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Cognitive decline in Parkinson disease

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Abstract | Dementia is a frequent problem encountered in advanced stages of Parkinson disease (PD). In recent years, research has focused on the pre-dementia stages of cognitive impairment in PD, including mild cognitive impairment (MCI). Several longitudinal studies have shown that MCI is a harbinger of dementia in PD, although the course is variable, and stabilization of cognition — or even reversal to normal cognition — is not uncommon. In addition to limbic and cortical spread of Lewy pathology, several other mechanisms are likely to contribute to cognitive decline in PD, and a variety of biomarker studies, some using novel structural and functional imaging techniques, have documented *in vivo* brain changes associated with cognitive impairment. The evidence consistently suggests that low cerebrospinal fluid levels of amyloid- β_{42} , a marker of comorbid Alzheimer disease (AD), predict future cognitive decline and dementia in PD. Emerging genetic evidence indicates that in addition to the *APOE** ϵ 4 allele (an established risk factor for AD, *GBA* mutations and *SCNA* mutations and triplications are associated with cognitive decline in PD, whereas the findings are mixed for *MAPT* polymorphisms. Cognitive enhancing medications have some effect in PD dementia, but no convincing evidence that progression from MCI to dementia can be delayed or prevented is available, although cognitive training has shown promising results.

Introduction

Parkinson disease (PD) is one of the most common age-related brain disorders. PD is defined primarily as a movement disorder, with the typical symptoms being resting tremor, rigidity, bradykinesia and postural instability, and is pathologically characterized by degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (misfolded α -synuclein) in the surviving neurons. In addition to the defining dopamine-related motor symptoms, however, PD is increasingly recognized as a heterogeneous multisystem disorder involving other neurotransmitter systems, such as the serotonergic, noradrenergic and cholinergic circuits. Thus, a wide variety of nonmotor symptoms (NMS) linked with these neurotransmitters are commonly observed in patients with PD. In light of this variability, subtyping of PD has been proposed, including a subtype based on time of onset and ongoing rate of cognitive decline¹.

Cognitive decline is among the most common and important NMS, and in this article we review the current status of knowledge regarding cognitive impairment in PD. Robust evidence indicates that in comparison with age-matched groups without PD, people with PD exhibit more rapid decline in a

number of cognitive domains — in particular, executive, attentional and visuospatial domains, but also memory. The full spectrum of cognitive abilities can be observed in PD, from normal cognition, through early mild subjective and objective decline (mild cognitive impairment (MCI)), to mild, moderate and even severe PD dementia (PDD). Studies from the 1990s onwards convincingly demonstrated a much higher cumulative risk of dementia in people with PD than in the general population, and systematic reviews showed that the point prevalence of dementia was 25–30%. Several long-term longitudinal studies have indicated that the majority of patients with PD will develop dementia if they survive for more than 10 years after diagnosis. On the basis of numerous, varied studies, we now know that dementia in PD has important adverse implications for functioning, quality of life, caregiver burden, and health-related costs².

The timing, profile and rate of cognitive decline vary widely among individuals with PD, so identifying and predicting future cognitive decline in this population is crucial for researchers and clinicians alike. Identification of clinical and biological markers that can predict which patients are at increased risk of early and rapid cognitive decline is important for communicating the prognosis and managing patients clinically and, thus, is a focus of this article. Established demographic and clinical risk factors include increasing age and more severe parkinsonism, in particular, non-tremor features². Here, we focus on cognitive and biomarker features as potential predictors of cognitive decline in PD.

Cognitive syndromes in PD

Subjective cognitive decline

In recent years, interest has focused on subjective cognitive decline (SCD), in which cognitive impairments are noted by the patient, family members or health personnel, but cognitive test performance is in the normal range. In the general population, SCD is associated with an increased risk of future cognitive decline, that is, progression to MCI or dementia, including Alzheimer disease (AD). Relatively little is known about SCD in PD, and there are no established criteria for this syndrome. No reliable method of capturing SCD in PD yet exists, possibly owing partly to the confounding effects of motor symptoms and NMS. Nevertheless, SCD has been reported in patients with PD, and might be a harbinger of further cognitive decline in this population¹⁴.

MCI and the risk of PD dementia

The two most common cognitive syndromes in patients with PD, PDD and PD-MCI, were operationally defined in diagnostic and assessment guidelines from the International Parkinson and Movement Disorder Society (MDS)^{3,4}. In PDD, but not in PD-MCI, the cognitive deficits are severe enough to impair daily life (for example, social and occupational functioning, and personal care), independently of the impairment ascribable to motor or autonomic symptoms.

Among PD patients without dementia, approximately 25–30% have MCI, which is evident at the time of diagnosis in 10–20% of patients². Presence of MCI is associated with a shorter time to progression to a dementia diagnosis, although considerable variability is observed, with some patients remaining stable and some even reverting to normal cognition. For example, in one study of patients with early PD⁵, over 20% of those with MCI reverted to normal cognition after 1 year, although persistent MCI was associated with a much lower remission rate.

Early studies indicated that the mean time to dementia after PD diagnosis was approximately 10 years. This figure is supported by more recent studies, including some that monitored patients from the time of PD diagnosis (TABLE 1), which reported dementia prevalence of 15–20% after 5 years and 46% at 10 years⁶. However, lower dementia rates (5% after 4 years) have been reported elsewhere⁷. One study that selected only PD patients with normal cognition reported that nearly 50% had developed cognitive decline after 6 years⁸. Some studies⁹ suggest that cortical posterior cognitive deficits (that is, memory and language impairment), but not frontally based dysfunction, indicate a higher risk of dementia, leading to the ‘dual syndrome hypothesis’ of cognition in PD. Discrepancies between studies are likely to be attributable to a variety of factors, including differences in case

selection, whether duration was measured from onset of symptoms or diagnosis, use of different criteria for PD-MCI and PDD, and loss to follow-up.

Clinical challenges

Cognitive decline in PD is a continuous process affecting nearly all patients over time, and the demarcations between the four cognitive groups — cognitively normal, SCD, PD-MCI and PDD — are not strict. The distribution of patients in these four groups vary markedly among different studies, depending on factors including the case selection procedures, the criteria applied, the study design (cross-sectional or longitudinal), and the cognitive measurement procedures utilized. A recent study, which attempted to define the optimal criteria for PD-MCI, found that impairment (>1.5 SD below the normative mean) on two tests within the same cognitive domain — rather than across different domains — was the best predictor of progression to dementia during the next 4 years¹⁵. As highlighted above, the separation between MCI and dementia hinges on whether the functional impact of cognitive impairment is 'severe enough to impair daily life', a criterion that is difficult to operationalize and requires an element of clinical judgement.

Another clinical challenge is the distinction between PDD and dementia with Lewy bodies (DLB), owing to their clinical and pathological overlap. The '1-year rule', in which PDD is defined as dementia that occurs at least 1 year after onset of PD motor symptoms, whereas dementia occurring prior to, simultaneously with, or within the first year of onset of parkinsonism is classified as DLB, is often difficult to apply, as a substantial proportion of patients lie within the grey zone, and categorization is usually performed retrospectively. In addition, prodromal PD and DLB symptoms overlap; for example, REM sleep behaviour disorder (RBD) can evolve into either PD or DLB. Recent evidence indicates that cognitive impairment can be present in prodromal PD, further blurring the distinction between PD and DLB¹⁶. The recently revised MDS clinical diagnostic criteria for PD propose that PD can be diagnosed regardless of when dementia occurs in relation to parkinsonism onset, and in cases where parkinsonism subsequently develops in a patient with dementia, the diagnosis 'PD (DLB subtype)' is recommended¹⁷. The relationship between PD and DLB requires further exploration. For example, recent findings indicate several nonmotor subtypes of PD, including cognitive and non-cognitive forms, which can occur in early untreated motor disease in late-onset PD, as well as in early-onset PD^{18,19}. From a practical perspective, an algorithm in which premotor NMS such as RBD are channelled towards potential transformation to motor PD, including cognitive phenotypes, has been proposed¹⁹.

Visual hallucinations and dementia risk

Several longitudinal studies have identified visual hallucinations and illusions as risk factors for cognitive decline and dementia in PD, with the time frame depending on the study design. In one study, a history of visual hallucinations at baseline was found to increase the risk of dementia at 8 years (OR 3.1, 95% CI 1.6–6.2)²⁰, and another group found that baseline visual hallucinations (OR 10.2, 90% CI 2.4–44.0) or illusions (OR 8.2, 90% CI 2.4–28.4) increased the risk of dementia at 4–5 years²¹. The association between visual hallucinations and dementia that has been observed in prospective studies might reflect progression of cognitive dysfunction, which seems to be present before or coincident with hallucination onset²².

Mechanisms

A variety of mechanisms, in addition to the classic nigrostriatal α -synuclein misfolding and dopaminergic neuronal loss, contribute to the brain changes associated with PD (BOX 1). PD is now recognized to involve multisystem, multiprotein neurodegeneration, with non-dopaminergic degeneration having a crucial role.

Compared with the motor symptoms, little is known about the mechanisms underlying cognitive decline in PD, and several key questions remain unresolved. First, is cognitive decline merely a result of more severe and widespread involvement of primary PD neuropathophysiology? Second, are some

of the PD-related mechanisms particularly relevant for cognitive decline? Last, is cognitive impairment related to regional involvement or specific mechanisms?

Information on the mechanisms underlying cognitive decline in PD has come from a variety of sources. In addition to post-mortem studies, *in vivo* studies, including clinicopathological studies and biomarker studies involving electrophysiological, imaging, electrophysiology and biofluid analyses, and genetic studies, have all contributed to an increased understanding. However, animal models for PD-related cognitive deficits have been difficult to develop.

Evidence from pathological studies

The pathological contributions to dementia in PD have been studied in some detail, and have been reviewed in detail elsewhere²³. Good evidence from post-mortem studies indicates that limbic and cortical Lewy body pathology is the main pathological correlate of dementia in PD. In most cases, α -synuclein pathology seems to spread from sites in the lower brainstem or olfactory bulb — or even extracranially from the gut or other areas innervated by the vagus nucleus¹ — to the midbrain, forebrain and limbic structures and, finally, neocortical regions²⁴.

In addition, there is strong evidence that the extent of amyloid plaque pathology is a significant contributor to dementia in up to one-third of PD patients, whereas the role of tau-related pathology is less clear. Importantly, the three proteinopathies in combination seem to have an additive effect over and above the effect of any single pathology^{25,26}. This finding is in line with basic neuroscience studies, which show an interaction between the processing of these three proteins. For example, transgenic mice with double pathology (that is, overexpression of α -synuclein on a background of amyloid- β (A β) or tau pathology) show more severe Lewy body pathology than mice overexpressing α -synuclein pathology only²⁷. Clinically, these effects manifest as earlier and more rapid cognitive decline in patients with combined Lewy body and amyloid pathology²⁸. The roles of other pathologies, including cerebrovascular disease, hippocampal sclerosis and cerebral amyloid angiopathy, are also beginning to be explored.

Synaptic pathology and cognition

The structural pathologies described above are relevant, but only partially explain the variance in cognitive decline in patients with PD. A better understanding of the disease substrate is needed for targeted drug discovery and to enable better monitoring of disease progression. Changes in synaptic function followed by synaptic loss are likely to be early and key events in neurodegenerative diseases: in AD, loss of synapses was found to be more robustly correlated with cognitive decline than was morphological pathology²⁹. Less is known regarding the role of synaptic dysfunction in cognition in PD, but synaptic alterations have been demonstrated (reviewed elsewhere³⁰).

In PD, mounting evidence indicates that the initial damage in dopaminergic nigral neurons occurs at the synapse, with subsequent retrograde axonal damage and, finally, somatic degeneration, leading to the typical motor symptoms of PD (reviewed elsewhere³¹). Similar mechanisms might underlie limbic and cortical involvement in PD. These events probably involve α -synuclein, which is mainly located synaptically and regulates synaptic homeostasis, vesicles and neurotransmitter release, and initially aggregates at the synaptic terminal during PD pathogenesis³². Of note, several other proteins implicated in PD — in particular, PINK1, Parkin, leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2) and DJ1 — are also involved in synaptic regulation. We have found that reduced neocortical level of ZnT3, a marker of synaptic plasticity, and two key synaptic proteins, neurogranin and SNAP25^{33,34}, are associated with cognition in PD. These findings suggest that cortical synaptic changes lead to cognitive decline in PD, consistent with imaging findings (see below), and preliminary work indicates that synaptic changes are also reflected in the cerebrospinal fluid (CSF). Neurogranin levels were found to be increased in the CSF in AD³⁵, probably due to increased intracellular sequestration, and similar findings have been reported — and linked with cognitive decline — in PD³⁶. Thus, CSF levels of synaptic proteins are potential biomarkers of future cognitive decline.

Neurotransmitters

Convincing evidence is available that mesolimbic and mesocortical dopaminergic activity is associated with cognitive functioning. The association between dopaminergic drugs and cognition is complex, however, and antiparkinson drugs can improve, worsen or have no influence on cognition³⁷. In addition, a number of non-dopaminergic transmitter systems are affected in PD, and are likely to contribute to cognitive impairment²³. For example, good evidence from post-mortem and imaging studies indicates that the cholinergic system is affected relatively early in PD and contributes to the cognitive decline. Interestingly, whereas Lewy body and amyloid plaque pathologies were associated with earlier onset of dementia, cholinergic deficits were more pronounced in individuals with dementia occurring later in the disease course^{28,38}. These observations provide a rationale for the positive effects of cholinesterase inhibitors in PD (see treatment section below), as well as the worsening cognition associated with the use of medications with anticholinergic activity³⁹.

Non-dopaminergic monoaminergic nuclei such as the noradrenergic locus coeruleus and the serotonergic raphe nuclei, with their long and widespread mesocortical connections, may affect cognition due to their influence on the activity of synaptic networks. This hypothesis was supported in a recent study, which showed that the ability of atomoxetine-mediated noradrenergic or citalopram-mediated serotonergic reuptake inhibition to improve response inhibition — a frontal executive task relevant to impulsivity — in patients with PD could be predicted by differences in brain activation, as measured by functional imaging⁴⁰. In the serotonin system, several receptors are associated with cognition, including the 5-HT_{1B} receptor, which was found to be downregulated in early PD in a recent PET study using a novel ligand, but was not associated with executive or attentional functioning⁴¹.

Striatal GABAergic neurons express adenosine A_{2A} receptors, which have become a drug target to improve motor functioning in PD. These receptors are also located in the thalamus and neocortex, and some evidence indicates that increased receptor activity is associated with worsening cognition. Adenosine A_{2A} antagonists may increase dopamine activity in the prefrontal cortex, and preliminary evidence suggests that they can improve cognition, in particular working memory, in PD^{42,43}.

Mitochondrial activity

Mitochondrial dysfunction occurs in PD, but little is known regarding its potential role in cognitive decline. However, mitochondrial pathology seems to contribute to cognitive decline in AD, and a recent post-mortem study showed that deficiency in mitochondrial complex 1 activity and reduced mitochondrial DNA levels in the prefrontal cortex were more pronounced in PDD than in PD without dementia⁴⁴. Mitochondrial activity is particularly high at the synapse, and is crucial to synaptic activity. A relationship between α -synuclein and mitochondrial activities at the level of synapses has been demonstrated, but their causal relationship needs to be further explored. Therapeutic approaches targeting mitochondrial activity, including complex 1 deficiency, are being developed, and manipulation of mitochondrial retrograde signalling has shown promising results in animal studies⁴⁵. The role of mitochondrial dysfunction in cognitive decline in PD needs to be further explored.

Inflammation and neurotrophic factors

Neuroinflammation is relevant for both AD and PD, and might have important implications for cognitive decline in PD⁴⁶, with a potential for novel treatment targets. Increased microglial activation is thought to lead to cell death in AD and PDD⁴⁷, and inflammation markers represent possible prognostic biomarkers. Interestingly, CSF levels of cytokines are found to be associated with cognitive impairment in PD⁴⁸ and, thus, represent possible biomarkers (see below).

Findings from many different sources convincingly demonstrate a link between diabetes, insulin resistance and PD, possibly via mechanisms involving neuroinflammation and mitochondrial dysfunction⁴⁹. A recent imaging study in a cohort of 36 patients, 12 of whom had diabetes, reported an association between diabetes, grey matter loss and cognitive impairment in PD⁵⁰, indicating a possible role for antidiabetic drugs in the treatment or prevention of cognitive decline in PD, as has been suggested in AD.

Neurotrophic factors are crucial for neuronal plasticity and, thus, learning and other cognitive functions. A longitudinal study showed that cognitive impairment in PD was associated with reduced levels of growth factors, such as brain-derived neurotrophic factor and epidermal growth factor, in CSF⁵¹ and plasma⁵².

Summary

In addition to α -synuclein, tau and amyloid pathologies, a number of other mechanisms, including different neurotransmitter systems, early synaptic changes, inflammation, and mitochondrial dysfunction, are likely to contribute to cognitive decline in PD. The roles of these as well as other potentially relevant mechanisms for cognitive impairment, such as the unfolded protein response⁵³, the ubiquitin–proteasome system⁵⁴, and increased neurogenesis (for example, in response to neurotrophic factors)⁵⁵, need to be explored further (see Management section below).

Genetic contributions

The link between risk genes for cognitive impairment and decline in PD has been the subject of several detailed reviews^{2,23,56}. BOX 2 provides a summary of genes examined to date, and the discussion below focuses on those with the largest bodies of evidence.

Genetic variants that cause monogenic forms of PD have been extensively investigated with respect to their effects on the clinical presentation of PD, including cognition and susceptibility to dementia. The *LRRK2* Gly2019Ser substitution is the most commonly studied mutation, and has been shown in the majority of studies to either have no effect on cognition or to be protective^{57–65}. However, the sample sizes of the studies were restricted by the rarity of *LRRK2* mutations, so an association with cognitive impairment cannot be ruled out. Moreover, limited longitudinal follow-up, along with assessment tools that lack the sensitivity to detect subtle changes, might mask true associations. α -Synuclein gene (*SNCA*) mutations are another major cause of autosomal dominant PD and, in contrast to *LRRK2* mutations, most seem to have deleterious effects on cognition, with the exception of duplications, which produce a clinical presentation similar to sporadic PD^{66–69}.

Polymorphisms in *SNCA* also confer a risk of sporadic PD, but examination of one risk variant (rs356219) in a large study failed to find any evidence of a relationship with cognition⁷⁰. However, the recent identification of a haplotype in intron 4 of the gene and its association with PDD raises the possibility that *SNCA*-related mechanisms are associated with cognition in sporadic PD, warranting additional studies in longitudinally assessed cohorts⁷¹.

Most other research in sporadic PD has largely focused on four candidate genes: glucosylceramidase (*GBA*), microtubule-associated protein tau (*MAPT*), apolipoprotein E (*APOE*) and catechol-*O*-methyltransferase (*COMT*). Of these, *GBA* has the strongest evidence base for association with cognitive measures: heterozygous mutations in this gene have been reliably shown to increase the risk of dementia^{72–76} and less severe impairments in frontal cognitive domains⁷⁷. *GBA* is a highly polymorphic gene, and two large independent studies found that the type of mutation modulates the relationship with cognitive decline, furthering the possibility for disease subtyping on the basis of genetic status^{78,79}.

The strong association between *APOE* and AD has led to extensive investigation of the relationship between AD risk alleles and cognition in PD. Tentative conclusions were drawn from a large meta-analysis showing a relationship with dementia⁸⁰, and some^{70,81,82} — but not all^{83,84} — subsequent studies have reported effects on cognition, as measured by a variety of neuropsychological tests. These findings point to potential genetic overlap between AD and PD, a position strengthened by recent research leveraging PD genome-wide association study data, which found evidence of genetic pleiotropy at the *MAPT* locus⁸⁵. Whether these findings provide a mechanistic explanation specifically for cognitive impairment in PD remains to be fully established.

Regional and cognitive domain-specific alterations in cortical activation associated with *MAPT*, *APOE* and *COMT* variants have been reported in two neuroimaging studies^{86,87}. These findings complement those from neuropsychological studies, and might also go some way towards explaining the inconsistent results. In particular, although neuropsychological associations may not always be

detected owing to low statistical power or lack of sensitivity of the measures used, evidence is accumulating that genetic variation drives mechanistic alterations that are consistent with different patterns of cognitive deficits. These findings warrant clinical studies with larger sample sizes, conducted with cognitive batteries specific to the neural correlates of the genes of interest.

Despite some compelling findings, experiments designed to examine the effects of single genes can only capture a small proportion of the variance of complex traits such as cognition. Genome-wide association studies go some way towards addressing this issue by simultaneously genotyping markers across the genome. One such study conducted in PD cognition found no genome-wide significant hits but, with only 443 cases, was underpowered⁸⁸. The application of genome-wide methods in other diseases across neurology and psychiatry has generated promising findings^{85,89}, but much larger data sets are needed in PD. The availability of such samples — and, consequently, the potential to conduct more powerful genetic analyses — is increasing.

Biomarkers of cognitive decline in PD

Cerebrospinal fluid biomarkers

The variety of CSF-based markers in PD, and the biological factors that influence their levels in the CSF, was recently reviewed¹⁰⁵. The most commonly studied markers have been the AD markers A β ₄₂ (a marker of A β pathology), total tau (t-tau, a marker of neurodegeneration) and phosphorylated tau (p-tau, a marker of tau pathology), and the PD marker α -synuclein. In a comprehensive review of biomarkers and cognition in PD, Lin and Wu¹⁰⁶ identified 18 CSF studies. The most consistent finding was an association between reduced CSF A β ₄₂ levels and cognitive impairment, which was reported in 14 of 15 studies. By contrast, findings for t-tau and p-tau were inconsistent, with some studies reporting an association between increased CSF levels and cognitive impairment, but most reporting no associations. Subsequently, several more studies were published, including longitudinal studies reporting an association between CSF markers and future cognitive decline — a particularly relevant question for clinicians. In AD, CSF markers can accurately predict which patients with MCI will develop AD dementia in the near future, and CSF markers to predict accelerated cognitive decline in PD are an important priority. Two cross-sectional studies reported an association between low CSF A β ₄₂ levels and cognitive impairment in PD^{107,108}. In addition, four longitudinal studies reported that reduced A β ₄₂ predicted more rapid cognitive decline^{109–112}, confirming previous findings^{113–115} (TABLE 2). DeNoPa, a multimodal biomarker study in *de novo* PD¹¹⁶, found no link between PD progression and CSF markers, but the results could have been confounded by the low number of participants agreeing to serial CSF sampling, variations in CSF sample preparation, and the demographics of the cohort.

Several studies of CSF levels of total α -synuclein have been published. Most reported low values in PD, as confirmed by a recent meta-analysis¹¹⁸, but the association with cognition continues to be inconsistent, with both low¹⁰⁷ and high values^{110,117} found to be associated with cognitive decline in different studies. The discrepant findings might be explained by differences in disease stage. CSF α -synuclein levels may increase with disease stage, and the association between high levels and cognitive impairment was found in more advanced disease but not early disease stages. In one study of CSF biomarker change with time, Hall *et al.*¹¹⁹ found that levels of t-tau, p-tau, total α -synuclein, neurofilament and YKL-40 (a marker of inflammation), but not A β ₄₂, increased over a 2-year period and were associated with worsening cognition, and the increase was particularly marked in patients with longer disease duration. These findings are consistent with reports that α -synuclein levels increase with more severe neurodegeneration. However, the DeNoPa study reported no change in α -synuclein or other CSF markers during a 24-month study period¹¹⁶. In addition to total α -synuclein, post-translationally modified forms of α -synuclein, including phosphorylated, nitrated and ubiquitinated forms, as well as oligomers, have been identified, and show some promise as markers of disease progression in PD^{120–122}, but further research is needed to confirm their diagnostic and prognostic utility as markers for cognitive impairment in PD.

Neuroimaging

Over the past decade, structural, functional and molecular neuroimaging techniques such as MRI¹²³

and PET^{124–126} have considerably advanced our understanding of the complex mechanisms underlying the development of cognitive impairment in PD^{123,126}. Two large, ongoing 5-year observational biomarker studies, PPMI and COPPADIS, are using a range of imaging assessments, and are expected to yield important information on the utility of MRI to detect brain pathology in PD patients with cognitive impairment¹²⁷. In such patients, PET imaging has provided *in vivo* evidence for the interplay between several pathological processes, including degeneration of subcortical cholinergic and dopaminergic projections, microglial activation, and neocortical pathology associated with misfolded protein deposition or vascular pathology^{47,124,128}. Also, functional polymorphisms in the *COMT* gene, which influence dopamine storage, might contribute to cognitive deficits in PD¹²⁹.

MRI measures of cortical and subcortical volume loss. Structural MRI can localize differences in regional cortical and subcortical tissue volume between groups of individuals. In PD patients without a formal diagnosis of PD-MCI or PDD, loss of tissue volume in frontal and parietal cortices has been associated with worse performance in decision-making, facial expression recognition, visual memory and executive function^{130–132}. Studies in patients with PD-MCI have demonstrated a pattern of cortical volume loss in posterior, parietal and frontal cortices, and atrophy in the hippocampus, that correlates with memory deficits^{133–135}. Longitudinal assessments of cortical thickness and subcortical volumes in patients with PD-MCI have indicated progression of cortical thinning in temporal, occipital, parietal and frontal cortices, and further loss of hippocampal volume that is associated with cognitive decline^{134,136}. Retrospective analysis of structural MRI scans has demonstrated that in PD patients without cognitive impairment, this technique can predict conversion to PD-MCI status at 6 months on the basis of baseline hippocampal atrophy¹³⁷, at 18 months on the basis of baseline temporal cortex thinning¹³⁴, and at 2 years on the basis of baseline prefrontal thinning, and insular and caudate volume loss¹³⁸. At the time when a PDD diagnosis is established, the pattern of cortical thinning becomes more severe in parietal, occipital, temporal and frontal cortices, and the volume loss in the hippocampus is substantial, including atrophy of parahippocampus, insula and cingulate gyrus that are associated with further decline of cognitive functions^{139–142}. The pattern of cortical thinning has been also suggested to differentiate PDD, which shows a predominant frontal cortex thinning, from DLB, which shows a predominant parietal and occipital cortices thinning¹⁴³.

MRI-based structural and functional connectivity. Diffusion tensor imaging measures the magnitude (mean diffusivity) and direction (fractional anisotropy) of water molecule flow in brain tissue. Neurodegenerative disorders are characterized by damage to white matter tracts (structural connectivity) that results in increased mean diffusivity and decreased fractional anisotropy. In PD patients without a formal diagnosis of PD-MCI or PDD, increased mean diffusivity in the hippocampus, and frontal and parietal white matter tracts is associated with worse performance in terms of verbal and visuospatial memory, semantic fluency and other executive functions^{132,144–146}. Also, decreased hippocampal fractional anisotropy correlates with measures of global cognitive decline¹⁴⁶.

Resting state functional MRI (fMRI) measures blood-oxygen-level dependent (BOLD) signal in the brain without an externally prompted task, and is useful to explore the functional organization of networks (functional connectivity) in the human brain. PD patients without a formal diagnosis of PD-MCI or PDD exhibited progressive loss of resting state functional connectivity over a period of 3 years in multiple brain regions, especially the posterior parts of the brain, which correlated with decreasing cognitive performance¹⁴⁷. Studies have demonstrated that cognitive decline in PDD is associated with disruption of corticostriatal and frontal cortex functional connectivity^{148,149}. As seen with the pattern of cortical thinning on structural MRI, the pattern of functional connectivity disruption can differentiate PDD, which is characterized by predominant frontal cortex disruption, from DLB, which is characterized by predominant disruption of parietal and occipital cortices¹⁴³. Further studies are needed to replicate these findings, and specifically to pinpoint the structural and functional brain networks that underlie cognitive decline in patients with PD.

Perfusion imaging. Arterial spin labelling (ASL) is an MRI-based technique that allows quantification of altered cerebral blood flow. ASL studies have demonstrated patterns of hypoperfusion in patients with PDD compared with cognitively normal PD patients¹⁵⁰. The pattern of brain hypoperfusion in PDD largely overlaps with the hypoperfusion observed in the posterior cingulate gyrus, precuneus and occipital regions in patients with AD, but differs in the temporal lobes (AD < PDD) and right frontal cortex (PDD < AD)¹⁵¹. ASL is a promising technique that merits additional study in patients with PD and cognitive impairment.

Dopaminergic molecular imaging. Studies involving dopamine decarboxylase and vesicular monoamine transporter 2 PET imaging have demonstrated decline in regional mesolimbic and mesocortical monoaminergic capacity in patients with PDD^{152,153}. These patients show only subtle loss of monoaminergic capacity in the anterior cingulate, ventral striatum and caudate, which can be detected at a single-voxel level¹⁵². Visual or semi-quantitative assessment of dopamine transporters by PET or single-photon emission CT (SPECT) imaging reveals nigrostriatal degeneration in patients with PDD, and reduced caudate dopamine transporter uptake has been associated with impairment of executive functions^{154,155}. However, dopaminergic molecular imaging can detect only subtle differences between PDD and PD, and no differences between PDD and DLB have been reported to date.

PET imaging of glucose metabolism. Studies using PET to image glucose metabolism have demonstrated metabolic decreases in the parietal, temporal, cingulate and frontal cortices in PD-MCI and PDD^{156–158}. PDD and DLB are characterized by similar patterns of glucose metabolic changes¹⁵⁹. When PDD and AD were compared, however, patients with PDD showed greater metabolic reduction in the visual cortex and relative preservation of metabolism in the medial temporal cortex^{156,157,159}. The use of more sophisticated PET analysis has allowed the identification of PD-related metabolic brain networks underlying cognitive dysfunction in PD, including smaller areas, detected at the single-voxel level, in the occipital, parietal and frontal cortices¹⁶⁰. However, even with advanced methods, discrimination between PDD and DLB has been difficult in view of the aforementioned similarities in metabolic network patterns, with the exception that metabolic decrease in the anterior cingulate is greater in patients with DLB than in those with PDD¹⁶¹.

Cholinergic PET molecular imaging. The cholinergic system has a key role in functional and structural remodelling of the cortical circuits that underlie cognitive processing¹⁶². Cholinergic PET imaging studies seem to be consistent with post-mortem evidence suggesting that loss of cholinergic function, in the forebrain, is associated with the manifestation of PDD^{38,163–165}. PET molecular imaging of acetylcholinesterase (AChE) activity has indicated that cholinergic denervation of the cerebral cortex is an early phenomenon in the course of PD, and is more widespread and profound in patients with PDD^{38,163}. AChE PET imaging studies have demonstrated mean cortical AChE loss of 20–30% in patients with PDD, compared with 11–13% in patients with PD^{38,164–166}. In PDD, loss of cholinergic function is evident in the temporal, frontal and medial occipital cortices, and in the thalamus^{38,164,167}. A similar pattern is seen in DLB^{153,167}, and to a lesser extent in AD¹⁶⁵; however, thalamic cholinergic denervation is not observed in AD¹⁶⁷. Cholinergic PET might also be sensitive also to subclinical dementia. In PD patients without a diagnosis of cognitive impairment, lower cortical AChE PET activity was associated with reduced cognitive performance scores for attention, memory and executive functions^{162,165,168}. A number of molecular targets related to the cholinergic system can be evaluated with PET, and further studies are needed to understand cholinergic system involvement in the development of cognitive impairment in PD.

Amyloid- β and tau PET in PDD. PET imaging of A β plaques *in vivo* has demonstrated that most AD cases and a subset of DLB cases show increased cortical A β retention¹⁶⁹. A β PET imaging (FIG. 1) indicates that cortical and striatal A β pathology is relatively infrequent (incidence 15–20%) in patients with PDD^{169–172}, but is sometimes uncovered by histopathology at post mortem¹⁷³. Compared with

cortical β -amyloidopathy alone, the combined presence of striatal and cortical A β plaques was associated with worse cognitive impairment in PD¹⁷⁴. A β retention in patients with PD-MCI predicted an increased risk of future cognitive decline¹⁷⁵.

A recent tau PET study has shown increased signal in the inferior temporal gyrus and precuneus in patients with PDD, which was associated with heightened cognitive impairment. These findings suggest that tau cortical aggregates are present in patients with PDD, and that tau PET data could be a marker of cognitive impairment¹⁷⁶.

As regards future research, application of novel neuroimaging techniques, including molecular imaging of α -synuclein, and of mitochondrial and non-TSPO (translocator protein) neuroinflammatory targets, could enhance our understanding of the mechanisms underlying cognitive impairment in PD, and accelerate the development of novel therapeutics.

Electrophysiology

Several studies, using a range of EEG and cognitive measures, have reported associations between slowing of the EEG in PD and cognitive deficits. The findings include associations between executive dysfunction¹⁷⁷ or Mini-Mental State Examination (MMSE) score¹⁷⁸ and spectral ratio (the ratio of fast to slow activity), between performance deficits in attention, executive function and memory and increased delta power¹⁷⁹ or decreased EEG median frequency¹⁸⁰, and between clinical ratings of background EEG slowing and combined MMSE and clock drawing test scores¹⁸¹. An increase in low-frequency (delta and theta) EEG spectral power distinguishes PDD from PD and AD¹⁸².

Indices of EEG slowing are predictive of the transition to dementia at 5 years (HR 13)¹⁸³. Peak frequency magnetoencephalogram (MEG) slowing is also predictive of the transition to dementia (hazard ratio 3.9 at 7 years)¹⁴⁷; however, unlike EEG studies, greater MEG predictive power was found at higher, beta band frequencies (HR 5.2). Interestingly, combining MEG and cognitive markers improved the prognostic power over and above the single markers, with a very high hazard ratio (>27)¹⁴⁷. A recent review of evoked potential studies in PD has suggested that a delayed (but not decreased-amplitude) P3b component in classic oddball tasks is a trait-like marker of PD cognitive impairment and dementia¹⁸⁴. The review also noted that the mismatch negativity component of pre-attentive deviance detection tasks might be reduced more in PDD than in AD or DLB¹⁸⁴.

Combination of biomarkers

As described above, the mechanisms underlying cognitive decline in PD are heterogeneous and, thus, the various biomarker modes show different yet connected brain changes. Creation of multiple models, by combining different types of markers, may provide complementary information and improve the prognostic accuracy for cognitive decline in PD. CSF or blood-based markers can inform the biochemical changes underlying volume reductions identified in imaging studies, as shown with some success in AD¹⁸⁵.

Compta and colleagues reported interesting associations between structural imaging and CSF protein changes. In a cross-sectional study, high t-tau and p-tau and low A β ₄₂ values were associated with reduced grey matter volume in patients with PDD, but not in PD and non-PD controls¹⁸⁶. Similar findings were reported by a different group¹⁸⁷. In a subsequent longitudinal study, low CSF A β ₄₂ was associated with cortical thinning, and a combination of biomarker pathologies was a stronger predictor of cognitive decline and dementia than was a single biomarker pathology¹¹⁴. Finally, low CSF α -synuclein was associated with frontal cortical thinning in PD patients without dementia and in a group with idiopathic RBD, whereas in patients with PDD, cortical atrophy was associated with increased total CSF α -synuclein and t-tau¹⁰⁶.

In two studies combining CSF biomarkers and SPECT striatal dopamine transporter uptake in early PD, reduced striatal uptake was associated with low CSF levels of t-tau and p-tau¹⁸⁸ but not α -synuclein¹⁸⁹. In an fMRI study, activity in motor-related networks correlated with CSF total α -synuclein, indicating that α -synuclein contributes to motor-related resting state networks in PD. In PD patients without dementia, CSF α -synuclein was associated with the dorsal attentional network, suggesting that

α -synuclein is also involved in cognition. No associations between resting state fMRI networks and CSF A β were found¹⁹⁰.

Taken together, these studies support the hypothesis that the cognition-related volume loss in PD is related to three key pathologies: α -synuclein, tau and amyloid. This idea is consistent with post-mortem studies demonstrating that amyloid, tau and α -synuclein pathologies contribute to neuronal loss and cognitive decline from relatively early disease stages.

Management

Antidementia drugs for PDD

Robust evidence is available to support the use of cholinesterase inhibitors to treat dementia in PD¹⁹¹. The best evidence came from the EXPRESS study of rivastigmine¹⁹², and supportive data for donepezil were reported in the EDON study¹⁹³. Memantine was tested in two medium-sized studies including both PDD and DLB cohorts^{194,195}; only one of these studies found an effect in the PDD group¹⁹⁴. Effect sizes were relatively small, for example, the difference in MMSE scores between patients treated with rivastigmine and placebo was 1.0 (REF. 192), with an SD of 3.8 in the treated group, indicating a Cohen's *d* effect size between 0.25 and 0.30. A meta-analysis¹⁹¹ indicated that antidementia drugs did not increase mortality, and the drop-out rates did not differ between donepezil, rivastigmine, memantine and placebo groups. Compared with placebo, rivastigmine — but not donepezil or memantine — was associated with an increased incidence of adverse events. Preservation of frontoparietal and default mode cholinergic networks was recently reported to be associated with a positive response to cholinergic agents¹⁹⁶, and might enable the identification of patients who are likely to benefit from this treatment.

Potential treatments for PD-MCI

As yet, no disease-modifying treatments with effects on cognition in PD are available, and there is no robust evidence that progression to dementia can be impeded. Epidemiological studies indicate that green tea and coffee can influence the risk of PD and, thus, a potential preventive role has been explored, although the effects on cognitive decline are unclear^{197,198}.

In the first trial in PD-MCI, rivastigmine patch offered some benefit, although the primary outcome measure — clinical impression of change — was not significantly affected¹⁹⁹. However, significant effects were observed on one of the secondary outcomes, a scale measuring everyday cognitive activities. Of note, the study had a cross-over design, and included only 26 patients. Further studies of rivastigmine or other cholinesterase inhibitors for PD-MCI are warranted.

Theoretical and preliminary empirical evidence supports the hypothesis that rasagiline, a selective monoamine oxidase B inhibitor with effects on motor symptoms in PD, also has a positive cognitive effect. In a relatively large, placebo-controlled, randomized trial over 24 weeks, however, rasagiline did not significantly improve cognitive functioning in patients with PD-MCI²⁰⁰.

In a study focusing on depression, atomoxetine, a selective noradrenaline reuptake inhibitor, was associated with some cognitive benefit in patients with PD²⁰¹. On a relatively insensitive screening instrument such as the MMSE, the placebo group worsened by 0.5 points whereas the atomoxetine group improved by 0.8 points, a statistically significant difference. Further support for the use of atomoxetine or other noradrenergic agents was provided in a single-dose, placebo-controlled study, which showed that 40 mg atomoxetine improved selected tests of decision-making and attention in PD²⁰². We are not aware of any systematic studies of serotonergic agents in the context of cognition in PD, but vortioxetine, a novel agent that acts on a number of serotonergic receptors in addition to inhibiting serotonin reuptake, has produced cognitive improvement in elderly patients with depression²⁰³ and is a candidate for trials in PD. Various studies are ongoing, including trials of 5-HT₆ receptor antagonists and donepezil for PD-MCI. 5-HT₆ receptor antagonists might exert effects on cognition and mood owing to enhancement of cholinergic, glutamatergic, noradrenergic and dopaminergic neurotransmission, and the SYNAPSE study is exploring the effects of these agents in PDD.

Disease-modifying agents that slow disease progression in PD, including delaying the onset of dementia, are an urgent unmet need. The most interesting approaches include passive and active immunotherapies targeting A β , tau and α -synuclein, which might be particularly relevant for diseases such as PD, which are characterized by accumulation and prion-like propagation of toxic protein aggregates²⁰⁴. Other potential strategies include drugs addressing mitochondrial dysfunction, anti-inflammatory agents, GBA-active agents, stimulation of neurogenesis, and neurotrophic factors⁵⁵. As amyloid pathology has a prominent role in dementia development in PD, strategies to reduce A β toxicity — for example, by influencing clusterin-associated pathways²⁰⁵ — might be relevant in this context. Interestingly, apomorphine, which is used to treat motor complications in PD, has been shown in animal studies to reduce A β accumulation and toxicity, possibly via antioxidative mechanisms²⁰⁶. In a recent post-mortem study, PD patients without dementia who had received apomorphine treatment showed reduced A β deposition compared with untreated patients²⁰⁷, and in a comparative open-label trial, apomorphine infusion was associated with improvement of several NMS²⁰⁸. Thus, placebo-controlled clinical trials to test whether apomorphine can delay dementia onset in PD are warranted.

Non-pharmacological approaches

Cognitive training. Studies employing systematic cognitive training to improve cognition have been conducted in AD and, more recently, in PD. A review and meta-analysis²⁰⁹ based on seven studies involving 272 patients with PD (MMSE scores 27–29) showed small but statistically significant improvements in working memory, processing speed and executive functioning after cognitive training. Large multicentre studies are needed to confirm these encouraging findings.

Physical exercise. Aerobic physical exercise has a range of beneficial effects on the brain, with potential relevance to cognition. A review based on seven studies concluded that physical exercise can improve motor symptoms and several NMS in PD²¹⁰, possibly by improving perfusion, or by promoting growth hormone release or angiogenesis. In one relatively large study, 51 PD patients without dementia were randomly assigned to a progressive strengthening exercise training programme or to a simpler programme focusing on stretching, balance, breathing and non-progressive strengthening, administered twice a week for 24 months²¹¹. No differences between the groups were observed, although both groups showed evidence of improvement of attention and working memory after 24 months. Larger studies with carefully designed control conditions are needed to test whether physical exercise can improve cognition in PD.

Neurostimulation. Deep brain stimulation of the subthalamic nucleus is an established practice in PD. However, cognition might be adversely affected, not only postoperatively, with accelerated decline of executive functions being reported²¹². By contrast, there is some preliminary evidence of positive cognitive effects after stimulation of the cholinergic nucleus basalis of Meynert in patients with AD²¹³. Given the probable contribution of cholinergic deficits to cognitive impairment in PD, this approach might be relevant in the PD context²¹⁴, and studies are ongoing.

Conclusions

In addition to the well-known high risk of dementia in the later stages of PD, recent research has established the high frequencies of SCD and MCI as harbingers of dementia in PD. Cognitive impairment might occur very early in the disease course, even before the onset of motor symptoms in the prodromal state. A variety of mechanisms contributing to cognitive decline in PD are gradually being revealed; in addition to α -synuclein toxicity, the potential contributions of other pathologies, mitochondrial disturbances, inflammatory changes and genetic factors are currently under investigation. Related to these changes, a number of imaging, electrophysiological and CSF-based biomarkers have already been shown to be associated with cognitive impairment in PD, and studies consistently show that reduced CSF A β ₄₂ concentrations predict more rapid cognitive decline. However, following the demonstration of efficacy of a cholinesterase inhibitor for the treatment of PDD more than 10 years ago, no additional convincing evidence has emerged regarding the treatment

or prevention of PD-MCI and PDD. Therapies for PDD remain a key avenue for future investigations, and several promising candidates are now being explored.

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Author contributions

All authors contributed equally to all aspects on manuscript preparation.

Competing interests

[Au: are you happy for us to use the same competing interests statement as for your psychosis Review?]

Commented [DÅ1]: yes

Review criteria

We comprehensively searched MEDLINE and PubMed, for articles published in English up to 20 May 2016 [Au: did you add any papers from after this date when you revised the manuscript?], using the search term "Parkinson" combined with "cognition", "cognitive impairment", "dementia", "antidementia agents", "acetylcholinesterase inhibitors", "memantine", "electrophysiology", "EEG", "biomarker", "imaging", "cerebrospinal fluid", "gene", "SNCA", "MAPT", "GBA", "APOE", "COMT" and "pathology". We read relevant papers in full, searched their reference lists, and selected the most relevant on the basis of design, findings, and time of publication. We also searched the NIH online clinical trial registry, ClinicalTrials.gov, for relevant ongoing trials focusing on cognition in Parkinson disease. Further prioritization of identified papers for inclusion in the article was based on several additional criteria, including high-quality reviews, sample size and longitudinal follow-up.

Commented [DÅ2]: yes, selected one, including our own, how can we formulate this,

Key points

- The full spectrum of cognitive impairment, from subjective cognitive decline to dementia [Au: OK?], has been observed in Parkinson disease (PD)
- Mild cognitive impairment in PD [Au: OK?] usually progresses to dementia, but can be stable and even revert in some patients
- The aetiology of cognitive impairment in PD has not been fully elucidated, but limbic and cortical Lewy body pathology seems to be the main cause
- Amyloid plaque pathology also contributes to cognitive decline in PD [Au: OK?], and amyloid pathology detected by cerebrospinal fluid analysis and imaging can predict subsequent dementia
- Other probable mechanisms include genetics, synaptic pathology, neurotransmitter changes and inflammation

- Cholinesterase inhibitors have symptomatic effects, but no disease-modifying treatments are available to reduce the risk of dementia in PD

Box 1 | Mechanisms of cognitive decline

The following mechanisms are proposed to contribute to cognitive decline in Parkinson disease:

- Protein misfolding (α -synuclein, amyloid and tau)
- Neurotransmitter activity
- Synaptic dysfunction and loss
- Neuroinflammation and diabetes
- Mitochondrial dysfunction and retrograde signalling
- Microglial and astroglial changes
- Genetics
- Epigenetics
- Adenosine receptor activation [Au: OK?]
- Cerebral network disruption

Box 2 | Potential genetic risk factors for cognitive impairment in PD [Au: I have reformatted this item as a box — we generally avoid two-column tables, unless there is no other alternative]

GBA (glucosylceramidase)

Mutations are associated with greater cognitive impairment and risk of dementia in patients with Parkinson disease (PD) [Au: OK?]^{72–77}.

MAPT (microtubule-associated protein tau)

Mixed findings for cognitive impairment: the H1 haplotype is associated with an increased risk of dementia and [Au: OK?] modulation of temporal–parietal activation, as measured by functional MRI (fMRI)^{11,70,81,82,86,87,90,91}.

APOE (apolipoprotein E)

The *APOE** ϵ 4 allele was associated with cognition in most (but not all) studies: evidence of distinct word list learning and semantic verbal fluency deficits; mixed evidence for dementia risk; associated with modulation of temporal–parietal activation, as measured by fMRI^{70,80–83,86,92}.

LRRK2 (leucine-rich repeat serine/threonine-protein kinase 2)

No association in the majority of studies, but some larger studies reported a reduced prevalence of cognitive impairment and dementia in carriers of *LRRK2* mutations [Au: changes OK?]^{57–65,93,94}.

SNCA (α -synuclein)

One study found no association between the rs356219 polymorphism and cognition in sporadic PD, but multiplications and disease-causing mutations are associated with cognitive decline and dementia in monogenic PD^{66,67,70,95}.

COMT (catechol-O-methyltransferase)

Mixed findings for cognition; some evidence that the Met allele is associated with impairment on frontal-dependent tasks; no evidence for dementia risk; associated with modulation of frontal networks^{5,9,73,81,82,86,96,97}.

BDNF (brain-derived neurotrophic factor)

Mixed findings: one of three studies reported an association between cognitive impairment and the Gly196Ala polymorphism^{98–100}.

UBQLN1 (ubiquilin-1)

No association with cognitive impairment [Au: OK here and below?]¹⁰¹.

FMR1 (fragile X mental retardation protein 1)

No association with cognitive impairment¹⁰².

Immune/inflammatory genes: IL10, IL17A, IUL-18 [Au: I can't find any reference to this gene in the literature or the gene databases — please can you check that the name is correct?], IFNG

Mixed findings: *IL10* was associated with lower risk of cognitive impairment and *IL17A* was associated with greater risk in one study¹⁰³, but not in a subsequent study¹⁰⁴.

Figure 1 | Amyloid-β PET scans in Parkinson disease dementia. Axial slices from two patients with Parkinson disease dementia, showing **a** | absence and **b** | presence of amyloid-β binding. ¹¹C-PiB, ¹¹C-labelled Pittsburgh compound B.

Figure 2 | Overview of risk factors for Parkinson disease dementia. Three different categories of risk factors for Parkinson disease dementia (PDD) — clinical, molecular, and structural/functional imaging — are illustrated. Factors with evidence from longitudinal studies are shaded red, and factors with evidence from cross-sectional studies are shaded grey [Au: changes to this sentence OK?]. Interrelationships between factor categories (bidirectional arrows) and temporal relationships between cross-sectional factors and PDD (unidirectional arrows) remain unclear. MCI, mild cognitive impairment; MEG, magnetoencephalogram.

Table 1 | Development of MCI and dementia from time of PD diagnosis: longitudinal studies

Study	N	Duration (years)	MCI at baseline (%)	MCI at follow-up (%)	Dementia during study (%)	Comments	MCI and risk of dementia	Refs
Pigott, K. <i>et al.</i> (2015)	141	4.4	0	47.4*	28	Normal cognition at baseline	–	8
PARKWEST Pedersen, K. F. <i>et al.</i> (2013)	182	5	20.3	–	19.2	–	RR 39.2, $P < 0.001$	5
Amsterdam Broeders, M. <i>et al.</i> (2013)	123	5	35	50 [†]	13.8	–	“All patients who progressed to PD dementia had MCI at a previous assessment”	10
PPMI Weintraub, D <i>et al.</i> (unpublished work) [Au: OK?]	423	3	10	15–21 [§]	3–6 [§]	–	–	–
CamPaIGN Williams-Gray, C. H. <i>et al.</i> (2013)	142	10	36 [‡]	62 at 3 years	46 (17 at 5 years)	–	Reduced semantic fluency (HR 3.05) and pentagon copying (HR [Au: OK?] 2.55)	11
DeNoPa Mollenhauer, B <i>et al.</i> (personal communication) [Au: OK? If this is not your own work, we require written consent from the original authors for inclusion of this information]	118	2	26	27	18.6	–	–	–
Napoli Santangelo, G. <i>et al.</i> (2015)	76	4	32.9	38.2	5.4	50% MCI at 4 years	–	7
NYPUM Domellöf, M. E. <i>et al.</i> (2015)	147	5	42.6	–	27.6	–	MCI at baseline 6.5 x increased risk for dementia	12
Sydney Hely, M. A. <i>et al.</i> (2008)	136	20	–	–	83	MCI criteria not available at study start	–	13

*Any cognitive impairment. [†]Of those without dementia. [§]Using different criteria. ^{||}Cognitive impairment rather than MCI. MCI, mild cognitive impairment; N, number of participants; PD, Parkinson disease.

Table 2 | Predictive effects of CSF markers on cognitive decline in PD: longitudinal studies

Study	N	Baseline MMSE score	Disease duration (years)	Duration of follow-up (years)	CSF markers studied (in addition to total tau, phosphorylated tau and A β ₄₂)	Outcome measures [Au: OK?]	Results	Refs
Compta, Y. <i>et al.</i>	27	28	10	1.5	–	De—mentia	Low A β ₄₂ predicted dementia	114
Siderowf, A. <i>et al.</i>	45	DRS score: 133	11	1.5	–	DRS score	Low A β ₄₂ predicted more rapid decline on DRS	113
Parnetti, L. <i>et al.</i>	44	27	3	3	α -Synuclein (total, oligomer)	MMSE and Montreal Cognitive Assessment score	Low A β ₄₂ predicted more rapid decline	115
Alves, G. <i>et al.</i>	104	28	<i>De novo</i>	5	–	Dementia	Low A β predicted early dementia	111
Bäckström, D. C. <i>et al.</i>	99	29	1.4	5–9	α -Synuclein total, NFL, H-FABP	Dementia	Low A β ₄₂ , NFL and H-FABP predicted dementia	109
Hall, S. <i>et al.</i>	42	29	7	2	α -Synuclein total, NFL	Dementia	Low A β predicted memory decline, high α -synuclein predicted reduced cognitive speed	110
Terrelonge, M. <i>et al.</i>	341	–	0.6	2	α -Synuclein total	Four domains: memory, visuospatial, working memory—executive function, [Au: OK, for consistency with the original paper?] and attention processing speed	Low A β ₄₂ predicted cognitive impairment at follow-up	112
Stewart, T. <i>et al.</i>	403	28.9	2.1	1.8	α -Synuclein total	Tests of verbal memory, cognitive	Lower α -synuclein predicted	117

						processing speed, and visuospatial working memory	better preservation of cognitive function	
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A β , amyloid- β ; CSF, cerebrospinal fluid; DRS, Dementia Rating Scale; H-FABP, fatty acid-binding protein, heart; MMSE, Mini-Mental State Examination; *N*, number of participants; NFL, neurofilament light chain protein; PD, Parkinson disease.

Author biographies [Au: is it OK if we use the same wording for your biographies as in the psychosis Review?]

Commented [DÅ3]: YES

Dag Aarsland - Dag Aarsland MD, PhD, is Professor of Old Age Psychiatry at IoPPN, Visiting professor at the Alzheimer's Disease Research Centre at Karolinska Institutet and Research Director at Centre for Age-Related Medicine, Stavanger University Hospital. He is a psychiatrist and has worked as a senior consultant in geriatric psychiatry for most of his career. His main research interest is the neuropsychiatric aspects of patients with neurodegenerative diseases, in particular translational studies on cognitive decline in Parkinson's disease and dementia with Lewy bodies.

Byron Creese - Byron Creese is a research fellow at the University of Exeter Medical School. Prior to this he completed his PhD at the Wolfson Centre for Age-Related Diseases, King's College London before undertaking post-doctoral work at the South London and the Maudsley NIHR Biomedical Research Centre. His interests focus on using genome-wide approaches to understanding the aetiology of neuropsychiatric symptoms and cognitive decline in dementia and Parkinson's disease.

Marios Politis - Marios Politis (MD MRCP MSc DIC PhD FEAN) is a Senior Academic Neurologist, and the Head of Neurodegeneration Imaging Group at King's College London. His research involves the use of molecular (PET) and functional (fMRI) imaging as a method of investigating aetiology, pathophysiology, and effects and complications of novel therapies in Neurodegenerative disorders. He has achieved a large number of awards and distinctions including awards from the Movement Disorders Society, the Society of Nuclear Medicine and Molecular Imaging, and the European Academy of Neurology.

K Ray Chaudhuri - Prof K Ray Chaudhuri is the Clinical Director of the National Parkinson Foundation International Centre of Excellence at King's College and King's College Hospital London, Lead of the King's Neuroscience Research and Development unit and Chairman of the Movement Disorders Society Non-motor Study Group at Denmark Hill Campus in London. He also sits on the Nervous Systems Committee of the UK Department of Health, National Institute of Health Research, and serves as a member of the Scientific Programme Committee of the International Parkinson's and Movement Disorders Society. In addition, he serves as a member of clinical advisory groups to Parkinson's UK and the European Parkinson's Disease Association. He has published over 300 papers and co-edited 4 books on Parkinson's disease and restless legs syndrome, and currently serves on the editorial board of numerous international journals including Basal Ganglia, the Journal of Parkinson's Disease and is the editor in chief of the newly launched Nature Parkinson's Journal. His particular expertise is non-motor aspects of Parkinson's disease focused on subtyping, sleep and pain.

Dominic ffytche - Dr ffytche is Reader in Visual Psychiatry at the Institute of Psychiatry, Psychology and Neuroscience, King's College London and Consultant at the Maudsley Hospital where he runs a specialist clinic for visual perceptual disorders. He has published extensively on clinical and

neuroscientific aspects of visual hallucinations and is an international expert on Charles Bonnet Syndrome. He is joint chief investigator for the National Institute of Health Research funded SHAPED programme (Study of Hallucinations in Parkinson's disease, Eye disease and Dementia).

D Weintraub - Dr. Weintraub is Professor of Psychiatry and Neurology at the University of Pennsylvania and Psychiatrist at the Parkinson's Center at the Philadelphia Veterans Affairs (VA) Medical Center. A board-certified geriatric psychiatrist, he conducts clinical research in the psychiatric and cognitive complications of Parkinson's disease and related disorders. He completed a NIMH Career Development Award related to depression in PD, and has been PI on grants from NIH, VA, Penn, the Fox Foundation, and several industry-sponsored studies, and is currently Director of the Clinical Core of the Penn Udall Center focused on cognitive impairment in PD. He also is Associate Editor of Movement Disorders Journal.

Clive Ballard - Clive Ballard has recently joined the University Exeter as executive Dean of Medicine and pro vice chancellor. He was previously Professor of Age Related Disease and Director of the Biomedical Research Unit for Dementia at the Institute of Psychiatry, Psychology and Neuroscience, King's College London. He leads a diverse programme of research ranging from basic science and post-mortem studies to drug discovery and clinical trials focussing on Alzheimer's disease and non-Alzheimer dementias. Key interests include neuropsychiatric symptoms in dementia, clinical trials of drug and non-drug therapies, genome wide association studies, non-Alzheimer dementias and on-line intervention studies.