Cognitive Impairment in Parkinson's Disease: What We Know so Far

This article was published in the following Dove Press journal:
Research and Reviews in Parkinsonism

Celia Painous

Maria J Marti

Parkinson and Movement Disorders Unit,
Neurology Service, Hospital Clínic
Universitari, Institut d'Investigacions
Biomèdiques August Pi i Sunyer
(IDIBAPS), University of Barcelona;
Centro de Investigación Biomédica en
Red de Enfermedades
Neurodegenerativas (CIBERNED),
Barcelona, Catalonia, Spain

Abstract: One of the most impactful non-motor manifestations of Parkinson's disease (PD) is cognitive impairment. Cognitive decline in PD exists as a continuum, with symptoms ranging from normal cognition to mild cognitive impairment (MCI) and finally dementia (PDD). MCI is clinically heterogeneous and its progression varies with cases reverting to normal cognition. On the contrary, when dementia occurs, the decline is usually rapid and stereotyped. The combination of Lewy and Alzheimer's disease pathology is the most robust pathological correlate of PDD. There are no approved drugs for PD-MCI and the benefit from the only approved symptomatic treatment for PDD is modest. This review aims to present the aspects in which greater evidence exists and summarize the epidemiology, pathogenesis, clinical features, diagnostic approach, and treatment of cognitive dysfunction and dementia in PD.

Keywords: Parkinson, dementia, mild cognitive impairment, review, biomarker, diagnosis, treatment

Introduction

Parkinson's disease (PD) has been traditionally considered a motor disorder but non-motor symptoms including cognitive impairment and dementia, depression, psychosis, autonomic disturbances, and sleep disorders have increasingly been recognized. Cognitive dysfunction and dementia can have a greater effect than motor symptoms on the quality of life of the patient and caregivers,¹ as well as being a risk factor for nursing home admission² and early mortality.³ Due to all these impactful consequences cognition in PD has been the subject of extensive research, covering multiple perspectives and promoting an enormous amount of literature.

In the text that follows we review the epidemiology, pathogenesis, CSF biomarkers, clinical features, diagnostic approach, and treatment of cognitive dysfunction and dementia in PD aiming to present the aspects in which greater evidence exists. **Box 1** highlights the key points of this review.

Epidemiology

Cognitive deficits are common in PD even in early stages and over 75% of PD patients may eventually develop dementia (PDD) over time.⁴⁻⁶ Cognitive decline in PD exists as a continuum, with symptoms ranging from normal cognition to subjective cognitive changes with normal neuropsychological assessment, mild cognitive impairment (PD-MCI), and finally dementia. The classification into those groups among different studies vary depending on the design of the study and the criteria applied.^{7,8}

Correspondence: Maria J Marti
Parkinson's Disease & Movement
Disorders Unit, Hospital Clínic de
Barcelona, Hospital Clínic, 170 Villarroel
Street, Barcelona, Catalonia 08036, Spain
Tel +34 932275785
Email mjmarti@clinic.cat

Box I Key Points

Cognitive deficits are common in PD even in early stages and over 75% of PD patients will present dementia over time.⁴⁻⁶

The combination of Lewy pathology and Alzheimer's disease (AD) pathologies (ie beta-amyloid plaques and neurofibrillary tangles) is the most robust pathological correlate of PDD.

Pathological and neuroimaging studies consistently support an association for a cholinergic deficit with cognition in PD³³⁻³⁸

Specific diagnostic clinical criteria have been established for PD-MCI and PDD.^{9,10}

The difference between MCI and PDD is based on the extent to which cognitive impairment interferes with daily life activities.^{9,10}

PD-MCI entails an increased risk of dementia. However, some patients with PD-MCI will revert to normal cognition.

Older age, postural instability-gait disorder phenotype, psychiatric symptoms as psychosis, hallucinations, and depression, REM sleep behavior disorder, and diurnal sleepiness have been associated with PD cognitive worsening.^{10,18-21}

Low levels of A β and increased levels of tau in the CSF at baseline might predict future cognitive decline in patients with PD.⁵⁶⁻⁵⁹

Rivastigmine has been designated as clinically useful in PDD.¹¹²

There is insufficient evidence for the use of other anticholinesterase inhibitors in PD-MCI.

In the last decade, the International Parkinson and Movement Disorder Society (MDS) has proposed formal diagnostic criteria for both PD-MCI and PDD.^{9,10} For PD-MCI cognitive deficits should be present on neuropsychological testing and should not interfere with functional autonomy. Estimates of the prevalence of PD-MCI vary widely with a recent estimate of around 26%.¹¹ Two cross-sectional studies have estimated MCI prevalence in 33% and 64% respectively.^{12,13} A pooled analysis of data from eight different cohorts comprising 1346 non-demented PD patients showed that 25.8% of patients had MCI.¹⁴

Specific diagnostic clinical criteria have also been established for possible and probable PD-associated dementia.¹⁰ Diagnosis of dementia must be based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuospatial functions) documented by clinical and cognitive examination, and be severe enough to affect normal functioning. A systematic review of the prevalence of PDD including 12 selected studies found a point prevalence of 24 to 35%.¹⁵ Different studies have indicated an association between the prevalence of dementia and disease duration. In the CamPaIGN study, a dementia prevalence rate of 15 to 20% after 5 years and 46% at 10 years was reported.^{6,16} Although progression to dementia seems not to be inevitable, it develops in about 80% of PD patients with disease duration, especially longer than 20 years.¹⁷ Older age, postural instability-gait disorder phenotype, psychiatric symptoms as psychosis, hallucinations, and depression, REM sleep behavior disorder, and diurnal sleepiness have been associated with PD cognitive worsening.^{10,18-21} As for genetic causes of PD, α -synuclein duplication and triplication, DJ1, GBA, and MAPT mutations

have been linked to prominent cognitive dysfunction and dementia while LRRK2 and Parkin mutations have not.²²⁻²⁴

Pathogenesis of PDD

Although the exact neurobiological basis of PDD is not known, dementia in PD probably occurs as a result of progressive involvement of subcortical and cortical structures by Lewy-type pathology and associated Alzheimer histological changes. Other factors such as vascular pathology, among others, may contribute to the development of PDD in some cases.

Neuropathological Correlates

Neuropathological studies using α -synuclein immunohistochemistry have demonstrated that cortical and limbic involvement by Lewy bodies (LB) and Lewy neurites are the dominant and primary substrate of PDD.¹⁷ In a recent systematic review including 41 autopsy studies of pathologically-verified PD cases with dementia, α -synuclein pathology almost invariably extended to the limbic system or neocortex and neocortical involvement was more frequent than in non-demented PD patients.²⁵ The severity of cognitive impairment correlated with Lewy body densities in the frontal, straight, angular, cingulate, and middle temporal gyri. In PDD brains, Alzheimer's disease (AD) -type and LB-type pathologies frequently coexist, suggesting there are interactions between α -synuclein, tau, and amyloid- β (A β) proteins aggregates. In fact, in combined Lewy-Alzheimer transgenic mice models, both enhancement of α -synuclein aggregation by A β peptides²⁶ and exacerbation of tau and A β accumulation by α -synuclein, lead to the acceleration of neuropathology and cognitive

decline.²⁷ In the above mentioned systematic review²⁵, tau and A β pathologies in demented PD cases were typically moderate to severe only in the entorhinal cortex and mild in the hippocampus. The neocortex was variably affected by amyloid- β . In contrast, what is happening in AD, tau pathology was more prevalent in prefrontal than in the temporal cortex. As for the relative contribution of AD pathology to dementia in PD, tau lesions have been independently associated in one study²⁸ but A β , in contrast, was not independently related to dementia in any study but moderate to severe deposition has been associated with a more rapid cognitive decline^{29,30} and earlier mortality.³¹ In another pathological study coexistence of LB-type and tau and A β pathologies was found to be a better predictor of dementia than the severity of a single pathology.³²

Neurochemical Deficits in PDD

Degeneration of subcortical nuclei in PD leads to dopaminergic, cholinergic, noradrenergic, and serotonergic deficits. Of them, cholinergic deficits due to degeneration of the nucleus basalis of Meynert (NBM) have been the most involved in PDD. In early neuropathological studies, PDD patients showed more NBM cholinergic neuronal depletion when compared with AD and non-demented PD.^{33,34} A greater reduction of choline acetyltransferase activity (indicative of cholinergic innervation) in frontal and temporal cortex was found in PDD than in PD without dementia.³⁵ Mattila et al reported reduced choline acetyltransferase activity in the hippocampus, prefrontal cortex, and temporal cortex in PD. Reduction in the frontal cortex correlated significantly with the degree of cognitive impairment.³⁶ Not only pathological studies but also neuroimaging studies have pointed out a role for a cholinergic deficit in cognition in PD. Both PD and PDD have cholinergic neuron deficits with vesicular acetylcholine transporter (VACHT) and acetylcholinesterase (AChE)^{37,38} imaging being the decreased VACHT more important and extensive in the cerebral cortex of PDD subjects.³⁹

As for the dopaminergic system, evidence indicates that it may contribute to some of the cognitive problems in PDD. Executive dysfunction has been associated with denervation of striatal dopamine and D2 receptor deficiency in the insula lobe region in PD-MCI⁴⁰ and with degeneration of nigrostriatal dopaminergic neurons in early PD, but not with memory and visual-spatial functions.⁴¹ Another study, however, using ¹¹C-DTBZ and ¹¹C-FLB 457 PET imaging, demonstrated that memory-impaired PD patients had more significant reductions in D2 receptor binding in the insular cortex,

anterior cingulate cortex, and the right parahippocampal gyrus compared to healthy controls and patients cognitively normal.⁴²

There are not consistent findings supporting an association between dementia and other monoaminergic systems.

Cerebro-Vascular Pathology

The contribution of cerebral vascular lesions in PDD is controversial. In an 18 months prospective study we found that progression to dementia was more frequent in PD patients with moderate to severe parieto-occipital white matter hyperintensities (WMH) and low CSF A β levels.⁴³ Others have reported increased burden of WMH in PD subjects later progressing to dementia⁴⁴ and the WMH volume has been found to predict longitudinal cognitive decline among PD patients with MCI⁴⁵ and early PD.⁴⁶ However, in a multicenter study, no differences were observed in early PD and normal controls⁴⁷ and more recently a pathological study found no correlation between the severity of subcortical small vessel disease and dementia.⁴⁸ A possible explanation of these apparent discrepancies is that the presence of cerebrovascular lesions might be modest cross-sectionally but it might have a role in cognitive worsening with the progression of the disease.

CSF Biomarkers in PDD

Many studies on CSF aimed to identify biomarkers reflecting the abnormal protein aggregates associated with PDD. In the majority of them, the level of A β was found reduced^{49–52} whereas the levels of total (t-tau) and phosphorylated tau (ptau) were increased^{49,50,53,54} or unchanged^{52,55} in PDD. The use of more or less strict definition for dementia and the inclusion of more or fewer patients with “AD- memory problems” can partially account for the discrepancies in the tau level reported.

Based on the data from cross-sectional and longitudinal studies there is the strongest evidence that low levels of A β and increased levels of tau in the CSF at baseline might predict future cognitive decline in patients with PD.^{56–59}

We performed a longitudinal study in non-demented PD patients including CSF, neuropsychological and MRI at baseline and 18 months follow-up.⁶⁰ We found that a combination of lower CSF A β , reduced verbal learning, semantic fluency, and visuo-perceptual scores, as well as cortical thinning in superior-frontal/anterior cingulate and precentral regions, were predictive for PDD. In this sense, different studies have shown that a combination of clinical, biological, and

neuroimaging markers could be predictive for deterioration in cognition in PD with good accuracy.^{59,61,62}

Several studies of CSF levels of total α -synuclein have been published, most of them reporting low values in PD, which has been confirmed by a recent meta-analysis performed by Eusebi et al.⁶³ However, the relationship between α -synuclein levels and cognitive decline remains uncertain. Both high^{64,65} and low⁶⁶ CSF levels have been observed as significant predictors of cognitive impairment in PD. In general, the association between high levels and cognitive impairment was found in more advanced disease stages. In other studies, no prognostic effect was observed. In addition to total α -synuclein, post-translationally modified forms such as oligomeric α -synuclein, have been analyzed concerning PD cognition. Hansson et al found levels of CSF α -synuclein oligomers significantly higher in patients with PDD and DLB compared with patients with AD and controls.⁶⁷ Compta et al determined CSF oligomeric- and total- α -synuclein in patients with idiopathic REM-sleep behavior disorder (iRBD) and non-demented PD and PDD intended to reflect the premotor-motor-dementia PD continuum. CSF oligomeric- α -synuclein was higher in non-demented than iRBD and PDD than iRBD and controls and correlated with UPDRS-III, MMSE, semantic fluency and visuosperceptive scores.⁶⁸ Although promising further research is needed to confirm the diagnostic and prognostic utility as markers of oligomeric and other forms of α -synuclein for cognitive impairment in PD.

Clinical Characteristics

The difference between MCI and PDD is based on the extent to which cognitive impairment interferes with daily life activities.^{9,10} PD-MCI is clinically heterogeneous with a range of cognitive domains affected. PD-MCI can be classified into single or multiple domains, being the domains attention, executive, language, memory, and visuospatial functions. If neuropsychological assessment includes one test for each of the five domains it is considered as level 1 assessment for detecting MCI-PD, whereas a level 2 assessment includes at least two tests for each domain and allow for MCI subtyping.⁹ Using level II criteria, multi-domain MCI is more frequent than a single domain.^{9,69} Non-amnestic is the most frequent subtype in PD-MCI single domain according to several studies.^{8,9,70} In PD-MCI multi-domain, the most affected domains are executive, visuospatial, memory, and attention tasks.⁸ Although less frequently, language impairment has also been observed in some studies.⁷¹ The “dual syndrome hypothesis” has been proposed to distinguish between MCI: 1) in some, there is a predominant frontal-

striatal impairment (disturbances in planning, working memory, and response inhibition), modulated by dopamine, that may be present even in very early phases of PD and frequently with little progression over time; 2) patients with predominant temporal and posterior cortical dysfunction (attentional, semantic verbal fluency, and visual-spatial difficulties) which are more likely to progress to dementia.^{72,73} PD-MCI usually precedes PDD and patients with PD-MCI present a higher risk (19%–62%) of developing dementia when they are followed from 2 to 5 years after diagnosis.⁷⁴ However, some patients with PD-MCI will revert to normal cognition during follow-up. In a community-based cohort study that assessed 115 newly diagnosed patients with PD found that having MCI at baseline (n: 49, 42.6%) increased the risk of developing PDD (n: 25, 51%) within 5 years 6.5 times (Hazard ratio: 6.5, 95% CI 2.60–16.13, $p < 0.001$).⁷⁵ Besides, six patients (12.40%) that were initially classified as MCI reversed back to normal cognition and ten patients fluctuated between MCI and normal cognition at different assessments.⁷⁵ Another prospective cohort study with 178 PD patients at baseline evidenced that 39.1% of patients with PD-MCI progressed to dementia. Those who had persistent PD-MCI (OR: 16.6, 95% CI: 5.1–54.7) and those who converted from normal cognition to PD-MCI (OR: 6.4, 95% CI: 1.7–23.8) at the 1-year follow-up presented an increased risk to develop dementia compared to those with normal cognition.⁷⁶ Finally, a recent meta-analysis showed that 20% (95% CI 13–30%) PD-MCI patients converted to dementia while 28% (95% CI 20–37%) reverted to a state of normal cognitive function. When the study follow-up was equal or greater than 3 years, rates to MCI and dementia were higher, and reversion rates lower.⁷⁷

PDD is characterized by a more devastating cognitive impairment and is a common late manifestation in PD. Unlike MCI, when dementia occurs the decline is usually more rapid and stereotyped.⁷⁸ Dementia involves executive, attention, visuospatial, and memory impairment, with the language being usually preserved.¹⁰ Executive dysfunction is at the root of most cognitive changes in PD and is characterized by impairment in planning, abstract thinking, mental flexibility, verbal fluency, and apathy. Patients with impaired attention may present difficulties to follow a conversation and present drowsiness and reduced arousal. The attentional deficit has been shown to interfere significantly in the patient's quality of life.⁷⁹ Regarding memory, PDD patients typically present poor performance in free recall with benefit from cueing, but some patients may also present impaired recognition similar to what is seen in

Alzheimer's disease.⁸⁰ Visuospatial problems include both visuospatial and visuoperceptive deficits and present high sensitivity to detect the conversion to PDD.^{73,81}

PDD is often accompanied by neuropsychiatric symptoms such as mood disorders, psychosis, and hallucinations. Visual hallucinations are typically complex, with well-formed figures such as people, animals or objects and often with preserved insight.⁸²

Sleep problems like excessive daytime sleepiness or insomnia and autonomic disturbances including urinary incontinence and orthostatic and postprandial hypotension are also frequent in PDD.

Diagnostic Approach

Differential diagnosis between DLB and PDD has been based on an arbitrary distinction between the time of onset of motor and cognitive symptoms.⁸³ Thus, the Movement Disorders Society does not consider any more the presence of dementia in an early phase as an exclusion criterion for PD.⁸⁴ A diagnosis of PDD is based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuospatial functions) and those have to be severe enough to impair activities of daily living.¹⁰ For the differential diagnosis with other kinds of dementia, the neuropsychological battery is the gold standard. It is recommended, at least, to cover cognitive domains most frequently affected and to use more than 1 test per domain to increase sensitivity.⁸⁵

The assessment of cognition with cognitive rating scales is frequent and can be useful for screening and monitoring in clinical practice. A recent systematic review by the Movement Disorders Society classified the Montreal Cognitive Assessment (MoCA), the Mattis Dementia Rating Scale Second Edition (DRS-2), and the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) as recommended scales.⁸⁵ The MoCA is a brief (10–30 minutes), 30-point, cognitive test which was developed as a screening measure for MCI. It covers visuospatial and executive functions, attention and memory, language, and orientation.⁸⁶ Cutoff points have been established in 25/26 for PD-MCI and 20/21 for PDD.⁸⁷ The DRS-2 is a global cognitive function test, administered in 20–30 minutes, for patients with neurodegenerative diseases.⁸⁸ It assesses different cognitive areas like attention, initiation-perseveration, construction, conceptualization, and memory. Cutoff scores have been established at 132/144 for PDD and 139/144 for PD-MCI.^{89,90} The PD-CRS is a brief scale, specifically designed to capture the whole spectrum of cognitive functions impaired throughout Parkinson's disease. It is

composed of frontal and subcortical tasks (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate and delayed free recall verbal memory) and posterior cortical tasks (confrontation naming and clock copying).⁹¹ Administration time is about 20 minutes. Overall, these three scales have been validated and show good test-retest and interrater reliability.^{85,91,92} The Mini-Mental State Examination (MMSE) has been traditionally used as a standard bedside clinical test for cognitive dysfunction. However, it is not recommended as the first option of neuropsychological evaluation because it evaluates cortical cognitive aspects, which are usually preserved in PDD, but its sensitivity to detect executive dysfunction is low.

Neuroimaging

Structural and functional imaging is not recommended in the differential diagnosis between PDD and other types of dementia. However, studies have reported some differences between PD with cognitive problems and control groups.

Cross-sectional studies have indicated higher regional brain atrophy in PDD and PD-MCI when comparing with control groups (healthy subjects, PD patients without cognitive impairment or subjects with other dementias), specifically in the frontal, temporal, parietal and basal forebrain areas.^{93,94} Subcortical volume loss has also been observed, mostly in hippocampus, parahippocampus, amygdala, and insula, even in MCI patients.^{94–98} MRI analysis of cortical thickness has also shown a prognostic value with greater thinning showing an increased risk of developing dementia.^{99–101} A longitudinal study revealed that patients with PD-MCI showed more extensive atrophy and a greater percentage of cortical thinning compared to PD with no cognitive impairment.¹⁰² Regarding resting-state functional MRI a 3 years follow-up period study demonstrated a progressive loss of resting-state functional connectivity for multiple brain regions, but mostly posterior regions, and a strong correlation with decreasing cognitive performance.¹⁰³ A recent meta-analysis showed that PD patients with cognitive impairment presented reduced connectivity in specific brain regions that are part of the default mode network.¹⁰⁴

Treatment

Symptomatic Drugs

According to several meta-analyses, there is robust evidence to support the use of acetylcholinesterase inhibitors in patients with Parkinson's disease and dementia.^{105–107}

Acetylcholinesterase inhibitors, specifically rivastigmine and in a minor degree donepezil, have been shown to improve cognitive function.^{108–111} In a large randomized placebo-controlled study, with 541 PDD patients, the rivastigmine treated group presented a moderate but significant improvement in cognition. Patients receiving rivastigmine had a mean improvement of 2.1 points in the Alzheimer's Disease Assessment Scale (ADAS-cog), whereas those receiving placebo had a mean decline of 0.7 points over 6 months. Rivastigmine treated group also presented a better score in the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change.¹¹¹ Regarding donepezil, its efficacy was tested in another large randomized placebo-controlled study.¹⁰⁸ Although the primary endpoint was not achieved, the treated group presented a significant improvement in cognition and global status. Because of the failure to achieve the primary end-point, donepezil has been considered only as “possibly useful” in a recent systematic review.¹¹² Galantamine is another acetylcholinesterase inhibitor, but its efficacy has not been proved consistently.¹⁰⁶ There is insufficient evidence for the use of acetylcholinesterase inhibitors drugs in MCI-PD.¹¹²

Results in memantine, a glutamatergic modulator, have been inconsistent^{113,114} and it is not considered as a good candidate for the treatment of PDD.

Overall, these drugs are safe and higher frequency of adverse events between the treatment group and the placebo group have only been reported with rivastigmine.¹¹¹

Frequently, patients with PDD can associate psychosis and hallucinations. In front of these symptoms, the first step, especially when the onset is acute, is to rule out secondary causes as infections or toxic-metabolic etiologies. The next step should be discontinuing any non-essential non-antiparkinsonian drug, for example, anticholinergics, benzodiazepines, or opioids. If this is not enough, reducing and simplifying parkinsonian treatment should be considered.¹¹⁵ If there is still no optimal improvement of psychotic symptoms, adding an atypical antipsychotic should be considered. There is robust evidence to recommend clozapine for psychosis in PD. Randomized controlled trials^{116–118} have proven its efficacy. However, it is associated with agranulocytosis, a rare but severe life-threatening adverse event, so proper close monitoring is required. Quetiapine, an atypical dibenzothiazepine, despite having less supportive evidence, it is very used in the clinical practice. Two randomized controlled trials, rater-blinded, compared quetiapine with clozapine without finding significant differences.^{118,119} However, there have been

numerous placebo-controlled trials showing inconsistent results.^{120–122} Despite this, physicians have generally positive clinical experiences with quetiapine¹²³ because it is generally well-tolerated, does not require monitoring, and is equally effective as clozapine in some studies. In a recent systematic review, it has been considered as “possibly useful” for psychosis in PD patients.¹¹² Finally, pimavanserin, is a novel antipsychotic with selective serotonin 5-HT_{2A} inverse agonist activity, which is effective for psychosis treatment and does not worsen motor function.^{124,125}

Acetylcholinesterase inhibitors drugs have been proposed for psychosis and hallucinations management, as a prior step to antipsychotics, by some authors.

Non-Pharmacological Interventions

Non-pharmacological interventions for PDD and PD-MCI include cognitive training, physical exercise, music, and art therapy, and non-invasive brain stimulation techniques. Overall, there is little evidence about the efficacy of these therapies.

Although the number of studies is relatively small, cognitive training could be useful according to a meta-analysis.¹²⁶ In this work, seven randomized controlled trial studies, with relatively small sample sizes, were analyzed. They found an overall improvement in global cognition with the largest effect size in working memory, executive function, and processing speed. Regarding exercise, a systematic review of nine randomized clinical trials, performed within the last decade, found significant effects of physical exercises on cognitive function in PD patients. Trials included in this review studied a different kind of therapies such as tango, cognitive training associated with motor training, and treadmill training. Programs promoted a positive effect on global cognitive function, processing speed, sustained attention, and mental flexibility.¹²⁷ Literature relating to the impact of non-invasive brain stimulation techniques is limited, with very few studies with a control group. More well-deigned studies and powered populations are needed to elucidate the efficacy of these therapies.^{128,129}

Conclusions

Cognitive symptoms represent an important aspect of the clinical spectrum of PD even in early stages and can lead to a significant reduction in the quality of life of patients and caregivers. Lewy pathology is generally considered to be an important etiopathogenic factor in the development of cognitive impairment in PD, however, the combination of Lewy pathology and AD pathologies is the most robust

pathological correlate of PDD. Studies highlight the clinical heterogeneity and progression variability of cognitive impairment in PD patients. Currently, we have formal diagnostic criteria for both mild cognitive impairment and dementia associated with PD. Although neuropsychological battery covering the four core cognitive domains (attention, memory, executive and visuospatial functions) is the gold standard, the assessment of cognition with cognitive rating scales like MoCa, DRS-2, and PD-CRS, can be useful in the clinical practice. Finally, patients with PDD should be considered for acetylcholinesterase inhibitors drugs which have been shown to present modest effects. Finding successful disease-modifying therapies and clarifying the underlying pathophysiology are still unmet needs of paramount importance.

Abbreviations

AChE, acetylcholinesterase; AD, Alzheimer disease; ADAS-cog, Alzheimer's Disease Assessment Scale; A β , Amyloid- β ; iRBD, idiopathic REM-sleep behavior disorder; LB, Lewy bodies; DRS-2, Mattis Dementia Rating Scale Second Edition; MCI, mild cognitive impairment; MCI-PD, mild cognitive impairment in the context of Parkinson's disease; MMSE, Mini-Mental State Examination; MoCa, Montreal Cognitive Assessment; NBM, nucleus basalis of Meynert; PD, Parkinson's disease; PD-CRS, Parkinson's Disease-Cognitive Rating Scale; PDD, Parkinson's disease dementia; ptau, phosphorylated tau; t-tau, total tau; VACHT, vesicular acetylcholine transporter; WMH, white matter hyperintensities.

Funding

The authors received no specific funding for this work.

Disclosure

CP: received a grant Rio Hortega from Instituto de Salud Carlos III (CM18/00072). MJM: Honoraria for consulting and lectures from Merz Pharma and Allergan SA; grants from the MJ Fox Foundation (CP041639), Fundacio la Marato de TV3 (288/C/2014) and Fondo de Investigaciones Sanitarias (FIS)-ISCIII (PI17/00096). The authors report no other conflicts of interest in this work.

References

- Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry*. 1999;14:866–874. doi:10.1002/(SICI)1099-1166(199910)14:10<866::AID-GPS38>3.0.CO;2-Z
- Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc*. 2000;48(8):938–942. doi:10.1111/j.1532-5415.2000.tb06891.x
- Levy G, Tang MX, Louis ED, et al. The association of incident dementia with mortality in PD. *Neurology*. 2002;59:1708–1713. doi:10.1212/01.WNL.0000036610.36834.E0
- Santangelo G, Vitale C, Picillo M, et al. Mild cognitive impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. *Parkinsonism Relat Disord*. 2015;21(10):1219–1226. doi:10.1016/j.parkreldis.2015.08.024
- Hely A, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord*. 2005;20(2):190–199. doi:10.1002/mds.20324
- Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry*. 2013;84(11):1258–1264. doi:10.1136/jnnp-2013-305277
- Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. *Nat Rev Neurol*. 2017;13(4):217–231. doi:10.1038/nrneurol.2017.27
- Dalrymple-Alford JC, Livingston L, MacAskill MR, et al. Characterizing mild cognitive impairment in Parkinson's disease. *Mov Disord*. 2011;26(4):629–636. doi:10.1002/mds.23592
- Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Mov Disord*. 2012;27:349–356. doi:10.1002/mds.24893
- Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22(12):1689–1707. doi:10.1002/mds.21507
- Litvan I, Aarsland D, Adler CH, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord*. 2011;26(10):1814–1824. doi:10.1002/mds.23823
- Marras C, Armstrong MJ, Meaney CA, et al. Measuring mild cognitive impairment in patients with Parkinson's disease. *Mov Disord*. 2013;28:626–633. doi:10.1002/mds.25426
- Lawrence BJ, Gasson N, Loftus AM. Prevalence and subtypes of mild cognitive impairment in Parkinson's disease. *Sci Rep*. 2016;6:33929. doi:10.1038/srep33929
- Aarsland D, Bronnick K, Williams-Gray C, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*. 2010;75(12):1062–1069. doi:10.1212/WNL.0b013e3181f39d0e
- Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. *Mov Disord*. 2005;20(10):1255–1263. doi:10.1002/mds.20527
- Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132(11):2958–2969. doi:10.1093/brain/awp245
- Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008;23(6):837–844. doi:10.1002/mds.21956
- Jozwiak N, Postuma RB, Montplaisir J, et al. REM sleep behavior disorder and cognitive impairment in Parkinson's disease. *Sleep*. 2017;40:8. doi:10.1093/sleep/zsx101
- Vendette M, Gagnon JF, Décary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*. 2007;69(19):1843–1849. doi:10.1212/01.wnl.0000278114.14096.74

20. Goldman JG, Ghode RA, Ouyang B, Bernard B, Goetz CG, Stebbins GT. Dissociations among daytime sleepiness, night time sleep, and cognitive status in Parkinson's disease. *Parkinsonism Relat Disord.* **2013**;19:806–811. doi:10.1016/j.parkreldis.2013.05.006
21. Goldman JG, Stebbins GT, Leung V, Tilley BC, Goetz CG. Relationships among cognitive impairment, sleep, and fatigue in Parkinson's disease using the MDS-UPDRS. *Parkinsonism Relat Disord.* **2014**;20(11):1135–1139. doi:10.1016/j.parkreldis.2014.08.001
22. Mata IF, Leverenz JB, Weintraub D, et al. APOE, MAPT, and SNCA genes and cognitive performance in parkinson disease. *JAMA Neurol.* **2014**;71(11):1405–1412. doi:10.1001/jamaneurol.2014.1455
23. Morley JF, Xie SX, Hurtig HI, et al. Genetic influences on cognitive decline in Parkinson's disease. *Mov Disord.* **2012**;27:512–518. doi:10.1002/mds.24946
24. Piredda R, Desmarais P, Masellis M, Gasca-Salas C. Cognitive and psychiatric symptoms in genetically determined Parkinson's disease: a systematic review. *Eur J Neurol.* **2020**;27(2):229–234. doi:10.1111/ene.14115
25. Smith C, Malek N, Grosset K, Cullen B, Gentleman S, Grosset DG. Neuropathology of dementia in patients with Parkinson's disease: a systematic review of autopsy studies. *J Neurol Neurosurg Psychiatry.* **2019**;90(11):1234–1243. doi:10.1136/jnnp-2019-321111
26. Masliah E, Rockenstein E, Veinbergs I, et al. Beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. *Proc Natl Acad Sci U S A.* **2001**;98(21):12245–12250. doi:10.1073/pnas.211412398
27. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci.* **2010**;30(21):7281–7289. doi:10.1523/JNEUROSCI.0490-10.2010
28. Horvath J, Herrmann FR, Burkhard PR, Bouras C, Kövari E. Neuropathology of dementia in a large cohort of patients with Parkinson's disease. *Parkinsonism Relat Disord.* **2013**;19(10):864. doi:10.1016/j.parkreldis.2013.05.010
29. Ruffmann C, Calboli FC, Bravi I, et al. Cortical Lewy bodies and Aβ burden are associated with prevalence and timing of dementia in Lewy body diseases. *Neuropathol Appl Neurobiol.* **2016**;42(5):436–450. doi:10.1111/nan.12294
30. Sabbagh MN, Adler CH, Lahti TJ, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. *Alzheimer Dis Assoc Disord.* **2009**;23(3):295–297. doi:10.1097/WAD.0b013e31819c5ef4
31. Kotzbauer PT, Cairns NJ, Campbell MC, et al. Pathologic accumulation of α-synuclein and Aβ in Parkinson disease patients with dementia. *Arch Neurol.* **2012**;69(10):1326–1331. doi:10.1001/archneurol.2012.1608
32. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer type pathologies in Parkinson's disease dementia: which is more important? *Brain.* **2011**;134(5):1493–1505. doi:10.1093/brain/awr031
33. Perry EK, Curtis M, Dick DJ. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* **1985**;48:413–421. doi:10.1136/jnnp.48.5.413
34. Whitehouse PJ, Hedreen JC, White CL, Price DL. Basal forebrain neurons in the dementia of Parkinson's disease. *Ann Neurol.* **1983**;13:243–248. doi:10.1002/ana.410130304
35. Perry RH, Tomlinson BE, Candy JM, et al. Cortical cholinergic deficit in mentally impaired Parkinsonian patients. *Lancet.* **1983**;2:789–790. doi:10.1016/S0140-6736(83)92317-6
36. Mattila PM, Roytta M, Lonnberg P, Marjamäki P, Helenius H, Rinne JO. Choline acetyltransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. *Acta Neuropathol.* **2001**;102:160–166. doi:10.1007/s004010100372
37. Pillon J, Kahan J, Zrinzo L, et al. The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? *Neurosci Biobehav Rev.* **2013**;37(10):2676–2688. doi:10.1016/j.neubiorev.2013.09.003
38. Silbert LC, Kaye J. Neuroimaging and cognition in Parkinson's disease dementia. *Brain Pathol.* **2010**;20(3):646–653. doi:10.1111/j.1750-3639.2009.00368.x
39. Kuhl DE, Minoshima S, Fessler et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Ann Neurol.* **1996**;40(3):399–410. doi:10.1002/ana.410400309
40. Christopher L. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain.* **2014**;137(2):565–575. doi:10.1093/brain/awt337
41. Siepel FJ, Brönnick KS, Booi et al. Cognitive executive impairment and dopaminergic deficits in de novo Parkinson's disease. *Mov Disord.* **2014**;29(14):1802–1808. doi:10.1002/mds.26051
42. Christopher L, Duff-Canning S, Koshimori Y, et al. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. *Ann Neurol.* **2015**;77(2):269–280. doi:10.1002/ana.24323
43. Compta Y, Buongiorno M, Bargalló N, et al. White matter hyperintensities, cerebrospinal amyloid-β and dementia in Parkinson's disease. *J Neurol Sci.* **2016**;367:284–290. doi:10.1016/j.jns.2016.06.009
44. González-Redondo R, Toledo J, Clavero P, et al. The impact of silent vascular brain burden in cognitive impairment in Parkinson's disease. *Eur J Neurol.* **2012**;19(8):1100–1107. doi:10.1111/j.1468-1331.2012.03682.x
45. Sunwoo MK, Jeon S, Ham JH, et al. The burden of white matter hyperintensities is a predictor of progressive mild cognitive impairment in patients with Parkinson's disease. *Eur J Neurol.* **2014**;21(6):922–e50. doi:10.1111/ene.12412
46. Chahine LM, Dos SC, Fullard M, et al. Modifiable vascular risk factors, white matter disease, and cognition in early Parkinson's disease. *Eur J Neurol.* **2019**;26(2):246–e18. doi:10.1111/ene.13797
47. Dalaker TO, Larsen JP, Dwyer MG, et al. White matter hyperintensities do not impact cognitive function in patients with newly diagnosed Parkinson's disease. *Neuroimage.* **2009**;47(4):2083–2089. doi:10.1016/j.neuroimage.2009.06.020
48. Schwartz RS, Halliday GM, Soh D, Cordato DJ, Kril JJ. Impact of small vessel disease on severity of motor and cognitive impairment in Parkinson's disease. *J Clin Neurosci.* **2018**;58:70–74. doi:10.1016/j.jocn.2018.10.029
49. Compta Y, Martí MJ, Ibarretxe-Bilbao N, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. *Mov Disord.* **2009**;24(15):2203–2210. doi:10.1002/mds.22594
50. Gmitterová K, Gawinecka J, Llorens F, Varges D, Valkovič P, ZI. Cerebrospinal fluid markers analysis in the differential diagnosis of dementia with Lewy bodies and Parkinson's disease dementia. *Eur Arch Psychiatry Clin Neurosci.* **2020**;270(4):461–470. doi:10.1007/s00406-018-0928-9
51. Maetzler W, Liepelt I, Reimold M, et al. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. *Neurobiol Dis.* **2009**;34:107–112. doi:10.1016/j.nbd.2008.12.008
52. Modreanu R, Cerquera SC, Martí MJ, et al. Cross-sectional and longitudinal associations of motor fluctuations and non-motor predominance with cerebrospinal τ and Aβ as well as dementia-risk in Parkinson's disease. *J Neurol Sci.* **2017**;373:223–229. doi:10.1016/j.jns.2016.12.064

53. Hall S, Öhrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. *Arch Neurol*. 2012;69(11):1445–1452. doi:10.1001/archneurol.2012.1654
54. Vranová HP, Hényková E, Kaiserová M, et al. Tau protein, beta-amyloid 1–42 and clusterin CSF levels in the differential diagnosis of Parkinsonian syndrome with dementia. *J Neurol Sci*. 2014;343:120–124. doi:10.1016/j.jns.2014.05.052
55. Parnetti L, Tiraboschi P, Lanari A, et al. Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies. *Biol Psychiatry*. 2008;64:850–855. doi:10.1016/j.biopsych.2008.02.016
56. Johar I, Mollenhauer B, Aarsland D. Cerebrospinal fluid biomarkers of cognitive decline in Parkinson's disease. *Int Rev Neurobiol*. 2017;132:275–294.
57. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid 1-42 predicts cognitive decline in Parkinson disease. *Neurology*. 2010;75(12):1055–1061. doi:10.1212/WNL.0b013e3181f39a78
58. Terrelonge M, Marder KS, Weintraub D, Alcalay RN. CSF β -amyloid 1-42 predicts progression to cognitive impairment in newly diagnosed Parkinson disease. *J Mol Neurosci*. 2016;58(1):88–92. doi:10.1007/s12031-015-0647-x
59. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. *Lancet Neurol*. 2016;16(1):66–75. doi:10.1016/S1474-4422(16)30328-3
60. Compta Y, Pereira JB, Ríos J, et al. Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. *Parkinsonism Relat Disord*. 2013;19(8):717–724. doi:10.1016/j.parkreldis.2013.03.009
61. Bäckström DC, Eriksson Domellöf M, Linder J, et al. Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease. *JAMA Neurol*. 2015;72:1175–1182. doi:10.1001/jamaneurol.2015.1449
62. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain*. 2017;140(7):1959–1976. doi:10.1093/brain/awx118
63. Eusebi P, Giannandrea D, Biscetti L, et al. Diagnostic utility of cerebrospinal fluid α -synuclein in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2017;32(10):1389–1400. doi:10.1002/mds.27110
64. Hall S, Surova Y, Öhrfelt A, et al. CSF biomarkers and clinical progression of Parkinson disease. *Neurology*. 2015;84:57–63. doi:10.1212/WNL.0000000000001098
65. Stewart T, Liu C, Ghingina C, et al. Cerebrospinal fluid α -Synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort. *Am J Pathol*. 2014;184:966–975. doi:10.1016/j.ajpath.2013.12.007
66. Pagano G, De Micco R, Yousaf T, Wilson H, Chandra A, Politis M. REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease. *Neurology*. 2018;91(10):894–906. doi:10.1212/WNL.00000000000006134
67. Hansson O, Hall S, Öhrfelt A, et al. Levels of cerebrospinal fluid α -synuclein oligomers are increased in Parkinson's disease with dementia and dementia with Lewy bodies compared to Alzheimer's disease. *Alzheimers Res Ther*. 2014;6:25. doi:10.1186/alzrt255
68. Compta Y, Valente J, Saura J, et al. Correlates of cerebrospinal fluid levels of oligomeric- and total- α -synuclein in premotor, motor and dementia stages of Parkinson's disease. *J Neurol*. 2015;262(2):294–306. doi:10.1007/s00415-014-7560-z
69. Cammisuli DM, Crowe S. Spatial disorientation and executive dysfunction in elderly nondemented patients with Parkinson's disease. *Neuropsychiatr Dis Treat*. 2018;14:2531–2539. doi:10.2147/NDT.S173820
70. Kalbe E, Rehberg SP, Heber I, et al. Subtypes of mild cognitive impairment in patients with Parkinson's disease: evidence from the LANDSCAPE study. *J Neurol Neurosurg Psychiatry*. 2016;87:1099–1105. doi:10.1136/jnnp-2016-313838
71. Peran P, Rascol O, Demonet JF, et al. Deficit of verb generation in nondemented patients with Parkinson's disease. *Mov Disord*. 2003;18:150–156. doi:10.1002/mds.10306
72. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain*. 2007;130(7):1787–1798. doi:10.1093/brain/awm111
73. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. *Neurodegener Dis*. 2013;11(2):79–92. doi:10.1159/000341998
74. Wood KL, Myall DJ, Livingston L, et al. Different PD-MCI criteria and risk of dementia. *NPJ Parkinsons Dis*. 2016;2(1):15027. doi:10.1038/npjparkd.2015.27
75. Domellof ME, Ekman U, Forsgren L, Elgh E. Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurol Scand*. 2015;132:79–88. doi:10.1111/ane.12375
76. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study. *Neurology*. 2017;88(8):767–774. doi:10.1212/WNL.0000000000003634
77. Saredakis D, Collins-Praino LE, Gutteridge DS, Stephan BCM, Keage HAD. Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord*. 2019;65:20–31. doi:10.1016/j.parkreldis.2019.04.020
78. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. *Brain*. 2010;133(6):1755–1762. doi:10.1093/brain/awq059
79. Bronnick K, Ehrh U, Emre M, et al. Attentional deficits affect activities of daily living in dementia-associated with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77(10):1136–1142. doi:10.1136/jnnp.2006.093146
80. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. *Cogn Behav Neurol*. 2004;17(4):195–200.
81. Cumming JL, Huber SJ. Visuospatial abnormalities in Parkinson's disease. In: Huber SJ, Cummings JL, editors. *Parkinson's Disease. Neurobehavioral Aspects*. New York: Oxford University Press; 1992:59–73.
82. Aarsland D, Brønnick K, Ehrh U, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *J Neurol Neurosurg Psychiatry*. 2007;78(1):36–42. doi:10.1136/jnnp.2005.083113
83. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65:1863–1872. doi:10.1212/01.wnl.0000187889.17253.b1
84. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591–1601. doi:10.1002/mds.26424
85. Skorvanek M, Goldman JG, Jahanshahi M, et al. Global scales for cognitive screening in Parkinson's disease: critique and recommendations. *Mov Disord*. 2018;33(2):208–218. doi:10.1002/mds.27233
86. Nasreddine Z, Phillips N, Bäckdrian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x
87. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology*. 2010;75(19):1717–1725. doi:10.1212/WNL.0b013e3181fc29c9

88. Jurica PJ, Leitten CL, Mattis S. Psychological assessment resources, 2001. Dementia Rating Scale-2 (DRS-2). *Arch Clin Neuropsychol*. 2004;19:145–147. doi:10.1016/j.acn.2003.07.003
89. Matteau E, Dupre N, Langlois M, Provencher P, Simard M. Clinical validity of the Mattis Dementia Rating Scale-2 in Parkinson disease with MCI and dementia. *J Geriatr Psychiatry Neurol*. 2012;25:100e6.
90. Bezdicek O, Michalec J, Nikolai T, et al. Clinical validity of the Mattis Dementia Rating Scale in differentiating mild cognitive impairment in Parkinson's disease and normative data. *Dement Geriatr Cogn Disord*. 2015;39(5–6):303–311. doi:10.1159/000375365
91. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Mov Disord*. 2008;23:998–1005. doi:10.1002/mds.22007
92. Nie K, Zhang Y, Wang L, et al. A pilot study of psychometric properties of the Beijing version of Montreal Cognitive Assessment in patients with idiopathic Parkinson's disease in China. *J Clin Neurosci*. 2012;19:1497–1500. doi:10.1016/j.jocn.2011.11.039
93. Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. *Neurology*. 2007;69(8):747–754. doi:10.1212/01.wnl.0000269666.62598.1c
94. Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, et al. Correlations between gray matter reductions and cognitive deficits in dementia with Lewy bodies and Parkinson's disease with dementia. *Mov Disord*. 2009;24(12):1740–1746. doi:10.1002/mds.22488
95. Junqué C, Ramírez-Ruiz B, Tolosa E, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. *Mov Disord*. 2005;20(5):540–544. doi:10.1002/mds.20371
96. Pagonabarraga J, Corcuera-Solano I, Vives-Gilabert Y, et al. Pattern of regional cortical thinning associated with cognitive deterioration in Parkinson's disease. *PLoS One*. 2013;8(1):e54980. doi:10.1371/journal.pone.0054980
97. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain*. 2004;127(Pt 4):791–800. doi:10.1093/brain/awh088
98. Rektorova I, Biundo R, Marecek R, Weis L, Aarsland D, Antonini A. Grey matter changes in cognitively impaired Parkinson's disease patients. *PLoS One*. 2014;9(01):e85595. doi:10.1371/journal.pone.0085595
99. Segura B, Baggio HC, Marti MJ, et al. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. *Mov Disord*. 2014;29(12):1495–1503. doi:10.1002/mds.25982
100. Gasca-Salas C, García-Lorenzo D, García-García D, et al. Parkinson's disease with mild cognitive impairment: severe cortical thinning antedates dementia. *Brain Imaging Behav*. 2019;13:180–188. doi:10.1007/s11682-017-9751-6
101. Zarei M, Ibarretxe-Bilbao N, Compta Y, et al. Cortical thinning is associated with disease stages and dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2013;84(8):875–881. doi:10.1136/jnnp-2012-304126
102. Mak E, Su L, Williams GB, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study. *Brain*. 2015;138(10):2974–2986. doi:10.1093/brain/awv211
103. Olde Dubbelink KT, Schoonheim MM, Deijlen JB, Twisk JW, Barkhof F, Berendse HW. Functional connectivity and cognitive decline over 3 years in Parkinson disease. *Neurology*. 2014;83(22):2046–2053. doi:10.1212/WNL.0000000000001020
104. Wolters AF, SCF VDW, Leentjens AFG, Duits AA, Jacobs HIL, Kuijff ML. Resting-state fMRI in Parkinson's disease patients with cognitive impairment: a meta-analysis. *Parkinsonism Relat Disord*. 2019;62:16–27. doi:10.1016/j.parkreldis.2018.12.016
105. Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev*. 2012;(3):CD006504.
106. Wang HF, Yu JT, Tang SW, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry*. 2015;86:135–143. doi:10.1136/jnnp-2014-307659
107. Meng YH, Wang PP, Song YX, Wang JH. Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: a meta-analysis. *Exp Ther Med*. 2019;17(3):1611–1624. doi:10.3892/etm.2018.7129
108. Dubois B, Tolosa E, Katzschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov Disord*. 2012;27(10):1230–1238. doi:10.1002/mds.25098
109. Aarsland D, Laake K, Larsen JP, Janvin C. Donepezil for cognitive impairment in parkinson's disease: a randomised controlled study. *J Neurol Neurosurg Psychiatry*. 2002;72(6):708–712.
110. Mamikonyan E, Xie SX, Melvin E, Weintraub D. Rivastigmine for mild cognitive impairment in Parkinson disease: a placebo-controlled study. *Mov Disord*. 2015;30(7):912–918. doi:10.1002/mds.26236
111. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*. 2004;351(24):2509–2518. doi:10.1056/NEJMoa041470
112. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Mov Disord*. 2019;34(2):180–198. doi:10.1002/mds.27602
113. Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. *Mov Disord*. 2009;24(8):1217–1221. doi:10.1002/mds.22495
114. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol*. 2009;8(7):613–618. doi:10.1016/S1474-4422(09)70146-2
115. Caballol N, Martí MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. *Mov Disord*. 2007;22(17):S358–366. doi:10.1002/mds.21677
116. Factor S, Friedman J, Lannon M, Oakes D, Bourgeois K, Group PS. Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial. *Mov Disord*. 2001;16:135–139. doi:10.1002/1531-8257(200101)16:1<135::AID-MDS1006>3.0.CO;2-Q
117. Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry*. 2004;75(5):689–695. doi:10.1136/jnnp.2003.029868
118. Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol*. 2004;27:153–156. doi:10.1097/01.wnf.0000136891.17006.ec
119. Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. *Clin Neuropharmacol*. 2006;29(6):331–337. doi:10.1097/01.WNF.0000236769.31279.19

120. Ondo W, Tintner R, Young K, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord.* 2005;20:958–963. doi:10.1002/mds.20474
121. Rabey J, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord.* 2007;22(3):313–318. doi:10.1002/mds.21116
122. Fernandez HH, Okun MS, Rodriguez RL, et al. Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. *Int J Neurosci.* 2009;119:2196–2205. doi:10.3109/00207450903222758
123. Schneider RB, Iourinets J, Richard IH. Parkinson's disease psychosis: presentation, diagnosis and management. *Neurodegener Dis Manag.* 2017;7(6):365–376. doi:10.2217/nmt-2017-0028
124. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin (2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology.* 2010;35(4):881–892. doi:10.1038/npp.2009.176
125. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled Phase 3 trial. *Lancet.* 2014;383(9916):533–540. doi:10.1016/S0140-6736(13)62106-6
126. Leung IH, Walton CC, Hallock H, Lewis SJ, Valenzuela M, Lampit A. Cognitive training in Parkinson disease: a systematic review and meta-analysis. *Neurology.* 2015;85(21):1843–1851. doi:10.1212/WNL.0000000000002145
127. da Silva FC, Iop RDR, de Oliveira LC, et al. Effects of physical exercise programs on cognitive function in Parkinson's disease patients: a systematic review of randomized controlled trials of the last 10 years. *PLoS One.* 2018;13(2):e0193113. doi:10.1371/journal.pone.0193113
128. Rektorová I, Anderková E. Noninvasive brain stimulation and implications for nonmotor symptoms in Parkinson's disease. *Int Rev Neurobiol.* 2017;134:1091–1110.
129. Dinkelbach L, Brambilla M, Manenti R, Brem AK. Non-invasive brain stimulation in Parkinson's disease: exploiting crossroads of cognition and mood. *Neurosci Biobehav Rev.* 2017;75:407–418. doi:10.1016/j.neubiorev.2017.01.021

Research and Reviews in Parkinsonism

Dovepress

Publish your work in this journal

Research and Reviews in Parkinsonism is an online, open access, peer-reviewed journal. The journal publishes review articles, historical reviews, original research articles, case reports, letters to the editor, clinical teaching cases, neuroradiology highlights, neuropathology highlights, neuropsychiatry highlights, autobiographies,

conference proceedings, abstracts and book reviews. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/research-and-reviews-in-parkinsonism-journal>