1 **Neuroimaging correlates of cognitive impairment and dementia in Parkinson's**
2 **disease**

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1 **ABSTRACT**

2 There has been a gradual shift in the definition of Parkinson's disease, from a movement
3 disorder to a neurodegenerative condition affecting multiple cognitive domains. Mild
4 cognitive impairment (PD-MCI) is a frequent comorbidity in PD that is associated with
5 progression to dementia (PDD) and debilitating consequences for patients and caregivers.
6 At present, the pathophysiology underpinning cognitive impairment in PD is not
7 established, although emerging evidence has suggested that multi-modal imaging
8 biomarkers could be useful in the early diagnosis of PD-MCI and PDD, thereby
9 identifying at-risk patients to enable treatment at the earliest stage possible. Structural
10 MRI studies have revealed prominent grey matter atrophy and disruptions of white matter
11 tracts in PDD, although findings in non-demented PD have been more variable. There is a
12 need for further longitudinal studies to clarify the spatial and temporal progression of
13 morphological changes in PD, as well as to assess their underlying involvement in the
14 evolution of cognitive deficits. In this review, we discuss the aetiology and
15 neuropsychological profiles of PD-MCI and PDD, summarize the putative imaging
16 substrates in light of evidence from multi-modal neuroimaging studies, highlight
17 limitations in the present literature, and suggest recommendations for future research.

18

1 INTRODUCTION

2 Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting over 4
3 million people above the age of 50, with prevalence in Western Europe and the world's
4 10 most populous nations expected to double to between 8.7 and 9.3 million by 2030 [1].
5 Although PD is classically conceptualized by its cardinal motor deficits, it is increasingly
6 associated with a variable spectrum of cognitive impairment, most prominently in
7 executive function, attention and working memory, visuospatial and language domains
8 [2]. In addition, the trajectory of cognitive decline in up to 80% of PD patients progresses
9 over time to mild cognitive impairment (PD-MCI) and dementia (PDD) [3].

10

11 Cognitive impairment in PD has an adverse impact on quality of life [4], contributes to
12 increased caregiver burden [5], and has been associated with depression and mortality
13 [6]. Collectively, these negative consequences underscore the need to establish
14 biomarkers, which would facilitate our on-going efforts to identify patients at risk of
15 dementia, and develop disease-modifying treatments. In addition, early detection of
16 dementia in PD will permit patients and their caregivers to make optimal plans for the
17 future and monitor symptoms more closely.

18

19 At present, the neuropathophysiology underlying cognitive impairments in PD has not
20 been established, although accumulating evidence has suggested that multi-modal
21 imaging biomarkers could be useful in the early diagnosis of PD-MCI and PDD. In this
22 review, we outline current and emerging concepts of MCI and dementia in PD, discuss

putative neural substrates in light of evidence from neuroimaging studies, and highlight limitations in the present literature.

COGNITIVE IMPAIRMENT IN PD

Prevalence and epidemiology of PD-MCI and PDD

Mild cognitive impairment, defined as cognitive decline that is more severe than expected for age but with preserved functional activities, is common in non-demented PD subjects with a prevalence of 20 – 50% [2,7]. PD-MCI subjects are also at increased risk of future dementia. In a prospective longitudinal study, Aarsland and colleagues reported that more than 80% of PD patients developed dementia over the course of the disease [3]. For the purpose of this review paper, we adopt the definition of PDD proposed by the MDS Task Force: PDD is diagnosed when dementia develops within the context of established PD [8]. There is substantial overlap of pathological and clinical features between PDD and dementia with Lewy bodies (DLB), indicating that both conditions are most likely two clinical entities along a spectrum of Lewy body diseases. In this regard, the Third Report of the DLB Consortium has recommended a diagnosis of DLB when dementia occurs before or concurrently with parkinsonism [9]. Several clinical and demographic risk factors for the development of PDD have also been described, including postural instability gait difficulty [10], neuropsychiatric symptoms such as depression and visual hallucinations, disease duration, and advanced age [11].

Neuropsychological profiles

1 Cognitive deficits in PD have traditionally been conceptualized as ‘subcortical’ in nature
2 [12], but accumulating evidence points to a heterogeneous profile featuring deficits in
3 executive function, attention, processing speed, visuospatial ability, and memory [7],
4 even during the earliest stages of the disease [13]. For instance, a community-based
5 cohort of 159 newly diagnosed PD patients (CamPaIGN study) revealed deficits in
6 frontostriatal-based tasks (12%), temporal lobe-based tasks (8%), and global cognition
7 (15%) [14].

8

9 Given the near ubiquitous nature of cognitive deficits in PD, the relative importance of
10 various cognitive profiles in the development of PDD is a topic of continuing debate.
11 Although executive deficits and attention have been implicated in the development of
12 PDD [15,16], a 3.5-years follow-up of the CamPaIGN cohort further clarified the
13 evolution of cognitive deficits in PD by showing that cognitive deficits with a posterior
14 cortical basis (i.e. semantic fluency and visuospatial ability) are most associated with
15 progressive global decline [17]. Of note, these findings were also backed by genetic
16 variations, with tau H1 haplotype associated with posterior deficit and increased risk of
17 dementia, whereas the COMT genotype was associated with executive impairment but
18 not dementia. Specifically, the pentagon copying test, a measure of visuospatial ability,
19 was also proposed as a predictor of cognitive decline in PD while other studies have
20 similarly reported that constructional deficits, most likely reflecting parietal lobe
21 dysfunction, herald dementia in PD [18]. These inconsistencies warrant further
22 investigation, although they could be attributed to varying definitions of PDMCI and
23 PDD and sample heterogeneity.

1 *Neuropathological substrates of cognitive impairment*

2 Immunohistochemical methods, particularly staining with anti-alpha-synuclein antibodies
 3 have allowed the investigation and recognition of cortical Lewy bodies (LB) as the
 4 primary substrate driving cognitive impairment in PD [19,20]. A longitudinal study that
 5 prospectively followed 22 PD subjects until their deaths found that instead of
 6 neurofibrillary tangles (NFTs), the severity of LB was the only pathological measure that
 7 significantly correlated with rates of cognitive decline [19]. A strong association was also
 8 found between dementia severity and regional LB scores in the entorhinal cortex of 22
 9 elderly PD subjects in whom parkinsonism preceded cognitive decline by 3 years [21].
 10 Similarly, as retrospective study of 45 PD subjects revealed a significant association,
 11 particularly in the frontal and cingulate gyrus, between the severity of cognitive
 12 impairment and cortical Lewy bodies that was independent of AD [22]. However, there is
 13 also evidence – inconclusive as yet – that amyloid beta plaques and tau neurofibrillary
 14 tangles (NFTs) also underlie cognitive impairment in PDD [23,24]. These
 15 clinicopathological findings have provoked an on-going debate regarding a possible
 16 synergistic relationship between AD and LB pathology that is linked with progressive
 17 cognitive decline in PD. Evidence in support for this hypothesis has come from a
 18 previous study that showed that a combination of measures including cortical LB, NFTs,
 19 and amyloid plaques was most closely associated with PDD over any single pathological
 20 marker [23].

21

22 Elucidating the neurochemical bases of cognitive impairment in PD-MCI and PDD is
 23 challenging, as it is most likely a consequence of multiple factors that may or may not be

1 independent of one another. Several theories have been proposed, including an imbalance
2 in the dopamine-acetylcholine synergistic function leading to synaptic impairments [25].
3 In addition, the heterogeneous profile of cognitive deficits could also reflect extensive
4 neurochemical deficits beyond the dopaminergic system, including the cholinergic
5 system [26] which has been implicated in the presence of dementia in PD [27,28], as well
6 as cortical deafferentation of other ascending monoaminergic systems, such as the
7 noradrenergic and serotonergic pathways [29]. These pathological and neurochemical
8 abnormalities are commonly associated with morphological brain changes, including
9 atrophy, which could be detected *in vivo* by structural MRI studies.

10
11 Considered together in the context of identifying targets for drug discovery in PDD, these
12 findings highlight the complex and multifactorial nature of the pathogenesis underlying
13 dementia in PD, although it can be argued that LB pathology should be considered as a
14 the main pathological substrate of cognitive impairment in PD. Future research for targets
15 in drug discovery endeavours should aim to delineate the relative contribution of other
16 factors, such as ageing, concomitant AD pathology, as well as genetic susceptibility.

17 18 **STRUCTURAL NEUROIMAGING IN PD**

19 With the prospect of disease modifying therapies and the recent characterization of PD-
20 MCI as a distinct clinical entity [7], concerted efforts have been made to identify
21 biomarkers that are capable of quantifying pathological changes in a sensitive and
22 reproducible manner. Advances in computational analyses have allowed the investigation
23 of subtle regional atrophy, contributing to the recognition of structural magnetic

1 resonance imaging (MRI) as a validated biomarker for AD [30] and MRI is also
 2 increasingly adopted as an outcome measure in clinical trials for AD [31]. In the
 3 following sections, we summarize principle findings from multiple imaging modalities
 4 across the cognitive spectrum of PD. A summary of candidates for neuroimaging
 5 correlates in PD-MCI and PDD can be found in Table 1.

6 7 *MR studies of grey matter changes in PDD*

8 The general consensus from the structural imaging literature suggests widespread cortical
 9 atrophy in PDD, although it is less severe compared to AD and DLB [32,33]. Using
 10 voxel-based morphometry (VBM) and cortical thickness analyses, the assessment of grey
 11 matter changes in PDD has also revealed a linear progression of atrophy across the
 12 cognitive stages in PD, affecting temporal, frontal, parietal [32,34–39], and less
 13 commonly, occipital regions [32].

14
 15 Regarding subcortical involvement, VBM and region of interest (ROI) studies in PDD
 16 have also revealed atrophy of the hippocampus [34,40–42], though less extensive than in
 17 AD [39]. Importantly, this finding is also consistent with clinicopathologic evidence
 18 indicating that the hippocampus is a major target for Lewy body inclusions in PD [43].
 19 Other atrophic subcortical structures in PDD include the thalamus [32], putamen [32],
 20 amygdala [34,41], and the caudate [32,42].

21
 22 Imaging studies have also compared atrophy profiles between DLB and PDD. These
 23 results have converged to reveal a pattern of more pronounced grey matter loss in DLB

1 compared to PDD. Despite similar severity of dementia, DLB subjects had more cortical
 2 atrophy compared to subjects with PDD [33]. Reductions of grey matter volumes in
 3 prefrontal areas have been reported in DLB compared to PDD [44], while decreased GM
 4 volume in associative areas such as the precuneus and the inferior frontal lobe also
 5 correlated with visual hallucinations in DLB but not in PDD [45]. Together, these
 6 findings support the hypothesis that PDD and DLB represent two distinct subtypes of a
 7 spectrum of Lewy body diseases.

8

9 *MR studies of grey matter changes in PD-MCI*

10 Although grey matter atrophy is well established in PDD, the extent of grey matter
 11 changes in non-demented PD subjects continues to be a topic of contentious debate.
 12 Compared to PD subjects with no cognitive impairment (PD-NC), atrophy in temporal,
 13 parietal, and frontal cortices has been observed in PD-MCI using VBM [35,46]. In
 14 addition, thalamic [47] and hippocampal changes have also been implicated in PD-MCI
 15 while the latter has been associated with deficits in memory-encoding performance [36].
 16 Interestingly, a study assessing volumetric changes in hippocampal subfields
 17 demonstrated preferential atrophy of the CA2-3 and CA4-dentate gyrus subfields in non-
 18 demented PD compared to controls, which correlated with learning deficits [48].

19

20 However, atrophy of grey matter structures in PD-MCI remains to be established, as it
 21 has not been universally reported [42,49–51]. This may reflect the limitations of VBM, in
 22 that it may not be highly sensitive for detecting subtle cortical atrophy in the early stages
 23 of PD [52]. In fact, surfaced-based analyses of cortical thickness appeared to be more

1 sensitive in detecting pathology-related grey matter changes in PD than VBM [53]. For
2 instance, compared to PD-NC, cortical thinning in temporal and parietal regions has been
3 demonstrated in PD-MCI by several studies [37,54,55] (Figure 1).

4
5 Recent longitudinal analyses of cortical thinning patterns have suggested that frontal
6 cortical thinning could be an early indicator for further cognitive decline to PDD [56].
7 Another longitudinal study of 35 months duration found that, while cortical thickness was
8 similar between non-demented PD and controls at baseline, the PD group presented a
9 more aggressive rate of cortical thinning than controls with a bilateral fronto-temporal
10 pattern, extending to the parietal cortex [57]. This pattern of accelerated cortical thinning
11 is corroborated by another longitudinal study of a shorter follow-up period (20 months),
12 where faster rates of thinning were found in the frontal and temporal cortices, as well as
13 the insular and supplementary motor areas [58]. The same study also demonstrated the
14 clinical relevance of cortical thinning in PD, by revealing significant associations
15 between rates of global cognitive decline and cortical thinning in the temporal and medial
16 occipital lobe [58].

17 *Longitudinal assessment of global atrophy rates*

18 The rate of whole brain atrophy on serial MRI is increasingly recognized as a sensitive
19 and objective marker of disease progression in several neurodegenerative diseases [59].
20 Accelerating rates of atrophy previously have been shown with increasing severity of
21 dementia in AD, DLB and vascular dementia [60]. To date, there is only 1 study
22 assessing global atrophy rates in PDD, which reported higher rates of global atrophy in
23

1 PDD (1.12%) compared to PD-NC (0.31%) and controls (0.34%) [61]. However, whether
 2 PD without dementia is also characterized by accelerating global atrophy rate remains to
 3 be established. Although one study has found significantly higher annual atrophy rates
 4 (0.81% vs -0.04%) in non-demented PD compared to controls [62], several other studies
 5 have found no significant difference in global atrophy rates [61,63]. These differences
 6 could be accounted for by sample heterogeneity, as PD-MCI was not distinguished from
 7 the PD cohorts. Furthermore, it is also noteworthy that three previous studies have
 8 reported similar rates of global atrophy in DLB compared to controls [64–66]. Indeed,
 9 considering the evidence that increased atrophy rates in AD may predate dementia by 3
 10 years [67], further research is warranted to investigate the potential clinical utility of
 11 atrophy rates in predicting progression from PD-MCI to PDD.

12 *Diffusion weighted imaging*

14 Diffusion weighted imaging (DWI) is commonly used to evaluate the microstructural
 15 integrity of white matter tracts. Contrary to inconclusive findings of grey matter atrophy
 16 in non-demented PD, numerous studies have demonstrated white matter deficits across
 17 the full spectrum of cognitive function in PD. In PD-NC, white matter abnormalities have
 18 been frequently found in the frontal and temporal regions [68–70].

19
 20 Relative to controls, reduced fractional anisotropy values – an index of altered structural
 21 integrity of white matter – have been found in major white matter tracts in PD-MCI and
 22 PDD [49]. Importantly, white matter integrity may serve as a possible neural substrate for
 23 cognitive impairment in PD, with evidence suggesting an association with global

1 cognition [49,71] and executive impairment [72,73]. Interestingly, a previous study that
2 performed a joint analysis of grey matter and white matter profiles in the same PD cohort
3 also found extensive white matter abnormalities in subjects with PD-MCI and PDD
4 whereas grey matter atrophy was only evident in the PDD group [49]. Given the earlier
5 negative findings regarding grey matter reductions in PD-MCI, these consistent DWI
6 findings challenge the classical view that white matter degeneration, including loss of
7 axons and myelin, occurs secondary to grey matter pathology, and, in turn, raise the
8 intriguing possibility that white matter alterations in PD might be a sensitive precedent
9 for neuronal loss in associated grey matter regions. While the comparability of these
10 findings might be hindered by different levels of sensitivity associated with each imaging
11 modality [74], this view is also consistent with immunocytochemical evidence for the
12 presence of ubiquitin and alpha-synuclein inclusions in the axons of Lewy body disease
13 cases, which is presumed to impair axonal transport before cell body damage [75].
14 Alternatively, white matter abnormalities in PD may also be associated with activation of
15 microglia [76].

16
17 Compared to PDD, more extensive white matter pathology in DLB was also found in
18 temporal and visual association fibres extending into the occipital areas despite
19 comparable global cognitive profiles [77], a finding that is in keeping with previous
20 evidence of more severe grey matter atrophy in DLB compared to PDD.

21
22 With the development of prospective neuroprotective agents, further longitudinal
23 investigations are necessitated to establish the clinical utility of DWI as a biomarker

1 sensitive to early pathology, during which interventions might be most effective, as well
2 as sensitivity to change over time.

4 *White matter hyperintensities*

5 Cognitive impairment in PD has been associated with cerebrovascular diseases, including
6 white matter hyperintensities (WMH) [78–80], which are present in 30% of patients with
7 PD [81]. WMH have been described to contribute to cognitive deficits in the elderly [82]
8 and are highly associated with AD [83,84]. Increasing evidence, although inconclusive as
9 yet, has suggested that WMH are also associated with cognitive impairment in PD. WMH
10 burden is increased in PD-MCI and is also a significant predictor of conversion to PDD
11 [85–89]. A previous study has reported higher levels of periventricular and deep WMH in
12 PDD compared to a group of non-demented PD despite comparable cerebrovascular risk
13 factors and other covariates such as education, age, and gender. Furthermore, deep WMH
14 was significantly associated with MMSE scores [79]. However, the role of WMH in
15 cognitive dysfunction, particularly in non-demented PD, remains a contentious topic with
16 previous reports of similar WMH severity between PD-NC, PD-MCI and controls [90–
17 92]. Furthermore, a previous study did not find any significant differences in WMH
18 progression over one year between PD and controls, and change in WMH did not
19 correspond to global cognitive decline [93]. It is possible that cognitive effects of WMH
20 may be more easily detectable in advanced stages of neurodegeneration such as in PDD.
21 The involvement of WMH in PD should also be interpreted in light of current theories of
22 the underlying pathology of WMH. This is likely multifactorial, involving vascular
23 damages [94], reductions in myelin density due to Wallerian degeneration [95] as well as

hypotension [96]. As such, further longitudinal studies are needed to confirm these findings and investigate the impact of small vessel diseases on cognition in PD.

Quantitative MRI

Based on relaxometric parameters of MRI, quantitative MRI can potentially provide information at cellular and molecular levels, which are much smaller than the spatial scale of a MRI voxel [97]. In transgenic mouse models of dementia, ultra high-resolution T1 and T2 (longitudinal / transverse relaxation time) maps have been routinely used to visualise beta-amyloid deposition and iron load *in vivo* [98]. More recently, the application of quantitative MRI has been extended to investigate distinct biochemical properties of human brain tissues in Lewy body diseases such as PD (Bunzeck et al., 2013) and DLB (Su et al., 2014). Quantitative MRI provides additional information over and above conventional volumetric MRI, tapping into cellular and molecular levels of PD pathology. A previous study has revealed increased $T_{1\rho}$ (an alternative MRI contrast mechanism – spin lattice relaxation time constant in the rotating frame) in the bilateral hippocampus in PDD compared to controls [101], most likely reflecting a complex interaction between multiple factors including iron-induced local field inhomogeneities due to neurodegenerative processes. Given these promising findings in PD and related dementias, further studies should investigate the potential of other quantitative MRI parameters such as T2 and T2* in diagnosing PD / PDD, and their roles in disease progression and conversion from PD-MCI to PDD.

FUNCTIONAL NEUROIMAGING IN PD

1

2 *Resting-state fMRI*

3 With recent developments in computational neuroimaging, the study of neural substrates
4 underlying cognitive processes has witnessed a gradual shift from the focus of localized
5 brain areas to an interconnected model of brain function [102]. This shift has also
6 coincided with an exponential proliferation of resting-state studies in PD over the last few
7 years, with the default mode network (DMN) emerging as a key functional substrate for
8 cognitive deficits in PD [103,104]. Tessitore and colleagues [105] found decreased
9 functional connectivity of the right medial temporal lobe and bilateral inferior parietal
10 cortex within the DMN.

11

12 Other resting-state networks have also been examined. In a previous study, PD-MCI had
13 a reduction in connectivity between right frontoinsula regions and the dorsal attention
14 network, which was also correlated with attention and executive deficits. Interestingly,
15 functional connectivity was increased between posterior cortical regions and the default
16 mode network, which was also associated with visuo-perceptual deficits [106]. Using a
17 graph-theory approach on the same subject sample, the same group demonstrated
18 widespread deficits of long-range connectivity in PD-MCI between major cortical and
19 subcortical areas. In contrast, increases in short-range connectivity, possibly reflecting
20 compensatory mechanisms, were also observed within the fronto-temporal regions [107].
21 Rektorova and colleagues reported significant decreases of connectivity in the right
22 inferior frontal gyrus in PDD compared to non-demented PD and healthy controls. The

1 PDD group also demonstrated reductions in the connectivity in the left and right inferior
2 occipital gyrus compared to healthy controls [108].

4 *Task based fMRI*

5 Functional imaging experiments have studied a range of cognitive dysfunctions with
6 task-related brain activations. Abnormal fronto-striatal response during executive task
7 performance was found in cognitively impaired PD compared to PD-NC [109]. Studies
8 focussing on set-shifting paradigms have also found both hypoactivity and hyperactivity
9 of prefrontal regions, depending on the involvement of the caudate nucleus [110].
10 Another fMRI study assessing working memory found increased prefrontal and parietal
11 activations during the working memory task performance, which were positively
12 correlated with errors made during the task [111]. These patterns of neural activations
13 agree with those reported in a large incident PD cohort (ICICLE-PD study) [112], which
14 revealed associations between regionally specific activations and deficits in executive
15 function (prefrontal and caudate nuclei activation), visuospatial function (parietal
16 activation), and memory encoding (hippocampal activation). Impaired deactivation of the
17 default mode network during executive task performance has also been reported
18 [113,114], suggesting that executive deficits in PD could arise from increased
19 susceptibility to extraneous and irrelevant interference.

21 *Proton MR spectroscopy*

22 Magnetic resonance spectroscopy is a non-invasive technique that has been used to
23 evaluate a range of metabolic changes in PD. In particular, the N-acetyl aspartate (NAA)

and creatine (Cr) ratio is a reliable marker of neuronal integrity, and studies in non-demented PD have demonstrated that lower NAA/Cr ratios in the anterior and posterior cingulate cortices are associated with executive deficits [115] and mild memory impairment respectively [116]. However, these findings should be considered with the caveat that longitudinal studies evaluating NAA/Cr ratios make the assumption that creatine levels remain constant over time. Fewer studies have investigated brain metabolism in PDD. Compared to PD-NC and controls, Summerfield and colleagues demonstrated reduced NAA levels in the occipital regions in PDD, which were correlated with neuropsychological scores on backward digit span and block design tests [117].

RADIONUCLIDE IMAGING TECHNIQUES

Nuclear imaging modalities such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) represent well established, reliable imaging methods to assess molecular deficits in PD. There is compelling SPECT and PET evidence indicating more severe striatal presynaptic dopaminergic deficiencies in PDD compared to non-demented PD, particularly in the caudate [118,119]. A previous longitudinal study also demonstrated increased rates of decline in striatal binding in PD and PDD, which were positively associated with global cognition at baseline [120]. Together, these findings are supported by frequent reports of associations between reductions in caudate dopaminergic tracer uptake and cognitive functions, such as verbal and visual memory [121] and executive functions [122]. In accordance with previous neuropsychological evidence suggesting that impairments with posterior cortical bases are predictors of future dementia in PD [17], a longitudinal PET study found that reduced

1 glucose metabolism in occipital and posterior cingulate regions heralded future
 2 conversion to PDD [123].

3
 4 The contribution of amyloid pathology to cognitive deficits in Lewy body diseases is still
 5 unclear, although differences in cortical amyloid burden between DLB and PDD have
 6 been investigated. There is a growing consensus from ^{11}C -Pittsburgh compound B (PIB)
 7 findings that PDD and DLB may be differentiated by relatively lower amyloid burden in
 8 the former group. Edison and colleagues reported increased amyloid pathology in DLB
 9 relative to PDD [124], a finding that is in keeping with the presence of greater cortical
 10 AD pathology in DLB [125]. At present, there is no conclusive evidence that PD and
 11 PDD patients show elevated amyloid load in the brain [124,126], although a recent
 12 review suggested that a subset of PDD subjects (35%) have increased cortical amyloid
 13 burden [127]. A previous study of 3 individuals with PDD who had both *in vivo* ^{11}C -PIB
 14 PET imaging and autopsy found that 2 of the 3 subjects showed elevated cortical uptake
 15 of ^{11}C -PIB [128]. Underscoring the specificity of ^{11}C -PIB for fibrillar amyloid in ante-
 16 mortem studies, the PIB-negative individual had abundant LB, diffuse plaques, no
 17 neurotic plaques and low NFT burden. Importantly, these finding raises an important
 18 future consideration to utilize ^{11}C -PIB PET as an *in vivo* marker as for the identification
 19 of PDD subjects exhibiting an elevated amyloid profile for whom novel anti-amyloid
 20 strategies might be most effective.

21 22 **CURRENT LIMITATIONS AND FUTURE DIRECTIONS**

23 *Heterogeneous characteristics of subject samples*

1 While it is generally established that PDD is associated with significant morphological
 2 changes, studies in non-demented PD samples have yielded conflicting findings [35,129].
 3 The inconsistency in the findings could, at least in part, be due to sources of
 4 heterogeneity in samples, such as variability of disease stages and differing severity of
 5 cognitive impairment. Therefore, the failure to stratify non-demented PD groups into PD-
 6 NC and PD-MCI will predictably limit the sensitivity of imaging analyses to detect
 7 differences in cognitive and morphological profiles.

8

9 *Ambiguity of PD-MCI classification*

10 Although the recent formalization of the MDS criteria has addressed some of ambiguity
 11 surrounding the concept of PD-MCI, it remains a controversial topic for a number of
 12 reasons. For instance, the definition of PD-MCI implies a strict dichotomization of a
 13 continuous variable (i.e. memory scores), and the cut-off criteria may lead to an
 14 underestimation or overestimation of cognitive impairment in PD patients. This concern
 15 is particularly relevant for highly functioning persons, whose cognitive abilities might be
 16 considered normal despite a worrying decline from premorbid functioning. There is also
 17 continuing debate about the number of tests that should be used to define PD-MCI.
 18 Future studies will also need to adhere to homogenous criteria (e.g. deciding between
 19 1SD – 2SD below normative values) to minimize discrepancies between results.

20

21 *Methodological differences across imaging analyses*

1 There are also inherent limitations in current imaging analyses. Although the VBM
2 technique is by far the most widely used approach to evaluate grey matter atrophy in PD,
3 its sensitivity is limited by mis-registration errors during the segmentation process, which
4 could be misinterpreted as cortical folding or thickness reductions. There are also
5 inconsistencies across studies over the selection of covariates to control for potential
6 cofounds. By default, we recommend that all imaging studies must include age and
7 gender as covariates. Correction for inter-subject variability in head sizes should also be
8 accounted if necessary.

9 The association of WMH with cognitive impairment in PD remains controversial due to
10 highly conflicting findings, partly owing to methodological differences in measurement
11 of WMH. Semi-quantitative visual ratings [79] and fully-automated volumetric analyses
12 [130] are commonly used to evaluate WMH in PD. Although visual ratings have the
13 advantage of ease of use, it requires subjective judgments. Furthermore, the ordinal
14 grading (e.g. 4 – 10 being the most severe) precludes accurate information about the
15 location or volume of the lesions. Furthermore, the use of different visual rating systems
16 makes it challenging to compare WMH findings in the literature. The majority of studies
17 have assessed global WMH scores, which might be insensitive to cognitive deficits that
18 are topographically associated to the location of WMH. The development of a fully
19 automated technique to segment and localize WMH will increase reproducibility of
20 studies, and allow robust longitudinal analyses of within-subject WMH progression over
21 time. Finally, statistical analysis and modeling for DTI and quantitative MRI data remain
22 a challenge, and robust methods to systematically integrate data from multimodal dataset
23 still await future research and validation.

1 *Lack of histopathological validation*

2 While there is still a lack of histopathological gold standard in PD [131], most of the
 3 studies in the literature have relied on clinical diagnosis, though we acknowledge that this
 4 is a common drawback in ante mortem studies. The combination of both post-mortem
 5 and *in vivo* imaging studies would be highly desirable to establish the neuroanatomical
 6 correlates of cognitive impairment in PD. To increase diagnostic confidence, a
 7 longitudinal design should include repeated monitoring of clinical symptoms to verify
 8 diagnosis at each time-point.

9

10 *Scarcity of longitudinal studies*

11 Lastly, there is a paucity of longitudinal studies to support cross-sectional findings.
 12 Additional longitudinal evidence is warranted to determine the progression of pathology,
 13 and how its trajectory relates to cognitive decline. There are also several advantages with
 14 a longitudinal design. As each subject serves as his or her own control, a longitudinal
 15 design can reduce the confounding effect of inter-individual morphological variability,
 16 thereby increasing statistical power. More importantly, monitoring non-demented PD
 17 subjects over a period of time offers an ideal opportunity to study the earliest regional
 18 morphological changes (biomarkers) underlying dementia.

19

20 **CONCLUSION**

21 Accumulating evidence from various neuroimaging approaches has increased our
 22 understanding of the neural substrates underlying cognitive impairment in PD. Specific

patterns of grey matter atrophy and white matter disruptions, as well as their associations with specific cognitive profiles have been well documented. There is increasing evidence that white matter abnormalities as revealed by DTI precede for grey matter atrophy in non-demented PD, although the role of WMH in cognitive decline in PD is still debated. More recently, functional neuroimaging (i.e. connectivity deficits of the default mode network) have emerged as promising candidates for biomarkers for PD-MCI and PDD but further studies are needed to confirm their prognostic utility. Considering the heterogeneous profile of cognitive deficits in PD, multimodal neuroimaging studies, for example, analyzing brain grey matter changes along with diffusion and perfusion imaging) could provide novel insights regarding the relative contributions of pathologic processes to cognitive impairment, especially with regards conversion to PDD.

COMPETING INTERESTS

Elijah Mak has no conflict of interests.

Li Su has no conflict of interests.

Guy Williams has no conflict of interests.

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24 Figure Legends

25 Figure 1. Vertex-wise comparisons of cortical thickness between (a) controls (CTR) and
26 cognitively normal patients with Parkinson disease (PD-CN), (b) controls and patients
27 with PD and mild cognitive impairment (PD-MCI), and (c) PD-CN and PD-MCI. The
28 color scale bar shows the logarithmic scale of p values. Lh = left hemisphere; MDS =
29 Movement Disorders Society; Rh = right hemisphere.

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