

The diagnosis relies on the presence of the following five criteria:

- 1. Parkinson’s disease**
- 2. PD developed prior the onset of dementia**
- 3. PD associated with a decreased global cognitive efficiency:** test proposed: MMSE. It is proposed because it is a simple and universally applied scale)
- 4. Cognitive deficiency severe enough to impair daily life:** impact on daily living activities that cannot be attributed to motor or autonomic symptoms in case of PDD).
- 5. Impairment in more than one cognitive domain:** profile of cognitive deficits, typical of those described for PDD, in two or more of four domains (attention, executive function, visuoconstructive ability and memory).

Memory impairment is not a prerequisite for the diagnosis of PDD and a preservation of language function (that can be evaluated during the general neurological examination and patient interview) is usual in PDD.

Supportive features

Although behavioral symptoms are not required, the presence of at least one of the following behavioral symptoms (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PDD.

Features making the diagnosis of probable PDD uncertain

The presence of major depression or delirium or any other abnormality which may by itself cause significant cognitive impairment makes the diagnosis uncertain.

1	A diagnosis of Parkinson's disease based on the Queen's Square Brain Bank criteria for PD
2	PD developed prior to the onset of dementia
3	MMSE below 26
4	Cognitive deficits severe enough to impact daily living (Caregiver interview or Pill Questionnaire)
5	Impairment in at least two of the following tests: Months reversed or Seven backward Lexical fluency or Clock drawing MMSE Pentagons 3-Word recall
The presence of one of the following behavioral symptoms: apathy or depressed mood or delusions or excessive daytime sleepiness may support the diagnosis of probable PDD.	
The presence of major depression or delirium or any other abnormality which may by itself cause significant cognitive impairment makes the diagnosis uncertain.	

Table 11. Algorithm for diagnosing Parkinson's disease with dementia (PDD) at Level I²²⁹

MDS proposes a diagnostic rating sheet for checking the presence of the diagnostic features of probable PDD (Table 12).

	YES	NO
1. Parkinson's disease	☐	☐
2. Parkinson's disease developed before dementia	☐	☐
3. MMSE<26	☐	☐
4. Dementia has Impact on ADLs	☐	☐
5. Impaired cognition (For Yes, at least of 2 of 4 tests below are abnormal)	☐	☐
Mark which Tests are abnormal		
☐ Months reversed or sevens backwards		
☐ Lexical fluency or clock drawing		
☐ MMSE pentagons		
☐ 3-word recall		
6. Absence of major depression	☐	☐
7. Absence of delirium	☐	☐
8. Absence of other abnormalities that obscure diagnosis	☐	☐
Probable PDD (items 1–8 must all be YES)	☐	☐

Table 12. Diagnostic rating sheet for probable Parkinson's disease with dementia (PDD), recommended by the Movement Disorder Task Force²²⁹

2.4.2 Neuropsychological testing

Neuropsychological tests are validated standardized tests with adequate population norms. Raw test scores are especially influenced by age and education level. Based on the norms, raw test scores are transformed, correcting for influences, such as age and education, into z-scores or equivalents¹¹.

A primary consideration in the selection of specific tests is the psychometric properties of the tests, specifically the availability of good normative data representative of the population and the reliability, validity, sensitivity, specificity and predictive values of tests in PD in particular²³⁵.

Test selection should consider the patient's cognitive, emotional, motor, and sensory capacity to cooperate with evaluation²³⁵.

In PD, cognitive tests are often sought that minimize potentially confounding motor demands. Furthermore, motor fluctuations and fatigability should be considered when deciding the length of a test battery²³⁵.

In terms of detailed neuropsychological testing, there is no optimal battery to detect cognitive changes in PD for the time being¹¹⁸.

Different neuropsychological tests and norms are used across centers and for different research studies and for clinical assessment. However, preliminary work has been performed to guide future efforts to establish an efficient neuropsychological battery¹¹⁸.

Goldman et al (2015)²³⁸ investigated how many and which neuropsychological tests could be recommended to diagnose PD-MCI by MDS Task Force criteria. Out of 19 MDS-recommended scales representing five cognitive domains, the two best performing tests for each cognitive domain were determined with 2 SDs below norms on these tests suggested to be highly sensitive and specific for PD-MCI diagnosis.

Nevertheless, a multi-site study by the MDS Study Group for Validation of MCI in PD, which included 2908 PD patients and 1247 healthy controls, did not provide strong support for this threshold²³⁹. Different sites were using different normative scores for neuropsychological tests, which led to a high variability in cognitive performance across

study sites. This variability was reduced when comparisons involved healthy controls that were matched with the patients for education, language, test version, test procedures, and source population within the studies. The study group outlined the need to unify existing guidelines for test procedures, including matched healthy controls, and developing more extensive normative data for tests to account for age, education, sex, ethnicity and race to allow comparability of findings in research²³⁹.

Tests are most frequently divided into five domains (attention and working memory, executive, language, memory, and visuospatial functions).

Examples of tests that are useful to proceed with a comprehensive neuropsychological assessment (Level II) are provided in the MDS consensus PD-MCI paper²²⁵ and in the MDS PDD recommended diagnostic procedures paper²²⁹.

Level II (PD-MCI Comprehensive Assessment)²²⁵

For the diagnosis of PD-MCI by level II criteria and PD-MCI subtyping, the MDS task force recommends formal, comprehensive neuropsychological testing that includes at least two tests for each of the five cognitive domains previously listed (Table 10).

Impairment should be present:

- on at least two tests, either within a single cognitive domain or across different cognitive domains

Impairment on neuropsychological tests may be demonstrated in several ways:

- performance between 1 to 2 SDs below age, education, gender, and culturally appropriate norms, or
- significant decline on serial cognitive testing, or
- significant decline from estimated premorbid levels.

Subtype Classification for PD-MCI²²⁵

Classification of PD-MCI subtypes is important for research purposes and to explore whether impairments in different cognitive domains have a different neurobiological substrate and course.

Presence of two abnormal tests within a single cognitive domain, with the other domains unimpaired, represents a **single-domain subtype**.

If at least one test in two or more cognitive domains is impaired, then PD-MCI should be **subtyped** as **multiple domain**.

Level II (PDD Comprehensive Assessment)²²⁹

The MDS PDD task force suggested a comprehensive neuropsychological assessment to provide a more detailed series of assessments that will allow characterization of the components of PDD and the monitoring of elements that may be responsive to interventions.

These investigations are qualitative and have no diagnostic cutoff scores.

The same Level II assessments may also be utilized when the diagnosis of PDD remains uncertain or equivocal at the end of Level I process, for example where the cognitive deficits are patchy and relatively mild or when depression is present.

The Level II evaluation assesses four domains: 1) global cognitive efficiency; 2) subcortico-frontal features of PDD (executive functions, apathy and long-term memory process and retrieval ability); 3) instrumental (cortically mediated) functions (language, visuoconstructive, visuospatial and visuoceptive functions); 4) and neuropsychiatric features (apathy, depression, visual hallucinations and psychosis) (Table 13).

Domains	Cognitive tests
Global efficiency	Mattis DRS
Executive functions	
Working memory	Digit span Spatial span (CANTAB) Digit ordering test
Conceptualization	Similarities (WAIS-III) Wisconsin CST
Set activation	Verbal fluency (C, F, L)
Set shifting	TMT
Set maintenance	Stroop test Odd man out test
Behavioral control	Prehension behavior
Memory	RAVLT Free and cued recall test
Instrumental functions	
Language	Boston naming test

Visuoconstructive	Copy of the clock
Visuospatial	Benton line orientation test
	Cube analysis (VOSP)
Visuoperceptive	Benton face recognition test
	Fragmented letters (VOSP)
Neuropsychiatric functions	
Apathy	Apathy scale
Depression	MADRS
	Hamilton
	Beck depression inventory
	GDS-15
Visual hallucination	PPQ6
Psychosis	NPI

Table 13. Summary of tests at Level II testing for Parkinson's disease with dementia (PDD)²²⁹

According to the MDS task force²²⁹, the dissociation between the mediotemporal component (predominantly impaired in Alzheimer's disease) and the subcortico-frontal component (predominantly impaired in PDD) is of central importance in understanding the patterns of memory deficit found in different dementia syndromes.

2.4.2.1 Cutoffs for neuropsychological tests

Differences in cut-off scores utilized have led to a wide range of prevalence estimates for PD-MCI and PDD.

Studies of MCI have commonly utilized a range of cut-off scores at 1 to 2 SD or more below the mean using normative data²²⁵.

One issue in using a rigid cut-off score, such as -1.5 SD, is that high-functioning people (e.g., those scoring at least 0.5 SD above the mean relative to an appropriate normative sample premorbidly) would have to experience a decline of >2 SDs to meet a -1.5 -SD cutoff²²⁵.

Assuming a normal distribution of test scores, 30% of people scoring 0.5 SD or more above the mean premorbidly would not be detected as having experienced a marked decline in cognition, even with a 1.5 -SD decline in performance (i.e., false negatives), whereas 7% scoring 1.5 or more SD below the mean premorbidly would be falsely assumed to have cognitive decline, even without any change in performance over time (i.e., false positives)²²⁵.

Dalrymple-Alford et al (2011)¹⁶⁷ found that the best criterion to minimize the inclusion of cognitively normal patients as having MCI was to require deficits of at least -1.5 SD in two scores within any single domain (resulting in 30% PD-MCI) or deficits of at least -1.5 SD in two scores from different domains (37% PD-MCI).

The proposed MDS PD-MCI criteria are consistent with these cut-off scores, but because of potential differences among tests and premorbid patient function, MDS PD-MCI task force proposed a less-rigid recommendation of a range of 1 to 2 SDs below appropriate norms²²⁵.

2.4.2.2 Assessing function related to cognition

Impairment on the patient's ability to carry out instrumental activities of daily living (IADL) is an essential feature for establishing the severity of cognitive impairment²³⁵.

This is especially relevant for nondemented PD subjects in whom some aspects of altered functioning in IADL may appear unnoticeable before the diagnosis of dementia without a formal examination²³⁵.

The presence of significant functional deficiency due to cognitive impairment is part of the current criteria to support the diagnosis of PDD²²⁴. Moreover, the major formal differentiation of MCI from dementia has typically required cognitive deficits not to interfere significantly with the patient's ability to implement IADL²²⁵.

Nevertheless, Rosenthal et al (2010)²⁴⁰ investigated the association between cognition and function in patients with PD with and without dementia and they concluded that a certain degree of functional impairment in IADL can also be identified in PD-MCI subjects.

The lack of a recommendable instrument, capable of measuring the specific impact of cognitive decline in PD minimizing the motor symptoms of the disease, have made it challenging to set a standard for what is meant by 'significantly' (ie, dementia) or 'subtly reduced' (ie, MCI) functional performance²²⁵.

According to Marras et al (2014)²³⁵, filling this gap appears important not only to help with clinical management of patients suspected to have PD-MCI, but to facilitate the design of cognitive therapeutic trials that move to enroll milder, non-demented PD patients and will

require evidence that improvement in cognitive measures is accompanied by functional benefit.

The MDS task force²²⁹ and Martinez-Martin (2013)²⁴¹ proposed the Pill Questionnaire for detecting functional impairment in PDD. However, it has been shown insensitive to identify non-demented individuals diagnosed with PD-MCI²⁴².

Marras et al (2014)²³⁵ suggested two PD-specific instruments, the PD-Cognitive Function Rating Scale (PD-CFRS), and the Brief Penn Daily Activities Questionnaire (PDAQ). The authors referred that these two instruments may help fill the need for assessments of IADLs that are sensitive to cognitive impairment in PD while minimizing the motor aspects of the disease.

2.4.2.3 Interpreting the results

Cognitive test results must be interpreted in the context of the mental and physical health of the individual²³⁵.

In PD, the potential for other medical issues to influence cognitive performance is high. Common confounding factors are depression, apathy, anxiety, delirium related to adverse effects of medication and hour to hour fluctuations in the state of effectiveness of dopaminergic replacement therapy²³⁵.

Nonetheless, it is recommended that patients be tested in their optimal motor state, using tests that minimize motor demands²²⁵.

2.4.2.4 Considerations in test administration

Troster & Browner (2013)²⁴³ have outlined some possible considerations and modifications in standard test administration procedures in persons with movement disorders.

Patients with marked dysarthria may need to be tested over multiple, brief sessions if they are asked to repeat responses. Alternatively, test requiring pointing responses may be employed. Similarly, hypophonia may be compensated for by an amplification device²⁴³.

Marked tremor, dyskinesia, dystonia or apraxia may require that tests requiring a written response, even as simple as marking across on a questionnaire, are administered orally. On

tasks such as card sorting or tower tests, the examiner may need to hold and move the cards or blocks/beads as instructed by the patient (standard timing cannot be used in such cases)²⁴³.

Interview of the patient or caregiver prior to the appointment can be used to ascertain timing of motor fluctuations and the typical time of day when the patients shows the best motor on state or is less likely to be affected by choreiform or dystonic dyskinesias and allow planning for test breaks and timing²⁴³.

Unless there is a specific need to compare performances “on” and “off” medications, it is recommended that patients be tested while on their antiparkinsonian medications (though anticholinergics and potentially cognitively offending medications are best discontinued and tapered prior to evaluation if medically feasible)²⁴³.

2.4.2.5 Alternative testing for severely impaired PD patients

Alternative testing is recommended for patients who, according to the best clinical judgment of the study investigators or clinician, are not capable of completing a comprehensive neuropsychological testing²⁴⁴.

As a group, the late-stage PD patients are difficult to evaluate, largely due to floor effects on cognitive testing. Some severely impaired subjects are not able even to complete the screening tests²⁴⁴.

Nevertheless, there is the possibility to proceed with a caregiver-based qualitative cognitive assessment to make conclusions mainly on PDD in patients with these typical late-stage physical/motor disabilities, otherwise, we risk underestimating cognitive impairment in these late PD stages.

3. Aims of the thesis

The aim of this thesis was to contribute to the growing knowledge on the cognitive functioning in Parkinson's disease.

Our research intends to summarize the current evidence of dementia frequency in PD and to characterize the cognitive profile of LSPD patients.

In order to address our research proposal, our study objectives were the following:

1. To evaluate the frequency of PDD reported in published observational studies and to examine the impact of methodological, clinical, and demographic characteristics of the studies and PD patients in dementia frequency;
2. To examine the most used instruments to assess cognition in LSPD and to propose a neuropsychological battery adapted to the special characteristics of this population;
3. To assess the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD;
4. To characterize the cognitive profile of LSPD patients by using a selection of neuropsychological tests proposed by MDS task force on PDD diagnostic procedures, and to examine clinical, demographic, and cognitive variables that are associated with PDD diagnosis.

4. Research projects

To achieve the aims purposed, four research projects were planned. The first (aim 1) was a quantitative research synthesis, based on systematic review and meta-analysis. The second (aim 2) was again a quantitative research synthesis, also based on systematic review. The third (aim 3) was based on a cross-sectional study. The last research project (aim 4) was based on another cross-sectional study, developed with the same LSPD population.

Research project 1: Systematic review and meta-analysis of observational studies available in EMBASE and MEDLINE databases, from inception to May 2019. The outcome of interest was the number of PDD among a population of PD patients. Pooled estimates of dementia frequency and 95% confidence intervals (CI) were derived by random effects meta-analysis. We proceeded to a subgroup analysis of the dementia frequency according to the methodological, clinical, and demographic characteristics of the included studies. Meta-regression was used to determine whether a significant difference was present between subgroups. The study protocol was registered at PROSPERO: CRD42020140044.

Research project 2: Systematic review of observational studies available in EMBASE and MEDLINE databases, from inception to May 2019. The outcome of interest was the cognitive tests used in a population of LSPD patients. We grouped them according to the respective cognitive demands described in the studies. We selected the four most used cognitive tests in each cognitive domain and we verified their global characteristics in order to propose a battery of cognitive instruments, brief in their utilization but covering all relevant cognitive domains, that require as little as possible the use of paper and pencil and preferably not timed (minimized motor demands), and possible to be used in the patient's home.

Research project 3: Cross-sectional study designed to evaluate the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD. The primary objective was to evaluate the frequency of dementia by using MDS clinical criteria for “probable” and “possible” PDD, operationalized according to the Level II procedures outlined by Dubois et al.¹¹ which were based on neuropsychological tests, functional autonomy as well as clinical interview. The secondary objective was to evaluate the frequency of dementia by using different diagnostic criteria (MDS PDD Level I, DSM-IV, and DSM-5 criteria).

Research project 4: Cross-sectional study designed to examine the cognitive functioning of the same LSPD study population. The primary objective was to examine the cognitive performance of LSPD patients by using MDS Level II criteria and the suggested neuropsychological tests to diagnose PDD. The secondary objectives were to examine the cognitive profiles according to the pattern of cognitive impairment and to investigate the associated clinical, demographic, and cognitive variables with PDD diagnosis.

5. Thesis outline

In chapter I, we described the background of cognitive impairment in Parkinson's disease. We also described the most common cognitive and neuropsychiatric associated profiles, and the international accepted criteria and procedures to diagnose cognitive impairment in PD (MCI and PDD).

In chapter II, we systematically reviewed the available evidence on observational studies regarding dementia frequency in Parkinson's disease. Additionally, we performed a subgroup analysis and we included the methodological characteristics of the studies and clinical and demographic characteristics presented by the participants to analyze dementia frequency according to these variables. Meta-regression was used to determine whether a significant difference was present between subgroups. A sensitivity analysis of the data was performed by study quality. Studies with a low, moderate, or high risk of bias were combined using meta-analysis and compared to determine whether significant differences were present in dementia frequency based on study quality.

In chapter III, we explored the most used neuropsychological instruments in LSPD populations in order to propose a neuropsychological battery which take into account the special characteristics of LSPD patients and possible to be used for research purpose and also in clinical practice.

In chapter IV, we presented data from the cross-sectional study regarding dementia frequency in LSPD patients according to MDS PDD Level II criteria and according to another dementia criteria frequently used in research studies (MDS PDD Level I criteria, DSM-IV, and DSM-5).

In chapter V, we explored the cognitive functioning of LSPD patients, by analyzing their cognitive performance using the MDS Level II criteria and the suggested neuropsychological tests to diagnose PDD. Secondly, we explored the profile of the cognitive impairment by analyzing its pattern (subcortical, cortical, or global impairment) and, finally, we investigated if there were clinical, demographic, and cognitive variables associated with PDD diagnosis.

Finally, in chapter VI we discussed the results obtained, their implication for clinical practice and research, and explore future steps in this field.

Chapter II. Frequency of dementia in observational studies - systematic review and meta-analysis

Paper:

Frequency of dementia in Parkinson's disease: A systematic review and meta-analysis

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J Neurol Sci. 2021 Dec 3;432:120077. doi: 10.1016/j.jns.2021.120077

Impact factor: 3.181

Catarina Severiano e Sousa participated in the conception and design of the project, data acquisition, analysis, and interpretation, as well as drafting and revising final manuscript critically.

Frequency of dementia in Parkinson's disease: A systematic review and meta-analysis

Abstract

Background: There is a considerable variation in the reported frequency of dementia in Parkinson's disease (PDD). The aim of this study was to evaluate the frequency of PDD reported in published studies and to examine the different methodological, clinical, and demographic factors that may contribute to this variation.

Methods: We conducted a systematic review, searching EMBASE and MEDLINE databases for relevant articles on PDD frequency published before May 2019. A global estimation of PDD was calculated. Different subgroup analyses were performed for methodological, clinical, and demographic characteristics. Meta-regression was also conducted to identify any significant differences within the subgroups.

Results: We included 295 studies. The global pooled dementia frequency was 26.3%. These estimations varied according to methodological (14%-55%), clinical (18%-46%), and demographic (21%-43%) variables. The declared primary objective of the studies (to study PDD), the follow-up length (≥ 7 years), the age of the participants (≥ 75 years), Parkinson's disease (PD) duration (> 10 years), and the Hoehn & Yahr (H&Y) stage (> 3) were important factors affecting reported dementia frequency.

Conclusions: This systematic review found that approximately one-quarter of the PD patients were diagnosed with PDD. Dementia frequency varied according to methodological, clinical and demographic variables. We cannot examine PDD frequency without considering all these variables that have an impact on it.

Keywords: Parkinson's disease, dementia frequency, systematic review

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that has been classically defined by motor dysfunction. Currently, we understand that PD is a heterogeneous disorder, comprising a range of motor and non-motor symptoms. Cognitive decline, in particular, is a common non-motor feature of the disease, which can have a high impact on the quality of life of patients and carers³⁸, as well as being a risk factor for early mortality²⁴⁵. As such, the identification of the specific features that may predict the progression of cognitive impairment could have important implications for the treatment planning and clinical management of PD patients.

Although it is estimated that the prevalence of Parkinson's disease dementia (PDD) is around 24-31%⁷⁰, several studies have reported a considerable variation in their results, ranging from 8%⁷⁴ to 83%²⁵, thus making it difficult to accurately estimate dementia frequency in this population.

Methodological characteristics of the studies and clinical and demographic characteristics of PD patients have been associated with this variability. Important methodological features include the analytical design used (cross-sectional versus longitudinal), tests to assess cognition (screening scales versus comprehensive neuropsychological assessment), definitions of dementia, and the criteria for diagnosing PDD and selecting patients. Most of the previous studies on PDD also included patients at varying disease stages.

Although it seems clear from the published literature that the prevalence of dementia increases with older age^{37,71}, greater severity of motor impairment⁷¹, and longer PD duration²⁴⁶, the frequency of PDD at different disease stages, ages, and disease duration remains unclear.

The primary objective of the present systematic review and meta-analysis was to estimate the frequency of dementia within PD. Secondary objectives were to estimate the frequency of dementia according to the methodological, clinical, and demographic characteristics of the included studies and PD patients.

2. Methods

This systematic review was performed according to the Cochrane Collaboration recommended procedures²⁴⁷ and the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)²⁴⁸.

2.1 Eligibility Criteria

We included original observational studies (cross-sectional, prospective cohort, and case-control studies), published in English, French, or Spanish without publication date restriction, which reported patients with confirmed PD diagnosis and dementia that developed one year after the confirmed PD diagnosis. The one-year rule was used to distinguish PDD from dementia with Lewy-bodies (DLB)^{224,231}, in order to carefully minimize the risk of involuntary inclusion of DLB patients.

2.2 Information Sources and Search Methods

We searched both EMBASE and MEDLINE databases, from their inception to May 2019, using a pre-defined search strategy (Supplementary Figure 1). The search strategy combined standardized subject terms and text words, with relevant Boolean operators implemented. A citation chaining was also conducted to ensure that no articles were overlooked.

2.3 Data Extraction

Two authors independently assessed the titles and abstracts of retrieved publications to identify studies that met the inclusion criteria. Any disagreement over the eligibility of studies was resolved through a consensus discussion with a third author.

The outcome of interest was the number of PDD among a population of PD patients.

A standard data collection form was created to extract methodological data from the studies and demographic and clinical information on the PD patients.

2.4 Subgroup Analysis

We performed a subgroup analysis.

In this subgroup analysis, we included the methodological characteristics of the studies (year of the study development [classified as year of study], study design, study primary objective,

follow-up length, dementia diagnosis criteria, and methodology used to assess cognition) and clinical and demographic characteristics presented by the participants (PD severity [Hoehn & Yahr stage, H&Y²⁸]), PD duration, age, and education).

We performed an additional analysis within each of the categories of the PD severity subgroup to analyze dementia frequency according to these variables.

2.4.1 Year of Study

At the end of 2007, the International Movement Disorders Society (MDS) recommended criteria to diagnose dementia²²⁹. It was an important milestone because until then PDD was diagnosed without an internationally accepted recommendation.

We, therefore, analyzed studies published before and after 2008, to investigate any changes that have occurred, especially methodologically, and whether this had an impact on the reporting of dementia frequency.

2.4.2 Study Design

We grouped the studies according to the three main analytical designs used in observational research: 1) cross-sectional; 2) cohort; and 3) case-control studies.

2.4.3 Studies' Primary Objectives

We grouped the studies into three main categories according to their declared primary objective: 1) study PDD; 2) study cognitive functioning, which we classified as study cognition; and 3) other (i.e., studies which primarily investigated other conditions and reported dementia frequency as a secondary result).

2.4.4 Follow-up Length

We grouped the studies into seven categories of reported follow-up length (in years): 1) ≤ 1 ; 2) $>1 \leq 2$; 3) $>2 < 5$; 4) $\geq 5 < 7$; 5) $\geq 7 < 10$; 6) $\geq 10 < 15$; and 7) ≥ 15 .

For studies with multiple follow-ups, we entered the dementia frequency of the last assessment.

2.4.5 Dementia Diagnosis Criteria

We grouped the studies into seven main categories, according to the PDD diagnosis criteria used: 1) MDS Level I; 2) MDS Level II; 3) DSM-III/IV (due to their similarities, we included ICD-9/10 criteria in this category); 4) The best clinical judgement criteria with a comprehensive neuropsychological assessment (NPA) and with a well-defined definition of cognitive impairment, were classified as “NPA criteria”; 5) Screening scales criteria (screening scales cut-offs); 6) The best clinical judgement criteria made by a single qualified clinician or through consensus by a team of clinicians, were classified as “Clinical assessment criteria”; and 7) The studies that failed to describe the criteria used were classified as “Not specified”.

For studies that compared different diagnostic criteria, we entered data concerning to dementia frequency obtained with their primary criteria.

2.4.6 Methodology Used to Assess Cognition

We grouped the studies into three main categories, according to the methodology used to assess cognition: 1) Screening scales; 2) NPA; and 3) Not specified (studies that failed to describe the methodology used).

2.4.7 PD Severity

We grouped the studies that reported the H&Y stages of PD patients into three categories: 1) $H\&Y \leq 2$ (early stages, with mild motor impairment); 2) $H\&Y > 2 \leq 3$ (intermediate/advanced stages, with moderate motor impairment); and 3) $H\&Y > 3$ (late stages, with severe motor impairment).

2.4.8 PD Duration

We grouped the studies that reported PD duration (number of years since PD was diagnosed) into five categories (in years): 1) ≤ 3.5 ; 2) $> 3.5 \leq 5$; 3) $> 5 \leq 10$; 4) $> 10 < 15$; and 5) ≥ 15 .

2.4.9 Age

We grouped the studies that reported the age of the PD patients into three categories (in years old): 1) ≤ 60 ; 2) $> 60 < 75$; and 3) ≥ 75 .

2.4.10 Education

The studies that reported participants' education levels were grouped into four categories (in years): 1) ≤ 4 ; 2) $> 4 \leq 9$; 3) $> 9 \leq 12$; and 4) > 12 .

We entered the H&Y stage, PD duration, and age presented by PD patients at the baseline assessment, in cross-sectional studies, and at the last follow-up assessment, in the longitudinal studies.

2.5 Quality Assessment

The quality of the included studies was assessed using a scale adapted from Hoy and colleagues^{249,250}. The risk of bias of the studies was categorized as “low risk” (0-3 points), “moderate risk” (4-6 points), or “high risk” (7-9 points)²⁵⁰ (see Supplementary Figure 2 for quality criteria used).

2.6 Data Synthesis

We used descriptive statistics to characterize the methodological, clinical, and demographic information of the included studies. Variables were described through absolute and relative frequencies (%).

Dementia frequency and 95% confidence intervals (CI95%) were calculated based on the number of dementia cases and PD patients included.

We proceeded to a subgroup analysis of the dementia frequency according to the methodological, clinical, and demographic characteristics of the included studies. Data were organized into several categories within each subgroup according to the criteria explained above.

We calculated the Cochrane Q statistic (with $p < 0.10$ indicating statistically significant heterogeneity) and used I^2 (with $< 40\%$ indicating heterogeneity might not be important and $> 75\%$ indicating considerable heterogeneity) to quantify the magnitude of heterogeneity between studies²⁵¹. As a way of standardizing the results of the analyzed studies, a meta-analysis was used to calculate dementia frequency and 95% confidence intervals by using the DerSimonian and Laird random-effects model²⁵².

Meta-regression was used to determine whether a significant difference was present between subgroups. A sensitivity analysis of the data was performed by study quality. Studies with a low, moderate, or high risk of bias were combined using meta-analysis and compared to determine whether significant differences were present in dementia frequency based on study quality.

The descriptive statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL). Meta-analysis and meta-regression were performed using OpenMetaAnalyst software²⁵³. A p-value <0.005 was considered statistically significant.

3. Results

3.1 Search

The results of the literature search are summarized in Supplementary Figure 3. Of the 3326 screened studies, 1261 were excluded following abstract screening, while 1770 were excluded following full-text screening. In total, 295 studies reported dementia frequency in PD according to our inclusion criteria and were included in our review.

3.2 Study Characterization

Of the included studies, 64.1% were published after 2008 and were mainly cohort studies (66.4%). Among the studies that reported a follow-up period (N=159), most were between 2 and 5 years (41.5%). For 35.9% of the studies, the primary objective was to study dementia, 41.7% used DSM-III/IV criteria to diagnose PDD, and 46.8% assessed patients' cognition using screening scales (Figure 5).

Interestingly, only one study followed DSM-5 criteria to diagnose PDD. As this study used full NPA, which is similar to the DSM-5 criteria, we included it in the subgroup of studies that used NPA criteria to diagnose PDD.

54.6% of the included studies had a moderate risk of bias (Supplementary Figure 2).

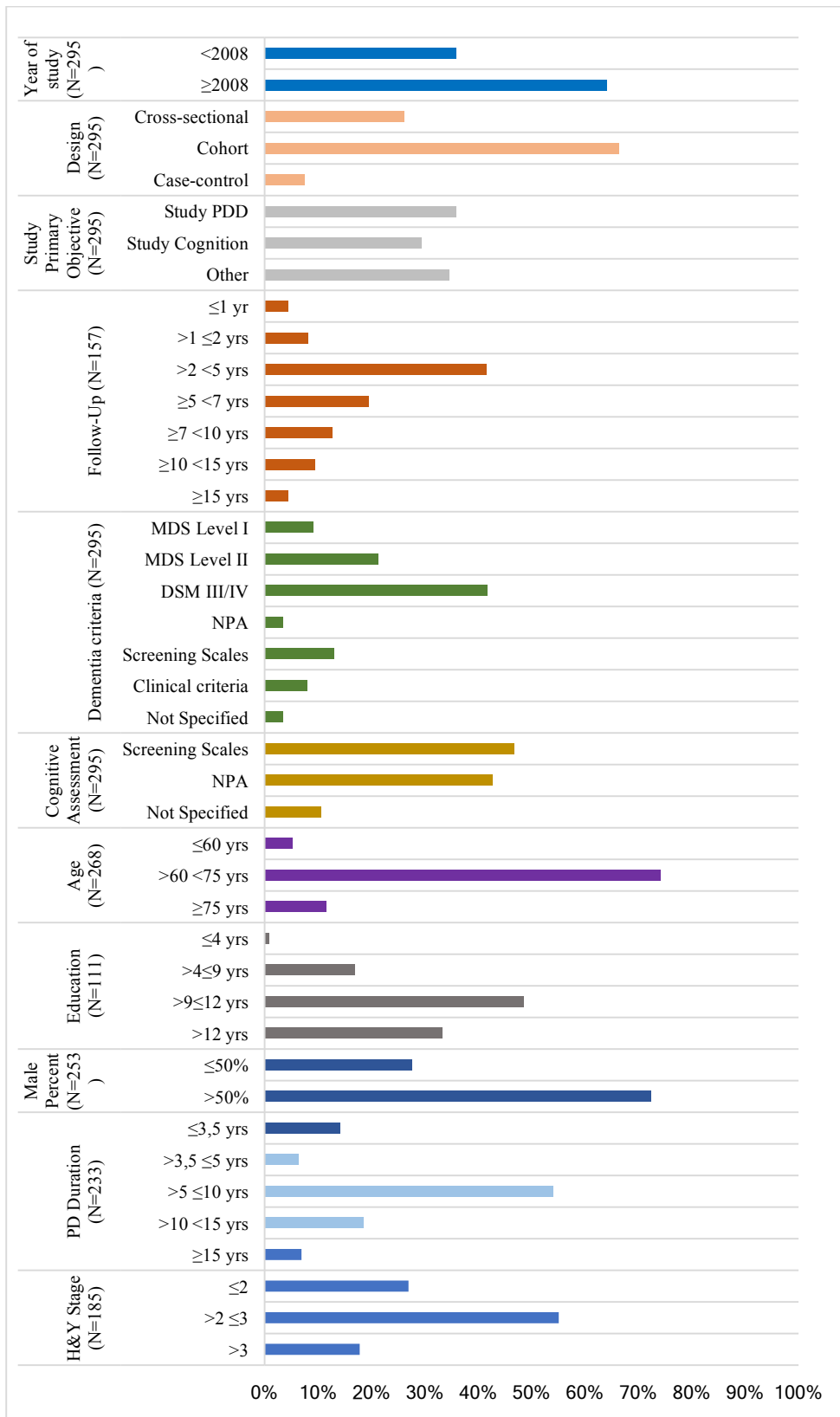


Figure 5. Studies' characterization

PD- Parkinson's disease

PDD- Parkinson's disease dementia

MDS- Movement disorder society

NPA- Neuropsychological assessment

H&Y- Hoehn and Yahr

3.3 Patient Characterization

In total, 54 107 patients with PD were included. Most of the studies included participants aged between 60 and 75 years (81.7%), more than 50% men (72.4%), with between 9 and 12 years of education (48.6%), a PD duration between 5 and 10 years (54.1%), and a H&Y stage between 2 and 3 (55.1%).

3.4 Dementia Frequency

Of the 54 107 PD patients included in the meta-analysis, 12 262 were diagnosed with dementia (26.3%). We observed a high heterogeneity between the studies (higher than 75%) (Figure 6).

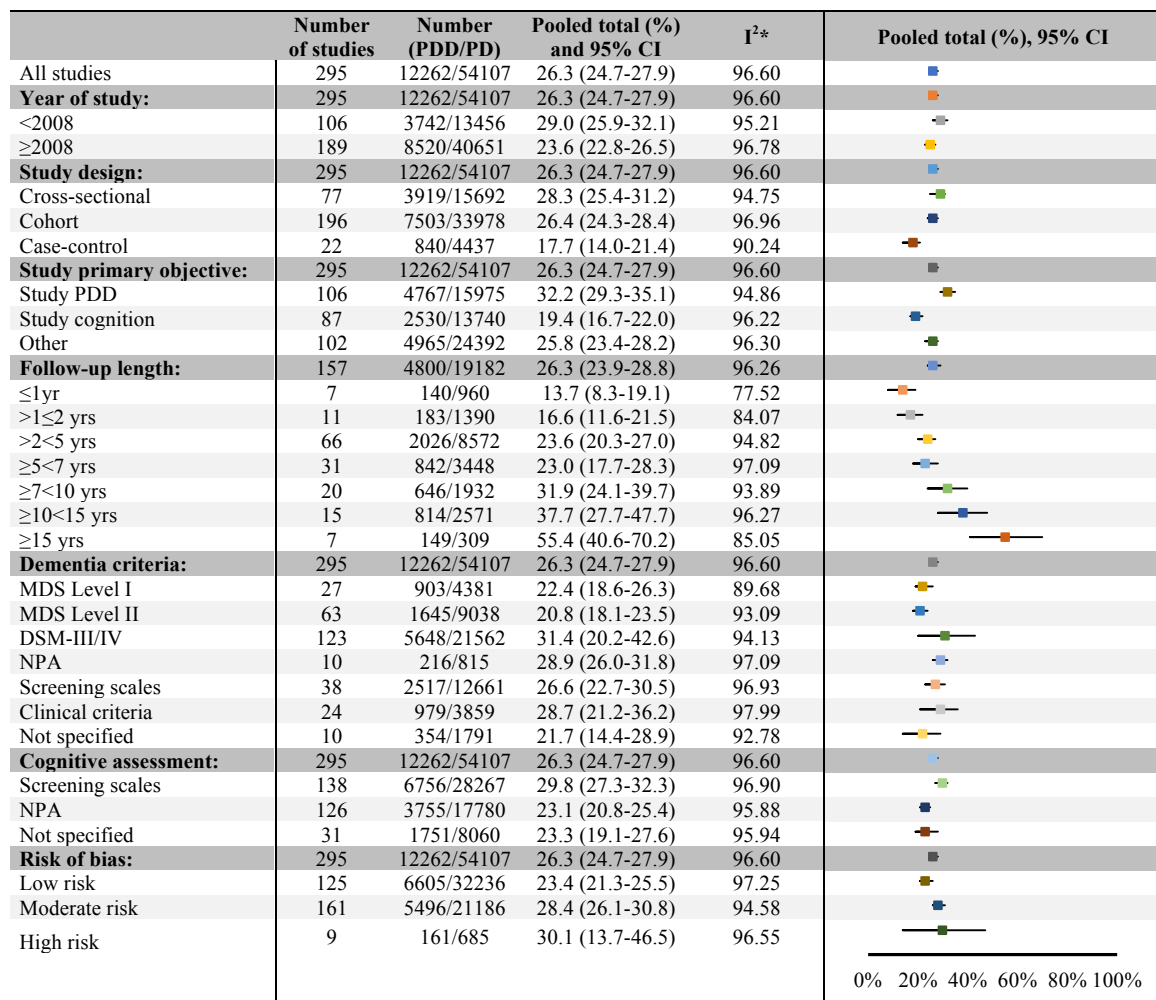


Figure 6. Meta-analysis of dementia frequency by methodological subgroups

*<40% heterogeneity might not be important; >75% considerable heterogeneity²⁵¹

PD- Parkinson's disease; PDD- Parkinson's disease dementia; MDS- Movement disorder society; NPA- Neuropsychological assessment

3.5 Subgroup Analysis

3.5.1 Methodological Aspects and Dementia Frequency

When we analyzed dementia frequency according to the year of study publication, although not statistically significant, we observed that before 2008 (N=106) dementia frequency was higher than after 2008 (29.0% vs 24.6%) (Figure 6). In this period, the proportion of studies focused on other conditions and reporting dementia frequency as a secondary result was higher (45.3%), followed by studying PDD (39.6%). They mainly used DSM-III/IV criteria (67.0%) and screening scales to assess cognition (56.6%) (Supplementary Table 1).

After 2008 (N=189), more studies reported dementia frequency, but their focus had changed. The primary objective that prevailed was to study cognitive functioning (37.6%). The same was observed with the methodology used to diagnose dementia and to assess cognition. MDS Level II criteria and full NPA were the most used (33.3% and 49.7% respectively).

When we analyzed dementia frequency according to study design, we observed a variation between 17.7% and 28.3%. Cross-sectional studies had the higher values (28.3%, $p=0.005$) (Figure 6).

Although confirmed PD diagnosis and PD without cognitive impairment prevailed as inclusion criteria across all the study design categories, we observed high heterogeneity in the inclusion criteria. The cross-sectional category had more studies with advanced/late-stage PD, PD patients in nursing homes, and cognitive complaints as inclusion criteria than the cohort and case-control categories (15.6% vs 13.2%, and 0%, respectively).

Considering the follow-up length, dementia frequency varied between 13.7% and 55.4%. We observed a global trend of increased frequency of dementia with increased study follow-up length, mainly with a follow-up length between 7 and 10 years (7-10 years, $p=0.006$; 10-15 years and higher than 15 years, $p<0.001$).

When we analyzed dementia frequency according to the study's primary objective, we observed a variation between 19.4% and 32.2%. It was higher when the primary objective was to study PDD (32.2%, $p<0.001$).

Regardless of the focus, the studies were mainly cohorts (Supplemental Table 1). The follow-up length that prevailed was similar in the studies that primarily studied PDD or cognition (between 2 and 5 years, 52.4% and 43.1%, respectively).

In the studies whose primary objective was to study PDD, the most used dementia diagnosis criteria were the DSM-III/IV (50.9%), with screening scales (47.2%), and NPA (46.2%) used to assess cognition.

The distribution of the age of the PD patients was similar regardless of the study focus (to study dementia, cognition, or other issues). The same applied to PD duration and H&Y stage distribution. Most participants were between 60 and 75 years old (80.2%, 85.9%, and 79.8%, for each study focus, respectively), had had PD for between 5 and 10 years (56.1%, 59.4%, and 47.6%, respectively), and were in the advanced H&Y stage (between 2 and 3) (57.1%, 56.9%, and 52.1%, respectively).

Inclusion criteria, although highly heterogeneous, were similar regardless of the study focus. Most had PD diagnosis and no cognitive impairment as inclusion criteria.

By analyzing dementia frequency according to the criteria used to diagnose PDD, we observed a variation between 20.8% and 31.4%. Although not statistically significant, higher results were observed when DSM-III/IV criteria were used (Figure 6).

Similar results were found when we analyzed dementia frequency according to the methodology used to assess cognition. It varied between 23.1% and 29.8%. Once more, this was not statistically significant, higher results were observed when screening scales were used.

The studies that most used the DSM-III/IV criteria to diagnose PDD and screening scales to assess cognition were the studies in which participants were PD patients aged between 60 and 75 years (74.3% and 77.7%, respectively) or more than 75 years (19.5% and 19.2%, respectively), with more than 5 years of PD duration (89% and 80.9%, respectively), and in the advanced (64% and 54.1%, respectively) and late stages (22.7% and 26.5%, respectively) of PD.

We observed, in general, that with increasing age, PD duration, and H&Y stage, there was an increased tendency to use brief methodologies to diagnose PDD (e.g., MDS Level I,

DSM-III/IV, screening scales cut-offs, and clinical assessment without NPA) and screening scales to assess cognition.

3.5.2 The Clinical and Demographic Aspects and Dementia Frequency

With regards to dementia frequency according to the H&Y stages, we observed a variation between 19.8% and 45.9%. The frequency was higher in the late disease stage ($p<0.001$) (Figure 7).

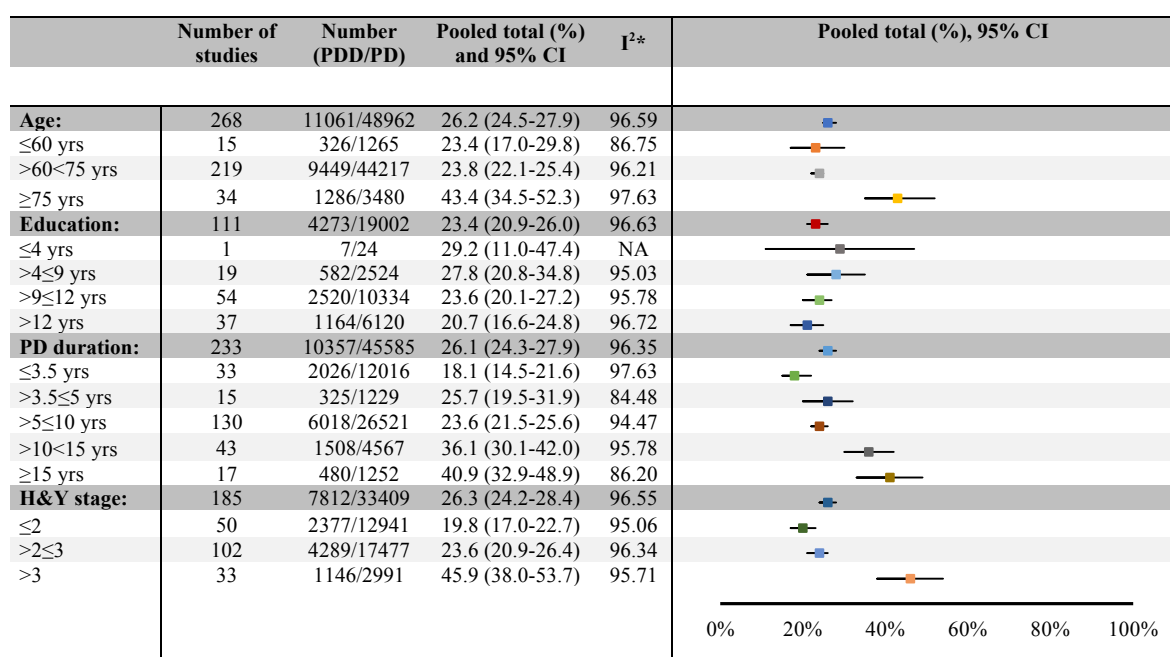


Figure 7. Meta-analysis of dementia frequency by clinical and demographic subgroups

*<40% heterogeneity might not be important; >75% considerable heterogeneity²⁵¹

PD- Parkinson's disease

PDD- Parkinson's disease dementia

H&Y- Hoehn and Yahr

Considering the criteria used to diagnose dementia, we found that in those studies that included participants in the early disease stages, although not statistically significant, higher frequencies of dementia were observed with MDS Level I criteria (33.3%) and when screening scales were used to assess cognition (25.6%) (Supplementary Table 2).

In those studies that had participants mainly in the advanced and late stages, higher dementia frequencies were observed when NPA criteria were used (33.3%, without statistical significance and 54.6%, $p=0.011$ respectively), with full NPA to assess cognition (24.8%, without statistical significance and 50.4%, $p<0.001$, respectively).

In the early H&Y stages, the most used dementia diagnosis criteria were MDS Level II, with full NPA (44.0% and 56.0%, respectively), while in studies that had participants in the advanced and late stages the most used criteria were the DSM-III/IV, with screening scales (47.1% and 51.5%, and 52% and 78.8%, respectively) (Supplementary Table 1).

Regardless of the H&Y stage, participants had a similar age distribution (mainly between 60 and 75 years old) (95.8%, 87.1%, and 59.4% in the early, advanced, and late stages, respectively), a similar level of education (mainly between 9 and 12 years) (56.7%, 40.0%, and 40.0%, respectively) and PD duration (mainly between 5 and 10 years) (50.0%, 66.3%, and 39.3%, respectively). However, in the early-stage subgroup, there were more participants in the categories with less than 5 years of PD duration (47.7%). In the late-stage category, participants were more distributed between the older categories ($>60<75$ and ≥ 75 years old, 59.4%, and 34.4%, respectively) and were more present in the categories with more than 10 years of PD duration (60.7%).

We observed a trend of an increased number of women with the increase of H&Y stages. In the early stages, 12.8% of the studies had more women participants ($\leq 50\%$ men percent category), in the advanced stages it was 34.8%, and in the late stages, 44.8%.

With regards to dementia frequency according to PD duration, we observed that dementia frequency increased in relation to PD duration and varied between 18.1% and 40.9%. The highest values were for patients who had PD for between 10 and 15 years (36.1%, $p<0.001$) and more than 15 years of PD (40.9%, $p=0.019$) (Figure 7).

The same was observed when we analyzed dementia frequency according to age (between 23.4% and 43.4%). PD patients over 75 years old had the highest frequency of dementia ($p<0.001$).

Most studies had a greater percentage of women in the over 75 years old category than in the younger age categories (≤ 60 years old and between 60 and 75 years old) (53.3% vs. 16.7% and 25.4%, respectively).

Dementia frequency decreased with increasing education levels, varying between 20.7% and 29.2%. Although not statistically significant, the higher values were observed in the lower levels of education (where patients had less than 4 years (29.2%) and between 4 and 9 years of education (27.8%)).

4. Discussion

The aim of this systematic review was to investigate the frequency of dementia in patients with PD. We also investigated which variables could help estimate this frequency, in this way we hope to contribute to the comprehension of dementia variability reported in the literature.

Of the 295 included studies, most were published after the publication of the MDS recommendations for diagnosing PDD. They were mainly cohort studies, with between two and five years of follow-up, and used the DSM-III/IV criteria with screening scales to diagnose PDD. Most studies included PD patients who were between 60 and 75 years old, patients were mainly men, with between 9 and 12 years of education, with a PD duration between 5 and 10 years, and in an advanced H&Y stage.

Despite the high heterogeneity that we already expected to find (higher than 75%²⁵¹), due to the observational design of the studies, for exploratory purposes, we decided to proceed with a global and subgroup meta-analysis.

Of the included 54 107 PD patients, 12 262 were diagnosed with PDD (26.3%). This result is in accordance with the majority of previously published studies that found similar frequencies of PDD²⁵⁴⁻²⁵⁸.

In the subgroup meta-analysis, we investigated dementia frequency according to the methodological, clinical, and demographic characteristics of the studies and participants.

Dementia frequency varied in all subgroups. However, the 95% CI, in some of the subgroups did not allow us to draw any conclusions, especially in the dementia criteria subgroup. Taking both this and the high heterogeneity of studies into consideration, the frequency of dementia reported according to the subgroups meta-analysis must only be interpreted qualitatively.

We observed higher dementia frequencies in studies published before 2008, in cross-sectional studies, when the primary objective was to study dementia, studies with a longer follow-up, and when DSM-III/IV criteria were used to diagnose PDD with screening scales to assess cognition. The same was observed in the clinical and sociodemographic variables.

The meta-analysis revealed a rising frequency of dementia in relation to increasing age, PD duration, and H&Y stage, and with decreasing levels of education.

Before 2008, most studies focused on studying other conditions and reported dementia as a secondary result, using DSM-III/IV criteria and screening scales to assess cognition.

After 2008, the focus of studies changed. The primary objective that prevailed was to study cognition. The same occurred with the methodology used to diagnose dementia and assess cognition. MDS Level II criteria and full NPA were the most used tools.

The distribution of age (between 60 and 75 years old), level of education (between 9 and 12 years), PD duration (between 5 and 10 years), and H&Y stage (between 2 and 3) that prevailed were similar in both periods. However, before 2008, there were more PD patients in the older category, in the categories of higher PD duration (more than 10 years), and in the advanced and late-stage H&Y categories. This led us to conclude that PD patients who participated in the studies before 2008 tended to be older and suffered from greater motor impairment. On the other hand, after 2008, PD patients were more evenly distributed between the categories of higher levels of education ($9 \leq 12$ and >12 years). These results may explain why dementia frequency was higher before 2008.

The risk of bias analysis revealed that most studies had a moderate risk. With the sensitivity analysis that we performed by study quality, we observed that dementia frequency tends to increase with the increasing risk of bias ($p=0.005$). This result is in accordance with what we expected. According to Rosenthal (1991)²⁵⁹, extracting data from published studies may bias results in favor of a significant effect, because studies with non-significant results are less likely to be published.

Analysis within each category of the subgroup of primary objectives revealed interesting information. Regardless of the primary objective, studies were mainly cohorts, with a follow-up length between 2 and 5 years in the studies that primarily investigated PDD or cognition. Curiously, inclusion criteria, although heterogeneous, were similar regardless of the study focus. Most had PD diagnosis and no cognitive impairment as inclusion criteria.

As they were mainly published after 2008, contrary to our expectations, the studies whose primary objective was to study PDD used DSM-III/IV criteria to diagnose dementia. Interestingly, the methodology used to assess cognition was distributed between screening

scales and full NPA. In the same way, the studies that investigated PDD as a secondary objective also used the DSM-III/IV criteria to diagnose PDD, but mainly with screening scales to assess cognition.

The main clinical and demographic characteristics of PD patients were similar regardless of study focus (between 60 and 75 years old, with between 5 and 10 years of PD duration, and in a H&Y stage between 2 and 3). However, when we analyzed the second most frequent categories, we observed that studies that focused on PDD had more PD patients in the older age categories and with longer PD duration. The same was observed with studies that investigated PDD as a secondary objective, these also had more participants in the late-stage H&Y category. However, despite their similarities, the frequency of dementia was lower than the frequency found in studies that sought to study PDD. Methodological issues may explain these results. Abbreviated methodologies to assess cognition may produce false negatives in the late stages of PD. The fact that NPA used to assess cognition was more frequently used in the studies that primarily studied PDD, may have contributed to the reduction of false negatives and explain the higher dementia frequency found in this subgroup.

These results led us to contemplate the sensitivity of screening scales used to assess PDD. In the early stages of PD, when dysexecutive syndrome and attentional deficits are more common, it is possible that a brief methodology to diagnose dementia and assess cognition as the only diagnostic tool for PDD may lead to a significant proportion of misdiagnoses because of type I (false positives) diagnostic errors²⁶⁰. On the other hand, false positives can occur due to the interference of psychological variables such as mood disturbances (anxiety, depression) that may occur due to concern about the consequences and implications of PD and about how it will evolve and be managed²⁶¹. Maintaining a positive attitude towards living with PD is a challenge for PD patients, especially in the early stages, due to the progressive losses that start in the initial phases²⁶¹⁻²⁶⁴. In the late stages of PD, misdiagnoses can also occur but in a different manner. When PD patients are more educated and/or do not have memory deficits, the brief methodology may lead a type II (false negatives) diagnostic errors²⁶⁵. False-positives and false negatives cases can bias the prevalence estimates and decrease the power of analytical estimates^{167,266}.

Disease severity is frequently reported as one important variable, which is associated with PDD^{78,258,267}. As such, we decided to analyze how dementia frequency varies within each of

the H&Y stage categories according to the different characteristics of the studies and PD patients.

As we expected, dementia frequency varied according to the H&Y stage. It was higher in the late stages. The same was observed depending on the criteria used to diagnose dementia and the methodology used to assess cognition. In the early stages, dementia frequency was higher when the MDS Level I criteria were used, with brief cognitive assessment. In the advanced and late stages, dementia frequency was higher when NPA criteria were used, with full cognitive assessment. Once again, these results confirm that, as mentioned above, possible misdiagnoses are associated with the methodology used to assess cognition and depend on the PD stage of the patients.

Interestingly, in the early stages, MDS Level II criteria and full NPA to assess cognition were the most used. In the advanced and late stages, DSM-III/IV criteria and the screening scales prevailed. As we know, with increased disease severity, motor and non-motor symptoms also tend to increase, making cognitive assessment difficult. On the other hand, NPA is more time-consuming, which is a constraint especially in studies with larger samples. In our opinion, these were the reasons why we observed that as PD severity progresses, the tendency was to abbreviate the methodology to assess cognition.

We also observed that with an increasing H&Y stage, there was a tendency to increase the number of women among the participants. In the late stages, almost half of the studies included more than 50% of women in their participants. The literature describes the male sex as a predictor factor of PDD^{246,268,269,270}. Having dementia a risk factor for mortality²⁷¹, we can hypothesize that men are diagnosed with dementia and die earlier, before reaching the late stages of the disease, being a women is a protective factor for late-stage PD.

The meta-regression analysis that we undertook revealed that methodological, clinical, and demographic variables were important for the estimation of dementia frequency. The definition of the study primary objective (to study PDD), the follow-up length (higher than 7 years), the age of the participants (mainly older than 75 years), PD duration (more than 10 years), and the H&Y stage (higher than 3) were important for dementia frequency.

Most of the studies did not report how or if they investigated vascular diseases and the presence of other comorbidities (i.e., Alzheimer's disease, Lewy-body dementia, etc.) that

may contribute to dementia frequency. According to a recent systematic review¹⁰³, coexistent pathologies are common. Between one-fifth and one-third of PD cases had comorbid Alzheimer's disease. The differentiation of dementia type is important for clinical research, as treatments are specifically targeted against the different pathological substrates of the disease.

Our study has limitations. As we said above, the high heterogeneity between studies and the overlap of the 95% confidence intervals in most of our subgroup meta-analyses prevented us from drawing precise conclusions. As such, our results should be read with caution. This heterogeneity emphasizes the importance of standardizing methods used in future studies.

5. Conclusions

The overall estimated dementia frequency was 26.3%. However, this estimation varied according to the methodological, clinical and demographic variables of the studies and PD patients.

We can speculate that in the early stages of PD, with participants between 60 and 75 years old and between 5 and 10 years of PD duration, by using MDS Level II criteria and NPA to assess cognition, dementia frequency varies between 16% and 20%. In the advanced stages, also with participants between 60 and 75 years old but with between 10 and 15 years of PD duration, by using a similar methodology to diagnose dementia and assess cognition, dementia frequency varies between 20% and 30%. Finally, in the late stages, we can speculate that with participants over 75 years old and with more than 15 years of PD duration, dementia frequency may vary between 50% and 60%.

A study's primary objective, follow-up length, methodology to assess cognition, age, PD duration, and H&Y stage are important to this variability.

To assess dementia, we must consider methodological aspects like a clear definition of the main objective and inclusion criteria, diagnostic criteria that must be actualized and adapted to the particularities of PD, and methodology to assess cognition, which must be based on a full cognitive assessment to avoid misdiagnoses. In the same way, increasing age, PD duration, and H&Y stage of PD patients tend to lead to higher dementia frequency. It is important to define at what stage of PD we want to assess dementia frequency and, according to this, define the methodological aspects. We cannot compare dementia frequency in PD as

a whole without considering all of these different study aspects because dementia frequency varies according to all these variables.

Chapter III. Cognitive testing in LSPD population – critical appraisal

Paper:

Cognitive testing in late-stage Parkinson's disease: a critical appraisal of available instruments

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App Neuropsychol Adult. 2022 Aug 26;1-12. doi: 10.1080/23279095.2022.2114355

Impact factor: 2.050

Catarina Severiano e Sousa participated in the conception and design of the project, data acquisition, analysis, and interpretation, as well as drafting and revising final manuscript critically.

Cognitive testing in late-stage Parkinson's disease: a critical appraisal of available instruments

Abstract

Objective: For patients with Parkinson's disease (PD), cognitive impairment is one of the most disabling non-motor symptoms, particularly in the late disease stages (LSPD). Without a common cognitive assessment battery, it is difficult to estimate its prevalence and limits comparisons across studies. In addition, some instruments traditionally used in PD may not be adequate for use in LSPD. We sought to identify instruments used to assess cognition in LSPD and to investigate their global characteristics and psychometric properties in order to recommend a cognitive battery for the LSPD population.

Method: We conducted a literature search of EMBASE and MEDLINE for articles reporting the use of cognitive tests in LSPD. The global characteristics and psychometric properties of the four most used cognitive tests in each cognitive domain were verified in order to recommend a cognitive assessment battery.

Results: Of 60 included studies, 71.7% used screening scales to assess cognition. Of the 53 reported instruments, the Montreal Cognitive Assessment, the Digit Span, the Trail Making Test, the Semantic Fluency test, the Rey Auditory Verbal Learning Test, the Brief Visuospatial Memory Test-Revised, the Boston Naming Test, the Judgment of Line Orientation, and the Clock Drawing Test corresponded best overall to the requirements considered important for selecting instruments in LSPD.

Conclusion: Screening scales are frequently used to assess cognition in LSPD. We recommend a cognitive assessment battery that considers the special characteristics of the LSPD population, including being quick and easy to use, with minimized motor demands, and covering all relevant cognitive domains.

Keywords: Parkinson disease; Neuropsychological tests; Cognitive assessment; Cognitive tests; Cognitive function; Critical review

1. Introduction

Parkinson's disease (PD) is a complex progressive neurodegenerative disorder with a wide variety of clinical symptoms. Although motor symptoms classically define PD, non-motor symptoms (NMS) form an important part of the disease²⁷², mainly in the late disease stages.

Coelho e Ferreira (2012)³³ proposed the term “late-stage” to describe PD patients who progressed in severity of treatment-resistant motor and non-motor symptoms, are highly dependent on caregivers for activities of daily life (ADL), and require specialist medical care. According to these authors, the phenotype of PD changes considerably in later stage, and the symptoms that contribute most to disability differ from those in early and advanced stages. Late-stage PD is a good clinical model to identify the symptoms that cause most disability and mortality, highlighting the symptoms that should be targeted at an earlier stage of disease.

Cognitive impairment is among the most common and severe and disabling NMS. Dementia, in particular, has been associated with increasing disability²⁴, mortality⁵⁴, and caregiver burden²⁷³.

Estimates of the incidence of cognitive impairment in PD vary considerably. The different methodological characteristics of studies, as well as the different clinical and demographic characteristics of PD patients, likely contribute to this variability. Important methodological features that vary between studies include the tests used to assess cognition (screening scales versus comprehensive neuropsychological assessment) and the criteria for diagnosing Parkinson's disease dementia (PDD). Clinical and demographic features that vary between studies include disease duration and severity, as well as the age of the PD patients²⁷⁴.

Given the deleterious effects of cognitive impairment and the increasing emphasis on the cognitive features of PD, mainly in the late disease stages, there is a compelling need for a standardised approach to neuropsychological assessment in this population.

Indeed, patients with late-stage PD (LSPD) are a poorly studied population due to their typically severe motor and non-motor symptoms that often complicate cognitive assessment. Most studies of this population are neuropathological studies²⁷⁵, assess cognition using cognitive screening tests⁴⁰, or do not make a detailed description of cognitive performance²⁷⁶.

The lack of a common core assessment battery limits comparisons across studies. In addition, some instruments traditionally used in PD may not be adequate for use in LSPD due to the particular characteristics of these patients (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for activities of daily living [ADL])³³.

It is of the utmost importance that a comprehensive neuropsychological assessment takes into account these special characteristics of the LSPD population, ideally includes cognitive instruments validated in PD, preferably quick and easy to use and requiring minimal use of paper and pencil. This is a major determinant to a better understanding of the pattern of cognitive impairment in LSPD, which is necessary to improve our understanding of the therapeutic and supportive strategies that must be implemented at earlier disease stages when they are more likely to be effective.

The primary objective of the present critical review was to identify which instruments have been used to assess cognition in LSPD. Secondary objectives were: 1) to verify the global characteristics of the most used cognitive instruments, including their psychometric properties, and 2) based on the most used cognitive instruments, recommend a neuropsychological assessment (NPA) battery for use in the LSPD population, taking into account the global characteristics and the psychometric properties of the instruments for the PD population and the particular characteristics of LSPD patients cited above.

2. Materials and Methods

This review did not require direct intervention or interaction with human subjects, nor was personal, private information identifiable, and was therefore exempt from institutional review. It was not registered in any international register platform of systematic reviews.

2.1 Eligibility Criteria

We included original studies, published in English, French, or Spanish with no publication date restrictions, which reported cognitive tests used for the cognitive assessment of patients with a confirmed PD diagnosis, in the late-stage of the disease³³ (patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or non-motor symptoms, with a Hoehn and Yahr scale (H&Y) score >3 ²⁸, and/or a Schwab and England scale (S&E) score $<50\%$ ⁴⁵ in the MED ON condition).

2.2 Information Sources and Search Methods

We searched both EMBASE and MEDLINE databases, from their inception to May 2019, using a pre-defined search strategy (Supplementary Figure 4). The search strategy combined standardized subject terms and text words, with relevant Boolean operators implemented. Citation chaining was also conducted to ensure that no articles were overlooked.

2.3 Data Extraction

One author (C.S.S.) assessed the titles and abstracts of retrieved publications to identify studies that met the inclusion criteria. The relevant studies for this critical appraisal were then reviewed in detail to determine suitability for inclusion.

The outcome of interest was the cognitive tests used in a population of LSPD patients.

A standard data collection form was created to extract data on the cognitive tests used. We grouped tests according to the respective cognitive demands as described in the studies.

We selected the four most used cognitive tests in each cognitive domain and verified their global characteristics, based on requirements considered important for cognitive testing and the selection of instruments²⁷⁷: 1) the instrument, on the whole, is accurate and sensitive to changes ranging from no cognitive impairment to mild cognitive impairment (MCI) in PD, 2) up-to-date normative data are available, 3) the instrument is included in the Movement Disorder Society (MDS) task force guidelines to diagnose PD-MCI²²⁵ or PDD²²⁹, 4) motor demands are minimized, 5) quick to use, and 6) covered all domains relevant for obtaining a diagnosis of MCI²²⁵ or PDD²²⁹ according to MDS criteria (attention, executive function, memory, language, and visuospatial functions).

To examine the accuracy of cognitive tests to discriminate PD-MCI patients from patients with PD without cognitive impairment (PD-noCI) we searched for the cut-off points, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and area under the receiver operating characteristic (ROC) curve with 95% confidence interval (AUC 95% CI) of the cognitive instruments.

Sensitivity and specificity refer to the proportion of individuals correctly classified as having or not having a particular symptom. The PPV refers to the probability of people with a

positive test result actually having the condition of interest. The NPV refers to the probability of people with a negative result not having the condition of interest. AUC is an effective way to summarize the overall diagnostic accuracy of one test. An AUC of 0.5 suggests no discrimination (i.e., inability to diagnose patients with or without the disease or condition based on the test), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding^{278,279}. Whenever possible, we based our selection of instruments upon the maximum combined sensitivity and specificity (preferably based upon the commonly regarded acceptable values, 80%, and 60%, respectively²⁸⁰ and AUC>0.7).

Our recommendation for a battery of cognitive instruments took into account these requirements as well as the accuracy of the cognitive tests and the special characteristics of LSPD patients. In addition, to ensure translatability into clinical practice, we ensured that each of the cognitive instruments was widely used and available, easy and quick to administer while covering all relevant cognitive domains, requiring as little as possible the use of paper and pencil, preferably not timed (minimized motor demands), and possible to be used in the patient's home.

Additional information describing the methodological characteristics of the included studies and the clinical and demographic characteristics of the PD patients was collected and introduced in the standard data collection form:

1) Methodological data from the studies: study design; study's primary objective [I) study PDD, II) study cognitive functioning, which we classified as study cognition, and III) other (i.e., studies which primarily investigated other conditions and reported dementia frequency as a secondary result)]; follow-up length; dementia diagnosis criteria [I) MDS diagnostic procedures Level I²²⁹, II) MDS Level II²²⁹, III) DSM-III/IV^{281,282} (due to their similarities, we included ICD-9/10 criteria in this category), IV) The best clinical judgement criteria with a comprehensive NPA and with a well-defined definition of cognitive impairment, were classified as "NPA criteria", V) Screening scales criteria (screening scales cut-offs), VI) The best clinical judgement criteria made by a single qualified clinician or through consensus by a team of clinicians, were classified as "Clinical assessment criteria", and VII) the studies that failed to describe the criteria used were classified as "Not specified"]]; methodology used to assess cognition [I) screening scales, II) comprehensive NPA, and III) not specified (studies that failed to describe the cognitive tests used)]; cognitive domains assessed.

2) Demographic and clinical information on the LSPD patients: PD duration; age; education; cognitive domains impaired.

2.4 Data Synthesis

We used descriptive statistics to characterize the number of studies using each cognitive test and the methodological, clinical, and demographic information of the included studies. Variables were described through absolute and relative frequencies (%).

The descriptive statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL).

3. Results

3.1 Search

The results of the literature search are summarized in Figure 8. Of the 3326 screened studies, 1261 were excluded following abstract screening, while 2005 were excluded following full-text screening, resulting in 60 studies being included in our review. Study and patient characteristics are described in Supplementary Figure 5.

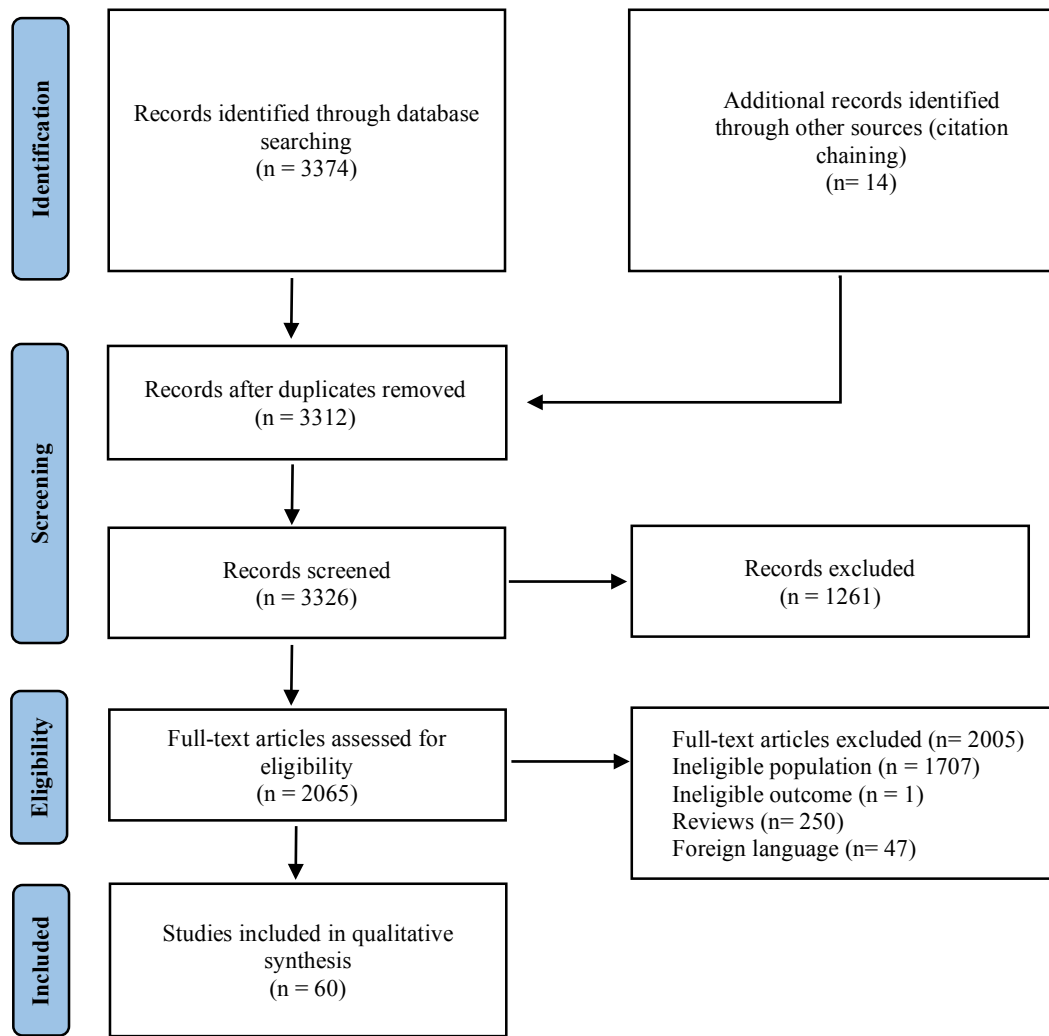


Figure 8. PRISMA review flowchart

3.2 Frequency of Use of Cognitive Assessment Instruments

Forty-three (71.7%) studies assessed cognition exclusively with screening scales (global cognitive assessment). The remaining 17 (28.3%) proceeded with a neuropsychological assessment, the majority (15.0%) assessed four cognitive domains (Table 14).

Assessed Cognitive Domains	Studies N (%)
Global Cognitive Assessment	43 (71.7)
2 cognitive domains	1 (1.7)
Executive function, Memory	1 (1.7)
3 cognitive domains	3 (5.0)
Executive Function, Memory, Visuospatial Function	2 (3.3)
Memory, Language, Visuospatial Function	1 (1.7)
4 cognitive domains	9 (15.0)
Attention and Working Memory, Executive Function, Memory, Language	3 (5.0)
Attention and Working Memory, Executive Function, Memory, Visuospatial Function	4 (6.7)

Attention and Working Memory, Executive Function, Language, Visuospatial Function	1 (1.7)
Executive Function, Memory, Language, Visuospatial Function	1 (1.7)
5 cognitive domains	4 (6.7)
Attention and Working Memory, Executive Function, Memory, Language, Visuospatial Function	4 (6.7)

Table 14. Frequency of assessment of cognitive domains

We identified 53 different neuropsychological instruments that have been used to assess cognition in LSPD (Table 15).

Cognitive Assessment Instruments	Studies N(%)
Global Cognitive Assessment (N=57)	
Mini-Mental State Examination (MMSE)	50(87.7)
Clinical Dementia Rating (CDR)	5(8.8)
Mattis Dementia Rating Scale (MDRS)	4(7.0)
Montreal Cognitive Assessment (MoCA)	3(5.3)
Scales for Outcome in Parkinson's Disease-Cognition (SCOPA-COG)	3(5.3)
Frontal Assessment Battery (FAB)	2(3.5)
Cognitive Abilities Screening Instrument (CASI)	1(1.8)
Cambridge Cognitive Assessment (CAMCOG)	1(1.8)
Addenbrooke's Cognitive Examination-Revised (ACE-R)	1(1.8)
Milan Overall Dementia Assessment (MODA)	1(1.8)
Verbal fluency (phonemic and semantic)	1(1.8)
Brief informant interview to detect dementia (AD8)	1(1.8)
Wechsler Adult Intelligence Scales (WAIS)	1(1.8)
Attention and Working Memory (N=12)	
Wechsler Adult Intelligence Scales 3 rd edition (WAIS-III) Digit span (forward and backward)	4(33.3)
Verbal fluency	3(25.0)
Semantic Fluency	3(25.0)
Phonemic Fluency	3(25.0)
Stroop Test	3(25.0)
Stroop Test (word reading)	3(25.0)
Stroop Test (color naming)	3(25.0)
Stroop Test (word-color interference)	2(16.7)
Trail Making Test (TMT)	3(25.0)
Part A	3(25.0)
Part B	2(16.7)
Map search	1(8.3)
Digit Ordering	1(8.3)
Neuropsychological Test Battery Vienna (NTBV) (attention sub-scale)	1(8.3)
Alters Konzentrations Test	1(8.3)
Cerebral Insufficiency Test (symbol counting task)	1(8.3)
Raven Progressive Matrices (RPM)	1(8.3)
Austin-Maze Test	1(8.3)
Wisconsin Card Sorting Test (WCST)	1(8.3)
Symbol Digit Modalities Test (SDMT)	1(8.3)
Paced auditory serial addition Test (PASAT)	1(8.3)
Not specified	2(16.7)
Executive Function (N=16)	
Verbal Fluency	8(50.0)
Phonemic Fluency	8(50.0)
Semantic Fluency	6(37.5)
Stroop Test	5(31.3)

Stroop Test (word reading)	3(18.8)
Stroop Test (color naming)	3(18.8)
Stroop Test (word-color interference)	5(31.3)
Trail Making Test (TMT)	4(25.0)
Part A	3(18.8)
Part B	4(25.0)
Wechsler Adult Intelligence Scales 3 rd edition (WAIS-III) Digit span (difference between forward and backward)	2(12.5)
Austin-Maze Test	2(12.5)
Wisconsin Card Sorting Test (WCST)	2(12.5)
Controlled Oral Word Association Test (COWAT)	1(6.3)
Category Switching	1(6.3)
Neuropsychological Test Battery Vienna (NTBV) (executive functions sub-scale)	1(6.3)
Cerebral Insufficiency Test (interference task)	1(6.3)
Raven Progressive Matrices (RPM)	1(6.3)
Wechsler Adult Intelligence Scales (WAIS) Similarities	1(6.3)
Symbol Digit Modalities Test (SDMT)	1(6.3)
Paced Auditory Serial Addition Test (PASAT)	1(6.3)
Frontal Assessment Battery (FAB)	1(6.3)
Not specified	2(13.3)
Memory (N=16)	
Visual Episodic Memory	
Benton Visual Retention Test (BVRT)	2(12.5)
Rey Complex Figure Test (RCFT) (immediate recall)	2(12.5)
Copy and Delayed Recall of Two Simple Figures (Massachusetts General Hospital of Boston)	1(6.3)
Spatial Memory	
Austin-Maze Test	1(6.3)
Verbal Episodic Memory	
Rey Auditory Verbal Learning Test (RAVLT) (immediate recall, learning, delayed recall and recognition)	7(43.8)
California Verbal Learning Test (CVLT) (immediate recall, learning, delayed recall and recognition)	2(12.5)
Selective Reminding Test (SRT) (immediate recall, total recall, delayed recall and recognition)	1(6.3)
Buschke Free and Cued Selective Reminding Test	1(6.3)
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory	1(6.3)
Controlled Oral Word Association Test (COWAT)	1(6.3)
Free and Cued Selective Reminding Test (immediate recall)	1(6.3)
Wechsler Memory Scale (WMS)	1(6.3)
Not specified	2(12.5)
Language (N=10)	
Boston Naming Test (BNT)	8(80.0)
Verbal Fluency	4(40.0)
Phonemic Fluency	4(40.0)
Semantic Fluency	3(30.0)
Western Aphasia Battery (WAB)	1(10.0)
Neuropsychological Test Battery Vienna (NTBV) (language sub-scale) (verbal fluency-phonemic and semantic, and Boston Naming Test)	1(10.0)
Not specified	1(10.0)
Visual Function (N=13)	
Visuospatial Function	
Judgment of Line Orientation Test (JoLO)	3(23.1)
Visual Object and Space Perception Test (VOSP)	3(23.1)
Wechsler Block Design	2(15.4)
Fragmented Letters	1(7.7)
Copy of the Three-Loop Spiral	1(7.7)
Hooper Visual Organization Test	1(7.7)
Poppelreuter-Ghent Test	1(7.7)
Visuoconstructive Function	

Clock Drawing Test (CDT)	3(23.1)
Visuoperceptive Function	
Rey Complex Figure Test (RCFT) (copy)	2(15.4)

Table 15. Frequency of use of cognitive assessment instruments

The four most used cognitive tests to perform a global cognitive assessment (screening scales, used in 57 studies) were: the Mini-Mental State Examination (MMSE) (87.7%), the Clinical Dementia Rating (CDR) (8.8%), the Mattis Dementia Rating Scale (Mattis DRS) (7.0%), and the Montreal Cognitive Assessment (MoCA) (5.3%).

The four most used neuropsychological instruments assessing different cognitive domains were:

- 1) Attention and Working Memory (assessed in 12 studies) – Digit Span task of Wechsler Adult Intelligence Scales third edition (WAIS-III) (33.3%), Verbal Fluency (25.0%), Stroop Test (25.0%), and Trail Making Test (TMT) (25.0%);
- 2) Executive Function (assessed in 16 studies) – Verbal Fluency (50.0%), Stroop Test (31.3%), TMT (25.0%), and Digit Span task of WAIS-III (12.5%);
- 3) Memory (assessed in 16 studies) – Rey Auditory Verbal Learning Test (RAVLT) (43.8%), California Verbal Learning Test (CVLT) (12.5%), Benton Visual Retention Test (BVRT) (12.5%), and immediate recall of Rey Complex Figure Test (RCFT) (12.5%);
- 4) Language (assessed in 10 studies) – Boston Naming Test (BNT) (80.0%), Verbal Fluency (40.0%), and Western Aphasia Battery (10.0%);
- 5) Visuospatial Function (assessed in 13 studies) – Judgment of Line Orientation Test (JoLO) (23.1%), Visual Object and Space Perception Test (VOSP) (23.1%), Clock Drawing Test (CDT) (23.1%), and copy of RCFT (15.4%).

3.3 Global Characteristics of Cognitive Assessment Instruments

Of the four screening scales most used to perform a global cognitive assessment, the MoCA was the cognitive test that best corresponded to our aforementioned requirements (Table 16). The MoCA was the only test that had all the following characteristics: accurate and sensitive to changes in PD from no cognitive impairment to MCI, had available up-to-date normative

data, was included in the MDS guidelines for diagnosing PD-MCI or PDD, was quick and easy to use while covering all relevant cognitive domains (attention and executive functions, memory, language, and visuospatial functions), required little motor demands, and could be used in the patient's home.

Of the four neuropsychological instruments most used to assess different cognitive domains, we observed that attention and working memory and executive function were assessed more frequently with the same instruments. As such, we grouped them in a single domain. The Digit Span Backwards of WAIS-III, the TMT, and the Semantic Fluency test were the cognitive tests that globally best corresponded to the requirements considered important for the selection of the instruments (Table 16).

To assess memory, RAVLT was the only cognitive test that met all requirements. Visual episodic memory tests (BVRT and immediate recall of RCFT) appeared in the four cognitive tests most used to assess memory but did not meet our requirements. There is no available information about the assessment of accuracy and sensitivity to change of the BVRT in PD; the immediate recall of RCFT is not sensitive in distinguishing between no cognitive impairment and MCI. For language assessment, the BNT was the cognitive test that best met the requirements, while for visuospatial assessment the JoLO and the CDT were the best instruments (Table 16).

					Recommended cut-off scores and performance of instruments					
					PD population					
Cognitive Assessment Scales	Accurate for detecting PD-MCI	Available up-to-date normative data	Minimized motor demands	Suggested by MDS in PD-MCI ²²⁵ or PDD ²²⁹ diagnostic procedures	Cut-off score (for MCI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (CI 95%)
Global Cognitive Assessment										
MMSE	Yes	Yes	Yes	Yes	29/30 ²⁸³	94	45	59	91	0.7 (0.53-0.87)
CDR (sum of boxes)	No	Yes	Yes	No	1-4 ²⁸⁴	71	82	Na	Na	0.5 (0.43-0.54)
Mattis DRS	Yes	Yes	No	Yes	137/138 ²⁸³	72	86	81	79	0.8 (0.69-0.96)
MoCA	Yes	Yes	Yes	Yes	26/27 ²³⁷	83	53	Na	Na	0.7 (0.64-0.85)
Attention and Executive Function										
WAIS-III Digit span										
Forward	No	Yes	Yes	Yes	Na* ²⁸⁵	Na*	Na*	Na*	Na*	Na*
Backward	Yes	Yes	Yes	Yes	<4 ²⁸⁵	85	44	39	87	0.7 (0.60-0.80)
Stroop Test										
Words	Yes	Yes	No	Yes	15/16 ²⁸⁶	84	60	68	79	0.8 (0.69-0.88)
Color	Yes	Yes	No	Yes	12/13 ²⁸⁶	87	58	67	81	0.8 (0.69-0.88)
Word-Color	Yes	Yes	No	Yes	27/28 ²⁸⁶	82	53	64	75	0.8 (0.68-0.87)
Errors	Yes	Yes	No	Yes	0/1 ²⁸⁶	80	58	65	74	0.8 (0.68-0.87)
Interference	Yes	Yes	Yes	Yes	1.9/2.0 ²⁸⁶	82	38	57	68	0.7 (0.55-0.77)
TMT										
Part A	Yes	Yes	No	Yes	>33 ²⁸⁵	74	69	51	86	0.7 (0.61-0.81)
Part B	Yes	Yes	No	Yes	>162 ²⁸⁵	68	93	85	82	0.8 (0.70-0.87)
Part (B-A)	Yes	Yes	Yes	Yes	>97 ²⁸⁵	68	91	76	87	0.8 (0.69-0.87)
Verbal Fluency										
Semantic Fluency	Yes	Yes	No	Yes	<44 ²⁸⁵	74	53	40	82	0.7 (0.55-0.75)
Phonemic Fluency	No	Yes	No	Yes	<32 ²⁸⁵	56	69	44	79	0.6 (0.53-0.74)
Memory										
Benton Visual Retention Test	Na [#]	Yes	No	No	NA	NA	NA	NA	NA	NA
Rey Complex Figure Test (immediate recall)	No	Yes	No	No	Na* ²⁸⁵	Na*	Na*	Na*	Na*	Na*
RAVLT										
Immediate Recall	Yes	Yes	Yes	Yes	<40.3 ²⁸⁵	68	78	57	85	0.7 (0.62-0.82)
Delayed Recall	Yes	Yes	Yes	Yes	<8.9 ²⁸⁵	74	64	46	85	0.7 (0.57-0.77)

California Verbal Learning Test										
Immediate Recall	Na [#]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Learning	Na [#]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Delayed Recall	Na [#]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Recognition	Na [#]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Language										
Boston Naming Test (short version)	Yes	Yes	Yes	Yes	26 ²⁸⁷	67	89	88	70	0.8 (0.61-0.92)
Verbal Fluency										
Phonemic Fluency	No	Yes	No	No**	<32 ²⁸⁵	56	69	44	79	0.6 (0.53-0.74)
Semantic Fluency	Yes	Yes	No	No**	<44 ²⁸⁵	74	53	40	82	0.7 (0.55-0.75)
Western Aphasia Battery	Na [#]	Yes	No	No	NA	NA	NA	NA	NA	NA
Visuospatial Function										
JoLO	Yes	Yes	Yes	Yes	22/23 ²⁸⁸	59	78	73	66	0.7 (0.59-0.83)
VOSP	Na [#]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Clock Drawing Test (10-point score)	Yes	Yes	No	Yes#	8/9 ²⁸⁹	78	74	94	41	0.9 (Na)
Rey Complex Figure Test (copy)	Yes	Yes	No	No	<29 ²⁸⁵	59	96	87	85	0.8 (0.67-0.85)

Table 16. Global characteristics and psychometric properties of cognitive tests

MDS- Movement Disorder Society; PD-MCI- Parkinson's Disease Mild Cognitive Impairment; PDD- Parkinson's Disease Dementia; PPV- Positive Predictive Value; NPV- Negative Predictive Value; AUC (CI 95%)- Area under the receiver operating characteristic (ROC) curve with 95% confidence interval; NA- Not applicable; Na- Not available; Na*- Not available: no differences were found between PD patients without cognitive impairment vs PD-MCI patients (Biundo et al., 2013); Na[#]- Not available (There is no available information about the assessment of accuracy and sensitivity to change in PD); ** This test is recommended to assess another cognitive domain; # Copying version; MMSE- Mini-Mental State Examination; CDR- Clinical Dementia Rating; Mattis DRS- Mattis Dementia Rating Scale; MoCA- Montreal Cognitive Assessment; WAIS-III- Wechsler Adult Intelligence Scale-3rd edition; TMT- Trail Making Test; RAVLT- Rey Auditory Verbal Learning Test; JoLO- Judgement of Line Orientation Test; VOSP- Visual Object and Space Perception Test

3.4 Recommendation of Cognitive Instruments to be used in LSPD

Based on the global characteristics of the cognitive instruments and LSPD requirements, we recommend a battery of instruments for assessing all relevant cognitive domains. The recommended instruments had the best global characteristics and, cumulatively, minimized motor demands and were quick and easy to use (Table 17): the MoCA Test for global cognitive assessment and visuospatial function (by using the copy of the cube subtest), the Digit Span Backwards of WAIS and the TMT (difference between parts B and A, to remove the speed element from the test evaluation) to assess attention and executive function, the Semantic Fluency test to assess attention and executive functions and language, the RAVLT to assess verbal memory, the BNT to assess language, the JoLO to assess visuospatial function, and the CDT to assess attention and executive function and visuospatial function. To assess memory, we recommend the RAVLT. As visual episodic memory is an important memory demand and the most used cognitive tests did not meet the requirements, we suggest the BVMT-R (Table 17).

	Global Cognitive Assessment	Attention and Executive Functions	Memory	Language	Visuospatial Functions
MoCA Test	X				X*
WAIS Digit Span Backward		X			
TMT (Part B-A)		X			
Semantic Fluency		X		X	
RAVLT			X		
BVMT-R			X		X
BNT (short version)				X	
JoLO					X
CDT (10-point score)#		X			X

Table 17. Recommendation of cognitive domains to be assessed in LSPD and the respective cognitive instruments.

*Copy of the cube; #Sunderland et al., 1989; MoCA- Montreal Cognitive Assessment; WAIS- Wechsler Adult Intelligence Scale; TMT- Trail Making Test; RAVLT- Rey Auditory Verbal Learning Test; BVMT-R- Brief Visuospatial Memory Test-Revised; BNT- Boston naming Test; JoLO- Judgement of Line Orientation Test; CDT- Clock drawing Test

4. Discussion

The typical severe motor and non-motor LSPD patient's symptoms often complicate cognitive assessment. However, this is determinant to better understand the pattern of cognitive impairment, which is necessary to improve our understanding of the therapeutic

and supportive strategies that must be implemented at earlier disease stages when they are more likely to be effective. As such, the recommendation of a suitable cognitive battery for this population is of utmost clinical interest.

This review aimed to identify the instruments most used to assess cognition in LSPD. We also investigated the global characteristics and the psychometric properties of the most used cognitive instruments in order to recommend a NPA battery that takes into account the special characteristics of the LSPD population (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL).

We identified 53 different instruments that have been used to assess cognition in LSPD.

Most of the studies assessed LSPD patients' cognition with screening scales, namely with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Mattis Dementia Rating Scale (Mattis DRS), and Montreal Cognitive Assessment (MoCA).

In the studies that used a comprehensive NPA, we grouped the instruments assessing different cognitive domains according to their respective cognitive demands as described in the studies. Interestingly, we observed that the four cognitive tests most used to assess attention, working memory, and executive function were the same (Digit Span task of Wechsler Adult Intelligence Scales third edition (WAIS-III), Stroop Test, Trail Making Test (TMT), and Verbal Fluency).

For assessing memory, the Rey Auditory Verbal Learning Test (RAVLT), the California Verbal Learning Test (CVLT), the Benton Visual Retention Test (BVRT), and the immediate recall of Rey Complex Figure Test (RCFT) were the most used. Language was most frequently assessed with the Boston Naming Test (BNT), Verbal Fluency, and the Western Aphasia Battery, and visuospatial functions were most frequently assessed with the Judgment of Line Orientation Test (JoLO), the Visual Object and Space Perception Test (VOSP), the Clock Drawing Test (CDT), and the copy of RCFT.

As we expected, we observed that different cognitive tests can vary considerably in terms of their cognitive demands, although it is clear that no human neuropsychological test is uniquely associated with damage to a specific brain region¹³⁸.

Based on the global characteristics and the psychometric properties of the most used cognitive instruments (accurate and sensitive for the changes from no cognitive impairment to MCI in PD, available up-to-date normative data, suggested by MDS for diagnosing PD-MCI or PDD, minimized motor demands, quick and easy to use, all domains relevant for PD-MCI or PDD diagnosis are considered, sensitivity and specificity preferably higher than 80% and 60%, respectively, and $AUC > 0.7$), we recommended a NPA battery to diagnose PD-MCI and PDD, that took into account the special characteristics of the LSPD population. Whereas MDS-MCI and PDD criteria are internationally accepted criteria, with high discriminative validity in the detection of PD-MCI^{287,288}, we considered it important to standardize the methodology used to assess cognition in PD in order to reduce the variability in the frequency of cognitive impairment attributed to methodological aspects. As is recommended in these criteria, we also ensured that each of the cognitive domains was assessed with at least two cognitive instruments to address all cognitive domains equally, increase sensitivity and specificity, and allow full subtyping of PD-MCI. According to Goldman et al (2015)²³⁸, a neuropsychological battery with two tests per domain provides a practical, efficient, sensitive and robust approach to diagnosing cognitive impairment in PD.

Of the four cognitive tests most used to perform a global cognitive assessment, MoCA was the cognitive test that globally best corresponded to the requirements considered important for the selection of the instruments. MoCA has adequate psychometric properties as a screening instrument for the detection of MCI or dementia in PD^{237,279}, is quick and easy to use, and covers all significant cognitive domains that need to be assessed in PD, contrarily to the MMSE that is incomplete in covering cognitive domains, and the Mattis DRS that is too long to be appropriate for use as a screening test in LSPD population.

Although most of the studies assessed LSPD patients' cognition with screening scales, these are known to have several limitations. According to some authors²⁶⁰, a screening methodology that is the only cognitive tool used to assess cognition may lead to a significant proportion of misdiagnoses. In LSPD, misdiagnoses can occur when PD patients are more educated and/or do not have memory deficits. In these cases, the screening methodology may lead to type II (false negatives) diagnostic errors²⁶⁵. False negative cases can bias the prevalence estimates and decrease the power of analytical estimates^{167,266}.

On the other hand, screening scales do not allow for an understanding of the pattern of LSPD cognitive impairment, which is of the utmost importance for improving our understanding

of the therapeutic and supportive strategies that must be implemented at an earlier stage of disease when they are more likely to be effective. Mattis DRS scale is an exception. Although it is internationally accepted and classified as a screening scale, with its five subscales it allows to better comprehend the pattern of cognitive impairment. However, it is too long to be used as a screening scale with LSPD patients and is incomplete to be used as a cognitive battery to perform a complete and comprehensive neuropsychological assessment.

The Digit Span Backward of WAIS, TMT (difference between part B and part A), and Semantic Fluency were the instruments that best corresponded to the requirements to assess attention and executive function. The Digit Span Backward and TMT are described as some of the instruments with the best discrimination diagnostic power to diagnose MCI in PD^{285,287,288}. Although the TMT motor demands are not minimized, this test allows us to remove the speed element from the test evaluation through a derived score obtained by the difference between parts B and A of the test²⁹⁰. Semantic Fluency is one of the instruments most used to assess executive function, providing information about attention, short-term memory, initiation, mental flexibility, response inhibition, processing speed, and semantic memory²⁹¹. It is described as an efficient test that can discriminate PD-MCI from no cognitive impairment^{285,288}.

For assessing memory, the RAVLT was the only cognitive test that corresponded to our requirements. The dissociation between the mediotemporal component (frequently impaired in Alzheimer's disease) and the subcortico-frontal component (frequently impaired in PDD) is of central importance in understanding the patterns of memory deficit found in different dementia syndromes²²⁹. The RAVLT is an episodic memory test that allows us to make conclusions about the impairment in these two memory demands (encoding and retrieval demands and the strategic aspects involved in these encoding and retrieval demands)²²⁹. According to some authors^{285,287}, the RAVLT is among the tests that have proven high discriminative validity in PD-MCI. In late-stage PD, memory is a cognitive domain frequently impaired. The RAVLT proved to be applicable to this population and allowed to analyse the patterns of their memory deficit, a fact that revealed very important to better characterize the LSPD patients cognitive profile²⁹². Visual episodic memory also appeared as a memory demand frequently assessed in the reviewed studies. However, the cognitive tests most used to assess this cognitive feature did not meet our requirements. As such, we

propose the inclusion of the Brief Visuospatial Memory Test-Revised (BVMT-R). It is proposed by the MDS guidelines to diagnose MCI. According to Litvan et al. (2012)²²⁵, most visual memory tests are less appropriate for PD-MCI diagnosis because they require motor responses or evaluate other memory demands less sensitive to memory decline. BVMT-R is an exception because, with its copy condition, it allows for assessment of the motor component²⁹³. This optional copy trial allows clinicians to identify visuoconstructional difficulties that may impact BVMT-R performance, and may also be important to consider the impact of slower processing speed on BVMT-R learning and memory performance²⁹⁴.

The Boston Naming Test (short version) was the cognitive test that best corresponded to the requirements to assess language. It is an instrument widely used, easy-to-administer, is generally well accepted by patients, and had high discriminative validity in PD-MCI^{238,287}. To complement the language assessment, we proposed the use of the Semantic Fluency test which, in an ecological view (more information with less resources), in addition to evaluating executive functions, allows us to understand the fluency and organization of verbal language²⁹¹.

Lastly, to assess visuospatial functions, the JoLO and the CDT were the instruments that best corresponded to our requirements. The CDT is a quick and economic cognitive test, initially developed to detect frontoparietal deficits, which rely primarily on executive function and visuospatial abilities²⁹⁵. Therefore, CDT completion requires several cognitive domains, including comprehension, motor programming, abstraction, attention, and concentration^{295,296}, which for a multidomain ecological cognitive assessment is very important. As there is no international consensus about the scoring methods that must be used, we propose the 10-point Sunderland²⁹⁷ scoring system because is efficient in detecting PD-MCI²⁸⁹ and is the scoring system recommended by Dubois et al. (2007)²²⁹ in the diagnostic procedures for PDD diagnosis.

The recommended cognitive instruments battery is not a fixed test battery. It contains a small easy-to-administer core battery of widely available cognitive tests that, in our opinion, can be adjusted by adding or subtracting cognitive instruments, depending upon the goals of the cognitive assessment (research or clinical practice), patient and caregiver concerns, and the patient's ability to cooperate with or complete given tests²⁹⁸. Importantly, it is a battery that despite not being validated particularly for this population, it has been utilized and has proven to be possible to use with most LSPD patients²⁶⁵.

The test selection should consider the LSPD patient's cognitive, emotional, motor, and sensory capacities to cooperate with evaluation²³⁵. In PD, one often requires cognitive tests that minimize confounding motor demands. In this late stage of PD, when patients are often at an advanced age, with treatment-resistant motor and non-motor symptoms, the motor fluctuations, neuropsychiatric symptoms, and fatigability must be considered when deciding on the test battery. According to Marras et al. (2014)²³⁵, interview of the caregiver can be useful to ascertain timing of motor fluctuations and define the best time of day to proceed with the cognitive assessment, which should be when the patients are less likely to be affected by motor and non-motor symptoms, while on their antiparkinsonian medications.

In addition, observations made during testing are critical when utilizing a process approach to assessment that seeks to elucidate the cognitive mechanisms underlying test success and failure²⁹⁹. It is important to know, especially in timed tests, such as the Semantic Fluency test, if the eventual low scores are due to executive function or language impairment or are due, for example, to speech and voice disabilities, like dysarthria, a frequent treatment-resistant motor symptom in LSPD³⁰⁰, that may compromise verbal fluency.

In these worst cases, when severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) makes NPA impossible, we consider it important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients, to avoid underestimating this important non-motor symptom.

Our study has limitations. Although the battery we recommend has been applied and has demonstrated to be feasible to use with most LSPD patients, there is no data on their psychometric properties, and it has not been validated particularly for this population, a fact that should be considered for future studies. Additionally, although it was not our objective, it would have been of interest to assess the frequency of use of neuropsychiatric instruments to assess mood and behavioral symptoms (depression, apathy, hallucinations, and delusions). They are frequent in LSPD^{39,40}, may impact cognition and, according to some authors^{301,302}, may be considered to be characteristics that support a diagnosis of PDD. In the same way, it would also have been important to verify the frequency of use of instruments to assess functionality related to cognition. Understanding the impact of cognitive deficits on the patient's ability to implement instrumental ADL is important not only for differentiating MCI from PDD^{225,229} but also for informing treatment decisions if one wants to directly intervene to treat impairments that have an impact on ADL from the patient's and

caregiver's point of view²³⁵. Finally, it would also have been of interest to verify if the studies mentioned in which condition the patients were evaluated (on or off their antiparkinsonian medications).

5. Conclusion

Of the 60 included studies, we identified 53 different instruments to assess cognition in LSPD.

The MoCA to assess global cognitive assessment, the Digit Span Backwards of WAIS and the TMT to assess attention and executive function, the Semantic Fluency test to assess attention and executive function and language, the RAVLT and BVMT-R to assess memory, the BNT to assess language, the JoLO to assess visuospatial function, and the CDT to assess attention, and executive and visuospatial functions were the cognitive instruments that best corresponded globally to the requirements considered important for instrument selection.

We recommend a NPA battery that takes into account the special characteristics of the LSPD population (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL), quick and easy to use while covering all relevant cognitive domains for obtaining a diagnosis of PD-MCI or PDD, requiring little use of paper and pencil, preferably not timed (minimized motor demands) and suitable for home use.

When severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) make NPA impossible, we considered it important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients and to avoid underestimating this important non-motor symptom.

Chapter IV. Frequency of dementia in late-stage Parkinson's disease

Paper:

Clinical diagnostic criteria have a high impact on the frequency of dementia in late-stage Parkinson's disease

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Front Neurol. 2021 May 20;12:652424. doi:10.3389/fneur.2021.652424

Impact factor: 3.552

Catarina Severiano e Sousa participated in the conception and design of the project, data acquisition, analysis, and interpretation, as well as drafting and revising final manuscript critically.

Clinical diagnostic criteria have a high impact on the frequency of dementia in late-stage Parkinson's disease

Abstract

Background: Cognitive impairment is a potential late feature of Parkinson's disease (PD). However, studies in patients with late-stage PD are lacking due to the particular characteristics of this population.

Objectives: To evaluate the frequency of dementia in late-stage PD patients and to assess the impact of using different diagnostic criteria.

Methods: We conducted a cross-sectional study to estimate the frequency of dementia in late-stage PD patients using the International Parkinson and Movement Disorders Society (MDS) (Level II) clinical diagnostic criteria as the primary outcome. We also applied other diagnostic criteria (MDS (Level I), DSM-IV, and DSM-5 criteria) to determine their applicability and impact on dementia frequency.

Results: 93 participants with a mean age of 75.8 years (SD 6.8) and 16.5 years (SD 7.5) of disease duration were included. 64.3% were classified as demented using the International Parkinson and Movement Disorders Society (MDS) (Level II) clinical diagnostic criteria. We observed a high discrepancy on the frequency of dementia depending on the criteria applied (6.2% with MDS (Level I), 58.8% with DSM-IV, and 72.0% with DSM-5 criteria).

Conclusions: We found a frequency of dementia below what was observed in similar populations. The particular characteristics of our sample may have contributed as protective factors for late-stage dementia. Dementia frequency varied depending on the criteria used mainly due to the presence of major depression.

Keywords: Parkinson's disease, late-stage, dementia, cognitive impairment, diagnostic criteria

1. Introduction

Cognitive impairment is a late clinically feature of Parkinson's disease (PD). Dementia is a potential late-stage complication of PD, which may affect multiple cognitive domains²⁵ causing disability³³ and patient institutionalization^{35,38,76,303}. However, there is no consensus on dementia frequency partly because the diagnostic criteria that have been used vary from the DSM-IV criteria with brief cognitive assessment^{33,75} to quantitative neuropsychological assessment^{24,276}.

The International Parkinson and Movement Disorder Society (MDS) recommends clinical diagnostic criteria for “probable” and “possible” Parkinson's disease dementia (PDD)²²⁴ and specific diagnostic procedures based on a two-level process, depending on the clinical scenario and evaluator expertise²²⁹: Level I) short algorithm to be used as a screening tool, with a checklist format; Level II) a detailed neuropsychological assessment (NPA), with proposed cognitive tests that can confirm PDD, characterize its components, and facilitate the differential diagnosis between PDD and other diagnoses.

Although it is already well-accepted that MDS PDD Level II clinical criteria are the gold standard for PDD diagnosis, to our knowledge, there are no published studies on the dementia frequency by using updated PDD diagnostic criteria with late-stage PD patients (LSPD), which is a special population, often understudied due to its particular characteristics. As such, the current study was designed to evaluate the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD.

2. Materials and Methods

2.1 Recruitment

In this cross-sectional study, consecutive LSPD patients attending the Movement Disorders Unit of the University Hospital of Santa Maria (Lisbon) were recruited.

All participants and their formal/informal caregivers were informed about the study objectives and procedures and were asked for their written informed consent. The informed consent of cognitively impaired patients was signed by the caregiver. The study was approved by the local ethics committee.

2.2 Inclusion/Exclusion Criteria

Inclusion criteria were 1) Idiopathic PD according to the UK Brain Bank criteria³⁰⁴; 2) LSPD³³ (patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or non-motor symptoms, with a Hoehn and Yahr scale (H&Y) score $>3^{28}$ and/or a Schwab and England scale (S&E) score $<50\%^{45}$ in the MED ON condition) and 3) signed informed consent.

Exclusion criteria were 1) dementia before PD onset and 2) dementia within 1 year following PD diagnosis.

2.3 Outcomes

2.3.1 Primary Outcome

The frequency of dementia was determined using MDS clinical criteria for “probable” and “possible” PDD, operationalized according to the Level II procedures outlined by Dubois et al.²²⁹ which were based on neuropsychological tests, functional autonomy as well as clinical interview. Briefly, involved the following: 1) PD; 2) PD before dementia; 3) decreased global cognitive efficiency evidenced by education-adjusted Mini-Mental State Exam (Portuguese cutoff: score < 22 (0-2 yrs); <24 (3-6 yrs); <27 (≥ 7 yrs)); 4) cognitive deficits that impact activities of daily life (ADL); 5) deficits in two or more cognitive domains documented by a detailed NPA; 6) the presence of at least one behavioral symptom (apathy, depressed mood, hallucinations, delusions, or excessive daytime sleepiness) supports the diagnosis of probable PDD; 7) the presence of any abnormality which may by itself cause significant cognitive impairment (e.g., delirium, relevant vascular disease) but judged not to be the cause of dementia makes the diagnosis uncertain and supports the diagnosis of possible PDD.

2.3.2 Secondary Outcomes

Frequency of dementia according to three other diagnostic criteria:

- 1) MDS PDD Level I²²⁹ - Level I and Level II are broadly the same criteria but Level I has some particularities: 1) the methodology to assess cognition is brief and 2) the absence of major depression, *delirium*, and abnormalities that may obscure PDD diagnosis is

mandatory to diagnose probable PDD. In the presence of these abnormalities, dementia is not excluded but we have to perform the Level II NPA to diagnose possible PDD.

2) DSM-IV criteria²⁸¹ - Although the DSM-5 is already published, which makes DSM-IV criteria no longer clinically relevant, we considered it important to use them because most of the previous studies used the DSM-IV criteria to diagnose PDD and we intended to perform a comparative analysis of the frequency of dementia with other studies that used similar samples.

3) DSM-5 criteria³⁰⁵ - Briefly, these criteria required the following steps:

- I) Distinction between mild and major Neurocognitive Disorder (NCD). Major NCD corresponds to the diagnosis of dementia. Its main feature is the presence of a significant acquired cognitive decline, which may be documented by:
 - a) detailed NPA, considered as cognitive impairment performance values below 2 standard deviations (SD) on age-and-educated normative scores in one or more cognitive domains, or
 - b) brief but quantitative cognitive assessment.
- II) Identification of behavioral symptoms that support the diagnosis of PDD.
- III) Specification of the level of certainty of dementia diagnosis: major NCD probably due to PD vs major NCD possibly due to PD. What distinguishes them is the presence of abnormalities that may obscure diagnosis.

We compared dementia frequency obtained through the two DSM-5 possible approaches (NPA vs brief cognitive evaluation), also testing its applicability in LSPD.

2.4 Measures

2.4.1 Neurologic and Functional Assessment

Neurological assessment was performed by a neurologist with expertise in movement disorders and included the investigation of vascular problems. Disease severity and disability were assessed using H&Y²⁸ and S&E⁴⁵ scales, respectively.

2.4.2 Neuropsychiatric and Behavioral Assessment

The neuropsychiatric assessment was performed by the neurologist and included neuropsychiatric functions (behavioral symptoms and major depression). The neuropsychiatric inventory³⁰⁶ (NPI) and the geriatric depression scale³⁰⁷ (GDS) were used, respectively.

To diagnose *delirium*, we used the DSM-5 criteria³⁰⁵ as the MDS criteria²²⁹ omit the methodology that we were to use.

2.4.3 Neuropsychological Assessment

The NPA was performed by a neuropsychologist. It took place in a single session, at the patients' homes, in order to ensure the presence of the usual amenities, and to reduce as far as possible any interference, malaise, or interfering in the patients' lives.

A clinical interview was undertaken with caregiver collaboration to obtain the following information: 1) demographics; 2) educational history; 3) temporal relationship of PD diagnosis and the onset of cognitive complaints; 4) disease duration; 5) objective and subjective cognitive complaints; 6) pattern of PD and cognitive complaints progression; 7) impact of cognitive impairment on ADL; 8) history of abnormalities that may obscure the diagnosis (ex. delirium, vascular or other neurological diseases); 9) current comorbidities.

To assess the impact of cognitive impairment on ADL, two approaches were taken: 1) patient and caregiver clinical interview, using a checklist with cognitive ADL tasks and, 2) the Pill Questionnaire, with the assumption that if the patient was able to manage his/her treatment in the past, the inability to describe one's own medication regimen was equivalent to an impairment in ADL²²⁹. Whenever one of these sources of information was suggestive of dysfunction, the patient was classified as having impaired ADL.

To assess cognition using MDS PDD Level II criteria²²⁹, we proceeded with NPA with a set of cognitive tests selected from their proposal (Table 18), according to the following criteria: 1) existence of normative data for the Portuguese population, 2) tests predictably less sensitive to PD manifestations, and 3) expected time consumed by the test (only one test for each cognitive task whose performance would have a shorter estimated duration, to ensure the minimum tiredness interference). We considered cognitive impairment performance values below 1 SD on age-and-educated-adjusted normative scores in two or more cognitive domains. We applied neuropsychological tests in the same order for all patients.

To assess cognition following MDS PDD Level I criteria²²⁹, we used the proposed cognitive tests (Table 18), adapted to the Portuguese population.

Cognitive Domains/Tasks	MDS PDD Level I Cognitive Tests	MDS PDD Level II Cognitive Tests
-Global Efficiency	. MMSE ^{308,309}	. MMSE ³⁰⁸⁻³¹¹
-Attention	. Serial 3's of the MMSE ³⁰⁸	
-Executive Functions	. Phonologic Fluency (P) ^{312,313}	
. Working Memory		. Digit Span ^{314,315}
. Conceptualization		. Similarities (WAIS-III) ^{316,317}
. Set Activation		. Phonologic Fluency (P,M,R) ^{312,313}
. Set Shifting		. TMT (A and B) ^{290,318}
. Set Maintenance		. Odd Man Out Test ³¹⁹
. Behavioral Control		. Prehension Behavior (FAB) ^{320,321}
-Memory	. 3-Word Recall of the MMSE ³⁰⁸	. RAVLT ^{322,323}
-Instrumental Functions		
. Language		. Boston Naming Test ³²⁴
. Visuoconstructive	. Drawing of the MMSE Pentagons ³⁰⁸	. Copy of the Clock ²⁹⁷
. Visuospatial		. Benton Line Orientation Test ³²⁵
. Visuoperceptive		. Benton Face Recognition Test ³²⁶

Table 18. Neuropsychological tests used to assess cognition according to MDS PDD Level I and Level II criteria.

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force²²⁹.

MMSE- Mini-Mental State Exam

TMT (A and B)- Trail Making Test A and B

WAIS-III- Wechsler Adult Intelligence Scale 3rd Edition

FAB- Frontal Assessment Battery

RAVLT- Rey Auditory and Verbal Learning Test

To assess cognition according to the DSM-IV criteria²⁸¹, we used MMSE sub-scales³⁰⁸ to assess memory, aphasia, agnosia and apraxia (retention and evocation, language and construction sub-scales, respectively). To assess executive function, we used WAIS-III similarities sub-scale³¹⁷, MMSE attention and calculation sub-scale³⁰⁸, phonologic fluency

test (P,M,R letters)³¹³ and information collected in the clinical interview (impact of cognitive impairment on ADL such as the ability to plan daily activities).

For DSM-5 detailed NPA³⁰⁵, we used the same tests selected from MDS PDD Level II²²⁹ but we strictly followed the DSM-5 proposed cognitive domains organization and cognitive impairment definition. As social cognition is a cognitive domain that is not included in the proposed MDS criteria, we followed the DSM-5 assessment methodology and, to guarantee the non-interference of poor insight, we assessed it during the clinical interview with the contribution of the caregiver. As the evaluation of this domain was qualitative, we considered as a reference for impairment the examples of major symptoms made available by the DSM-5.

For brief DSM-5 cognitive assessment³⁰⁵, we used the MMSE³⁰⁸ even though it is less effective in assessing global PD cognition. This decision was mainly due to two reasons: 1) the MMSE is commonly used due to its quick and ease of use and access and 2) the MMSE was proposed by the MDS PDD criteria²²⁹ as a measure of global cognitive efficiency. As it is validated for the Portuguese population and there are several cutoff proposals, we decided to perform a comparative analysis with the cutoff that is the most used in clinical practice (adjusted for education³⁰⁹, age and education³¹⁰, dementia diagnosis³¹¹).

2.5. Statistical Methods

2.5.1 Sample Size

Assuming an expected LSPD dementia frequency of approximately 50%³³, with a 95% confidence interval and an error level of approximately 10%, a sample of 100 patients was estimated necessary.

2.5.2 Statistical Analysis

Statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL).

We used descriptive statistics to characterize demographic and clinical information. Categorical variables were described through absolute and relative frequencies (%) and continuous variables through the mean value and standard deviation (SD).

The frequency of dementia was analyzed using descriptive statistics. We presented the absolute and relative frequency (%) of LSPD dementia cases, according to the different criteria for dementia that we used.

The agreement analysis between our gold-standard and the other criteria for PDD was performed using Cohen's Kappa (>0.6 is significant)³²⁷. We calculated sensitivity, specificity, positive predictive value, and negative predictive value for each PDD diagnostic criteria.

We considered a confidence interval of 95%.

3. Results

3.1 Patient Demographics and Clinical Characteristics

One hundred and twenty-one LSPD patients were initially recruited (Figure 9). Following motor assessment but before the proposed NPA, 12 patients died and 16 declined to participate in the NPA (13 patients refused to perform it and three were unable to due to the unavailability of the caregiver). A total of 93 LSPD patients agreed to perform the NPA. However, when patients were visited at home, the neuropsychologist found that it would not be possible to carry out the NPA of eight patients due to their physical/motor disability. Of these eight patients, we only collected information through the neurological and neuropsychiatric evaluation, and through the clinical history that we performed with the help of the caregiver (Table 19).

In total, 85 patients underwent complete NPA (Figure 9). 49 (57.6%) were women, with a mean age of 75.4 years (SD 6.9), 6.5 years (SD 4.5) of education, 16.9 years (SD 7.5) of disease duration, age at PD onset (58.5 years; SD 10.9), a mean H&Y of 4.1 (SD 0.9) and loss of independence assessed by the S&E corresponding to 36.7% (SD 13.6) (Table 19).

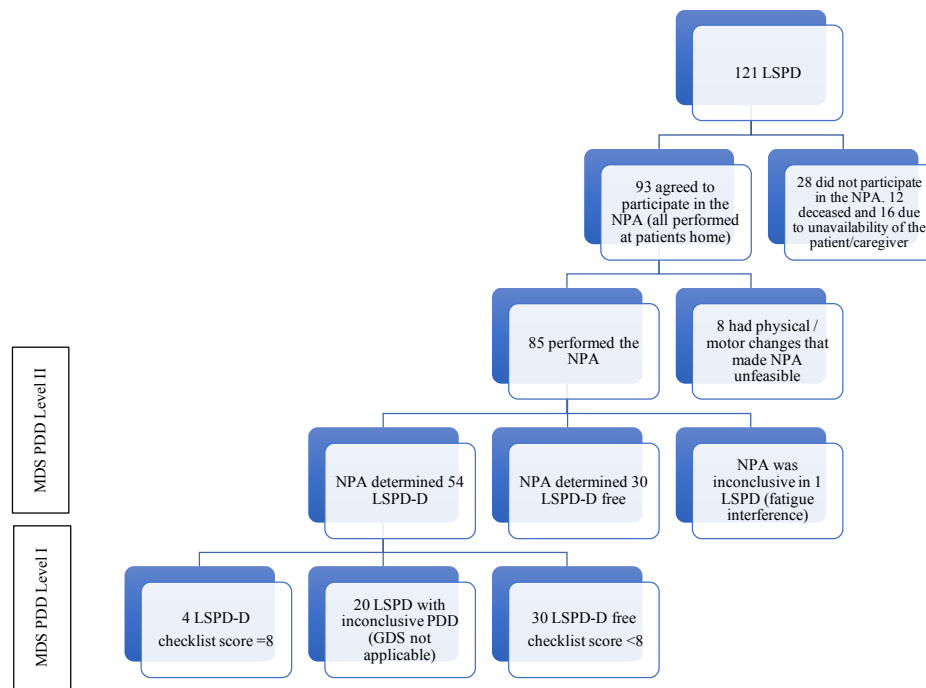


Figure 9. Patients and assessments flowchart

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force²²⁹.

LSPD- Late-stage Parkinson's Disease patients

LSPD-D- Late-stage Parkinson's Disease dementia patients

NPA- Neuropsychological assessment

GDS- Geriatric Depression Scale

	LSPD (N=85) Mean (SD)	LSPD (N=8)* Mean (SD)	LSPD (N=93) Mean (SD)
Gender (m/f)	36/49	4/4	40/53
Age (yrs)	75.4 (6.9)	80.3 (4.7)	75.8 (6.8)
Education (yrs)	6.5 (4.5)	3.1 (1.6)	6.4 (4.6)
Disease duration (yrs)	16.9 (7.5)	12.0 (6.5)	16.5 (7.5)
Age at onset (yrs)	58.5 (10.9)	66.3 (4.6)	59.1 (10.8)
Hoehn & Yahr stage (0/5)	4.1 (0.9)	5 (0)	4.2 (0.9)
Schwab & England (0/100%)	36.7 (13.6)	15.71 (7.9)	35.1 (14.3)
NPI delusions (0/12) (Cutoff ≥ 3)	1.3 (2.6)	0.3 (0.8)	1.3 (2.5)
NPI hallucinations (0/12) (Cutoff ≥ 3)	1.7 (2.7)	1.7 (1.9)	1.7 (2.7)
NPI depression (0/12) (Cutoff ≥ 3)	3.3 (2.4)	1.8 (2.0)	3.2 (2.4)
NPI apathy (0/12) (Cutoff ≥ 3)	3.6 (3.6)	3.8 (4.3)	3.6 (3.6)
NPI sleep disorders (0/12) (Cutoff ≥ 3)	2.5 (3.3)	1.0 (1.5)	2.4 (3.3)
Pill Questionnaire (0/3) (Cutoff ≥ 2)	2.2 (1.1)	3 (0)	2.3 (1.0)

GDS Score (0/30) (Cutoff 11-20: mild depression; 21-30: severe depression)	13.8 (6.8)	NA	NA
MMSE Score (0/30) (Cutoff: 0-2 yrs education- 22 pt; 3-6 yrs education- 24 pt; ≥7 yrs education- 27 pt)	21.6 (6.1)	NA	NA

Table 19. Demographic and clinical characteristics of LSPD patients

LSPD- Late-stage Parkinson's Disease

NPI- Neuropsychiatric Inventory

GDS- Geriatric Depression Scale

MMSE- Mini-Mental State Exam

NA- Not applicable due to physical/motor impairment

* These 8 patients did not perform the neuropsychological assessment due to the physical and motor limitations they presented. This information was collected through the caregiver-based clinical interview that we performed.

3.2 Dementia Frequency According to MDS PDD Level II Criteria

54 (64.3%) patients met the criteria for PDD (27/36 men (75%), 27/49 women (55%)): 47 (55.9%) were diagnosed with probable PDD and seven (8.3%) with possible PDD due to the abnormalities that made the diagnostic uncertain (3 LSPD had a stroke significantly before PD, three were submitted to undergo deep brain stimulation after PD and one had an oncological disease and was undergoing chemotherapy after the beginning of cognitive impairment). According to the caregiver, none of these abnormalities was associated with the onset of worsening cognitive impairment. One patient had inconclusive PDD due to the interference of tiredness during NPA.

69.4% LSPD presented an MMSE score lower than the education cutoff. The mean score obtained was 21.6 (SD 6.1), with an interval ranging from eight to 30 points. 67.9% of LSPD had impaired cognition in two or more cognitive domains and 87.1% presented cognitive changes severe enough to impair ADL.

We observed at least one behavioral symptom with significant expression in 74.7% of LSPD (Table 20). The most common was depressive mood (57.8%), followed by apathy (51.8%), excessive daytime sleepiness (36.1%), hallucinations (25.3%), and delusions (18.1%).

Of the eight patients who could not undergo NPA, it was possible to confirm through the clinical history collected from the caregivers that before the worsening of the physical/motor impairment significant global cognitive impairment with impact on ADL had occurred, leading us to suspect the existence of PDD. They were older patients, less educated, and

who, despite having fewer years of PD, had worse disease severity and dysfunction (Table 19).

If we were to consider them as having PDD, we would have observed a frequency of dementia of 67.4% (Table 21).

LSPD (N=85)	MDS PDD Level I	MDS PDD Level II
	Yes (%)	Yes (%)
1- Parkinson's disease	100	100
2- Parkinson's disease developed before dementia	100	100
3- MMSE** <22 (0-2 yrs education); <24 (3-6 yrs education); <27 (≥7 yrs education)	69.4	69.4
4- Dementia has impact on ADLs	87.1	87.1
5- Impaired cognition (for yes, at least of 2 of 4 cognitive domains below are abnormal)	79.1	67.9
5 a) Attention	48.2	*
5 b) Executive Function	87.1	56.5
B1) Working memory	*	25.9
B2) Conceptualization	*	11.8
B3) Set activation	*	68.7
B4) Set shifting	*	85.9
B5) Set maintenance	*	55.2
B6) Behavioral control	*	30.1
5 c) Instrumental Functions	*	55.6
C1) Language	*	11.1
C2) Visuo-Constructive	65.5	60.8
C3) Visuo-Spatial	*	67.1
C4) Visuo-Perceptive		61.1
5 d) Memory	62.4	68.7
D1) Only medial temporal/hippocampal component	*	18.1
D2) Only subcortico-frontal component	*	15.7
D3) Both components		44.6
6- Absence of major depression	18.6	*
7- Absence of <i>delirium</i>	98.8	*
8- Absence of other abnormalities that obscure diagnosis	89.4	89.4
Behavioral symptoms (one of delusions, hallucinations, depression, excessive daytime sleepiness)	74.7	74.7
Probable PDD (items 1-8 must all be YES)	6.2	55.9***
Probable PDD Inconclusive	23.5	1.2
Possible PDD	0	8.3
Total Score (0/8) Mean (SD)	6.3 (1.0)	*

Table 20. Diagnostic rating sheet for Probable PDD recommended by the MDS Task Force

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force²²⁹.

PDD- Parkinson's Disease dementia

MMSE- Mini-Mental State Exam

ADLs- Activities of daily living

*Not applicable in this Level

** We considered education-adjusted MMSE cutoff scores (Portuguese population)

*** Items 6 and 7 not applicable for MDS PDD Level II

3.3 Dementia Frequency According to Three Other PDD Diagnostic Criteria

The frequency of dementia differed markedly according to the diagnostic criteria used. Dementia frequency rated by MDS Level I was consistently the lowest. Only 6.2% of the LSPD met all screening checklist clinical criteria to be diagnosed as probable PDD (Table 20). All patients identified by the screening checklist as having PDD were confirmed by Level II criteria (100% specificity). However, Level II criteria identified more patients with PDD than the screening checklist (sensitivity 8.8%) (Table 22). Although 79.1% of LSPD presented impaired cognition in two or more cognitive domains and 87.1% of LSPD presented cognitive changes severe enough to impair ADL, we observed the absence of major depression that is mandatory for Level I PDD diagnosis only in 18.6% of LSPD. In the same way, 23.5% of LSPD had Level I PDD inconclusive due to comprehension difficulties that made GDS not applicable and impossible to conclude about the absence of major depression.

Although less markedly, we also observed discrepant results in dementia frequency between DSM-IV diagnostic criteria (58.8%) and Level II criteria (64.3%).

Using DSM-5 with full NPA criteria, once again, we observed discrepant results (72.0% vs 64.3%). Three patients (3.5%) were given an inconclusive dementia diagnosis due to the interference of tiredness which did not allow differential diagnosis between Mild Cognitive Impairment and PDD (Table 21).

When we used the DSM-5 criteria with MMSE, we observed results quite similar to Level II criteria (62.4% with education adjustment, 68.2% with age and education adjustment, and 60.0% with dementia adjustment vs 64.3% respectively).

Diagnostic criteria	LSPD (N=85) (%)	LSPD (N=93)* (%)
MDS PDD Level I	6.2	16.4
Inconclusive (major depression not assessed - difficulty GDS items comprehension)	23.5	
MDS PDD Level II	64.3	67.4
Probable PDD	55.9	
Possible PDD	8.3	
Inconclusive (fatigue interference did not allow to confirm PDD diagnosis)	1.2	
DSM-IV	58.8	62.4
DSM-5		
With MMSE adjusted for education	62.4	65.6
Major NCD Probably due to PD with behavioral disturbance	48.2	
Major NCD Probably due to PD without behavioral disturbance	7.1	
Major NCD Possibly due to PD	7.1	
With MMSE adjusted for age and education	68.2	70.9
Major NCD Probably due to PD with behavioral disturbance	52.9	
Major NCD Probably due to PD without behavioral disturbance	8.2	
Major NCD Possibly due to PD	7.1	
With MMSE adjusted for dementia	60.0	63.4
Major NCD Probably due to PD with behavioral disturbance	47.1	
Major NCD Probably due to PD without behavioral disturbance	5.9	
Major NCD Possibly due to PD	7.1	
With NPA	72.0	74.4
Major NCD Probably due to PD with behavioral disturbance	56.1	
Major NCD Probably due to PD without behavioral disturbance	7.3	
Major NCD Possibly due to PD	8.5	
Inconclusive (fatigue interference did not allow differential diagnosis between MCI and PDD)	3.5	

Table 21. Dementia frequency according to different diagnostic criteria

LSPD- Late-stage Parkinson's Disease patients

PDD- Parkinson's Disease dementia

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force²²⁹.

DSM-IV- Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition²⁸¹.

DSM-5- Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition³⁰⁵.

NCD- Neurocognitive disorder

GDS- Geriatric Depression Scale

MMSE- Mini-Mental State Exam

NPA- Neuropsychological assessment

MCI- Mild cognitive impairment

*If we considered as PDD the 8 LSPD who could not perform the NPA due to physical/motor disabilities, based on the clinical history collected from the caregiver.

When we analyzed the agreement between Level II and DSM-5 criteria (Table 22), we observed the significant similarity seen in clinical practice. The DSM-5 was very sensitive in identifying demented LSPD, either through the use of the NPA (100%) or through the use of MMSE (adjusted for education 96.3%; age and education 100%; diagnosis of dementia 90.7%).

The specificity of the DSM-5 with MMSE adjusted for age and education (90.0%) and with NPA (82.1%) was lower than the specificity obtained with MMSE adjusted only for education and for the diagnosis of dementia because the first diagnosed more dementia than the MDS Level II criteria, so they presented a higher number of false positives.

Classification	MDS PDD Level I	DSM- IV	DSM-5 MMSE adjusted for education	DSM-5 MMSE adjusted for age and education	DSM-5 MMSE adjusted for dementia	DSM-5 NPA
True positive	3	45	52	54	49	54
False positive	0	5	0	3	2	5
True negative	30	25	30	27	28	23
False negative	31	9	2	0	5	0
PPV (%)	100	90.0	100	94.7	96.1	91.5
NPV (%)	49.2	73.5	93.8	100	84.8	100
Sensitivity (%)	8.8	83.3	96.3	100	90.7	100
Specificity (%)	100	83.3	100	90.0	93.3	82.1
Kappa coefficient*	0.1	0.6	0.9	0.9	0.8	0.9

Table 22. Classification of LSPD by different diagnostic criteria using MDS PDD Level II criteria as the gold-standard.

LSPD- Late-stage Parkinson's Disease patients

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force²²⁹.

DSM-IV- Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition²⁸¹.

DSM-5- Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition³⁰⁵.

MMSE- Mini-Mental State Exam

NPA- Neuropsychological assessment

PPV- Positive Predictive Value

NPV- Negative Predictive Value

*Kappa coefficient >0,6 is significant

4. Discussion

Our results conclude that by using MDS Level II²²⁹ clinical diagnosis criteria, slightly more than half of the 85 LSPD (64.3%) meet dementia criteria. Considering the high frequency of dementia (80%) reported by Reid et al.²⁷⁶ who studied a sample of PD with 20 years of disease, we expected to find similar results. When we compared the frequency of dementia that we obtained through the same diagnostic criteria used by Reid et al.²⁷⁶, we observed a greater discrepancy (58.8% vs. 80%). We hypothesized that this discrepancy could be due in part to the fact that Reid et al.²⁷⁶ diagnosed PDD using the DSM-IV criteria with full NPA to assess cognition, contrary to what we did in our study where we strictly followed the DSM-IV criteria using a brief cognitive assessment methodology mainly with MMSE subscales, which, as is well known, is not the best methodology for assessing cognition in PD. However, our analysis of agreement between diagnosis criteria allowed us to conclude that the MMSE proved to be a reliable tool to diagnose dementia in LSPD. The discrepancy that we observed may have been due in part to the clinical and socio-demographic characteristics of our sample that should be noted.

Our participants had been living with PD for an average of 17 years, with an early age at PD onset (<60 years) and there was a higher proportion of women (58%) than expected based on gender prevalence of PD. Forsaa et al.³⁵ developed a long-term study about mortality and associated risk factors in a population-based cohort with PD and found that approximately 70% of patients with a median survival from motor onset of 16 years and 20 years after disease onset had died. They concluded that higher age at onset, male sex, and dementia were independent risk factors for mortality. Cholerton et al.³²⁸ compared baseline cognitive, demographic, and clinical characteristics of participants who remained cognitively stable and those who progressed throughout follow-up in a large, well-characterized PD cohort and found that the primary predictive factor in the transition from no cognitive impairment to cognitive impairment was male sex. They also found that female participants progressed more slowly to cognitive impairment than male participants. We believe that approximately 64% of PDD we have identified through our gold standard may be due to this conjuncture of characteristics, namely the fact that about 58% of the participants were female. Of the 36 (42.4%) men who participated, 27 (75%) were diagnosed with PDD and of the 49 (57.6%) participating women, 27 (55%) obtained the same diagnosis, which corroborates the results found by Cholerton et al.³²⁸ and may justify the fact that our population was mostly female.

This may be another peculiarity of LSPD. It can be hypothesized that female gender may be a protective factor.

On the other hand, the participants had a level of education (mean of 6 years) that is not representative of the aged Portuguese population who is poorly educated. According to the National Institute of Statistics (Source: PORDATA), in 2019 only about 4.6% of the general population over 65 years had 6 years of schooling. The remaining 73% had no education or only up to four years of schooling and about 22.5% had nine or more years of schooling. Considering that the results of cognitive tests were corrected in general for age and education based on the mean values obtained for the general aged Portuguese population, education may also have contributed to the lower frequency of dementia found.

As we expected, the frequency of dementia was partly dependent on the diagnostic criteria used. We found a significant discrepancy between the results obtained with the MDS PDD Level I and Level II criteria²²⁹ (6.2% vs 64.3%, respectively). The checklist proposed at Level I proved to be quite specific in identifying non-demented LSPD but very unresponsive in identifying demented LSPD. The agreement between the two diagnostic criteria was not significant. The mandatory absence of major depression was largely responsible for different dementia frequency and for the lack of significant agreement among the two levels. Only 18.6% of the LSPD was not diagnosed with major depression and 23.5% had an inconclusive diagnosis due to their difficulty in understanding the GDS³⁰⁷ items. These results are concordant with the results published by Barton et al.³⁰¹ who identified similar results.

When we used the DSM-5 criteria³⁰⁵, we observed less discrepancy. The agreement analysis demonstrate a significant concordance between DSM-5 and Level II criteria. However, with the NPA, there was an increase in dementia frequency (72.0% vs 64.3%, respectively). The lowest number of impaired cognitive domains that DSM-5 criteria considers sufficient to diagnose dementia justified it.

When we used DSM-5 criteria³⁰⁵ with the MMSE, the frequency of dementia was quite similar (62.4% with education adjustment, 68.2% with age and education adjustment, 60.0% with dementia adjustment). These results revealed that MMSE assessed cognitive domains (like orientation and complex orders comprehension) that were not included in NPA and proved important in the cognitive profile of these patients, which is more similar to normal aging, with global impairment.

In terms of clinical translation and practical application, the good specificity of Level I criteria proved that this is a time-efficient method to exclude PDD. However, as the absence of major depression is mandatory to perform the Level I diagnosis, future studies in similar populations will be important to confirm whether major depression is a frequent comorbidity and characteristic of late-stage PD, as this influences how we should evaluate it and to conclude about the applicability of MDS Level I criteria in this population. Such an evaluation should likely be performed based on a semi-structured clinical interview.

On the other hand, DSM-5 criteria proved to be more efficient to diagnose dementia, with a high positive predictive value and good specificity in identifying non-demented patients. However, due to the false positives that may be diagnosed with these criteria, conclusions about dementia diagnosis must be cautious and well supported by a robust clinical interview with the caregiver collaboration to assess the clinical manifestations and the impact of cognitive impairment in ADL.

None of the criteria used to diagnose dementia applied to the eight patients with severe physical/motor disabilities for whom NPA was impossible. In the future, we consider it important that caregiver-based qualitative assessment methodology be developed to make conclusions on PDD in patients with these typical late-stage physical/motor disabilities, otherwise, we risk underestimating it.

The strengths of our study were the high number of LSPD patients who participated in the NPA and were assessed at home. Considering their disease severity, we believe it was a huge effort and willingness to collaborate in our study.

Given the particular clinical and demographic characteristics of our sample, we believe that our results may be compared with future studies with similar populations to inform about the presence of eventual protective factors associated with the late-stage PD dementia.

This study has also some limitations that we must consider. Firstly, given that the present data come from outpatients attending a specialist movement disorder unit, the results need to be validated in a community sample. Secondly, we used a cross-sectional design and, to confirm the validity of PDD diagnosis procedures, it would be of interest to have a prospective cohort and longitudinal data. Finally, the inexistence of a no-late-stage control

group (e.g. advanced stage) didn't allow us to validate the cognitive assessment methodology that we used and analyze the frequency of dementia in a different stage of PD.

In conclusion, our study indicates that below what we would expect, slightly more than half the participants meet dementia criteria. This must have been due to the particular characteristics of our LSPD sample (early age at PD onset, female sex, higher educational level in relation to the general aged Portuguese population), which may have been protective factors for late-stage PD dementia. The estimates of late-stage dementia frequency were partly dependent on the diagnostic criteria. When screening for PDD in LSPD it is important to consider the possibility of using a caregiver-based qualitative methodology assessment to make conclusions on patients with severe physical/motor disabilities for whom neuropsychological tools cannot be used.

Chapter V. Cognitive functioning in late-stage Parkinson's disease

Paper:

Profile of cognitive impairment in late-stage Parkinson's disease

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Brain Behav. 2022 Apr;12(4):e2537. doi:10.1002/brb3.2537

Impact factor: 2.71

Catarina Severiano e Sousa participated in the conception and design of the project, data acquisition, analysis, and interpretation, as well as drafting and revising final manuscript critically.

Profile of cognitive impairment in late-stage Parkinson's disease

Abstract

Introduction: The profile of cognitive impairment associated with the late stages of Parkinson's disease (LSPD) is rarely reported. Its characterization is necessary to better understand the cognitive changes that occur as the disease progresses and to better contribute to its management.

Methods: In this cross-sectional study, we characterized the cognitive profile of LSPD patients using the comprehensive assessment methodology proposed by the International Parkinson and Movement Disorders Society Task Force. The association of clinical and demographic variables with dementia diagnosis was also investigated using binary logistic regression analysis.

Results: Eighty-four LSPD patients were included (age 75.4 ± 6.9 ; disease duration 16.9 ± 7.5). 54 (64.3%) were classified as demented and presented a global impairment cognitive profile. In the non-demented group (N=30), 25 (83.3%) LSPD patients met the diagnostic criteria for mild cognitive impairment, mostly with multiple domain impairment (96.0%) and a heterogeneous profile. Memory was the most frequent and severely impaired cognitive domain in both groups. Disease disability, orientation, complex order comprehension, verbal learning and visuoconstructive abilities were significantly associated with dementia diagnosis ($p < 0.05$).

Conclusions: Cognitive impairment in multiple domains was common in LSPD patients. The most frequent and prominent deficits were in the memory domain, with a strong interference from attention impairment. Disease disability, orientation, complex order comprehension, verbal learning and visuoconstructive abilities proved to be important determinants for dementia diagnosis.

Keywords: Parkinson's disease, late-stage, cognitive impairment

1. Introduction

Cognitive dysfunction is one of the most prevalent non-motor symptoms associated with Parkinson's disease (PD) and has been widely studied in an attempt to better describe the pattern of impairment and the cognitive profile of PD patients. However, there are few published studies on late-stage Parkinson's disease (LSPD). Indeed, LSPD is a poorly studied population due to the typically severe motor and non-motor symptoms that often complicate cognitive assessment. This may be the reason why studies including this population are neuropathological studies²⁷⁵, assess cognition using cognitive screening tests⁴⁰, or do not make a detailed description of cognitive performance²⁷⁶. It is common to observe the inclusion of this population in heterogeneous groups regarding the motor dysfunction/severity associated with PD, without providing a particular description of their cognitive profile.

Dementia has been described as a non-motor symptom that is almost inevitable, mainly in the advanced stages of PD²⁷⁶. It is a crucial determinant of reduced life expectancy in patients with PD. Defining the pattern of the cognitive impairment that is prodromal of Parkinson's disease dementia (PDD) is an area of active research owing to its predictive value and the possibility that these deficits could respond better to treatments used in dementia³²⁹.

Therefore, a greater understanding of the cognitive disorders present in LSPD is of the utmost importance due to their high frequency in these patients. In the same way, studying cognition in LSPD will help to better understand the pattern of cognitive impairment across the different PD stages.

The current study sought to help clarify these issues by examining the cognitive performance of LSPD patients. To assess dementia we followed the methodology suggested by MDS PDD Level II²²⁹ and examined cognitive profiles according to the pattern of cognitive impairment. We also investigated clinical, demographic, and cognitive variables that are associated with PDD diagnosis.

2. Methods

2.1 Subjects

In this cross-sectional study, consecutive LSPD patients attending the Movement Disorders Unit of the University Hospital of Santa Maria (Lisbon) were recruited.

All participants and their formal/informal caregivers were informed about the study objectives and procedures and were asked for their written informed consent. The informed consent of cognitively impaired patients was signed by the caregiver. The study was approved by the local ethics committee.

The inclusion criteria were 1) Idiopathic PD according to the UK Brain Bank criteria³⁰⁴; 2) late-stage Parkinson's disease³³ (Hoehn and Yahr scale (H&Y) score $>3^{28}$ and a Schwab and England scale (S&E) score $<50\%^{45}$ in the ON condition) and 3) signed informed consent. Patients were excluded if they presented dementia before PD onset or dementia within 1 year of PD diagnosis.

2.2 Measures

Neurologic and Functional Assessment

Neurological assessment was performed by a neurologist with expertise in movement disorders and included the investigation of vascular problems. It took place at the the Movement Disorders Unit of the University Hospital of Santa Maria or, whenever this was not possible (due to difficulties in patients' mobility), it took place at patients' home. The Movement Disorders Society – Unified Parkinson Disease Rating Scale (MDS_UPDRS) (Parts I-IV)³³⁰ was administered to assess PD motor and non-motor features. We specified clarity of handwriting and tremor item results (Part II 2.7 and 2.10 items) to better analyse the results, particularly of paper and pencil cognitive tests. The neuropsychiatric functions were assessed by the same neurologist and included behavioral symptoms and major depression, using the neuropsychiatric inventory³⁰⁶ (NPI) and the geriatric depression scale³⁰⁷ (GDS), respectively. *Delirium* was diagnosed according to the DSM-5 criteria³⁰⁵.

Neuropsychological Assessment

The neuropsychological assessment (NPA) was performed by a neuropsychologist. It took place in a single session, at the patients' homes, to ensure the presence of the usual amenities and to reduce as far as possible any interference in the patients' lives.

A clinical interview was undertaken, with caregiver collaboration, to obtain each LSPD patient's socio-demographic and clinical information.

To assess the impact of cognitive impairment on activities of daily living (ADL), two approaches were taken: 1) a patient and caregiver clinical interview and 2) the Pill Questionnaire²²⁹. Whenever one of these sources of information was suggestive of dysfunction, the patient was classified as having impaired ADL.

The LSPD patient's cognitive performance was described by using a neuropsychological battery which was applied in the same order for all patients and included a set of cognitive tests selected from the MDS PDD Level II proposal (Table 23), according to the following criteria: 1) existence of normative data for the Portuguese population and 2) expected time consumed by the test (only one test for each cognitive task whose performance would have a shorter estimated duration, to minimise interfering with tiredness). According to the MDS Level II recommendations, the memory domain was dissociated into two components to better understand the pattern of its impairment: 1) subcortical-frontal component (strategic aspects of explicit memory) and 2) mediotemporal component (encoding and retrieval abilities).

Cognitive Domains/Tasks	MDS PDD Level II Cognitive Tests
-Global Efficiency	. MMSE ^{308,309}
-Executive Functions	
. Working Memory	. Digit Span ^{314,315}
. Conceptualization	. Similarities (WAIS-III) ^{316,317}
. Set Activation	. Phonologic Fluency (P,M,R) ^{312,313}
. Set Shifting	. TMT (A and B) ^{290,318}
. Set Maintenance	. Odd Man Out Test ³¹⁹
. Behavioral Control	. Prehension Behavior (FAB) ^{320,321}
-Memory	. RAVLT ^{322,323}
-Instrumental Functions	
. Language	. Boston Naming Test ^{324,331}
. Visuo-constructive	. Copy of the Clock ²⁹⁷
. Visuospatial	. Benton Line Orientation Test ³³²
. Visuo-perceptive	. Benton Face Recognition Test ³³²

Table 23. Neuropsychological tests used to assess cognition according to MDS PDD Level II criteria²²⁹

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force.

MMSE- Mini-Mental State Exam

TMT (A and B)- Trail Making Test A and B

WAIS-III- Wechsler Adult Intelligence Scale 3rd Edition

FAB- Frontal Assessment Battery

RAVLT- Rey Auditory and Verbal Learning Test

Raw scores for cognitive tests were transformed into z-scores based upon normative data for the Portuguese population and upon manual tests, which were adjusted for age, education, and, when possible, for sex. Each LSPD patient's cognitive performance was obtained by composite scores for each cognitive domain, which were calculated by averaging individual cognitive z-scores within each of the specific domains.

We considered a cognitive test/domain as impaired if its z-score was more than 1 standard deviation (SD) below the adjusted normative scores ($z\text{-score} < -1$).

The cognitive profile was described based on the organization of cognitive domains proposed by the MDS PDD Level II²²⁹ and the respective pattern of cognitive impairment: 1) subcortical profile - included patients with executive function impairment and only subcortical-frontal memory component impairment; 2) cortical profile - included patients with instrumental function impairment and only in the mediotemporal memory component. The patients who did not present, or presented changes in the cognitive domains that did not fulfill a specific cognitive profile, were classified as having a heterogeneous profile. The patients who manifested changes in both subcortical and cortical mediated cognitive domains were classified as having a global impairment profile. The LSPD patient's cognitive profile was drawn through composite scores which were obtained by averaging the cognitive domains z-score within each of the specific cognitive profiles.

2.3 Cognitive categorization

LSPD patients were classified as demented or non-demented. Dementia was diagnosed according to the MDS PDD Level II criteria²²⁹ based on neuropsychological and functional autonomy assessment and a clinical interview.

For exploratory purposes, we examined the frequency of mild cognitive impairment (MCI) by using the MDS MCI Level II criteria (comprehensive assessment)²²⁵.

2.4 Statistical analysis

To describe the cognitive performance of LSPD patients, we compared clinical and demographic variables, and neuropsychological z-scores of the demented and non-demented patients by using the Chi-square, Mann-Whitney U, and Wilcoxon tests, as appropriate ($p < 0.05$).

Subsequently, we analysed cognitive profile sub-groups by comparing clinical and cognitive variables in each of the demented and non-demented groups and between groups, using Chi-square, Wilcoxon, Mann-Whitney U, and Kruskal-Wallis tests with post-hoc pairwise analysis with Bonferroni correction of ($p < 0.05$), as appropriate.

Finally, to examine the contribution of the clinical, demographic and neuropsychological measures for dementia diagnosis, binary logistic regression analysis with a forward conditional procedure was run with all of the variables that reached statistical significance ($p < 0.05$) between demented and non-demented groups as independent variables and with presence or absence of dementia as the dependent variable. Per block step, the improvement of the regression model was compared using the likelihood ratio test. The goodness of fit of the model was assessed with the Hosmer-Lemeshow test.

All statistical analyses were performed using SPSS software version 26 (IBM SPSS, Chicago, IL).

3. Results

3.1 Patient demographics and clinical characteristics

Eighty-four LSPD patients performed the NPA. Forty-eight (57.1%) were women, with a mean age of 75.4 years (± 6.9), 6.5 years (± 4.5) of education, 16.9 years (± 7.5) of disease duration, and 58.5 years (± 10.9) at PD onset. 97.3% were on levodopa treatment (Table 24).

According to MDS PDD Level II criteria, 54 (64.3%) LSPD patients met the criteria for PDD (27/36 men (75%), 27/49 women (55%)).

There were no statistically significant differences between demented and non-demented groups concerning sex, age, education, disease duration, age at PD onset, or levodopa treatment profile. We highlight the fact that there were no significant differences in the MDS_UPDRS tremor item, which arose in both groups with sufficiently low frequency or

intensity to cause no impact on function, as well as in motor complications (MDS_UPDRS Part IV), whose frequency and severity was between mild and moderate in both groups (Table 24).

	LSPD (N=84) Mean (SD)	LSPD-NoD (N=30) Mean (SD)	LSPD-D (N=54) Mean (SD)	p
Gender (M/F)	36/49	9/21	27/27	0.08
Age (yrs)	75.4 (6.9)	75.8 (5.2)	75.2 (7.7)	0.92
Education (yrs)	6.5 (4.5)	5.7 (4.4)	7.1 (4.5)	0.14
Disease duration (yrs)	16.9 (7.5)	16.9 (7.7)	16.9 (7.6)	0.86
Age at onset (yrs)	58.5 (10.9)	58.9 (10.2)	58.2 (11.2)	0.94
MDS_UPDRS Part I	20.6(6.9)	17.1(6.4)	22.6(6.4)	0.00
MDS_UPDRS Part II	33.6(9.5)	29.9(9.0)	35.9(9.3)	0.00
MDS_UPDRS Part II 2.7 (clarity of handwriting)	3.3(0.9)	3.0(0.9)	3.4(0.9)	0.02
MDS_UPDRS Part II 2.10 (tremor)	1.0(1.2)	1.1(1.1)	1.0(1.2)	0.72
MDS_UPDRS Part III	58.9(16.6)	52.2(15.4)	63.1(16.1)	0.00
MDS_UPDRS Part IV	5.1(4.4)	4.8(4.6)	5.1(4.2)	0.74
Levodopa (% yes)	97.3	100	95.8	0.29
Hoehn & Yahr stage (0/5)	4.1 (0.9)	3.8 (0.9)	4.2 (0.9)	0.03
Schwab & England (0/100%)	36.7 (13.6)	44.7 (14.8)	32.2 (10.7)	0.00
NPI delusions (0/12) (Cutoff ≥ 3)	1.3 (2.6)	0.6 (2.0)	1.8 (2.8)	0.00
NPI hallucinations (0/12) (Cutoff ≥ 3)	1.7 (2.7)	0.8 (2.2)	2.2 (2.9)	0.01
NPI depression (0/12) (Cutoff ≥ 3)	3.3 (2.4)	2.9 (2.5)	3.6 (2.3)	0.13
NPI apathy (0/12) (Cutoff ≥ 3)	3.6 (3.6)	2.2 (3.1)	4.5 (3.6)	0.00
NPI sleep disorders (0/12) (Cutoff ≥ 3)	2.5 (3.3)	1.9 (2.6)	2.9 (3.6)	0.47
Pill questionnaire (0/3) (Cutoff ≥ 2)	2.2 (1.1)	1.5 (1.1)	2.6(0.8)	0.00
GDS score (0/30) (Cutoff 11-20: mild depression; 21-30: severe depression)	13.8 (6.8)	13.9 (5.3)	17.0 (5.9)	0.03
MMSE score (0/30) (cutoff: 0-2 yrs education- 22 pt; 3-6 yrs education- 24 pt; ≥ 7 yrs education- 27 pt)	21.6 (6.1)	27.1 (2.0)	18.4 (5.3)	0.00

Table 24. Demographic and clinical characteristics of LSPD patients

Sub-groups were compared using Chi-squared (nominal variables) and Mann-Whitney U tests (continuous variables) ($p < 0.05$ is significant).

LSPD- Late-Stage Parkinson's Disease

LSPD-NoD- Late-Stage Parkinson's Disease patients without dementia

LSPD-D- Late-Stage Parkinson's Disease patients with dementia

MDS_UPDRS- Movement Disorder Society Unified Parkinson's Disease Rating Scale

NPI- Neuropsychiatric Inventory

GDS- Geriatric Depression Scale

MMSE- Mini-Mental State Exam

3.2 Cognitive performance of LSPD patients

In the non-demented group (N=30), 5 (16.7%) LSPD patients did not present changes in cognitive domains. The remaining 25 (83.3%) had impairment on at least two neuropsychological tests, meeting criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple domain impairment).

Memory emerged as the most frequently impaired cognitive domain (34.5% of the non-demented group) (Figure 10).

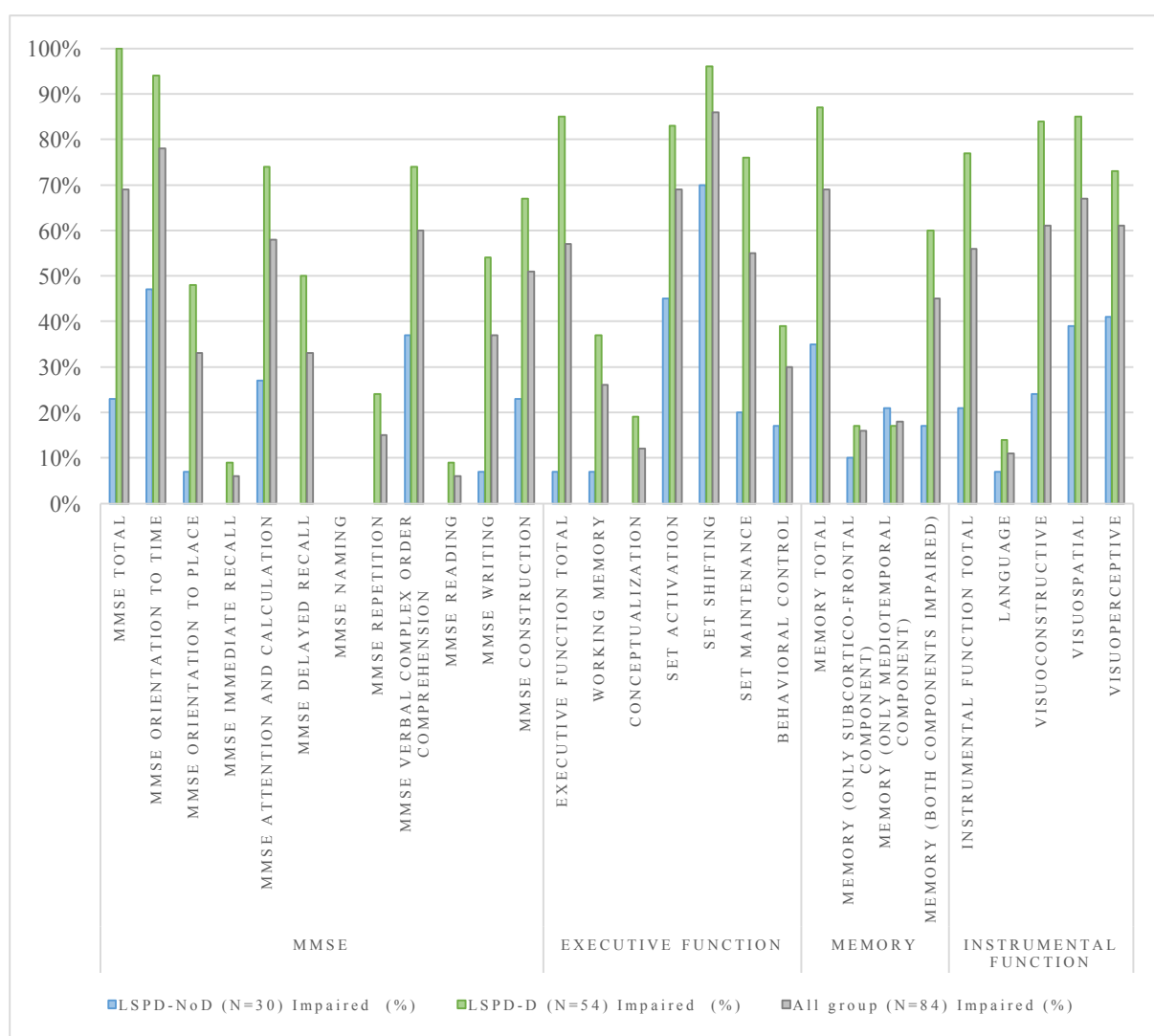


Figure 10. Frequency of cognitive impairment in LSPD patients

MMSE- Mini-Mental State Exam

LSPD-NoD- Late-Stage Parkinson's disease patients without dementia

LSPD-D- Late-Stage Parkinson's disease patients with dementia

When dissociating memory into its two components to analyze the memory deficit pattern, we observed that the mediotemporal component was the most frequently affected (20.7%), with an accentuated impairment (mean z-score -1.7 ± 0.5) (Figure 11) particularly in the long-term percent retention. We also observed a high frequency of intrusions in immediate and delayed retrieval (60.0% with more than five intrusions).

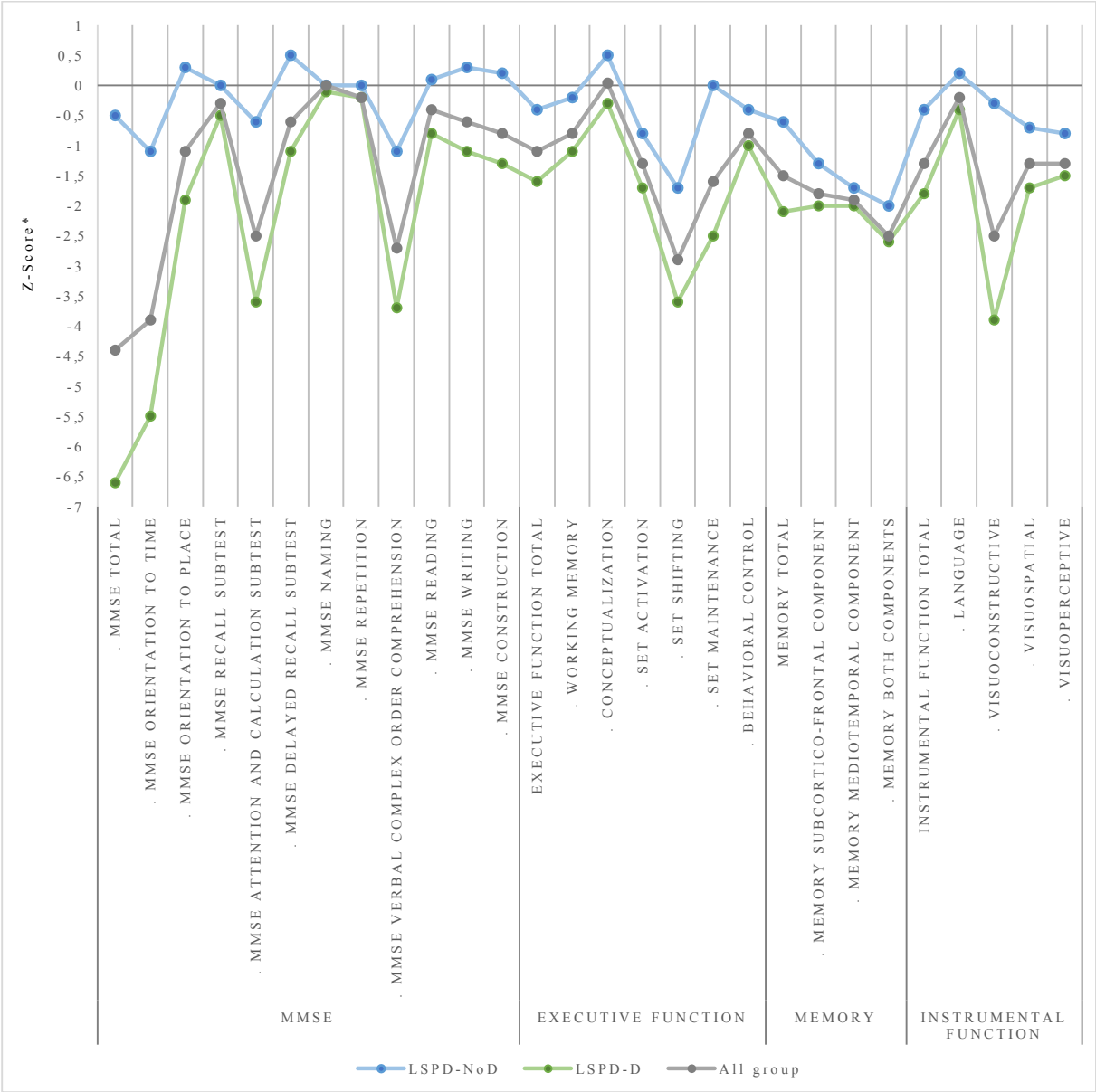


Figure 11. Cognitive performance of LSPD patients

MMSE- Mini-Mental State Exam

LSPD-NoD- Late-Stage Parkinson's disease patients without dementia

LSPD-D- Late-Stage Parkinson's disease patients with dementia

*We considered a cognitive test/domain as impaired if its z-score was more than 1 standard deviation below the adjusted normative scores (z-score<-1).

Instrumental function was also impaired in non-demented LSPD (LSPD-NoD) patients (20.7%), mainly visuoperceptive (40.7%) and visuospatial (39.3%) functions. Executive function was the least impaired cognitive domain in this group (6.7%). However, when we analyzed it in detail, we observed a high frequency of impairment in attention tasks, mainly in set shifting (70.4%) and set activation (44.8%).

In the demented group (N=54), 40.7% of LSPD patients reported changes in multiple domains and 59.3% in all cognitive domains.

The memory cognitive domain was the most frequently impaired (86.8%). We dissociated it into its two components to analyze its deficit patterns, observing that the majority of demented LSPD (LSPD-D) patients (60.4%) presented changes in both components, and that impairment was accentuated (mean z-score -2.6 ± 0.7), with a high frequency of intrusions (73.6% LSPD-D patients with more than five intrusions).

For executive function, the second most impaired LSPD-D cognitive domain (85.2%), we observed a pattern of changes similar to those in the non-demented group (mainly affecting attention) but with a much more pronounced frequency and impairment severity in all executive function cognitive tasks ($p < 0.05$).

Also, the instrumental function cognitive domain was significantly more impaired in the demented group ($p = 0.00$). When we looked at its pattern of changes, visuospatial was the function that was most frequently impaired (85.1%), followed by visuoconstructive (83.7%), two cognitive functions where there was also the most pronounced impairment (mean z-score -3.9 ± 2.6) ($p < 0.05$) (Supplementary Table 3).

3.3 Cognitive profile of LSPD according to the pattern of cognitive impairment

The LSPD patients were classified according to their cognitive profile, based on the pattern of cognitive impairment.

As required by definition, most of the non-demented group (73.3%) did not present significant changes in the cognitive tasks underlying each cognitive profile. They presented a heterogeneous cognitive profile. Only 6.7% of LSPD patients were classified as having a subcortical profile, 6.7% as having a cortical profile and, 13.3% as having a global impairment profile (Figure 12).

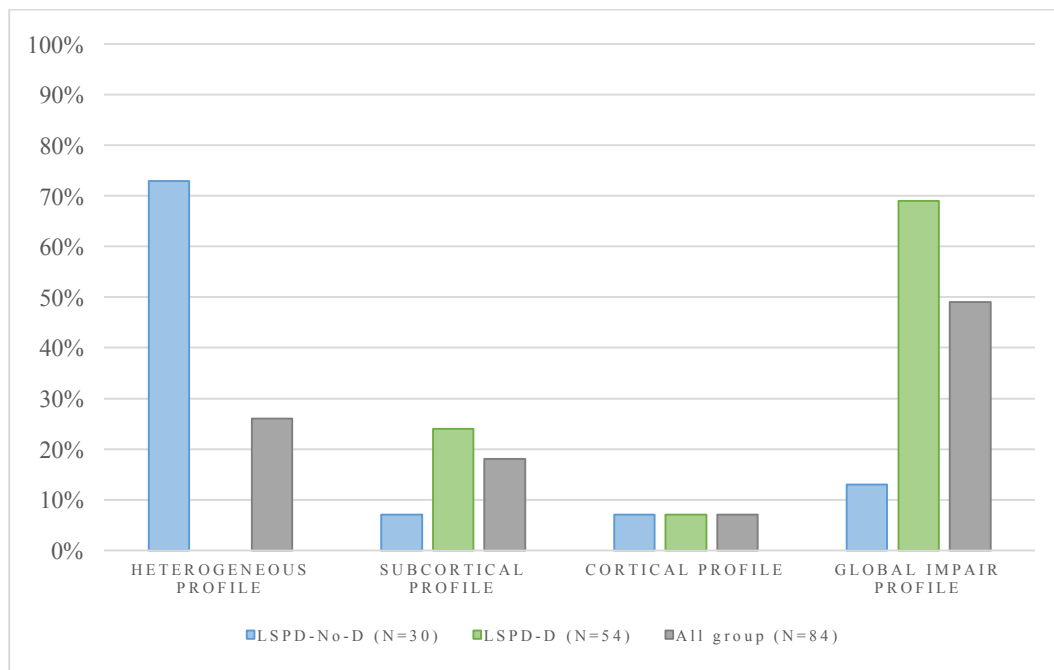


Figure 12. Frequency of cognitive profile of LSPD patients

LSPD-NoD- Late-Stage Parkinson's disease patients without dementia

LSPD-D- Late-Stage Parkinson's disease patients with dementia

In the demented group, 24.1% of LSPD patients were classified as having a subcortical profile, 7.4% as having a cortical profile, and 68.5% as having a global impairment profile.

As the cognitive profile sub-groups were small, no statistically significant differences were found within and between the non-demented and demented groups regarding demographic, clinical, and most of the distribution of cognitive variables distribution (Supplementary Table 4).

3.4 Variables associated with PDD

The hierarchical logistic regression analysis, with presence/absence of PDD as the dependent variable and clinical and neuropsychological measures as independent variables, showed that 1) the MMSE sub-scales scores of orientation in time (OR=0.54, beta=-0.63; 95% confidence interval [CI]=0.35-0.83; p=0.00), orientation in space (OR=0.35, beta=-1.04; 95% CI=0.15-0.86; p=0.02), language (complex order comprehension) (OR=0.61, beta=-0.50; 95% CI=0.43-0.87; p=0.00), and construction (OR=0.48, beta=-0.73; 95% CI=0.25-0.93; p=0.03), 2) S&E disability scale (OR=0.91, beta=-0.09; 95% CI=0.85-0.98; p=0.00), 3) RAVLT verbal learning (OR=0.33, beta=-1.11; 95% CI=0.12-0.91; p=0.03), and 4) Copy

of the clock test (OR=0.62, beta=-0.47; 95% CI=0.45-0.87; p=0.00) were associated with the condition of dementia, with reduced scores supporting the dementia diagnosis.

4. Discussion

Our results indicate that 54 (64.3%) LSPD patients met the criteria for PDD. Of the 30 (35.7%) LSPD-NoD patients, 5 (16.7%) did not present cognitive impairment. The remaining 25 (83.3%) met criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple-domain impairment). Reid et al. (2011)²⁷⁶ investigated a sample of PD who had 20 years of disease and found that 80% of PD patients had dementia. Based on these results, we expected to find a higher frequency of PDD. This discrepancy may be due in part to some clinical and socio-demographic characteristics of our sample. Phongpreecha et al. (2020)¹³¹ studied the associations between biological, clinical, and cognitive factors and they found that the primary factors associated with PDD were male sex, the glucocerebrosidase gene, later age at PD onset, and disease duration. In our study, although there were no statistically significant differences between the groups of demented and non-demented patients with regard to socio-demographic variables (probably due to the small size of the non-demented group, which will have reduced power of statistical analysis), our sample has an earlier age at PD onset and a higher proportion of women (58%) than expected based on previous reports. On the other hand, the participants had a level of education (mean of 6 years) that is not representative of the elderly Portuguese population who is poorly educated (up to four years in the population over 65 years), a fact that may have contributed to the lower frequency of dementia found.

Analysis of the cognitive performance of LSPD patients indicated that most of the demented and non-demented patients presented impairment in multiple cognitive domains.

Memory was the cognitive domain most frequently impaired, and the severity of the changes was also the most pronounced in both groups. Analysis by components showed that in the non-demented group impairment prevailed in the mediotemporal component, with more frequent changes in long-term retention, with a high frequency of intrusions in immediate and differed evocation, which also reveals that LSPD-NoD patients have difficulty maintaining the distinction between information coming from the outside and their own associations²⁹¹. These results are supported by some studies which report that the performance of PD patients in explicit memory tests is significantly decreased in those tasks

which require the organization of the to-be-remembered material³³³. Internal control of attention, required to generate spontaneously efficient encoding and retrieval strategies, is impaired in PD¹⁸⁷. Recall deficit is not primarily due to a memory disruption but rather to difficulties in activating the neuronal processes involved in the functional use of memory stores¹⁸⁷. PD patients are not unable to acquire mental sets but have difficulty maintaining newly acquired sets against competing alternatives, suggesting again a deficit of internal control of attention¹⁸⁷.

In the demented group, we observed a global memory impairment with changes both in learning and retention, and there was a high frequency of intrusions. These results revealed a global impairment in the different stages of information storage, whose severity was much more accentuated than that manifested by the non-demented group.

For instrumental function, the visuoperceptive abilities were the most frequently impaired in non-demented patients. Some neuroimaging studies report that these changes often arise in association with posterior cortical dysfunction¹⁸³.

In the demented group, visuo-constructive and visuospatial functions were the most frequently impaired. The LSPD-D patients correctly identified the clock design but manifested great difficulty in copying it, thereby revealing a visuo-constructive apraxia. PDD patients may be at an enhanced risk of visuospatial impairments that also reflect disrupted praxis and disrupted visuoperception over and above the contributions of motor dysfunction¹⁸².

We highlight the low frequency of language changes (in both groups), assessed by the Boston Naming Test. Errors on this test, although infrequent, sometimes arose due to visuoperceptive changes and not due to an impairment in naming. These findings go against what is reported in the literature. Naming is not frequently reported as an impaired cognitive task in PD³³⁴.

Executive function, the cognitive domain often reported as most frequently impaired in PD, was the third most frequently impaired in the non-demented group and the second in the demented group. This discrepancy may be due to two reasons: 1) the decline in executive function occurs in the early stages and then tapers off during the mid-stages of PD³³⁵; 2) almost all LSPD patients were medicated with levodopa which may improve executive

function and attention³³⁶. By contrast, visuospatial function³³⁷, visual recognition memory, conditional associative learning, and verbal memory seem to be dopamine-independent and unaffected by medication status^{338,339}. However, we highlight the changes we observed in attention both in frequency and severity of impairment. It was in the set shifting that LSPD patients manifested greater difficulties, even removing the speed element from the test evaluation. In the same way, in both groups, we observed changes in the set activation and the set maintenance. These changes may be attributed to the difficulty in maintaining and adapting a strategy against other competing possibilities due to frontal cortical and basal ganglia lesions³¹⁹.

When we grouped the cognitive domains into cognitive profiles to better characterize the substrate of cognitive impairment, we observed that the majority of LSPD-NoD patients manifested a heterogeneous cognitive profile. Some authors suggest that this heterogeneity might be at least partly explained by uneven dopamine loss across the basal ganglia circuitry^{340,341} and neurodegenerative hallmarks such as the emergence of cortical Lewy bodies and non-Parkinson's disease features as a consequence of ageing⁴³, which might interact with the putative pathological processes that underlies dementia. As such, there have been very few LSPD-NoD patients in cognitive profile subgroups, which made it impossible for us to have a reliable comparative analysis between them.

In the demented group, most patients exhibited widespread cognitive deficits, which we classified as a global impairment cognitive profile. For this reason, once again, the comparative analysis with the remaining demented and non-demented subgroups proved delicate given their small size. For purely exploratory reasons, we observed that LSPD-D patients in the global impairment group tended to be older, less educated, and have later PD age onset, greater disease disability, and overall greater frequency and severity of neuropsychiatric symptoms. It has been suggested that older age³⁴², later disease onset (after the age of 60 years)^{268,343}, and low educational attainment²⁶⁸ are associated with greater cognitive decline. Our results went in this direction. When we compared them with the other demented cognitive profile subgroups, we found that they present, overall, greater impairment in cognitive domains.

Hobson & Meara (2004)³⁴⁴ in their elderly PD cohort (mean age of 78 years) ascribed memory deficits to the possible development of Alzheimer's disease (AD). Similarly, our elderly LSPD patients, mainly PDD patients with global cognitive impairment, appeared to

present cognitive performance characterized by both AD (with memory (encoding) and orientation deficits) and PDD-typical impairments (executive function, memory (retrieving) and visuospatial abilities). Although AD cannot be diagnosed in the presence of PD because, according to the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria³⁴⁵, early parkinsonian signs rule this diagnosis out, Bothe et al. (2010)²⁷⁷ maintain that these existing criteria are quite restrictive and they disregard the neuropathological findings of the Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS, 2001)³⁴⁶, who mentioned that the majority of demented patients aged over 70 years present with more than one kind of severe neurodegenerative pathology.

A final finding of our study was that among the socio-demographic and clinical variables, only disease disability was significantly associated with PDD. Regarding the cognitive variables, we also found that orientation in time and space, complex order comprehension and construction MMSE sub-scales revealed an important association with PDD. The same was observed with verbal learning and with the copy of the clock test. These findings are consistent with previous studies that reported associations between language, memory³⁴⁴, and visuo-constructive function impairment¹³⁸ with PDD.

There are several strengths in the current study. To the best of our knowledge, this is the first study that applies the MDS PDD criteria in a sample exclusively consisting of LSPD patients, examined in their homes with a complete neuropsychological assessment.

Our study has some limitations. Firstly, we used a cross-sectional design and, to conclude on the cognitive changes with disease progression, it would be of interest to have a prospective cohort and longitudinal data. Secondly, the inexistence of a non-late-stage control group did not allow us to compare the pattern of the cognitive impairment in a different stage of PD by using the same assessment methodology.

In conclusion, almost all non-demented patients meet clinical criteria for MCI with multiple-domain impairment. Memory was the most frequently impaired cognitive domain, with a strong contribution of attention deficit. The cognitive profiles were heterogeneous, without any meaningful pattern over the cognitive domains. Most demented patients presented a global impairment profile, with both AD and PDD-typical impairments. Disease disability,

orientation, complex order comprehension, verbal learning, and visuo-construction were associated with PDD diagnosis.

Future studies with larger LSPD cohorts will be important to conclude about the eventual protective effect of socio-demographic variables for LSPD dementia and their typical cognitive profiles.

Chapter VI. General Discussion and future steps

This dissertation thesis came as a result of our finding that there is a considerable heterogeneity in the frequency of dementia reported by research studies and due to the lack of information about cognitive functioning in LSPD patients.

A number of studies have investigated the prevalence of cognitive impairment in PD patients. This estimation can range from 8%⁷⁴ to 83%²⁵, thus making it difficult to accurately estimate dementia frequency in this population.

Methodological characteristics of the studies and clinical and demographic characteristics of PD patients have been associated with this variability. The prevalence of cognitive impairment depends on a number of factors, including whether the cohort is incident or prevalent, hospital or community based, the selection of neuropsychological tests employed, and the criteria used to define cognitive impairment¹⁶⁶.

It was on the basis of these issues that we have decided to develop a systematic review and meta-analysis on the frequency of dementia in PD.

Although it seems clear from the published literature that the prevalence of dementia increases with older age^{37,71}, greater severity of motor impairment⁷¹, and longer PD duration²⁴⁶, the frequency of PDD at different disease stages, ages, and disease duration remained unclear.

Our primary objective was to estimate the frequency of dementia within PD. Secondly, we intended to estimate the frequency of dementia according to the methodological, clinical, and demographic characteristics of the included studies and PD patients.

We included 295 studies. Despite the high heterogeneity that we found (higher than 75%²⁵¹) due to the observational design of the studies, only for exploratory purposes we decided to proceed with a global and subgroup meta-analysis. Of the included 54 107 PD patients, 12 262 were diagnosed with PDD (26.3%). This result was in accordance with the majority of previously published studies that found similar frequencies of PDD²⁵⁴⁻²⁵⁸.

In the subgroup meta-analysis, we investigated dementia frequency according to the methodological, clinical, and demographic characteristics of the studies and participants.

Dementia frequency varied in all subgroups. However, the 95% CI, in some of the subgroups did not allow us to draw any conclusions, especially in the dementia criteria subgroup. Taking both this and the high heterogeneity of studies into consideration, the frequency of dementia reported according to the subgroups meta-analysis must only be interpreted qualitatively.

This systematic review allowed us to speculate that in the early stages of PD, with participants between 60 and 75 years old and between 5 and 10 years of PD duration, by using MDS Level II criteria and NPA to assess cognition, dementia frequency varies between 16% and 20%. In the advanced stages, also with participants between 60 and 75 years old but with between 10 and 15 years of PD duration, by using a similar methodology to diagnose dementia and assess cognition, dementia frequency varies between 20% and 30%. Finally, in the late stages, we can speculate that with participants over 75 years old and with more than 15 years of PD duration, dementia frequency may vary between 50% and 60%. These results are in accordance with what we observed in our cross-sectional study on dementia frequency in LSPD patients.

A study's primary objective, follow-up length, methodology to assess cognition, age, PD duration, and H&Y stage are important to this variability.

To assess dementia, we must consider methodological aspects like a clear definition of the main objective and inclusion criteria, diagnostic criteria, that must be actualized and adapted to the particularities of PD, and methodology to assess cognition, which must be based on a full cognitive assessment to avoid misdiagnoses. In the same way, increasing age, PD duration, and H&Y stage of PD patients tend to lead to higher dementia frequency. It is important to define at what stage of PD we want to assess dementia frequency and, according to this, define the methodological aspects. We cannot compare dementia frequency in PD as a whole without considering all of these different study aspects because dementia frequency varies according to all these variables.

Secondarily, we considered important to explore the most used instruments to assess cognition in LSPD, also to propose a battery that could be used with this population.

Although there were already recommendations about the number of tests to use mainly to diagnose MCI (two tests per domain)²²⁵, we considered that following these quantitative

suggestion we would get a very long battery that very likely would easily be interfered with by tiredness and poor adherence of LSPD patients, jeopardizing or hindering their cognitive assessment.

As such, we conducted a critical appraisal by searching for relevant articles which reported cognitive tests used for cognitive assessment of LSPD patients.

We selected the four most used cognitive tests in each cognitive domain and we verified their global characteristics and psychometric properties in order to recommend a cognitive assessment battery taking into account the special characteristics of LSPD population (often in an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL).

We included 60 studies which reported 53 different neuropsychological instruments used with LSPD patients. Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Mattis Dementia Rating Scale (Mattis DRS), and Montreal Cognitive Assessment (MoCA) were on top four for global cognitive assessment.

In the studies that used comprehensive neuropsychological assessment, we grouped the instruments assessing different cognitive domains according to their respective cognitive demands described in the studies. Interestingly, we observed that the four most used cognitive tests described to assess attention and working memory and executive functions were the same (Digit Span task of Wechsler Adult Intelligence Scales third edition (WAIS-III), Stroop Test, Trail Making Test (TMT), and Verbal Fluency).

For assessing memory, Rey's Auditory Verbal Learning Test (RAVLT), California Verbal Learning Test (CVLT), Benton Visual Retention Test (BVRT), and memory of Rey Complex Figure Test (RCFT) were the most used. Language was more frequently assessed with Boston Naming Test (BNT), Verbal Fluency, and Western Aphasia Battery, and visuospatial functions with Judgment of Line Orientation Test (JoLO), Visual Object and Space Perception Test (VOSP), Clock Drawing Test (CDT), and Copy of RCFT.

As we observed, different cognitive tests can vary considerably in terms of their cognitive demands, although it is clear that no human neuropsychological test is uniquely associated with damage to a specific brain region¹³⁸.

Based on the global characteristics and the psychometric properties of the most used cognitive instruments (accurate and sensitive for the changes from no cognitive impairment to MCI in PD, available up-to-date normative data, suggested by MDS for diagnosing PD-MCI or PDD, minimized motor demands, quick and easy to use, all domains relevant for PD-MCI or PDD diagnosis are considered, sensitivity and specificity preferably higher than 80% and 60%, respectively, and $AUC > 0.7$), we recommended a NPA battery that took into account the special characteristics of the LSPD population. Whereas MDS-MCI and PDD criteria are internationally accepted criteria, we considered it important to standardize the methodology used to assess cognition in PD in order to reduce the variability in the frequency of cognitive impairment attributed to methodological aspects.

Of the four most used cognitive tests to perform a global cognitive assessment, MoCA was the cognitive test that globally best corresponded to the requirements considered important for the selection of the instruments, Digit Span Backwards of WAIS and TMT, to assess attention and executive function, Semantic Fluency, to assess attention and executive functions and language, RAVLT and BVMT-R, to assess memory, BNT, to assess language, JoLO, to assess visuospatial function, and CDT, to assess attention and executive function and visuospatial function

This cognitive instruments battery that we recommend is not a fixed test battery. It contains a small easy-to-administer core battery of widely available cognitive tests that, in our opinion, can be adjusted by adding or by subtracting cognitive instruments, depending upon the goals of the cognitive assessment (if there is for researching or clinical practice), the patient and caregiver concerns, and the patient's ability to cooperate with or complete given tests²⁹⁸.

The test selection should consider the LSPD patient's cognitive, emotional, motor, and sensory capacity to cooperate with evaluation²³⁵. In PD, one often sought for cognitive tests that minimize potentially confounding motor demands. In this particular late-stage of PD, when patients are often in an advanced age, with treatment-resistant motor and non-motor symptoms, the motor fluctuations, neuropsychiatric symptoms and fatigability must be considered when deciding the test battery.

In addition, observations made during testing are critical when utilizing a process approach to assessment that seeks to elucidate the cognitive mechanisms underlying test success and

failure²⁹⁹. It is important to know, especially in timed tests, such as semantic fluency test, if the eventual low scores are due to executive function or language impairment or are due, for example, to speech and voice disabilities, like dysarthria, a frequent treatment-resistant motor symptom in LSPD³⁰⁰, that may compromise verbal fluency.

We recommended a NPA battery taking into account the special characteristics of LSPD population, brief in its utilization, that required as little as possible the use of paper and pencil and preferably not timed (minimized motor demands), and possible to be used in the patient's home.

In these worst cases, when severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) makes NPA impossible, we considered it important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients, to avoid underestimating this important non-motor symptom.

Considering this background and the scarcity of information about cognition particularly in late-stages of PD, we decided to explore dementia frequency in a cohort of LSPD patients.

Cognitive impairment is a potential late feature of Parkinson's disease (PD). However, the LSPD is a poorly studied population due to its typically severe motor and non-motor symptoms that often complicate cognitive assessment. As such, we developed a cross-sectional study to evaluate the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD. Although it is already well-accepted that MDS PDD Level II clinical criteria are the gold standard for PDD diagnosis, to our knowledge, there were no published studies on the dementia frequency by using updated PDD diagnostic criteria with LSPD patients.

We included 93 participants with a mean age of 75.8 years (SD 6.8) and 16.5 years (SD 7.5) of disease duration. We concluded that by using MDS Level II²²⁹ clinical diagnosis criteria, slightly more than half of the LSPD (64.3%) meet dementia criteria.

We also observed that the estimates of late-stage dementia frequency were partly dependent on the diagnostic criteria. We observed a high discrepancy on the frequency of dementia depending on the criteria applied (6.2% with MDS (Level I), 58.8% with DSM-IV, and 72.0% with DSM-5 criteria), mainly when we applied the MDS Level I criteria²²⁹. The checklist proposed at Level I proved to be quite specific in identifying non-demented LSPD

but very unresponsive in identifying demented LSPD. The agreement between the two diagnostic criteria was not significant. The mandatory absence of major depression was largely responsible for different dementia frequency and for the lack of significant agreement among the two levels. Only 18.6% of the LSPD was not diagnosed with major depression and 23.5% had an inconclusive diagnosis due to their difficulty in understanding the GDS³⁰⁷ items. These results are concordant with the results published by Barton et al. (2012)³⁰¹ who identified similar results.

In terms of clinical translation and practical application, the good specificity of Level I criteria proved that this is a time-efficient method to exclude PDD. However, as the absence of major depression is mandatory to perform the Level I diagnosis, future studies in similar populations will be important to confirm whether major depression is a frequent comorbidity and characteristic of late-stage PD, as this influences how we should evaluate it and to conclude about the applicability of MDS Level I criteria in this population.

MDS Level II criteria were applicable to most LSPD patients and we verified that there was accordance between the selection of instruments that we made and the most used cognitive tests in LSPD populations.

Nevertheless, none of the criteria used to diagnose dementia were applicable to eight patients which had severe physical/motor disabilities and for whom NPA was impossible. In the future, we consider it important that caregiver-based qualitative assessment methodology be developed to make conclusions on PDD in patients with these typical late-stage physical/motor disabilities, otherwise, we risk underestimating it.

Previous systematic reviews reported frequencies of dementia in PD between 24% and 31%⁷⁰. However, in these systematic reviews, dementia frequency was not reported according to the methodology used in the studies, mainly to diagnose PDD and assess cognition, and according to the clinical characteristics of PD patients (like PD duration and PD severity).

As such, we decided to compare our results with the results of other studies that assessed dementia frequency in PD by using similar methodology and in patients with similar clinical characteristics.

Considering the high frequency of dementia (80%) reported by Reid et al. (2011)²⁷⁶ who studied a sample of PD with 20 years of disease, we expected to find similar results. When we compared the frequency of dementia that we obtained through the same diagnostic criteria used by Reid et al. (2011)²⁷⁶ (DSM-IV criteria), we observed a huge discrepancy (58.8% vs. 80%). We hypothesized that this discrepancy may have been due in part to the clinical and socio-demographic characteristics of our sample that should be noted (early age at PD onset, female sex, higher educational level in relation to the general aged Portuguese population), which could have been protective factors for late-stage PD dementia. However, we have not overlooked that the Reid et al. (2011)²⁷⁶ study was a clinical trial study, which aim was to compare the efficacy and side effects of low-dose L-dopa with low-dose bromocriptine. It was a clinical trial with another main objective that reported dementia frequency as a secondary objective, by using non-specific PDD diagnostic criteria and a cognitive tests battery not covering all the significant cognitive domains, facts that together may also have contributed to the discrepancy found.

As one of the most severe and disabling non-motor symptoms of PD, cognitive impairment, particularly dementia, has been statistically associated with mortality⁵⁴, impairs social function, intensifies caregiver burden and the costs of disease-related medical care⁵⁵.

According to Gonzalez-Latapi et al (2021)¹¹⁸, the timing, profile and rate of cognitive decline varies widely among individuals with PD. As such, it is important to better comprehend the clinical profile of cognitive impairment in PD as well as the risk factors for developing these cognitive changes. This understanding is crucial clinically for communicating prognosis and managing patients. A better understanding of these factors also allows for optimization of research efforts, particularly clinical trial design¹¹⁸.

Given the morbidity associated with cognitive decline, preventative and disease modifying strategies would have great impact and may be found through knowledge of such factors¹¹⁸.

Therefore, a greater understanding of the cognitive disorders present in LSPD is of the utmost importance due to their high frequency in these patients.

Based on this findings, we decided to develop a cross-sectional study with the same LSPD population, in order to explore the clinical profile associated with their cognitive impairment

and the clinical, demographic, and cognitive variables that are associated with PDD diagnosis.

Eighty-four LSPD patients were included (age 75.4 ± 6.9 ; disease duration 16.9 ± 7.5). As we described above, 54 (64.3%) LSPD patients met the criteria for PDD. Of the 30 (35.7%) LSPD-NoD patients, 5 (16.7%) did not present cognitive impairment. The remaining 25 (83.3%) met criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple-domain impairment).

Analysis of the cognitive performance of LSPD patients indicated that most of the demented and non-demented patients presented impairment in multiple cognitive domains.

Memory was the cognitive domain most frequently impaired, and the severity of the changes was also the most pronounced clinically in both groups. Analysis by components showed that in the non-demented group impairment prevailed in the mediotemporal component, with more frequent changes in long-term retention, with a high frequency of intrusions in immediate and differed evocation, which also reveals that LSPD-NoD patients have difficulty maintaining the distinction between information coming from the outside and their own associations²⁹¹. These results are supported by some studies which report that the performance of PD patients in explicit memory tests is significantly decreased in those tasks which require the organization of the to-be-remembered material³³³. Internal control of attention, required to generate spontaneously efficient encoding and retrieval strategies, is impaired in PD¹⁸⁷. Recall deficit is not primarily due to a memory disruption but rather to difficulties in activating the neuronal processes involved in the functional use of memory stores¹⁸⁷. PD patients are not unable to acquire mental sets but have difficulty maintaining newly acquired sets against competing alternatives, suggesting again a deficit of internal control of attention¹⁸⁷.

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We highlight the low frequency of language changes (in both groups), assessed by the Boston Naming Test. Errors on this test, although infrequent, sometimes arose due to visuoperceptive changes and not due to an impairment in naming. These findings go against what is reported in the literature. Naming is not frequently reported as an impaired cognitive task in PD³³⁴.

Executive function, the cognitive domain often reported as most frequently impaired in PD, was the third most frequently impaired in the non-demented group and the second in the demented group. This discrepancy may be due to two reasons: 1) the decline in executive function occurs in the early stages and then tapers off during the mid-stages of PD³³⁵; 2) almost all LSPD patients were medicated with levodopa which may improve executive function and attention³³⁶. By contrast, visuospatial function³³⁷, visual recognition memory, conditional associative learning, and verbal memory seem to be dopamine-independent and unaffected by medication status^{338,339}. However, we highlight the changes we observed in attention both in frequency and severity of impairment. It was in the set shifting that LSPD patients manifested greater difficulties, even removing the speed element from the test evaluation. In the same way, in both groups, we observed changes in the set activation and the set maintenance. These changes may be attributed to the difficulty in maintaining and adapting a strategy against other competing possibilities due to frontal cortical and basal ganglia lesions³¹⁹.

When we grouped the cognitive domains into cognitive profiles to better characterize the substrate of cognitive impairment, we observed that the majority of LSPD-NoD patients manifested a heterogeneous cognitive profile. Some authors suggest that this heterogeneity

might be at least partly explained by uneven dopamine loss across the basal ganglia circuitry^{340,341} and neurodegenerative hallmarks such as the emergence of cortical Lewy bodies and non-Parkinson's disease features as a consequence of ageing⁴³, which might interact with the putative pathological processes that underlies dementia. As such, there have been very few LSPD-NoD patients in cognitive profile subgroups, which made it impossible for us to have a reliable comparative analysis between them.

In the demented group, most patients exhibited widespread cognitive deficits, which we classified as a global impairment cognitive profile. For this reason, once again, the comparative analysis with the remaining demented and non-demented subgroups proved delicate given their small size. For purely exploratory reasons, we observed that LSPD-D patients in the global impairment group tended to be older, less educated, and have later PD age onset, greater disease disability, and overall greater frequency and severity of neuropsychiatric symptoms. It has been suggested that older age³⁴², later disease onset (after the age of 60 years)^{268,343}, and low educational attainment²⁶⁸ are associated with greater cognitive decline. Our results went in this direction. When we compared them with the other demented cognitive profile subgroups, we found that they present, overall, greater impairment in cognitive domains.

Hobson & Meara (2004)³⁴⁴ in their elderly PD cohort (mean age of 78 years) ascribed memory deficits to the possible development of Alzheimer's disease (AD). Similarly, our elderly LSPD patients, mainly PDD patients with global cognitive impairment, appeared to present cognitive performance characterized by both AD (with memory (encoding) and orientation deficits) and PDD-typical impairments (executive function, memory (retrieving) and visuospatial abilities). Although AD cannot be diagnosed in the presence of PD because, according to the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria³⁴⁵, early extrapyramidal signs rule this diagnosis out, Bothe et al. (2010)²⁷⁷ maintain that these existing criteria are quite restrictive and they disregard the neuropathological findings of the Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS, 2001)³⁴⁶, who mentioned that the majority of demented patients aged over 70 years present with more than one kind of severe neurodegenerative pathology.

A final finding of our study was that among the socio-demographic and clinical variables, only disease disability was significantly associated with PDD. Regarding the cognitive

variables, we also found that orientation in time and space, complex order comprehension and construction MMSE sub-scales revealed an important association with PDD. The same was observed with verbal learning and with the copy of the clock test. These findings are consistent with previous studies that reported associations between language, memory³⁴⁴, and visuo-constructive function impairment¹³⁸ with PDD.

Conclusions

- Through a systematic review and meta-analysis, we observed that the global pooled frequency of dementia in observational studies is 26.3%.
- Dementia frequency may vary with methodological, clinical and demographic characteristics of the studies and PD patients.
- We can speculate that in the early stages of PD, with participants between 60 and 75 years old and between 5 and 10 years of PD duration, by using MDS Level II criteria and NPA to assess cognition, dementia frequency varies between 16% and 20%. In the advanced stages, also with participants between 60 and 75 years old but with between 10 and 15 years of PD duration, by using a similar methodology to diagnose dementia and assess cognition, dementia frequency varies between 20% and 30%. Finally, in the late stages, we can speculate that with participants over 75 years old and with more than 15 years of PD duration, dementia frequency may vary between 50% and 60%.
- The declared primary objective of the studies (to study PDD), the follow-up length (≥ 7 years), the age of the participants (≥ 75 years), Parkinson's disease (PD) duration (> 10 years), and the Hoehn & Yahr (H&Y) stage (> 3) were important factors affecting reported dementia frequency.
- In order to propose a brief cognitive assessment battery taking into account the special characteristics of the LSPD patients, we proceeded with a critical appraisal of the available instruments.
- Based on the global characteristics and the psychometric properties of the most used cognitive instruments, we proposed MoCA Test, to assess global cognitive assessment, Digit Span Backwards of WAIS and TMT, to assess attention and executive function, Semantic Fluency, to assess attention and executive functions and language, RAVLT and BVMRT-R, to assess memory, BNT, to assess language, JoLO, to assess visuospatial function, and CDT, to assess attention and executive function and visuospatial function.
- In the worst cases, when severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) makes NPA impossible, we considered it

important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients, to avoid underestimating this important non-motor symptom.

- Through a cross-sectional study, developed to evaluate the frequency of PDD and verify the applicability and impact of using different diagnostic criteria in LSPD patients, we observed that slightly more than half of the LSPD patients (64.3%) meet dementia diagnosis by using MDS Level II criteria.
- These results are in accordance with what we observed in our systematic review and meta-analysis on dementia frequency in LSPD patients.
- The estimates of LSPD dementia frequency were partly dependent on the diagnostic criteria, mainly when MDS Level I were applied.
- The checklist proposed at Level I proved to be quite specific in identifying non-demented LSPD but very unresponsive in identifying demented LSPD. The mandatory absence of major depression was largely responsible for different dementia frequency and for the lack of significant agreement among the two levels.
- The good specificity of Level I criteria proved that this is a time-efficient method to exclude PDD. However, as the absence of major depression is mandatory to perform the Level I diagnosis, future studies in similar populations will be important to confirm whether major depression is a frequent co-morbidity and characteristic of late-stage PD, as this influences how we should evaluate it and to conclude about the applicability of MDS Level I criteria in this population.
- MDS Level II PDD criteria were applicable to most LSPD patients. We verified the accordance between the selection of instruments that we made and the most used cognitive tests in LSPD populations.
- Nevertheless, none of the criteria used to diagnose dementia were applied to the eight patients with severe physical/motor disabilities for whom NPA was impossible.
- In the future, we consider it important that caregiver-based qualitative assessment methodology be developed to make conclusions on PDD in patients with these typical late-stage physical/motor disabilities, otherwise, we risk underestimating it.
- Clinical diagnostic criteria are important and may explain in part the heterogeneity in results of dementia frequency but this seems not to be the only factor that could justify the discrepancy in dementia frequency.

- Through a cross-sectional study, developed with the same LSPD population, which aim was, beyond exploring dementia frequency, to explore the clinical profile associated with their cognitive impairment, and the clinical, demographic and cognitive variables that may be associated with PDD diagnosis, we observed that most of the LSPD patients presented impairment in multiple cognitive domains.
- 83.3% of the non-demented patients met criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple-domain impairment).
- Memory was the most frequently and severely impaired cognitive domain in demented and non-demented LSPD patients.
- Non-demented patients manifested a heterogeneous cognitive profile.
- Demented patients manifested a global impairment cognitive profile.
- Demented patients with global impairment cognitive profile appeared to present a cognitive performance characterized by both AD and PDD-typical impairments.
- Disease disability, orientation in time and space, complex order comprehension and construction MMSE sub-scales, verbal learning and copy of the clock, revealed an important association with PDD.
- The studies main conclusions are schematically represented in figure 14.

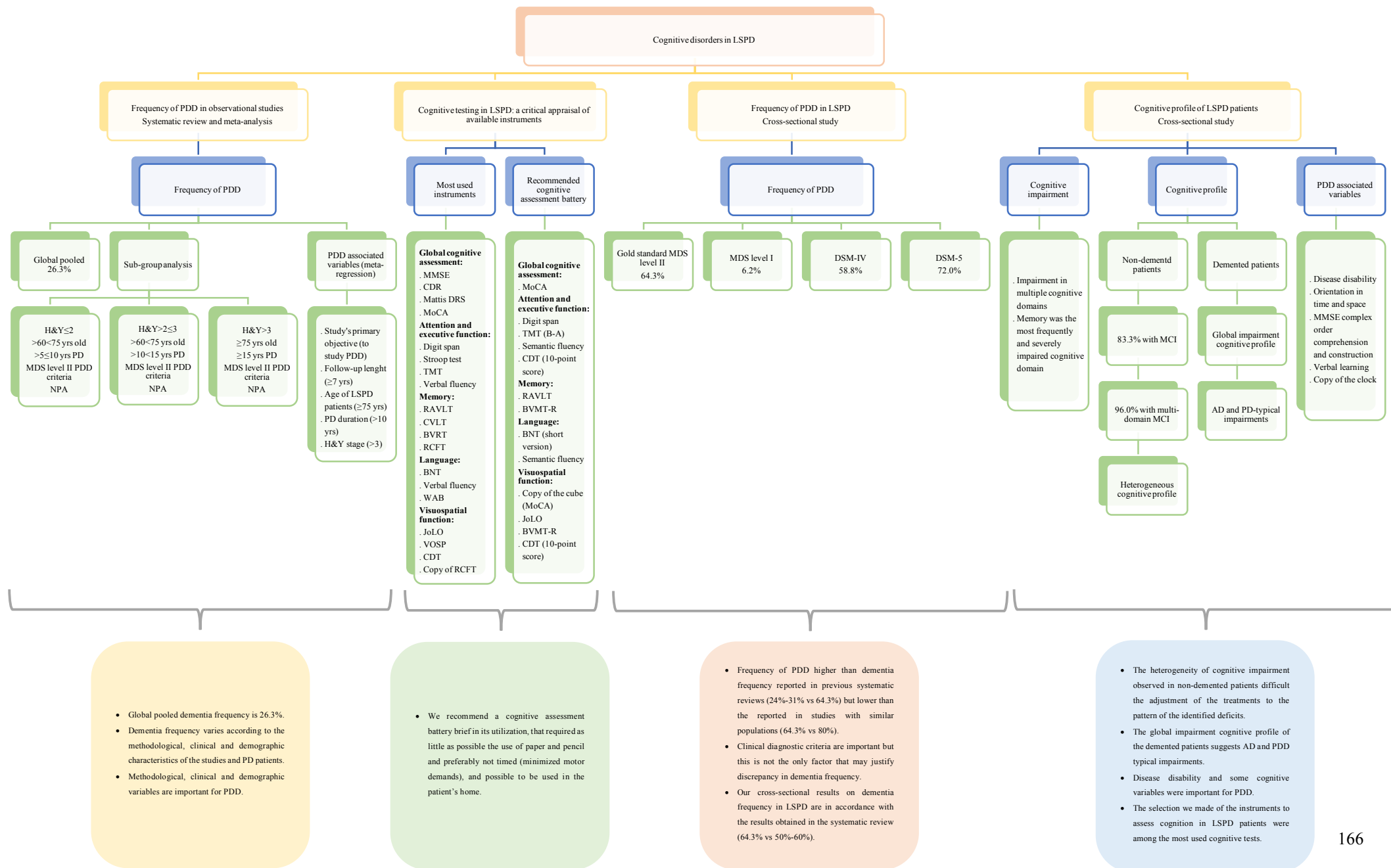


Figure 13. Scheme of the main conclusions

Implications for clinical practice

Comprehensive evaluation of individual cognitive domains is crucial for estimating the underlying pathophysiology and subsequently lead to development of effective treatments.

As the neurodegenerative progression continues in PD, cognitive changes also advance. The frequency of patients with MCI increases, and those with MCI are at a higher risk for the development of dementia. Although some studies reported that dementia may seem almost inevitable after 20 years following the diagnosis of PD, with dementia prevalence reaching 80%, the rate of progression to dementia is highly variable¹¹⁸.

With our studies, we concluded that although the frequency of cognitive impairment is high in LSPD, most of these patients are possible to be assessed by using a comprehensive neuropsychological battery. However, this battery must consider the special characteristics of these patients and can not be the same in type and number of cognitive tests as the batteries used in early stages of PD. As such, our proposed neuropsychological battery allows for an appropriately broad and harmonized assessment of cognition that is not overly burdensome to LSPD patients, and can be tailored to specific clinical and research interests. On the other hand, our study draws attention to the non-exclusion of patients with severe motor and non-motor impairments that compromise the neuropsychological assessment from the epidemiological studies on PD cognitive impairment, in order to avoid its underestimation.

The additional high variability for the affected cognitive domains and the severity of the cognitive decline that we observed in our studies makes it challenging to make predictions about the progression and underlying pathologies.

Implications for research

Although there are currently no pharmacological treatments to delay or prevent cognitive decline in PD, from a research perspective it is important to be able to detect the patients at risk before the onset of severe cognitive decline and to monitor the progression to determine the rate of decline.

Detecting such patients and progression rates will enable the development of effective strategies to prevent or delay progression to dementia in PD.

Future steps

Cognitive impairment has a major impact over the course of Parkinson's disease and contributes substantially to disease burden, particularly as the disease progresses but even early in the disease. As such there is increasing interest in understanding the factors associated with the development of PD-MCI and PDD in order to develop preventive or modifying strategies.

To date, there is conflicting evidence for most environmental and genetic factors that have been studied. Contributing methodological issues include the use of inconsistent criteria to define PD-MCI and PDD, the use of different instruments to measure cognition. In addition, cognition is a multifaceted function that is complex to measure, and many studies lack a comprehensive neuropsychological assessment. This hinders the description of specific cognitive patterns associated with specific risk factors. As such, it would be of great importance the standardization of the clinical criteria and cognitive instruments that should be used to diagnose cognitive impairment in PD.

Although the development of cognitive impairment has been well documented for some genetic forms of PD, such as *GBA*, the effect of other genetic variants and environmental exposures is much less clear. Regarding genetic variants, the role of less frequent variants, such as *SNCA* or *PINK1* variants is unclear, mainly due to the small number of cases reported. Importantly, most of the studies analyzing genetic risk factors have included mostly Caucasian subjects. As such, the role of these genes in other populations still needs to be ascertained. The same can be said for variants in genes such as *COMT*, *APOE*, *BDNF*. Our understanding of the role of environmental factors is similarly limited; while factors such as traumatic brain injury and pesticide exposure have been extensively studied as risk factors for the development of PD, the specific role they play in cognition, other aspects of the symptom complex of PD and PD progression needs to be better understood.

One additional issue is the timing of exposure; there may be an etiologically relevant time window where a given exposure may be causally related to disease onset. In this way, measurement of lifetime exposure to environmental factors can provide information related to cognitive decline onset, while exposure to the same factors once cognitive decline has started may give us information on how these contribute to disease course. The complication

lies in identifying the correct time window, which has been historically difficult in PD given its long prodromal phase and long symptomatic course.

Even less is known about protective factors. Cohort studies focused on prodromal PD may provide an opportunity to explore this, by prospectively documenting lifestyle, dietary and other environmental risk factors prior to the onset of or early in the course of cognitive decline. In particular, identification of modifiable risk factors, such as specific diet patterns, dietary supplementations or exercise regimens should be prioritized, as this will allow for potential interventions even in established PD. Evidence for a role of ongoing environmental exposures in accelerating or decelerating the progression of PD provide an important basis for targeted interventions or counselling to improve the lives of people living with PD. Adding further complexity, there is increasing awareness of interactions between gene and environment as determinants of disease phenotype, and this large field has been practically unexplored regarding cognition and PD. As genetic testing becomes more accessible, the elucidation of risk variants may allow for the identification of at-risk individuals who may benefit most from interventions.

Molecular and imaging biomarkers have been studied in PD-associated cognitive impairment. Most studies, however, have been small and have lacked detailed neuropsychological testing, prospective longitudinal evaluations, and independently validated data. Future validation of biomarker candidates is highly desired and may lead to revised criteria of cognitive impairment in PD. An anticipated biomarker for PD-MCI should be detectable at diagnosis, easily and widely accessible, and validated in independent cohorts. There is a need for prospective, longitudinal assessments of accessible biomarkers (including cerebrospinal fluid, blood, and neuroimaging) that also incorporate neuropathological correlation. Though the National Institute on Aging Alzheimer's Association MCI criteria committee has incorporated biomarkers into research criteria for MCI and Alzheimer's disease, the field of PD has not advanced sufficiently to consider biomarkers as criteria for cognitive decline at present²²⁵.

Finally, it would be of interest to study larger community-based groups of LSPD patients, in order to observe if clinical and demographic variables (such as sex, age at PD onset) could be protective factors for late-stage PD dementia, and in order to validate the proposed battery to assess cognition in LSPD patients.

Acknowledgments

I decided to acknowledge in portuguese, my native language, as the cultural and emotional dimensions of language and speech may be lost in translation.

Ao Professor Doutor Joaquim Ferreira, o meu orientador. A pessoa que mais responsabilidade tem pelo meu reingresso na vida académica. Aquele que desde o início me deu esta oportunidade e acreditou em mim. Um verdadeiro líder, inspirador quer do ponto de vista profissional como do ponto de vista das relações humanas. Aquele que representa, defende e protege a sua equipa de modo ímpar. Um verdadeiro líder, exemplo das boas práticas, rigor, seriedade, exigência, capacidade de trabalho, que me orientou nos momentos turbulentos, quando surgiram as crises existenciais, os momentos de incerteza, quando me questioneei se conseguiria algum dia corresponder com sucesso a tamanha exigência. Aquele que com as suas provocações me ajudou a crescer como profissional e como pessoa. O meu sentimento de gratidão é imenso agora e sempre.

À Professora Doutora Isabel Pavão Martins, minha co-orientadora, por me ter acolhido tão bem desde o primeiro momento, pelo seu exemplo de boas práticas e rigor científico, pela disponibilidade e sugestões que foram tão importantes e indispensáveis para o sucesso dos meus trabalhos.

Aos meus colegas que me acolheram no início deste desafio. À Catarina Godinho, à Margherita Fabbri, à Rita Simões, pelo apoio incondicional e pelo contributo indispensável para a concretização dos trabalhos. Ao Professor Miguel Coelho, pelo apoio, disponibilidade e partilha de conhecimentos.

À equipa do Laboratório de Farmacologia Clínica e Terapêutica, pelo acolhimento, apoio e partilha de conhecimentos. Um agradecimento especial às minhas colegas e amigas Mariana Alves e Raquel Bouça, companheiras de travessia, com quem tantas vezes partilhei as minhas dificuldades e angústias mas também chorei de tanto rir, a quem tantas vezes pedi ajuda, verdadeiros exemplos de capacidade de organização e trabalho, sempre disponíveis para ajudar.

Ao serviço de neurologia do Hospital de Santa Maria, na pessoa do Professor Doutor José Ferro, por ter autorizado e facilitado o acesso aos participantes dos estudos.

À Faculdade de Medicina da Universidade de Lisboa, ao Instituto de Medicina Molecular e ao Centro Académico de Medicina de Lisboa, por me terem acolhido e proporcionado o contacto e a aprendizagem com personalidades científicas de excelência e por terem contribuído para o meu enriquecimento teórico.

À Fundação para a Ciência e Tecnologia, pela atribuição da bolsa de doutoramento, indispensável para que me pudesse dedicar exclusivamente à investigação. Estou certa de que foi um apoio decisivo e indispensável para a conclusão dos trabalhos com sucesso.

Ao Centro Hospitalar do Oeste, a instituição que há 22 anos me deu a oportunidade de iniciar a minha atividade profissional enquanto psicóloga, onde cresci desmesuravelmente enquanto profissional e enquanto pessoa e que permitiu que me ausentasse durante o período da bolsa para que fosse possível a concretização deste projeto.

Deixo para o final propositadamente o meu agradecimento áqueles que foram verdadeiramente decisivos e dão sentido a este percurso pessoal e académico, a minha fonte de inspiração e motivação. Aos doentes de Parkinson e seus cuidadores. Pessoas a quem dei tanto de mim mas de quem tanto recebi, com quem muito aprendi, pessoas verdadeiramente inspiradoras pelo espírito de sacrifício, luta e perseverança, que me abriram a porta e receberam de modo tão caloroso naquele que é o seu ambiente mais recatado e privado, no seu lar.

Finalmente, aos meus. Àqueles que são a minha vida. À minha família. Aos meus filhos Martim e Mariana que comigo viveram empolgadamente o meu regresso à escola, que me inspiram e me fazem lembrar todos os dias que seja qual for a travessia em que nos encontramos, o segredo do sucesso é nunca deixarmos de ser quem somos dando sempre o melhor que temos dentro de nós. Ao meu marido, pela paciência e apoio nos dias em que precisei que tivessem mais do que 24 horas. À minha irmã, pelo apoio, carinho e palavras de motivação e perseverança. Aos meus pais, por estarem sempre lá, pelo apoio incondicional, por me terem inculcado que o céu é o limite e por me terem ensinado a acreditar que com trabalho e empenho o impossível não existe.

Nunca foi sorte ... 

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List of publications

- Severiano E Sousa C, Alarcão J, Pavão Martins I, Ferreira JJ. Frequency of dementia in Parkinson's disease: A systematic review and meta-analysis. *J Neurol Sci.* 2021 Dec 3;432:120077. doi: 10.1016/j.jns.2021.120077. **Impact factor: 3.181**
- Severiano E Sousa C, Alarcão J, Pavão Martins I, Ferreira JJ. Cognitive testing in late-stage Parkinson's disease: a critical appraisal of available instruments. *App Neuropsychol Adult.* 2022 Aug 26;1-12. doi: 10.1080/23279095.2022.2114355. **Impact factor: 2.050**
- Severiano E Sousa C, Fabbri M, Godinho C, Simões R, Chendo I, Coelho M, Martins IP, Ferreira JJ. Clinical Diagnostic Criteria Have a High Impact on the Frequency of Dementia in Late-Stage Parkinson's Disease. *Front Neurol.* 2021 May 20;12:652424. doi: 10.3389/fneur.2021.652424. **Impact factor: 3.552**
- Severiano E Sousa C, Fabbri M, Godinho C, Moiron Simões R, Chendo I, Coelho M, Pavão Martins I, Ferreira JJ. Profile of cognitive impairment in late-stage Parkinson's disease. *Brain Behav.* 2022 Apr;12(4):e2537. doi: 10.1002/brb3.2537. **Impact factor: 2.71**

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Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Frequency of dementia in Parkinson's disease: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Parkinson's disease
Dementia frequency
Systematic review

ABSTRACT

Background: There is a considerable variation in the reported frequency of dementia in Parkinson's disease (PDD). The aim of this study was to evaluate the frequency of PDD reported in published studies and to examine the different methodological, clinical, and demographic factors that may contribute to this variation.**Methods:** We conducted a systematic review, searching EMBASE and MEDLINE databases for relevant articles on PDD frequency published before May 2019. A global estimation of PDD was calculated. Different subgroup analyses were performed for methodological, clinical, and demographic characteristics. Meta-regression was also conducted to identify any significant differences within the subgroups.**Results:** We included 295 studies. The global pooled dementia frequency was 26.3%. These estimations varied according to methodological (14%–55%), clinical (18%–46%), and demographic (21%–43%) variables. The declared primary objective of the studies (to study PDD), the follow-up length (≥ 7 years), the age of the participants (≥ 75 years), Parkinson's disease (PD) duration (> 10 years), and the Hoehn & Yahr (H&Y) stage (> 3) were important factors affecting reported dementia frequency.**Conclusions:** This systematic review found that approximately one-quarter of the PD patients were diagnosed with PDD. Dementia frequency varied according to methodological, clinical and demographic variables. We cannot examine PDD frequency without considering all these variables that have an impact on it.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that has been classically defined by motor dysfunction. Currently, we understand that PD is a heterogeneous disorder, comprising a range of motor and non-motor symptoms. Cognitive decline, in particular, is a common non-motor feature of the disease, which can have a high impact on the quality of life of patients and carers [1], as well as being a risk factor for early mortality [2]. As such, the identification of the specific features that may predict the progression of cognitive impairment could have important implications for the treatment planning and clinical management of PD patients.

Although it is estimated that the prevalence of Parkinson's disease dementia (PDD) is around 24–31% [3], several studies have reported a

considerable variation in their results, ranging from 8% [4] to 83% [5], thus making it difficult to accurately estimate dementia frequency in this population.

Methodological characteristics of the studies and clinical and demographic characteristics of PD patients have been associated with this variability. Important methodological features include the analytical design used (cross-sectional versus longitudinal), tests to assess cognition (screening scales versus comprehensive neuropsychological assessment), definitions of dementia, and the criteria for diagnosing PDD and selecting patients. Most of the previous studies on PDD also included patients at varying disease stages.

Although it seems clear from the published literature that the prevalence of dementia increases with older age [6,7], greater severity of motor impairment [6], and longer PD duration [8], the frequency of

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<https://doi.org/10.1016/j.jns.2021.120077>

Received 30 September 2021; Received in revised form 24 November 2021; Accepted 27 November 2021

Available online 3 December 2021

0022-510X/© 2021 Published by Elsevier B.V.

PDD at different disease stages, ages, and disease duration remains unclear.

The primary objective of the present systematic review and meta-analysis was to estimate the frequency of dementia within PD. Secondary objectives were to estimate the frequency of dementia according to the methodological, clinical, and demographic characteristics of the included studies and PD patients.

2. Methods

This systematic review was performed according to the Cochrane Collaboration recommended procedures [9] and the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [10].

2.1. Eligibility criteria

We included original observational studies (cross-sectional, prospective cohort, and case-control studies), published in English, French, or Spanish without publication date restriction, which reported patients with confirmed PD diagnosis and dementia that developed one year after the confirmed PD diagnosis. The one-year rule was used to distinguish PDD from dementia with Lewy-bodies (DLB) [11,12], in order to carefully minimize the risk of involuntary inclusion of DLB patients.

2.2. Information sources and search methods

We searched both EMBASE and MEDLINE databases, from their inception to May 2019, using a pre-defined search strategy (Supplementary Fig. 1). The search strategy combined standardized subject terms and text words, with relevant Boolean operators implemented. A citation chaining was also conducted to ensure that no articles were overlooked.

2.3. Data extraction

Two authors independently assessed the titles and abstracts of retrieved publications to identify studies that met the inclusion criteria. Any disagreement over the eligibility of studies was resolved through a consensus discussion with a third author.

The outcome of interest was the number of PDD among a population of PD patients.

A standard data collection form was created to extract methodological data from the studies and demographic and clinical information on the PD patients.

2.4. Subgroup analysis

We performed a subgroup analysis.

In this subgroup analysis, we included the methodological characteristics of the studies (year of the study development [classified as year of study], study design, study primary objective, follow-up length, dementia diagnosis criteria, and methodology used to assess cognition) and clinical and demographic characteristics presented by the participants (PD severity [Hoehn & Yahr stage, H&Y [13]], PD duration, age, and education).

We performed an additional analysis within each of the categories of the PD severity subgroup to analyze dementia frequency according to these variables.

2.4.1. Year of study

At the end of 2007, the International Movement Disorders Society (MDS) recommended criteria to diagnose dementia [14]. It was an important milestone because until then PDD was diagnosed without an internationally accepted recommendation.

We, therefore, analyzed studies published before and after 2008, to investigate any changes that have occurred, especially methodologically, and whether this had an impact on the reporting of dementia frequency.

2.4.2. Study design

We grouped the studies according to the three main analytical designs used in observational research: 1) cross-sectional; 2) cohort; and 3) case-control studies.

2.4.3. Studies' primary objectives

We grouped the studies into three main categories according to their declared primary objective: 1) study PDD; 2) study cognitive functioning, which we classified as study cognition; and 3) other (i.e., studies which primarily investigated other conditions and reported dementia frequency as a secondary result).

2.4.4. Follow-up length

We grouped the studies into seven categories of reported follow-up length (in years): 1) ≤ 1 ; 2) $> 1 \leq 2$; 3) $> 2 < 5$; 4) $\geq 5 < 7$; 5) $\geq 7 < 10$; 6) $\geq 10 < 15$; and 7) ≥ 15 .

For studies with multiple follow-ups, we entered the dementia frequency of the last assessment.

2.4.5. Dementia diagnosis criteria

We grouped the studies into seven main categories, according to the PDD diagnosis criteria used: 1) MDS Level I; 2) MDS Level II; 3) DSM-III/IV (due to their similarities, we included ICD-9/10 criteria in this category); 4) The best clinical judgement criteria with a comprehensive neuropsychological assessment (NPA) and with a well-defined definition of cognitive impairment, were classified as "NPA criteria"; 5) Screening scales criteria (screening scales cut-offs); 6) The best clinical judgement criteria made by a single qualified clinician or through consensus by a team of clinicians, were classified as "Clinical assessment criteria"; and 7) The studies that failed to describe the criteria used were classified as "Not specified".

For studies that compared different diagnostic criteria, we entered data concerning to dementia frequency obtained with their primary criteria.

2.4.6. Methodology used to assess cognition

We grouped the studies into three main categories, according to the methodology used to assess cognition: 1) Screening scales; 2) NPA; and 3) Not specified (studies that failed to describe the methodology used).

2.4.7. PD severity

We grouped the studies that reported the H&Y stages of PD patients into three categories: 1) H&Y ≤ 2 (early stages, with mild motor impairment); 2) H&Y $> 2 \leq 3$ (intermediate/advanced stages, with moderate motor impairment); and 3) H&Y > 3 (late stages, with severe motor impairment).

2.4.8. PD duration

We grouped the studies that reported PD duration (number of years since PD was diagnosed) into five categories (in years): 1) ≤ 3.5 ; 2) $> 3.5 \leq 5$; 3) $> 5 \leq 10$; 4) $> 10 < 15$; and 5) ≥ 15 .

2.4.9. Age

We grouped the studies that reported the age of the PD patients into three categories (in years old): 1) ≤ 60 ; 2) $> 60 < 75$; and 3) ≥ 75 .

2.4.10. Education

The studies that reported participants' education levels were grouped into four categories (in years): 1) ≤ 4 ; 2) $> 4 \leq 9$; 3) $> 9 \leq 12$; and 4) > 12 .

We entered the H&Y stage, PD duration, and age presented by PD

patients at the baseline assessment, in cross-sectional studies, and at the last follow-up assessment, in the longitudinal studies.

2.5. Quality assessment

The quality of the included studies was assessed using a scale adapted from Hoy and colleagues [15,16]. The risk of bias of the studies was categorized as "low risk" (0–3 points), "moderate risk" (4–6 points), or "high risk" (7–9 points) [16] (see Supplementary Fig. 2 for quality criteria used).

2.6. Data synthesis

We used descriptive statistics to characterize the methodological, clinical, and demographic information of the included studies. Variables were described through absolute and relative frequencies (%).

Dementia frequency and 95% confidence intervals (CI95%) were calculated based on the number of dementia cases and PD patients included.

We proceeded to a subgroup analysis of the dementia frequency according to the methodological, clinical, and demographic characteristics of the included studies. Data were organized into several

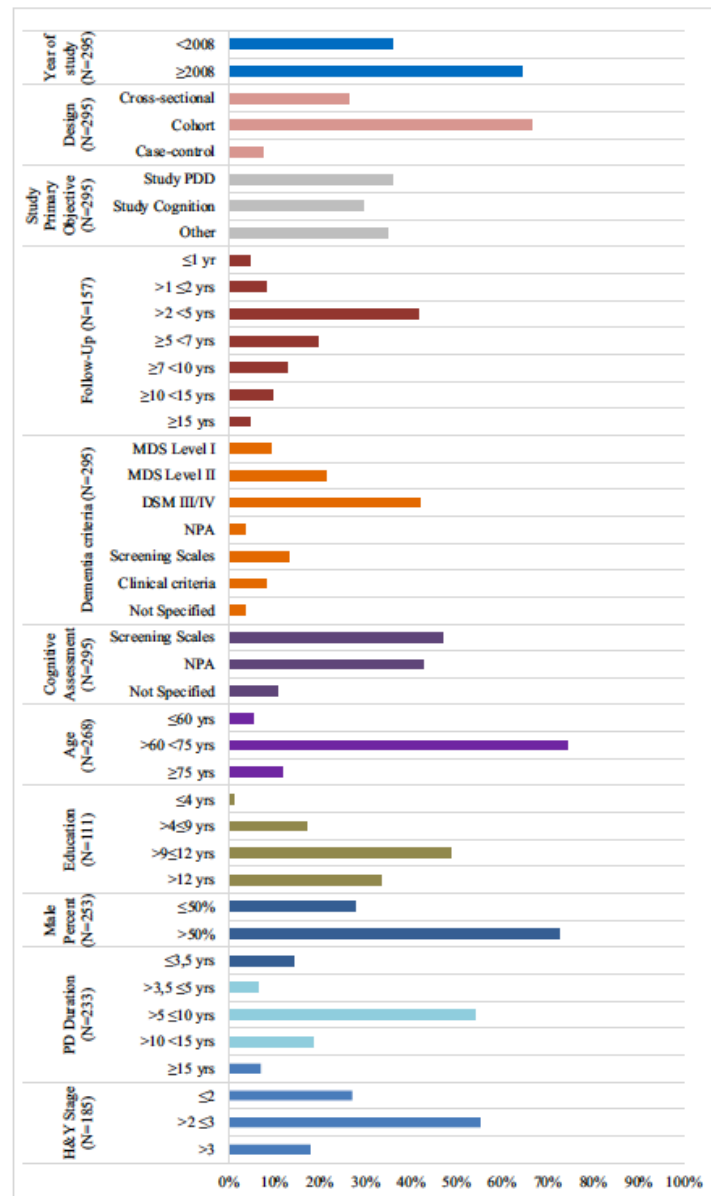


Fig. 1. Studies' characterization.
PD- Parkinson's disease.
PDD- Parkinson's disease dementia.
MDS- Movement disorder society.
NPA- Neuropsychological assessment.
H&Y- Hoehn and Yahr.

categories within each subgroup according to the criteria explained above.

We calculated the Cochrane Q statistic (with $p < 0.10$ indicating statistically significant heterogeneity) and used I^2 (with $<40\%$ indicating heterogeneity might not be important and $>75\%$ indicating considerable heterogeneity) to quantify the magnitude of heterogeneity between studies [17]. As a way of standardizing the results of the analyzed studies, a meta-analysis was used to calculate dementia frequency and 95% confidence intervals by using the DerSimonian and Laird random-effects model [18]. Meta-regression was used to determine whether a significant difference was present between subgroups. A sensitivity analysis of the data was performed by study quality. Studies with a low, moderate, or high risk of bias were combined using meta-analysis and compared to determine whether significant differences were present in dementia frequency based on study quality.

The descriptive statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL). Meta-analysis and meta-regression were performed using OpenMetaAnalyst software [19]. A p -value <0.005 was considered statistically significant.

3. Results

3.1. Search

The results of the literature search are summarized in Supplementary Fig. 3. Of the 3326 screened studies, 1261 were excluded following abstract screening, while 1770 were excluded following full-text screening. In total, 295 studies reported dementia frequency in PD according to our inclusion criteria and were included in our review.

3.2. Study characterization

Of the included studies, 64.1% were published after 2008 and were mainly cohort studies (66.4%). Among the studies that reported a follow-up period ($N = 159$), most were between 2 and 5 years (41.5%). For 35.9% of the studies, the primary objective was to study dementia, 41.7% used DSM-III/IV criteria to diagnose PDD, and 46.8% assessed patients' cognition using screening scales (Fig. 1).

Interestingly, only one study followed DSM-5 criteria to diagnose PDD. As this study used full NPA, which is similar to the DSM-5 criteria, we included it in the subgroup of studies that used NPA criteria to diagnose PDD.

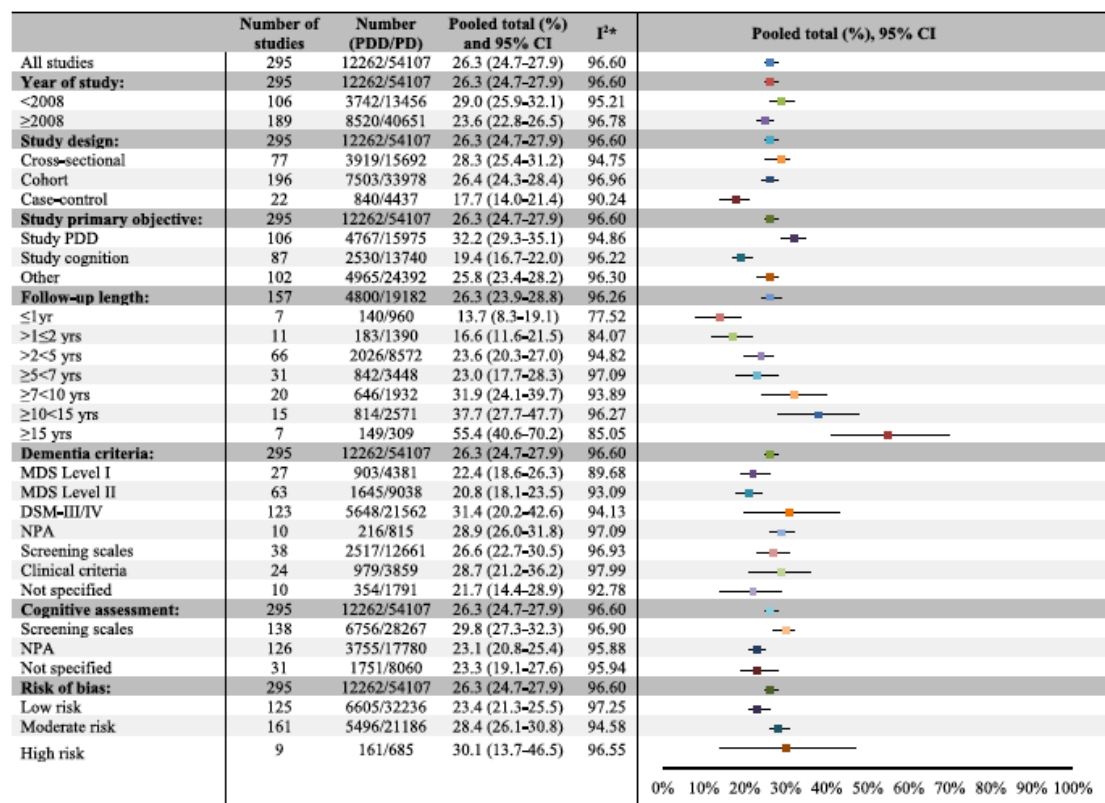


Fig. 2. Meta-analysis of dementia frequency by methodological subgroups.

* $<40\%$ heterogeneity might not be important; $>75\%$ considerable heterogeneity¹⁷.

PD- Parkinson's disease.

PDD- Parkinson's disease dementia.

MDS- Movement disorder society.

NPA- Neuropsychological assessment.

54.6% of the included studies had a moderate risk of bias (Supplementary Fig. 2).

3.3. Patient characterisation

In total, 54,107 patients with PD were included. Most of the studies included participants aged between 60 and 75 years (81.7%), more than 50% men (72.4%), with between 9 and 12 years of education (48.6%), a PD duration between 5 and 10 years (54.1%), and a H&Y stage between 2 and 3 (55.1%).

3.4. Dementia frequency

Of the 54,107 PD patients included in the meta-analysis, 12,262 were diagnosed with dementia (26.3%). We observed a high heterogeneity between the studies (higher than 75%) (Fig. 2).

3.5. Subgroup analysis

3.5.1. Methodological aspects and dementia frequency

When we analyzed dementia frequency according to the year of study publication, although not statistically significant, we observed that before 2008 ($N = 106$) dementia frequency was higher than after 2008 (29.0% vs 24.6%) (Fig. 2). In this period, the proportion of studies focused on other conditions and reporting dementia frequency as a secondary result was higher (45.3%), followed by studying PDD (39.6%). They mainly used DSM-III/IV criteria (67.0%) and screening scales to assess cognition (56.6%) (Supplementary Table 1).

After 2008 ($N = 189$), more studies reported dementia frequency, but their focus had changed. The primary objective that prevailed was to study cognitive functioning (37.6%). The same was observed with the methodology used to diagnose dementia and to assess cognition. MDS Level II criteria and full NPA were the most used (33.3% and 49.7% respectively).

When we analyzed dementia frequency according to study design, we observed a variation between 17.7% and 28.3%. Cross-sectional studies had the higher values (28.3%, $p = 0.005$) (Fig. 2).

Although confirmed PD diagnosis and PD without cognitive impairment prevailed as inclusion criteria across all the study design categories, we observed high heterogeneity in the inclusion criteria. The cross-sectional category had more studies with advanced/late-stage PD, PD patients in nursing homes, and cognitive complaints as inclusion criteria than the cohort and case-control categories (15.6% vs 13.2%, and 0%, respectively).

Considering the follow-up length, dementia frequency varied between 13.7% and 55.4%. We observed a global trend of increased frequency of dementia with increased study follow-up length, mainly with a follow-up length between 7 and 10 years (7–10 years, $p = 0.006$; 10–15 years and higher than 15 years, $p < 0.001$).

When we analyzed dementia frequency according to the study's primary objective, we observed a variation between 19.4% and 32.2%. It was higher when the primary objective was to study PDD (32.2%, $p < 0.001$).

Regardless of the focus, the studies were mainly cohorts (Supplementary Table 1). The follow-up length that prevailed was similar in the studies that primarily studied PDD or cognition (between 2 and 5 years, 52.4% and 43.1%, respectively).

In the studies whose primary objective was to study PDD, the most used dementia diagnosis criteria were the DSM-III/IV (50.9%), with screening scales (47.2%), and NPA (46.2%) used to assess cognition.

The distribution of the age of the PD patients was similar regardless of the study focus (to study dementia, cognition, or other issues). The same applied to PD duration and H&Y stage distribution. Most participants were between 60 and 75 years old (80.2%, 85.9%, and 79.8%, for each study focus, respectively), had had PD for between 5 and 10 years (56.1%, 59.4%, and 47.6%, respectively), and were in the advanced

H&Y stage (between 2 and 3) (57.1%, 56.9%, and 52.1%, respectively).

Inclusion criteria, although highly heterogeneous, were similar regardless of the study focus. Most had PD diagnosis and no cognitive impairment as inclusion criteria.

By analyzing dementia frequency according to the criteria used to diagnose PDD, we observed a variation between 20.8% and 31.4%. Although not statistically significant, higher results were observed when DSM-III/IV criteria were used (Fig. 2).

Similar results were found when we analyzed dementia frequency according to the methodology used to assess cognition. It varied between 23.1% and 29.8%. Once more, this was not statistically significant, higher results were observed when screening scales were used.

The studies that most used the DSM-III/IV criteria to diagnose PDD and screening scales to assess cognition were the studies in which participants were PD patients aged between 60 and 75 years (74.3% and 77.7%, respectively) or more than 75 years (19.5% and 19.2%, respectively), with more than 5 years of PD duration (89% and 80.9%, respectively), and in the advanced (64% and 54.1%, respectively) and late stages (22.7% and 26.5%, respectively) of PD.

We observed, in general, that with increasing age, PD duration, and H&Y stage, there was an increased tendency to use brief methodologies to diagnose PDD (e.g., MDS Level I, DSM-III/IV, screening scales cut-offs, and clinical assessment without NPA) and screening scales to assess cognition.

3.5.2. The clinical and demographic aspects and dementia frequency

With regards to dementia frequency according to the H&Y stages, we observed a variation between 19.8% and 45.9%. The frequency was higher in the late disease stage ($p < 0.001$) (Fig. 3).

Considering the criteria used to diagnose dementia, we found that in those studies that included participants in the early disease stages, although not statistically significant, higher frequencies of dementia were observed with MDS Level I criteria (33.3%) and when screening scales were used to assess cognition (25.6%) (Supplementary Table 2).

In those studies that had participants mainly in the advanced and late stages, higher dementia frequencies were observed when NPA criteria were used (33.3%, without statistical significance and 54.6%, $p = 0.011$ respectively), with full NPA to assess cognition (24.8%, without statistical significance and 50.4%, $p < 0.001$, respectively).

In the early H&Y stages, the most used dementia diagnosis criteria were MDS Level II, with full NPA (44.0% and 56.0%, respectively), while in studies that had participants in the advanced and late stages the most used criteria were the DSM-III/IV, with screening scales (47.1% and 51.5%, and 52% and 78.8%, respectively) (Supplementary Table 1).

Regardless of the H&Y stage, participants had a similar age distribution (mainly between 60 and 75 years old) (95.8%, 87.1%, and 59.4% in the early, advanced, and late stages, respectively), a similar level of education (mainly between 9 and 12 years) (56.7%, 40.0%, and 40.0%, respectively) and PD duration (mainly between 5 and 10 years) (50.0%, 66.3%, and 39.3%, respectively). However, in the early-stage subgroup, there were more participants in the categories with less than 5 years of PD duration (47.7%). In the late-stage category, participants were more distributed between the older categories ($>60 < 75$ and ≥ 75 years old, 59.4%, and 34.4%, respectively) and were more present in the categories with more than 10 years of PD duration (60.7%).

We observed a trend of an increased number of women with the increase of H&Y stages. In the early stages, 12.8% of the studies had more women participants ($\leq 50\%$ men percent category), in the advanced stages it was 34.8%, and in the late stages, 44.8%.

With regards to dementia frequency according to PD duration, we observed that dementia frequency increased in relation to PD duration and varied between 18.1% and 40.9%. The highest values were for patients who had PD for between 10 and 15 years (36.1%, $p \leq 0.001$) and more than 15 years of PD (40.9%, $p = 0.019$) (Fig. 3).

The same was observed when we analyzed dementia frequency according to age (between 23.4% and 43.4%). PD patients over 75 years

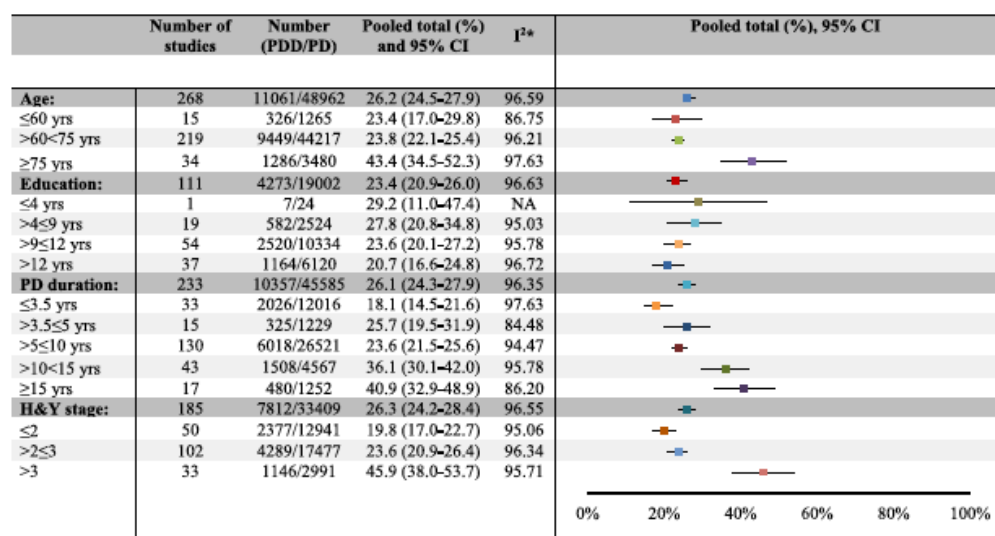


Fig. 3. Meta-analysis of dementia frequency by clinical and demographic subgroups.

* < 40% heterogeneity might not be important; >75% considerable heterogeneity¹⁷.

PD- Parkinson's disease.

PDD- Parkinson's disease dementia.

H&Y- Hoehn and Yahr.

old had the highest frequency of dementia ($p < 0.001$).

Most studies had a greater percentage of women in the over 75 years old category than in the younger age categories (≤60 years old and between 60 and 75 years old) (53.3% vs. 16.7% and 25.4%, respectively).

Dementia frequency decreased with increasing education levels, varying between 20.7% and 29.2%. Although not statistically significant, the higher values were observed in the lower levels of education (where patients had less than 4 years (29.2%) and between 4 and 9 years of education (27.8%)).

4. Discussion

The aim of this systematic review was to investigate the frequency of dementia in patients with PD. We also investigated which variables could help estimate this frequency, in this way we hope to contribute to the comprehension of dementia variability reported in the literature.

Of the 295 included studies, most were published after the publication of the MDS recommendations for diagnosing PDD. They were mainly cohort studies, with between two and five years of follow-up, and used the DSM-III/IV criteria with screening scales to diagnose PDD. Most studies included PD patients who were between 60 and 75 years old, patients were mainly men, with between 9 and 12 years of education, with a PD duration between 5 and 10 years, and in an advanced H&Y stage.

Despite the high heterogeneity that we already expected to find (higher than 75% [17]), due to the observational design of the studies, for exploratory purposes, we decided to proceed with a global and subgroup meta-analysis.

Of the included 54,107 PD patients, 12,262 were diagnosed with PDD (26.3%). This result is in accordance with the majority of previously published studies that found similar frequencies of PDD [20-24].

In the subgroup meta-analysis, we investigated dementia frequency according to the methodological, clinical, and demographic characteristics of the studies and participants.

Dementia frequency varied in all subgroups. However, the 95% CI, in some of the subgroups did not allow us to draw any conclusions, especially in the dementia criteria subgroup. Taking both this and the high heterogeneity of studies into consideration, the frequency of dementia reported according to the subgroups meta-analysis must only be interpreted qualitatively.

We observed higher dementia frequencies in studies published before 2008, in cross-sectional studies, when the primary objective was to study dementia, studies with a longer follow-up, and when DSM-III/IV criteria were used to diagnose PDD with screening scales to assess cognition. The same was observed in the clinical and sociodemographic variables. The meta-analysis revealed a rising frequency of dementia in relation to increasing age, PD duration, and H&Y stage, and with decreasing levels of education.

Before 2008, most studies focused on studying other conditions and reported dementia as a secondary result, using DSM-III/IV criteria and screening scales to assess cognition.

After 2008, the focus of studies changed. The primary objective that prevailed was to study cognition. The same occurred with the methodology used to diagnose dementia and assess cognition. MDS Level II criteria and full NPA were the most used tools.

The distribution of age (between 60 and 75 years old), level of education (between 9 and 12 years), PD duration (between 5 and 10 years), and H&Y stage (between 2 and 3) that prevailed were similar in both periods. However, before 2008, there were more PD patients in the older category, in the categories of higher PD duration (more than 10 years), and in the advanced and late-stage H&Y categories. This lead us to conclude that PD patients who participated in the studies before 2008 tended to be older and suffered from greater motor impairment. On the other hand, after 2008, PD patients were more evenly distributed between the categories of higher levels of education (>9 ≤ 12 and > 12 years). These results may explain why dementia frequency was higher before 2008.

The risk of bias analysis revealed that most studies had a moderate risk. With the sensitivity analysis that we performed by study quality, we

observed that dementia frequency tends to increase with the increasing risk of bias ($p = 0.005$). This result is in accordance with what we expected. According to Rosenthal (1991) [25], extracting data from published studies may bias results in favor of a significant effect, because studies with non-significant results are less likely to be published.

Analysis within each category of the subgroup of primary objectives revealed interesting information. Regardless of the primary objective, studies were mainly cohorts, with a follow-up length between 2 and 5 years in the studies that primarily investigated PDD or cognition. Curiously, inclusion criteria, although heterogeneous, were similar regardless of the study focus. Most had PD diagnosis and no cognitive impairment as inclusion criteria.

As they were mainly published after 2008, contrary to our expectations, the studies whose primary objective was to study PDD used DSM-III/IV criteria to diagnose dementia. Interestingly, the methodology used to assess cognition was distributed between screening scales and full NPA. In the same way, the studies that investigated PDD as a secondary objective also used the DSM-III/IV criteria to diagnose PDD, but mainly with screening scales to assess cognition.

The main clinical and demographic characteristics of PD patients were similar regardless of study focus (between 60 and 75 years old, with between 5 and 10 years of PD duration, and in a H&Y stage between 2 and 3). However, when we analyzed the second most frequent categories, we observed that studies that focused on PDD had more PD patients in the older age categories and with longer PD duration. The same was observed with studies that investigated PDD as a secondary objective, these also had more participants in the late-stage H&Y category. However, despite their similarities, the frequency of dementia was lower than the frequency found in studies that sought to study PDD. Methodological issues may explain these results. Abbreviated methodologies to assess cognition may produce false negatives in the late stages of PD. The fact that NPA used to assess cognition was more frequently used in the studies that primarily studied PDD, may have contributed to the reduction of false negatives and explain the higher dementia frequency found in this subgroup.

These results led us to contemplate the sensitivity of screening scales used to assess PDD. In the early stages of PD, when dysexecutive syndrome and attentional deficits are more common, it is possible that a brief methodology to diagnose dementia and assess cognition as the only diagnostic tool for PDD may lead to a significant proportion of misdiagnoses because of type I (false positives) diagnostic errors [26]. On the other hand, false positives can occur due to the interference of psychological variables such as mood disturbances (anxiety, depression) that may occur due to concern about the consequences and implications of PD and about how it will evolve and be managed [27]. Maintaining a positive attitude towards living with PD is a challenge for PD patients, especially in the early stages, due to the progressive losses that start in the initial phases [27–30]. In the late stages of PD, misdiagnoses can also occur but in a different manner. When PD patients are more educated and/or do not have memory deficits, the brief methodology may lead to a type II (false negatives) diagnostic errors [31]. False-positives and false negatives cases can bias the prevalence estimates and decrease the power of analytical estimates [32,33].

Disease severity is frequently reported as one important variable, which is associated with PDD [24,34,35]. As such, we decided to analyze how dementia frequency varies within each of the H&Y stage categories according to the different characteristics of the studies and PD patients.

As we expected, dementia frequency varied according to the H&Y stage. It was higher in the late stages. The same was observed depending on the criteria used to diagnose dementia and the methodology used to assess cognition. In the early stages, dementia frequency was higher when the MDS Level I criteria were used, with brief cognitive assessment. In the advanced and late stages, dementia frequency was higher when NPA criteria were used, with full cognitive assessment. Once again, these results confirm that, as mentioned above, possible misdiagnoses are associated with the methodology used to assess cognition

and depend on the PD stage of the patients.

Interestingly, in the early stages, MDS Level II criteria and full NPA to assess cognition were the most used. In the advanced and late stages, DSM-III/IV criteria and the screening scales prevailed. As we know, with increased disease severity, motor and non-motor symptoms also tend to increase, making cognitive assessment difficult. On the other hand, NPA is more time-consuming, which is a constraint especially in studies with larger samples. In our opinion, these were the reasons why we observed that as PD severity progresses, the tendency was to abbreviate the methodology to assess cognition.

We also observed that with an increasing H&Y stage, there was a tendency to increase the number of women among the participants. In the late stages, almost half of the studies included more than 50% of women in their participants. The literature describes the male sex as a predictor factor of PDD [8,36–38]. Having dementia a risk factor for mortality [39], we can hypothesize that men are diagnosed with dementia and die earlier, before reaching the late stages of the disease, being a women is a protective factor for late-stage PD.

The meta-regression analysis that we undertook revealed that methodological, clinical, and demographic variables were important for the estimation of dementia frequency. The definition of the study primary objective (to study PDD), the follow-up length (higher than 7 years), the age of the participants (mainly older than 75 years), PD duration (more than 10 years), and the H&Y stage (higher than 3) were important for dementia frequency.

Most of the studies did not report how or if they investigated vascular diseases and the presence of other comorbidities (i.e., Alzheimer's disease, Lewy-body dementia, etc.) that may contribute to dementia frequency. According to a recent systematic review [40], coexistent pathologies are common. Between one-fifth and one-third of PD cases had comorbid Alzheimer's disease. The differentiation of dementia type is important for clinical research, as treatments are specifically targeted against the different pathological substrates of the disease.

Our study has limitations. As we said above, the high heterogeneity between studies and the overlap of the 95% confidence intervals in most of our subgroup meta-analyses prevented us from drawing precise conclusions. As such, our results should be read with caution. This heterogeneity emphasizes the importance of standardizing methods used in future studies.

5. Conclusions

The overall estimated dementia frequency was 26.3%. However, this estimation varied according to the methodological, clinical and demographic variables of the studies and PD patients.

We can speculate that in the early stages of PD, with participants between 60 and 75 years old and between 5 and 10 years of PD duration, by using MDS Level II criteria and NPA to assess cognition, dementia frequency varies between 16% and 20%. In the advanced stages, also with participants between 60 and 75 years old but with between 10 and 15 years of PD duration, by using a similar methodology to diagnose dementia and assess cognition, dementia frequency varies between 20% and 30%. Finally, in the late stages, we can speculate that with participants over 75 years old and with more than 15 years of PD duration, dementia frequency may vary between 50% and 60%.

A study's primary objective, follow-up length, methodology to assess cognition, age, PD duration, and H&Y stage are important to this variability.

To assess dementia, we must consider methodological aspects like a clear definition of the main objective and inclusion criteria, diagnostic criteria, that must be actualized and adapted to the particularities of PD, and methodology to assess cognition, which must be based on a full cognitive assessment to avoid misdiagnoses. In the same way, increasing age, PD duration, and H&Y stage of PD patients tend to lead to higher dementia frequency. It is important to define at what stage of PD we want to assess dementia frequency and, according to this, define the

methodological aspects. We cannot compare dementia frequency in PD as a whole without considering all of these different study aspects because dementia frequency varies according to all these variables.

Funding

This work was supported by a Doctoral Fellowship from Fundação para a Ciência e Tecnologia, Portugal [SFRH/BD/139853/2018], which was assigned to Catarina Severiano e Sousa.

Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article.

Credit authorship contribution statement

Catarina Severiano e Sousa: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft; Joana Alarcão: Data curation, Resources, Writing – review & editing; Isabel Pavão Martins: Writing – review & editing; Joaquim J. Ferreira: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

Catarina Severiano e Sousa: no conflict of interest to report. No additional disclosures to report.

Joana Alarcão: no conflict of interest to report. No additional disclosures to report.

Isabel Pavão Martins: no conflict of interest to report. No additional disclosures to report.

Joaquim J. Ferreira: no conflict of interest to report. He has received grants from GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Novartis, Medtronic. He received consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion Pharmaceuticals, Zambon, Affiris. He has also participated in advisory boards for Bial and provided expert testimony to Novartis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2021.120077>.

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Cognitive testing in late-stage Parkinson's disease: A critical appraisal of available instruments

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To cite this article: Catarina Severiano e Sousa, Joana Alarcão, Isabel Pavão Martins & Joaquim J. Ferreira (2022): Cognitive testing in late-stage Parkinson's disease: A critical appraisal of available instruments, *Applied Neuropsychology: Adult*, DOI: [10.1080/23279095.2022.2114355](https://doi.org/10.1080/23279095.2022.2114355)

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Cognitive testing in late-stage Parkinson's disease: A critical appraisal of available instruments

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ABSTRACT

Objective: For patients with Parkinson's disease (PD), cognitive impairment is one of the most disabling non-motor symptoms, particularly in the late disease stages (LSPD). Without a common cognitive assessment battery, it is difficult to estimate its prevalence and limits comparisons across studies. In addition, some instruments traditionally used in PD may not be adequate for use in LSPD. We sought to identify instruments used to assess cognition in LSPD and to investigate their global characteristics and psychometric properties to recommend a cognitive battery for the LSPD population.

Method: We conducted a literature search of EMBASE and MEDLINE for articles reporting the use of cognitive tests in LSPD. The global characteristics and psychometric properties of the four most used cognitive tests in each cognitive domain were verified to recommend a cognitive assessment battery.

Results: Of 60 included studies, 71.7% used screening scales to assess cognition. Of the 53 reported instruments, the Montreal Cognitive Assessment, the Digit Span, the Trail Making Test, the Semantic Fluency test, the Rey Auditory Verbal Learning Test, the Brief Visuospatial Memory Test-Revised, the Boston Naming Test, the Judgment of Line Orientation, and the Clock Drawing Test corresponded best overall to the requirements considered important for selecting instruments in LSPD.

Conclusion: Screening scales are frequently used to assess cognition in LSPD. We recommend a cognitive assessment battery that considers the special characteristics of the LSPD population, including being quick and easy to use, with minimized motor demands, and covering all relevant cognitive domains.

KEYWORDS

Cognitive assessment;
cognitive function; cognitive
tests; critical review;
neuropsychological tests;
Parkinson's disease

Introduction

Parkinson's disease (PD) is a complex progressive neurodegenerative disorder with a wide variety of clinical symptoms. Although motor symptoms classically define PD, non-motor symptoms (NMS) form an important part of the disease (Chaudhuri et al., 2006), mainly in the late disease stages.

Coelho and Ferreira (2012) proposed the term "late-stage" to describe PD patients who progressed in the severity of treatment-resistant motor and non-motor symptoms, are highly dependent on caregivers for activities of daily life (ADL), and require specialized medical care. According to these authors, the phenotype of PD changes considerably in a later stage, and the symptoms that contribute most to disability differ from those in early and advanced stages. Late-stage PD is a good clinical model to identify the symptoms that cause most disability and mortality, highlighting the

symptoms that should be targeted at an earlier stage of the disease.

Cognitive impairment is among the most common and severe and disabling NMS. Dementia, in particular, has been associated with increasing disability (Hely et al., 2005), mortality (Levy et al., 2002), and caregiver burden (Aarsland et al., 1999).

Estimates of the incidence of cognitive impairment in PD vary considerably. The different methodological characteristics of studies, as well as the different clinical and demographic characteristics of PD patients, likely contribute to this variability. Important methodological features that vary between studies include the tests used to assess cognition (screening scales versus comprehensive neuropsychological assessment) and the criteria for diagnosing Parkinson's disease dementia (PDD). Clinical and demographic features that vary between studies include disease duration and

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 Supplemental data for this article is available online at <https://doi.org/10.1080/23279095.2022.2114355>

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severity, as well as the age of the PD patients (Severiano E Sousa, Alarcão, et al., 2021).

Given the deleterious effects of cognitive impairment and the increasing emphasis on the cognitive features of PD, mainly in the late disease stages, there is a compelling need for a standardized approach to neuropsychological assessment in this population.

Indeed, patients with late-stage PD (LSPD) are a poorly studied population due to their typically severe motor and non-motor symptoms that often complicate cognitive assessment. Most studies of this population are neuropathological studies (Braak et al., 2005), assess cognition using cognitive screening tests (Coelho et al., 2015), or do not make a detailed description of cognitive performance (Reid et al., 2011).

The lack of a common core assessment battery limits comparisons across studies. In addition, some instruments traditionally used in PD may not be adequate for use in LSPD due to the particular characteristics of these patients (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for activities of daily living [ADL]) (Coelho & Ferreira, 2012).

It is of the utmost importance that a comprehensive neuropsychological assessment takes into account these special characteristics of the LSPD population, ideally including cognitive instruments validated in PD, preferably quick and easy to use and requires minimal use of paper and pencil. This is a major determinant to a better understanding of the pattern of cognitive impairment in LSPD, which is necessary to improve our understanding of the therapeutic and supportive strategies that must be implemented at earlier disease stages when they are more likely to be effective.

The primary objective of the present critical review was to identify which instruments have been used to assess cognition in LSPD. Secondary objectives were: (1) to verify the global characteristics of the most used cognitive instruments, including their psychometric properties, and (2) based on the most used cognitive instruments, to recommend a neuropsychological assessment (NPA) battery for use in the LSPD population, taking into account the global characteristics and the psychometric properties of the instruments for the PD population and the particular characteristics of LSPD patients cited above.

Materials and methods

This review did not require direct intervention or interaction with human subjects, nor was personal, private information identifiable, and was therefore exempt from institutional review. It was not registered in any international register platform of systematic reviews.

Eligibility criteria

We included original studies, published in English, French, or Spanish with no publication date restrictions, which reported cognitive tests used for the cognitive assessment of

patients with a confirmed PD diagnosis, in the late-stage of the disease (9) (patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or non-motor symptoms, with a Hoehn and Yahr scale (H&Y) score >3 (Goetz et al., 2004), and/or a Schwab and England scale (S&E) score <50% (Schwab & England, 1969) in the MED ON condition).

Information sources and search methods

We searched both EMBASE and MEDLINE databases, from their inception to May 2019, using a pre-defined search strategy (Supplementary Figure 1). The search strategy combined standardized subject terms and text words, with relevant Boolean operators implemented. Citation chaining was also conducted to ensure that no articles were overlooked.

Data extraction

One author (C.S.S.) assessed the titles and abstracts of retrieved publications to identify studies that met the inclusion criteria. The relevant studies for this critical appraisal were then reviewed in detail to determine suitability for inclusion.

The outcome of interest was the cognitive tests used in a population of LSPD patients.

A standard data collection form was created to extract data on the cognitive tests used. We grouped tests according to the respective cognitive demands as described in the studies.

We selected the four most used cognitive tests in each cognitive domain and verified their global characteristics, based on requirements considered important for cognitive testing and the selection of instruments (Bothe et al., 2010): (1) the instrument, on the whole, is accurate and sensitive to changes ranging from no cognitive impairment to mild cognitive impairment (MCI) in PD, (2) up-to-date normative data are available, (3) the instrument is included in the Movement Disorder Society (MDS) task force guidelines to diagnose PD-MCI (Litvan et al., 2012) or PDD (Dubois et al., 2007), (4) motor demands are minimized, (5) quick to use, and (6) covered all domains relevant for obtaining a diagnosis of MCI (Litvan et al., 2012) or PDD (Dubois et al., 2007) according to MDS criteria (attention, executive function, memory, language, and visuospatial functions).

To examine the accuracy of cognitive tests to discriminate PD-MCI patients from patients with PD without cognitive impairment (PD-noCI) we searched for the cutoff points, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and area under the receiver operating characteristic (ROC) curve with 95% confidence interval (AUC 95% CI) of the cognitive instruments.

Sensitivity and specificity refer to the proportion of individuals correctly classified as having or not having a particular symptom. The PPV refers to the probability of people with a positive test result actually having the condition of interest. The NPV refers to the probability of people with a

negative result not having the condition of interest. AUC is an effective way to summarize the overall diagnostic accuracy of one test. An AUC of 0.5 suggests no discrimination (i.e., inability to diagnose patients with or without the disease or condition based on the test), 0.7–0.8 is considered acceptable, 0.8–0.9 is considered excellent, and more than 0.9 is considered outstanding (Mandrekar, 2010; Mazancova et al., 2020). Whenever possible, we based our selection of instruments upon the maximum combined sensitivity and specificity (preferably based upon the commonly regarded acceptable values, 80 and 60%, respectively (Stolwyk et al., 2014) and AUC > 0.7).

Our recommendation for a battery of cognitive instruments took into account these requirements as well as the accuracy of the cognitive tests and the special characteristics of LSPD patients. In addition, to ensure translatability into clinical practice, we ensured that each of the cognitive instruments was widely used and available, easy and quick to administer while covering all relevant cognitive domains, requiring as little as possible the use of paper and pencil, preferably not timed (minimized motor demands), and possible to be used in the patient's home.

Additional information describing the methodological characteristics of the included studies and the clinical and demographic characteristics of the PD patients was collected and introduced in the standard data collection form:

1. Methodological data from the studies: *study design*; *study's primary objective* [(I) study PDD, (II) study cognitive functioning, which we classified as study cognition, and (III) other (i.e., studies which primarily investigated other conditions and reported dementia frequency as a secondary result)]; *follow-up length*; *dementia diagnosis criteria* [(I) MDS diagnostic procedures Level I (Dubois et al., 2007), (II) MDS Level II (Dubois et al., 2007), (III) DSM-III/IV (APA, 1980, 1994) (due to their similarities, we included ICD-9/10 criteria in this category), (IV) The best clinical judgment criteria with a comprehensive NPA and with a well-defined definition of cognitive impairment, were classified as "NPA criteria," (V) Screening scales criteria (screening scales cutoffs), (VI) The best clinical judgment criteria made by a single qualified clinician or through consensus by a team of clinicians, were classified as "Clinical assessment criteria," and (VII) the studies that failed to describe the criteria used were classified as "Not specified"]; *methodology used to assess cognition* [(I) screening scales, (II) comprehensive NPA, and (III) not specified (studies that failed to describe the cognitive tests used)]; *cognitive domains assessed*.
2. Demographic and clinical information on the LSPD patients: *PD duration*; *age*; *education*; *cognitive domains impaired*.

Data synthesis

We used descriptive statistics to characterize the number of studies using each cognitive test and the methodological,

clinical, and demographic information of the included studies. Variables were described through absolute and relative frequencies (%).

The descriptive statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL, USA).

Results

Search

The results of the literature search are summarized in Figure 1. Of the 3326 screened studies, 1261 were excluded following abstract screening, while 2005 were excluded following the full-text screening, resulting in 60 studies being included in our review. Study and patient characteristics are described in Supplementary Figure 2.

Frequency of use of cognitive assessment instruments

Forty-three (71.7%) studies assessed cognition exclusively with screening scales (global cognitive assessment). The remaining 17 (28.3%) proceeded with a neuropsychological assessment, the majority (15.0%) assessed four cognitive domains (Table 1).

We identified 53 different neuropsychological instruments that have been used to assess cognition in LSPD (Table 2).

The four most used cognitive tests to perform a global cognitive assessment (screening scales, used in 57 studies) were: the Mini-Mental State Examination (MMSE) (87.7%), the Clinical Dementia Rating (CDR) (8.8%), the Mattis Dementia Rating Scale (Mattis DRS) (7.0%), and the Montreal Cognitive Assessment (MoCA) (5.3%).

The four most used neuropsychological instruments assessing different cognitive domains were:

1. *Attention and Working Memory* (assessed in 12 studies)—Digit Span task of Wechsler Adult Intelligence Scales third edition (WAIS-III) (33.3%), Verbal Fluency (25.0%), Stroop Test (25.0%), and Trail Making Test (TMT) (25.0%);
2. *Executive Function* (assessed in 16 studies)—Verbal Fluency (50.0%), Stroop Test (31.3%), TMT (25.0%), and Digit Span task of WAIS-III (12.5%);
3. *Memory* (assessed in 16 studies)—Rey Auditory Verbal Learning Test (RAVLT) (43.8%), California Verbal Learning Test (CVLT) (12.5%), Benton Visual Retention Test (BVRT) (12.5%), and immediate recall of Rey Complex Figure Test (RCFT) (12.5%);
4. *Language* (assessed in 10 studies)—Boston Naming Test (BNT) (80.0%), Verbal Fluency (40.0%), and Western Aphasia Battery (10.0%);
5. *Visuospatial Function* (assessed in 13 studies)—Judgment of Line Orientation Test (JoLO) (23.1%), Visual Object and Space Perception Test (VOSP) (23.1%), Clock Drawing Test (CDT) (23.1%), and copy of RCFT (15.4%).

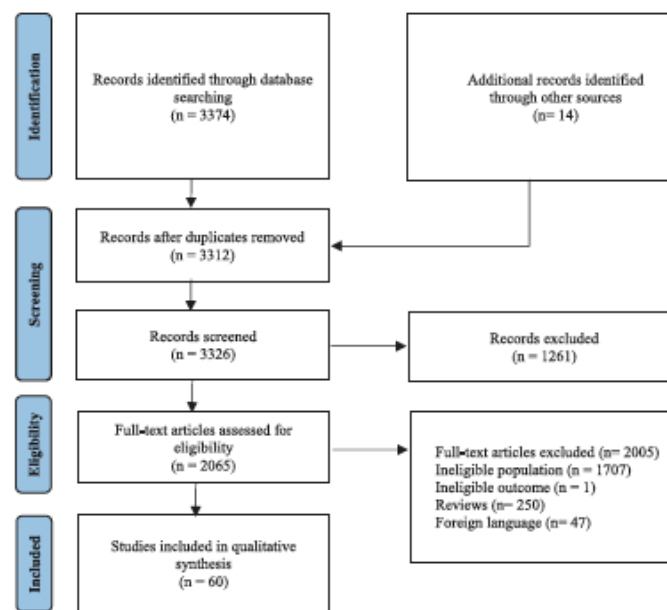


Figure 1. PRISMA review flowchart.

Table 1. Frequency of assessment of cognitive domains.

Assessed cognitive domains	Studies N (%)
Global cognitive assessment	43 (71.7)
2 Cognitive domains	1 (1.7)
Executive function, memory	1 (1.7)
3 Cognitive domains	3 (5.0)
Executive function, memory, visuospatial function	2 (3.3)
Memory, language, visuospatial function	1 (1.7)
4 Cognitive domains	9 (15.0)
Attention and working memory, executive function, memory, language	3 (5.0)
Attention and working memory, executive function, memory, visuospatial function	4 (6.7)
Attention and working memory, executive function, language, visuospatial function	1 (1.7)
Executive function, memory, language, visuospatial function	1 (1.7)
5 Cognitive domains	4 (6.7)
Attention and working memory, executive function, memory, language, visuospatial function	4 (6.7)

Global characteristics of cognitive assessment instruments

Of the four screening scales most used to perform a global cognitive assessment, the MoCA was the cognitive test that best corresponded to our aforementioned requirements (Table 3). The MoCA was the only test that had all the following characteristics: accurate and sensitive to changes in PD from no cognitive impairment to MCI, had available up-to-date normative data, was included in the MDS guidelines for diagnosing PD-MCI or PDD, was quick and easy to use while covering all relevant cognitive domains (attention and executive functions, memory, language, and visuospatial functions), required little motor demands, and could be used in the patient's home.

Of the four neuropsychological instruments most used to assess different cognitive domains, we observed that

attention and working memory, and executive function were assessed more frequently with the same instruments. As such, we grouped them in a single domain. The Digit Span Backwards of WAIS-III, the TMT, and the Semantic Fluency test were the cognitive tests that globally best corresponded to the requirements considered important for the selection of the instruments (Table 3).

To assess memory, RAVLT was the only cognitive test that met all requirements. Visual episodic memory tests (BVRT and immediate recall of RCFT) appeared in the four cognitive tests most used to assess memory but did not meet our requirements. There is no available information about the assessment of accuracy and sensitivity to change of the BVRT in PD; the immediate recall of RCFT is not sensitive in distinguishing between no cognitive impairment and MCI. For language assessment, the BNT was the cognitive test that best met the requirements, while for

Table 2. Frequency of use of cognitive assessment instruments.

Cognitive assessment instruments	Studies N (%)
Global cognitive assessment (N = 57)	50 (87.7)
Mini-Mental State Examination (MMSE)	5 (8.8)
Clinical Dementia Rating (CDR)	4 (7.0)
Mattis Dementia Rating Scale (MDRS)	3 (5.3)
Montreal Cognitive Assessment (MoCA)	3 (5.3)
Scales for Outcome in Parkinson's Disease-Cognition (SCOPA-COG)	2 (3.5)
Frontal Assessment Battery (FAB)	1 (1.8)
Cognitive Abilities Screening Instrument (CASI)	1 (1.8)
Cambridge Cognitive Assessment (CAMCOG)	1 (1.8)
Addenbrooke's Cognitive Examination-Revised (ACE-R)	1 (1.8)
Milam Overall Dementia Assessment (MODA)	1 (1.8)
Verbal fluency (phonemic and semantic)	1 (1.8)
Brief informant interview to detect dementia (AD8)	1 (1.8)
Wechsler Adult Intelligence Scales (WAIS)	1 (1.8)
Attention and working memory (N = 12)	
Wechsler Adult Intelligence Scales 3rd edition (WAIS-III) Digit span (forward and backward)	4 (33.3)
Verbal fluency	3 (25.0)
Semantic fluency	3 (25.0)
Phonemic fluency	3 (25.0)
Stroop Test	3 (25.0)
Stroop Test (word reading)	3 (25.0)
Stroop Test (color naming)	3 (25.0)
Stroop Test (word-color interference)	2 (16.7)
Trail Making Test (TMT)	3 (25.0)
Part A	3 (25.0)
Part B	2 (16.7)
Map search	1 (8.3)
Digit ordering	1 (8.3)
Neuropsychological Test Battery Vienna (NTBV) (attention sub-scale)	1 (8.3)
Alters Konzentrations Test	1 (8.3)
Cerebral Insufficiency Test (symbol counting task)	1 (8.3)
Raven Progressive Matrices (RPM)	1 (8.3)
Austin-Maze Test	1 (8.3)
Wisconsin Card Sorting Test (WCST)	1 (8.3)
Symbol Digit Modalities Test (SDMT)	1 (8.3)
Paced auditory serial addition Test (PASAT)	1 (8.3)
Not specified	2 (16.7)
Executive function (N = 16)	
Verbal fluency	8 (50.0)
Phonemic fluency	8 (50.0)
Semantic fluency	6 (37.5)
Stroop Test	5 (31.3)
Stroop Test (word reading)	3 (18.8)
Stroop Test (color naming)	3 (18.8)
Stroop Test (word-color interference)	5 (31.3)
Trail Making Test (TMT)	4 (25.0)
Part A	3 (18.8)
Part B	4 (25.0)
Wechsler Adult Intelligence Scales 3rd edition (WAIS-III) Digit span (difference between forward and backward)	2 (12.5)
Austin-Maze Test	2 (12.5)
Wisconsin Card Sorting Test (WCST)	2 (12.5)
Controlled Oral Word Association Test (COWAT)	1 (6.3)
Category Switching	1 (6.3)
Neuropsychological Test Battery Vienna (NTBV) (executive functions sub-scale)	1 (6.3)
Cerebral Insufficiency Test (interference task)	1 (6.3)
Raven Progressive Matrices (RPM)	1 (6.3)
Wechsler Adult Intelligence Scales (WAIS) Similarities	1 (6.3)
Symbol Digit Modalities Test (SDMT)	1 (6.3)
Paced Auditory Serial Addition Test (PASAT)	1 (6.3)
Frontal Assessment Battery (FAB)	1 (6.3)
Not specified	2 (13.3)
Memory (N = 16)	
Visual episodic memory	
Benton Visual Retention Test (BVRT)	2 (12.5)
Rey Complex Figure Test (RCFT) (immediate recall)	2 (12.5)
Copy and Delayed Recall of Two Simple Figures (Massachusetts General Hospital of Boston)	1 (6.3)
Spatial memory	
Austin-Maze Test	1 (6.3)
Verbal episodic memory	
Rey Auditory Verbal Learning Test (RAVLT) (immediate recall, learning, delayed recall and recognition)	7 (43.8)
California Verbal Learning Test (CVLT) (immediate recall, learning, delayed recall and recognition)	2 (12.5)
Selective Reminding Test (SRT) (immediate recall, total recall, delayed recall and recognition)	1 (6.3)
Buschke Free and Cued Selective Reminding Test	1 (6.3)

(continued)

Table 2. Continued.

Cognitive assessment instruments	Studies N (%)
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory	1 (6.3)
Controlled Oral Word Association Test (COWAT)	1 (6.3)
Free and Cued Selective Reminding Test (immediate recall)	1 (6.3)
Wechsler Memory Scale (WMS)	1 (6.3)
Not specified	2 (12.5)
Language (N = 10)	
Boston Naming Test (BNT)	8 (80.0)
Verbal fluency	4 (40.0)
Phonemic fluency	4 (40.0)
Semantic fluency	3 (30.0)
Western Aphasia Battery (WAB)	1 (10.0)
Neuropsychological Test Battery Vienna (NTBV) (language sub-scale) (verbal fluency- phonemic and semantic, and Boston Naming Test)	1 (10.0)
Not specified	1 (10.0)
Visual function (N = 13)	
Visuospatial function	
Judgment of Line Orientation Test (JoLO)	3 (23.1)
Visual Object and Space Perception Test (VOSP)	3 (23.1)
Wechsler Block Design	2 (15.4)
Fragmented Letters	1 (7.7)
Copy of the Three-Loop Spiral	1 (7.7)
Hooper Visual Organization Test	1 (7.7)
Poppelreuter-Ghent Test	1 (7.7)
Visuoconstructive function	
Clock Drawing Test (CDT)	3 (23.1)
Visuoperceptive function	
Rey Complex Figure Test (RCFT) (copy)	2 (15.4)

visuospatial assessment the JoLO and the CDT were the best instruments (Table 3).

Recommendation of the cognitive instruments to be used in LSPD

Based on the global characteristics of the cognitive instruments and LSPD requirements, we recommend a battery of instruments for assessing all relevant cognitive domains. The recommended instruments had the best global characteristics and, cumulatively, minimized motor demands and were quick and easy to use: the MoCA Test for global cognitive assessment and visuospatial function (by using the copy of the cube subtest), the Digit Span Backwards of WAIS and the TMT (difference between parts B and A, to remove the speed element from the test evaluation) to assess attention and executive function, the Semantic Fluency test to assess attention and executive functions and language, the BNT to assess language, the JoLO to assess visuospatial function, and the CDT to assess attention and executive function and visuospatial function. To assess memory, we recommend the RAVLT. As visual episodic memory is an important memory demand and the most used cognitive tests did not meet the requirements, we suggest the BVMT-R (Table 4).

Discussion

The typical severe motor and non-motor LSPD patient's symptoms often complicate cognitive assessment. However, this is determinant to a better understanding of the pattern of cognitive impairment, which is necessary to improve our understanding of the therapeutic and supportive strategies that must be implemented at earlier disease stages when they are more likely to be effective. As such, the

recommendation of a suitable cognitive battery for this population is of utmost clinical interest.

This review aimed to identify the instruments most used to assess cognition in LSPD. We also investigated the global characteristics and the psychometric properties of the most used cognitive instruments to recommend an NPA battery that takes into account the special characteristics of the LSPD population (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL).

We identified 53 different instruments that have been used to assess cognition in LSPD.

Most of the studies assessed LSPD patients' cognition with screening scales, namely with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Mattis Dementia Rating Scale (Mattis DRS), and Montreal Cognitive Assessment (MoCA).

In the studies that used a comprehensive NPA, we grouped the instruments assessing different cognitive domains according to their respective cognitive demands as described in the studies. Interestingly, we observed that the four cognitive tests most used to assess attention, working memory, and executive function were the same (Digit Span task of Wechsler Adult Intelligence Scales third edition (WAIS-III), Stroop Test, Trail Making Test (TMT), and Verbal Fluency).

For assessing memory, the Rey Auditory Verbal Learning Test (RAVLT), the California Verbal Learning Test (CVLT), the Benton Visual Retention Test (BVRT), and the immediate recall of Rey Complex Figure Test (RCFT) were the most used. The language was most frequently assessed with the Boston Naming Test (BNT), Verbal Fluency, and the Western Aphasia Battery, and visuospatial functions were most frequently assessed with the Judgment of Line

Table 3. Global characteristics and psychometric properties of cognitive tests.

Cognitive assessment scales	Accurate for detecting PD-MCI	Available up-to-date normative data	Minimized motor demands	Suggested by MDS in PD-MCI ^a or PDD ^b diagnostic procedures	Recommended cutoff scores and performance of instruments					
					PD population					
					Cutoff score (for MCI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (CI 95%)
Global cognitive assessment										
MMSE	Yes	Yes	Yes	Yes	29/30 ^d	94	45	59	91	0.7 (0.53–0.87)
CDR (sum of boxes)	No	Yes	Yes	No	1–4 ^d	71	82	Na	Na	0.5 (0.43–0.54)
Mattis DRS	Yes	Yes	No	Yes	137/138 ^c	72	86	81	79	0.8 (0.69–0.96)
MoCA	Yes	Yes	Yes	Yes	26/27 ^a	83	53	Na	Na	0.7 (0.64–0.85)
Attention and executive function										
WAIS-III Digit span										
Forward	No	Yes	Yes	Yes	Na ^{af}	Na ^a	Na ^a	Na ^a	Na ^a	Na ^a
Backward	Yes	Yes	Yes	Yes	<4 ^f	85	44	39	87	0.7 (0.60–0.80)
Stroop Test										
Words	Yes	Yes	No	Yes	15/16 ^g	84	60	68	79	0.8 (0.69–0.88)
Color	Yes	Yes	No	Yes	12/13 ^g	87	58	67	81	0.8 (0.69–0.88)
Word-color	Yes	Yes	No	Yes	27/28 ^g	82	53	64	75	0.8 (0.68–0.87)
Errors	Yes	Yes	No	Yes	0/1 ^g	80	58	65	74	0.8 (0.68–0.87)
Interference	Yes	Yes	Yes	Yes	1.9/2.0 ^g	82	38	57	68	0.7 (0.55–0.77)
TMT										
Part A	Yes	Yes	No	Yes	>33 ^f	74	69	51	86	0.7 (0.61–0.81)
Part B	Yes	Yes	No	Yes	>16 ^f	68	93	85	82	0.8 (0.70–0.87)
Part (B-A)	Yes	Yes	Yes	Yes	>9 ^f	68	91	76	87	0.8 (0.69–0.87)
Verbal fluency										
Semantic fluency	Yes	Yes	No	Yes	<44 ^f	74	53	40	82	0.7 (0.55–0.75)
Phonemic fluency	No	Yes	No	Yes	<32 ^f	56	69	44	79	0.6 (0.53–0.74)
Memory										
Benton Visual Retention Test	Na ^a	Yes	No	No	NA	NA	NA	NA	NA	NA
Rey Complex Figure Test (immediate recall)	No	Yes	No	No	Na ^{af}	Na ^a	Na ^a	Na ^a	Na ^a	Na ^a
RAVLT										
Immediate Recall	Yes	Yes	Yes	Yes	<40.3 ^f	68	78	57	85	0.7 (0.62–0.82)
Delayed Recall	Yes	Yes	Yes	Yes	<8.9 ^f	74	64	46	85	0.7 (0.57–0.77)
California Verbal Learning Test										
Immediate recall	Na ^a	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Learning	Na ^a	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Delayed recall	Na ^a	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Recognition	Na ^a	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Language										
Boston Naming Test (short version)	Yes	Yes	Yes	Yes	26 ^b	67	89	88	70	0.8 (0.61–0.92)
Verbal fluency										
Phonemic fluency	No	Yes	No	No ^{**}	<32 ^f	56	69	44	79	0.6 (0.53–0.74)
Semantic fluency	Yes	Yes	No	No ^{**}	<44 ^f	74	53	40	82	0.7 (0.55–0.75)
Western Aphasia Battery	Na ^a	Yes	No	No	NA	NA	NA	NA	NA	NA
Visuospatial function										
JoLO	Yes	Yes	Yes	Yes	22/23 ⁱ	59	78	73	66	0.7 (0.59–0.83)
VOSP	Na ^a	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Clock Drawing Test (10-point score)	Yes	Yes	No	Yes ^h	8/9 ^j	78	74	94	41	0.9 (Na)
Rey Complex Figure Test (copy)	Yes	Yes	No	No	<29 ^f	59	96	87	85	0.8 (0.67–0.85)

MDS: Movement Disorder Society; PD-MCI: Parkinson's Disease Mild Cognitive Impairment; PDD: Parkinson's Disease Dementia; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC (CI 95%): area under the receiver operating characteristic (ROC) curve with 95% confidence interval; NA: not applicable; Na: not available; Na^a: not available: no differences were found between PD patients without cognitive impairment vs. PD-MCI patients (Biundo et al., 2013); Na^{af}: not available (there is no available information about the assessment of accuracy and sensitivity to change in PD); MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating; Mattis DRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment; WAIS-III: Wechsler Adult Intelligence Scale-3rd edition; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Test; JoLO: Judgment of Line Orientation Test; VOSP: Visual Object and Space Perception Test.

^{**}This test is recommended to assess another cognitive domain.

^aCopying version.

^bUitvan et al. (2012).

^cDubois et al. (2007).

^dVilleneuve et al. (2011).

^eWyman-Chick and Scott (2015).

^fHoops et al. (2009).

^gBiundo et al. (2013).

^hBezdzicek et al. (2015).

ⁱBezdzicek, Sulc, et al. (2017).

^jBezdzicek, Nikolai, et al. (2017).

^kLolkha et al. (2021).

Table 4. Recommendation of cognitive domains to be assessed in LSPD and the respective cognitive instruments.

	Global cognitive assessment	Attention and executive functions	Memory	Language	Visuospatial functions
MoCA Test	X				X*
WAIS Digit Span Backward		X			
TMT (Part B-A)		X			
Semantic fluency		X		X	
RAVLT			X		
BVMT-R			X		X
BNT (short version)				X	
JoLO					X
CDT (10-point score)*		X			X

MoCA: Montreal Cognitive Assessment; WAIS: Wechsler Adult Intelligence Scale; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; BNT: Boston naming Test; JoLO: Judgment of Line Orientation Test; CDT: Clock drawing Test.

*Copy of the cube.

*Sunderland et al. (1989).

Orientation Test (JoLO), the Visual Object and Space Perception Test (VOSP), the Clock Drawing Test (CDT), and the copy of RCFT.

As we expected, we observed that different cognitive tests can vary considerably in terms of their cognitive demands, although it is clear that no human neuropsychological test is uniquely associated with damage to a specific brain region (Williams-Gray et al., 2007).

Based on the global characteristics and the psychometric properties of the most used cognitive instruments (accurate and sensitive for the changes from no cognitive impairment to MCI in PD, available up-to-date normative data, suggested by MDS for diagnosing PD-MCI or PDD, minimized motor demands, quick and easy to use, all domains relevant for PD-MCI or PDD diagnosis are considered, sensitivity and specificity preferably higher than 80 and 60%, respectively, and $AUC > 0.7$), we recommended an NPA battery to diagnose PD-MCI and PDD, that took into account the special characteristics of the LSPD population. Whereas MDS-MCI and PDD criteria are internationally accepted criteria, with high discriminative validity in the detection of PD-MCI (Bezdzicek, Nikolai, et al., 2017; Bezdzicek, Sulc, et al., 2017), we considered it important to standardize the methodology used to assess cognition in PD to reduce the variability in the frequency of cognitive impairment attributed to methodological aspects. As is recommended in these criteria, we also ensured that each of the cognitive domains was assessed with at least two cognitive instruments to address all cognitive domains equally, increase sensitivity and specificity, and allow full subtyping of PD-MCI. According to Goldman et al. (2015), a neuropsychological battery with two tests per domain provides a practical, efficient, sensitive, and robust approach to diagnosing cognitive impairment in PD.

Of the four cognitive tests most used to perform a global cognitive assessment, MoCA was the cognitive test that globally best corresponded to the requirements considered important for the selection of the instruments. MoCA has adequate psychometric properties as a screening instrument for the detection of MCI or dementia in PD (Hoops et al., 2009; Mazancova et al., 2020), is quick and easy to use, and covers all significant cognitive domains that need to be assessed in PD, contrarily to the MMSE that is incomplete in covering cognitive domains, and the Mattis DRS that is

too long to be appropriate for use as a screening test in LSPD population.

Although most of the studies assessed LSPD patients' cognition with screening scales, these are known to have several limitations. According to some authors (Di Battista et al., 2011), a screening methodology that is the only cognitive tool used to assess cognition may lead to a significant proportion of misdiagnoses. In LSPD, misdiagnoses can occur when PD patients are more educated and/or do not have memory deficits. In these cases, the screening methodology may lead to type II (false negatives) diagnostic errors (Severiano E Sousa, Fabbri, et al., 2021). False negative cases can bias the prevalence estimates and decrease the power of analytical estimates (Dalrymple-Alford et al., 2011; Rosca & Simu, 2020).

On the other hand, screening scales do not allow for an understanding of the pattern of LSPD cognitive impairment, which is of the utmost importance for improving our understanding of the therapeutic and supportive strategies that must be implemented at an earlier stage of the disease when they are more likely to be effective. Mattis DRS scale is an exception. Although it is internationally accepted and classified as a screening scale, with its five subscales it allows to better comprehend the pattern of cognitive impairment. However, it is too long to be used as a screening scale with LSPD patients and is incomplete to be used as a cognitive battery to perform a complete and comprehensive neuropsychological assessment.

The Digit Span Backward of WAIS, TMT (difference between part B and part A), and Semantic Fluency were the instruments that best corresponded to the requirements to assess attention and executive function. The Digit Span Backward and TMT are described as some of the instruments with the best discrimination diagnostic power to diagnose MCI in PD (Bezdzicek, Nikolai, et al., 2017; Bezdzicek, Sulc, et al., 2017; Biundo et al., 2013). Although the TMT motor demands are not minimized, this test allows us to remove the speed element from the test evaluation through a derived score obtained by the difference between parts B and A of the test (Cavaco et al., 2013). Semantic Fluency is one of the instruments most used to assess executive function, providing information about attention, short-term memory, initiation, mental flexibility, response inhibition, processing speed, and semantic memory (Lezak et al., 2012). It is described as an efficient and useful test that can

discriminate PD-MCI from no cognitive impairment (Bezdicsek, Nikolai, et al., 2017; Biundo et al., 2013).

For assessing memory, the RAVLT was the only cognitive test that corresponded to our requirements. The dissociation between the mediotemporal component (frequently impaired in Alzheimer's disease) and the subcortico-frontal component (frequently impaired in PDD) is of central importance in understanding the patterns of memory deficit found in different dementia syndromes (Dubois et al., 2007). The RAVLT is an episodic memory test that allows us to make conclusions about the impairment in these two memory demands (encoding and retrieval demands and the strategic aspects involved in these encoding and retrieval demands) (Dubois et al., 2007). According to some authors (Bezdicsek, Sulc, et al., 2017; Biundo et al., 2013), the RAVLT is among the tests that have proven high discriminative validity in PD-MCI. In late-stage PD, memory is a cognitive domain frequently impaired. The RAVLT proved to be applicable to this population and allowed to analyze the patterns of their memory deficit, a fact that revealed very important to better characterize the LSPD patient's cognitive profile (Severiano E Sousa et al., 2022). Visual episodic memory also appeared as a memory demand frequently assessed in the reviewed studies. However, the cognitive tests most used to assess this cognitive feature did not meet our requirements. As such, we propose the inclusion of the Brief Visuospatial Memory Test-Revised (BVM-T-R). It is proposed by the MDS guidelines to diagnose MCI. According to Litvan et al. (2012), most visual memory tests are less appropriate for PD-MCI diagnosis because they require motor responses or evaluate other memory demands less sensitive to memory decline. BVM-T-R is an exception because, with its copy condition, it allows for the assessment of the motor component (Benedict, 1997). This optional copy trial allows clinicians to identify visuoconstructional difficulties that may impact BVM-T-R performance, and may also be important to consider the impact of slower processing speed on BVM-T-R learning and memory performance (Tam & Schmitter-Edgecombe, 2013).

The Boston Naming Test (short version) was the cognitive test that best corresponded to the requirements to assess language. It is an instrument widely used, easy to administer, is generally well accepted by patients, and had high discriminative validity in PD-MCI (Bezdicsek, Sulc, et al., 2017; Goldman et al., 2015). To complement the language assessment, we proposed the use of the Semantic Fluency test which, in an ecological view (more information with less resources), in addition to evaluating executive functions, allows us to understand the fluency and organization of verbal language (Lezak et al., 2012).

Lastly, to assess visuospatial functions, the JoLO and the CDT were the instruments that best corresponded to our requirements. The CDT is a quick and economic cognitive test, initially developed to detect frontoparietal deficits, which rely primarily on executive function and visuospatial abilities (Freedman et al., 1994). Therefore, CDT completion requires several cognitive domains, including comprehension, motor programming, abstraction, attention, and

concentration (Freedman et al., 1994; Ismail et al., 2010), which for a multidomain ecological cognitive assessment is very important. As there is no international consensus about the scoring methods that must be used, we propose the 10-point Sunderland (Sunderland et al., 1989) scoring system because is efficient in detecting PD-MCI (Lolekha et al., 2021) and is the scoring system recommended by Dubois et al. (2007) in the diagnostic procedures for PDD diagnosis.

The recommended cognitive instruments battery is not a fixed test battery. It contains a small easy-to-administer core battery of widely available cognitive tests that, in our opinion, can be adjusted by adding or subtracting cognitive instruments, depending upon the goals of the cognitive assessment (research or clinical practice), patient and caregiver concerns, and the patient's ability to cooperate with or complete given tests (Fields & Troster, 2013). Importantly, it is a battery that despite not being validated particularly for this population, it has been utilized and has proven to be possible to use with most LSPD patients (Severiano E Sousa, Fabbri, et al., 2021).

The test selection should consider the LSPD patient's cognitive, emotional, motor, and sensory capacities to cooperate with evaluation (Marras et al., 2014). In PD, one often requires cognitive tests that minimize confounding motor demands. In this late stage of PD, when patients are often at an advanced age, with treatment-resistant motor and non-motor symptoms, the motor fluctuations, neuropsychiatric symptoms, and fatigability must be considered when deciding on the test battery. According to Marras et al. (2014), an interview of the caregiver can be useful to ascertain the timing of motor fluctuations and define the best time of day to proceed with the cognitive assessment, which should be when the patients are less likely to be affected by motor and non-motor symptoms, while on their antiparkinsonian medications.

In addition, observations made during testing are critical when utilizing a process approach to assessment that seeks to elucidate the cognitive mechanisms underlying test success and failure (Kaplan, 1988). It is important to know, especially in timed tests, such as the Semantic Fluency test, if the eventual low scores are due to executive function or language impairment or are due, for example, to speech and voice disabilities, like dysarthria, a frequent treatment-resistant motor symptom in LSPD (Fabbri et al., 2017), that may compromise verbal fluency.

In these worst cases, when severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) makes NPA impossible, we consider it important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients, to avoid underestimating this important non-motor symptom.

Our study has limitations. Although the battery we recommend has been applied and has demonstrated to be feasible to use with most LSPD patients, there is no data on their psychometric properties, and it has not been validated particularly for this population, a fact that should be considered for future studies. Additionally, although it was not our objective, it would have been of interest to assess the

frequency of use of neuropsychiatric instruments to assess mood and behavioral symptoms (depression, apathy, hallucinations, and delusions). They are frequent in LSPD (Coelho et al., 2015; Fabbri et al., 2020), may impact cognition, and according to some authors (Barton et al., 2012; Dujardin et al., 2009), may be considered to be characteristics that support a diagnosis of PDD. In the same way, it would also have been important to verify the frequency of use of instruments to assess functionality related to cognition. Understanding the impact of cognitive deficits on the patient's ability to implement instrumental ADL is important not only for differentiating MCI from PDD (Dubois et al., 2007; Litvan et al., 2012) but also for informing treatment decisions if one wants to directly intervene to treat impairments that have an impact on ADL from the patient's and caregiver's point of view (Marras et al., 2014). Finally, it would also have been of interest to verify if the studies mentioned in which condition the patients were evaluated (on or off their antiparkinsonian medications).

Conclusion

Of the 60 included studies, we identified 53 different instruments to assess cognition in LSPD.

The MoCA to assess global cognitive assessment, the Digit Span Backwards of WAIS and the TMT to assess attention and executive function, the Semantic Fluency test to assess attention and executive function and language, the RAVLT and BVMRT to assess memory, the BNT to assess language, the JoLO to assess visuospatial function, and the CDT to assess attention, and executive and visuospatial functions were the cognitive instruments that best corresponded globally to the requirements considered important for instrument selection.

We recommend an NPA battery that takes into account the special characteristics of the LSPD population (often at an advanced age, with treatment-resistant motor and non-motor symptoms, and highly dependent on caregivers for ADL), quick and easy to use while covering all relevant cognitive domains for obtaining a diagnosis of PD-MCI or PDD, requiring little use of paper and pencil, preferably not timed (minimized motor demands) and suitable for home use.

When severe physical/motor disabilities and severe neuropsychiatric symptoms (apathy, hallucinations, delusions) make NPA impossible, we considered it important to conduct a caregiver-based interview to make conclusions on cognitive impairment in LSPD patients and to avoid underestimating this important non-motor symptom.

Disclosure statement

Catarina Severiano e Sousa, Joana Alarcão, and Isabel Pavão Martins: no conflict of interest to report. No additional disclosures to report. Joaquim J. Ferreira: no conflict of interest to report. He has received grants from GlaxoSmithKline, Grünenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Novartis, Medtronic. He received consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie,

Sunovion Pharmaceuticals, Zambon, Affiris. He has also participated in advisory boards for Bial and provided expert testimony to Novartis.

Funding

This work was supported by a Doctoral Fellowship from Fundação para a Ciência e Tecnologia, Portugal [SFRH/BD/139853/2018], which was assigned to CSS.

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Clinical Diagnostic Criteria Have a High Impact on the Frequency of Dementia in Late-Stage Parkinson's Disease

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OPEN ACCESS

Edited by:

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Reviewed by:

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Specialty section:

This article was submitted to
Movement Disorders,
a section of the journal
Frontiers in Neurology

Received: 12 January 2021

Accepted: 21 April 2021

Published: 20 May 2021

Citation:

Severiano e Sousa C, Fabbri M,
Godinho C, Simões R, Chendo I,
Coelho M, Martins IP and Ferreira JJ
(2021) Clinical Diagnostic Criteria
Have a High Impact on the Frequency
of Dementia in Late-Stage Parkinson's
Disease. *Front. Neurol.* 12:652424.
doi: 10.3389/fneur.2021.652424

Background: Cognitive impairment is a potential late feature of Parkinson's disease (PD). However, studies in patients with late-stage PD are lacking due to the particular characteristics of this population.

Objectives: To evaluate the frequency of dementia in late-stage PD patients and to assess the impact of using different diagnostic criteria.

Methods: We conducted a cross-sectional study to estimate the frequency of dementia in late-stage PD patients using the International Parkinson and Movement Disorders Society (MDS) (Level II) clinical diagnostic criteria as the primary outcome. We also applied other diagnostic criteria [MDS (Level I), DSM-IV, and DSM-5 criteria] to determine their applicability and impact on dementia frequency.

Results: 93 participants with a mean age of 75.8 years (SD 6.8) and 16.5 years (SD 7.5) of disease duration were included. 64.3% were classified as demented using the International Parkinson and Movement Disorders Society (MDS) (Level II) clinical diagnostic criteria. We observed a high discrepancy on the frequency of dementia depending on the criteria applied [6.2% with MDS (Level I), 58.8% with DSM-IV, and 72.0% with DSM-5 criteria].

Conclusions: We found a frequency of dementia below what was observed in similar populations. The particular characteristics of our sample may have contributed as protective factors for late-stage dementia. Dementia frequency varied depending on the criteria used mainly due to the presence of major depression.

Keywords: Parkinson's disease, late-stage, dementia, cognitive impairment, diagnostic criteria

INTRODUCTION

Cognitive impairment is a late clinically feature of Parkinson's disease (PD). Dementia is a potential late-stage complication of PD, which may affect multiple cognitive domains (1) causing disability (2) and patient institutionalisation (3–6). However, there is no consensus on dementia frequency partly because the diagnostic criteria that have been used vary from the DSM-IV criteria with brief cognitive assessment (2, 7) to quantitative neuropsychological assessment (8, 9).

The International Parkinson and Movement Disorder Society (MDS) recommends clinical diagnostic criteria for "probable" and "possible" Parkinson's disease dementia (PDD) (10) and specific diagnostic procedures based on a two-level process, depending on the clinical scenario and evaluator expertise (11): Level (I) short algorithm to be used as a screening tool, with a checklist format; Level (II) a detailed neuropsychological assessment (NPA), with proposed cognitive tests that can confirm PDD, characterise its components, and facilitate the differential diagnosis between PDD and other diagnoses.

Although it is already well-accepted that MDS PDD Level II clinical criteria are the gold standard for PDD diagnosis, to our knowledge, there are no published studies on the dementia frequency by using updated PDD diagnostic criteria with late-stage PD patients (LSPD), which is a special population, often understudied due to its particular characteristics. As such, the current study was designed to evaluate the frequency of dementia and determine the applicability and impact of using different diagnostic criteria in LSPD.

MATERIALS AND METHODS

Recruitment

In this cross-sectional study, consecutive LSPD patients attending the Movement Disorders Unit of the University Hospital of Santa Maria (Lisbon) were recruited.

All participants and their formal/informal caregivers were informed about the study objectives and procedures and were asked for their written informed consent. The informed consent of cognitively impaired patients was signed by the caregiver. The study was approved by the local ethics committee.

Inclusion/Exclusion Criteria

Inclusion criteria were (1) Idiopathic PD according to the UK Brain Bank criteria (12); (2) LSPD (2) [patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or non-motor symptoms, with a Hoehn and Yahr scale (H&Y) score >3 (13) and/or a Schwab and England scale (S&E) score $<50\%$ (14) in the MED ON condition] and (3) signed informed consent.

Exclusion criteria were (1) dementia before PD onset and (2) dementia within 1 year following PD diagnosis.

Outcomes

Primary Outcome

The frequency of dementia was determined using MDS clinical criteria for "probable" and "possible" PDD, operationalized according to the Level II procedures outlined by Dubois

et al. (11) which were based on neuropsychological tests, functional autonomy as well as clinical interview. Briefly, involved the following: (1) PD; (2) PD before dementia; (3) decreased global cognitive efficiency evidenced by education-adjusted Mini-Mental State Exam [Portuguese cutoff: score <22 (0–2 yrs); <24 (3–6 yrs); <27 (≥ 7 yrs)]; (4) cognitive deficits that impact activities of daily life (ADL); (5) deficits in two or more cognitive domains documented by a detailed NPA; (6) the presence of at least one behavioural symptom (apathy, depressed mood, hallucinations, delusions, or excessive daytime sleepiness) supports the diagnosis of probable PDD; (7) the presence of any abnormality which may by itself cause significant cognitive impairment (e.g., delirium, relevant vascular disease) but judged not to be the cause of dementia makes the diagnosis uncertain and supports the diagnosis of possible PDD.

Secondary Outcomes

Frequency of dementia according to three other diagnostic criteria:

- 1) MDS PDD Level I (11) — Level I and Level II are broadly the same criteria but Level I has some particularities: (1) the methodology to assess cognition is brief and (2) the absence of major depression, *delirium*, and abnormalities that may obscure PDD diagnosis is mandatory to diagnose probable PDD. In the presence of these abnormalities, dementia is not excluded but we have to perform the Level II NPA to diagnose possible PDD.
- 2) DSM-IV criteria (15) — Although the DSM-5 is already published, which makes DSM-IV criteria no longer clinically relevant, we considered it important to use them because most of the previous studies used the DSM-IV criteria to diagnose PDD and we intended to perform a comparative analysis of the frequency of dementia with other studies that used similar samples.
- 3) DSM-5 criteria (16) — Briefly, these criteria required the following steps:
 - I Distinction between mild and major Neurocognitive Disorder (NCD). Major NCD corresponds to the diagnosis of dementia. Its main feature is the presence of a significant acquired cognitive decline, which may be documented by:
 - a. detailed NPA, considered as cognitive impairment performance values below 2 standard deviations (SD) on age-and-educated normative scores in one or more cognitive domains, or
 - b. brief but quantitative cognitive assessment.
 - II Identification of behavioural symptoms that support the diagnosis of PDD.
 - III Specification of the level of certainty of dementia diagnosis: major NCD probably due to PD vs. major NCD possibly due to PD. What distinguishes them is the presence of abnormalities that may obscure diagnosis.

We compared dementia frequency obtained through the two DSM-5 possible approaches (NPA vs. brief cognitive evaluation), also testing its applicability in LSPD.

Measures

Neurologic and Functional Assessment

Neurological assessment was performed by a neurologist with expertise in movement disorders and included the investigation of vascular problems. Disease severity and disability were assessed using H&Y (13) and S&E (14) scales, respectively.

Neuropsychiatric and Behavioural Assessment

The neuropsychiatric assessment was performed by the neurologist and included neuropsychiatric functions (behavioural symptoms and major depression). The neuropsychiatric inventory (17) (NPI) and the geriatric depression scale (18) (GDS) were used, respectively.

To diagnose *delirium*, we used the DSM-5 criteria (16) as the MDS criteria (11) omit the methodology that we were to use.

Neuropsychological Assessment

The NPA was performed by a neuropsychologist. It took place in a single session, at the patients' homes, in order to ensure the presence of the usual amenities, and to reduce as far as possible any interference, malaise, or interfering in the patients' lives.

A clinical interview was undertaken with caregiver collaboration to obtain the following information: (1) demographics; (2) educational history; (3) temporal relationship of PD diagnosis and the onset of cognitive complaints; (4) disease duration; (5) objective and subjective cognitive complaints; (6) pattern of PD and cognitive complaints progression; (7) impact of cognitive impairment on ADL; (8) history of abnormalities that may obscure the diagnosis (e.g., delirium, vascular or other neurological diseases); (9) current comorbidities.

To assess the impact of cognitive impairment on ADL, two approaches were taken: (1) patient and caregiver clinical interview, using a checklist with cognitive ADL tasks and, (2) the Pill Questionnaire, with the assumption that if the patient was able to manage his/her treatment in the past, the inability to describe one's own medication regimen was equivalent to an impairment in ADL (11). Whenever one of these sources of information was suggestive of dysfunction, the patient was classified as having impaired ADL.

To assess cognition using MDS PDD Level II criteria (11), we proceeded with NPA with a set of cognitive tests selected from their proposal (Table 1), according to the following criteria: (1) existence of normative data for the Portuguese population, (2) tests predictably less sensitive to PD manifestations, and (3) expected time consumed by the test (only one test for each cognitive task whose performance would have a shorter estimated duration, to ensure the minimum tiredness interference). We considered cognitive impairment performance values below 1 SD on age-and-educated-adjusted normative scores in two or more cognitive domains. We applied neuropsychological tests in the same order for all patients.

To assess cognition following MDS PDD Level I criteria (11), we used the proposed cognitive tests (Table 1), adapted to the Portuguese population.

To assess cognition according to the DSM-IV criteria (15), we used MMSE sub-scales (19) to assess memory, aphasia, agnosia and apraxia (retention and evocation,

language and construction sub-scales, respectively). To assess executive function, we used WAIS-III similarities sub-scale (28), MMSE attention and calculation sub-scale (19), phonologic fluency test (P, M, R letters) (24) and information collected in the clinical interview (impact of cognitive impairment on ADL such as the ability to plan daily activities).

For DSM-5 detailed NPA (16), we used the same tests selected from MDS PDD Level II (11) but we strictly followed the DSM-5 proposed cognitive domains organisation and cognitive impairment definition. As social cognition is a cognitive domain that is not included in the proposed MDS criteria, we followed the DSM-5 assessment methodology and, to guarantee the non-interference of poor insight, we assessed it during the clinical interview with the contribution of the caregiver. As the evaluation of this domain was qualitative, we considered as a reference for impairment the examples of major symptoms made available by the DSM-5.

For brief DSM-5 cognitive assessment (16), we used the MMSE (19) even though it is less effective in assessing global PD cognition. This decision was mainly due to two reasons: (1) the MMSE is commonly used due to its quick and ease of use and access and (2) the MMSE was proposed by the MDS PDD criteria (11) as a measure of global cognitive efficiency. As it is validated for the Portuguese population and there are several cutoff proposals, we decided to perform a comparative analysis with the cutoff that is the most used in clinical practise [adjusted for education (20), age and education (21), dementia diagnosis (22)].

Statistical Methods

Sample Size

Assuming an expected LSPD dementia frequency of ~50% (2), with a 95% confidence interval and an error level of ~10%, a sample of 100 patients was estimated necessary.

Statistical Analysis

Statistical analysis was performed using SPSS software version 26 (IBM SPSS, Chicago, IL).

We used descriptive statistics to characterise demographic and clinical information. Categorical variables were described through absolute and relative frequencies (%) and continuous variables through the mean value and standard deviation (SD).

The frequency of dementia was analysed using descriptive statistics. We presented the absolute and relative frequency (%) of LSPD dementia cases, according to the different criteria for dementia that we used.

The agreement analysis between our gold-standard and the other criteria for PDD was performed using Cohen's Kappa (>0.6 is significant) (40). We calculated sensitivity, specificity, positive predictive value, and negative predictive value for each PDD diagnostic criteria.

We considered a confidence interval of 95%.

TABLE 1 | Neuropsychological tests used to assess cognition according to MDS PDD Level I and Level II criteria.

Cognitive domains/tasks	MDS PDD Level I cognitive tests	MDS PDD Level II cognitive tests
Global efficiency	MMSE (19, 20)	MMSE (19–22)
Attention	Serial 3's of the MMSE (19)	
Executive functions	Phonologic fluency (P) (23, 24)	
Working memory		Digit span (25, 26)
Conceptualisation		Similarities (WAIS-III) (27, 28)
Set activation		Phonologic fluency (P, M, R) (23, 24)
Set shifting		TMT (A and B) (29, 30)
Set maintenance		Odd man out test (31)
Behavioural control		Prehension behaviour (FAB) (32, 33)
Memory	3-Word Recall of the MMSE (19)	RAVLT (34, 35)
Instrumental functions		
Language		Boston naming test (36)
Visuoconstructive	Drawing of the MMSE Pentagons (19)	Copy of the clock (37)
Visuospatial		Benton line orientation test (38)
Visuoperceptive		Benton face recognition test (39)

MDS PDD, Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force (11); MMSE, Mini-Mental State Exam; TMT (A and B), Trail Making Test A and B; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; FAB, Frontal Assessment Battery; RAVLT, Ray Auditory and Verbal Learning Test.

RESULTS

Patient Demographics and Clinical Characteristics

One hundred and twenty-one LSPD patients were initially recruited (Figure 1). Following motor assessment but before the proposed NPA, 12 patients died and 16 declined to participate in the NPA (13 patients refused to perform it and three were unable to due to the unavailability of the caregiver). A total of 93 LSPD patients agreed to perform the NPA. However, when patients were visited at home, the neuropsychologist found that it would not be possible to carry out the NPA of eight patients due to their physical/motor disability. Of these eight patients, we only collected information through the neurological and neuropsychiatric evaluation, and through the clinical history that we performed with the help of the caregiver (Table 2).

In total, 85 patients underwent complete NPA (Figure 1). Forty-nine (57.6%) were women, with a mean age of 75.4 years (SD 6.9), 6.5 years (SD 4.5) of education, 16.9 years (SD 7.5) of disease duration, age at PD onset (58.5 years; SD 10.9), a mean H&Y of 4.1 (SD 0.9) and loss of independence assessed by the S&E corresponding to 36.7% (SD 13.6) (Table 2).

Dementia Frequency According to MDS PDD Level II Criteria

Fifty-four (64.3%) patients met the criteria for PDD [27/36 men (75%), 27/49 women (55%)]; 47 (55.9%) were diagnosed with probable PDD and seven (8.3%) with possible PDD due to the abnormalities that made the diagnostic uncertain (3 LSPD had a stroke significantly before PD, three were submitted to undergo deep brain stimulation after PD and one had an oncological disease and was undergoing chemotherapy after the beginning of cognitive impairment). According to the caregiver, none of these abnormalities was associated with

the onset of worsening cognitive impairment. One patient had inconclusive PDD due to the interference of tiredness during NPA.

69.4% LSPD presented an MMSE score lower than the education cutoff. The mean score obtained was 21.6 (SD 6.1), with an interval ranging from eight to 30 points. 67.9% of LSPD had impaired cognition in two or more cognitive domains and 87.1% presented cognitive changes severe enough to impair ADL.

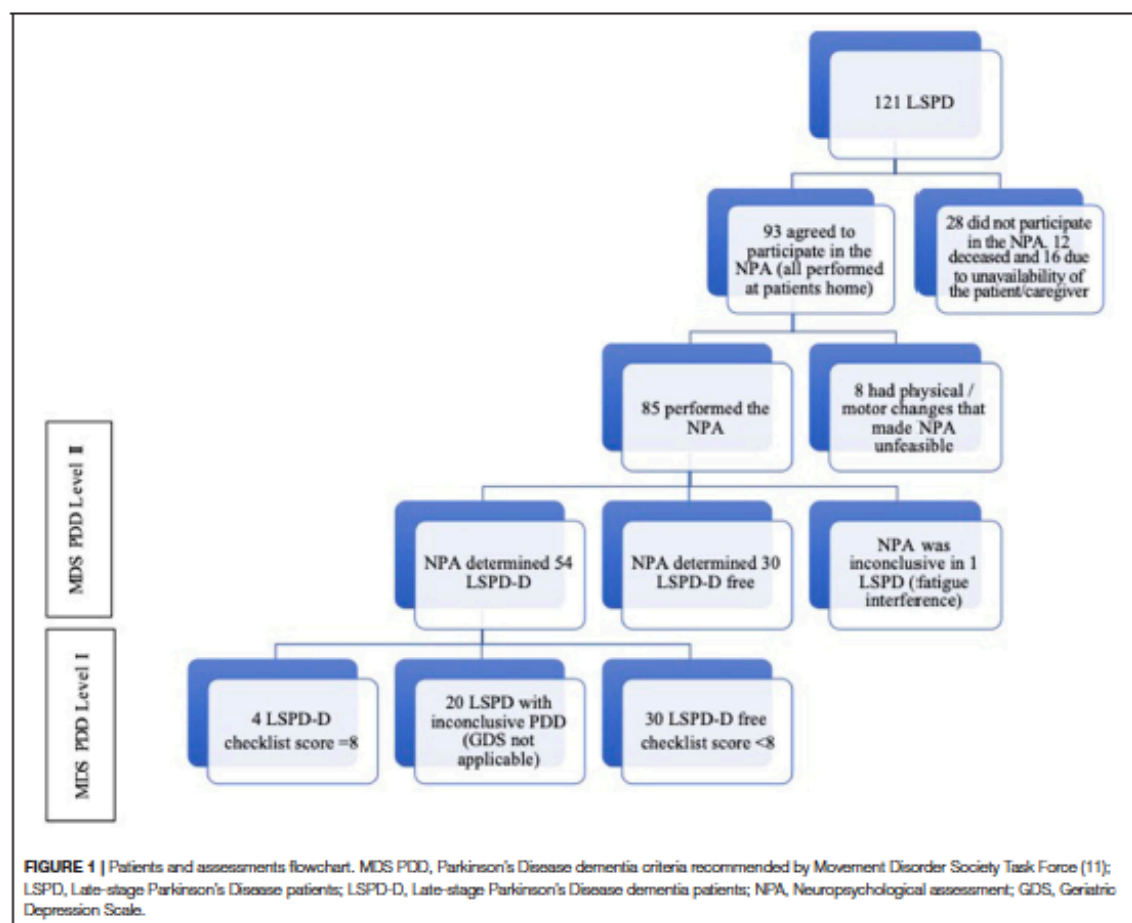
We observed at least one behavioural symptom with significant expression in 74.7% of LSPD (Table 3). The most common was depressive mood (57.8%), followed by apathy (51.8%), excessive daytime sleepiness (36.1%), hallucinations (25.3%), and delusions (18.1%).

Of the eight patients who could not undergo NPA, it was possible to confirm through the clinical history collected from the caregivers that before the worsening of the physical/motor impairment significant global cognitive impairment with impact on ADL had occurred, leading us to suspect the existence of PDD. They were older patients, less educated, and who, despite having fewer years of PD, had worse disease severity and dysfunction (Table 2).

If we were to consider them as having PDD, we would have observed a frequency of dementia of 67.4% (Table 4).

Dementia Frequency According to Three Other PDD Diagnostic Criteria

The frequency of dementia differed markedly according to the diagnostic criteria used. Dementia frequency rated by MDS Level I was consistently the lowest. Only 6.2% of the LSPD met all screening checklist clinical criteria to be diagnosed as probable PDD (Table 3). All patients identified by the screening checklist as having PDD were confirmed by Level II criteria



(100% specificity). However, Level II criteria identified more patients with PDD than the screening checklist (sensitivity 8.8%) (Table 5). Although 79.1% of LSPD presented impaired cognition in two or more cognitive domains and 87.1% of LSPD presented cognitive changes severe enough to impair ADL, we observed the absence of major depression that is mandatory for Level I PDD diagnosis only in 18.6% of LSPD. In the same way, 23.5% of LSPD had Level I PDD inconclusive due to comprehension difficulties that made GDS not applicable and impossible to conclude about the absence of major depression.

Although less markedly, we also observed discrepant results in dementia frequency between DSM-IV diagnostic criteria (58.8%) and Level II criteria (64.3%).

Using DSM-5 with full NPA criteria, once again, we observed discrepant results (72.0 vs. 64.3%). Three patients (3.5%) were given an inconclusive dementia diagnosis due to the interference

of tiredness which did not allow differential diagnosis between Mild Cognitive Impairment and PDD (Table 4).

When we used the DSM-5 criteria with MMSE, we observed results quite similar to Level II criteria (62.4% with education adjustment, 68.2% with age and education adjustment, and 60.0% with dementia adjustment vs. 64.3%, respectively).

When we analysed the agreement between Level II and DSM-5 criteria (Table 5), we observed the significant similarity seen in clinical practise. The DSM-5 was very sensitive in identifying demented LSPD, either through the use of the NPA (100%) or through the use of MMSE (adjusted for education 96.3%; age and education 100%; diagnosis of dementia 90.7%).

The specificity of the DSM-5 with MMSE adjusted for age and education (90.0%) and with NPA (82.1%) was lower than the specificity obtained with MMSE adjusted only for education and for the diagnosis of dementia because the first diagnosed more

TABLE 2 | Demographic and clinical characteristics of LSPD patients.

	LSPD (N = 85) Mean (SD)	LSPD (N = 8)* Mean (SD)	LSPD (N = 93) Mean (SD)
Gender (m/f)	36/49	4/4	40/53
Age (yrs)	75.4 (8.9)	80.3 (4.7)	75.8 (8.8)
Education (yrs)	6.5 (4.5)	3.1 (1.6)	6.4 (4.6)
Disease duration (yrs)	16.9 (7.5)	12.0 (6.5)	16.5 (7.5)
Age at onset (yrs)	58.5 (10.9)	68.3 (4.6)	59.1 (10.8)
Hoehn and Yahr stage (0/5)	4.1 (0.9)	5 (0)	4.2 (0.9)
Schwab and England (0/100%)	36.7 (13.6)	15.71 (7.9)	35.1 (14.3)
NPI delusions (0/12) (Cutoff ≥ 3)	1.3 (2.6)	0.3 (0.8)	1.3 (2.5)
NPI hallucinations (0/12) (Cutoff ≥ 3)	1.7 (2.7)	1.7 (1.9)	1.7 (2.7)
NPI depression (0/12) (Cutoff ≥ 3)	3.3 (2.4)	1.8 (2.0)	3.2 (2.4)
NPI apathy (0/12) (Cutoff ≥ 3)	3.6 (3.6)	3.8 (4.3)	3.6 (3.6)
NPI sleep disorders (0/12) (Cutoff ≥ 3)	2.5 (3.3)	1.0 (1.5)	2.4 (3.3)
Fill Questionnaire (0/3) (Cutoff ≥ 2)	2.2 (1.1)	3 (0)	2.3 (1.0)
GDS Score (0/30) (Cutoff 11–20: mild depression; 21–30: severe depression)	13.8 (8.8)	NA	NA
MMSE Score (0/30) (Cutoff: 0–2 yrs education-22 pt; 3–6 yrs education- 24 pt; ≥ 7 yrs education-27 pt)	21.6 (8.1)	NA	NA

LSPD, Late-stage Parkinson's Disease; NPI, Neuropsychiatric Inventory; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exam; NA, Not applicable due to physical/motor impairment.

*These 8 patients did not perform the neuropsychological assessment due to the physical and motor limitations they presented. This information was collected through the caregiver-based clinical interview that we performed.

dementia than the MDS Level II criteria, so they presented a higher number of false positives.

DISCUSSION

Our results conclude that by using MDS Level II (11) clinical diagnosis criteria, slightly more than half of the 85 LSPD (64.3%) meet dementia criteria. Considering the high frequency of dementia (80%) reported by Reid et al. (9) who studied a sample of PD with 20 years of disease, we expected to find similar results. When we compared the frequency of dementia that we obtained through the same diagnostic criteria used by Reid et al. (9), we observed a greater discrepancy (58.8 vs. 80%). We hypothesized that this discrepancy could be due in part to the fact that Reid et al. (9) diagnosed PDD using the DSM-IV criteria with full NPA to assess cognition, contrary to what we did in our study where we strictly followed the DSM-IV criteria using a brief cognitive assessment methodology mainly with MMSE subscales, which, as is well-known, is not the best methodology for assessing cognition in PD. However, our analysis of agreement between diagnosis criteria allowed us to conclude that the MMSE proved to be a reliable tool to diagnose dementia in LSPD. The discrepancy that we observed may have been due in part to the clinical and socio-demographic characteristics of our sample that should be noted.

Our participants had been living with PD for an average of 17 years, with an early age at PD onset (<60 years) and there was a higher proportion of women (58%) than expected based on gender prevalence of PD. Forsaa et al. (4) developed a long-term study about mortality and associated risk

factors in a population-based cohort with PD and found that approximately 70% of patients with a median survival from motor onset of 16 and 20 years after disease onset had died. They concluded that higher age at onset, male sex, and dementia were independent risk factors for mortality. Cholerton et al. (41) compared baseline cognitive, demographic, and clinical characteristics of participants who remained cognitively stable and those who progressed throughout follow-up in a large, well-characterized PD cohort and found that the primary predictive factor in the transition from no cognitive impairment to cognitive impairment was male sex. They also found that female participants progressed more slowly to cognitive impairment than male participants. We believe that ~64% of PDD we have identified through our gold standard may be due to this conjuncture of characteristics, namely the fact that about 58% of the participants were female. Of the 36 (42.4%) men who participated, 27 (75%) were diagnosed with PDD and of the 49 (57.6%) participating women, 27 (55%) obtained the same diagnosis, which corroborates the results found by Cholerton et al. (41) and may justify the fact that our population was mostly female. This may be another peculiarity of LSPD. It can be hypothesized that female gender may be a protective factor.

On the other hand, the participants had a level of education (mean of 6 years) that is not representative of the aged Portuguese population who is poorly educated. According to the National Institute of Statistics (Source: PORDATA), in 2019 only about 4.6% of the general population over 65 years had 6 years of schooling. The remaining 73% had no education or only up to 4 years of schooling and about 22.5% had nine or more years

TABLE 3 | Diagnostic rating sheet for Probable PDD recommended by the MDS Task Force.

LSPD (N = 85)	MDS PDD Level I	MDS PDD Level II
	Yes (%)	Yes (%)
1. Parkinson's disease	100	100
2. Parkinson's disease developed before dementia	100	100
3. MMSE** <22 (0-2 yrs education); <24 (3-6 yrs education); <27 (>7 yrs education)	69.4	69.4
4. Dementia has impact on ADLs	87.1	87.1
5. Impaired cognition (for yes, at least of 2 of 4 cognitive domains below are abnormal)	79.1	67.9
5 a) Attention	48.2	*
5 b) Executive Function	87.1	56.5
B1) Working memory	*	25.9
B2) Conceptualization	*	11.8
B3) Set activation	*	68.7
B4) Set shifting	*	85.9
B5) Set maintenance	*	55.2
B6) Behavioral control	*	30.1
5 c) Instrumental Functions	*	55.6
C1) Language	*	11.1
C2) Visuo-Constructive	65.5	60.8
C3) Visuo-Spatial	*	67.1
C4) Visuo-Perceptive	*	61.1
5 d) Memory	62.4	68.7
D1) Only medial temporal/hippocampal component	*	18.1
D2) Only subcortico-frontal component	*	15.7
D3) Both components	*	44.6
6. Absence of major depression	18.6	*
7. Absence of delirium	98.8	*
8. Absence of other abnormalities that obscure diagnosis	89.4	89.4
Behavioral symptoms (one of delusions, hallucinations, depression, excessive daytime sleepiness)	74.7	74.7
Probable PDD (items 1-8 must all be YES)	6.2	55.9***
Probable PDD Inconclusive	23.5	1.2
Possible PDD	0	8.3
Total Score (D/B) Mean (SD)	6.3 (1.0)	*

MDS PDD, Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force (11); PDD, Parkinson's Disease dementia; MMSE, Mini-Mental State Exam; ADLs, Activities of daily living.

*Not applicable in this Level. **We considered education-adjusted MMSE cutoff scores (Portuguese population). ***Items 6 and 7 not applicable for MDS PDD Level II.

of schooling. Considering that the results of cognitive tests were corrected in general for age and education based on the mean values obtained for the general aged Portuguese population, education may also have contributed to the lower frequency of dementia found.

As we expected, the frequency of dementia was partly dependent on the diagnostic criteria used. We found a significant discrepancy between the results obtained with the MDS PDD Level I and Level II criteria (11) (6.2 vs. 64.3%, respectively). The checklist proposed at Level I proved to be quite specific in identifying non-demented LSPD but very unresponsive in identifying demented LSPD. The agreement between the two diagnostic criteria was not significant. The

mandatory absence of major depression was largely responsible for different dementia frequency and for the lack of significant agreement among the two levels. Only 18.6% of the LSPD was not diagnosed with major depression and 23.5% had an inconclusive diagnosis due to their difficulty in understanding the GDS (18) items. These results are concordant with the results published by Barton et al. (42) who identified similar results.

When we used the DSM-5 criteria (16), we observed less discrepancy. The agreement analysis demonstrate a significant concordance between DSM-5 and Level II criteria. However, with the NPA, there was an increase in dementia frequency (72.0 vs. 64.3%, respectively). The lowest number of impaired cognitive

TABLE 4 | Dementia frequency according to different diagnostic criteria.

Diagnostic criteria	LSPD (N = 85) (%)	LSPD (N = 93)* (%)
MDS PDD Level I	6.2	16.4
Inconclusive (major depression not assessed - difficulty GDS items comprehension)	23.5	
MDS PDD Level II	64.3	67.4
Probable PDD	55.9	
Possible PDD	8.3	
Inconclusive (fatigue interference did not allow to confirm PDD diagnosis)	1.2	
DSM-IV	58.8	62.4
DSM-5		
With MMSE adjusted for education	62.4	65.6
Major NCD Probably due to PD with behavioural disturbance	48.2	
Major NCD Probably due to PD without behavioural disturbance	7.1	
Major NCD Possibly due to PD	7.1	
With MMSE adjusted for age and education	68.2	70.9
Major NCD Probably due to PD with behavioural disturbance	52.9	
Major NCD Probably due to PD without behavioural disturbance	8.2	
Major NCD Possibly due to PD	7.1	
With MMSE adjusted for dementia	60.0	63.4
Major NCD Probably due to PD with behavioural disturbance	47.1	
Major NCD Probably due to PD without behavioural disturbance	5.9	
Major NCD Possibly due to PD	7.1	
With NPA	72.0	74.4
Major NCD Probably due to PD with behavioural disturbance	56.1	
Major NCD Probably due to PD without behavioural disturbance	7.3	
Major NCD Possibly due to PD	8.5	
Inconclusive (fatigue interference did not allow differential diagnosis between MCI and PDD)	3.5	

LSPD, Late-stage Parkinson's Disease patients; PDD, Parkinson's Disease dementia; MDS PDD, Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force (11); DSM-IV, Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (15); DSM-5, Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (16); NCD, Neurocognitive disorder; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exam; NPA, Neuropsychological assessment; MCI, Mild cognitive impairment.

*If we considered as PDD the 8 LSPD who could not perform the NPA due to physical/motor disabilities, based on the clinical history collected from the caregiver.

domains that DSM-5 criteria considers sufficient to diagnose dementia justified it.

When we used DSM-5 criteria (16) with the MMSE, the frequency of dementia was quite similar (62.4% with education adjustment, 68.2% with age and education adjustment, 60.0% with dementia adjustment). These results revealed that MMSE assessed cognitive domains (like orientation and complex orders comprehension) that were not included in NPA and proved important in the cognitive profile of these patients, which is more similar to normal ageing, with global impairment.

In terms of clinical translation and practical application, the good specificity of Level I criteria proved that this is a time-efficient method to exclude PDD. However, as the absence of major depression is mandatory to perform the Level I diagnosis, future studies in similar populations will be important to confirm whether major depression is a frequent co-morbidity and characteristic of late-stage PD, as this influences how we should evaluate it and to conclude about the applicability of MDS Level I criteria in this population. Such an evaluation should likely be performed based on a semi-structured clinical interview.

On the other hand, DSM-5 criteria proved to be more efficient to diagnose dementia, with a high positive predictive value and good specificity in identifying non-demented patients. However, due to the false positives that may be diagnosed with these criteria, conclusions about dementia diagnosis must be cautious and well-supported by a robust clinical interview with the caregiver collaboration to assess the clinical manifestations and the impact of cognitive impairment in ADL.

None of the criteria used to diagnose dementia applied to the eight patients with severe physical/motor disabilities for whom NPA was impossible. In the future, we consider it important that caregiver-based qualitative assessment methodology be developed to make conclusions on PDD in patients with these typical late-stage physical/motor disabilities, otherwise, we risk underestimating it.

The strengths of our study were the high number of LSPD patients who participated in the NPA and were assessed at home. Considering their disease severity, we believe it was a huge effort and willingness to collaborate in our study.

TABLE 5 | Classification of LSPD by different diagnostic criteria using MDS PDD Level II criteria as the gold-standard.

Classification	MDS PDD Level I	DSM-IV	DSM-5 MMSE adjusted for education	DSM-5 MMSE adjusted for age and education	DSM-5 MMSE adjusted for dementia	DSM-5 NPA
True positive	3	45	52	54	49	54
False positive	0	5	0	3	2	5
True negative	30	25	30	27	28	23
False negative	31	9	2	0	5	0
PPV (%)	100	90.0	100	94.7	96.1	91.5
NPV (%)	49.2	73.5	93.8	100	84.8	100
Sensitivity (%)	8.8	83.3	96.3	100	90.7	100
Specificity (%)	100	83.3	100	90.0	93.3	82.1
Kappa coefficient*	0.1	0.6	0.9	0.9	0.8	0.9

LSPD, Late-stage Parkinson's Disease patients; MDS PDD, Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force (11); DSM-IV, Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (15); DSM-5, Parkinson's Disease dementia criteria recommended by Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (16); MMSE, Mini-Mental State Exam; NPA, Neuropsychological assessment; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

*Kappa coefficient >0.6 is significant.

Given the particular clinical and demographic characteristics of our sample, we believe that our results may be compared with future studies with similar populations to inform about the presence of eventual protective factors associated with the late-stage PD dementia.

This study has also some limitations that we must consider. Firstly, given that the present data come from outpatients attending a specialist movement disorder unit, the results need to be validated in a community sample. Secondly, we used a cross-sectional design and, to confirm the validity of PDD diagnosis procedures, it would be of interest to have a prospective cohort and longitudinal data. Finally, the inexistence of a no-late-stage control group (e.g., advanced stage) didn't allow us to validate the cognitive assessment methodology that we used and analyze the frequency of dementia in a different stage of PD.

In conclusion, our study indicates that below what we would expect, slightly more than half the participants meet dementia criteria. This must have been due to the particular characteristics of our LSPD sample (early age at PD onset, female sex, higher educational level in relation to the general aged Portuguese population), which may have been protective factors for late-stage PD dementia. The estimates of late-stage dementia frequency were partly dependent on the diagnostic criteria. When screening for PDD in LSPD it is important to consider the possibility of using a caregiver-based qualitative methodology assessment to make conclusions on patients with severe physical/motor disabilities for whom neuropsychological tools cannot be used.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Centro Académico de Medicina de Lisboa (Centro Hospitalar Lisboa Norte/Faculdade de Medicina de Lisboa/Instituto de Medicina Molecular João Lobo Antunes). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS: conception, organisation, and execution of the research project, design and execution of the statistical analysis, and writing of the first draught and review and critique of the manuscript preparation. MF, CG, and IC: execution of the research project and review and critique of the manuscript preparation. RS: execution of the research project, review and critique of the statistical analysis, and review and critique of the manuscript preparation. MC: organisation of the research project and review and critique of the manuscript preparation. IM: conception and organisation of the research project, design of the statistical analysis, and review and critique of the manuscript preparation. JF: conception and organisation of the research project, review and critique of the statistical analysis, and review and critique of the manuscript preparation. All authors contributed to the article and approved the submitted version.

FUNDING

CS received a Doctoral Fellowship (SFRH/BD/139853/2018) from Fundação para a Ciência e Tecnologia, Portugal, in which context the research of this article took place.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Profile of cognitive impairment in late-stage Parkinson's disease

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Funding information

This work was supported by a doctoral fellowship (SFRH/BD/139853/2018) from Fundação para a Ciência e Tecnologia, Portugal, which was assigned to Catarina Severiano e Sousa.

Abstract

Introduction: The profile of cognitive impairment associated with the late stages of Parkinson's disease (LSPD) is rarely reported. Its characterization is necessary to better understand the cognitive changes that occur as the disease progresses and to better contribute to its management.

Methods: In this cross-sectional study, we characterized the cognitive profile of LSPD patients using the comprehensive assessment methodology proposed by the International Parkinson and Movement Disorders Society Task Force. The association of clinical and demographic variables with dementia diagnosis was also investigated using binary logistic regression analysis.

Results: Eighty-four LSPD patients were included (age 75.4 ± 6.9 ; disease duration 16.9 ± 7.5). Fifty-four (64.3%) were classified as demented and presented a global impairment cognitive profile. In the nondemented group ($N = 30$), 25 (83.3%) LSPD patients met the diagnostic criteria for mild cognitive impairment, mostly with multiple domain impairment (96.0%) and a heterogeneous profile. Memory was the most frequent and severely impaired cognitive domain in both groups. Disease disability,

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Brain Behav. 2022;32:2537.

<https://doi.org/10.1002/brb3.2537>

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orientation, complex order comprehension, verbal learning, and visuoconstructive abilities were significantly associated with dementia diagnosis ($p < .05$).

Conclusions: Cognitive impairment in multiple domains was common in LSPD patients. The most frequent and prominent deficits were in the memory domain, with a strong interference from attention impairment. Disease disability, orientation, complex order comprehension, verbal learning, and visuoconstructive abilities proved to be important determinants for dementia diagnosis.

KEYWORDS

cognitive impairment, late-stage, Parkinson's disease

1 | INTRODUCTION

Cognitive dysfunction is one of the most prevalent nonmotor symptoms associated with Parkinson's disease (PD) and has been widely studied in an attempt to better describe the pattern of impairment and the cognitive profile of PD patients. However, there are few published studies on late-stage Parkinson's disease (LSPD). Indeed, LSPD is a poorly studied population due to the typically severe motor and nonmotor symptoms that often complicate cognitive assessment. This may be the reason why studies including this population are neuropathological studies (Braak et al., 2005), assess cognition using cognitive screening tests (Coelho et al., 2015), or do not make a detailed description of cognitive performance (Reid et al., 2011). It is common to observe the inclusion of this population in heterogeneous groups regarding the motor dysfunction/severity associated with PD, without providing a particular description of their cognitive profile.

Dementia has been described as a nonmotor symptom that is almost inevitable, mainly in the advanced stages of PD (Reid et al., 2011). It is a crucial determinant of reduced life expectancy in patients with PD. Defining the pattern of the cognitive impairment that is prodromal of Parkinson's disease dementia (PDD) is an area of active research owing to its predictive value and the possibility that these deficits could respond better to treatments used in dementia (Kehagia et al., 2010).

Therefore, a greater understanding of the cognitive disorders present in LSPD is of the utmost importance due to their high frequency in these patients. In the same way, studying cognition in LSPD will help to better understand the pattern of cognitive impairment across the different PD stages.

The current study sought to help clarify these issues by examining the cognitive performance of LSPD patients. To assess dementia we followed the methodology suggested by MDS PDD Level II (Dubois et al., 2007a) and examined cognitive profiles according to the pattern of cognitive impairment. We also investigated clinical, demographic, and cognitive variables that are associated with PDD diagnosis.

2 | METHODS

2.1 | Subjects

In this cross-sectional study, consecutive LSPD patients attending the Movement Disorders Unit of the University Hospital of Santa Maria (Lisbon) were recruited.

All participants and their formal/informal caregivers were informed about the study objectives and procedures and were asked for their written informed consent. The informed consent of cognitively impaired patients was signed by the caregiver. The study was approved by the local ethics committee.

The inclusion criteria were (1) idiopathic PD according to the UK Brain Bank criteria (Hughes et al., 1992); (2) late-stage Parkinson's disease (Coelho & Ferreira, 2012) (Hoehn and Yahr scale [H&Y] score > 3 [Goetz et al., 2004] and a Schwab and England scale [S&E] score $< 50\%$ [Schwab & England, 1969] in the ON condition), and (3) signed informed consent. Patients were excluded if they presented dementia before PD onset or dementia within 1 year of PD diagnosis.

2.2 | Measures

2.2.1 | Neurologic and functional assessment

Neurological assessment was performed by a neurologist with expertise in movement disorders and included the investigation of vascular problems. It took place at the the Movement Disorders Unit of the University Hospital of Santa Maria or, whenever this was not possible (due to difficulties in patients' mobility), it took place at patients' home. The Movement Disorders Society—Unified Parkinson Disease Rating Scale (MDS-UPDRS) (Parts I and IV) (Goetz et al., 2008) was administered to assess PD motor and nonmotor features. We specified clarity of handwriting and tremor item results (Part II 2.7 and 2.10 items) to better analyse the results, particularly of paper and pencil cognitive tests. The

neuropsychiatric functions were assessed by the same neurologist and included behavioral symptoms and major depression, using the neuropsychiatric inventory (Cummings et al., 1994) (NPI) and the geriatric depression scale (Ertan et al., 2005) (GDS), respectively. *Delirium* was diagnosed according to the DSM-5 criteria (American Psychiatric Association, 2014).

2.2.2 | Neuropsychological assessment

The neuropsychological assessment (NPA) was performed by a neuropsychologist. It took place in a single session, at the patients' homes, to ensure the presence of the usual amenities and to reduce as far as possible any interference in the patients' lives.

A clinical interview was undertaken, with caregiver collaboration, to obtain each LSPD patient's sociodemographic and clinical information.

To assess the impact of cognitive impairment on activities of daily living (ADL), two approaches were taken: 1) a patient and caregiver clinical interview and 2) the Pill Questionnaire (Dubois et al., 2007a). Whenever one of these sources of information was suggestive of dysfunction, the patient was classified as having impaired ADL.

The LSPD patient's cognitive performance was described by using a neuropsychological battery which was applied in the same order for all patients and included a set of cognitive tests selected from the MDS PDD Level II proposal (Table 1), according to the following criteria: 1) existence of normative data for the Portuguese population and 2) expected time consumed by the test (only one test for each cognitive task whose performance would have a shorter estimated duration, to minimise interfering with tiredness). According to the MDS Level II recommendations, the memory domain was dissociated into two components to better understand the pattern of its impairment: 1) subcortical-frontal component (strategic aspects of explicit memory) and 2) mediotemporal component (encoding and retrieval abilities).

Raw scores for cognitive tests were transformed into z-scores based upon normative data for the Portuguese population and upon manual tests, which were adjusted for age, education, and, when possible, for sex. Each LSPD patient's cognitive performance was obtained by composite scores for each cognitive domain, which were calculated by averaging individual cognitive z-scores within each of the specific domains.

We considered a cognitive test/domain as impaired if its z-score was more than 1 standard deviation (SD) below the adjusted normative scores ($z\text{-score} < -1$).

The cognitive profile was described based on the organization of cognitive domains proposed by the MDS PDD Level II (Dubois et al., 2007a) and the respective pattern of cognitive impairment: (1) subcortical profile that included patients with executive function impairment and only subcortical-frontal memory component impairment and (2) cortical profile that included patients with instrumental function impairment and only in the mediotemporal memory component. The patients who did not present, or presented changes in the cognitive domains that did not fulfill a specific cognitive profile, were classified as having a heterogeneous profile. The patients who manifested changes in both subcortical and cortical mediated cognitive domains were clas-

TABLE 1 Neuropsychological tests used to assess cognition according to MDS PDD Level II criteria (Dubois et al., 2007a)

Cognitive domains/tasks	MDS PDD Level II Cognitive tests
Global efficiency	MMSE (Folstein et al., 1975; Morgado et al., 2009)
Executive functions	
Working memory	Digit span (Martins et al., 2013; Wechsler, 1997a)
Conceptualization	Similarities (WAIS-III) (Wechsler, 1997b; Wechsler, 2008)
Set activation	Phonologic fluency (P,M,R) (Benton & Hamsher, 1989; Cavaco et al., 2013a)
Set shifting	TMT (A and B) (Cavaco et al., 2013b; Reitan, 1958)
Set maintenance	Odd man out test (Flowers & Robertson, 1985)
Behavioral control	Prehension behavior (FAB) (Lhermitte et al., 1986; Lima et al., 2008)
Memory	RAVLT (Cavaco et al., 2015; Schmidt, 1996)
Instrumental functions	
Language	Boston naming test (Kaplan et al., 1983; Peña-Casanova et al., 2009)
Visuoconstructive	Copy of the clock (Sunderland et al., 1989)
Visuospatial	Benton line orientation test (Benton et al., 1994)
Visuoperceptive	Benton face recognition test (Benton et al., 1994)

MDS PDD, Parkinson's disease dementia criteria recommended by Movement Disorder Society Task Force; MMSE, Mini-Mental State Exam; TMT (A and B), trail making test A and B; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition; FAB, frontal assessment battery; RAVLT, Rey auditory and verbal learning test.

sified as having a global impairment profile. The LSPD patient's cognitive profile was drawn through composite scores which were obtained by averaging the cognitive domains z-score within each of the specific cognitive profiles.

2.3 | Cognitive categorization

LSPD patients were classified as demented or nondemented. Dementia was diagnosed according to the MDS PDD Level II criteria (Dubois et al., 2007a) based on neuropsychological and functional autonomy assessment and a clinical interview.

For exploratory purposes, we examined the frequency of mild cognitive impairment (MCI) by using the MDS MCI Level II criteria (comprehensive assessment) (Litvan et al., 2012).

2.4 | Statistical analysis

To describe the cognitive performance of LSPD patients, we compared clinical and demographic variables, and neuropsychological z-scores of the demented and nondemented patients by using the Chi-square, Mann-Whitney U, and Wilcoxon tests, as appropriate ($p < .05$).

Subsequently, we analysed cognitive profile subgroups by comparing clinical and cognitive variables in each of the demented and nondemented groups and between groups, using Chi-square, Wilcoxon, Mann-Whitney U, and Kruskal-Wallis tests with post-hoc pairwise analysis with Bonferroni correction of ($p < .05$), as appropriate.

Finally, to examine the contribution of the clinical, demographic and neuropsychological measures for dementia diagnosis, binary logistic regression analysis with a forward conditional procedure was run with all of the variables that reached statistical significance ($p < .05$) between demented and nondemented groups as independent variables and with presence or absence of dementia as the dependent variable. Per block step, the improvement of the regression model was compared using the likelihood ratio test. The goodness of fit of the model was assessed with the Hosmer-Lemeshow test.

All statistical analyses were performed using SPSS software version 26 (IBM SPSS, Chicago, IL).

3 | RESULTS

3.1 | Patient demographics and clinical characteristics

Eighty-four LSPD patients performed the NPA. Forty-eight (57.1%) were women, with a mean age of 75.4 years (± 6.9), 6.5 years (± 4.5) of education, 16.9 years (± 7.5) of disease duration, and 58.5 years (± 10.9) at PD onset. 97.3% were on levodopa treatment (Table 2).

According to MDS PDD Level II criteria, 54 (64.3%) LSPD patients met the criteria for PDD (27/36 men (75%), 27/49 women (55%)).

There were no statistically significant differences between demented and nondemented groups concerning sex, age, education, disease duration, age at PD onset, or levodopa treatment profile. We highlight the fact that there were no significant differences in the MDS-UPDRS tremor item, which arose in both groups with sufficiently low frequency or intensity to cause no impact on function, as well as in motor complications (MDS-UPDRS Part IV), whose frequency and severity were between mild and moderate in both groups (Table 2).

3.2 | Cognitive performance of LSPD patients

In the nondemented group ($N = 30$), 5 (16.7%) LSPD patients did not present changes in cognitive domains. The remaining 25 (83.3%) had impairment on at least two neuropsychological tests, meeting criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple domain impairment).

Memory emerged as the most frequently impaired cognitive domain (34.5% of the nondemented group) (Figure 1). When dissociating memory into its two components to analyze the memory deficit pattern, we observed that the mediotemporal component was the most frequently affected (20.7%), with an accentuated impairment (mean z-score -1.7 ± 0.5) (Figure 2) particularly in the long-term percent retention. We also observed a high frequency of intrusions in immediate and delayed retrieval (60.0% with more than five intrusions).

Instrumental function was also impaired in nondemented LSPD (LSPD-NoD) patients (20.7%), mainly visuoceptive (40.7%) and visuospatial (39.3%) functions. Executive function was the least impaired cognitive domain in this group (6.7%). However, when we analyzed it in detail, we observed a high frequency of impairment in attention tasks, mainly in set shifting (70.4%) and set activation (44.8%).

In the demented group ($N = 54$), 40.7% of LSPD patients reported changes in multiple domains and 59.3% in all cognitive domains.

The memory cognitive domain was the most frequently impaired (86.8%). We dissociated it into its two components to analyze its deficit patterns, observing that the majority of demented LSPD (LSPD-D) patients (60.4%) presented changes in both components, and that impairment was accentuated (mean z-score -2.6 ± 0.7), with a high frequency of intrusions (73.6% LSPD-D patients with more than five intrusions).

For executive function, the second most impaired LSPD-D cognitive domain (85.2%), we observed a pattern of changes similar to those in the nondemented group (mainly affecting attention) but with a much more pronounced frequency and impairment severity in all executive function cognitive tasks ($p < .05$).

Also, the instrumental function cognitive domain was significantly more impaired in the demented group ($p = .00$). When we looked at its pattern of changes, visuospatial was the function that was most frequently impaired (85.1%), followed by visuoconstructive (83.7%), two cognitive functions where there was also the most pronounced impairment (mean z-score -3.9 ± 2.6) ($p < .05$) (Table S1, supplementary material).

3.3 | Cognitive profile of LSPD according to the pattern of cognitive impairment

The LSPD patients were classified according to their cognitive profile, based on the pattern of cognitive impairment.

As required by definition, most of the nondemented group (73.3%) did not present significant changes in the cognitive tasks underlying each cognitive profile. They presented a heterogeneous cognitive profile. Only 6.7% of LSPD patients were classified as having a subcortical profile, 6.7% as having a cortical profile and, 13.3% as having a global impairment profile (Figure 3).

In the demented group, 24.1% of LSPD patients were classified as having a subcortical profile, 7.4% as having a cortical profile, and 68.5% as having a global impairment profile.

As the cognitive profile subgroups were small, no statistically significant differences were found within and between the nondemented and

TABLE 2 Demographic and clinical characteristics of LSPD patients

	LSPD (N = 84) Mean (SD)	LSPD-NoD (N = 30) Mean (SD)	LSPD-D (N = 54) Mean (SD)	p
Gender (M/F)	36/49	9/21	27/27	.08
Age (years)	75.4 (6.9)	75.8 (5.2)	75.2 (7.7)	.92
Education (years)	6.5 (4.5)	5.7 (4.4)	7.1 (4.5)	.14
Disease duration (years)	16.9 (7.5)	16.9 (7.7)	16.9 (7.6)	.86
Age at onset (years)	58.5 (10.9)	58.9 (10.2)	58.2 (11.2)	.94
MDS-UPDRS Part I	20.6(6.9)	17.1(6.4)	22.6(6.4)	.00
MDS-UPDRS Part II	33.6(9.5)	29.9(9.0)	35.9(9.3)	.00
MDS-UPDRS Part II 2.7 (clarity of handwriting)	3.3 (0.9)	3.0(0.9)	3.4(0.9)	.02
MDS-UPDRS Part II 2.10 (tremor)	1.0 (1.2)	1.1 (1.1)	1.0 (1.2)	.72
MDS-UPDRS Part III	58.9 (16.6)	52.2 (15.4)	63.1 (16.1)	.00
MDS-UPDRS Part IV	5.1 (4.4)	4.8 (4.6)	5.1 (4.2)	.74
Levodopa (% yes)	97.3	100	95.8	.29
Hoehn & Yahr stage (0/5)	4.1 (0.9)	3.8 (0.9)	4.2 (0.9)	.03
Schwab & England (0/100%)	36.7 (13.6)	44.7 (14.8)	32.2 (10.7)	.00
NPI delusions (0/12) (cutoff ≥3)	1.3 (2.6)	0.6 (2.0)	1.8 (2.8)	.00
NPI hallucinations (0/12) (cutoff ≥3)	1.7 (2.7)	0.8 (2.2)	2.2 (2.9)	.01
NPI depression (0/12) (cutoff ≥3)	3.3 (2.4)	2.9 (2.5)	3.6 (2.3)	.13
NPI apathy (0/12) (cutoff ≥3)	3.6 (3.6)	2.2 (3.1)	4.5 (3.6)	.00
NPI sleep disorders (0/12) (cutoff ≥3)	2.5 (3.3)	1.9 (2.6)	2.9 (3.6)	.47
Pill questionnaire (0/3) (cutoff ≥2)	2.2 (1.1)	1.5 (1.1)	2.6(0.8)	.00
GDS score (0/30) (cutoff 11–20: mild depression; 21–30: severe depression)	13.8 (6.8)	13.9 (5.3)	17.0 (5.9)	.03
MMSE score (0/30) (cutoff: 0–2 years education: 22 pts; 3–6 years education: 24 pts; ≥7 years education: 27 pts)	21.6 (6.1)	27.1 (2.0)	18.4 (5.3)	.00

Note: Subgroups were compared using chi-squared (nominal variables) and Mann–Whitney *U* tests (continuous variables) ($p < .05$ is significant).

LSPD, late-stage Parkinson's disease; LSPD-NoD, late-stage Parkinson's disease patients without dementia; LSPD-D, late-stage Parkinson's disease patients with dementia; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; NPI, neuropsychiatric inventory; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exam.

demented groups regarding demographic, clinical, and most of the distribution of cognitive variables distribution (Table S2, supplementary material).

3.4 | Variables associated with PDD

The hierarchical logistic regression analysis, with presence/absence of PDD as the dependent variable and clinical and neuropsycholog-

ical measures as independent variables, showed that (1) the MMSE subscales scores of orientation in time ($OR = 0.54$, $\beta = -0.63$; 95% confidence interval [CI] = 0.35–0.83; $p = .00$), orientation in space ($OR = 0.35$, $\beta = -1.04$; 95% CI = 0.15–0.86; $p = .02$), language (complex order comprehension) ($OR = 0.61$, $\beta = -0.50$; 95% CI = 0.43–0.87; $p = .00$), and construction ($OR = 0.48$, $\beta = -0.73$; 95% CI = 0.25–0.93; $p = .03$), (2) S&E disability scale ($OR = 0.91$, $\beta = -0.09$; 95% CI = 0.85–0.98; $p = .00$), (3) RAVLT verbal learning ($OR = 0.33$, $\beta = -1.11$; 95% CI = 0.12–0.91; $p = .03$), and (4) copy of the clock test ($OR = 0.62$,

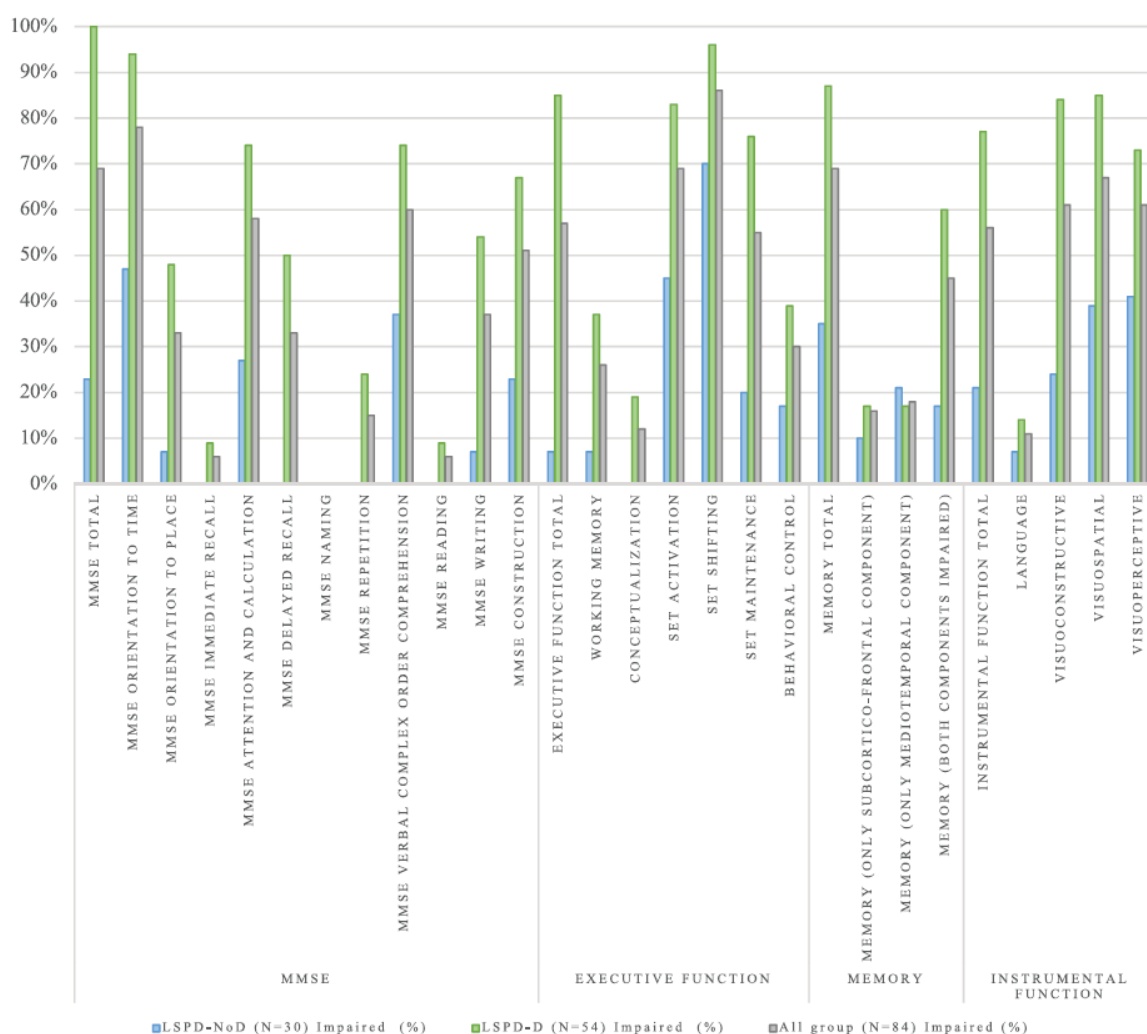


FIGURE 1 Frequency of cognitive impairment in LSPD patients. MMSE, Mini-Mental State Exam; LSPD-NoD, late-stage Parkinson's disease patients without dementia; LSPD-D, late-stage Parkinson's disease patients with dementia

$\beta = -0.47$; 95% CI = 0.45–0.87; $p = .00$) were associated with the condition of dementia, with reduced scores supporting the dementia diagnosis.

4 | DISCUSSION

Our results indicate that 54 (64.3%) LSPD patients met the criteria for PDD. Of the 30 (35.7%) LSPD-NoD patients, 5 (16.7%) did not present cognitive impairment. The remaining 25 (83.3%) met criteria for the diagnosis of MCI (4.0% with single-domain impairment and 96.0% with multiple-domain impairment). Reid et al. (2011) investigated a sample of PD who had 20 years of disease and found that 80% of PD patients had dementia. Based on these results, we expected to find a higher frequency of PDD. This discrepancy may be due in part to some clinical

and sociodemographic characteristics of our sample. Phongpreecha et al. (2020) studied the associations between biological, clinical, and cognitive factors and they found that the primary factors associated with PDD were male sex, the glucocerebrosidase gene, later age at PD onset, and disease duration. In our study, although there were no statistically significant differences between the groups of demented and nondemented patients with regard to sociodemographic variables (probably due to the small size of the nondemented group, which will have reduced power of statistical analysis), our sample has an earlier age at PD onset and a higher proportion of women (58%) than expected based on previous reports. On the other hand, the participants had a level of education (mean of 6 years) that is not representative of the elderly Portuguese population who is poorly educated (up to 4 years in the population over 65 years), a fact that may have contributed to the lower frequency of dementia found.

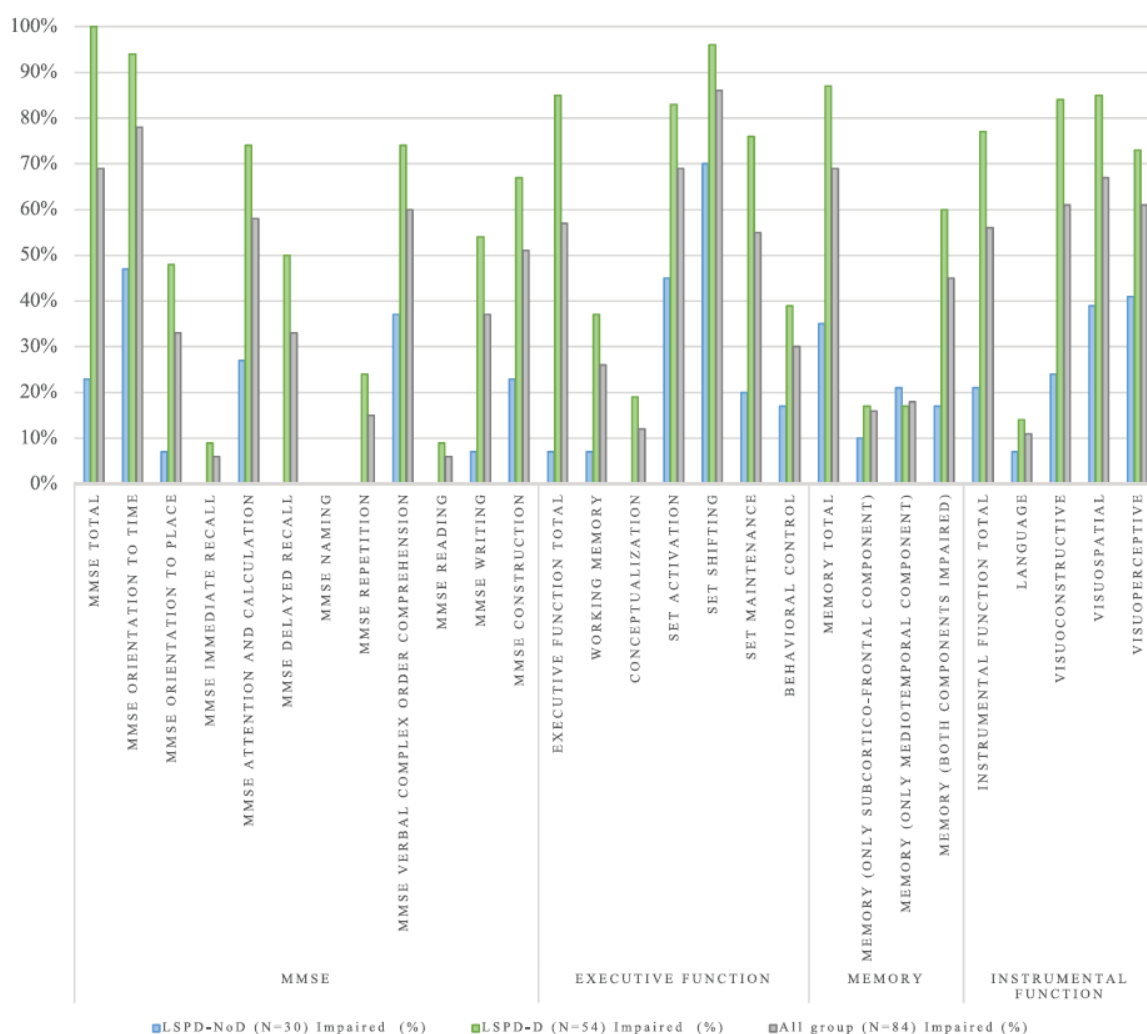


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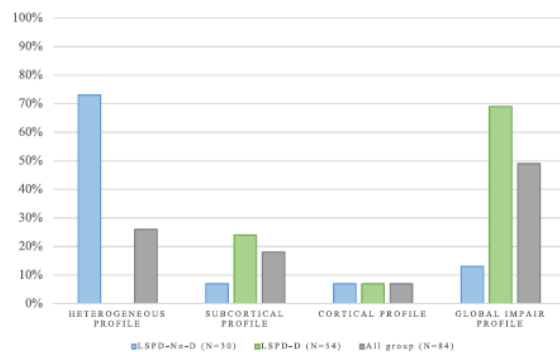


FIGURE 3 Frequency of cognitive profile of LSPD patients. LSPD-NoD, late-stage Parkinson's disease patients without dementia; LSPD-D, late-stage Parkinson's disease patients with dementia

suggesting again a deficit of internal control of attention (Dubois & Pillon, 1997).

In the demented group, we observed a global memory impairment with changes both in learning and retention, and there was a high frequency of intrusions. These results revealed a global impairment in the different stages of information storage, whose severity was much more accentuated than that manifested by the nondemented group.

For instrumental function, the visuoceptive abilities were the most frequently impaired in nondemented patients. Some neuroimaging studies report that these changes often arise in association with posterior cortical dysfunction (Abe et al., 2003).

In the demented group, visuoconstructive and visuospatial functions were the most frequently impaired. The LSPD-D patients correctly identified the clock design but manifested great difficulty in copying it, thereby revealing a visuoconstructive apraxia. PDD patients may be at an enhanced risk of visuospatial impairments that also reflect disrupted praxis and disrupted visuoception over and above the contributions of motor dysfunction (Troster, 2008).

We highlight the low frequency of language changes (in both groups), assessed by the Boston Naming Test. Errors on this test, although infrequent, sometimes arose due to visuoceptive changes and not due to an impairment in naming. These findings go against what is reported in the literature. Naming is not frequently reported as an impaired cognitive task in PD (Cummings et al., 1988).

Executive function, the cognitive domain often reported as most frequently impaired in PD, was the third most frequently impaired in the nondemented group and the second in the demented group. This discrepancy may be due to two reasons: (1) the decline in executive function occurs in the early stages and then tapers off during the mid-stages of PD (Muslimovic et al., 2007) and (2) almost all LSPD patients were medicated with levodopa, which may improve executive function and attention (Lange et al., 1992). By contrast, visuospatial function (Lee et al., 1998), visual recognition memory, conditional associative learning, and verbal memory seem to be dopamine-independent and unaffected by medication status (Owen et al., 1993; Sahakian et al., 1988). However, we highlight the changes we observed in attention both in frequency and severity of impairment. It was in the set shifting that

LSPD patients manifested greater difficulties, even removing the speed element from the test evaluation. In the same way, in both groups, we observed changes in the set activation and the set maintenance. These changes may be attributed to the difficulty in maintaining and adapting a strategy against other competing possibilities due to frontal cortical and basal ganglia lesions (Flowers & Robertson, 1985).

When we grouped the cognitive domains into cognitive profiles to better characterize the substrate of cognitive impairment, we observed that the majority of LSPD-NoD patients manifested a heterogeneous cognitive profile. Some authors suggest that this heterogeneity might be at least partly explained by uneven dopamine loss across the basal ganglia circuitry (Lewis & Barker, 2009; Sawamoto et al., 2008) and neurodegenerative hallmarks such as the emergence of cortical Lewy bodies and non-Parkinson's disease features as a consequence of ageing (Kempster et al., 2010), which might interact with the putative pathological processes that underlies dementia. As such, there have been very few LSPD-NoD patients in cognitive profile subgroups, which made it impossible for us to have a reliable comparative analysis between them.

In the demented group, most patients exhibited widespread cognitive deficits, which we classified as a global impairment cognitive profile. For this reason, once again, the comparative analysis with the remaining demented and nondemented subgroups proved delicate given their small size. For purely exploratory reasons, we observed that LSPD-D patients in the global impairment group tended to be older, less educated, and have later PD age onset, greater disease disability, and overall greater frequency and severity of neuropsychiatric symptoms. It has been suggested that older age (Palazzini et al., 1995), later disease onset (after the age of 60 years) (Glatt et al., 1996; Reid, 1992), and low educational attainment (Glatt et al., 1996) are associated with greater cognitive decline. Our results went in this direction. When we compared them with the other demented cognitive profile subgroups, we found that they present, overall, greater impairment in cognitive domains.

Hobson and Meara (2004) in their elderly PD cohort (mean age of 78 years) ascribed memory deficits to the possible development of Alzheimer's disease (AD). Similarly, our elderly LSPD patients, mainly PDD patients with global cognitive impairment, appeared to present cognitive performance characterized by both AD (with memory [encoding] and orientation deficits) and PDD-typical impairments (executive function, memory [retrieving], and visuospatial abilities). Although AD cannot be diagnosed in the presence of PD because, according to the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria (Dubois et al., 2007b), early parkinsonian signs rule this diagnosis out, Bothe et al. (2010) maintain that these existing criteria are quite restrictive and they disregard the neuropathological findings of the Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (2001), who mentioned that the majority of demented patients aged over 70 years present with more than one kind of severe neurodegenerative pathology.

A final finding of our study was that among the sociodemographic and clinical variables, only disease disability was significantly

associated with PDD. Regarding the cognitive variables, we also found that orientation in time and space, complex order comprehension, and construction MMSE subscales revealed an important association with PDD. The same was observed with verbal learning and with the copy of the clock test. These findings are consistent with previous studies that reported associations between language, memory (Hobson & Meara, 2004), and visuoconstructive function impairment (Williams-Gray et al., 2007) with PDD.

There are several strengths in the current study. To the best of our knowledge, this is the first study that applies the MDS PDD criteria in a sample exclusively consisting of LSPD patients, examined in their homes with a complete neuropsychological assessment.

Our study has some limitations. First, we used a cross-sectional design and, to conclude on the cognitive changes with disease progression, it would be of interest to have a prospective cohort and longitudinal data. Second, the inexistence of a nonlate-stage control group did not allow us to compare the pattern of the cognitive impairment in a different stage of PD by using the same assessment methodology.

In conclusion, almost all nondemented patients meet clinical criteria for MCI with multiple-domain impairment. Memory was the most frequently impaired cognitive domain, with a strong contribution of attention deficit. The cognitive profiles were heterogeneous, without any meaningful pattern over the cognitive domains. Most demented patients presented a global impairment profile, with both AD and PDD-typical impairments. Disease disability, orientation, complex order comprehension, verbal learning, and visuoconstruction were associated with PDD diagnosis.

Future studies with larger LSPD cohorts will be important to conclude about the eventual protective effect of sociodemographic variables for LSPD dementia and their typical cognitive profiles.

AUTHOR CONTRIBUTIONS

Catarina Severiano e Sousa: Conceptualization (equal), data extraction (lead), formal analysis (lead), funding acquisition, investigation (lead), methodology, project administration (equal), visualization, writing—original draft preparation. Margherita Fabbri: Data extraction, formal analysis, writing—review and editing. Catarina Godinho: Data extraction, formal analysis, writing—review and editing. Rita Moiron Simões: Data extraction, formal analysis, writing—review and editing. Inês Chendo: Writing—review and editing. Miguel Coelho: Writing—review and editing. Isabel Pavão Martins: Conceptualization (equal), methodology, supervision, writing—review and editing. Joaquim J. Ferreira: Conceptualization (equal), investigation, methodology (lead), project administration (equal), supervision (lead), writing—review, peer review (lead) and editing (lead).

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURES

Catarina Severiano e Sousa: No conflict of interest to report. No additional disclosures to report. Margherita Fabbri: No conflict of interest to report. No specific funding was received for this work. She has

received consultancy fees from AbbVie. No additional disclosures to report. Catarina Godinho: No conflict of interest to report. No specific funding was received for this work. No additional disclosures to report. Rita Simões: no conflict of interest to report. No specific funding was received for this work. She has received consultancy fees from BIAL—PORTELA & Ca, SA, Zambon, and AbbVie. No additional disclosures to report. Inês Chendo: No conflict of interest to report. No specific funding was received for this work. No additional disclosures to report. Miguel Coelho: No conflict of interest to report. No specific funding was received for this work. He has received consultancy fees from Zambon. No additional disclosures to report. Isabel Pavão Martins: No conflict of interest to report. No specific funding was received for this work. No additional disclosures to report. Joaquim J. Ferreira: No conflict of interest to report. No specific funding was received for this work. He has received grants from GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Novartis, Medtronic. He received consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion Pharmaceuticals, Zambon, Affiris. He has also participated in advisory boards for Bial and provided expert testimony to Novartis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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How to cite this article: Severiano e Sousa, C., Fabbri, M., Godinho, C., Moiron Simões, R., Chendo, I., Coelho, M., Pavão Martins, I., & Ferreira, J. J. (2022). Profile of cognitive impairment in late-stage Parkinson's disease. *Brain and Behavior*, e2537. <https://doi.org/10.1002/brb3.2537>

Annex – Supplementary data

Supplementary Tables

		Year of study (N=295)				Study's primary objective (N=295)						PD severity (N=185)					
		<2008		≥2008		Study PDD		Study cognition		Other		H&Y≤2		H&Y>2≤3		H&Y>3	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Methodological characteristics	Study design	106	100	189	100	106	100	87	100	102	100	50	100	102	100	33	100
	Cross-sectional	37	34.9	40	21.2	30	28.3	16	18.4	31	30.4	9	18.0	35	34.3	6	18.2
	Cohort	61	57.5	135	71.4	73	68.9	63	72.4	60	58.8	38	76.0	58	56.9	25	75.8
	Case-control	8	7.5	14	7.4	3	2.8	8	9.2	11	10.8	3	6.0	9	8.8	2	6.1
	Study primary objective	106	100	189	100	NA	NA	NA	NA	NA	NA	50	100	102	100	33	100
	Study PDD	42	39.6	64	33.9	NA	NA	NA	NA	NA	NA	17	34.0	36	35.3	10	30.3
	Study cognition	16	15.1	71	37.6	NA	NA	NA	NA	NA	NA	18	36.0	29	28.4	4	12.1
	Other	48	45.3	54	28.6	NA	NA	NA	NA	NA	NA	15	30.0	37	36.3	19	57.6
	Follow-up length	50	47.2	109	57.7	63	59.4	51	58.6	45	44.1	32	64.0	48	47.1	18	54.5
	≤1yr	4	8.0	3	2.8	1	1.6	5	9.8	1	2.2	2	6.3	3	6.3	0	0
	>1≤2yrs	2	4.0	11	10.1	4	6.3	7	13.7	2	4.4	4	12.5	2	4.2	2	11.1
	>2≤5yrs	24	48.0	42	38.5	33	52.4	22	43.1	11	24.4	14	43.8	21	43.8	5	27.8
	≥5<7yrs	9	18.0	22	20.2	9	14.3	10	19.6	12	26.7	8	25.0	8	16.7	3	16.7
	≥7<10yrs	5	10.0	15	13.8	7	11.1	4	7.8	9	20.0	3	9.4	7	14.6	2	11.1
	≥10<15yrs	5	10.0	10	9.2	6	9.5	2	3.9	7	15.6	1	3.1	5	10.4	4	22.2
	≥15yrs	1	2.0	6	5.5	3	4.8	1	2.0	3	6.7	0	0	2	4.2	2	11.1
	Dementia criteria	106	100	189	100	106	100	87	100	102	100	50	100	102	100	33	100
	MDS Level I	0	0	27	14.3	9	8.5	7	8.0	11	10.8	6	12.0	13	12.7	2	6.1
	MDS Level II	0	0	63	33.3	21	19.8	38	43.7	4	3.9	22	44.0	16	15.7	3	9.1
	DSM-III/IV	71	67.0	52	27.5	54	50.9	21	24.1	48	47.1	10	20.0	48	47.1	17	51.5
	NPA	5	4.7	5	2.6	6	5.7	2	2.3	2	2.0	0	0	4	3.9	2	6.1
	Screening scales	15	14.2	23	12.2	10	9.4	7	8.0	21	20.6	10	20.0	10	9.8	5	15.2
	Clinical criteria	10	9.4	14	7.4	4	3.8	8	9.2	12	11.8	0	0	7	6.9	3	9.1
	Not specified	5	4.7	5	2.6	2	1.9	4	4.6	4	3.9	2	4.0	4	3.9	1	3.0
	Cognitive assessment	106	100	189	100	106	100	87	100	102	100	50	100	102	100	33	100

Demographic characteristics	Screening scales	60	56.6	78	41.3	50	47.2	27	31.0	61	59.8	19	38.0	53	52.0	26	78.8
	NPA	32	30.2	94	49.7	49	46.2	59	67.8	18	17.6	28	56.0	38	37.3	6	18.2
	Not specified	14	13.2	17	9.0	7	6.6	1	1.1	23	22.5	3	6.0	11	10.8	1	3.0
	Age	91	85.8	177	93.7	96	90.6	78	89.7	94	92.2	48	96.0	101	99.0	32	97.0
	≤60yrs	5	5.5	10	5.6	3	3.1	5	6.4	7	7.4	0	0	5	5.0	2	6.3
	>60<75yrs	69	75.8	150	84.7	77	80.2	67	85.9	75	79.8	46	95.8	88	87.1	19	59.4
	≥75yrs	17	18.7	17	9.6	16	16.7	6	7.7	12	12.8	2	4.2	8	7.9	11	34.4
	Education	24	22.6	87	46.0	49	46.2	48	55.2	14	13.7	30	60.0	40	39.2	5	15.2
	≤4 yrs	0	0	1	1.1	0	0	0	0	1	7.1	0	0	1	2.5	0	0
	>4≤9 yrs	3	12.5	16	18.4	9	18.4	7	14.6	3	21.4	4	13.3	9	22.5	2	40.0
	>9≤12 yrs	18	75.0	36	41.4	28	57.1	19	39.6	7	50.0	17	56.7	16	40.0	2	40.0
	>12 yrs	3	12.5	34	39.1	12	24.5	22	45.8	3	21.4	9	30.0	14	35.0	1	20.0
	Men percent	85	80.2	168	88.9	94	88.7	73	83.9	86	84.3	47	94.0	92	90.2	29	87.9
	≤50%	34	40.0	36	21.4	33	35.1	8	11.0	29	33.7	6	12.8	32	34.8	13	44.8
	>50%	51	60.0	132	78.6	61	64.9	65	89.0	57	66.3	41	87.2	60	65.2	16	55.1
Clinical characteristics	PD duration	82	77.4	151	79.9	82	77.4	69	79.3	82	80.4	42	84.0	95	93.1	28	84.8
	≤3.5yrs	5	6.1	28	18.5	11	13.4	11	15.9	11	13.4	18	42.9	5	5.3	0	0
	>3.5≤5yrs	5	6.1	10	6.6	6	7.3	6	8.7	3	3.7	2	4.8	10	10.5	0	0
	>5≤10yrs	42	51.2	84	55.6	46	56.1	41	59.4	39	47.6	21	50.0	63	66.3	11	39.3
	>10<15yrs	22	26.8	21	13.9	14	17.1	9	13.0	20	24.4	1	2.4	16	16.8	11	39.3
	≥15yrs	8	9.8	8	5.3	5	6.1	2	2.9	9	11.0	0	0	1	1.1	6	21.4
	H&Y stage	65	61.3	120	63.5	63	59.4	51	58.6	71	69.6	NA	NA	NA	NA	NA	NA
	≤2	6	9.2	44	36.7	17	27.0	18	35.3	15	21.1	NA	NA	NA	NA	NA	NA
	>2≤3	42	64.6	60	50.0	36	57.1	29	56.9	37	52.1	NA	NA	NA	NA	NA	NA
	>3	17	26.2	16	13.3	10	15.9	4	7.8	19	26.8	NA	NA	NA	NA	NA	NA

Supplementary Table 1. Frequency of methodological, clinical and demographic characteristics by year of the study, study primary objective and PD severity.

PD- Parkinson's disease

PDD- Parkinson's disease dementia

MDS- Movement disorder society

NPA- Neuropsychological assessment

H&Y- Hoehn and Yahr

Hoehn and Yahr-specific PDD proportions												
	H&Y ≤2				H&Y >2≤3				H&Y >3			
	N studies	N (PDD/PD)	Pooled total (%) and 95% CI	I ² *	N studies	N (PDD/PD)	Pooled total (%) and 95% CI	I ² *	N studies	N (PDD/PD)	Pooled total (%) and 95% CI	I ² *
All studies	50	2377/12941	19.8 (17.0-22.7)	95.06	102	4289/17477	23.6 (20.9-26.4)	96.34	33	1146/2991	45.9 (38.0-53.7)	95.71
PDD criteria	50	2377/12941	19.8 (17.0-22.7)	95.06	102	4289/17477	23.6 (20.9-26.4)	96.34	33	1146/2991	45.9 (38.0-53.7)	95.71
MDS Level I	6	200/678	33.3 (15.8-50.8)	97.06	13	427/2453	16.4 (13.0-19.8)	72.79	2	29/77	37.6 (26.8-48.4)	0
MDS Level II	22	591/3370	16.4 (12.9-19.9)	87.87	16	251/1424	20.1 (14.3-25.9)	91.41	3	52/93	52.9 (25.6-80.2)	87.66
DSM-III/IV	10	443/3082	15.1 (11.7-18.4)	79.71	48	2591/9147	25.1 (20.2-30.0)	97.80	17	633/1498	46.3 (34.7-57.8)	96.04
NPA criteria	0	0	0	NA	4	98/298	33.3 (25.6-41.1)	52.62	2	45/106	54.6 (-1.2-110.5)	97.79
Screening scales cut-off	10	1127/5577	27.1 (18.7-35.5)	98.35	10	443/2013	24.2 (16.2-32.3)	94.82	5	232/823	40.8 (20.2-61.4)	97.33
Clinical criteria	0	0	0	NA	7	250/941	24.5 (18.0-31.0)	78.48	3	143/366	43.6 (32.2-54.9)	64.80
Not specified	2	16/234	6.3 (2.2-10.4)	43.86	4	229/1201	20.8 (15.4-26.2)	51.46	1	12/28	42.9 (24.5-61.2)	NA
Cognitive assessment	50	2377/12941	19.8 (17.0-22.7)	95.06	102	4289/17477	23.6 (20.9-26.4)	96.34	33	1146/2991	45.9 (38.0-53.7)	95.71
Screening scales	19	1596/8002	25.6 (20.2-31.0)	97.40	53	2512/10257	23.4 (19.5-27.3)	96.80	26	978/2595	45.2 (36.2-54.2)	96.21
NPA	28	738/4509	16.6 (13.5-19.7)	88.94	38	1109/4096	24.8 (19.4-30.2)	96.22	6	147/338	50.4 (30.8-70.0)	93.34
Not specified	3	43/430	10.8 (5.8-15.7)	52.40	11	668/3124	20.9 (15.6-26.2)	90.91	1	21/58	36.2 (23.8-48.6)	NA
Age group	48	2301/12578	19.8 (16.9-22.7)	95.21	101	4279/17433	23.6 (20.9-26.4)	96.37	32	1126/2915	46.5 (38.4-54.6)	95.81
≤60 yrs	0	0	0	NA	5	197/745	26.1 (22.6-29.6)	8.88	2	46/105	43.7 (34.3-53.2)	0
>60<75 yrs	46	2274/12469	19.5 (16.5-22.5)	95.35	88	3675/15537	22.8 (19.9-25.6)	96.35	19	624/1968	38.7 (31.7-45.6)	90.92
≥75 yrs	2	27/109	32.0 (-1.3-65.2)	90.81	8	407/1151	31.7 (20.3-43.1)	94.19	11	456/842	60.2 (45.0-75.5)	95.94
PD duration	42	1994/11551	19.4 (16.6-22.3)	94.51	95	4127/16259	24.2 (21.6-26.7)	94.17	28	977/2568	44.3 (35.7-52.9)	95.84
≤3.5 yrs	18	857/5908	16.4 (13.1-19.7)	91.67	5	547/1887	19.0 (2.5-35.6)	99.21	0	0	0	NA
>3.5≤5 yrs	2	41/162	28.0 (-8.8-64.7)	96.74	10	244/945	23.9 (18.6-29.3)	69.69	0	0	0	NA
>5≤10 yrs	21	899/5075	19.6 (15.5-23.7)	93.16	63	2874/11852	23.3 (20.6-26.1)	92.88	11	411/1371	35.8 (20.5-51.2)	97.72
>10<15 yrs	1	197/406	48.5 (43.7-53.4)	NA	16	437/1515	28.5 (24.8-32.2)	54.25	11	400/863	51.5 (40.9-62.1)	90.39
≥15 yrs	0	0	0	NA	1	25/60	41.7 (29.2-54.1)	NA	6	166/334	47.5 (38.7-56.3)	62.59

Supplementary Table 2. Meta-analysis of dementia frequency by H&Y stages

*<40% heterogeneity might not be important; >75% considerable heterogeneity²⁵¹

H&Y- Hoehn and Yahr; PD- Parkinson's disease; PDD- Parkinson's disease dementia; MDS- Movement disorder society; NPA- Neuropsychological assessment; NA- Not applicable

Cognitive domains	Cognitive tests	LSPD (N=84)		LSPD-NoD (N=30)		LSPD-D (N=54)		p
		Impaired (%)	z-score Mean (SD)	Impaired (%)	z-score Mean (SD)	Impaired (%)	z-score Mean (SD)	
MDS PDD								
Level II domains								
Global efficiency	. MMSE	69.4	-4.4(4.0)	23.3	-0.5(1.3)	100	-6.6(3.4)	0.00
1. Orientation	. MMSE Orientation subtest	61.2	-3.3(3.6)	20.0	-0.4(1.2)	85.2	-4.9(3.5)	0.00
1.1. orientation to time	. MMSE Orientation subtest	77.6	-3.9(3.7)	46.7	-1.1(2.0)	94.4	-5.5(3.6) ^f	0.00
1.2. orientation to place	. MMSE Orientation subtest	32.9	-1.1(2.4)	6.7	0.3(0.6)	48.1	-1.9(2.7)	0.00
2. Immediate recall	. MMSE Recall subtest	5.9	-0.3(1.1)	0	0.0(0.0)	9.3	-0.5(1.3)	0.03
3. Attention and calculation	. MMSE Attention and calculation subtest	57.6	-2.5(4.0)	26.7	-0.6(1.5)	74.1	-3.6(4.5) ^{d,e}	0.00
4. Delayed recall	. MMSE Delayed recall subtest	32.9	-0.6(1.3)	0	0.5(0.6)	50.0	-1.1(1.2) ^d	0.00
5. Language	. MMSE Language subtest	58.8	-2.6(3.1)	20.0	-0.3(1.3)	81.5	-3.8(3.2) ^d	0.00
5.1. naming	. MMSE Language subtest	0	-0.0(0.2)	0	0.0(0.0)	0	-0.1(0.2)	0.20
5.2. repetition	. MMSE Language subtest	15.3	-0.2(0.4)	0	0.0(0.0)	24.1	-0.2(0.4)	0.00
5.3. verbal complex order comprehension	. MMSE Language subtest	60.0	-2.7(3.5)	36.7	-1.1(2.4)	74.1	-3.7(3.7) ^g	0.00
5.4. reading comprehension	. MMSE Language subtest	5.9	-0.4(2.2)	0	0.1(0.2)	9.3	-0.8(2.7)	0.14
5.5. writing	. MMSE Language subtest	36.5	-0.6(1.5)	6.7	0.3(0.6)	53.7	-1.1(1.6)	0.00
6. Construction	. MMSE Construction subtest	50.6	-0.8(1.3)	23.3	0.2(1.2)	66.7	-1.3(1.0) ^d	0.00
Subcortical features								
1- Executive function		56.5	-1.1(0.8)	6.7	-0.4(0.5)	85.2	-1.6(0.7)	0.00
. working memory	. Digit Span	25.9	-0.8(0.9)	6.7	-0.2(0.7)	37.0	-1.1(1.0) ^h	0.00
. conceptualization	. Similarities (WAIS-III)	11.8	0.04(1.0)	0	0.5(0.7)	18.5	-0.3(1.0)	0.00
. set activation	. Phonological Fluency (P,M,R)	68.7	-1.3(1.0)	44.8	-0.8(1.0)	83.0	-1.7(0.9) ^{h,i}	0.00
. set shifting	. TMT (B-A)	85.9	-2.9(1.8)	70.4	-1.7(1.2)	95.5	-3.6(1.8)	0.00
. set maintenance	. Odd Man Out Test	55.2		20.0		76.2		
	Trial 1		-1.8(2.6)		0.4(1.0)		-3.2(2.4)	0.00
	Trial 2		-0.6(1.6)		0.8(0.6)		-1.4(1.5)	0.00
	Trial 3		-0.9(1.8)		0.5(1.3)		-1.8(1.4)	0.00
	Trial 4		-1.3(1.7)		-0.1(1.4)		-1.9(1.5)	0.00
	Trial 5		-1.4(1.9)		-0.0(1.6)		-2.2(1.5)	0.00
	Trial 6		-1.4(1.6)		-0.3(1.6)		-2.1(1.3)	0.00

	Trial 7		-2.4(2.1)		-0.8(2.2)		-3.3(1.3)	0.00
	Trial 8		-1.5(1.4)		-0.7(1.5)		-2.0(1.0)	0.00
	Trial 9		-2.9(3.9)		0.7(2.5)		-5.0(3.0)	0.00
	Trial 10		-1.4(1.7)		-0.2(1.2)		-2.2(1.3)	0.00
	Total		-1.6(1.8)		0.0(1.2)		-2.5(1.4) ^h	0.00
. behavioral control	. Prehension Behavior (FAB)	30.1	-0.8(1.1)	16.7	-0.4(0.9)	38.5	-1.0(1.2)	0.05
2- Memory ^a	. RAVLT (Total)	68.7	-1.5(1.2) ^c	34.5	-0.6(0.9)	86.8	-2.1(1.1) ^c	0.00
2.1- Memory (only subcortical-frontal component)	. RAVLT (Total component)	15.7	-1.8(0.8)	10.3	-1.3(0.3)	17.0	-2.0(0.9)	0.15
	. Total learning	100	-2.5(1.0)	100	-1.5(0.1)	100	-2.8(1.0) ^j	0.02
	. Learning over trials index	46.2	-1.2(1.0)	66.7	-1.2(0.5)	44.4	-1.3(1.2)	0.73
Cortical features								
2.2- Memory (only mediotemporal component)	. RAVLT (Total component)	18.1	-1.9(0.6)	20.7	-1.7(0.5)	17.0	-2.0(0.7)	0.53
	. Long term percent retention index	80.0	-2.1(1.5)	83.3	-1.9(1.2)	77.8	-2.3(1.7)	0.86
	. Delayed recognition	60.0	-1.6(0.8)	50.0	-1.5(0.9)	66.7	-1.6(0.7)	0.96
2.3- Memory (both components impaired) ^b	. RAVLT (Total component)	44.6	-2.5(0.7)	17.2	-2.0(0.6)	60.4	-2.6(0.7)	0.07
	. Total learning	100	-2.9(0.8)	100	-1.9(0.2)	100	-3.1(0.8)	0.00
	. Learning over trials index	67.6	-1.4(1.1)	40.0	-1.3(1.6)	71.9	-1.5(1.0) ^k	0.37
	. Long term percent retention index	89.2	-3.2(1.3)	80.0	-2.5(1.3)	90.6	-3.3(1.3)	0.14
	. Delayed recognition	100	-2.6(0.8)	100	-2.1(0.4)	100	-2.6(0.9) ^k	0.23
3- Instrumental function		55.6	-1.3(1.1)	20.7	-0.4(0.8)	76.5	-1.8(1.0) ^c	0.00
. language	. Boston Naming Test	11.1	-0.2(0.9)	6.9	0.2(1.0)	13.7	-0.4(0.8)	0.01
. visuo-constructive	. Copy of the Clock	60.8	-2.5(2.9)	24.1	-0.3(1.7)	83.7	-3.9(2.6)	0.00
. visuospatial	. Benton Line Orientation Test	67.1	-1.3(1.0)	39.3	-0.7(1.1)	85.1	-1.7(0.8) ^l	0.00
. visuoperceptive	. Benton Face Recognition Test	61.1	-1.3(1.0)	40.7	-0.8(1.1)	73.3	-1.5(0.8) ^l	0.00
Single domain		1.2		3.3		0		
Multiple domain		92.4		80.0		100		

Supplementary Table 3. Cognitive performance of LSPD patients

Sub-groups were compared using the Mann-Whitney U and Wilcoxon tests (p<0.05 is significant).

LSPD-NoD Late-Stage Parkinson's Disease patients without dementia

LSPD-D Late-Stage Parkinson's Disease patients with dementia

MDS PDD- Parkinson's Disease dementia criteria recommended by Movement Disorder Society Task Force

MMSE- Mini-Mental State Exam

TMT (A and B)- Trail Making Test A and B

WAIS-III- Wechsler Adult Intelligence Scale 3rd Edition

FAB- Frontal Assessment Battery

RAVLT- Rey Auditory and Verbal Learning Test

^a Cognitive domain not considered as subcortical feature and for subcortical composite z-score calculation

^b Cognitive domain not considered as cortical feature and for cortical composite z-score calculation

^c $p < 0.05$, different from executive function

^d $p < 0.05$, different from orientation

^e $p < 0.05$, different from delayed recall

^f $p < 0.05$, different from orientation to place

^g $p < 0.05$, different from writing

^h $p < 0.05$, different from set shifting

ⁱ $p < 0.05$, different from working memory

^j $p < 0.05$, different from learning over trials index

^k $p < 0.05$, different from long-term percent retention index

^l $p < 0.05$, different from visuoconstructive

	LSPD-NoD (N=30) Mean (SD)									LSPD-D (N=54) Mean (SD)						
Clinical and cognitive description	Heterogeneous profile (N=22)		Subcortical profile (N=2)		Cortical profile (N=2)		Global impair profile (N=4)		p	Subcortical profile (N=13)		Cortical profile (N=4)		Global impair profile (N=37)		p
	Impair (%)	z-score Mean (SD)	Impair (%)	z-score Mean (SD)	Impair (%)	z-score Mean (SD)	Impair (%)	z-score Mean (SD)		Impair (%)	z-score Mean (SD)	Impair (%)	z-score Mean (SD)	Impair (%)	z-score Mean (SD)	
Gender (M/F)	7/15		1/1		0/2		1/3		0.72	6/7		1/3		20/17		0.52
Age		76.8(5.1)		73.5(0.7)		73.0(7.1)		73.0(6.1)	0.47		74.1(7.7)		70.0(16.1)		76.2(6.4)	0.61
Education		5.5(4.1)		5.0(1.4)		3.5(0.7)		8.3(7.7)	0.55		7.9(4.6)		7.0(4.8)		6.8(4.6)	0.74
Disease duration (yrs)		17.5(7.8)		15.0(5.7)		9.0(1.4)		18.5(9.1)	0.26		18.8(8.3)		18.0(11.9)		16.2(6.9)	0.66
Age at onset (yrs)		59.3 (11.1)		58.5(5.0)		64.0(8.5)		54.5(8.2)	0.61		55.3 (10.5)		52.0 (26.6)		60.0(9.5)	0.48
MDS_UPDRS 1		16.0(5.5)		25.5 (10.6)		15.0(8.5)		20.0(6.9)	0.33		23.5(5.7)		19.0(3.7)		22.7(6.9)	0.28
MDS_UPDRS 2		30.0(8.7)		34.0(11.3)		17.5(5.0)		33.5(7.2)	0.20		33.8(8.0)		32.0(14.4)		37.1(9.2)	0.34
MDS_UPDRS 2.7		3.1(0.9)		2.5(2.1)		2.0(0.0)		3.3(1.0)	0.37		3.3(0.9)		3.3(1.5)		3.5(0.8)	0.83
MDS_UPDRS 2.10		1.4(1.2)		0.0(0.0)		0.5(0.7)		0.3(0.5)	0.10		0.9(0.8)		1.5(1.3)		1.0(1.4)	0.51
MDS_UPDRS 2.13		2.2(1.6)		3.5(0.7)		2.0(2.8)		3.5(1.0)	0.32		2.6(1.2)		3.0(2.0)		2.7(1.5)	0.56
MDS_UPDRS 3		51.5 (14.0)		66.5 (26.1)		34.0(7.1)		58.0 (16.8)	0.13		57.5 (14.9)		66.5(31.0)		64.8(14.5)	0.25
MDS_UPDRS 4		3.9(4.4)		9.0(2.8)		4.5(6.4)		8.0(4.3)	0.18		6.4(4.6)		5.5(6.4)		4.5(3.9)	0.44
Levodopa (% yes)	100		100		100		100		1.00	100		50.0		100		0.00
Hoehn & Yahr stage (0/5)		3.8(0.9)		3.5(2.1)		4.0(0.0)		3.9(1.0)	0.99		4.0(1.1)		4.3(1.0)		4.3(0.9)	0.57
Schwab & England (0/100%)		44.6 (14.4)		40.0 (28.3)		49.0(0.0)		40.0 (14.1)	0.34		32.3(9.3)		37.5(15.0)		31.6(10.9)	0.58
NPI delusions (0/12) (Cutoff ≥3)	4.5	0.2(0.9)	50.0	4.5(6.4)	0	0	25.0	1.5(3.0)	0.11	15.4	0.9(1.5)	25.0	2.0(4.0)	25.7	2.0(3.0)	0.48
NPI hallucinations (0/12) (Cutoff ≥3)	4.5	0.3(1.3)	50.0	4.5(6.4)	0	1.0(1.4)	25.0	1.8(2.9)	0.10	30.8	1.9(2.3)	0	0	40.0	2.5(3.2)	0.15
NPI depression (0/12) (Cutoff ≥3)	40.9	2.8(2.4)	100	6.0(4.2)	0	1.0(0.0)	25.0	2.8(2.2)	0.27	84.6	3.8(1.6)	50.0	3.3(3.6)	65.7	3.6(2.4)	0.84
NPI apathy (0/12) (Cutoff ≥3)	27.3	1.8(2.6)	50.0	7.0(7.1)	0	0	50.0	3.5(3.0)	0.11	61.5	3.7(3.0)	50.0	3.5(3.3)	68.6	4.9(3.9)	0.65
NPI sleep disorders (0/12) (Cutoff ≥3)	27.3	1.9(2.5)	100	6.5(3.5)	0	1.0(1.4)	0	0.3(0.5)	0.11	61.5	4.0(3.1)	0	0.5(1.0)	40.0	2.9(3.9)	0.08
Pill questionnaire (0/3) (Cutoff ≥2)	50.0	1.4(1.1)	100	2.5(0.7)	0	1.0(0.0)	25.0	1.5(1.0)	0.23	76.9	2.2(1.1)	75.0	1.8(0.5)	97.2	2.8(0.6) ^{b,c}	0.00
GDS score (0/30) (Cutoff 11-20: mild depression; 21-30: severe depression)	76.2	13.5(5.3)	100	18.0(0.0)	50.0	9.0(1.4)	100	17.0(5.4)	0.27	91.7	19.3(6.7)	100	14.3(3.1)	80.0	15.7(5.2)	0.12
MMSE score	18.2	-0.4(1.3)	0	-0.7(1.2)	0	0.7(1.6)	75.0	-1.4(0.7)	0.19	100	-5.0(4.3) ^d	100	-3.1(1.2)	100	7.5(2.8) ^{b,c,e}	0.00
Orientation	9.1	-0.1(0.9)	100	-2.8(1.3) ^a	0	0.6(0.0)	50.0	-1.2(1.4)	0.04	92.3	-3.7(2.9)	50.0	-1.5(1.5)	86.5	-5.7(3.6) ^{c,e}	0.03

Orientation to time	40.9	-0.7(1.5)	100	-5.3(2.4)	0	0.4(0.1)	75.0	-1.9(2.0)	0.08	100	-4.4(2.8) ^f	75.0	-2.2(1.8)	94.6	-6.3(3.7) ^{c,f}	0.08
Orientation to place	4.5	0.4(0.4)	0	0.4(0.1)	0	0.5(0.1)	25.0	-0.3(1.4)	0.69	46.2	-1.8(3.0)	25.0	-0.6(1.6)	51.4	-2.1(2.7)	0.64
Immediate recall	0	0.0(0.0)	0	0	0	0.0(0.0)	0	0.0(0.0)	1.00	0	-0.1(0.3)	0	0	13.5	-0.6(1.6)	0.40
Attention and calculation	22.7	-0.5(1.4)	50.0	-1.2(2.6)	50.0	-0.3(1.9)	25.0	-0.6(1.6)	0.97	69.2	-3.4(4.7)	50.0	-0.6(1.1)	78.4	-4.0(4.6) ^{g,i}	0.19
Delayed recall	0	0.5(0.6)	0	0.7(0.4)	0	1.2(0.4)	0	0.0(0.8)	0.20	30.8	-0.4(1.4)	25.0	-0.3(1.0)	59.5	1.5(1.1) ^{b,e,g}	0.00
Language	18.2	-0.5(1.4)	0	0.7(0.2)	0	0.5(0.5)	50.0	-0.7(1.5)	0.32	53.8	-3.1(4.8)	50.0	-3.8(4.3)	94.6	-4.1(2.3) ^{e,g}	0.09
Naming	0	0	0	0	0	0	0	0	1.00	0	0	0	0	0	-0.1(0.3)	0.49
Repetition	0	0	0	0	0	0	0	0	1.00	0	0	0	0	35.1	-0.4(0.5) ^b	0.02
Verbal complex order comprehension	36.4	-1.4(2.7)	0	0.4(0.1)	50.0	-0.5(1.3)	50.0	-0.8(1.3)	0.41	53.8	-3.9(5.8)	75.0	-4.5(4.6)	81.1	-3.5(2.7) ^e	0.73
Reading comprehension	0	0.1(0.2)	0	0	0	0.2(0.2)	0	0	0.45	0	0.0(0.4)	0	0.1(0.2)	13.5	-1.1(3.2) ^h	0.83
Writing	0	0.3(0.3)	0	0.5(0.2)	0	1.0(0.6)	50.0	-0.6(1.0) ^e	0.03	23.1	-0.5(1.7)	50.0	-1.4(2.6)	64.9	-1.3(1.4) ^h	0.17
Construction	13.6	0.4(1.1)	50.0	-0.6(2.0)	50.0	0.1(1.8)	50.0	-0.6(1.3)	0.28	53.8	-1.0(1.2)	75.0	-2.0(0.8)	70.3	-1.4(0.9) ^g	0.30
Executive function	0	-0.3(0.4)	50.0	-0.9(0.2)	0	-0.3(0.2)	25.0	-1.0(0.7) ^a	0.03	76.9	-1.1(0.4) ^j	25.0	-0.5(0.5)	94.6	1.8(0.6) ^{b,e,c}	0.00
Working memory	9.1	-0.2(0.7)	0	-0.3(1.1)	0	-0.3(0.4)	0	-0.6(0.3)	0.51	46.2	-1.0(1.0)	0	0.4(1.0) ^b	37.8	-1.2(0.9) ^{c,k}	0.03
Conceptualization	0	0.6(0.8)	0	0.7(0.5)	0	0.2(0.2)	0	0.4(0.5)	0.76	23.1	-0.1(1.2)	0	0.2(0.9)	18.9	-0.4(0.9)	0.31
Set activation	38.1	-0.6(1.1)	50.0	-1.2(0.4)	0	-0.5(0.3)	100	-1.5(0.4)	0.23	69.2	-1.4(0.8) ^k	75.0	-1.5(0.8)	88.9	-1.8(1.0) ^k	0.35
Set shifting	65.0	-1.4(0.9)	100	-2.9(0.4)	100	-2.1(0.0)	75.0	-2.8(1.9)	0.08	100	-2.7(0.7)	100	-1.5(0.1)	93.8	-4.0(1.9) ^c	0.02
Set maintenance	10.5	0.4(0.8)	100	-3.0(0.0)	0	0.4(0.0)	50.0	-1.0(1.3)	0.06	22.2	-0.9(1.1)	66.7	-1.5(2.4)	93.3	3.1(0.9) ^{b,e,k}	0.00
Behavioral control	18.2	-0.5(0.9)	0	0	0	0	25.0	-0.5(1.0)	0.72	33.3	-0.8(1.1)	0	0	44.4	-1.1(1.3) ^k	0.20
Memory	28.6	-0.4(0.8)	50.0	-0.7(0.4)	0	-0.4(0.3)	75.0	-1.7(1.2)	0.22	69.2	-1.3(1.2)	50.0	-1.1(0.5)	97.2	-2.4(0.8) ^{b,c,l}	0.00
Memory (only subcortical-frontal component)	9.5	-1.2(0.1)	50.0	-1.6(0.0)	0	0	0	0	0.67	53.8	-2.2(1.0)	0	0	5.6	-1.5(0.5)	0.50
. Total learning	100	-1.4(0.1)	100	-1.6(0.0)	0	0	0	0	0.67	100	-2.8(1.1)	0	0	100	-2.8(1.1)	1.0
. Learning over trials	50	-0.9(0.4)	100	-1.7(0.0)	0	0	0	0	0.67	57.1	-1.6(1.2)	0	0	0	-0.3(0.1)	0.06
Memory (only mediotemporal component)	14.3	-2.0(0.6)	50.0	-1.1(0.0)	50.0	-1.8(0.0)	25.0	-1.5(0.0)	0.47	7.7	-1.6(0.0)	100	-1.7(0.8)	11.1	-2.3(0.7)	0.32
. Long term percent retention index	100	-2.6(1.2)	100	-1.6(0.0)	100	-1.6(0.0)	0	-0.4(0.0)	0.22	100	-1.1(0.0)	75.0	-2.3(2.0)	75.0	-2.6(1.7)	0.85
. Delayed recognition	33.3	-1.3(1.0)	0	-0.5(0.0)	100	-2.0(0.0)	100	-2.5(0.0)	0.47	100	-2.0(0.0)	25.0	-1.1(0.6)	100	-2.0(0.4)	0.16
Memory (both components impaired)	14.3	-1.6(0.2)	0	0	0	0	50.0	-2.6(0.5)	0.20	23.1	-1.7(0.1)	0	0	80.6	-2.7(0.6)	0.01
. Total learning	100	-1.8(0.1)	0	0	0	0	100	-2.0(0.4)	1.0	100	-2.1(0.2)	0	0	100	-3.2(0.7)	0.03
. Learning over trials	33.3	-0.7(0.7)	0	0	0	0	50.0	-2.3(2.4)	0.40	66.7	-1.0(0.2)	0	0	72.4	-1.5(1.0) ^m	0.38
. Long term percent retention index	66.7	-1.7(0.8)	0	0	0	0	100	-3.7(0.4)	0.20	100	-1.7(0.2)	0	0	89.7	-3.4(1.2)	0.04
. Delayed recognition	100	-2.0(0.5)	0	0	0	0	100	-2.3(0.4)	0.80	100	-1.8(0.3)	0	0	100	-2.7(0.9) ^m	0.04
Instrumental function	9.5	-0.2(0.6)	0	-0.1(0.2)	100	-1.3(0.3)	50.0	-1.4(1.0) ^a	0.02	16.7	-0.6(0.5)	75.0	-1.8(1.1)	97.2	-2.3(0.7) ^{b,l}	0.00
Language	4.5	0.4(1.0)	0	0.5(0.0)	0	-1.0(0.0)	25.0	-0.8(0.9)	0.05	0	0.2(0.8)	50.0	-1.1(1.0) ^b	14.3	-0.5(0.7)	0.02
Visuo-constructive	23.8	-0.1(1.5)	0	0.7(0.6)	50.0	-0.6(1.3)	25.0	-1.3(3.2)	0.47	40.0	-0.5(1.3)	100	-4.3(2.0)	94.3	-4.9(2.1) ^{b,c}	0.00
Visuospatial	28.6	-0.5(1.1)	50.0	-1.0(1.4)	100	-1.5(0.0)	75.0	-1.4(0.9)	0.53	60.0	-1.4(0.7)	75.0	-0.5(1.9)	94.1	-1.9(0.4) ^{b,n}	0.00
Visuoperceptive	30.0	-0.5(1.1)	0	-0.5(0.0)	100	-2.0(0.0)	100	-2.0(0.0) ^a	0.04	37.5	-0.8(1.1)	75.0	-1.4(0.9)	82.4	-1.7(0.6) ^{b,n}	0.04

Supplementary Table 4. Comparative analysis of the LSPD patients' cognitive performance according to their cognitive profile in non-dementia vs dementia groups.

Sub-groups were compared using the Chi-squared (nominal variables), Wilcoxon, and the Kruskal-Wallis tests with post hoc pairwise analysis and Mann-Whitney U test for pairwise comparison between non-dementia and dementia sub-groups (continuous variables) ($p < 0.05$ is significant)

LSPD- Late-Stage Parkinson's disease patients

NPI- Neuropsychiatric Inventory

GDS- Geriatric Depression Scale

MMSE- Mini-Mental State Exam

^a $p < 0.05$, different from heterogeneous group, with Bonferroni correction

^b $p < 0.05$, different from subcortical profile group, with Bonferroni correction

^c $p < 0.05$, different from cortical group, with Bonferroni correction

^d $p < 0.05$, different from subcortical profile non-demented group

^e $p < 0.05$, different from global impairment non-demented group

^f $p < 0.05$, different from orientation to place

^g $p < 0.05$, different from orientation

^h $p < 0.05$, different from verbal complex order comprehension

ⁱ $p < 0.05$, different from delayed recall

^j $p < 0.05$, different from instrumental function

^k $p < 0.05$, different from set shifting

^l $p < 0.05$, different from executive function

^m $p < 0.05$, different from long-term percent retention index

ⁿ $p < 0.05$, different from visuo-constructive

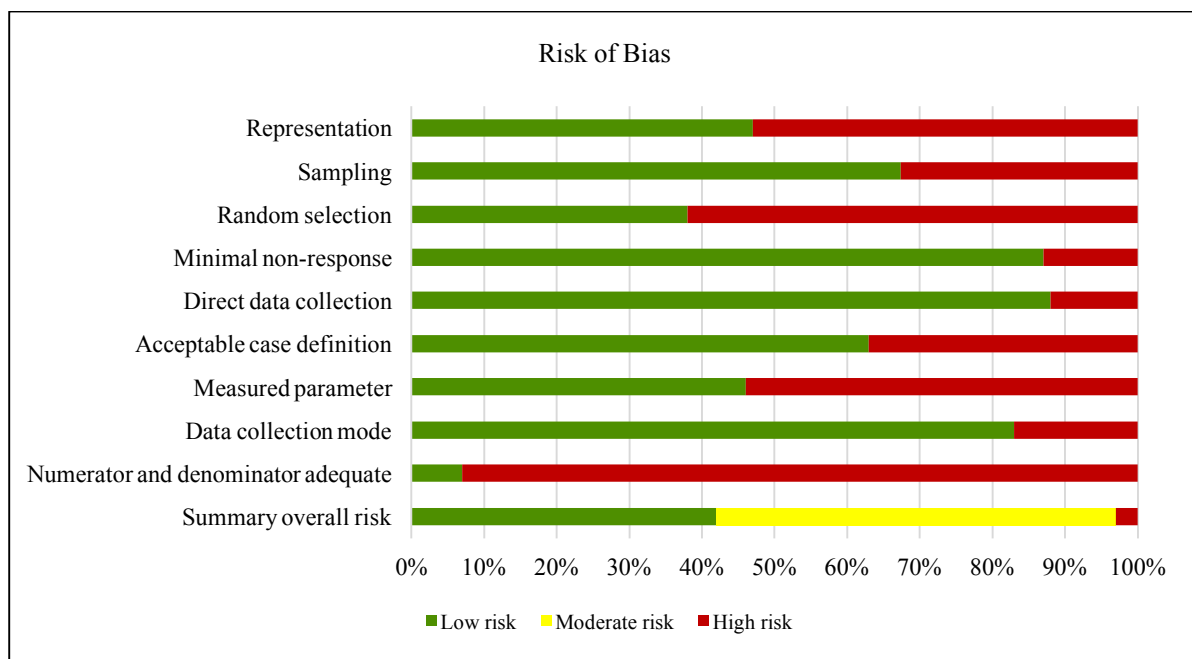
Supplementary Figures

Database: Embase <1974 to 2019 May 21>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 21, 2019>

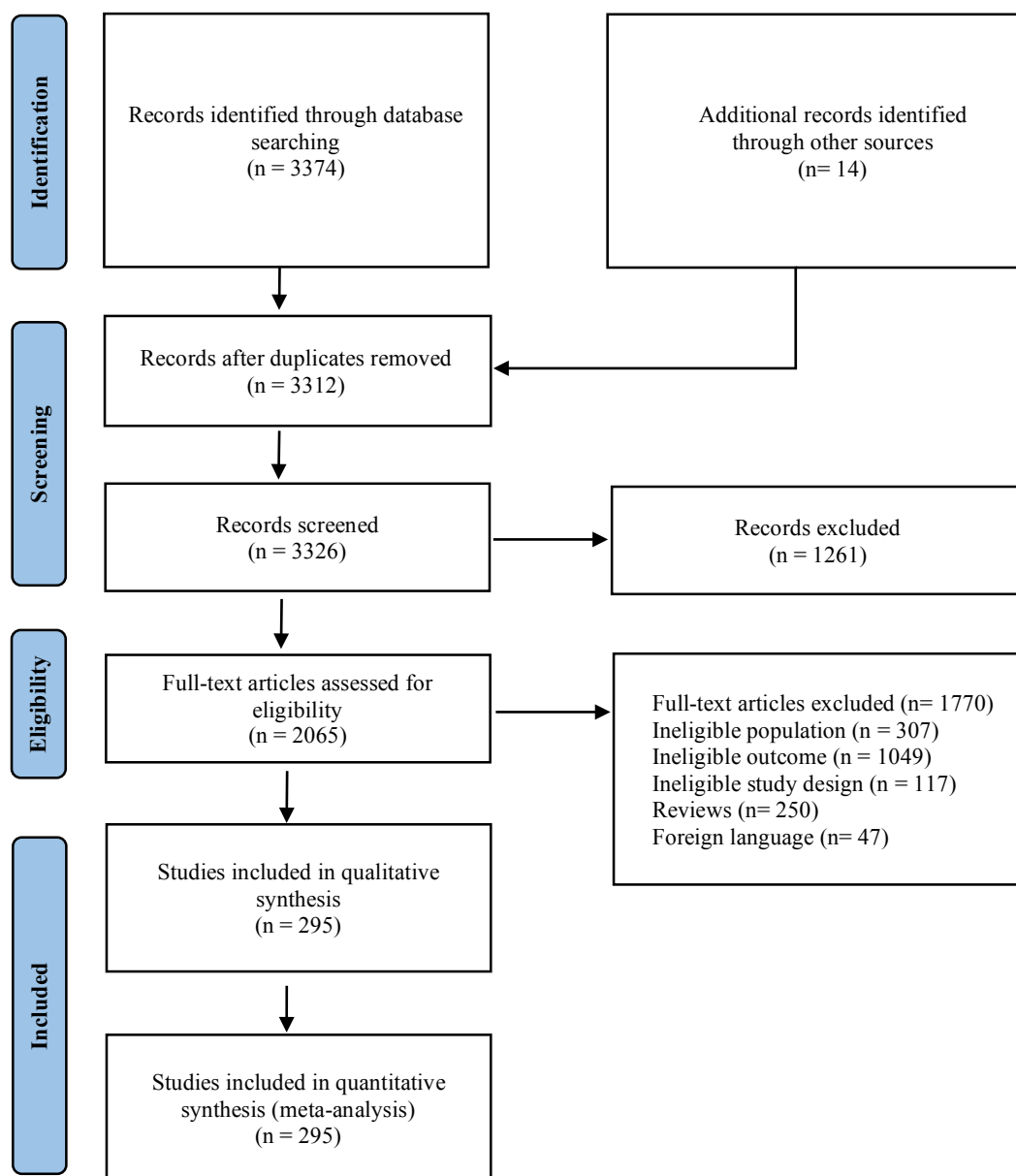
Search Strategy:

-
- 1 exp Parkinson disease/
 - 2 Parkinson's disease.ab,ti.
 - 3 Parkinson disease.ab,ti.
 - 4 Parkinsons disease.ab,ti.
 - 5 1 or 2 or 3 or 4
 - 6 exp Cognitive Dysfunction/
 - 7 exp dementia/
 - 8 non-motor symptoms.ab,ti.
 - 9 ((cognit* or neurocognit* or memory*) adj3 (impair* or declin* or deteriorat* or deficit*)).ab,ti.
 - 10 dementia.ab,ti.
 - 11 6 or 7 or 8 or 9 or 10
 - 12 exp incidence/
 - 13 exp prevalence/
 - 14 exp epidemiology/
 - 15 exp cohort analysis/
 - 16 exp longitudinal study/
 - 17 exp prospective study/
 - 18 exp follow up/
 - 19 cohort*.ab,ti.
 - 20 longitudinal.ab,ti.
 - 21 prospective.ab,ti.
 - 22 prevalen*.ab,ti.
 - 23 inciden*.ab,ti.
 - 24 exp animals/ not humans.sh.
 - 25 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
 - 26 5 and 11 and 25
 - 27 26 not 24
 - 28 remove duplicates from 27

Supplementary Figure 1. Search strategy



Supplementary Figure 2. Risk of Bias evaluation

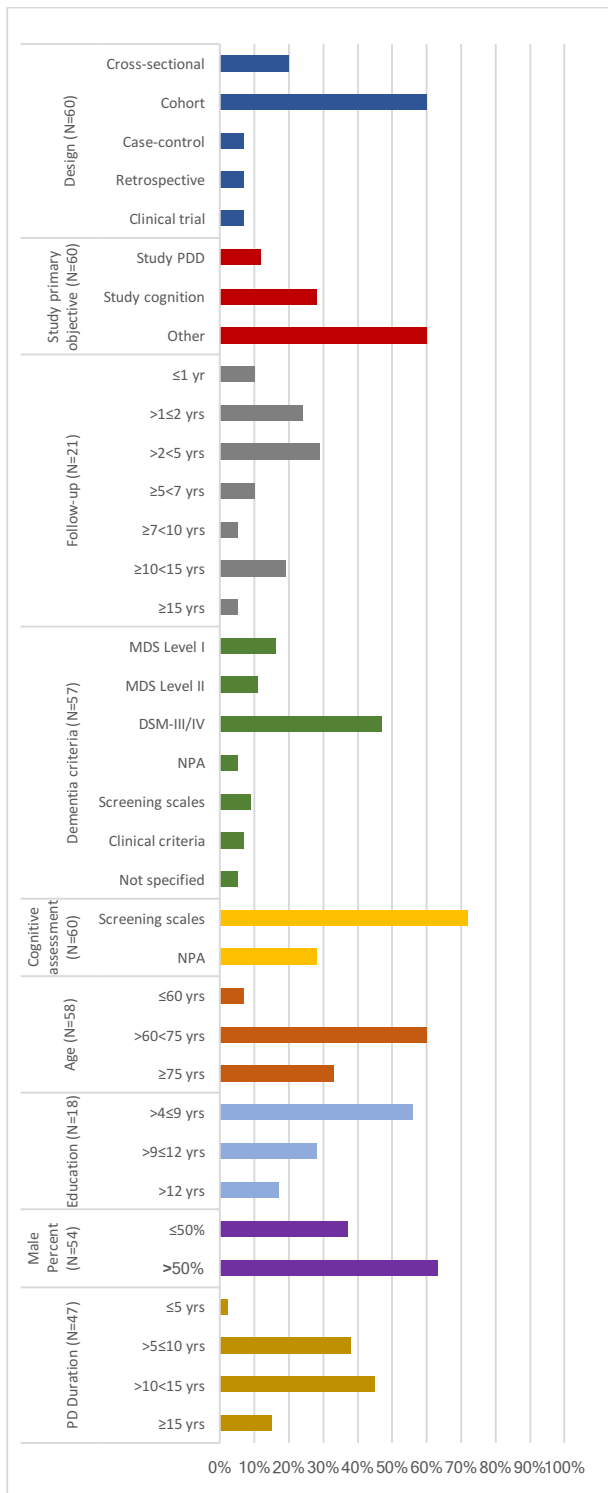


Supplementary Figure 3. PRISMA Systematic review flowchart

Database: Embase <1974 to 2019 May 21>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 21, 2019>
Search Strategy:

-
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 - 7 exp dementia/
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 - 9 ((cognit* or neurocognit* or memory*) adj3 (impair* or declin* or deteriorat* or deficit*)).ab,ti.
 - 10 dementia.ab,ti.
 - 11 6 or 7 or 8 or 9 or 10
 - 12 exp incidence/
 - 13 exp prevalence/
 - 14 exp epidemiology/
 - 15 exp cohort analysis/
 - 16 exp longitudinal study/
 - 17 exp prospective study/
 - 18 exp follow up/
 - 19 cohort*.ab,ti.
 - 20 longitudinal.ab,ti.
 - 21 prospective.ab,ti.
 - 22 prevalen*.ab,ti.
 - 23 inciden*.ab,ti.
 - 24 exp animals/ not humans.sh.
 - 25 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
 - 26 5 and 11 and 25
 - 27 26 not 24
 - 28 remove duplicates from 27

Supplementary Figure 4. Search strategy



Supplementary Figure 5. Studies' and PD patients' characterization

PD- Parkinson's disease; PDD-Parkinson's disease dementia; MDS-Movement Disorder Society; NPA-Neuropsychological assessment; H&Y- Hoehn and Yahr