Parkinson disease-associated cognitive impairment

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Abstract | Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting >1% of the population ≥65 years of age and with a prevalence set to double by 2030. In addition to the defining motor symptoms of PD, multiple non-motor symptoms occur; among them, cognitive impairment is common and can potentially occur at any disease stage. Cognitive decline is usually slow and insidious, but rapid in some cases. Recently, the focus has been on the early cognitive changes, where executive and visuospatial impairments are typical and can be accompanied by memory impairment, increasing the risk for early progression to dementia. Other risk factors for early progression to dementia include visual hallucinations, older age and biomarker changes such as cortical atrophy, as well as Alzheimer-type changes on functional imaging and in cerebrospinal fluid, and slowing and frequency variation on EEG. However, the mechanisms underlying cognitive decline in PD remain largely unclear. Cortical involvement of Lewy body and Alzheimer-type pathologies are key features, but multiple mechanisms are likely involved. Cholinesterase inhibition is the only high-level evidence-based treatment available, but other pharmacological and non-pharmacological strategies are being tested. Challenges include the identification of disease-modifying therapies as well as finding biomarkers to better predict cognitive decline and identify patients at high risk for early and rapid cognitive impairment.

Parkinson disease (PD) is the most common movement disorder and the second most common neurodegenerative disorder after Alzheimer disease (AD). The neuropathological hallmarks of PD are neuronal loss in the substantia nigra, which causes striatal dopaminergic deficiency, and α-synuclein accumulation in intraneuronal inclusions. However, multiple mechanisms and pathway dysfunctions play a role in the pathogenesis of PD, including oxidative stress, dysfunctional mitochondria, cellular calcium imbalance, neuroinflammation and other neurotransmitter system deficits[1].

Apart from its cardinal motor features, such as bradykinesia (slowness of movement), rigidity and resting tremor, PD is associated with a heterogeneous spectrum of non-motor symptoms that contribute greatly to the overall disease burden. Cognitive impairment is up to six times more common in individuals with PD than in the healthy population[2] and is one of the most important non-motor manifestations of PD, integral to the natural history of the disease. Cognitive impairment can severely affect quality of life (QOL) and function and has been shown to have substantial economic consequences over and above the motor symptoms, even at the early stages of PD[3–5], thereby representing a high priority for both patients and care partners.

The full spectrum of cognitive impairment occurs in individuals with PD, from subjective cognitive decline (SCD) and mild cognitive impairment (PD-MCI) to dementia (PDD). SCD is a self-perceived decline in cognitive ability, unrelated to an acute event, together with normal age-adjusted, sex-adjusted and education-adjusted performance on standardized cognitive tests[6]. By contrast, PD-MCI is a gradual decline in cognitive ability reported by either a patient with PD or an informant or observed by the clinician, associated with cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities[7]. Subtle difficulties on complex functional tasks may be present[7] and, based on the number of affected cognitive domains, PD-MCI can be classified as single or multiple domain[7]. PDD is defined as cognitive impairment in a patient with PD with deficits in at least two of four cognitive domains (executive abilities, attention, visuospatial abilities and memory) that are severe enough to significantly affect normal functioning beyond impairment caused by disease-related motor and autonomic symptoms[8,9]. PDD can be denoted as mild (mild effect on daily functioning), moderate and severe (inability for independent living) dementia. Multiple cognitive domains are affected in those with cognitive impairment and PD, including

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memory, attention, visuospatial abilities and especially executive functions (mental flexibility, set-shifting, switching, efficiently planning future actions and solving problems)[10]. Of note, dementia with Lewy bodies (DLB) is a disorder characterized by limbic and cortical Lewy body pathology and dementia occurring before or within 1 year after the onset of motor parkinsonism[11]; a specific prodromal, pre-dementia stage has been described[12]. DLB and PDD are thus very similar and distinguished only by the relative timing of motor and cognitive symptoms, although this is under debate[13].

Despite increased research over the past two decades, the knowledge and treatment of cognitive difficulties in PD lag far behind our knowledge and treatment of its motor features. Continued efforts for a better comprehension of this complex feature of PD are required, particularly as there is no treatment to prevent or delay cognitive decline in PD, no effective treatments for PD-MCI, and only one treatment (cholinesterase inhibitors) approved for PDD[14,15].

This Primer describes the epidemiology of PD-associated cognitive impairment and what is known about its mechanisms and pathophysiological changes. In addition, it reviews the diagnostic criteria, procedures and biomarkers to identify patients with PD at increased risk for early and rapid cognitive decline. Finally, this Primer concludes with an overview of the status of pharmacological and non-pharmacological therapeutic strategies and an outline of the most promising breakthroughs that are likely to drive future research pathways.

Epidemiology

Cognitive decline can occur prior to[16] or at the time of a diagnosis of PD or a few years or decades after diagnosis and has high variability in its clinical severity, the cognitive domains involved and the rate of progression (FIG. 1). Longitudinal cohort studies have found that people with PD have a 2.5–6-times higher risk of developing dementia than people without PD of similar age[2,17]. However, the epidemiology of cognitive impairment in PD is not entirely clear, as population-based studies of PD rarely include PDD or PD-MCI and most studies assess the prevalence and incidence of cognitive impairment in established PD cohorts. In this Primer, we focus on longitudinal studies with relatively large and, when possible, community-based cohorts, using consensus criteria for cognitive impairment classification, based on cognitive testing and clinical interviews.

Dementia

The cross-sectional proportion of patients with PD who have dementia is 24–31%[18]. Although findings vary among studies, the cumulative prevalence of PDD in patients with a mean age at diagnosis from 54 to 70.2 years is 17% at 5 years after diagnosis[19], 46% at 10 years after diagnosis[20] and 83% 20 at years after diagnosis[21,22] (TABLE 1), compared with a global prevalence of 5–7% of dementia in the general population >60 years of age[23]. Thus, despite variability, there is a high risk of dementia in PD, with nearly half of patients having dementia within 10 years after diagnosis and the vast majority of patients having dementia within >20 years after diagnosis. Of note, there is a large variation in time to dementia, as some patients develop dementia within the first few years after diagnosis whereas others remain without dementia for decades. Although several risk factors for cognitive impairment in individuals with PD have been identified (see 'Risk Factors', below), further understanding of the mechanisms driving this difference and identifying those with a high risk of early dementia to allow for closer monitoring and management is crucial. Importantly, the rate of cognitive decline in PDD is similar to that in AD[24] and many patients with PDD will become fully dependent on care and support from others and need nursing home placement[25].

Mild cognitive impairment

During the past decade, there has been increased focus on the pre-dementia stages of cognitive impairment in individuals with PD, in particular MCI, as has been the case in AD and, more recently, also in DLB[12]. Cross-sectional studies suggest that 25.8% of patients with PD without dementia have MCI[26], whereas data from the incidence cohort of the ParkWest Study (a prospective longitudinal multicentre study of patients with incident PD in Norway) and other studies found that ~20.2% of patients have MCI at the time of diagnosis (mean age 71.3 ± 7.5 SD), which increases to 40–50% after 5 years of follow-up[27–30] (TABLE 1). By contrast, the estimated prevalence of MCI in the general older population (aged 60–90 years) ranges between 16% and 20%[31].

MCI is often described as a transitory stage between normal cognition (PD-NC) and dementia and it is important to understand the progression from MCI to dementia. Conversion rates for PDD are markedly increased in those with MCI; for the ParkWest cohort, this was reported to be almost 60% at 5 years of follow-up for those with PD-MCI[27]. The MCI course is variable and stabilization of cognitive function or even reversion from PD-MCI to PD-NC has been reported, the latter in approximately 25% of patients[27]. However, the long-term risk for dementia is still increased in patients with PD who revert from MCI to normal cognition[27,32]. Importantly, the prognostic value of MCI for the development of PDD is influenced by the diagnostic criteria chosen for MCI (see Diagnosis, screening and prevention, below)[33].

Subjective cognitive decline

The emerging concept of SCD[6] is also arising from the field of AD and has been a novel focus of PD research in the past few years. In one of the first studies assessing whether subjective memory complaints in patients with de novo PD (defined as either newly diagnosed patients or patients not receiving dopaminergic medications) could predict cognitive decline, 30.3% of patients complained of memory issues and were more likely to develop MCI within 2 years of follow-up compared with patients who did not complain of memory issues[34]; subsequent studies have supported this[35], although several factors, such as affective symptoms[36], may contribute to progression to MCI (see Diagnosis, screening and prevention, below).

Risk factors

Given the wide variation in the time to and rate of cognitive decline in PD, a key research priority is to identify predictors of the future cognitive course for patients with PD[37]. Several clinical features are associated with an increased risk of cognitive decline and, thus, it is possible to predict the risk for future cognitive impairment or dementia using various algorithms that combine demographic, clinical and genetic features[38], which may assist the clinician in identifying patients with PD who have a high risk of early dementia. The following predictors, ranked in descending order of weight, were independently associated with the development of cognitive impairment or dementia: presence of hallucinations, older age, overall severity of motor symptoms, presence of speech impairment, older age at PD onset, bradykinesia severity, higher Hoehn and Yahr stage (a descriptive, 5-stage scale commonly used to describe PD severity[39]), axial impairment (for example, postural instability and gait difficulty features), a low level of education, presence of depression and male sex[40]. There are also indications that, in addition to MCI being a risk for dementia, deficits in different cognitive domains may have different predictive power. The CamPaIGN study found that posterior cortical deficits were closely related to incident dementia in PD[41]. Meanwhile, other studies showed that frontal/executive dysfunction and frontal atrophy were associated with a higher risk for dementia conversion[42–44]. The discrepancies might be ascribed to different genetic or ethnic backgrounds. In the general population, ~40% of all dementia cases are estimated to be associated with potentially modifiable risk factors, including education, hearing loss, traumatic brain injury, hypertension, diabetes, physical inactivity, excessive alcohol consumption, obesity, smoking, depression, social contact and air pollutants[45], indicating a potential for prevention. However, it is unclear whether all the risk factors identified for dementia in the general population are also applicable to PDD.

Prodromal PD phenotypes and conversion

Recent evidence suggests that individuals with prodromal features of PD, such as hyposmia (loss of smell), REM sleep behaviour disorder (RBD) and reduced dopamine transporter binding, may present with worse

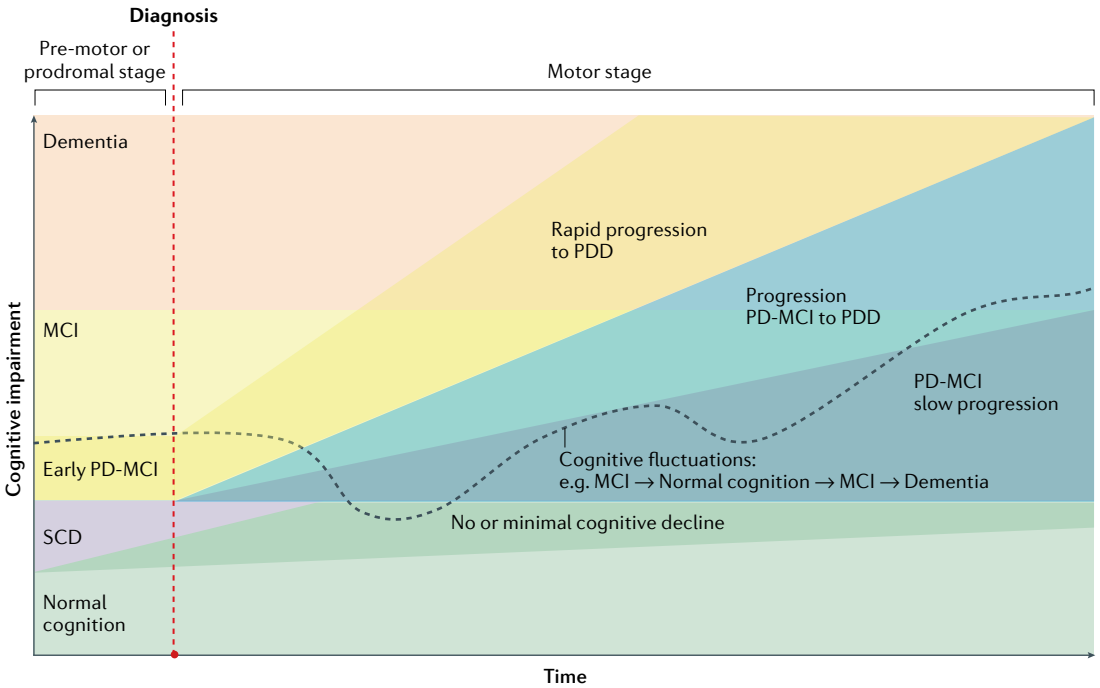

Fig. 1 | **The cognitive spectrum and the heterogeneity of progression of cognitive impairment in Parkinson disease.** Cognitive changes, mostly in the form of subjective cognitive decline (SCD) or mild cognitive impairment (MCI) can occur prior to or at the time of Parkinson disease (PD) diagnosis or even decades later, with high variability in the rate of progression. Cognitive fluctuations may also occur, in which, for example, some patients with PD-associated MCI (PD-MCI) may revert to normal cognition and then develop cognitive impairment later in the disease course, typically accompanied by motor progression and the occurrence of other non-motor symptoms. PDD, Parkinson disease dementia.

cognitive performance compared with people without any or with only one of these features[46–48]. Interestingly, prodromal PD and DLB[12] may overlap and it is not yet known how to distinguish between those who will develop PD versus those who will develop DLB. Of note, cognitive deficit has been recently defined as a new prodromal marker and has been included in the last update of the research criteria for prodromal PD[49].

Mechanisms/pathophysiology

By definition, all patients with PD have the neuropathology of PD with early loss of dopaminergic neurons in the substantia nigra and abnormal deposition of α-synuclein in Lewy bodies, initially in cholinergic and monoaminergic brainstem neurons and in the olfactory system, causing significant synaptic pathology[50]. In patients with coexisting AD pathology, which is common in and related to cognitive impairment in PD, α-synuclein deposition and synaptic pathology are found in limbic rather than brainstem regions, but the mechanisms of α-synuclein proteostasis, degradation and overall prion-like propagation that affects synapses are not thought to differ to those of PD[51].

Cognitive decline can occur due to functional brain changes but cognitive decline in PD is thought to relate to neurodegenerative brain changes that differ from those identified in PD-NC. A great variety of theoretical constructs are proposed to underlie the tissue changes associated with cognitive decline in PD, with evidence that multiple degenerative changes and mechanisms may be involved.

Degeneration of neurotransmitter systems

More widespread dopaminergic deficits in the brain. By definition, all patients with PD have a moderate-to-severe loss of dopaminergic neurons in the nigrostriatal projection pathway. More widespread degeneration of dopaminergic terminals in the striatum — particularly denervation of dopaminergic terminals in the associative dorsal caudate nucleus — occurs in those with PD-MCI than in those with PD without cognitive impairment[52] (FIG. 2). However, in patients with PD-MCI, there is relative preservation of other dopaminergic systems in the brain[52], whilst those with PDD have a considerable loss of the lateral dopaminergic system to frontal, parietal and temporal cortical regions[52] (FIG. 2). In healthy individuals, cortical dopamine modulation can boost working memory as well as visuospatial and attentional processing, and promotes cognitive effort[53,54], suggesting a key role for dopamine in cognitive function.

Table 1 | **Longitudinal cohort studies (*n* >100) reporting prevalence and cumulative prevalence of CI (MoCA <26), MCI and dementia in Parkinson disease**

Study	Cohort selection	*n* (at baseline)	Cognitive outcome	Frequency (%)	Refs
Sydney Multicenter Study	Research, de novo[a]	136	Dementia	83% at 20 years	21
Stavanger Study	Prevalence[b]	233	Dementia	27% at baseline and 60% at 12 years (80–90% by age 90)	22
Norwegian ParkWest	Incidence[c]	178	MCI	20.2% at baseline, 28.1% at 1 year, 38.8% at 3 years and 43.3% at 5 years	27,277
			Dementia	17.4% at 4 years	27
CamPalGN	Incidence[c]	142	Dementia	17% at 5 years and 46% at 10 years	19,20
CARPA	Research, de novo[d]	123	MCI	35% at baseline, 53% at 3 years and 50% at 5 years	278
			Dementia	17% at 5 years	278
NYPUM	Incidence[c]	134	MCI	42.6% at baseline and 72.6% at 5 years	29
			Dementia	27.6% at 5 years	29
Pennsylvania University	Convenience[e]	141	MCI	7.8% at 1 year, 18.5% at 2 years, 28% at 3 years, 36.1% at 4 years and 43% at 6 years	279
			Dementia	0.7% at 1 year, 3.5% at 2 years, 7.5% at 3 years, 12.9% at 4 years and 28% at 6 years	279
ICICLE-PD	Incidence[c]	212	MCI	20% at baseline[f], 14% at 1.5 years[f] and16% at 3 years[f]	28
PPMI	Research, de novo[d]	423	CI (MoCA <26)	21% at baseline, 61.8% at 1 year[g], 69.8% at 2 years[g], 67.3% at 3 years[g], 69.9% at 4 years[g] and 68.2% at 5 years[g]	280

CI, cognitive impairment; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment. [a]De novo university-based research cohort. [b]Prevalence community-based population-representative cohort. [c]Incident community-based population-representative cohort. [d]Research cohort, de novo patients. [e]Convenience cohort at University clinic. [f]Cumulative prevalence assessed using modified level II diagnostic criteria to classify Parkinson disease-associated MCI (1.5 SD below normative values) for cognitive tests. [g]Percentage of patients with symptoms at previous visit who remained symptomatic 1 year later, out of patients with data available at both years.

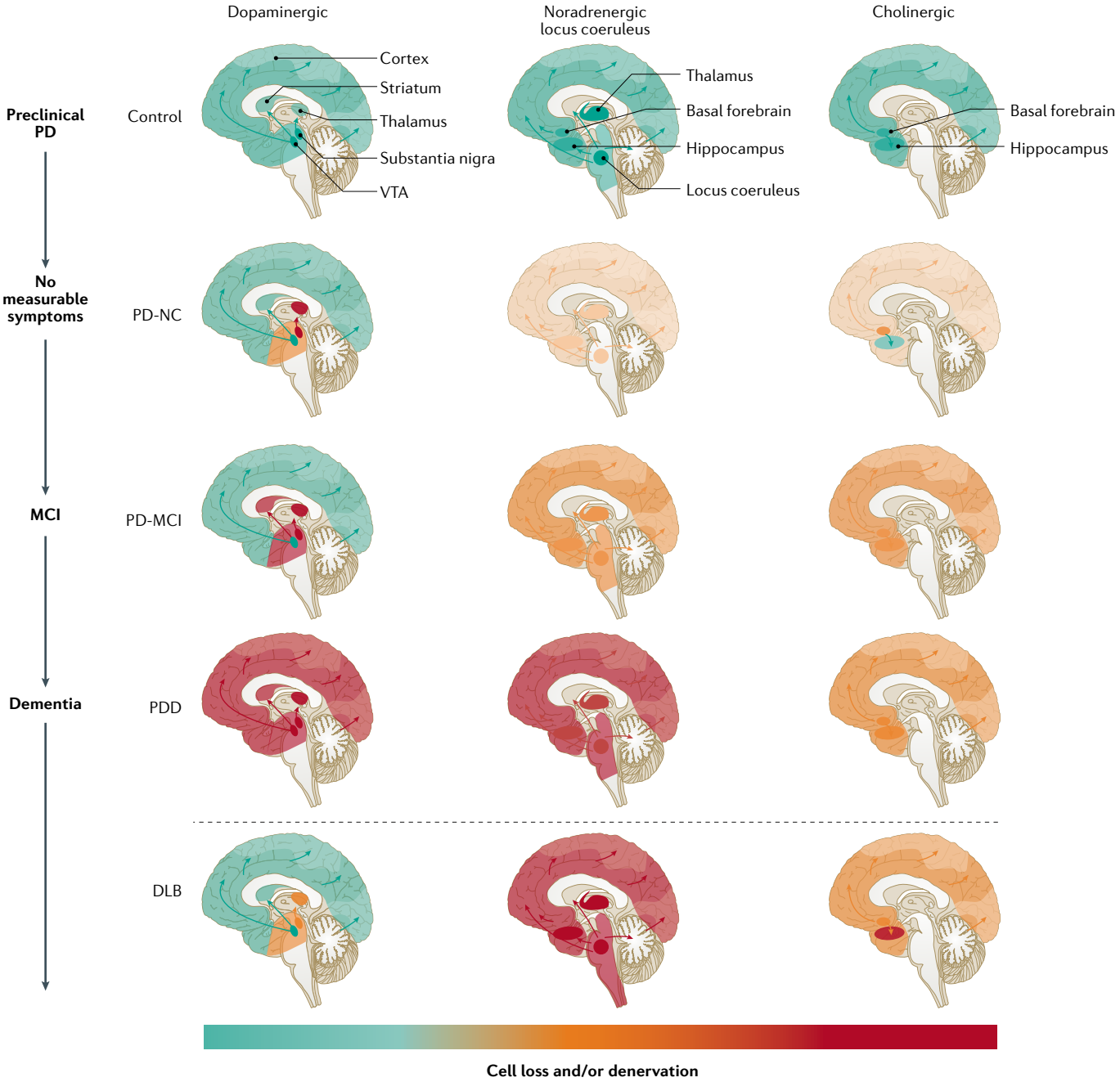

Fig. 2 | **Neurotransmitter deficits associated with cognitive decline in PD and DLB.** The dopaminergic deficit is widespread initially in the caudate nucleus in Parkinson disease (PD) with mild cognitive impairment (PD-MCI), later progressing to limbic and neocortical brain region in PD dementia (PDD). Dopaminergic deficits are usually more restricted and less severe in dementia with Lewy bodies (DLB). Similar to dopamine, deficits in noradrenaline occur in the brain in PD with normal cognition (PD-NC) but widespread noradrenergic deficits are progressively found with increasing severity of cognitive impairment in PD. Similarly, there are widespread cholinergic deficits in PD-NC but increasing deficits targeting the hippocampus occur with the increasing severity of cognitive decline in PD. Noradrenergic and cholinergic deficits are more severe in DLB. Note that serotonin deficits can occur in PD but are not directly related to cognitive decline. VTA, ventral tegmental area.

Noradrenergic locus coeruleus and sympathetic systems. The locus coeruleus contains noradrenaline-synthesizing neurons that, in humans, produce neuromelanin pigment as a by-product[55]. These neurons promote waking and arousal and are involved in sensory signal detection and modulation of various aspects of cognition but particularly in attention, behavioural flexibility, working and long-term memory[56]. Two areas of dense noradrenergic innervation originating in the locus coeruleus — the frontal cortex and hippocampus — are particularly important for cognitive behaviours[56]. At the first diagnosis of PD, there is an association between a reduction in the neuromelanin-sensitive MRI signal of the locus and the presence of PD-MCI[57] (FIG. 2). In addition, there is a

similar association between a reduction in MRI signal in the locus coeruleus and RBD[58] and, in those patients with PD and RBD, this signal reduction is associated with cognitive deterioration and orthostatic hypotension[59]. Moreover, a reduction in brain noradrenaline transporter availability correlates with cognitive decline and orthostatic hypotension in PD[59] and neurogenic orthostatic hypotension in PD owing to noradrenergic denervation of the heart is independently associated with cognitive decline[60]. The underlying mechanism of this association is due to cerebral hypoperfusion caused by orthostatic hypotension, which impairs cognitive function, with noradrenaline-enhancing drugs recommended for the treatment of orthostatic hypotension[61,62]. Of note, the properties of noradrenergic neurons make them more susceptible to oxidative DNA damage compared with other neurons[63], an increasing problem in patients with reduced blood flow during orthostasis. The evaluation of dopaminergic, noradrenergic and serotonergic markers in CSF and serum in a spectrum of patients with PD shows increasing alterations in noradrenergic markers that differentiate controls from PD and PD from PDD cases[64], with only noradrenergic markers significantly reduced in all brain tissue regions from people with PDD[65] (FIG. 2). Collectively, data from these studies identify the association of increasing loss of brain noradrenaline and cognitive decline in individuals with PD. On the basis of these data, locus coeruleus imaging and plasma noradrenaline levels are being assessed as potential biomarkers for cognitive decline in a variety of neurodegenerative diseases, including PD[66].

Basal forebrain cholinergic systems. The basal forebrain cholinergic neurons are the major source of cholinergic innervation to the neocortex, hippocampus and amygdala[67,68]. These neurons provide important control over circuit dynamics underlying cognitive processing, in particular attention and executive and memory functions[67]. In newly diagnosed patients with PD and in those further into their disease, a reduction in the volume and density of the basal forebrain cholinergic region and their projections to the neocortex, hippocampus and amygdala is associated with cognitive decline over a 2-year period[69–71] and is predictive of cognitive decline in those with PD-NC over 5 years[72]. Of note, the loss of cholinergic fibres is more marked than the loss of cholinergic neurons in PDD[73]. While the loss of cortical cholinergic innervation is independently associated with cognitive decline in PD, it also interacts with the greater loss of dopamine in the caudate nucleus to contribute to greater cognitive decline[70,74]. This could be due to the heavy innervation of the basal forebrain cholinergic region by dopamine terminals from midbrain dopaminergic neurons[75]. In terms of memory dysfunction, the loss of basal forebrain cholinergic projections to the hippocampus correlates with memory deficits and conversion to PDD (FIG. 2)[71,76]. Loss of hippocampal cholinergic fibres and activity occurs in patients with PD-MCI, whereas those with PDD have a subsequent increase in α-synuclein deposition and dysfunction in both the basal forebrain and hippocampal systems[77,78].

The mechanisms underlying the degeneration of the basal forebrain cholinergic system are not clear. Unlike the dopaminergic system, the involvement of variations in genes regulating cholinergic function has not been assessed and the cholinergic neurons are not as susceptible to oxidative damage as the noradrenergic locus coeruleus[63]. In addition, increased α-synuclein deposition occurs only after the reduction in cholinergic fibres in the cortex[78] and the widespread aggregation of α-synuclein in many neurotransmitter neuronal types does not suggest any selectivity of vulnerability for cholinergic neurons. Of note, there is a selective increase in the innervation of basal forebrain cholinergic neurons by galanin-containing fibres with the development of PD-MCI and progression to PDD, which is thought to be a response to injury, potentially from the cellular increase in α-synuclein[73]. This hyperinnervation is lost with increasing cortical AD pathology[73]. Further research is required to determine the mechanisms underpinning the insult to the basal forebrain cholinergic system in PD-MCI.

Serotonergic dysfunction is not directly related to cognitive decline. Although the loss of brainstem serotonergic neurons occurs preclinically and prior to the loss of dopamine neurons in PD, there is no clear relationship between the degeneration of serotonergic neurons and cognitive decline[79], with both disease progression and older age affecting the severity of degeneration in serotonergic neurons[80]. The degeneration of serotonergic neurons in PD is linked to motor and other non-motor features such as sleep dysfunction, depression and anxiety[81,82]. In PD, the loss of brain serotonergic structures relates directly to the deposition of β-amyloid, and medications that increase serotonin neurotransmission reduce β-amyloid peptide generation and reduce the risk of cognitive decline[83].

Neuropathology

In addition to the deposition of α-synuclein in Lewy pathologies, other prevalent age-related pathologies can coexist with PD and DLB to affect cognition (FIG. 3)[84]. Of note, neuroinflammation is not a substantive feature of individuals with Lewy pathologies in the absence of AD pathologies[85]. The most common neuropathology in PDD is limbic and/or neocortical Lewy pathology, with few documented cases without this pathology[86].

α-synuclein. The abnormal deposition of α-synuclein in vulnerable brainstem and olfactory structures is a definitive feature of PD and can occur prodromally (for example, in those with RBD) and preclinically[50,87]. The question is when and where α-synuclein may have a significant effect on cognition. Atrophy of the entorhinal cortex is associated with memory performance in people with PD-MCI[88] and with MCI in those without PD[89] and, in PD, the density of α-synuclein pathology in this region differentiates those progressing to dementia[90] (FIG. 4). However, the infiltration of α-synuclein pathology into limbic (parahippocampal) and neocortical (frontal and temporal association) regions is considered a major determinant of PDD and DLB[91] (FIG. 4). Indeed,

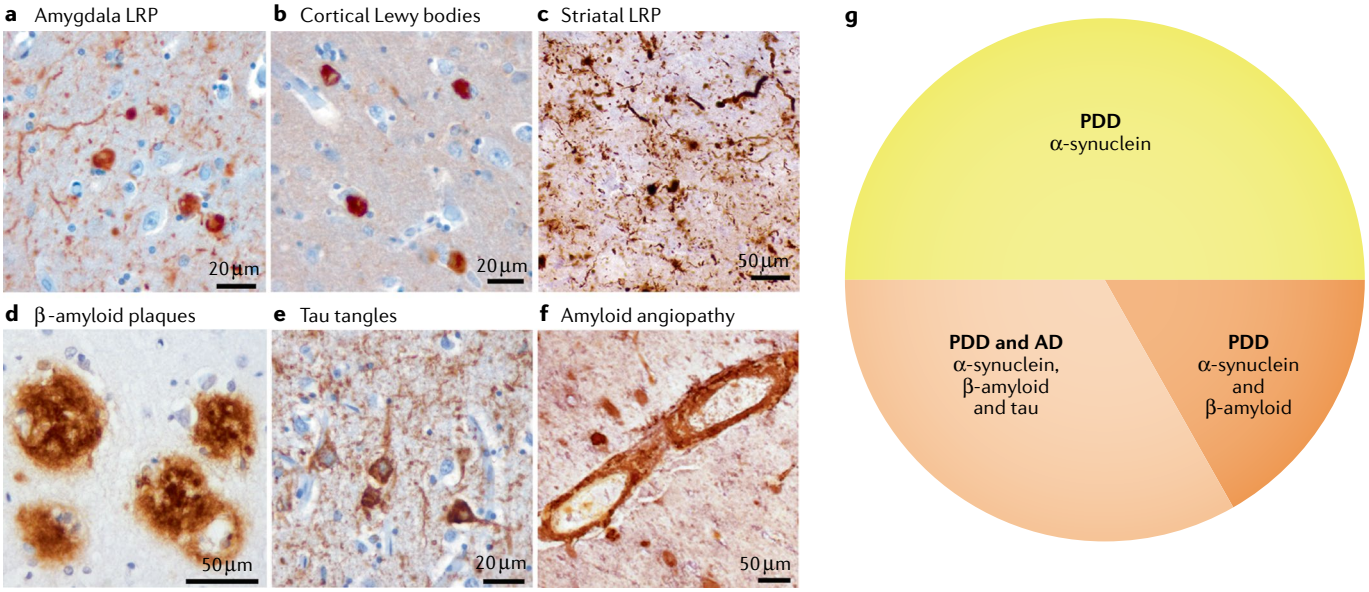

Fig. 3 | **The most common neuropathologies associated with PDD.** All patients with Parkinson disease dementia (PDD) have α-synuclein Lewy pathologies, particularly in medial temporal lobe regions (panel **a**), but over time there is an increase in neocortical and subcortical Lewy-related pathology (LRP) (panels **b** and **c**). Approximately 50% of patients with PDD have β-amyloid plaques in the cortex (panel **d**), which are indicative of pathological changes of Alzheimer disease (AD)[290]. Two-thirds of these patients also have phosphorylated tau deposition (panel **e**) in cortical tangles indicative of AD, often with amyloid angiopathy (panel **f**) and neuroinflammation[86] (panel **g**).

individuals with neocortical infiltration of α-synuclein pathology have almost twice the yearly decline in cognition compared with those without neocortical infiltration[92] and a meta-analysis found that neocortical α-synuclein pathology has the strongest association with PDD compared with all other pathologies[86].

α-Synuclein interacts with neuronal DNA in PD, which may affect DNA repair[93], and with mitochondria in DLB, drawing mitochondria into α-synuclein aggregates and reducing their numbers in cells[94]. This difference in α-synuclein interactions may reflect genetic variation in its coding gene, *SNCA*, which differs between DLB and PD[95–97], thereby affecting the type of *SNCA* transcripts and α-synuclein levels and isoforms in these diseases[98]. These molecular differences in α-synuclein between PD and DLB are likely to influence the different types of α-synuclein strains that have been documented in these diseases[99] (FIG. 4). Methods to identify these α-synuclein strains in real-time are being standardized[100]; whether these methods will be helpful in predicting cognitive decline in PD remains to be determined.

Other pathology. The most common age-related pathologies in individuals with PD and cognitive impairment are those associated with AD, extracellular β-amyloid and intracellular tau deposition (FIG. 3). Of note, these pathologies have a different distribution in the brain than Lewy pathologies. One of the earliest age-related pathological markers is the deposition of extracellular β-amyloid in association cortices; however, it has been shown that the prevalence of positive β-amyloid PET scans in PD-MCI (5–11%) is not different to that in aged-matched controls[101–103], suggesting that the initiation of cognitive decline in PD is not due to significant β-amyloid deposition. Positive β-amyloid PET scans precede the substantial tau deposition that together are diagnostic for AD[104].

As may be expected by the prevalence of cortical β-amyloid in PD-MCI, about one-third of patients with PDD have a positive β-amyloid PET[101], potentially consistent with the age prevalence of conversion from MCI to AD over time. In addition, a meta-analysis of more sensitive histological analyses on post-mortem brain tissue found moderate-to-severe extracellular β-amyloid in cortical and subcortical regions in about half of samples with PDD and severe tau pathology in hippocampal and neocortical regions in around one-third of samples with PDD[86] (FIG. 3). Coexisting AD pathology in patients with PD increases the amount of limbic and neocortical α-synuclein pathology, such that the severity of α-synuclein and AD pathologies are correlated, but also independently predicts progression to PDD[86,105]. In patients with PDD who have coexisting AD pathology, amyloid angiopathy and neuroinflammation are common and cognitive decline is more rapid with earlier mortality than in PDD without pathological AD[86]. In addition, patients with PDD and AD pathology are older at PD onset[106] and have more impaired language than those without coexisting AD, with the severity of language dysfunction (measured with the Boston Naming Test) correlating with increased measures of tau and not of β-amyloid deposition[107]. Of note, cerebrovascular and TDP43 pathologies do not generally contribute to PDD[86].

Genetic factors

Genetic variation is considered to impact cognition both in PD[108–110] and more generally in the population. In terms of the most consistent pathologies, genetic variants

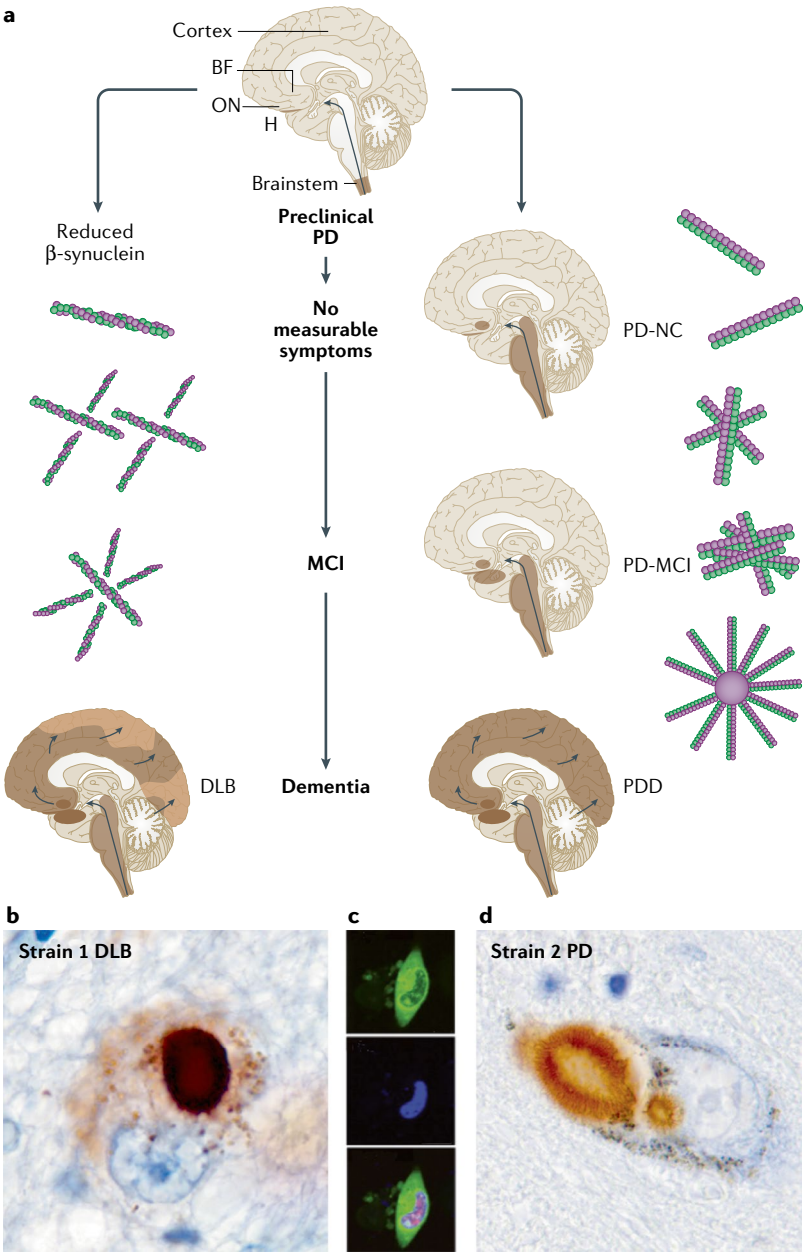

Fig. 4 | **Differences in the progression and types of α-synuclein pathologies in PD compared with DLB. a** | Increasing infiltration of α-synuclein pathologies into parahippocampal cortices occurs with increasing cognitive decline in Parkinson disease (PD) but there is also significant infiltration of α-synuclein pathology into limbic and neocortical brain regions in both PD dementia (PDD) and dementia with Lewy bodies (DLB). **b** | Photomicrograph of α-synuclein-labelled Lewy pathologies in cortical neurons in DLB (brown immunoperoxidase, Nissl counterstain). **c** | α-Synuclein-labelled nucleus and cytoplasm in cell culture (green labelling represents α-synuclein, blue labelling represents DAPI (4′,6-diamidino-2-phenylindole) staining showing nucleus). **d** | α-Synuclein-labelled Lewy pathologies in cortical neurons in PD (brown immunoperoxidase, Nissl counterstain). In PD, there is evidence that α-synuclein interacts with neuronal DNA whereas, in DLB, there is a decrease in β-synuclein with mitochondria drawn into the α-synuclein aggregates (see intracellular dot-like structures in DLB cortical neuron). Genetic variation in α-synuclein, β-synuclein and GBA1 affects the levels, isoforms and pathological seeding capacity of different α-synuclein strains documented in PD versus DLB. See REF.[50] for a review of the mechanistic aspects of α-synuclein proteostasis, degradation and prion-like propagation. BF, basal forebrain; H, hippocampus; MCI, mild cognitive impairment; ON, olfactory nerve; PD-NC, Parkinson disease with normal cognition; PD-MCI, Parkinson disease with mild cognitive impairment. Part **c** adapted with permission from (REF.[291]), Elsevier.

that affect α-synuclein levels, the lysosomal potassium channel TMEM175 and the lysosomal metabolism of α-synuclein are also implicated in increased α-synuclein pathology in PD and DLB[111,112]. *SNCA*, *TMEM175* and *GBA* (encoding β-glucosylceramidase) mutations that respectively increase α-synuclein, reduce potassium currents impairing lysosomal and mitochondrial function, and reduce glucocerebrosidase and lysosomal activity are risk factors for both PD and DLB[112]. The reduced potassium currents and glucocerebrosidase activity do not result directly in α-synuclein aggregation but respectively increase the phosphorylation of α-synuclein and cellular susceptibility to pathological α-synuclein seeds (FIG. 4)[112,113]. A particular single nucleotide polymorphism in *GBA* that reduces glucocerebrosidase expression, weakens its enzymatic activity and enhances α-synuclein deposition is associated with PD-MCI and PDD[114].

Progression and increased cognitive impairment in PD are associated with the *APOE* (encoding apolipoprotein E) ε4 allele and with no other genetic variants at the genome-wide level[108–110]. The *APOE* ε4 allele may predispose to β-amyloid deposition over time in these individuals as occurs in the general population.

Poorer cognition and reduced dopamine transmission in the general population has also been associated with genetic variation in *SLC6A3* (also known as *DAT*, encoding dopamine transporter)[115] as well as in genes involved in dopamine synthesis (*DDC*, encoding dopamine decarboxylase)[116], degradation enzymes (*COMT*, encoding catecholamine-O-methyltransferase)[117,118] and dopamine receptors (*DRD2*, encoding dopamine receptor 2)[119]. Collectively, these studies suggest that common genetic variations in a variety of proteins important for the production, metabolism and signalling of dopamine in the brain may predispose to cognitive deficits in PD.

Diagnosis, screening and prevention

Diagnosis

The accurate diagnosis of cognitive impairment in individuals with PD is important for clinical management, patient information and counselling, and research, including trial selection. The diagnosis can be made based on the evaluation of global cognitive function or on a more detailed neuropsychological assessment, which allows the assessment of attention, working memory, and executive, language, memory and visuospatial functions. A full medical examination is mandatory and biomarkers can be useful to identify the causes and predict the risk of cognitive decline, although their use in clinical practice is yet to be validated.

Screening. Screening of cognitive function in patients with PD is not performed regularly but should be part of routine clinical care. This screening requires less time, fewer resources, is more available and is less burdensome for patients compared with detailed neuropsychological assessments. Disadvantages of screening include limited information about the cognitive profile and reduced reliability compared with neuropsychological assessment.

Based on their clinimetric properties in PD[120], three scales for screening of cognitive function were recommended in a paper by the Movement Disorder

Society (MDS) Rating Scales Review Committee (the Montreal Cognitive Assessment (MoCA)[121], Mattis Dementia Rating Scale Second Edition (MDRS-2)[122] and Parkinson's Disease – Cognitive Rating Scale (PD-CRS)[123]) and two scales were classified as recommended with caveats (Mini-Mental Parkinson (MMP)[124] and Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG)[125])[120]. Although the Mini-Mental State Examination (MMSE) is frequently used, it is not suitable for cognitive screening in the early stage of PD owing to a ceiling effect[126] and the lack of sensitivity in detecting MCI.

The MoCA is the most frequently used screening instrument in PD research and clinical practice. The optimal cut-off point of 23/24 has a sensitivity of 0.41 and a specificity of 0.82, with 68% correct diagnoses of PD-MCI[127]. Based on the individual MoCA score or course of successive MoCA scores, a detailed neuropsychological assessment can be indicated, balancing this cut-off score with other factors such as education, previous level of functioning and availability of neuropsychological assessment.

Neuropsychological testing. Neuropsychological tests are validated standardized tests with adequate population norms. Raw test scores are especially influenced by age and education level. Based on the norms, raw test scores are transformed, correcting for influences, such as age and education, into z-scores or equivalents. Tests are most frequently divided into five domains (attention and working memory, executive, language, memory, and visuospatial functions). Examples of tests that are useful are provided in the MDS consensus PD-MCI paper[7]. There is large heterogeneity in the neuropsychological tests used in clinical practice. A study using pooled data across multiple international sites could not recommend with confidence a test battery that would be sensitive to detect mild cognitive deficits in patients with PD[128]. Therefore, the selection of tests should be done based on the presence of adequate local population norms.

Subjective and mild cognitive impairment. Research in healthy older adults has suggested that subjectively identified cognitive decline may indicate early changes in cognitive functioning that are not detected on neuropsychological tests. SCD can be reported by the patient, family members or friends, or clinicians. To our knowledge, there are no validated instruments to determine the presence of SCD in PD. However, tools developed for the assessment of non-motor symptoms, such as the Non-Motor Symptoms Scale (NMSS)[129], the MDS Non-Motor Rating Scale (MDS-NMS)[130] and the Non-Motor Symptoms Questionnaire (NMSQ)[131], include questions on the cognitive status as perceived by the patient. Nevertheless, the value of subjective cognitive complaints in patients with PD without objective impairment in formal neuropsychological testing is not well understood. Although the presence of SCD does not correspond well with objective cognitive impairment, it represents an increased risk for cognitive decline in some but not all studies[34,35]. Of note, as SCD can be due to anxiety or depression, screening and treatment of depression and anxiety is important in patients with subjective cognitive impairment in addition to the monitoring of cognitive function.

Diagnostic criteria for PD-MCI from the MDS[7] classify PD-MCI as SCD reported by patient, caregiver or clinician and impairments at neuropsychological assessment that do not significantly interfere with functional independence (BOX 1). A detailed patient interview is essential to differentiate the effects of cognitive and motor impairment on functioning and to distinguish between MCI and dementia. This can be done, for example, with the Parkinson's Disease – Cognitive Functional Rating Scale (PD-CFRS)[132] or Penn Parkinson's Daily Activities Questionnaire-15 (PDAQ-15)[133]. The PD-MCI criteria contain a two-level operational scheme of PD-MCI depending on the comprehensiveness of the clinical assessment, in which level I is based on an abbreviated assessment (such as screening of cognitive function or a limited battery of neuropsychological tests) and level II is based on comprehensive neuropsychological testing of five cognitive domains (BOX 1). The MDS PD-MCI criteria appeared to have prognostic validity for the development of PD dementia with both the level I limited test battery[134] and level II criteria[135]. In a meta-analysis, level I criteria were associated with a greater reversion estimate from PD-MCI to normal cognitive functioning[136]. However, different cut-offs for PD-MCI in neuropsychological testing, different global scales for cognitive screening and the limited battery of neuropsychological tests were all treated equally as level I in this meta-analysis. Therefore, we do not know precisely which level I operationalization led to the greater reversion. Overall, the sensitivity and specificity of level I testing are probably less adequate than those of level II testing, leading to

Box 1 | **Movement Disorder Society PD-MCI diagnostic criteria**[7,120]

Level I – Abbreviated assessment

- Impairment on Parkinson disease (PD)-appropriate global cognitive ability scale (such as Montreal Cognitive Assessment (MoCA), Parkinson's Disease – Cognitive Rating Scale (PD-CRS), Mattis Dementia Rating Scale Second Edition (MDRS-2))
- Impairment on at least two neuropsychological tests when a limited set of tests is used (less than two tests per domain or less than five cognitive domains assessed)

Level II – Comprehensive assessment

- Neuropsychological testing includes two tests per domain:
  - Attention and working memory
  - Executive functions
  - Language
  - Memory
  - Visuospatial skills
- Impairment on two tests in one domain or impairment on one test in two different domains
- Impairment shown by:
  - Score 1–2 SD below norm
  - Significant decline on serial testing
  - Significant decline from estimated premorbid functioning

PD with mild cognitive impairment (PD-MCI) subtype classification (comprehensive level II assessment required)

- Single domain: impairment on two or more tests in one domain
- Multiple domain: impairment on at least one test in each of two or more domains

Box 2 | **Diagnostic procedure Movement Disorder Society PDD criteria**[8,144]

Level I — Parkinson disease dementia (PDD)

- A diagnosis of Parkinson disease (PD) based on the UK Brain Bank criteria for PD
- PD developed prior to the onset of dementia
- Mini-Mental State Examination (MMSE) below 26
- Cognitive deficits severe enough to impact daily living (caregiver interview or Pill Questionnaire) independent of motor symptoms
- Impairment in more than one cognitive domain, that is, at least two of the following aspects:
  - Months Reversed or Seven Backward
  - Lexical Fluency or Clock Drawing
  - MMSE Pentagons
  - Three-Word Recall
- Absence of major depression
- Absence of delirium
- Absence of other abnormalities that obscure diagnosis

Level II — Comprehensive assessment for characterizing PDD

The level II evaluation assesses four domains:

- Decreased global cognitive efficiency
- Subcorticofrontal features of PDD
- Instrumental (cortically mediated) functions:
  - Language
  - Visuoconstructive
  - Visuospatial
  - Visuoperceptive
- Neuropsychiatric features:
  - Apathy
  - Depression
  - Visual hallucination
  - Psychosis

lower validity of the outcomes. Furthermore, reversion might be due to small fluctuations around the precise cut-off and not due to a reversion back to stable normal cognitive functioning.

The introduction of the MDS criteria reduced the heterogeneity in the reported epidemiology of PD-MCI, which was partially due to a previous lack of consensus guidelines, but there is still variability[137]. Indeed, the MDS criteria themselves create some variability owing to a lack of specificity about cut-off points for impairment in neuropsychological tests. In this regard, the most recent studies used a cut-off of ≤1.5 SD below the normative mean.

Parkinson disease dementia. Establishing the diagnosis of PDD is important for the management of patients and their caregivers, including personalized care packages, forward planning and use of medication. The main feature of the clinical MDS PDD criteria[8,9] (BOX 2) is an insidious decline in more than one cognitive domain that is severe enough to impair daily life and lasting for at least 6 months. Importantly, behavioural features (apathy, personality and mood alterations, hallucinations, excessive daytime sleepiness) may be present and are sometimes reported by the patient but most often by caregivers. Similar to the criteria for MCI, subjective and objective cognitive impairment are required and cognitive screening instruments are often sufficient to diagnose dementia due to a more marked impairment. Functional impairment due to cognitive impairment is essential and, as mentioned above, can be identified using the PD-CFRS and PDAQ-15 or during a clinical interview with the patient and an informant. Also similar to the PD-MCI criteria, the PDD criteria contain a two-level operational scheme depending on the comprehensiveness of the clinical assessment (BOX 2).

In dementia trials in PD, other rating scales have been used to assess the degree of cognitive impairment, its effect on activities of daily living and the clinical global impression of change, although none of them have been specifically designed nor recommended for PDD. These include the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)[138], the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL)[139] and the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)[140], all of which have been developed in the context of dementia due to AD.

In the context of a diagnosis of PDD, it is important to rule out other causes of cognitive impairment such as concomitant physical disease, drug use, depression or delirium. In addition to physical examination and history, basic blood tests (for example, thyroid function tests, vitamin B12 level and relevant tests for metabolic, infectious, autoimmune and other aetiologies)[141] and structural brain imaging with MRI should be performed to rule out other causes such as severe cerebrovascular disease. PDD is also associated with atrophy in brain MRI[142]; the regional atrophy pattern is variable, and temporal, parietal, frontal and occipital lobe atrophy is common[142,143]. See BOX 2 and REF.[144] for more details.

Of note, DLB and PDD share many pathological and clinical features and are usually considered as two clinical entities on a spectrum of Lewy body disease[8,11]. From a neuropsychological perspective, it has been shown that PDD and DLB may have different cognitive profiles, such as the presence of a more severe impairment in executive functions for PDD and in memory for DLB, and trajectories of cognitive decline, which appear to be more rapid for DLB in the language domain[145]. However, at the earliest stages of dementia, worse performance on tests of attention and executive functions and constructive abilities has been observed in DLB than in PDD[146]. Traditionally, the 1-year rule has been used to distinguish DLB from PDD: if dementia occurs more than 1 year after the diagnosis of PD, the diagnosis is PDD, whereas parkinsonism occurring after or simultaneously with dementia is classified as DLB. Diagnostic criteria of PD that proposed to include also parkinsonism in the context of established dementia were proposed in 2015 (REF.[13]). However, here, we refer to PDD using the traditional classification, that is, dementia occurring in a person who has been diagnosed with PD (see Outlook, below).

Computerized cognitive testing. Digital computerized cognitive testing, which can be carried out remotely from patients' homes, has become an interesting alternative to traditional pen-and-paper testing[147]. Benefits of computerized testing include the opportunity for frequent testing with less learning effects, which increases the sensitivity to detect decline[148], cost-efficiency and the

availability of large normative databases. Opportunities for conducting both remote functional assessments and digital interventions (such as cognitive training) on the same online platform are being studied[147,149].

For the MoCA, a telephone version is available without the visual elements and it can also be administered audiovisually via several media (www.mocatest.org). The Telephone Interview for Cognitive Status (TICS) has been used in several patient groups but hardly in those with PD[150]. In one systematic review, the MMSE, MoCA and several neuropsychological tests showed good teleneuropsychological validity compared with face-to-face testing, although the number of studies per test was limited[151]. However, many challenges in teleneuropsychology remain such as copyright issues, the need for publishers' permission to adjust tests for teleneuropsychology and the need for a stable internet connection. In addition, remote assessment is difficult in people with severe cognitive or motor symptoms and with hearing or visual impairment[152], and not all patients have internet access or electronic devices on which to perform this. Given these limitations, face-to-face testing is routine in clinical care and more research is needed to understand how computerized testing can provide additional and more reliable information.

Biomarkers of cognitive decline

Many of the pathologies associated with cognitive impairment can be identified in vivo using a variety of imaging and blood-based or CSF-based markers. These biomarkers can be used to provide an increased understanding of the mechanisms underlying cognitive impairment in PD and, from a clinical perspective, can identify patients with an increased risk of early and rapid cognitive decline[153].

One of the first identified predictive markers was temporo-parietal atrophy on MRI (which is indicative of AD pathology)[154], confirmed in many subsequent studies. In addition, basal forebrain atrophy observed using MRI is also associated with cognitive impairment in PD[71,72]. Hypometabolism in the medial frontal and parietal regions using FDG-PET is associated with a decline in executive and memory function[155]. More recent MRI techniques, such as diffusion tensor imaging, also hold promise as biomarkers of cognitive function[156]. For example, increased radial and axial diffusivity in the thalamus observed using diffusion tensor imaging was associated with a decline in MoCA scores[157].

In addition to general imaging biomarkers, markers for specific pathologies that are associated with cognitive impairment are available. For example, CSF markers of AD pathology can predict future cognitive decline[158]. Indeed, in one study, low amyloid-β_{1-42} (Aβ42) levels were associated with the development of MCI or dementia[153]. Evidence for an association between CSF total tau or phospho-tau levels and MCI or dementia in PD has been limited mostly to cross-sectional studies[159], although the potential of CSF total tau, in combination with CSF Aβ42 and caudate [^{123}I]FP-CIT uptake, in predicting the development of cognitive impairment has been reported[160]. A recent PET study did not report associations between tau pathology and cognition in PD[161].

An α-synuclein biomarker for cognitive impairment may prove difficult owing to the central role of α-synuclein in PD itself. CSF levels of total α-synuclein have been inconsistently associated with cognitive decline, with some studies reporting reduced concentrations whereas others report increased concentrations[162]. Possibly, early in PD, there is a reduced concentration of α-synuclein, linked to α-synuclein being included in the formation of Lewy bodies, followed by increased concentrations due to leakage of α-synuclein associated with more neurodegeneration[163]. Recent studies using seed technology (a group of highly sensitive protein amplification assays used for the detection of aggregates of misfolded proteins) for strains have reported clearer associations with Lewy body pathology and might provide a more accurate predictor of cognitive decline[164].

There is emerging evidence supporting the role of quantitative electroencephalography (EEG) as a diagnostic marker for DLB, with slower wave activity and variation in dominant frequency in patients with this disorder[11,12]. Similar changes, such as quantitative EEG background slowing-down and spectral power analysis performed with machine learning techniques, are associated with cognitive impairment in Lewy body disease[165,166] and preliminary studies have suggested EEG as a predictive biomarker of cognitive decline in PD[167]. In a subsequent study, an increased risk of dementia in patients with PD with low background rhythm frequency and increased theta median power was found[168].

Management

Pharmacotherapy for dementia

Most randomized controlled trials (RCTs) for cognition in PD have focused on patients with dementia (TABLE 2); however, as PDD together with DLB are often considered as part of a broader clinicopathological entity called Lewy body dementia, several RCTs have included both patients with PDD or DLB.

To date, the only unequivocally positive RCT for PDD was for the cholinesterase inhibitor (ChEI) rivastigmine[169]. ChEIs reversibly inhibit the enzyme acetylcholinesterase, which decreases the metabolism of acetylcholine and enhances cholinergic neurotransmission in the basal forebrain. In this trial, rivastigmine had statistically significant but clinically modest effects on a range of primary (ADAS-Cog) and secondary (such as ADCS-CGIC, ADCS-ADL, verbal fluency, attention, and visuospatial abilities) outcome measures. Accordingly, oral rivastigmine is FDA-approved and EMA-approved for the treatment of mild-to-moderate PDD but not of PD-MCI due to a lack of efficacy in a single randomized placebo-controlled trial[170]. Both rivastigmine capsules and transdermal patches have a similar efficacy in improving cognition and behavioural symptoms albeit with greater improvements observed for the oral formulation[171]. In terms of tolerability, in the pivotal placebo-controlled RCT, nausea, vomiting and tremor were statistically more common in the rivastigmine capsule group compared with placebo[169]. A large RCT of donepezil, another ChEI, for PDD produced an improvement in cognitive performance assessed using ADAS-Cog, although this did

Table 2 | **Published RCTs investigating treatments for mild cognitive impairment and dementia in Parkinson disease**

Treatment	Dose	*n*	Duration	Summary of primary results (active group vs placebo/control)	Ref.
Dementia					
Donepezil	10 mg/day	16	18 weeks	↔ global cognition, ↑ memory	281
Donepezil	10 mg/day	22	10 weeks	↔ global cognition	282
Donepezil	5/10 mg/day	550	24 weeks	↔ global cognition, ↑ clinician's global impression of change	172
Galantamine	16 mg/day	41	24 weeks	↑ global cognition, ↑ frontal lobe function, ↑ visuospatial function	283
IRL752	750 mg/day	32	4 weeks	↔ spatial working memory, ↑ executive functions (secondary outcomes)	219
Memantine	20 mg/day	25	16 weeks	↔ global cognition	284
Memantine	20 mg/day	40	24 weeks	↑ clinician's global impression of change	173
Memantine	20 mg/day	120	24 weeks	↔ clinician's global impression of change	174
Rivastigmine	12 mg/day	541	24 weeks	↑ global cognition, ↑ clinician's global impression of change	169
Mild cognitive impairment					
Cognitive rehabilitation therapy	2 hours/week	20	6 weeks	↑ attention, ↔ all other domain-specific tests	285
Cognitive rehabilitation therapy	135 minutes/week	31	4 weeks	↑ global cognition, ↑ memory, ↑ executive functions, ↔ all other domain-specific tests	286
Cognitive training therapy	135 minutes/week plus home exercises	46	4 weeks	↔ global cognition	287
Cognitive training therapy plus tDCS	120 minutes/week plus 80 minutes/week	24	4 weeks	↓ attention/executive functions, ↔ all other domain-specific tests	222
Standard cognitive training or tailored cognitive training with or without tDCS	Cognitive training: 135 minutes/week; tDCS: 20 minutes/week	42	4 weeks	↑ executive function, ↑ memory, ↑ attention/working memory, ↑ language, ↑ activities of daily living, ↑ quality of life	288
tDCS plus physical therapy	25 minutes/day	20	2 weeks	↑ global cognition	223
Atomoxetine	80 mg/daily	30	10 weeks	↔ all domain-specific tests	182
Creatine plus coenzyme Q10	10 g/day plus 300 mg/day	75	12–18 months	↑ global cognition, ↑ plasma phospholipid levels	214
Rasagiline	1 mg/day	55	12 weeks	↑ working memory, ↑ verbal fluency, ↔ all other domain-specific tests	289
Rasagiline	1 mg/day	170	24 weeks	↔ global cognition	178
Rivastigmine	9.5 mg/24 hours	28	10 weeks per treatment phase	↔ clinician's global impression of change	170

Only randomized controlled trials (RCTs) with total sample size ≥20 were included. All RCTs were placebo-controlled, except for REF.[283] (open-label) and REF.[288] (inactive group). ↑, statistically significant improvement; ↔, no statistically significant difference; ↓, statistically significant worsening; IRL752, cortical enhancer; tDCS, transcranial direct current stimulation.

not reach statistical significance[172]. No randomized, double-blind RCTs of galantamine, another ChEI, for PDD have been conducted. Although donepezil and galantamine have insufficient evidence for the treatment of PDD, they have been rated as 'possibly useful' by the International Parkinson and Movement Disorder Society Evidence-Based Medicine Committee because of their proven effects and regulatory approval for AD[15].

Memantine, an NMDA receptor antagonist that reduces glutamatergic neural transmission and glutamate toxicity in the brain, is approved by the FDA and EMA for the treatment of moderate-to-severe AD. The efficacy of memantine was investigated in two RCTs for Lewy body dementia: memantine was partially beneficial in terms of global clinical status for PDD in one study[173] but not in the other[174]. The effects of ChEIs and the inconsistent effects of memantine have been demonstrated in several meta-analyses[175].

The 5-HT6 antagonist SYN120, repurposed from AD, has also been evaluated for the treatment of cognitive impairment in PD but negative findings were reported (NCT02258152). Intepirdine, another 5-HT6 antagonist, did not show positive effects on cognition or parkinsonism in DLB (HEADWAY-DLB Study; NCT02669433). The management of psychiatric features associated with PDD, such as depression, hallucinations and other psychotic symptoms, has been extensively reviewed elsewhere[15,176].

Treatment of MCI

No approved treatments for PD-MCI are available, but the symptomatic treatment for this indication is of great interest to the PD community. As PD-MCI is often a transitional state to PDD, treatments are urgently needed to slow its progression to PDD, either through long-term symptomatic or disease-modification effects. The RCT landscape for PD-MCI has been quite limited[15,177], with failed studies for both a PD MAO-B inhibitor, rasagiline[178], and a ChEI patch, rivastigmine[170], although the latter study showed a secondary benefit on a performance-based measure of cognitive functioning (TABLE 2). In a psychosis prophylaxis study including patients without dementia on the basis of MMSE score ≥24, donepezil treatment was associated with better performance on the MMSE and on an auditory memory task over a period of nearly 2 years[179]. In addition, preliminary studies of atomoxetine, a selective noradrenaline reuptake inhibitor, showed cognitive benefit[180,181], yet a subsequent small RCT in PD-MCI did not find a benefit on cognitive tests despite significant improvements in subjective reporting[182]. Ongoing or planned studies for PD-MCI include a selective α7 nicotinic acetylcholine receptor agonist and multiple non-pharmacological treatments.

Non-pharmacological approaches

Non-pharmacological therapies for cognition in PD fall into four broad categories: cognitive interventions (such as engagement in cognitive and social activities, guided practice on tasks or mnemonic strategies, and individualized treatment plans that focus on compensatory strategies), physical exercise (such as treadmill training), non-invasive brain stimulation (either transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS)), and invasive brain stimulation (DBS) (TABLE 2). Although the sophistication of studies has improved over time, many studies have numerous severe methodological limitations such as small sample sizes and lack of application of diagnostic criteria for PD-MCI or PDD[183]. Another important limitation is the difficultly in conducting double-blind studies, thereby introducing the high likelihood of non-specific treatment effects for patients randomized to the active treatment arm; additionally, even in double-blind studies, the effectiveness of the blinding process is rarely reported.

Despite the study limitations, there is preliminary evidence from reviews or quantitative meta-analyses, albeit with mixed findings based on limited data of varying quality[184], that cognitive training[185,186], physical exercise[187,188] and non-invasive brain stimulation[189] may all lead to at least short-term benefit in some cognitive abilities, with the strongest evidence for executive function abilities. In terms of cognitive training, one systematic review found that the use of multi-domain, computer-based cognitive training at a frequency of 2–3 times per week over 3–12 weeks is associated with measurable improvements in executive functions, memory, processing speed and attention[190]. However, another systematic review and meta-analysis graded the evidence from published clinical trials on cognitive training as low and recommended further large-scale studies in PD[186]. Regarding exercise, some studies have suggested that aerobic exercise, among other types of physical exercise, provides specific benefits for memory, although studies vary widely in the amount of exercise studied (between 30 and 60 minutes per session, 1–3 times per week, for 4–26 weeks)[191]. In particular, aerobic and resistance exercise (such as treadmill training), and combined physical and cognitive training, have shown short-term maintainance/improvement of global cognition, processing speed, sustained attention, mental flexibility and memory in patients with PD[188].

In terms of the neural stimulation techniques that have been evaluated in PD, tDCS modulates neural activity by delivering low-intensity electrical currents to specific cortical regions[192], whereas rTMS induces an electrical field in the brain by using a magnetic field, thus leading to neuronal depolarization[193]. There is insufficient RCT evidence to recommend tDCS or rTMS for the treatment of cognitive impairment in PD[15]. For DBS, one small study used a sham-controlled, crossover, bilateral DBS of the nucleus basalis of Meynert in PDD and showed that the procedure was safe; however, the primary cognitive outcomes did not significantly improve, although there was evidence for improvement in neuropsychiatric symptoms with DBS[194].

Impact of PD treatments

The clinical choice of initial PD medication (levodopa, dopamine agonist or monoamine oxidase-B (MAO-B) inhibitor) at disease onset does not seem to make a difference in terms of cumulative dementia rates[195,196]. However, there is strong evidence that medications with anticholinergic properties (encompassing both PD anticholinergic medications, such as benztropine and trihexyphenidyl, and over-the-counter sleep medications or antihistamines, such as diphenhydramine), and particularly the long-term exposure to multiple medications or medications with greater anticholinergic properties, are associated with worse long-term cognition in the general population and patients with PD[197,198], and thus represent a target for clinical management[199]. In patients with PDD, simplification of antiparkinsonian treatment through a stepwise withdrawal of non-levodopa PD medications starting with anticholinergic drugs, followed by amantadine, selegiline, dopamine agonists and then catechol-O-methyltransferase inhibitors, might be useful, particularly if comorbid psychosis is present[176].

In addition, several studies have found that DBS can worsen cognitive functioning[200]; as a result, cognitive testing is recommended as part of the pre-DBS surgery evaluation process, and patients with severe cognitive impairment should not undergo brain surgery. However, the use of model-based stimulation parameters to minimize the spread of the electrical current to non-motor portions of the subthalamic nucleus reversed the cognitive decline that occurred after DBS in one study[201]. Encouragingly, a subsequent study of DBS in younger patients with shorter disease duration showed short-term cognitive tolerability similar to the best medical therapy[202].

Other device-aided PD treatments, such as continuous subcutaneous apomorphine infusion and intrajejunal levodopa infusion (IJLI), despite being avoided in those with PD-associated cognitive impairment, are now considered as potential therapeutic strategies even in patients with MCI (apomorphine and IJLI) and mild-to-moderate dementia (IJLI)[203,204]. Patients with cognitive complaints as part of non-motor fluctuations[205,206] could potentially benefit cognitively from adjustments to their PD treatments, although this remains to be demonstrated.

Indirect management strategies

Given the association between common non-motor symptoms, such as depression and RBD, and cognitive decline in PD, it is possible that treating these disorders may affect cognitive abilities in the short or long term, although this has not yet been demonstrated. Given the known associations between vascular risk factors[207,208] and pathology[209], orthostatic hypotension[210], obstructive sleep apnoea[211,212], excessive daytime sleepiness[213] and cognitive performance in PD is important in this regard. Indirect management strategies for cognitive impairment are based on treating the comorbid disorders and risk factors; for example, managing the comorbid disorders associated with cognitive impairment (such as depression, psychosis and RBD) and managing comorbid vascular disease and vascular risk factors (such as hypertension, diabetes mellitus and dyslipidemia) given the association between cognitive impairment and vascular pathology in PD[209]. Specifically, obstructive sleep apnoea should be treated using continuous positive airway pressure ventilation and symptomatic orthostatic hypotension should be treated with midodrine, fludrocortisone or droxidopa, given their association with impaired cognition in patients with PD[210,212]. In addition, another indirect management strategy is minimizing anticholinergic medication use, including using instruments such as the Anticholinergic Cognitive Burden Scale[198] to identify and rate anticholinergic medications.

Novel treatment approaches

In general, disease-modifying clinical trials for PD do not determine if patients meet diagnostic criteria for a cognitive disorder or assess cognitive performance or its change over time.

To date, there has been one completed neuroprotective RCT for cognitive function in PD — a study testing the combination of the purported neuroprotectants creatine and coenzyme Q10 (CoQ10)[214]. CoQ10 plays an important role in mitochondrial bioenergetics, protects the integrity of biological membranes, and acts as an intracellular antioxidant and free-radical scavenger[215], and creatine, an endogenous organic acid, is also an active component of mitochondrial metabolism and has antioxidant properties[216]. This 18-month study randomized patients with PD-MCI to either monohydrate creatine plus CoQ10 or placebo, and both cognitive function (assessed using the MoCA) and a treatment-related biological measure (plasma phospholipid level, a measure of cell membrane integrity) showed improvements in the treatment group compared with placebo. Although these results are promising, there was no mention of discontinuations, adverse events or other neuropsychological measures, and other studies of both compounds in PD were negative or did not provide enough evidence for their neuroprotective effects[217,218].

Other ongoing or recently completed studies for PDD with novel therapeutic approaches include testing a partial D1 positive allosteric modulator (NCT03305809), an antibiotic (ceftriaxone, NCT03413384), a pharmacological chaperone for glucocerebrosidase (ambroxol, NCT02914366), human plasma fractions (NCT03713957), an NMDAR modulator (NCT04148391), a cortical enhancer[219] and a sigma 1 receptor agonist[220]. The latter, in particular, was evaluated in a double-blind, multicenter, placebo-controlled phase II trial and showed positive results for multiple subtests of the Cognitive Drug Research computerized assessment system for the active group versus placebo[220]. However, these encouraging preliminary data need further validation in a larger RCT. For the related disorder of DLB, one completed phase II double-blind, placebo-controlled RCT found that the oral p38α kinase inhibitor neflamapimod significantly improved cognition on a hybrid (computerized and paper-and-pencil) neuropsychological battery[221], although conclusions on its efficacy and possible use in clinical practice will require positive results in a phase III clinical trial.

Given the multifactorial aetiology of cognitive impairment in PD, it is unlikely that one single treatment strategy is sufficient and combinations, for example, of pharmacological and non-pharmacological therapies, are likely to be more successful in managing and preventing cognitive decline. We are not aware of such studies but, for instance, studies combining cognitive training or physical therapy with tDCS do exist[222,223]. Combination therapies should therefore be further tested.

Quality of life

In addition to an association with increased mortality[224,225] and complicating the management of motor symptoms, the presence of cognitive impairment plays an important role in determining the health-related QOL (HRQOL) in people with PD. HRQOL in patients with PD is a pillar of assessment of health empowering the patient, with a crucial role in defining individual well-being and global health[226,227]. Validated tools for the assessment of HRQOL include the Parkinson's Disease Questionnaire-39 (PDQ-39)[228], the Parkinson's Disease Questionnaire-8 (PDQ-8)[229] and the European Quality of Life – Five Dimensions (EQ-5D)[230]. Caregiver stress can be evaluated by, for example, the Zarit Burden Interview[231,232]. However, of note, these tools address the cognitive related-aspects of HRQOL only indirectly through, for example, assessment of the experienced impairment in activities of daily living.

A number of factors contribute to reduced HRQOL in PD (FIG. 5). The burden of non-motor symptoms drives HRQOL, as demonstrated by a multicenter, international, cross-sectional study on 411 patients with PD that found that non-motor symptoms, including cognitive impairment, have, as a whole, a greater effect

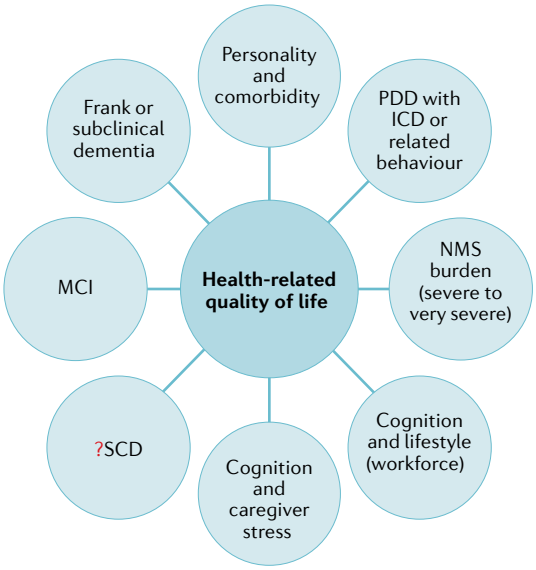

Fig. 5 | **Determinants of quality of life associated with cognitive impairment in PD.** The different cognitive syndromes associated with Parkinson disease (PD), PD dementia (PDD), mild cognitive impairment (MCI) or subjective cognitive decline (SCD) directly impact the health-related quality of life. In addition, an indirect effect of cognitive impairment on health-related quality of life can be exerted through their impact on other determinants of quality of life such as caregiver stress, comorbidities and overall non-motor symptom (NMS) burden. ICD, impulse control disorder.

on HRQOL than motor symptoms and that progression of non-motor symptoms contributes to HRQOL decline[226]. The authors of this study suggested that these findings might be explained by the fact that the presence of dopaminergic therapy and, therefore, the impact of the motor manifestations on HRQOL, may be neutralized by effective antiparkinsonian treatment[226]. In addition, only a minority of non-motor symptoms, due to their mainly non-dopaminergic nature, respond to dopaminergic therapy and this, together with a range of barriers in reporting non-motor symptoms among patients and clinicians[233], might prevent their effective management[226].

The HRQOL of patients with PD and cognitive impairment, and specifically regarding attention and memory deficits as assessed by the NMSS, is significantly worse compared to that of patients without these impairments[226]. The ICICLE cohort study showed that even PD-MCI leads to poorer QOL over 3 years of follow-up and specifically in those who developed dementia during follow-up[234]. In addition to global cognition, impaired attention was a particularly strong determinant of QOL, demonstrated by multivariate modelling showing that attentional deficits had the strongest predictive power[234].

Equally important is the impact of cognitive impairment on the caregiver. Both cognitive impairment[235] and other PD-related non-motor symptoms that are associated with PDD, including psychosis, apathy, depression and impulsive control disorders[236–239], contribute to the burden of caring for people with PD. For example, in one study including 584 pairs of patients with PD and their primary caregivers, the cumulative burden of neuropsychiatric symptoms coupled with dementia appeared to be a major determinant of QOL[240]. The perceived burden of care is closely linked to the positive quality of the relationship between the patient and the caregiver (mutuality). Indeed, mutuality is negatively influenced by cognitive impairment and, in turn, this effect on mutuality negatively affects the perceived burden of care[241]. In addition, cognitive impairment in patients with PDD significantly contributes to poorer mental health, stress, negative strain, resentment and overall higher levels of care burden in patients' spouses and life partners, who constitute the majority of caregivers[242,243].

Thus, HRQOL assessment and focus on the partner and the patient–carer relationship should be integral to any cognitive assessment, and specific personalized aspects need to be considered in people with PD and cognitive impairment.

HRQOL has now emerged as a key issue in the emergence of the long COVID/post-acute COVID-19 syndrome in patients with PD, and a new report suggests that cognitive impairment may play a key part in the symptoms that constitute long COVID in PD[244]. The overall effect of this phenomenon needs to be ascertained in longitudinal studies on patients affected by COVID-19 and some such studies have already started.

Outlook

Global burden of PD-associated cognitive impairment

PD is the fastest growing neurological disorder in the world in terms of prevalence, disability and deaths[245]. In 2016, it has been estimated that 6.1 million individuals had PD globally, compared with 2.5 million in 1990, and this number is expected to more than double by 2040 (REF.[246]). In light of what has been defined as the "Parkinson pandemic"[247], more attention has been focused in recent years on the impact of PD in lower-middle-income and low-income countries, where the largest increases in prevalence are expected[248–250]. On the other hand, the global number of individuals who lived with dementia has been estimated to be 43.8 million in 2016, expected to increase to over 100 million by 2050 (REF.[251]). However, while care inequalities in dementia care across the globe[252,253] and research challenges in developing countries are increasingly being recognized for both PD and dementia separately[254,255], data on the prevalence of PD-associated cognitive impairment, risk prediction, management and societal burden in these regions are lacking. Addressing these disparities with strategies to increase access to health care, research funding and public awareness on the topic is therefore mandatory and represents a global health priority.

Classification issues and prodromal stages

The proposal that dementia prior to or simultaneous with motor symptoms can be included in the diagnostic criteria for PD[13,256] has reopened the long-standing debate on whether PDD and DLB should be considered the same disease[257–260]. A deeper understanding of the pathophysiological processes underlying these two synucleinopathies, such as the relative contribution of

β-amyloid and tau pathology in cortex and striatum, the extent of cortical Lewy pathology and α-synuclein load in the hippocampus, the severity of neuronal loss in the substantia nigra, and cholinergic cell loss[260], is required to better understand the relationship between PD and DLB.

Although some risk factors for cognitive impairment have been identified[46,48,261], further research is needed to better identify any early evidence of cognitive impairment in genetic at-risk populations and in individuals with clinical features of prodromal PD to provide opportunities for prevention strategies and early precision therapy interventions.

Predictive biomarkers

Studies have identified a specific brain-clinical pattern that identifies people with RBD who developed rapid cognitive decline and DLB rather than PD. Based on routine MRI using partial least squares, atrophy in the basal ganglia, thalamus, amygdala, and frontotemporal grey and white matter as well as the expansion of CSF-filled spaces predicted cognitive decline in both RBD and PD[262]. In addition to imaging, CSF and EEG biomarkers for cognitive impairment, there is an increasing focus on exploring α-synuclein and other biomarkers in other biofluids and tissues such as skin, colon, submandibular gland, CSF, saliva and blood[263].

In this scenario, the development of plasma-based biomarkers for cognitive impairment in PD is particularly relevant given the recent progresses made in AD and the promise of neurofilament light and other plasma-based markers[264]. However, only one study has found significantly higher plasma total α-synuclein concentrations in people with PD, in particular in those with a more advanced disease stage and dementia[265]. Further longitudinal studies are needed to test the hypothesis that plasma α-synuclein could predict future cognitive decline in PD. Seed technology techniques using protein amplification assays, such as the Protein-Misfolding Cyclic Amplification (PMCA) and the Real-Time Quaking-Induced Conversion (RT-QuIC), are able to detect synucleinopathies with very high sensitivity and specificity even at the preclinical stage[164], although their potential use in the prediction of cognitive decline in PD needs to be explored. Another unmet need in biomarker development is represented by the lack of reliable α-synuclein PET ligands, which will allow the determination of the in vivo distribution of Lewy body pathology. Other novel imaging techniques also have huge potential to detect the earliest brain changes leading to cognitive impairment in PD[156].

The era of digital cognitive testing

The development of digital cognitive testing and the evolution of self-completed computerized assessments and wearable devices to assess cognitive functioning in daily life[147,149] provides an exciting opportunity to both improve clinical management and to obtain more sensitive outcome measures for clinical trials and will likely become a standard procedure in the future, given further technological improvements and increased access to the internet and digital devices. To reach this point, psychometric requirements (reliability, validity and normative data), documentation and technical problems, as well as their relation to traditional tests, need to be well known[266].

Management

Several questions on the direct and indirect management of cognitive symptoms in PD remain open.

Important challenges concern the role and long-term validity of non-pharmacological interventions, such as cognitive training, exercise-based therapy and non-invasive brain stimulation, in addressing and preventing cognitive dysfunction in PD. So far, clinical trials focused on these strategies, despite showing encouraging results, have been hindered by methodological issues, poor assessment of long-term effects and scarcity of pathophysiological correlates. In future trials, a more robust study design[186], longer intervention and follow-up durations as well as in vivo pathophysiological evidence (such as that provided by neuroimaging) will be the key components to establish the true role of such therapies.

The need for disease-modifying therapies

Numerous disease-modifying compounds targeting multiple pathophysiological processes are being tested in PD, although the process of bringing them into clinical use in PD remains a long-standing challenge[267].

Successful disease-modifying drugs for PD should also have cognitive benefit, although cognition has rarely been included in these studies. For instance, preclinical models suggest that immunotherapies targeting both β-amyloid and α-synuclein reduce AD and PD pathological burden, improve behaviours and may have an additive effect[268]. Active and passive immunotherapies targeting multiple pathologies, alone or in combination, therefore represent one of the most intriguing opportunities to tackle cognitive impairment in PD[269–271].

Diabetes-related pathways seem to play a role in the pathogenesis of PD, potentially through peripheral and cerebral insulin resistance leading to altered autophagy, mitochondrial function, cell proliferation and increased inflammation, which may have positive effects on memory and cognition[272]. The disease-modifying and neuroprotective potential in PD of antidiabetic agents is currently being explored in several trials[272]. Additional repurposed candidates include angiotensin receptor and calcium-channel blockers, tyrosine kinase inhibitors, immunomodulators, and GBA-related agents including ambroxol and anti-oxidants[273]. Most studies have been negative but still provide important lessons to learn, both regarding the most promising targets as well as trial designs.

Patient and public involvement

In the past years, there has been growing attention on the need to include patients, their caregivers and families in all stages of the research process[274]. The increasing contribution of patient and public involvement groups in defining research questions, designing and conducting clinical trials, disseminating outcomes, and shaping research roadmaps reflects the concept of research as a shared effort among all stakeholders. Although in PD research this concept is increasingly

being recognized[275], further involvement of patients and families, also inclusive of diverse patient populations, in research focused on PD-associated cognitive impairment is needed.

Improved clinical trial design

Clinical trials for therapies targeting cognition in PD may benefit from recent design improvements. More sensitive outcomes, including computerized cognitive testing and wearables to measure motor and other functions, together with the development of an internationally recognized set of core outcomes, as has been done for idiopathic PD[276], particularly focused on patients with cognitive impairment and on the effects of specific interventions (such as non-pharmacological interventions), will allow the reporting and comparison of research outcomes in a standardized manner. More targeted selection criteria using current diagnostic criteria[7,8] and recommended assessments[120], combined with both biomarkers and genetic risk factors aiming to assign the right person to the right intervention at an early disease stage, as well as biomarkers demonstrating target involvement, will offer opportunities for improved statistical power and cheaper trials.

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