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

Elijah Mak [a], Li Su [a], Guy B. Williams [b], John T. O'Brien [a, *]

[a] Department of Psychiatry, University of Cambridge, UK
[b] Wolfson Brain Imaging Centre, UK

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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.

1. 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.

2. Cognitive impairment in PD

2.1. 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

* Corresponding author. Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Level E4 Cambridge Biomedical Campus, Cambridge, CB2 0SP, UK.
E-mail addresses: fkm24@medschl.cam.ac.uk (E. Mak), ls514@cam.ac.uk (L. Su), gbw1000@wbic.cam.ac.uk (G.B. Williams), john.obrien@medschl.cam.ac.uk (J.T. O'Brien).

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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].

2.2. 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.

2.3. 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.

3. 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.

3.1. 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,

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