



Mild Cognitive Impairment in Parkinson's Disease—What Is It?

Rimona S. Weil^{1,2} · Alyssa A. Costantini² · Anette E. Schrag^{3,4}

© The Author(s) 2018. This article is an open access publication

Abstract

Purpose of Review Mild cognitive impairment is a common feature of Parkinson's disease, even at the earliest disease stages, but there is variation in the nature and severity of cognitive involvement and in the risk of conversion to Parkinson's disease dementia. This review aims to summarise current understanding of mild cognitive impairment in Parkinson's disease. We consider the presentation, rate of conversion to dementia, underlying pathophysiology and potential biomarkers of mild cognitive impairment in Parkinson's disease. Finally, we discuss challenges and controversies of mild cognitive impairment in Parkinson's disease.

Recent Findings Large-scale longitudinal studies have shown that cognitive involvement is important and common in Parkinson's disease and can present early in the disease course. Recent criteria for mild cognitive impairment in Parkinson's provide the basis for further study of cognitive decline and for the progression of different cognitive phenotypes and risk of conversion to dementia.

Summary Improved understanding of the underlying pathology and progression of cognitive change are likely to lead to opportunities for early intervention for this important aspect of Parkinson's disease.

Keywords Parkinson's disease · Mild cognitive impairment · Dementia

Abbreviations

MCI	Mild cognitive impairment
MOCA	Montreal cognitive assessment
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PD-MCI	Mild cognitive impairment in the context of Parkinson's disease

Introduction

Mild cognitive impairment (MCI) is a concept introduced in the 1980s to characterise mild cognitive deficits that did not amount to a diagnosis of dementia [1], in the context of

Alzheimer's disease. More recently, this concept has been used in the context of Parkinson's disease (PD), where cognitive deficits are common even at the point of diagnosis. However, there is considerable controversy on the use, definition, assessment and prognostic value of this concept. Here, we review current understanding of MCI in Parkinson's disease from the point of view of epidemiology, recently described definitions, underlying pathophysiology, detection methods and tracking the presence of cognitive involvement in PD and ongoing controversies in this area.

Why Does MCI Matter?

Dementia affects 50% of patients with Parkinson's within 10 years of diagnosis [2] but the timing and severity vary considerably between individuals. Identifying patients at risk of dementia and those at the earliest stages of cognitive involvement is important for three key reasons: (1) as new disease-modifying treatments in Parkinson's are emerging [3], early intervention to slow or prevent Parkinson's dementia is becoming a realistic prospect; (2) earlier detection of cognitive involvement offers the hope of prognostic information. This can allow an affected individual to better plan for their own future and enables policy makers and healthcare

This article is part of the Topical Collection on *Movement Disorders*

✉ Anette E. Schrag
a.schrag@ucl.ac.uk

¹ Dementia Research Centre, UCL, London, UK

² Department of Neurodegeneration, UCL, London, UK

³ Department of Clinical Neuroscience, UCL, London, UK

⁴ UCL Institute of Neurology, Rowland Hill Street, NW3 2PF, London, UK

providers to plan health and social needs for the population; (3) finding the earliest features of cognitive involvement may provide insights into underlying mechanisms of disease progression, ultimately leading to identification of novel therapeutic targets.

MCI in Individuals Without PD

MCI has been defined as a syndrome of cognitive decline that is greater than would be expected for an individual's age and level of education that does not interfere with that individual's ability to perform activities of daily life [4]. It is distinct as an entity from dementia, where cognitive difficulties are greater and have an impact on day-to-day functioning. The concept of MCI was described in the nineteenth century by Prichard [5] who noted that the earliest sign of dementia was loss of recent memories. Some degree of cognitive deficits were thought to be a normal part of ageing and various terms were used to describe this, including age-associated memory impairment, age-associated cognitive decline and benign senescent forgetfulness [6, 7]. With the advent of new scales to measure subjective and objective cognition, such as the Clinical Dementia Rating and the Global Deterioration Scale for Ageing and Dementia, in the 1980s, an intermediate phase between normal ageing and dementia became more widely recognised [8, 9]. At that point, it was defined as the presence of subtle deficits in cognition with some impairment in executive function. Following an expert international conference, the diagnosis and management of MCI was clarified [4] and later revised [10].

The prevalence of MCI is estimated to be 3–19% in the elderly population [11]. Conversion rates to dementia vary depending on the setting [12], with 11–33% conversion over 2 years. Notably, in a community setting, 44% of people with MCI were shown to return to normal after 1 year [11]. In contrast, higher rates of conversion to dementia are seen in patients tested in memory clinics, with estimates of 16–18% per year [13, 14]. Memory-led or amnesic MCI is particularly predictive of dementia, with rates as high as 41% after 1 year and 64% after 2 years for amnesic MCI [8, 15, 16]. Impairment of delayed recall is a strong predictor of progression to Alzheimer's disease in longitudinal studies [17, 18]. Patients with MCI in this context show quantitative differences from patients with no evidence of cognitive impairment, with reduced medial temporal lobe volumes [19, 20] and changes on PET imaging [21, 22]. In the field of Alzheimer's research and therapeutics, there is now pressure to intervene early to prevent the development of dementia and to start treatment in patients with MCI. However, clinical trials thus far have been disappointing [23].

MCI in PD

Cognitive deficits are common in PD, even early in the disease when there may be no cognitive complaints [2]. The concept of mild cognitive impairment in Parkinson's disease (PD-MCI) is therefore emerging as an intermediate stage between normal cognition and dementia, similar to amnesic MCI in AD.

Epidemiology

Epidemiological studies report prevalence rates of MCI in PD of 25–50% of patients [24–26], depending on the population and clinical setting. It is estimated to be as high as 20–42% at the time of diagnosis [25, 27, 28••].

PD-MCI Phenotypes

PD-MCI is a heterogeneous entity in phenotype, timing and progression, with a range of cognitive domains affected [28••]. Characteristically, where a single domain is involved, this is mostly a non-amnesic subtype [29, 30•]. However, subtypes with predominant deficits in attention, memory, executive function, psychomotor speed and visuospatial abilities have also been described [24, 26, 27, 31], and it frequently involves deficits across multiple domains [32–34].

One influential model for the pattern of cognitive deficits in PD was framed by Barker and colleagues as the dual syndrome hypothesis [35]. In their longitudinal CamPaIGN study [2, 36], they observed two distinct patterns of cognitive involvement in PD: a fronto-striatal/executive group and a posterior cortical/visuospatial cognitive phenotype [36]. One challenge, when comparing performance across cognitive domains, is maintaining the same level of difficulty across domains. Indeed, the relative preservation of visuospatial abilities in patients in some studies [27, 32] may be a result of the lack of sensitivity of the tests used, compared with more difficult tests of memory.

PD-MCI—New Proposed Definition

The definition of PD-MCI has varied between different studies, prompting a task force from the International Parkinson and Movement Disorder Society (MDS) to provide a unified definition based on a literature review and expert consensus [28••].

According to these new criteria (see Table 1), in patients with a diagnosis of PD, PD-MCI is defined as an insidious decline in cognitive abilities reported by patient or informant or observed by the clinician, not caused by other

Table 1 Criteria for the diagnosis of PD-MCI

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, or observed by the clinician
 Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities
 Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

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

PD-MCI level guidelines:

- A. Level I (abbreviated assessment)
- Impairment on a scale of global cognitive abilities validated for use in PD
 - or*
 - 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)
- B. 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 any one of the following:
 - Performance approximately 1 to 2 SDs below appropriate norms
 - Significant decline demonstrated on serial cognitive testing
 - Significant decline from estimated premorbid levels

Subtype classification for PD-MCI (optional, requires two tests from 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 or
 PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

From Litvan et al. (2012, with permission)

comorbidities. In contrast to dementia, cognitive deficits are present on testing but do not interfere with functional independence of the patient [28••].

In view of the varying availability of neuropsychological testing in different clinical settings, the Task Force proposed two levels of definition: level I uses a pragmatic approach that allows for the diagnosis of PD-MCI based on an abbreviated cognitive assessment, either with a global scale such as the Montreal Cognitive Assessment (MoCA) or a limited range of

neuropsychological tests. Within this level of definition, impairment must be present on a scale of global cognitive abilities or at least two out of a limited battery of neuropsychological tests.

Level II definition of PD-MCI is based on a more comprehensive assessment with at least two tests for each of the five cognitive domains (attention and working memory, executive, language, memory and visuospatial) and allows more accurate assessment. A range of suitable standard neuropsychological tests can be used for this assessment [28••]. Deficits need to be detected on at least two tests for each of the five cognitive domains. This can be either two tests within one cognitive domain or two tests across different cognitive domains. Impairment is defined as 1 to 2 standard deviations below population norms, a significant decline from previous testing or a significant decline from the individual's estimated premorbid level.

Further subtyping of PD-MCI by the task force is designed to enable future research into whether impairments in specific cognitive domains have distinct neurobiological substrates. Using this framework, PD-MCI can be divided into single or multiple domains, according to involvement of deficits on two tests within or across cognitive domains, respectively. Importantly, the task force recommended reporting exactly which cognitive domains are affected to enable differences between the subtypes to be studied.

Conversion from MCI to Parkinson's Disease Dementia

Generally, the presence of PD-MCI predicts the development of PD dementia (PDD) [28••], but longitudinal studies show heterogeneity in patterns of conversion to PDD and a notable proportion of patients with PD-MCI will revert to normal cognition during follow-up. In longitudinal studies, rates of conversion from PD-MCI to PDD are broadly similar: 62% after 4-year follow-up [37], compared with only 20% in patients without cognitive involvement; 50% at 5 years in a community-based Swedish study [38]; and 39% at 5-year follow-up in the Norwegian ParkWest study [39•]. Notably, rates of reversion back to normal cognition were 11% in the Swedish study [38] and 28% in the ParkWest study [39•]. The variability of these results is likely to reflect differences in study populations, assessment methods and definitions. The level II MDS PD-MCI definition as a predictor of PDD was recently validated in a longitudinal study, where conversion rates from PD-MCI to PDD varied depending on degree of cognitive deficit at baseline [40]: patients scoring between 1 and 1.5 SD below the mean in at least two cognitive tests had 12% rate of conversion to PD dementia during follow-up, compared with patients who fell below 2 SD from the mean

(in two tests) at baseline, of whom 50% developed PD dementia after follow-up.

MCI in Prodromal PD

Recent reports show that cognitive deficits, especially in fluency, can already be detected in the prodromal phase of PD, even before the onset of motor symptoms. Poor cognitive function, measured using letter-digit substitutions, Stroop colour test, verbal fluency and 15-word list learning tests, is associated with increased risk of developing PD [41••]. Cognitive deficits are even seen in people who do not yet have Parkinson's disease but are known to be at risk (e.g. due to hyposmia or REM sleep disorder [42, 43] and in the Parkinson's at Risk study, unaffected relatives of people with Parkinson's disease who had hyposmia and abnormal DaT scans also showed impaired performance in tests of attention, verbal fluency and processing speed [44].

How to Determine Who Is at Risk

Demographic and Clinical Risk Factors

Clinical factors associated with a higher risk of cognitive involvement in PD include the following: older age [38, 39] at diagnosis (age over 70 associated with odds ratio (OR) 5.2 in one study [45], akinetic rigid phenotype (freezing and/or falls, OR 1.8 [45], poor performance on verbal fluency tests and higher rates of comorbidity [2]. REM sleep behavioural disorder (OR 5.4 [45] and dysautonomia (OR 5.3 for systolic blood pressure drop [45]) are also associated with higher risk of developing dementia in PD [45, 46]. Other associated factors include male gender (OR 4.1 [45] and non-motor symptoms including depression and anxiety [47]. Lower apathy scores and higher Epworth Sleepiness scores were relatively protective, being associated with reversion to normal cognition at follow-up [39•]. Conversely, other studies have shown increased risk of PDD with excess daytime sleepiness [48]. Whether those that reverted to normal cognition had other causes of cognitive deficits will need to be tested in longitudinal studies.

Higher rates of conversion from PD-MCI to dementia are associated with, older age, depression and a non-tremor dominant phenotype [2, 37, 39•]. Consistent neuropsychological profiles of PD-MCI associated with higher conversion rates to dementia are non-amnesic MCI (affecting domains other than memory) [37] including deficits in fluency, mental flexibility and visuospatial domains, although memory deficits are also reported [2, 38]. The two groups defined by Barker et al. also differed in their rates of conversion to dementia: those with a frontal-executive phenotype had a higher rate of reversion to

normal cognition than those with visuo-perceptual deficits [2, 35]. As definitions of PD-MCI are increasingly refined and improved, more accurate predictions of the risk of development of dementia in PD based on cognitive profiles of PD-MCI are likely to be developed.

Biomarkers

Biomarkers, such as CSF proteins and imaging, are not currently part of the definition of PD-MCI, although they do form components of criteria for non-PD MCI [10]. They may become important in the future as our understanding of PD-MCI increases and as clinical trials to slow the progression of dementia in PD are developed.

CSF

Lower levels of CSF amyloid beta may reflect brain amyloid deposition [49]. Decreased CSF amyloid beta is found in patients with PDD and PD [50, 51] and correlates with scores in verbal learning and Stroop word colour tests [52]. CSF amyloid beta also correlates with risk of developing dementia in PD [53–55]. Importantly, lower levels of CSF amyloid beta are also seen in patients with PD before they develop PD-MCI and are therefore predictive of cognitive involvement in PD [54]. However, levels of amyloid beta are not lower in patients with PD-MCI than those with normal cognition in PD [55, 56]. This may reflect the wide definition of PD-MCI and its relative lack of specificity for future conversion to PDD.

The story is less clear for tau. Higher CSF tau is correlated with impaired performance on cognitive tests of naming and memory when tested in mixed groups of patients with PD and PDD [50, 53], and CSF tau is slightly higher in patients with PD and cognitive involvement (33/36 of whom had PD-MCI) [56]. But other studies in patients at earlier disease stages have showed no associations between CSF tau and cognition in PD [57].

Radioligand Imaging

Radioligand imaging can provide insights into mechanisms of cognitive involvement in PD-MCI and may have a potential role as a clinically useful biomarker of MCI in PD. Patients with PD-MCI show hypometabolism in posterior brain regions compared with PD patients with no evidence of cognitive involvement [58] and reduced metabolism is seen using FDG-PET in posterior cortical regions in PD patients who later developed PD dementia after 6 years of follow-up [59, 60].

Reduced dopamine transporter uptake correlates with executive function [61, 62], but executive dysfunction does not always progress to dementia in PD [63]. More recently, reduced caudate uptake on DAT-SPECT imaging was shown to

predict cognitive decline in PD, especially when combined with other measures including age and CSF [64]. Finally, ligands binding to amyloid may have a role in detecting PD-MCI as amyloid binding negatively correlates with cognition in PD [65, 66] and increased amyloid binding at baseline increases the likelihood of cognitive involvement in PD [65].

MRI

MRI structural differences in grey matter between patients with PD-MCI and patients without cognitive involvement show varying patterns of atrophy involving all cortical brain areas [67–69], as well as subcortical regions [68, 70, 71]. These differences are likely to be partly due to variation in MRI methodology to assess cortical thickness as well as differences in cognitive tests. However, a more fundamental reason for differences in findings is due to the low sensitivity of grey matter atrophy in detecting cognitive involvement in PD. Grey matter atrophy indexes neuronal cell death which is a relatively late event in PD dementia. Therefore, in order to detect the earliest signs of PD-MCI, measures that are sensitive to earlier pathological events are needed. These are likely to be techniques such as diffusion tensor imaging that detect axonal and synaptic changes [72] which occur at earlier stages in PD-MCI.

Diffusion-weighted imaging MRI techniques [73, 74] that provide information about white matter integrity are sensitive to axonal damage. Estimates of mean diffusivity (MD) and fractional anisotropy (FA) index the overall displacement of molecules and the pattern of restriction of diffusion of molecules, respectively. Indeed, white matter changes increase as cognition worsens in PD, as measured using FA and MD [73–75]. When measured concurrently, white matter alterations are seen in patients with PD *before* changes in grey matter atrophy [72, 74, 76]. New techniques for quantification of structural change across the entire network are emerging that are likely to show sensitivity for changes in PD-MCI [77].

Underlying Pathophysiology of MCI-PD

Alpha Synuclein

The precise pathophysiological mechanisms underlying cognitive involvement in PD are still not fully understood. There is only scarce data specific to PD-MCI, rather than dementia in PD. This is partly due to the fact that PD-MCI occurs relatively early in the disease, with only limited series of PD-MCI cases seen at post mortem (see [78] for review). It is becoming clear that PD-MCI is likely to be characterised by a combination of underlying pathologies [79, 80]. Lewy bodies (intracellular inclusions made up of alpha synuclein) are classically associated with PD and PDD [81, 82]. However, it is the *combination* of Lewy bodies with Alzheimer's pathology (fibrillary beta amyloid and intraneuronal tangles of

hyperphosphorylated tau) that is most strongly associated with dementia in Parkinson's disease [83–85]. Indeed, there seems to be synergistic effect between alpha synuclein and beta amyloid pathology. For example, a recent study showed a strong correlation between the extent of neurofibrillary tangles and alpha synuclein [86], and this observation is supported by mouse studies and in vitro model systems [87, 88].

Location of Pathological Accumulations

As well as accumulation of pathological proteins, the morphological characteristics and location of pathological accumulations within affected cells appear to be critical in patients with cognitive involvement in PD. The synapse may be important in the earlier stages of cognitive involvement in PD. The physiological form of alpha synuclein localises to the presynaptic terminal, and in both PD and DLB, alpha synuclein aggregates localise to the synapse [89, 90]. Consistent with this, reduced levels of two synaptic proteins (neurogranin and SNAP25) and neocortical ZnT3, a protein involved in synaptic zinc regulation, are all associated with cognitive involvement in PD [91, 92].

Axonal involvement also appears to be an important early feature of PD, with alpha synuclein accumulation starting in the axonal compartment, before neuronal loss is seen [93]. Moreover, neurones that are preferentially affected in PD-associated dementia show extreme length. For example, the cholinergic cells of the nucleus basalis of Meynert and the serotonergic cells of the raphe nucleus are both implicated in PDD and both show long, thin and complex branching axons [94–97].

Neurotransmitters

Changes in the levels of specific neurotransmitters may also have an important role in PD-MCI. There is a correlation between neuronal loss in the nucleus basalis of Meynert, cortical cholinergic deficits and the degree of cognitive impairment in PD [94]. Reduced choline acetyltransferase activity in frontal and temporal regions correlates with Lewy body load and with cognitive deficits [98]. In PD patients without dementia, cholinergic denervation is associated with impaired verbal learning and Stroop performance [99, 100]. These histopathological and neuroimaging findings are borne out by the observation that anticholinergic drugs that are used to treat motor symptoms in PD impair both memory [101] and frontal executive function [102]. Furthermore, treatment with cholinesterase inhibitors, which restore levels of acetyl choline [103], improve cognitive function in PDD and DLB, lending further support to the role of cholinergic neurotransmission in these conditions.

Noradrenergic pathways may also be involved in cognitive changes in PD. As well as early loss of peripheral noradrenergic neurones in PD [104], noradrenaline exerts central effects, possibly by integrating activity across brain regions

[105]. Alpha synuclein deposition is particularly heavy in the locus coeruleus, the chief source of noradrenergic projections in the brain [106]. This may form the basis of orthostatic hypotension, commonly seen in PD with associated cognitive deficits.

The relationship between dopamine and cognition is less clear-cut. Dopamine has beneficial effects on tasks sensitive to frontal lobe dysfunction [101, 107, 108] and uptake of dopamine transporter ligands may predict change in cognitive function in early PD [64]. However, visuospatial and memory tasks are not affected by dopaminergic medications [109], and a recent therapeutic trial of rasagiline that targets dopaminergic pathways did not show improved cognition in patients with PD-MCI [110].

In summary, cognitive involvement in PD-MCI is likely to arise from a combination of mechanisms. Pathological accumulation of alpha synuclein as well as tau and amyloid beta are of importance, especially within neurones with particularly long axons, and neurotransmitter changes especially involve loss of cholinergic function.

Current Challenges and Controversies

DLB and PDD

There is a longstanding debate as to whether PD dementia and dementia with Lewy bodies (DLB) are one or distinct entities [111]. Parkinson's disease dementia is defined as progressive cognitive decline in the context of established PD at least 1 year after onset of Parkinsonian motor symptoms [112]. Conversely, dementia occurring before, simultaneous to or within the first year of Parkinsonism is DLB [113]. The presence of cognitive deficits in prodromal and preclinical PD calls into question the very definition of DLB. If cognitive changes can be detected years before the onset of classical PD, this suggests that a cognitive phenotype is core to the diagnosis of PD itself and blurs the boundaries with DLB. This issue remains unresolved, although it is acknowledged in the current Movement Disorder Society criteria for both DLB and PD-MCI [28, 113]. As our understanding of the underlying mechanisms of cognitive involvement in Parkinson's disease increases, definitions of DLB, PDD and PD-MCI are likely to become clarified.

PD-Associated Comorbidities

Other factors commonly associated with PD may impact on cognition as well as general levels of alertness and attention. These include effects of medications, mood changes such as depression and apathy, as well as sleep disorders. Motor fluctuations can also influence cognition and an individual's global abilities in day-to-day functioning. These should all be

taken into consideration when assessing patients for potential PD-MCI. Where possible, therapeutic interventions should be targeted to optimise each of these factors.

Heterogeneity in PD-MCI

As currently defined, PD-MCI is a heterogeneous entity, encompassing patients with deficits in any cognitive domain, and with varying levels of impaired functioning. Evidence already suggests that some sub-groups, particularly those with deficits in visuospatial performance, are at the highest risk of developing PD dementia [2, 35]. Maintaining wide definitions, with poorly differentiated cognitive profiles, prevents accurate comparisons across studies. Critically, whilst these boundaries are blurred, clinically useful disease stratification will not be possible. There is clearly a need for better cognitive phenotyping to enable well-defined sub-groups that are more likely to show similar rates of disease progression. In part, this could be improved with more sensitive and more widely available measures of visuospatial function that are beginning to emerge [114].

Therapies to Treat PD-MCI

Pharmacological

There are currently no pharmacological treatments to improve cognition specifically in PD-MCI, although this is now an area of active research. A recent small cross-over study of the rivastigmine patch reported a trend for [115] improvement in the primary outcome measure of global improvement [116]. Recent trials of atomoxetine, a selective noradrenaline reuptake inhibitor, suggested improvement in global cognition in patients with depression in PD [117] as well as improved decision-making, attention and planning in patients with PD without dementia [118] supporting the potential role for noradrenergic pathways in PD-MCI.

Trials of disease-modifying therapies in Parkinson's are currently underway, with the ultimate aim of slowing the disease. Targets include the lysosomal pathway [119] and immunotherapies targeted against alpha synuclein [120] as well as repurposing of established drugs [3]. Whether these treatments will have specific effects on slowing cognitive involvement in PD or in PD-MCI will need to be tested.

Non-Pharmacological

Despite a large number reports of cognitive training to improve cognition in PD, the impact of these interventions is still not clear. A recent meta-analysis of seven studies, including 272 participants [121], found key methodological problems. For example, 6 out of 7 studies suffered from bias due to lack

of adherence to intention to treat analyses, and two out of 7 did not blind assessors. They concluded that the body of evidence is small but that there may be a small overall effect on cognition. They found no improvement in scores such as the MMSE or MoCA and that most gains were in executive skills such as planning. Notably, memory and visuospatial domains did not show significant improvement.

Interventions using physical exercise show more promise in improving cognitive outcomes in PD. Across several studies, moderate intensity aerobic exercises performed 2–3 times per week lead to some improvement in executive function [122–126] as well as language function [127]. Large-scale RCTs are now underway [128] and will be of critical importance to assess the effectiveness of these physical interventions in preventing or slowing cognitive involvement in PD and PD-MCI.

Conclusions

PD-MCI as a clinical entity has an important role in understanding the progression of PD both at an individual and a population level. Future work will require more longitudinal studies of the progression of cognitive change in PD, with more sensitive visuospatial measures. It is likely that definitions and biomarkers will begin to incorporate multimodal measures alongside neuropsychological tests. Recognising the earliest stages of cognitive involvement will allow disease stratification and personalised treatment, with the potential for early intervention. It will enable better-powered clinical trials, and potential outcome measures, ultimately to develop treatments to prevent the progression of dementia in PD.

Compliance with Ethical Standards

Conflict of Interest Rimona S. Weil and Alyssa A. Costantini declare no conflict of interest.

Anette E. Schrag has received grants from the National Institute of Health Research (NIHR), Economic and Social Research Council, GE Healthcare, Parkinson's UK, EU FP7, and the Movement Disorders Society and was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. Dr. Schrag has also received consultancy fees from Medtronic and owned shares in Astra Zeneca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Rubin EH, Morris JC, Grant EA, Vendegna T. Very mild senile dementia of the Alzheimer type. I. Clinical assessment. *Arch Neurol*. 1989 Apr;46:379–82.
2. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry*. 2013 Nov;84:1258–64.
3. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017 Aug 3;390:1664–75.
4. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. *Lancet*. 2006 Apr 15;367:1262–70.
5. Pritchard JC. A treatise on insanity. 1837.
6. Senescent KRALVA. forgetfulness: benign and malignant. *Can Med Assoc J*. 1962 Feb 10;86:257–60.
7. Levy R. Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. *Int Psychogeriatr*. 1994;6:63–8.
8. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology*. 1991 Jul;41:1006–9.
9. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry*. 1982 Sep;139:1136–9.
10. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270–9.
11. Ritchie K. Mild cognitive impairment: an epidemiological perspective. *Dialogues Clin Neurosci*. 2004 Dec;6:401–8.
12. Tomaszewski FS, Cahn-Weiner DA, Harvey DJ, et al. Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *Clin Neuropsychol*. 2009;23:446–61.
13. Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B. Neuropsychological prediction of decline to dementia in nondemented elderly. *J Geriatr Psychiatry Neurol*. 1999;12:168–79.
14. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005 Jun 9;352:2379–88.
15. Geslani DM, Tierney MC, Herrmann N, Szalai JP. Mild cognitive impairment: an operational definition and its conversion rate to Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2005;19:383–9.
16. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology*. 2001 Jan 9;56:37–42.
17. Artero S, Tierney MC, Touchon J, Ritchie K. Prediction of transition from cognitive impairment to senile dementia: a prospective, longitudinal study. *Acta Psychiatr Scand*. 2003 May;107:390–3.

18. Backman L, Small BJ, Fratiglioni L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain*. 2001 Jan;124:96–102.
19. Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999 Apr 22;52:1397–403.
20. Krasuski JS, Alexander GE, Horwitz B, Daly EM, Murphy DGM, Rapoport SI, et al. Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). *Biol Psychiatry*. 1998 Jan;43(1):60–8.
21. Chetelat G, Desgranges B, de IS V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology*. 2003;60:1374–7.
22. De SS, de Leon MJ, Rusinek H, et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging*. 2001 Jul;22:529–39.
23. Gold M. Phase II clinical trials of anti-amyloid beta antibodies: When is enough, enough? *Alzheimers Dement (NY)*. 2017;3:402–9.
24. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain*. 2004;127:550–60.
25. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*. 2010 Sep 21;75:1062–9.
26. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005 Oct 25;65:1239–45.
27. Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. *Neurology*. 2014 Jan 28;82:308–16.
28. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord*. 2012;27:349–56. **This paper describes the proposed diagnostic criteria for MCI in Parkinson's disease following a Movement Disorder Society commissioned task force. These are now the definitive criteria in use in studies of PD-MCI.**
29. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord*. 2011 Aug 15;26:1814–24.
30. 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;87:1099–105. **This is a large-scale prospective multicentre study of PD-MCI, including 269 patients. The authors demonstrate that the dominant phenotype is non-amnesic.**
31. Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*. 2006 Dec 26;67:2176–85.
32. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*. 2009 Mar 31;72:1121–6.
33. Marras C, Armstrong MJ, Meaney CA, Fox S, Rothberg B, Reginold W, et al. Measuring mild cognitive impairment in patients with Parkinson's disease. *Mov Disord*. 2013 May;28:626–33.
34. Cholerton BA, Zabetian CP, Wan JY, Montine TJ, Quinn JF, Mata IF, et al. Evaluation of mild cognitive impairment subtypes in Parkinson's disease. *Mov Disord*. 2014 May;29:756–64.
35. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. *Neurodegener Dis*. 2013;11:79–92.
36. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132:2958–69.
37. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord*. 2006;21:1343–9.
38. 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.
39. 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. **This is a prospective follow-up study of incident Parkinson's disease, including 178 patients. Importantly, the authors highlight the challenge of baseline MCI, as 27.8% of people with baseline PD-MCI had reverted to normal cognition at 5 year follow-up.**
40. Hoogland J, Boel JA, de Bie RMA, Geskus RB, Schmand BA, Dalrymple-Alford JC, et al. Mild cognitive impairment as a risk factor for Parkinson's disease dementia. *Mov Disord*. 2017 Jul;32:1056–65.
41. Darweesh SKL, Wolters FJ, Postuma RB, et al. Association Between Poor Cognitive Functioning and Risk of Incident Parkinsonism: The Rotterdam Study. *JAMA Neurol* 2017. **In this prospective cohort study of 7386 individuals without Parkinson's disease the authors showed that cognitive dysfunction was present before the onset of Parkinson's disease and that poor global cognition is a risk factor for the development of Parkinson's. This calls into question the very definition of Parkinson's dementia that is classically thought to arise after the onset of motor symptoms.**
42. Siderowf A, Stern MB. Premotor Parkinson's disease: clinical features, detection, and prospects for treatment. *Ann Neurol*. 2008 Dec;64(Suppl 2):S139–47.
43. Nagy A, Hardaker E, Bestwick JP, et al. Cognition in the PREDICT-PD cohort. 2017.
44. Weintraub D, Chahine LM, Hawkins KA, Siderowf A, Eberly S, Oakes D, et al. Cognition and the course of prodromal Parkinson's disease. *Mov Disord*. 2017 Oct 24;32:1640–5.
45. Anang JB, Nomura T, Romenets SR, Nakashima K, Gagnon JF, Postuma RB. Dementia predictors in Parkinson disease: a validation study. *J Parkinsons Dis*. 2017;7:159–62.
46. Jozwiak N, Postuma RB, Montplaisir J, Latreille V, Panisset M, Chouinard S, et al. REM sleep behavior disorder and cognitive impairment in Parkinson's disease. *Sleep*. 2017 Aug 1;40
47. Hu MT, Szezewczyk-Krolikowski K, Tomlinson P, et al. Predictors of cognitive impairment in an early stage Parkinson's disease cohort. *Mov Disord*. 2014;29:351–9.
48. Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. *Neurology*. 2002;58:1544–6.
49. Strozzyk D, Blennow K, White LR, Launer LJ. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology*. 2003;60:652–6.
50. Compta Y, Marti 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):2203–10.
51. Montine TJ, Shi M, Quinn JF, Peskind ER, Craft S, Ghingina C, et al. CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment. *Mov Disord*. 2010;25(15):2682–5.
52. Stav AL, Aarsland D, Johansen KK, Hessen E, Auning E, Fladby T. Amyloid-beta and alpha-synuclein cerebrospinal fluid

- biomarkers and cognition in early Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21:758–64.
53. Siderowf A, Xie SX, Hurtig H, Weintraub D, Duda J, Chen-Plotkin A, et al. CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease. *Neurology*. 2010 Sep 21;75:1055–61.
 54. Alves G, Lange J, Blennow K, Zetterberg H, Andreasson U, Forland MG, et al. CSF A β 42 predicts early-onset dementia in Parkinson disease. *Neurology*. 2014 May;82(20):1784–90.
 55. Backstrom DC, Eriksson DM, Linder J, et al. Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease. *JAMA Neurol*. 2015;72:1175–82.
 56. Yu SY, Zuo LJ, Wang F, Chen ZJ, Hu Y, Wang YJ, et al. Potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment: a cross-sectional study. *BMC Neurol*. 2014;14:113.
 57. Mollenhauer B, Zimmermann J, Sixel-Doring F, et al. Monitoring of 30 marker candidates in early Parkinson disease as progression markers. *Neurology*. 2016;87:168–77.
 58. Gonzalez-Redondo R, Garcia-Garcia D, Clavero P, et al. Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. *Brain*. 2014;137:2356–67.
 59. Bohnen NI, Koeppe RA, Minoshima S, Giordani B, Albin RL, Frey KA, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. *J Nucl Med*. 2011 Jun;52:848–55.
 60. Tard C, Demailly F, Delval A, Semah F, Defebvre L, Dujardin K, et al. Hypometabolism in posterior and temporal areas of the brain is associated with cognitive decline in Parkinson's disease. *J Parkinsons Dis*. 2015;5:569–74.
 61. Ekman U, Eriksson J, Forsgren L, Mo SJ, Riklund K, Nyberg L. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study. *Lancet Neurol*. 2012 Aug;11:679–87.
 62. Pellicchia MT, Picillo M, Santangelo G, Longo K, Moccia M, Erro R, et al. Cognitive performances and DAT imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study. *Acta Neurol Scand*. 2015;131:275–81.
 63. Moore SF, Barker RA. Predictors of Parkinson's disease dementia: towards targeted therapies for a heterogeneous disease. *Parkinsonism Relat Disord*. 2014;20(Suppl 1):S104–7.
 64. 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*. 2017 Jan;16:66–75.
 65. Gomperts SN, Locascio JJ, Marquie M, Santarlasci AL, Rentz DM, Maye J, et al. Brain amyloid and cognition in Lewy body diseases. *Mov Disord*. 2012 Jul;27:965–73.
 66. Akhtar RS, Xie SX, Chen YJ, Rick J, Gross RG, Nasrallah IM, et al. Regional brain amyloid-beta accumulation associates with domain-specific cognitive performance in Parkinson disease without dementia. *PLoS One*. 2017;12:e0177924.
 67. Song SK, Lee JE, Park HJ, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. *Mov Disord*. 2011 Feb 1;26:289–96.
 68. Melzer TR, Watts R, MacAskill MR, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2012 Feb;83:188–94.
 69. Pereira JB, Svenningsson P, Weintraub D, Bronnick K, Lebedev A, Westman E, et al. Initial cognitive decline is associated with cortical thinning in early Parkinson disease. *Neurology*. 2014 Jun 3;82:2017–25.
 70. Hanganu A, Bedetti C, Degroot C, Mejia-Constain B, Lafontaine AL, Soland V, et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. *Brain*. 2014 Apr;137:1120–9.
 71. Foo H, Mak E, Yong TT, Wen MC, Chander RJ, Au WL, et al. Progression of subcortical atrophy in mild Parkinson's disease and its impact on cognition. *Eur J Neurol*. 2017 Feb;24:341–8.
 72. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. *Hum Brain Mapp*. 2012 Mar;33:727–39.
 73. Melzer TR, Watts R, MacAskill MR, et al. White matter microstructure deteriorates across cognitive stages in Parkinson disease. *Neurology*. 2013;80:1841–9.
 74. Agosta F, Canu E, Stefanova E, Sarro L, Tomić A, Špica V, et al. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. *Hum Brain Mapp*. 2014;35:1921–9.
 75. Kamagata K, Motoi Y, Tomiyama H, Abe O, Ito K, Shimoji K, et al. Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis. *Eur Radiol*. 2013 Jul;23:1946–55.
 76. Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Brooks DJ, Barker RA, et al. Gray and white matter imaging: a biomarker for cognitive impairment in early Parkinson's disease? *Mov Disord*. 2016 Jan;31:103–10.
 77. Nigro S, Riccelli R, Passamonti L, Arabia G, Morelli M, Nisticò R, et al. Characterizing structural neural networks in de novo Parkinson disease patients using diffusion tensor imaging. *Hum Brain Mapp*. 2016;37:4500–10.
 78. Halliday GM, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. *Mov Disord*. 2014;29:634–50.
 79. Jellinger KA. Neuropathology in Parkinson's disease with mild cognitive impairment. *Acta Neuropathol*. 2010;120:829–30.
 80. Adler CH, Caviness JN, Sabbagh MN, Shill HA, Connor DJ, Sue L, et al. Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. *Acta Neuropathol*. 2010 Dec;120:827–8.
 81. Lewy F. Paralysis agitans. I. Pathologische Anatomie. In: Lewandowsky M, Abelsdorff G, editors. *Handbuch der Neurologie*. Berlin: Springer-Verlag; 1912. p. 920–33.
 82. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature*. 1997 Aug 28;388:839–40.
 83. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovicova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain*. 2011 May;134:1493–505.
 84. Sabbagh MN, Adler CH, Lahti TJ, Connor DJ, Vedders L, Peterson LK, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. *Alzheimer Dis Assoc Disord*. 2009 Jul;23:295–7.
 85. Howlett DR, Whitfield D, Johnson M, Attems J, O'Brien JT, Aarsland D, et al. Regional multiple pathology scores are associated with cognitive decline in Lewy body dementias. *Brain Pathol*. 2015 Jul;25:401–8.
 86. Irwin DJ, Grossman M, Weintraub D, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol*. 2017 Jan;16:55–65. **This is a retrospective study of 213 patients with Parkinson's followed-up to autopsy. The authors demonstrate that Alzheimer's-type pathology is frequently seen in patients with Parkinson's disease and that patients with higher burdens of Alzheimer's neuropathology developed dementia more rapidly and had shorter survival times.**
 87. Masliah E, Rockenstein E, Veinbergs I, Sagara Y, Mallory M, Hashimoto M, 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 Oct 9;98:12245–50.
88. Swirski M, Miners JS, de SR, et al. Evaluating the relationship between amyloid-beta and alpha-synuclein phosphorylated at Ser129 in dementia with Lewy bodies and Parkinson's disease. *Alzheimers Res Ther*. 2014;6:77.
 89. Kramer ML, Schulz-Schaeffer WJ. Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. *J Neurosci*. 2007 Feb 7;27:1405–10.
 90. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol*. 2010;120:131–43.
 91. Whitfield DR, Vallortigara J, Alghamdi A, Howlett D, Hortobágyi T, Johnson M, et al. Assessment of ZnT3 and PSD95 protein levels in Lewy body dementias and Alzheimer's disease: association with cognitive impairment. *Neurobiol Aging*. 2014;35:2836–44.
 92. Bereczki E, Francis PT, Howlett D, Pereira JB, Höglund K, Bogstedt A, et al. Synaptic proteins predict cognitive decline in Alzheimer's disease and Lewy body dementia. *Alzheimers Dement*. 2016;12:1149–58.
 93. Chung CY, Koprach JB, Siddiqi H, Isacson O. Dynamic changes in presynaptic and axonal transport proteins combined with striatal neuroinflammation precede dopaminergic neuronal loss in a rat model of AAV alpha-synucleinopathy. *J Neurosci*. 2009;29:3365–73.
 94. Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 1985 May;48:413–21.
 95. Gratwicke J, Kahan J, Zrinzo L, Hariz M, Limousin P, Foltynie T, et al. The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? *Neurosci Biobehav Rev*. 2013;37:2676–88.
 96. Wu H, Williams J, Nathans J. Complete morphologies of basal forebrain cholinergic neurons in the mouse. *elife*. 2014;3:e02444.
 97. Hale MW, Lowry CA. Functional topography of midbrain and pontine serotonergic systems: implications for synaptic regulation of serotonergic circuits. *Psychopharmacology*. 2011;213:243–64.
 98. Mattila PM, Roytta M, Lonnberg P, Marjamaki P, Helenius H, Rinne JO. Choline acetyltransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. *Acta Neuropathol*. 2001;102:160–6.
 99. Bohnen NI, Muller ML, Kotagal V, et al. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease. *Brain*. 2010 Jun;133:1747–54.
 100. Shimada H, Hirano S, Shinotoh H, Aotsuka A, Sato K, Tanaka N, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. *Neurology*. 2009;73:273–8.
 101. Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain*. 1992;115(Pt 6):1701–25.
 102. Dubois B, Pilon B, Lhermitte F, Agid Y. Cholinergic deficiency and frontal dysfunction in Parkinson's disease. *Ann Neurol*. 1990;28:117–21.
 103. 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.
 104. Orimo S, Uchihara T, Nakamura A, Mori F, Kakita A, Wakabayashi K, et al. Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. *Brain*. 2008;131:642–50.
 105. Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci*. 2009 Mar;10:211–23.
 106. Del TK, Braak H. Dysfunction of the locus coeruleus-norepinephrine system and related circuitry in Parkinson's disease-related dementia. *J Neurol Neurosurg Psychiatry*. 2013;84:774–83.
 107. Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology*. 1992;107:394–404.
 108. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol*. 2010;9:1200–13.
 109. Lee AC, Harris JP, Calvert JE. Impairments of mental rotation in Parkinson's disease. *Neuropsychologia*. 1998;36:109–14.
 110. Weintraub D, Hauser RA, Elm JJ, Pagan F, Davis MD, Choudhry A. Rasagiline for mild cognitive impairment in Parkinson's disease: a placebo-controlled trial. *Mov Disord*. 2016;31:709–14.
 111. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. Abolishing the 1-year rule: how much evidence will be enough? *Mov Disord*. 2016;31:1623–7.
 112. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689–707.
 113. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology*. 2017;89:88–100.
 114. Weil RS, Pappa K, Schade RN, Schrag AE, Bahrami B, Schwarzkopf DS, et al. The cats-and-dogs test: a tool to identify visuoperceptual deficits in Parkinson's disease. *Mov Disord*. 2017;32:1789–90.
 115. Li Z, Yu Z, Zhang J, Wang J, Sun C, Wang P, Zhang J. Impact of rivastigmine on cognitive dysfunction and falling in parkinson's disease patients. *Eur Neurol*. 2015;74(1-2):86–91.
 116. Mamikonyan E, Xie SX, Melvin E, Weintraub D. Rivastigmine for mild cognitive impairment in Parkinson disease: a placebo-controlled study. *Mov Disord*. 2015;30:912–8.
 117. Weintraub D, Mavandadi S, Mamikonyan E, Siderowf AD, Duda JE, Hurtig HI, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology*. 2010;75:448–55.
 118. Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. *Brain*. 2014 Jul;137:1986–97.
 119. Lindholm D, Pham DD, Cascone A, Eriksson O, Wennerberg K, Saarna M. C-Abl inhibitors enable insights into the pathophysiology and neuroprotection in Parkinson's disease. *Front Aging Neurosci*. 2016;8:254.
 120. Schenk DB, Koller M, Ness DK, Griffith SG, Grundman M, Zago W, et al. First-in-human assessment of PRX002, an anti-alpha-synuclein monoclonal antibody, in healthy volunteers. *Mov Disord*. 2017;32:211–8.
 121. 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;85:1843–51.
 122. Reynolds GO, Otto MW, Ellis TD, Cronin-Golomb A. The therapeutic potential of exercise to improve mood, cognition, and sleep in Parkinson's disease. *Mov Disord*. 2016;31:23–38.
 123. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol*. 2013;12:716–26.
 124. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand*. 2011;123:13–9.
 125. Uc EY, Doerschug KC, Magnotta V, Dawson JD, Thomsen TR, Kline JN, et al. Phase I/II randomized trial of aerobic exercise in

- Parkinson disease in a community setting. *Neurology*. 2014;83:413–25.
126. Nadeau A, Lungu O, Duchesne C, et al. A 12-week cycling training regimen improves gait and executive functions concomitantly in people with Parkinson's disease. *Front Hum Neurosci*. 2016;10:690.
127. Altmann LJ, Stegemoller E, Hazamy AA, et al. Aerobic exercise improves mood, cognition, and language function in Parkinson's disease: results of a controlled study. *J Int Neuropsychol Soc*. 2016;22:878–89.
128. van der Kolk NM, De Vries NM, Penko AL, et al. A remotely supervised home-based aerobic exercise programme is feasible for patients with Parkinson's disease: results of a small randomised feasibility trial. *J Neurol Neurosurg Psychiatry* 2017.