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

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Keywords: Lewy bodies, Parkinson's disease, neuroimaging, MRI, cognitive impairment.

ABSTRACT

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

INTRODUCTION

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

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

At present, the neuropathophysiology underlying cognitive impairments in PD has not been established, although accumulating evidence has suggested that multi-modal imaging biomarkers could be useful in the early diagnosis of PD-MCI and PDD. In this 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

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

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

Neuropathological substrates of cognitive impairment

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

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

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

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

STRUCTURAL NEUROIMAGING IN PD

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

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

MR studies of grey matter changes in PDD

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

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

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

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

MR studies of grey matter changes in PD-MCI

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

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

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

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

Longitudinal assessment of global atrophy rates

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

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

Diffusion weighted imaging

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

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

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

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

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

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

White matter hyperintensities

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

Resting-state fMRI

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

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

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

Task based fMRI

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

Proton MR spectroscopy

Magnetic resonance spectroscopy is a non-invasive technique that has been used to 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

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

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

CURRENT LIMITATIONS AND FUTURE DIRECTIONS

Heterogeneous characteristics of subject samples

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

Ambiguity of PD-MCI classification

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

Methodological differences across imaging analyses

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

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

Lack of histopathological validation

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

Scarcity of longitudinal studies

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

CONCLUSION

Accumulating evidence from various neuroimaging approaches has increased our 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.

John O'Brien has acted as a consultant for and received research funding from GE Healthcare and Avid/Lilly.

ACKNOWLEDGEMENTS

This work was supported by the NIHR Biomedical Research Unit in Dementia and the Biomedical Research Centre awarded to Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, and the NIHR Biomedical Research

Unit in Dementia and the Biomedical Research Centre awarded to Newcastle upon Tyne Hospitals NHS Foundation Trust and the Newcastle University. Elijah Mak was in receipt of a Gates Cambridge PhD studentship.

REFERENCES

[1] Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384–6. doi:10.1212/01.wnl.0000247740.47667.03.

[2] Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology 2014;82:308–16. doi:10.1212/WNL.0000000000000066.

[3] Aarsland D, Andersen K, Larsen JP, Lolk A. Prevalence and Characteristics of Dementia in Parkinson Disease. Arch Neurol 2003;60:387. doi:10.1001/archneur.60.3.387.

[4] Lawson R a, Yarnall AJ, Duncan GW, Khoo TK, Breen DP, Barker RA, et al. Quality of Life and Mild Cognitive Impairment in Early Parkinson's Disease: Does Subtype Matter? J Parkinsons Dis 2014:1–6. doi:10.3233/JPD-140390.

[5] Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 1999;14:866–74.

[6] Hughes TA, Ross HF, Mindham RHS, Spokes EGS. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand 2004;110:118–23. doi:10.1111/j.1600-0404.2004.00292.x.

[7] Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 2011;26:1814–24. doi:10.1002/mds.23823.

[8] Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689–707. doi:10.1002/mds.21507.

[9] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–72. doi:10.1212/01.wnl.0000187889.17253.b1.

[10] Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2006;77:585–9. doi:10.1136/jnnp.2005.081711.

[11] Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol 2010;20:633–9. doi:10.1111/j.1750-3639.2009.00369.x.

[12] Huber SJ, Paulson GW. The concept of subcortical dementia. Am J Psychiatry 1985;142:1312–7.

[13] Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009;72:1121–6. doi:10.1212/01.wnl.0000338632.00552.cb.

[14] Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127:550–60. doi:10.1093/brain/awh067.

[15] Janvin CC, Aarsland D, Larsen JP. Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study. J Geriatr Psychiatry Neurol 2005;18:149–54. doi:10.1177/0891988705277540.

[16] Pedersen KF, Larsen JP, Tysnes O-B, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol 2013;70:580–6. doi:10.1001/jamaneurol.2013.2110.

[17] Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130:1787–98. doi:10.1093/brain/awm111.

[18] Mahieux F, Fénelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998;64:178–83.

[19] Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: A prospective, community-based study. Ann Neurol 2005;58:773–6. doi:10.1002/ana.20635.

[20] Halliday GM, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. Mov Disord 2014;29:634–50. doi:10.1002/mds.25857.

[21] Kövari E, Gold G, Herrmann FR, Canuto A, Hof PR, Bouras C, et al. Lewy body densities in the entorhinal and anterior cingulate cortex predict cognitive deficits in Parkinson's disease. Acta Neuropathol 2003;106:83–8. doi:10.1007/s00401-003-0705-2.

[22] Mattila PM, Rinne JO, Helenius H, Dickson DW, Röyttä M. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. Acta Neuropathol 2000;100:285–90.

[23] Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011;134:1493–505. doi:10.1093/brain/awr031.

[24] Jellinger KA, Attems J. Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. Acta Neuropathol 2008;115:427–36. doi:10.1007/s00401-008-0347-5.

[25] Calabresi P, Picconi B, Parnetti L, Di Filippo M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. Lancet Neurol 2006;5:974–83. doi:10.1016/S1474-4422(06)70600-7.

[26] Bohnen NI, Müller MLTM, Kotagal V, Koeppe RA, Kilbourn MA, Albin RL, et al. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease. Brain 2010;133:1747–54. doi:10.1093/brain/awq079.

[27] Hilker R, Thomas A V, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology 2005;65:1716–22. doi:10.1212/01.wnl.0000191154.78131.f6.

[28] Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, Vollmar S, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. Neurology 2010;74:885–92. doi:10.1212/WNL.0b013e3181d55f61.

[29] Emre M. Dementia associated with Parkinson's disease. Lancet Neurol 2003;2:229–37.

[30] Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology 2011;76:1395–402. doi:10.1212/WNL.0b013e3182166e96.

[31] Prins ND, van der Flier W a, Knol DL, Fox NC, Brashear H, Nye JS, et al. The effect of galantamine on brain atrophy rate in subjects with mild cognitive impairment is modified by apolipoprotein E genotype: post-hoc analysis of data from a randomized controlled trial. Alzheimers Res Ther 2014;6:47. doi:10.1186/alzrt275.

[32] Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127:791–800. doi:10.1093/brain/awh088.

[33] Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. Neurology 2007;69:747–54. doi:10.1212/01.wnl.0000269666.62598.1c.

[34] Zarei M, Ibarretxe-Bilbao N, Compta Y, Hough M, Junque C, Bargallo N, et al. Cortical thinning is associated with disease stages and dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 2013;84:875–81. doi:10.1136/jnnp-2012-304126.

[35] Melzer TR, Watts R, MacAskill MR, Pitcher TL, Livingston L, Keenan RJ, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:188–94. doi:10.1136/jnnp-2011-300828.

[36] Weintraub D, Doshi J, Koka D, Davatzikos C, Siderowf AD, Duda JE, et al. Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol 2011;68:1562–8. doi:10.1001/archneurol.2011.725.

[37] Pagonabarraga J, Corcuera-Solano I, Vives-Gilabert Y, Llebaria G, García-Sánchez C, Pascual-Sedano B, et al. Pattern of regional cortical thinning associated with cognitive deterioration in Parkinson's disease. PLoS One 2013;8:e54980. doi:10.1371/journal.pone.0054980.

[38] Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007;78:254–9. doi:10.1136/jnnp.2006.093849.

[39] Tam CWC, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. Neurology 2005;64:861–5. doi:10.1212/01.WNL.0000153070.82309.D4.

[40] Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye J a. Parkinson's disease is associated with hippocampal atrophy. Mov Disord 2003;18:784–90. doi:10.1002/mds.10444.

[41] Junqué C, Ramírez-Ruiz B, Tolosa E, Summerfield C, Martí M-J, Pastor P, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. Mov Disord 2005;20:540–4. doi:10.1002/mds.20371.

[42] Apostolova LG, Beyer M, Green AE, Hwang KS, Morra JH, Chou Y-Y, et al. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. Mov Disord 2010;25:687–95. doi:10.1002/mds.22799.

[43] Churchyard A, Lees AJ. The relationship between dementia and direct involvement of the hippocampus and amygdala in Parkinson's disease. Neurology 1997;49:1570–6. doi:10.1212/WNL.49.6.1570.

[44] Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, Campdelacreu J, Gascon J, Falcon C, et al. Correlations between gray matter reductions and cognitive deficits in dementia with Lewy Bodies and Parkinson's disease with dementia. Mov Disord 2009;24:1740–6. doi:10.1002/mds.22488.

[45] Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, Campdelacreu J, Gascon J, Falcon C, et al. Frontal and associative visual areas related to visual hallucinations in dementia with Lewy bodies and Parkinson's disease with dementia. Mov Disord 2010;25:615–22. doi:10.1002/mds.22873.

[46] Song SK, Lee JE, Park H, Sohn YH, Lee JD. The Pattern of Cortical Atrophy in Patients with Parkinson ' s Disease According to Cognitive Status 2011;26:289–96. doi:10.1002/mds.23477.

[47] Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical atrophy is associated with cognitive impairment in mild Parkinson disease: a combined investigation of volumetric changes, cortical thickness, and vertex-based shape analysis. AJNR Am J Neuroradiol 2014;35:2257–64. doi:10.3174/ajnr.A4055.

[48] Pereira JB, Junqué C, Bartrés-Faz D, Ramírez-Ruiz B, Marti M-J, Tolosa E. Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. Hippocampus 2013;23:720–8. doi:10.1002/hipo.22131.

[49] Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 2012;33:727–39. doi:10.1002/hbm.21245.

[50] Dalaker TO, Zivadinov R, Larsen JP, Beyer MK, Cox JL, Alves G, et al. Gray matter correlations of cognition in incident Parkinson's disease. Mov Disord 2010;25:629–33. doi:10.1002/mds.22867.

[51] Mak E, Zhou J, Tan LCS, Au WL, Sitoh YY, Kandiah N. Cognitive deficits in mild Parkinson's disease are associated with distinct areas of grey matter atrophy. J Neurol Neurosurg Psychiatry 2014;85:576–80. doi:10.1136/jnnp-2013-305805.

[52] Jubault T, Gagnon J-F, Karama S, Ptito A, Lafontaine A-L, Evans AC, et al. Patterns of cortical thickness and surface area in early Parkinson's disease. Neuroimage 2011;55:462–7. doi:10.1016/j.neuroimage.2010.12.043.

[53] Pereira JB, Ibarretxe-bilbao N, Marti M, Bargallo N, Compta Y, Junque C. Assessment of Cortical Degeneration in Patients With Parkinson ' s Disease by

Voxel-Based Morphometry , Cortical Folding , and Cortical Thickness 2012;2534:2521–34. doi:10.1002/hbm.21378.

[54] Pereira JB, Svenningsson P, Weintraub D, Brønnick K, Lebedev A, Westman E, et al. Initial cognitive decline is associated with cortical thinning in early Parkinson disease. Neurology 2014:2017–25. doi:10.1212/WNL.0000000000000483.

[55] Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Garcia-Diaz AI, et al. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. Mov Disord 2014;00:1–9. doi:10.1002/mds.25982.

[56] Compta Y, Pereira JB, Ríos J, Ibarretxe-Bilbao N, Junqué C, Bargalló N, et al. Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. Parkinsonism Relat Disord 2013;19:717–24. doi:10.1016/j.parkreldis.2013.03.009.

[57] Ibarretxe-Bilbao N, Junque C, Segura B, Baggio HC, Marti MJ, Valldeoriola F, et al. Progression of cortical thinning in early Parkinson's disease. Mov Disord 2012;27:1746–53. doi:10.1002/mds.25240.

[58] Hanganu A, Bedetti C, Degroot C, Mejia-Constain B, Lafontaine A-L, Soland V, et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. Brain 2014;137:1120–9. doi:10.1093/brain/awu036.

[59] Fox NC, Freeborough PA. Brain atrophy progression measured from registered serial MRI: validation and application to Alzheimer's disease. J Magn Reson Imaging 1997;7:1069–75.

[60] O'Brien JT, Paling S, Barber R, Williams ED, Ballard C, McKeith IG, et al. Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia. Neurology 2001;56:1386–8.

[61] Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging. Mov Disord 2005;20:1571–6. doi:10.1002/mds.20652.

[62] Hu MT, White SJ, Chaudhuri KR, Morris RG, Bydder GM, Brooks DJ. Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline. J Neural Transm 2001;108:571–80.

[63] Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC. Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy. Brain 2006;129:1040–9. doi:10.1093/brain/awl021.

[64] Nedelska Z, Ferman TJ, Boeve BF, Przybelski SA, Lesnick TG, Murray ME, et al. Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies. Neurobiol Aging 2015;36:452–61. doi:10.1016/j.neurobiolaging.2014.07.005.

[65] Whitwell JL, Jack Jr. CR, Parisi JE, Knopman DS, Boeve BF, Petersen RC, et al. Rates of cerebral atrophy differ in different degenerative pathologies. Brain 2007;130:1148–58. doi:10.1093/brain/awm021.

[66] Mak E, Su L, Williams GB, Watson R, Firbank M, Blamire AM, et al. Longitudinal assessment of global and regional atrophy rates in Alzheimer's disease and dementia with Lewy bodies. NeuroImage Clin 2015;7:456–62. doi:10.1016/j.nicl.2015.01.017.

[67] Chan D, Janssen JC, Whitwell JL, Watt HC, Jenkins R, Frost C, et al. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. Lancet 2003;362:1121–2. doi:10.1016/S0140-6736(03)14469-8.

[68] Zhang K, Yu C, Zhang Y, Wu X, Zhu C, Chan P, et al. Voxel-based analysis of diffusion tensor indices in the brain in patients with Parkinson's disease. Eur J Radiol 2011;77:269–73. doi:10.1016/j.ejrad.2009.07.032.

[69] Karagulle Kendi a T, Lehericy S, Luciana M, Ugurbil K, Tuite P. Altered diffusion in the frontal lobe in Parkinson disease. AJNR Am J Neuroradiol 2008;29:501–5. doi:10.3174/ajnr.A0850.

[70] Gattellaro G, Minati L, Grisoli M, Mariani C, Carella F, Osio M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. AJNR Am J Neuroradiol 2009;30:1222–6. doi:10.3174/ajnr.A1556.

[71] Agosta F, Canu E, Stojković T, Pievani M, Tomić A, Sarro L, et al. The topography of brain damage at different stages of Parkinson's disease. Hum Brain Mapp 2013;34:2798–807. doi:10.1002/hbm.22101.

[72] Matsui H, Nishinaka K, Oda M, Niikawa H, Komatsu K, Kubori T, et al. Wisconsin Card Sorting Test in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 2007;116:108–12. doi:10.1111/j.1600-0404.2006.00795.x.

[73] Rae CL, Correia MM, Altena E, Hughes LE, Barker RA, Rowe JB. White matter pathology in Parkinson's disease: the effect of imaging protocol differences and relevance to executive function. Neuroimage 2012;62:1675–84. doi:10.1016/j.neuroimage.2012.06.012.

[74] Santillo AF, Mårtensson J, Lindberg O, Nilsson M, Manzouri A, Landqvist Waldö M, et al. Diffusion Tensor Tractography versus Volumetric Imaging in the Diagnosis of Behavioral Variant Frontotemporal Dementia. PLoS One 2013;8:1–9. doi:10.1371/journal.pone.0066932.

[75] Braak H, Sandmann-keil D, Gai W, Braak E. Extensive axonal Lewy neurites in Parkinson ' s disease : a novel pathological feature revealed by a -synuclein immunocytochemistry 1999;265:67–9.

[76] Teismann P, Schulz JB. Cellular pathology of Parkinson's disease: astrocytes, microglia and inflammation. Cell Tissue Res 2004;318:149–61. doi:10.1007/s00441-004-0944-0.

[77] Lee JE, Park H-J, Park B, Song SK, Sohn YH, Lee JD, et al. A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2010;81:320–6. doi:10.1136/jnnp.2009.184747.

[78] Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. Stroke 2012;43:2526–34. doi:10.1161/STROKEAHA.112.655803.

[79] Beyer MK, Aarsland D, Greve OJ, Larsen JP. Visual rating of white matter hyperintensities in Parkinson's disease. Mov Disord 2006;21:223–9. doi:10.1002/mds.20704.

[80] De Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000;47:145–51.

[81] Sohn YH, Kim JS. The influence of white matter hyperintensities on the clinical features of Parkinson's disease. Yonsei Med J 1998;39:50–5.

[82] Prins ND, Van Dijk EJ, Den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain 2005;128:2034–41. doi:10.1093/brain/awh553.

[83] Capizzano a a, Ación L, Bekinschtein T, Furman M, Gomila H, Martínez a, et al. White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75:822–7. doi:10.1136/jnnp.2003.019273.

[84] Provenzano F a, Muraskin J, Giuseppe T, Narkhede A, Wasserman BT, Griffith EY, et al. White Matter Hyperintensities and Cerebral Amyloidosis. Jama 2013. doi:10.1001/jamaneurol.2013.1321.

[85] Sunwoo MK, Jeon S, Ham JH, Hong JY, Lee JE, Lee J-M, et al. The burden of white matter hyperintensities is a predictor of progressive mild cognitive

impairment in patients with Parkinson's disease. Eur J Neurol 2014;21:922–e50. doi:10.1111/ene.12412.

[86] Choi S-A, Evidente VGH, Caviness JN, Shill HA, Sabbagh MN, Connor DJ, et al. Are there differences in cerebral white matter lesion burdens between Parkinson's disease patients with or without dementia? Acta Neuropathol 2010;119:147–9. doi:10.1007/s00401-009-0620-2.

[87] Kandiah N, Mak E, Ng A, Huang S, Au WL, Sitoh YY, et al. Cerebral white matter hyperintensity in Parkinson's disease: a major risk factor for mild cognitive impairment. Parkinsonism Relat Disord 2013;19:680–3. doi:10.1016/j.parkreldis.2013.03.008.

[88] Mak E, Dwyer MG, Ramasamy DP, Au WL, Tan LCS, Zivadinov R, et al. White matter hyperintensities and mild cognitive impairment in Parkinson's Disease. J Neuroimaging 2015. doi:10.1111/jon.12230.

[89] Kandiah N, Zainal NH, Narasimhalu K, Chander RJ, Ng A, Mak E, et al. Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease. Parkinsonism Relat Disord 2014:6–11. doi:10.1016/j.parkreldis.2014.08.024.

[90] Dalaker TO, Larsen JP, Dwyer MG, Aarsland D, Beyer MK, Alves G, et al. White matter hyperintensities do not impact cognitive function in patients with newly diagnosed Parkinson ' s disease. Neuroimage 2009;47:2083–9. doi:10.1016/j.neuroimage.2009.06.020.

[91] Lee S-J, Kim J-S, Yoo J-Y, Song I-U, Kim B-S, Jung S-L, et al. Influence of white matter hyperintensities on the cognition of patients with Parkinson disease. Alzheimer Dis Assoc Disord 2010;24:227–33. doi:10.1097/WAD.0b013e3181d71a13.

[92] Shin J, Choi S, Lee JE, Lee HS, Sohn YH, Lee PH. Subcortical white matter hyperintensities within the cholinergic pathways of Parkinson's disease patients according to cognitive status. J Neurol Neurosurg Psychiatry 2012;83:315–21. doi:10.1136/jnnp-2011-300872.

[93] Burton EJ, McKeith IG, Burn DJ, Firbank MJ, O'Brien JT. Progression of white matter hyperintensities in Alzheimer disease, dementia with lewy bodies, and Parkinson disease dementia: a comparison with normal aging. Am J Geriatr Psychiatry 2006;14:842–9. doi:10.1097/01.JGP.0000236596.56982.1c.

[94] Young VG, Halliday GM, Kril JJ. Neuropathologic correlates of white matter hyperintensities. Neurology 2008;71:804–11. doi:10.1212/01.wnl.0000319691.50117.54.

[95] Leys D, Pruvo JP, Parent M, Vermersch P, Soetaert G, Steinling M, et al. Could Wallerian degeneration contribute to “leuko-araiosis” in subjects free of any vascular disorder? J Neurol Neurosurg Psychiatry 1991;54:46–50.

[96] Ballard C, O’Brien J, Barber B, Scheltens P, Shaw F, McKeith I, et al. Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. Ann N Y Acad Sci 2000;903:442–5.

[97] Tofts PS. Quantitative MRI of the Brain: Measuring Changes Caused by Disease. John Wiley & Sons Ltd; 2004.

[98] Adlard PA, Tran BA, Finkelstein DI, Desmond PM, Johnston LA, Bush AI, et al. A review of β-amyloid neuroimaging in Alzheimer’s disease. Front Neurosci 2014;8:327. doi:10.3389/fnins.2014.00327.

[99] Bunzeck N, Singh-Curry V, Eckart C, Weiskopf N, Perry RJ, Bain PG, et al. Motor phenotype and magnetic resonance measures of basal ganglia iron levels in Parkinson’s disease. Parkinsonism Relat Disord 2013;19:1136–42. doi:10.1016/j.parkreldis.2013.08.011.

[100] Su L, Blamire AM, Watson R, He J, Aribisala B, O’Brien JT. Tissue microstructural changes in dementia with Lewy bodies revealed by quantitative MRI. J Neurol 2014. doi:10.1007/s00415-014-7541-2.

[101] Haris M, Singh A, Cai K, Davatzikos C, Trojanowski JQ, Melhem ER, et al. T1rho (T1ρ) MR imaging in Alzheimer’s disease and Parkinson's disease with and without dementia. J Neurol 2011;258:380–5. doi:10.1007/s00415-010-5762-6.

[102] Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 2009;10:186–98. doi:10.1038/nrn2575.

[103] Krajcovicova L, Mikl M, Marecek R, Rektorova I. The default mode network integrity in patients with Parkinson’s disease is levodopa equivalent dose-dependent. J Neural Transm 2012;119:443–54. doi:10.1007/s00702-011-0723-5.

[104] Yao N, Shek-Kwan Chang R, Cheung C, Pang S, Lau KK, Suckling J, et al. The default mode network is disrupted in parkinson’s disease with visual hallucinations. Hum Brain Mapp 2014;5666:5658–66. doi:10.1002/hbm.22577.

[105] Tessitore A, Esposito F, Vitale C, Santangelo G, Amboni M, Russo A, et al. Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. Neurology 2012;79:2226–32. doi:10.1212/WNL.0b013e31827689d6.

[106] Baggio H-C, Segura B, Sala-Llonch R, Marti M-J, Valldeoriola F, Compta Y, et al. Cognitive impairment and resting-state network connectivity in Parkinson's disease. Hum Brain Mapp 2014;00. doi:10.1002/hbm.22622.

[107] Baggio H-C, Sala-Llonch R, Segura B, Marti M-J, Valldeoriola F, Compta Y, et al. Functional brain networks and cognitive deficits in Parkinson's disease. Hum Brain Mapp 2014;35:4620–34. doi:10.1002/hbm.22499.

[108] Rektorova I, Krajcovicova L, Marecek R, Mikl M. Default mode network and extrastriate visual resting state network in patients with Parkinson's disease dementia. Neurodegener Dis 2012;10:232–7. doi:10.1159/000334765.

[109] Lewis SJG, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive Impairments in Early Parkinson ' s Disease Are Accompanied by Reductions in Activity in Frontostriatal Neural Circuitry 2003;23:6351–6.

[110] Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. J Neurosci 2004;24:702–10. doi:10.1523/JNEUROSCI.4860-03.2004.

[111] Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 2002;51:156–64.

[112] Nombela C, Rowe JB, Winder-Rhodes SE, Hampshire A, Owen AM, Breen DP, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain 2014;137:2743–58. doi:10.1093/brain/awu201.

[113] Tinaz S, Schendan HE, Stern CE. Fronto-striatal deficit in Parkinson's disease during semantic event sequencing. Neurobiol Aging 2008;29:397–407. doi:10.1016/j.neurobiolaging.2006.10.025.

[114] Van Eimeren T, Monchi O, Ballanger B, Strafella AP. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. Arch Neurol 2009;66:877–83. doi:10.1001/archneurol.2009.97.

[115] Lewis SJG, Shine JM, Duffy S, Halliday G, Naismith SL. Anterior cingulate integrity: executive and neuropsychiatric features in Parkinson's disease. Mov Disord 2012;27:1262–7. doi:10.1002/mds.25104.

[116] Camicioli R., Korzan J., Foster S., Fisher N., Emery D., Bastos a. ., et al. Posterior cingulate metabolic changes occur in Parkinson's disease patients without dementia. Neurosci Lett 2004;354:177–80. doi:10.1016/j.neulet.2003.09.076.

[117] Summerfield C, Gómez-Ansón B, Tolosa E, Mercader JM, Martí MJ, Pastor P, et al. Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study. Arch Neurol 2002;59:1415–20.

[118] O'Brien JT, Colloby S, Fenwick J, Williams ED, Firbank M, Burn D, et al. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch Neurol 2004;61:919–25. doi:10.1001/archneur.61.6.919.

[119] Ito K, Nagano-Saito A, Kato T, Arahata Y, Nakamura A, Kawasumi Y, et al. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[18F]fluoro-L-dopa PET study. Brain 2002;125:1358–65.

[120] Colloby SJ, Williams ED, Burn DJ, Lloyd JJ, McKeith IG, O'Brien JT. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT. Eur J Nucl Med Mol Imaging 2005;32:1176–85. doi:10.1007/s00259-005-1830-z.

[121] Jokinen P, Brück A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat Disord 2009;15:88–93. doi:10.1016/j.parkreldis.2008.03.005.

[122] Marié RM, Barré L, Dupuy B, Viader F, Defer G, Baron JC. Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. Neurosci Lett 1999;260:77–80.

[123] Bohnen NI, Koeppe R a, Minoshima S, Giordani B, Albin RL, Frey K a, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. J Nucl Med 2011;52:848–55. doi:10.2967/jnumed.111.089946.

[124] Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008;79:1331–8. doi:10.1136/jnnp.2007.127878.

[125] Halliday GM, Song YJC, Harding AJ. Striatal β-amyloid in dementia with Lewy bodies but not Parkinson's disease. J Neural Transm 2011;118:713–9. doi:10.1007/s00702-011-0641-6.

[126] Jokinen P, Scheinin N, Aalto S, Någren K, Savisto N, Parkkola R, et al. [(11)C]PIB-, [(18)F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia. Parkinsonism Relat Disord 2010;16:666–70. doi:10.1016/j.parkreldis.2010.08.021.

[127] Donaghy P, Thomas AJ, O'Brien JT. Amyloid PET Imaging in Lewy Body Disorders. Am J Geriatr Psychiatry 2013;23:23–37. doi:10.1016/j.jagp.2013.03.001.

[128] Gomperts SN, Rentz DM, Moran E, Becker J a, Locascio JJ, Klunk WE, et al. Imaging amyloid deposition in Lewy body diseases. Neurology 2008;71:903–10. doi:10.1212/01.wnl.0000326146.60732.d6.

[129] Dalaker TO, Larsen JP, Bergsland N, Beyer MK, Alves G, Dwyer MG, et al. Brain atrophy and white matter hyperintensities in early Parkinson's disease(a). Mov Disord 2009;24:2233–41. doi:10.1002/mds.22754.

[130] Firbank MJ, Minett T, O'Brien JT. Changes in DWI and MRS associated with white matter hyperintensities in elderly subjects. Neurology 2003;61:950–4.

[131] Uitti RJ, Calne DB, Dickson DW, Wszolek ZK. Is the neuropathological "gold standard" diagnosis dead? Implications of clinicopathological findings in an autosomal dominant neurodegenerative disorder. Park Relat Disord 2004;10:461–3. doi:10.1016/j.parkreldis.2004.10.001.

[132] Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical Atrophy Is Associated with Cognitive Impairment in Mild Parkinson Disease: A Combined Investigation of Volumetric Changes, Cortical Thickness, and Vertex-Based Shape Analysis. AJNR Am J Neuroradiol 2014. doi:10.3174/ajnr.A4055.

[133] Agosta F, Canu E, Stefanova E, Sarro L, Tomić A, Špica V, et al. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. Hum Brain Mapp 2014;35:1921–9. doi:10.1002/hbm.22302.

Figure Legends

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