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Morphological basis of Parkinson disease-associated cognitive impairment: an update

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Abstract

Cognitive impairment is one of the most salient non-motor symptoms of Parkinson disease (PD) that poses a significant burden on the patients and carers as well as being a risk factor for early mortality. People with PD show a wide spectrum of cognitive dysfunctions ranging from subjective cognitive decline and mild cognitive impairment (MCI) to frank dementia. The mean frequency of PD with MCI (PD-MCI) is 25.8% and the pooled dementia frequency is 26.3% increasing up to 83% 20 years after diagnosis. A better understanding of the underlying pathological processes will aid in directing disease-specific treatment. Modern neuroimaging studies revealed considerable changes in gray and white matter in PD patients with cognitive impairment, cortical atrophy, hypometabolism, dopamine/cholinergic or other neurotransmitter dysfunction and increased amyloid burden, but multiple mechanism are likely involved. Combined analysis of imaging and fluid markers is the most promising method for identifying PD-MCI and Parkinson disease dementia (PDD). Morphological substrates are a combination of Lewy- and Alzheimer-associated and other concomitant pathologies with aggregation of α-synuclein, amyloid, tau and other pathological proteins in cortical and subcortical regions causing destruction of essential neuronal networks. Significant pathological heterogeneity within PD-MCI reflects deficits in various cognitive domains. This review highlights the essential neuroimaging data and neuropathological changes in PD with cognitive impairment, the amount and topographical distribution of pathological protein aggregates and their pathophysiological relevance. Large-scale clinicopathological correlative studies are warranted to further elucidate the exact neuropathological correlates of cognitive impairment in PD and related synucleinopathies as a basis for early diagnosis and future disease-modifying therapies.

Keywords Parkinson disease · Mild cognitive impairment · Dementia · Neuroimaging · Neuropathology

Abbreviations

AD	Alzheimer disease
ADNC	Alzheimer disease-related neuropathological changes
aMCI	Amnestic mild cognitive impairment
Aβ	β-amyloid
αSyn	α-synuclein
CA	Cornu ammonis
CAA	Cerebral amyloid angiopathy
CI	Cognitive impairment
CMBs	Cerebral microbleeds
DLB	Dementia with lewy bodies
DMN	Default mode network
FA	Fractional anisotropy
FW	Free water
GM	Gray matter
GMV	Gray matter volume
LB	Lewy body
LBP	Lewy body pathology
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MRI	Magentic resonance imaging
naMCI	Non-amnestic mild cognitive impairment
NBM	Nucleus basalis of Meynert
NFT	Neurofibrillary tangle
PD	Parkinson disease
PDD	Parkinson disease dementia
PD-MCI	Parkinson disease with mild cognitive impairment
PD-NC	Parkinson disease with normal cognition
PDND	Parkinson disease-no dementia
PET	Positron emission tomography
SAN	Salience network

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SCD Subjective cognitive decline
SN Substantia nigra
WM White matter
WMH White matter hyperintensity
WMV White matter volume

Introduction

Parkinson disease (PD), the most common movement disorder and the second most common neurodegenerative disorder after Alzheimer disease (AD), is characterized by progressive degeneration not only of the dopaminergic striatonigral system but also by involvement of many other neurological systems and organs, due to widespread intraneuronal and neuritic deposition of abnormal phosphorylated α-synuclein (αSyn), forming intracytoplasmic Lewy bodies (LBs) and Lewy neurites, the morphological hallmarks of PD and related LB disorders. However, multiple mechanisms and pathways play a role in the pathogenesis of PD including oxidative stress, mitochondrial dysfunction, calcium imbalance, neuroinflammation, and multiple neurotransmitter deficits (Jellinger 2012a; Zaman et al. 2021): The resulting biochemical deficits cause a heterogeneous spectrum of motor and non-motor symptoms that contribute greatly to the overall disease burden of this multisystem/organ disorder (Dickson et al. 2009a; Jellinger 2012b). Cognitive impairment (CI) that has been recognized as an important part of PD since the historical description of Charcot (1877), shows a full spectrum ranging from subjective cognitive decline (SCD) and mild cognitive impairment (MCI) to full-blown dementia (PDD). It severely affects the quality of life, is a risk factor for early mortality (Oosterveld et al. 2015; Schrag et al. 2000), and has been shown to have substantial consequences over and above the motor symptoms, even at early stages of PD (Chandler et al. 2021; Leroi et al. 2012). SCD is a self-perceived decline in cognitive ability with normal age-, sex- and education-adjusted performance on standardized cognitive tests (Jessen et al. 2014); PD with MCI (PD-MCI) is a gradual decline in cognitive ability affecting single or multiple cognitive domains on complex functional tasks, including amnestic (aMCI) and non-amnestic (naMCI) phenotypes (Litvan et al. 2012; Petersen et al. 2009). It is a risk factor for PDD (Hoogland et al. 2017), which is defined as CI in PD patients with deficits in at least four cognitive domains (memory, attention, executive and visuospatial abilities) being severe enough to significantly affect routine functions of life (Emre et al. 2007; Goetz et al. 2008; Kiesmann et al. 2013). PDD can be denoted as mild, moderate and severe (inability for independent living). Cognitive decline may occur in presymptomatic stages (Fengler et al. 2017), at the time of diagnosis or a few years or decades after diagnosis of PD and has a high variability in its severity, rate of progression and involved cognitive domains (Aarsland et al. 2021). Mild neurocognitive deficits can occur even in the presymptomatic phase of PD (Bougea et al. 2019) and may precede the onset of dementia by up to 20 years. This is suggested to affect 19–30% of newly diagnosed, untreated (de novo) PD patients and may be associated with subtle changes of cognitive function that are not apparent to patients, families or clinicians. The most frequent phenotypes of MCI in prodromal PD are executive dysfunction and multidomain amnestic phenotypes (Pan et al. 2022), but not memory or attention (Speelberg et al. 2022). Although the estimated frequency of cognitive dysfunction in nondemented PD varies between 19 and 55%, it is underrecognized in practice (Barone et al. 2011). The cognitive symptoms experienced in PD are highly variable and may reflect both molecular, neurochemical, and morphological changes, such as αSyn- and Alzheimer-related and other pathologies, which will be critically reviewed. The relations between PDD and dementia with Lewy bodies (DLB) will not be discussed, since they have been reviewed recently (Jellinger 2018; Jellinger and Korczyn 2018).

Epidemiology

PD patients have a 2.5–6 times higher risk of developing dementia than people without PD of similar age (Aarsland et al. 2021; Perez et al. 2012). However, the epidemiology of CI in PD is not entirely clear, since population-based studies rarely include PD-MCI and PDD, and most studies assess the prevalence and incidence of CI in established PD cohorts. MCI is often described as a transitory stage between normal condition and dementia; conversion rates for PDD are markedly increased in those with MCI, and were reported to be almost 60% at 5 years of follow-up (Pedersen et al. 2017). Early onset PD patients exhibit a poorer cognitive performance than those with late onset PD (Kim et al. 2017). The frequency of PD-MCI ranges from about 21 to 70%, with a mean of 25.8% (Aarsland et al. 2021; Monastero et al. 2018; Nicoletti et al. 2019). A recent meta-analysis reported a pooled prevalence of 40% in a sample of 7053 PD patients (Baiano et al. 2020). Its estimated point prevalence is 30%, the cumulative prevalence is > 75% for PD patients surviving more than 10 years (Hely et al. 2008). The cumulative incidence of PD-MCI is 9.9% after 1 year, 23.2% after 3 years, and 28.9% after 5 years follow-up (Pedersen et al. 2017). Within 3 years, in PD with normal cognition (PD-NC), 25% (95% CI 20–30%) converted to PD-MCI and 2% (95% CI 1–7%) converted to PDD, whereas 28% (95% CI 20–37%) reverted back to normal cognitive function (Saredakis et al. 2019). A comprehensive meta-analysis of PD-MCI cognitive outcome and predictors in its conversion to PDD was published recently (Wallace et al. 2022). Approximately

20–30% have at least mild cognitive changes even at the time of diagnosis of PD (Poletti et al. 2012), increasing to 40–50% after 5 years' follow-up (Domellöf et al. 2015; Pedersen et al. 2017). By contrast, the estimated prevalence of MCI in the general population (age 60–90 years) ranges between 16 and 20% (Roberts and Knopman 2013). 59.1% of patients with persistent PD-MCI within 1 year develop PDD (Pedersen et al. 2017). Importantly, the value of MCI for the development of PDD is influenced by the diagnostic criteria chosen for MCI (Wood et al. 2016). About 30.3% of de novo PD patients complained of memory issues and were more likely to develop MCI within 2 years' follow-up compared to those who did not complain of memory issues (Purri et al. 2020), although other factors, such as affective symptoms, may contribute to progression of MCI (Chua et al. 2021). Cognitive deficits have been recently defined as a prodromal marker and have been included in the last research criteria of prodromal PD (Heinzel et al. 2019).

The global pooled frequency of PDD is 26.3% with variations according to the methodologies (14–55%) (Severiano et al. 2022), the estimated prevalence is 24–31% (Aarsland et al. 2005b), the cumulated prevalence in patients with a mean age of 54–70 years is 17% at 5 years after diagnosis, 83% at 20 years after diagnosis (Hely et al. 2008), and up to 95% by age 90 years (Rongve and Aarsland 2013). PDD has a relative risk of 2.47 (1.55–3.95) (Perez et al. 2012), a prevalence of 31.3% (95% CI 20.1–40.1) and incidence rates from 42.6 to 112.5/100,000 person-years (Marder 2010), indicating that around 10% of a PD population develop dementia per year (Hall and Lewis 2019). Systemic reviews suggest that 3–4% of the dementia in the general population would be due to PDD; its estimated prevalence in the population older than 65 years is 0.2–0.5% (Aarsland et al. 2005b).

Cognitive dysfunction/dementia in genetic forms of PD is variable, depending on the affected gene or genetic risk factors, e.g., DNA mutations, *LRRK2, GBA1, Parkin/PINK1, APOE ε4, MAPT/H1*, or other unknown factors, like additional genetic modifiers and environmental factors, which have been reviewed recently (Aarsland et al. 2021; Fan et al. 2021; Koros et al. 2022; Szwedo et al. 2022; Wise and Alcalay 2022). AD tau has been shown to be a prominent pathology in *LRRK2* PD (Henderson et al. 2019).

Neuroimaging findings in cognitive impairment in PD

Unlike clinical behavioral research and fluid biomarkers, brain imaging studies offer a unique opportunity to relate changes in brain structure and function, changes in cerebral blood flow, neuronal activation and neurochemical changes in the brain to cognition and cognitive impairment. Neuroimaging approaches to cognition in PD have been reviewed recently (Hall and Lewis 2019; Hou and Shang 2022; Montaser-Kouhsari et al. 2022; Weil et al. 2019). Although there is a continuum from PD-NC to SCD, PD-MCI and PDD, the major neuroimaging changes in the progression of normal to impaired cognition have been described separately.

Gray matter changes in early PD

While in noncomplicated PD, structural neuroimaging may be normal or shows only mild diffuse brain atrophy or temporal lobe changes in early PD (Martin et al. 2009; Pereira et al. 2014), voxel-based morphometry in PD patients with subjective memory complaints revealed reduced gray matter (GM) intensities in anterior cingulate and right parietal lobe than in uncomplicated ones (Hong et al. 2012). Earlier studies showed reduced gray matter volume (GMV) in frontal lobe in patients with PD and no dementia (PDND) compared with control subjects, while there was significant GM atrophy in the occipital lobe in PDD patients which extended from frontal areas to temporal, occipital and subcortical areas (Burton et al. 2004). Measurement of cortical thickness revealed distinct limbic and subtle GM atrophy in anterior cingulate, precuneus and temporal neocortex in PD-NC compared to healthy controls (Kunst et al. 2019).

Recent studies indicated that reduction of GM density in superior frontal gyrus and cerebellum were related with cognitive performance in early PD-MCI (Donzuso et al. 2021), while right entorhinal cortex atrophy was seen in early, drug-naive PD-MCI, which provided new evidence in differentiating the neuroanatomical states between PD-MCI and PD-NC (Jia et al. 2019).

Magentic resonance imaging (MRI) findings in PD-MCI (Table 1)

At baseline, compared with stable PD-NC cases, those with conversion to MCI showed cortical atrophy in the parietal and occipital lobes, similar to PD with stable MCI, while those with CI from the study entry showed additional involvement of the frontotemporal cortices (Weintraub et al. 2011). MCI is linked with a faster rate of cortical thinning in patients with PD longitudinally, as well as with significant diminishment of limbic subcortical structures (Hanganu et al. 2014). PD-MCI subjects revealed significant enlargement of bilateral temporal, occipital and left frontal lateral ventricles relative to PDND ones (Apostolova et al. 2012). GMV loss in MCI is characterized by prefrontal and occipital GM atrophy (Weintraub et al. 2011). A study using voxel-based morphometry, showed atrophy of the right entorhinal cortex in PD-MCI patients compared to PD-NC ones (Jia et al. 2019), while a resting-state functional MRI

Table 1 Neuroimaging changes in PD-MCI vs. PD-NC (modified from Hou and Shang 2022)

General
Mild diffuse brain atrophy or atrophy of prefrontal and temporal lobes
Enlargement of bilateral temporal and frontal lateral ventricles
GM
Reduced GM volume in left superior frontal and superior temporal gyri, bilateral dorsolateral frontal cortex, left cingulate, insular and parietal cortex, mid cingulate cortex, angular and supramarginal gyri
Atrophy in orbitofrontal regions, left superior parietal lobule, limbic and fronto-parieto-occipital neocortex
Reduced GM intensities in anterior cingulate and superior frontal gyrus
Atrophy hippocampal subregions (CA1), hippocampal-amygdaloid transition area; entorhinal cortex; amygdala, thalamus; accumbens nucleus; NBM
Reduced neuromelanin-sensitive MRI signal in substantia nigra and locus ceruleus
WM
WMH in frontal and interhemispheric WM (genu and body of corpus callosum)
Changes in prefrontal area and cingulum; smaller anisotropy in diffuse WM areas
Others
Loss of functional connectivity in salient networks without structural changes
Dysfunction of somatosensory and executive processing networks
Dysfunction of cortico-striatal networks; disruption of WM connections in frontal and posterior cortical regions
Reduced connections between mediodorsal thalamus and posterior cingulate cortex
Decreased connectivity of left caudate to frontal and cingulate cortex
Mild cortical Aβ-binding (5–11%) not significantly different from PDND and age-matched controls
Rather rare and mild cortical tau deposition

PDND Parkinson disease-no dementia, *PD-MCI* Parkinson disease with mild cognitive impairment, *PD-NC* Parkinson disease with normal cognition, *NBM* nucleus basalis of Meynert, *GM* gray matter, *WM* white matter, *Aβ* β-amyloid

study documented hyperactivity (reflecting a compensatory mechanism) in the right inferior frontal gyrus and hypoactivity in the occipital area in early PD with MCI (Wang et al. 2018). PD-MCI showed greater GM atrophy than PD-NC in orbitofrontal regions, left superior parietal lobule, more wide-spread limbic and fronto-parietal-occipital neocortical atrophy (Kunst et al. 2019). While frontostriatal atrophy may be a predictor for dementia in PD-MCI (Lee et al. 2010), other reduced GMV regions, including temporal and parietal cortices, amygdala, putamen and hippocampus have also been implicated (Melzer et al. 2012), the latter particularly associated with memory impairment (Chen et al. 2016; Weintraub et al. 2011).

A meta-analysis of around 1400 PD patients reported a significantly higher GM atrophy in bilateral prefrontal cortex, left angular gyrus, right supramarginal gyrus, left insula, and midcingulate cortex in the PD-MCI group, but atrophy of bilateral insula and right hippocampus in the PDD group (Mihaescu et al. 2019), while another meta-analysis reported severe GM atrophy in the left anterior insula, inferior and orbital-frontal gyrus (Zheng et al. 2019). Smaller cornu ammonis (CA) 1 region and hippocampal-amygdaloid transition area volumes have been observed in PD-MCI compared to PDND (Becker et al. 2021). Early PD-MCI showed reduction of GM density in superior frontal gyrus and cerebellum (Donzuso et al. 2021).

Longitudinal studies have shown a significantly greater progression of cortical thinning in posterior brain region in PD-MCI compared to PDND (Garcia-Diaz et al. 2018), while another 4-year follow-up study showed that both PDND and PD-MCI patients have a more severe decline in anterior and posterior hippocampus related to memory dysfunction (Uribe et al. 2018). Significant correlations were found between global cognitive status and lateral hippocampus volume, with significant reduction of bilateral CA4, and other subfields and right presubiculum, indicating selective regional vulnerability of the hippocampus in the progression of PD (Foo et al. 2016; Xu et al. 2020).

MRI findings in PD-MCI and PDD converters (Table 2)

Relative to PD-MCI patients who did not convert to PDD, the converters showed lower GM densities in prefrontal areas, insular caudate nucleus and lesser cortical thickness extending from the posterior cortical area into the frontal region and frontotemporal cortices (Chung et al. 2019; Filippi et al. 2020). PD-MCI is associated with a faster rate of GM thinning in temporal and medial occipital lobes as well as limbic subcortical structures (Hanganu et al. 2014); others observed early atrophy in temporal lobes and progressive atrophy in frontal lobes in patients who converted to PD-MCI (Zhou et al. 2020).

Table 2 a Neuroimaging changes in PD-MCI converters vs. non-converters (modified from Hou and Shang 2022), b Neuroimaging changes in PDD converters vs non-converters (modified from Hou and Shang 2022), c Neuroimaging changes in PDD converters vs PD-MCI non-converters (modified from Hou and Shang 2022)

a
GM atrophy temporal region, amygdala-hippocampus network at baseline; cortical thinning anterior cingulate cortex, temporal, parietal and occipital regions; accumbens nucleus; progressive atrophy frontal lobe; longitudinal WM volume reduction
Higher progressive atrophy thalamus, hippocampal subfields (CA 2/3), striatum, NBM
b
GM atrophy uncus, global hippocampus and hippocampal subfields (precuneus, cuneus, subiculum and CA1)
Cortical thinning mid superior frontal/olfactory cortex, superior frontal/anterior cingulate and precentral regions
Dysconnection between frontal and multiple other cortical and subcortical networks including cholinergic pathways
c
GM atrophy prefrontal areas, caudate nucleus and insula; cortical thinning from posterior into frontal regions
Atrophy of fronto-temporal, olfactory cortices, superior frontal/anterior cingulate and prefrontal region
Volume reduction global WM; progressive volume decrease hippocampus and substantia innominata

PDD Parkinson disease dementia, *PD-MCI* Parkinson disease with mild cognitive impairment, *PD-NC* Parkinson disease with normal cognition, *NBM* nucleus basalis of Meynert, *GM* gray matter, *WM* white matter

Few studies using longitudinal MRI metrics to predict MCI or dementia conversion in PD patients suggested that atrophy of fronto-temporal areas, hippocampus, thalamus and accumbens play a role in this process. Stratifying patients according to disease severity findings appeared partially controversial, although showing progressive atrophy of basal ganglia over one year of follow-up and a widespread cortical thinning over 3–6 years in patients with mild to moderate CI (Sarasso et al. 2021).

A longitudinal analysis showed that PD patients with stable MCI and those with no conversion to dementia accumulated the least cortical damage, while those with conversion to dementia showed progressive volume loss of right thalamus and hippocampus. PD patients with conversion to MCI had cortical thinning in the medial and superior frontal gyri, inferior temporal, precuneus, cingulate and supramarginal gyri bilaterally, whereas those with stable normal cognition showed cortical thinning progression mainly in parietal and occipital regions bilaterally. In general, cortical thinning was more prominent in the initial stage of PD cognitive decline, whereas involvement of the frontotemporoparietal regions, hippocampus and thalamus is associated with conversion to a more severe stage of CI (Filippi et al. 2020).

MRI in PDD (Table 3)

One study investigating whole brain atrophy in PDD showed a rate of atrophy of 1.12% in PDD patients, compared to 0.31% in non-demented ones and 0.34% in healthy age-matched controls. Rather surprisingly, it found no correlations between atrophy rate and dementia severity, which might be attributed to an insensitive scale used (Burton et al. 2005). One of the first identified predictive markers for cognitive decline in PD was temporo-parietal atrophy, which is indicative of AD pathology (Weintraub et al. 2012), confirmed by many subsequent studies (Hall and Lewis 2019). In addition, basal forebrain atrophy is also associated with CI in PD (Pereira et al. 2020; Ray et al. 2018). Memory impairment is correlated with frontal and hippocampal diffusivity impairments (Carlesimo et al. 2012; Gargouri et al. 2019; Melzer et al. 2013). Dorsomedial thalamus free water (FW) correlates with cognitive decline in early PD, while baseline hippocampal FW was associated with CI at 3 years, and baseline dorsomedial thalamic FW distinguished PD-NC from PD with cognitive impairment (Guttuso et al. 2022).

Cluster analysis of multimodal imaging data identified three PD subtypes, with prominent GM patterns and little white matter (WM) involvement: One group with widespread cortical and subcortical GMV and WM fractional anisotropy (FA) reductions and pronounced cognitive deficits; a second group with only cortical atrophy limited to orbitofrontal and temporal regions and more specific neuropsychological impairment, and a third one without detectable atrophy or CI and earlier disease onset (Inguanzo et al. 2021). Early onset PDD patients exhibit more severe atrophy in the left anterior cingulate and right inferior temporal gyrus with significantly decreased substantia innominata volume (Kim et al. 2017). These results are in line with recent results showing structural connectivity differences in PD subtypes (Abbasi et al. 2020).

A meta-analysis showed consistent GM loss bilaterally in the medial temporal lobes and the striatum (Pan et al. 2013). A discrimination analysis demonstrated that the volume of hippocampus, in combination with cortical thickness could identify PDD patients with an 80% accuracy (Zarei et al. 2013). PPD patients have GMV reduction in the superior temporal, inferior frontal lobe, insula and anterior cingulate cortex (Xu et al. 2016).

Table 3 Neuroimaging changes in PDD vs PD-NC (modified from Hou and Shang 2022)

General
Increased whole brain atrophy and enlargement of ventricular system
GM
Atrophy of basal forebrain, frontal, inferior and supratemporal lobes, anterior cingulate cortex and insula
GM loss in bilateral temporal lobes and striatum; cortical thinning frontal/supplementary motor area
Atrophy parieto-temporal and occipital cortices
Free water in dorsomedial thalamus and hippocampus
Degeneration of specific subregions of hippocampus
Reduced GMV in cholinergic nucleus basalis of Meynert
Reduced metabolism in temporoparietal, limbic, posterior cingulate cortex and hippocampus
WM
Considerable WMH burden, especially in deep cerebral WM
Microstructural change in corpus callosum, prefrontal area and cingulum
Fractional anisotropy decrease and mean diffusivity increase in bilateral cingulate, genu of corpus callosum and hippocampus
Abnormal diffusivity in subcortical and limbic WM; WMH in periventricular and deep WM areas
Others
Disruption of frontal cortical connectivity; reduced fractional anisotropy in hippocampus
Breakdown of connectivity of mediodorsal thalamus and cingulate cortex
Loss of interconnections between anterior insula and anterior cingulate cortex
Lesions of cholinergic pathways from the NBM to frontal cortex and from basal forebrain to hippocampus
Dysfunctional connections between subcortical frontoparietal and attention networks
Frequent and moderate to severe cortical Aβ deposition (around 52%)
Frequent and moderate to severe tau-deposition in cerebral cortex

GM gray matter, *GMV* gray matter volume, *WM* white matter, *WMH* white matter hyperintensity, *NBM* nucleus basalis of Meynert, *Aβ* β-amyloid

White matter (WM) changes in PD-MCI and PDD

Prominent WM changes are observed in both PD-MCI and PDD patients. Early changes in WM in PD-MCI patients with intact GMV have been reported (Agosta et al. 2014; Rektor et al. 2018). White matter hyperintensities (WMH) burden in PD-MCI patients was significantly different from that in PD-NC (Liu et al. 2021). WMH volume changed over time and was associated with impairment in global cognition, executive functions and language, whereas WM microstructural changes did not vary significantly with those clinical parameters (Scamarcia et al. 2022). However, significant reductions in WM volume have not been consistently found with PD-MCI compared with healthy controls (Butt et al. 2021; Hanning et al. 2019; Hattori et al. 2012; Yarnall et al. 2014). This suggests that the heterogeneous phenotypes seen in PD-MCI may impact on these distinctions and that either brain atrophy may not be as prominent in the early stages of PD-MCI (Hall and Lewis 2019). Moreover, microstructural damage in the main motor and associative WM tracts are present and rapidly progress, even in early phases of PD (Sarasso et al. 2021). PDD patients had a significantly higher burden of WMH, especially deep WMH, which might be an imaging marker for CI in PDD but not in PD-MCI (Liu et al. 2021). Whole brain studies revealed the involvement of the corpus callosum, cingulum and major association tracts in PD-MC patients, but not in PD-NC (Agosta et al. 2014; Chen et al. 2016; Hattori et al. 2012). PD-MCI shows increased hyperintensity in frontal and interhemispheric WM (genu and body of corpus callosum) (Agosta et al. 2014; Deng et al. 2013; Melzer et al. 2013). Thinning of corpus callosum in PDD compared to PD-MCI and PD-NC correlated with thickness of left orbitofrontal cortex in PD-MCI, while changes in corpus callosum in PDD occur in line with changes in the cortex in advanced disease stage (Owens-Walton et al. 2022). The corpus callosum, the cingulum bundle, and the corticospinal tract showed the same trend in the decline of cognitive function (Sang et al. 2022). In addition, the PDD group showed FA decrease and/or mean diffusivity increase in the bilateral cingulate tract (Kamagata et al. 2012; Matsui et al. 2007), in genu of corpus callosum (Chondrogiorgi et al. 2019; Kamagata et al. 2013), and hippocampus (Chen et al. 2015).

Correlation analyses between memory and voxel-based WM measures showed that PD-aMCI had smaller FA values than PD-NC in diffuse WM areas (Chen et al. 2019). Overall, WM abnormalities in PD patients with CI seem to be widespread (Hall and Lewis 2019), involving multiple brain regions with a heterogeneous pattern, abnormal diffusivity

variables being widely distributed in WM adjacent to cortices and limbic subcortices (Zhang and Burock 2020). PDD patients show a significantly higher burden of periventricular and deep WMHs compared to PD-NC (Beyer et al. 2006; Lee et al. 2010), which might be an imaging marker for CI in PDD but not in PD-MCI (Liu et al. 2021).

In summary, GM changes in PDD predominantly involve the temporal regions including the hippocampus, frontal and parietal areas as well as subcortical areas including thalamus and nucleus basalis of Meynert (NBM), while WM lesions are most typically observed in the corpus callosum and cingulate gyrus, inducing dysfunctions of cortico-cortical and cortico-subcortical networks, while local network analysis showed reduced efficiency predominantly in the frontal and parietal regions with the PD-MCI group (Colon-Perez et al. 2018). However, the clinical heterogeneity of MCI in PD is reflected in the variability of structural imaging findings and identifying a unique structural signature of PD-MCI remains challenging (Hall and Lewis 2019).

Degeneration of neurotransmitter systems

Dopaminergic system

Cognitive deficits in early PD are associated with impaired striatal and extrastriatal dopaminergic dysfunction (Siepel et al. 2014), which results in abnormal processing in the cortico-basal ganglia circuit with reduced prefrontal and parietal metabolism in PD-MCI (Bohnen et al. 2011; Ekman et al. 2012), in the salience network (SAN), and in the medial temporal lobe (Christopher et al. 2015), which contribute to memory impairment in PD, whereas mesocortical dopamine transmission appears to be preserved (Huang et al. 2008). Lower presynaptic dopamine uptake in striatum correlated with under-recruitment of anterior cingulate cortex suggesting frontostriatal dysfunction (Ekman et al. 2012). Functional MRI studies have shown frontostriatal and temporal lobe deficits in some PDD patients suggesting an involvement of both the nigrostriatal and the mesocortical dopaminergic pathways. Resting-state functional MRI studies that provide evidence of functional connectivity changes are consistent with the concept of two distinct cognitive syndromes in PD, which include dopaminergically mediated frontostriatal executive impairments and a "posterior cortical syndrome" more frequently associated with the later development of dementia (Baggio et al. 2015; Lebedev et al. 2014; Olde Dubbelink et al. 2014). Striatal dopamine transporter availability mediates the association between WMHs and CI in the visuospatial and memory domains (Jeong et al. 2022).

All patients with PD have a moderate to severe loss of dopaminergic neurons in the nigrostriatal pathway. More widespread degeneration of dopamine terminals in the striatum, particularly in the dorsal caudate nucleus, occurs in patients with PD-MCI than in those without CI. However, in PD-MCI patients there is relative preservation of the other dopaminergic systems in the brain, while those with PDD have a considerable loss of the lateral dopaminergic systems in frontal, parietal and temporal cortical regions (Sasikumar and Strafella 2020). Dysfunction of subcortical-cortical networks is the result of neuronal loss in the brainstem and limbic areas; cholinergic deficits in the cortex, thalamus, and NBM; striatal dopamine loss, decreased nicotinic acetylcholine receptors, and degeneration of the medial substantia nigra (SN) and striatofrontal and mesocorticolimbic loops. Dopaminergic differences in the SAN and the medial temporal lobes also contribute to memory impairment in PD (Christopher et al. 2015).

Forebrain cholinergic system

In vivo cholinergic forebrain atrophy predicts cognitive decline in de novo PD (Grothe et al. 2021; Ray et al. 2018). Microstructural alterations within the cholinergic NBM, detected by diffusion tensor imaging, have been identified as a strong predictor for development of CI in PD, and precede structural GM volume loss (Wilson et al. 2021). Volume loss of the NBM is specific to PD and progressive supranuclear palsy but not to multiple system atrophy (Rogozinski et al. 2022).

WM lesions were found in the cholinergic pathway projecting from the NBM to the cortex, associated with severe memory impairment (Park et al. 2015); these lesions were increased in PDD compared to PD-MCI and PD-NC, supporting the notion that memory dysfunction is related to cholinergic impairment (Schulz et al. 2018). Patients with smaller volumes of the NBM had a 3.5-fold greater risk of developing PD-MCI over about 5 years (Ray et al. 2018).

PDD is associated with selective destruction of corticostriatal resting functional MRI correlations (Seibert et al. 2012), while acetylcholinesterase-PET (positron emission tomography) demonstrated that posterior brain areas are related to cognitive decline in PD (Hirano et al. 2012). PD patients showed a reduction in volume and density of the forebrain cholinergic region and their projections to neocortex, hippocampus and amygdala, which was associated with CI over a 2-year period and predicted CI in those with PD-NC over 5 years (Bohnen et al. 2015; Ray et al. 2018; Schulz et al. 2018). The loss of the basal forebrain cholinergic projections to the hippocampus correlates with memory deficits and conversion to PDD (Gargouri et al. 2019; Pereira et al. 2020). Loss of hippocampal cholinergic fibers is seen in patients with PD-MCI, whereas those with PDD show a subsequent increase in αSyn deposition and dysfunction in both hippocampal and basal forebrain cholinergic systems (Hall et al. 2014; Liu et al. 2018). Significant subcortical

degeneration with neuronal loss and LBs in NBM may precede the onset of PDD due to cortical cholinergic denervation and αSyn pathology (Jellinger 2007a). Cortical cholinergic denervation and early posterior cortical atrophy induced by caudate dopaminergic denervation contribute to CI in PD (Bohnen et al. 2015; Sampedro et al. 2019). Reduction of cholinergic markers in PDD is due to early degeneration of the corticopetal basal forebrain projection involving both the NBM and the nucleus of the diagonal band of Broca (Liu et al. 2018; Ray et al. 2018; Schulz et al. 2018).

The noradrenergic locus ceruleus, serotonergic dorsal raphe nucleus and ventral tegmental area are also involved (Del Tredici and Braak 2013; Espay et al. 2014; Halliday et al. 2014; Tilley et al. 2021; Vermeiren and De Deyn 2017; Ye et al. 2022). PD-MCI patients showed a reduction in the neuromelanin-sensitive MRI signal of the locus ceruleus (Li et al. 2019; Prasuhn et al. 2021). MRI techniques sensitive to brain iron content found higher brain tissue iron content in cerebral cortices, hippocampus, thalamus, and putamen related to lower Montreal Cognitive Assessment scores in early and mid-stage PD (Thomas et al. 2020).

Connectivity and network degradation

Multimodal imaging studies showed a loss of functional connectivity and topological features without structural damage in the SAN in PD-MCI (Aracil-Bolaños et al. 2019), while recent studies revealed disrupted myelin networks in the cingulate cortex of PD (Xie et al. 2022).

Comparison of corticostriatal connectivity in PD-MCI showed decreased function between the striatal network and both the default mode (DMN), central executive and saliency (SAN) networks compared to PD/nonMCI and age-matched control subjects. This was explained partly by increased atrophy within the SAN in PD-MCI. The seed analysis revealed a relationship between higher MCI scores and lower connectivity of the left caudate head to the dorsal anterior cingulate and left middle frontal cortex, as well as to decreased connectivity of the right caudate head with the anterior cingulate cortex, precuneus, and left supramarginal gyrus, and increased connectivity to the left hippocampus and right cerebellar hemisphere. These results suggest that PD-MCI is associated with both global behavioral and cognitive symptoms in PD (Lang et al. 2020). Disrupted WM connectivity in frontal and posterior cortical regions, which correlates with frontal/executive dysfunction, are associated with early dementia conversion in PD-MCI (Chung et al. 2022). Furthermore, PD-MCI is associated with reduced connectivity of the mediodorsal thalamus with the paracingulate cortex, while also demonstrating increased functional connectivity of the mediodorsal thalamus with posterior cingulate cortex, compared to PDD. Structures with basal ganglia-thalamocortical circuits are implicated in CI and dementia in PD, which are associated with a breakdown in the connectivity of mediodorsal thalamus with para- and posterior cingulate regions, respectively (Owens-Walton et al. 2021). The brain regions involved in PD-MCI are associated with the somatosensory and executive processing networks (Mihaescu et al. 2019), and specific change in resting-state functional connections in frontostriatal and posterior cortical subtypes of PD-MCI (Devignes et al. 2022).

Reduced cognitive performance in PD patients was also associated with functional connectivity of the dorsal insular cortex with the DMN, highlighting the relevance of the insula in cognitive dysfunction in PD (Fathy et al. 2020). Tracts between dorsal anterior insular cortex and anterior cingulate cortex showed lower fractional anisotrophy and higher mean diffusivity in PD patients with lower working memory and executive functions, indicating a structural damage in the dorsal limbs of the SAN in PD, possibly due to loss of interconnecting anterior insular cortex subregions and anterior cingulate cortex. This provided evidence for clinically relevant structural damage to the cortical limbs of the SAN in PD due to extensive neuropathology and loss of interconnecting anterior insular and anterior cingulate cortex (Jonkman et al. 2021).

Studies of the connectivity within two distinct DMN systems—left-to-right hippocampal (LHC-RHC) and medial prefrontal cortex to posterior cingulate cortex (mPFC-PCC)—showed that LHC-RHC connectivity was significantly associated with global and domain-specific cognitive impairments, while the mPFC-PCC was associated with future global and episodic memory impairment. This suggests that there is a functionally distinct role of the hippocampal subsystems within the DMN resting state network and that intrinsic connectivity between the hippocampus is related to a broad range of cognitive functions in PD (Zarifkar et al. 2021). Reduced hippocampal FA correlating with global cortical decline in PD (Chen et al. 2015) is associated with disruption of cortex functional connectivity (Rektorova et al. 2012; Seibert et al. 2012) with predominant frontal cortical disruption, while others showed altered temporal properties in dynamic connectivity in PDD (Fiorenzato et al. 2019). Examination of altered (dynamic) functional interactions between brain networks relating to cognitive dysfunctions in PD patients showed that the severity of executive dysfunction was correlated with higher static and lower dynamic functional connectivity between deep GM regions and the frontoparietal network (DGM-FPN). Declining executive function was related to increasing static DGM-FPN connectivity,

together with changes of connectivity involving the dorsal attention network. These findings demonstrate that in PD patients, dysfunctional connections between subcortical fronto-parietal and attention networks mostly underlie worsening in executive functioning (Boon et al. 2020). In general, CI in PD is associated with reduced connectivity in networks relevant to cognition, most prominently to the DMN (Gratwicke et al. 2015; Wolters et al. 2019).

Brain positron emission tomography studies in PDD

^{18F}Fluorodeoxyglucose positron emission tomography (FDG-PET) studies showed hypometabolism in parietal, precuneus, hippocampus, and occipital lobes in PD with incident dementia (Bohnen et al. 2011), while hypometabolism in medial frontal and parietal regions was associated with decline in memory and executive functions (Huang et al. 2007), and reduced metabolism in posterior cortical regions was observed in PD-MCI patients (Schrag et al. 2017). Aβ PET studies showed higher rates of tracer retention in PDD but the degree of uptake was less than that seen in AD (Foster et al. 2010; Mashima et al. 2017; Oh et al. 2021; Villemagne et al. 2011), Patients who show higher degree of Aβ uptake are at higher risk of developing CI (Petrou et al. 2012; Shah et al. 2016). ^{18F}Florbetapir PET showed that severe Aβ deposition is common in PDD patients (52.4%), contributing to memory impairment and driving a faster rate of cognitive decline (Palermo et al. 2019). In other PET studies, prevalence of Aβ-positive cases was 0.34 (95% CI 0.13–0.56) in the PDD group and 0.05 (95% CI − 0.07 to 0.17) in the PD-MCI group (Petrou et al. 2015). Other groups did not find an association between Aβ deposition and CI in PD (Ko et al. 2017; Melzer et al. 2019). Frequency of positive Aβ PET scans in PD-MCI (5–11%) was not different from age-matched controls (Melzer et al. 2019; Petrou et al. 2015; Winer et al. 2018). The patterns of cortical Aβ and tau did not significantly differ between people with PD-NC, those with PD-MCI and healthy older adults. Thus, age, Aβ and tau did not differentiate patients with PD-NC and PD-MCI (Winer et al. 2018). A recent study showed that the Aβ-positive PD group had higher frequency of MCI, especially amnestic type, and lower dopaminergic activities in the left ventral striatum, suggesting that PD patients with Aβ positivity have AD-related cognitive changes (Na et al. 2020; Oh et al. 2021). In general, PDD patients have a lower incidence of Aβ deposition than DLB patients (Akhtar et al. 2016; Frey and Petrou 2015). No significant increase of tau-PET in SN or cortex brain flortaucipir uptake was seen across a 2-year follow-up in PD patients (Hansen et al. 2020). Preliminary tau-PET studies using ^{18F}flortaucipir (formerly called AV-1451) indicated a gradient of tau binding from PD-NC (none to minimal) via PD-MCI (minimal), PDD (low/modest) to DLB (intermediate/strong) to AD (highest) (Bohnen et al. 2017), uptake in PDD being intermediate between PDND and AD (Coughlin et al. 2020; Gomperts et al. 2016; Kantarci et al. 2017). Similar to postmortem data for tau pathology, increased flortaucipir uptake antemortem is also associated with dementia in PD (Smith et al. 2018). The recently described binding of ^{18F}flortaucipir uptake by neuromelanin (Marquie et al. 2017) and the relevance of radioiodinated benzimidazole derivates for selective imaging of αSyn aggregates (Alzghool et al. 2022; Roshanbin et al. 2022; Watanabe et al. 2017) deserve further confirmation.

Neuropathology of PD-MCI

Although the heterogeneous pathology of PDD and PD-MCI are well documented (Halliday et al. 2014; Molano et al. 2010; Sabbagh et al. 2009), there are few neuropathological studies of PD-MCI. Two neuropathological studies described 16 PD-MCI cases: among 365 autopsy-proven PD, eight (2.2%) met the criteria for PD-MCI (mean age 82.2, mean disease duration 11.4 years). Four patients had aMCI memory, three naMCI with frontal executive and one with executive and visuospatial dysfunction. Three cases were brainstem-dominant and brainstem-limbic-dominant, and two neocortical LB stage (Beach et al. 2009). Two patients with naMCI and one with aMCI showed multiple brain infarcts, emphasizing the role of co-existent cerebrovascular pathology (Adler et al. 2010). In addition, there was severe amyloid plaque intensity in the cortex; four with moderate to severe cerebral amyloid angiopathy (CAA), while one case each had moderate to severe CAA (Adler and Beach 2010). Among 233 autopsy-proven cases of PD (54.6% cognitively unimpaired), eight (3.4%) met the criteria for PD-MCI (mean 76.7, disease duration 13.4 years). Four patients were aMCI memory only; three naMCI with frontal dysexecution, and one multiple-domain aMCI. Two were brainstem, 5 brainstem-limbic, and one neocortical LB stage (Jellinger 2010a). Neuritic Braak stages ranged from I to III (mean 1.3); a few neuritic plaques and mild generalized CAA were detected in only two brains, while no diffuse plaques were seen in the basal ganglia. In the case of multidomain MCI, there was a correlation between amyloid and neuritic plaques and CAA (Jellinger 2010b), confirming the contribution of both Aβ plaque load and CAA to CI (Jellinger and Attems 2008). The neuropathological data in these 16 PD-MCI cases (8 aMCI-PD, 7 naMCI-PD, one amnestic multiple domain, mean age 78 years) can be summarized as follows: 50% were brainstem dominant LB disease, 31%

brainstem-limbic forms, 19% neocortical type. Neuritic Braak stage in aMCI was slightly higher than in naMCI (mean 2.7 vs 2.1); mild neuritic plaques were seen in 12%, moderate ones in 31%; mild CAA in 11%, lacunar state in 25%, and old cerebral infarcts in 12.5%. These data indicated a heterogeneous neuropathology in PD-MCI (Jellinger 2013). Recently the neuropathological findings of 49 cases (15 with the clinico-pathological diagnosis of PD) with amnestic aMCI and naMCI were compared, reporting the propensity of increased neurofibrillary tangles (NFT) in the aMCI group and increased LBs in the naMCI group (Dugger et al. 2015). In a recent study of 159 autopsy-confirmed PD cases, 25 had PD-MCI and 102 PDD. In the PD-MCI group 56% met criteria for aMCI and 44% of naMCI, showing no significant differences in age, gender, PD duration, etc. In the naMCI group, all were brainstem-limbic stage (III), which was significantly different from the aMCI group in which only 22% were at neocortical stage (IV). Concomitant non-AD tauopathy was present in 9 PD-MCI cases (42% aMCI and 18% naMCI). Both aging-related tau astrogliopathy (ARTAG) and argyrophilic grains were seen in 5 cases with no significant differences between both groups. Two aMCI cases also met neuropathological criteria of progressive supranuclear palsy. No differences were found in neuritic plaque density, total plaque density score, WM rarefaction, cerebral infarct volume. CAA score or *APOE* carrier frequency were similar between both groups (Knox et al. 2020). This study also confirmed a clear morphological heterogeneity in PD-MCI similar to that in MCI without PD (Markesbery 2010). In this cohort, 56% of the PD-MCI cases had aMCI with no preponderance of naMCI as reported in other series (Litvan et al. 2012). The aMCI cases had slightly higher Braak NFT stages, while a previous study of autopsy-proven PDD cases showed that 54.9% of them had concomitant AD, although there was little difference in their clinical dementia presentation (Sabbagh et al. 2009), while another recent study revealed an increase in LB pathology in naMCI (Knox et al. 2020). Furthermore, the presence of non-AD pathology in this PD-MCI cohort suggests that the role of tauopathies in PD-MCI and PDD should be further explored.

Neuropathology of PDD

There is a large number of extensive reports about the neuropathological substrates of PDD, most of them discussing the convergence and interactions of αSyn, tau and Aβ pathologies and their contribution to dementia pathogenesis, the relations between PD and AD, associated dysfunctions of various neurotransmitter systems, metabolic disorders (Compta et al. 2011; Coughlin and Irwin 2022; Hall et al. 2014; Halliday et al. 2014; Irwin et al. 2012, 2013; Jellinger 2012b; Kalaitzakis and Pearce 2009; Liu et al. 2019; Smith et al. 2019; Wills et al. 2010), the influence of co-pathologies on cognition in PD (Coughlin and Irwin 2022; Daida et al. 2018; Homma et al. 2015; Smith et al. 2019) or discussing specific changes, like protein pathology (Kouli et al. 2020; Tu et al. 2022), neuroinflammation (Kouli et al. 2020) or mitochondrial disorders in PDD (Garcia-Esparcia et al. 2018; Gatt et al. 2016).

Lewy/αSyn pathology

Although few cortical LBs are found in virtually all cases of sporadic PD, there is no consensus on the structural basis of CI in PD (Jellinger 2009; Sonnen et al. 2010). The function of αSyn remains under investigation, but it is localized in presynaptic neuronal membranes and regulated endocytosis and trafficking (Bendor et al. 2013; Vargas et al. 2014). Due to the ubiquitous deposition of αSyn in the central nervous system with high enrichment in presynaptic terminals, PD is denoted a synucleinopathy (Uversky 2009), showing specific synaptic pathology of αSyn aggregation (Schulz-Schaeffer 2010). The morphological substrate of PDD is heterogeneous and includes (1) Lewy/αSyn pathology in cortical, limbic, and subcortical structures, (2) AD-related neuropathological changes (ADNC) (diffuse and neuritic plaques, neurofibrillary tangles and CAA), and (3) a combination of these pathologies that has been shown to most robustly correlate with the severity of CI (Compta et al. 2011; Halliday et al. 2014; Irwin et al. 2012; Jellinger 2012b; Smith et al. 2019). Based on a large autopsy series of PD patients, a stereotypical pattern of spread of Lewy body pathology (LBP) from brainstem regions and olfactory bulb via limbic areas to neocortical areas was suggested (Braak et al. 2003), and later modified (Beach et al. 2009). The reasons for this selective vulnerability to accumulate LBP of these regions remains unclear but may be due to the fact that the longer, poorly myelinated axons or functionally connected networks may be prone to develop pathology and favor transsynaptic neuronal spread of pathogenic αSyn (Braak et al. 2004; Surmeier et al. 2017), suggesting a prion-like mechanism of αSyn pathology in PD.

Limbic and neocortical LBP are approximately 10 times higher in PDD cases than in PDND ones (Apaydin et al. 2002). CI in PD is often correlated with the density of LBs in frontal cortex and Lewy neurites and neuritic degeneration in hippocampus and periamygdaloid cortex, causing a disruption of the limbic loop similar to that described in AD (Mattila et al. 1999). The severity of LBP in the CA2/3 region of the hippocampus has been shown to correlate with episodic memory loss (Adamowicz et al. 2017; Harding

et al. 2002), although hippocampal atrophy and cell loss are not necessarily involved in memory impairment in PD (Joelving et al. 2006). The severity of CI correlates strongly with Braak PD stage (Braak et al. 2005). In a large autopsy series, 50% of PDD patients showed Braak Lewy neurite stages 4–6, particularly when cases with coexistent ADNC were excluded (Mattila et al. 2000). PDD cases also showed higher LBP in subcortical regions compared to PDND cases. In the striatum, insoluble αSyn levels were twice as high (Wills et al. 2010), while in the amygdala and hippocampus, LB density correlated with dementia severity (Apaydin et al. 2002; Churchyard and Lees 1997; Halliday et al. 2011; Mattila et al. 2000). Parahippocampal αSyn scores showed excellent sensitivity (91–93%) and specificity (84–88%) for separating PD cases with and without dementia (Harding and Halliday 2001). PDD cases usually showed higher LBP in subcortical regions relative to PDND ones. In a large study, the severity of cortical LBP was the factor that best correlated with dementia (Irwin et al. 2012), and in a community-based study of 872 autopsies, 103 showed neocortical LBP associated with increased odds of dementia and more rapid decline in all cognitive domains, whereas a limbic distribution was specifically associated with more rapid decline in visuospatial skills, which was not modified by coexistent AD pathology (Schneider et al. 2012). It should be considered, however, that not all patients with cortical LBP may develop dementia (Colosimo et al. 2003; Irwin et al. 2012; Kempster et al. 2010), although LB densities in temporal lobe were significantly higher in PDD compared to PDND cases, which was not observed in frontal or limbic cortical regions (Harding and Halliday 2001). The more severe increase of αSyn in inferior frontal gyrus in PDD patients compared to those without dementia (Wills et al. 2010), enhances the discussion in defining the underlying substrate of CI in PD, in particular with regard to the impact of neocortical LB burden (Jellinger 2007b; Kalaitzakis and Pearce 2009; Selikhova et al. 2009). However, the findings of more increased αSyn burden in the inferior frontal cortex in PDD subjects appear to favor increased LBP in neocortex contributing to dementia.

Insoluble αSyn in the striata being substantially higher than soluble levels in normal controls showed significant increase in both PDND and PDD, with much higher increase in PDD (176% vs. 141%) and in inferior frontal cortex (41- vs. 20-fold; $p < 0.019$), suggesting that there is a substantial increase of αSyn in both regions, being significantly greater in PDD (Wills et al. 2010). Striatal αSyn pathology in PDD was associated with Braak LB stage 3, and only mild striatal αSyn burden in PD brains scored LB Braak stages 3–5 (Jellinger and Attems 2006).

The strong association between extensive αSyn pathology and dementia was challenged by some studies that reported that 15–44.7% of cognitive intact PD patients were associated with severe neocortical LBP (Compta et al. 2011; Horvath et al. 2013; Irwin et al. 2012; Kempster et al. 2010), while a small study described PD cases without dementia despite limbic and neocortical LB pathology and concluded that no clear threshold of LB burden can distinguish PD cases with and without dementia (Colosimo et al. 2003). On the other side, few cases with dementia were described without LBs outside the brainstem and only mild or absent concomitant AD or cerebrovascular pathology (Libow et al. 2009), and dementia cases with αSyn pathology confined to the brainstem were observed in 14.7% of 109 PDD cases (Horvath et al. 2013), while other studies reported much lower figures (Aarsland et al. 2005a; Colosimo et al. 2003; Compta et al. 2011; Harding and Halliday 2001; Irwin et al. 2012; Kotzbauer et al. 2012; Sierra et al. 2016; Walker et al. 2015).

Role of AD pathology

Coexisting tau and Aβ pathology of varying severity is common in PD with CI and relates to a faster onset of dementia (Compta et al. 2011; Halliday et al. 2014; Howlett et al. 2015; Irwin et al. 2012, 2017; Jellinger et al. 2002). AD-related changes, severe enough for a secondary contribution to CI, were present in about 10% of PDND and in about 35% of PDD patients in various autopsy series (Irwin et al. 2012; Jellinger 2008; Smith et al. 2019). In general, both LBP and ADNC may occur and act synergistically (Colom-Cadena et al. 2017; Halliday et al. 2014; Hepp et al. 2016; Irwin et al. 2012, 2013; Jellinger 2009; Kotzbauer et al. 2012; Lashley et al. 2008; Nelson et al. 2010). In large autopsy series around 50% of PDD patients showed Braak LB stages 4–6 together with severe ADNC (Braak neuritic stages 5 and 6) (Irwin et al. 2013; Jellinger 2007a), while others suggested a significant positive relationship between cortical αSyn deposition and CI (Biundo et al. 2016; Petrou et al. 2012). ADNC has been considered by some to be a more specific correlate of dementia than cortical LBP, since the majority of PDD cases with sufficient numbers of cortical NFTs could be assigned a diagnosis of PD plus AD (Compta et al. 2011; Irwin et al. 2012). However, the proportion of PD with comorbid AD varies considerably. The four largest studies ($n = 88$ to $n = 200$) that defined AD as intermediate or high probability by NIA/AA (National Institute on Aging/Alzheimer's Association) criteria, showed reasonably consistent results: comorbid AD was diagnosed in 19.3–31.5% of total PD cases, while the rate of comorbid AD in PDD cases showed much higher variation between 21.5 and 89.4% (Braak et al. 2005; Irwin et al. 2012; Jellinger et al. 2002), tau pathologies in PDD cases affected the prefrontal cortex more severe than the temporal cortex, while the occipital cortex was rarely affected (Vermersch et al. 1993). Two

reports related advanced ADNC with severe dementia and concluded that PDD was particularly related to comorbid AD (Bancher et al. 1993; Jellinger et al. 1991), which was confirmed by later studies from the same research group (Jellinger et al. 2002; Jellinger and Attems 2008). The patterns of Aβ pathology and spread of NFTs in PDD are similar to that seen in typical AD, although in some cases the medial temporal lobe was relatively spared and there were some differences in neocortical tau burden (Coughlin et al. 2019b; Walker et al. 2015). The presence of co-existing ADNC relates to faster onset of dementia in PD (Compta et al. 2011; Halliday et al. 2014; Irwin et al. 2012, 2017; Jellinger et al. 2002). Moreover, AD co-pathology is related to older age at disease onset and decreased survival (Irwin et al. 2017; Kotzbauer et al. 2012; Sabbagh et al. 2009); some reports suggest that ADNC has a greater influence on dementia onset than αSyn pathology (Compta et al. 2014; Howlett et al. 2015). Co-existent ADNC has been shown to produce greater deficits in episodic memory (Coughlin et al. 2019a; Kraybill et al. 2005; Peavy et al. 2016).

A clinicopathological study identified three subgroups of PDD: (1) predominant synucleinopathy (LB Braak stages 5–6; 38%), (2) synucleinopathy with Aβ deposition but minimal or no tau pathology (59%), and (3) synucleinopathy with considerable to severe neocortical tau pathology (Braak neuritic stages 5–6; 3%). Patients in group II showed significantly shorter survival than those with pure synucleinopathy (Kotzbauer et al. 2012). Another study showed three groups with different LBP distributions: PD patients without comorbid AD, PD with AD (PD-AD) and DLB with AD (DLB-AD). The PD-AD group had ADNC with increased LBP; the DLB-AD group showed relative preservation of SN, while coincident ADNC was associated with increased LBP suggesting interaction of both. These cluster-defined groups were associated with different rate of progression to dementia (Toledo et al. 2016). LBP has typically been considered the most significant predictor of dementia in PD (Horvath et al. 2013; Irwin et al. 2012; Kövari et al. 2003; Ruffmann et al. 2016), while in some studies Aβ and tau pathologies were suggested to be independent predictors of dementia (Compta et al. 2011; Horvath et al. 2013). However, the additive or synergistic effect of αSyn on AD pathologies may influence clinical features of PDD, like shorter disease duration or more malignant course (Compta et al. 2011, 2014; Halliday et al. 2014; Irwin et al. 2017).

Contribution of αSyn, Aβ and tau to PDD

There is increasing evidence that abnormal αSyn, Aβ and tau are significant predictors of dementia in PD (Horvath et al. 2013; Irwin et al. 2012; Ruffmann et al. 2016). One study found that the variance in cognitive scores was related to LBP in entorhinal, anterior cingulate and temporal cortices, with smaller contributions from entorhinal and temporal Aβ (Kövari et al. 2003). Braak NFT stage remained independently associated with CI, while LBP was consistently the best predictor for dementia (Horvath et al. 2013). Another study of 104 PD cases found that the LB score alone was the best predictor for dementia (Ruffmann et al. 2016), while another study indicated that diagnostic accuracy was improved by addition of indicators of Aβ and tau pathology (Compta et al. 2011). A multivariate regression analysis examining dementia severity found that anterior cingulate and entorhinal LB burden together accounted for about 60%, while values for Aβ and tau were not significant (Kövari et al. 2003). A small study found that cognitive scores in PD patients were unrelated to any measure of Aβ, tau and αSyn, though the LB score predicted the annual rate of cognitive decline causing dementia in PD (Aarsland et al. 2005a, 2005b), whereas a study using multiple backward regressions showed that the best predictor of annual decline was a summated score incorporating both LB and AD pathologies that are both common, particularly in PDD cases in the prefrontal cortex (Howlett et al. 2015). There is convincing evidence that coexistence of limbic and neocortical αSyn pathology and notable ADNC contribute to dementia in PD, and we can reliably conclude that both tau and Aβ pathologies are common particularly in PDD cases. While one research group found advanced ADNC in most PDD cases (Bancher et al. 1993; Jellinger et al. 2002), in other studies ADNC was less frequent and less severe; while tau indices independently predicted dementia in PD cases in one study (Horvath et al. 2013), two other studies found no such association (Irwin et al. 2012; Ruffmann et al. 2016). In spite of some differences between study groups, the majority of results indicates that tau pathology contributes to dementia in a majority of PD cases, whereas Aβ was found not to be independently related to dementia in most studies. Thus, tau has a closer relationship with CI in PD than Aβ, which is consistent with observations in AD (Nelson et al. 2012). While Aβ deposition was not associated with dementia in PD, severe changes were linked with more rapid cognitive deterioration and earlier mortality (Compta et al. 2014; Halliday et al. 2011; Jellinger et al. 2002; Kotzbauer et al. 2012; Ruffmann et al. 2016; Sabbagh et al. 2009).

The relationship between αSyn deposition and dementia is strong despite some variations between studies. Global cortical αSyn burden was the best predictor of dementia (Horvath et al. 2013; Irwin et al. 2012; Kövari et al. 2003; Ruffmann et al. 2016), although the addition of tau and Aβ scores improved predicative accuracy for dementia (Compta et al. 2011). On the other hand, significant αSyn burden in limbic and neocortical areas were found in 15–45% of PD cases without CI (Compta et al. 2011; Irwin et al. 2012; Kempster et al. 2010) and other studies found severe αSyn

as well as Aβ and tau pathologies in elderly PD cases without CI (Parkkinen et al. 2005), which probably might be explained by higher cognitive reserve in these patients (Hindle et al. 2014). Human brain autopsy findings and both cell and animal model data provide evidence for a synergistic interaction of αSyn, tau and Aβ pathologies inducing each other and their spreading in the brain (Bassil et al. 2020, 2021).

In conclusion, whereas there has been a discussion about the role of individual pathologies causing dementia in PD, there is increasing evidence from multiple clinicopathological studies for a synergistic effect between αSyn pathology, age and ADNC (both tau and Aβ) as the main drive of cognitive decline in PD, suggesting a triad of neurodegeneration, the molecular pathogenesis remains to be further elucidated (Dickson et al. 2009b; Halliday et al. 2014; Jellinger 2011; Pletnikova et al. 2005; Wills et al. 2010). A recent study on the disease-specific patterns of αSyn multimer destabilization in PD, based on local regional neuronal vulnerability and "prion-like" aggregation transmission enabled by destabilization of local endogenous αSyn protein, revealed differences of the cytosolic unfolded, monomeric form of αSyn (αS^{U}) and helically folded multimeric form (αS^{H}) equilibrium comparing demented and cognitively intact PD patients (de Boni et al. 2022). These data suggest that different brain region-specific susceptibility of LBP might be important for development of cognitive impairment in PD.

Impact of other co-pathologies on cognition in PD

Other common neuropathologies associated with age can influence the course of PD. Cerebrovascular disease and WMHs have been demonstrated to be associated with cognitive dysfunction in PD (Chahine et al. 2019; Mak et al. 2015; Malek et al. 2016; Rektor et al. 2009), while other studies did not find such an association (González-Redondo et al. 2012; Haugarvoll et al. 2005). Among the different subtypes of cerebrovascular disease, cerebral small vessel disease has been associated with cortical thinning in the frontoparietal regions with concomitant decline in memory (Foo and Kandiah 2016). A meta-analysis of the influence of cerebral small vessel disease showed different effects on cognitive function in PD, most effective on executive ability, memory and overall cognitive function (Wan et al. 2022). Higher perivascular space in the basal ganglia and WMH severity are independent positive predictors of future cognitive decline in PD (Chen et al. 2022).

Cerebral microbleeds (CMB) related to hypertension also have been associated with cognitive decline (Qin et al. 2022), while others did not, but they were seen more frequently in PDD than in PDND patients (Daida et al. 2018; Ham et al. 2014). A regression analysis showed that the presence of lobar CMBs was strongly associated with PDD (Daida et al. 2018). Other recent studies showed that amyloid-related CMBs and reduced hippocampal volume are associated with PDD (Tsai et al. 2021); earlier studies also showed association of severe CAA with PDD (Compta et al. 2011; Irwin et al. 2012). While according to some authors, cerebrovascular and TDP 43 pathologies do not generally contribute to PDD (Smith et al. 2019), one study found hippocampal and entorhinal TDP-43 inclusions more often in subjects with PDD than in those with PDND and healthy controls. Furthermore, significant association between comorbid ADNC and TDP-43 was observed (Nakashima-Yasuda et al. 2007). Argyrophilic grain disease, another form of age-related tauopathy largely related to medial temporal lobe (Ferrer et al. 2008), appears to be rare in PD, but has been reported as an important factor affecting dementia in PD (Homma et al. 2015), while according to others, it was not associated with worse cognitive outcome (Aarsland et al. 2021; Irwin et al. 2012). Many of these pathologies can occur in advanced age and make it difficult to disentangle their individual contribution to cognitive decline (Compta et al. 2011; Coughlin et al. 2019b; Irwin et al. 2017). In general, there is likely a complex interaction of various neuropathologies in the expression of cognitive and other clinical features in PD (Buchman et al. 2019; Coughlin and Irwin 2022), which, however deserves further elucidation.

Conclusion and outlook

PD is a common and heterogeneous neurodegenerative disorder; it is much more than a movement disorder, and a wide range of nonmotor symptoms has been recognized. Among them, cognitive decline, in a wide range of severity and involved domains, is particularly important, due to its enormous impact on the quality of life of patients and caregivers, as well as the economic burden brought about by this severe condition. The morphological and molecular/biochemical basis of CI is heterogeneous, and modern neuroimaging studies revealed widespread changes in cerebral GM and WM, involving multiple brain areas and causing loss of functional connectivity between critical neuronal networks involved in cognitive and behavioral functions due to neurodegenerative changes. PD patients who exhibit 'AD-like' patterns of brain atrophy are at a greater risk for future cognitive decline. SPARE-AD (Spatial Pattern of Abnormality for Recognition of Early Alzheimer's disease), an MRI index capturing AD-related atrophy, has been shown to be higher in PD-MCI and PDD patients than in PD-NC and healthy controls (Charissé et al. 2022).

The majority of autopsy-based studies to date support the strong association of limbic and neocortical LBP with CI in

PD, while AD co-pathology is often observed as well and may play a synergistic role in the development of dementia with some unique cognitive features (episodic memory deficits and others). The global number of individuals who live with dementia has been expected to increase to 100 million by 2050 (Nichols and Collaborators 2019), and research challenges are increasingly being recognized for both PD and dementia, and further data on the prevalence of PD-associated CI are urgently warranted. The proposal that dementia prior to or simultaneous with or after development of motor symptoms might be included in the diagnosis of PD (Berg et al. 2014; Postuma et al. 2015) has reopened the discussion on whether PDD and DLB should be considered the same disease or phenotypes of a spectrum of LB diseases (Friedman 2018; Jellinger 2018; Jellinger and Korczyn 2018). A deeper understanding of the pathophysiological processes underlying these two synucleinopathies, such as the relative contribution of Aβ and tau pathologies in cortex and striatum, the extent of cortical and entorhinal LBP, the severity of neuronal loss in SN and other subcortical nuclei and the involvement of various neurotransmitter systems is required to better understanding the relationship between the different forms of CI in PD and related LB diseases. The prospective assessment and validation of CI in PD will be improved by combined assessment of neuroimaging and biomarker signatures, making decisions more homogenous. There is an urgent need for quantitative in vivo biomarkers and multicentered autopsy studies of well-characterized longitudinally followed patients to further elucidate the pathobiological contributions of different neuropathologies to CI and domain-specific features in PDD. These and other interdisciplinary efforts are critical to the development of meaningful disease-modifying therapies and preventive measures to slow or halt progression of PD and resultant cognitive deterioration.

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Declarations

Conflict of interest The author declares that he has no conflict of interest.

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