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White matter hyperintensities are linked to future cognitive decline in de novo Parkinson's disease patients

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ABSTRACT

White Matter Hyperintensities (WMHs) are associated with cognitive decline in aging and Alzheimer's disease. However, the pathogenesis of cognitive decline in Parkinson's disease (PD) is not as clearly related to vascular causes, and therefore the role of WMHs as a marker of small-vessel disease (SVD) in PD is less clear. Currently, SVD in PD is assessed and treated independently of the disease. However, if WMH as the major MRI sign of SVD has a higher impact on cognitive decline in PD patients than in healthy controls, vascular pathology needs to be assessed and treated with a higher priority in this population. Here we investigate whether the presence of WMHs leads to increased cognitive decline in de novo PD, and if these effects relate to cortical atrophy. WMHs and cortical thickness were measured in de novo PD patients and age-matched controls ($N_{PD} = 365$, $N_{Control} = 174$) from Parkinson's Progression Markers Initiative (PPMI) to study the relationship between baseline WMHs, future cognitive decline (follow-up: 4.09 ± 1.14 years) and cortical atrophy (follow-up: 1.05 ± 0.10 years). PD subjects with high baseline WMH loads had significantly greater cognitive decline than i) PD subjects with low WMH load, and ii) control subjects with high WMH load. Furthermore, in PD subjects, high WMH load resulted in more cortical thinning in the right frontal lobe. Theses results show that the presence of WMHs in de novo PD patients predicts greater future cognitive decline and cortical atrophy than in normal aging.

1. Introduction

While Parkinson's disease (PD) is typically characterized by motor symptoms, cognitive deficits occur in approximately 15% of patients in early drug-naïve stages (Poletti et al., 2012). Two decades after disease onset, this prevalence increases to over 80% (Hely et al., 2008). Early mild cognitive impairment (MCI) is a strong predictor of later development of dementia (Anang et al., 2014; Pedersen et al., 2017), which is a key determinant of mortality and poorer quality of life in PD (de Lau et al., 2005). Taken together, these epidemiological findings highlight the need to better understand cognitive impairment in PD and what biological underpinnings may shape the course of this decline. Progress has been made in recent years in understanding how subcortical dysfunction in early stages, followed by cortical α-synuclein pathology and loss of neurotransmitters, may relate to cognitive impairment in PD patients. Additionally, Compta et al. and Irwin et al. have underlined the relevance of neuropathological markers of Alzheimer's disease (AD) (i.e. amyloid beta and tau protein aggregates) present in ex-vivo samples of PD patients with dementia, indicating another potential co-morbid source of cognitive decline in PD (Compta et al., 2011; Irwin et al., 2012). More specifically, they report that high levels of cortical amyloid beta correlate with faster progression to dementia (Compta et al., 2011), and that in a cohort of samples obtained from 92 patients with a diagnosis of PD, almost a third had histopathologic findings associated with AD as a comorbidity (Irwin et al., 2012). Nevertheless, how vascular pathology (i.e., small-vessel disease (SVD) (Halliday et al., 2014; Merino & Hachinski, 2000)) - assessed by white matter changes or leukoaraiosis (Hachinski et al., 1987)- may

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contribute to cognitive dysfunction in PD remains unclear.

The term SVD is mainly related to two etiologies: age-related vascular disease, also referred as arteriolosclerosis, or vascular-risk-factor related SVD (de Leeuw et al., 2002; Debette & Markus, 2010), and cerebral amyloid angiopathy (Pantoni, 2010), which is also present in the small cortical vessels in AD pathology. Both etiologies play a crucial role in stroke, dementia and aging, and could also be relevant in PD. Therefore, early detection of WMHs and treatment of cardiovascular risk factors could have a positive impact on cognitive decline in PD (Dufouil et al., 2005; Hawkins et al., 2017; Biesbroek et al., 2017; Veselỳ & Rektor, 2016). One measure of SVD is white matter hyperintensities (WMHs) which are areas of increased signal in T2-weighted and FLAIR structural MRI (Pantoni & Garcia, 1997). Neuropathologic correlates of WMHs include loss of axons and glial cells, myelin rarefaction, spongiosis, perivascular demyelination, gliosis, subependymal glial accumulation and loss of the ependymal lining (Merino & Hachinski, 2000). Despite the various findings, consensus exists regarding the association of WMHs and SVD (Pantoni & Garcia, 1997).

In Alzheimer's disease (AD), WMHs have been extensively studied and strongly predict rapid cognitive decline in individuals with mild cognitive impairment (MCI) (Dubois et al., 2014; Tosto et al., 2014). In PD, the pathogenic role of vascular risk factors is less clear (de Lau et al., 2005) and results have been contradictory (Veselỳ & Rektor, 2016). WMHs might cause cognitive decline independent of PD, or the synergy between the two mechanisms may accelerate cognitive impairment (Veselỳ & Rektor, 2016). Alternatively, WMHs might aggravate the pathologic spread of misfolded α-synuclein or amyloid-β proteins. WMH burden can also precede neurological damage as indexed by cortical atrophy. Higher WMH load (WMHL) has been shown to correlate with lower cortical thickness in regions that are related to cognitive decline (Tuladhar et al., 2015). Cortical thinning caused by direct or indirect effects of WMHs might lead to cognitive decline in PD.

Of the few studies that have investigated WMHs and cognitive decline in PD, most are cross-sectional, include patients that are on dopaminergic medication, and are typically from cohorts that are at later stages of disease (Auning et al., 2014; Mak et al., 2015; Jones et al., 2017). Additionally, different groups implement different tests to assess cognition and many do not perform a comprehensive neuropsychological battery.

Capitalizing on the longitudinal assessment of cognitive abilities and neuroimaging biomarkers in the large-scale, multi-centre cohort of de novo PD patients from the Parkinson's Progression Markers Initiative (Marek et al., 2011), we investigated the relationship between WMH burden and: 1) cognitive decline over time, and 2) cortical grey matter changes over time (as indexed by cortical thinning) in early stages of PD.

2. Methods

2.1. Patients

The Parkinson's Progression Markers Initiative (PPMI) is a longitudinal multi-site clinical study of de novo PD patients and age-matched healthy controls (HC)(Marek et al., 2011) (http://www.ppmi-info.org). The study was approved by the institutional review board of all participating sites and written informed consent was obtained from all participants before inclusion in the study. In the present study, we included all subjects that had either FLAIR or T2-weighted MR images at their baseline visit and had follow-up visits for at least one year after the baseline scan (N_{PD} = 365, N_{HC} = 174). All subjects were regularly assessed (yearly follow-ups, mean total follow-up period of 4.09 ± 1.14 years) for clinical characteristics (motor, non-motor and neuropsychological performance) by site investigators, including Montreal Cognitive Assessment (MoCA), Hopkins Verbal Learning Test–Revised (HVLT), Benton judgement of line orientation test for visuospatial skills, Letter-Number Sequencing test for verbal working memory, and semantic fluency test to detect cognitive decline (Table 2). The executive function score is calculated as the sum of letter number sequencing and semantic fluency scores (Chan et al., 2008). To validate the correlation between these two components, we verified their relationship in the PD population ($r = 0.56$, $p < 0.0001$). For more information on clinical measurements, see supplementary material, section Cognitive Testing.

2.2. Procedures

All MR images were preprocessed using our standard pipeline (Aubert-Broche et al., 2013) in three steps: noise reduction, intensity non-uniformity correction, and intensity normalization. T2-weighted and FLAIR images were linearly co-registered to the T1-weighted images using a 6-parameter rigid registration. The T1-weighted images were first linearly and then nonlinearly registered to the standard template (MNI-ICBM-152). The WMHs were segmented using a previously validated automatic multi-modality segmentation technique in the native space of FLAIR or T2-weighted scans to avoid further blurring caused by resampling of the images (Dadar et al., 2017a; Dadar et al., 2017b). This technique uses a set of location and intensity features obtained from a library of manually segmented scans in combination with a random forest classifier to detect the WMHs in new images. The libraries used in this study were obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset since the T2-weighted and FLAIR sequences for the PPMI images follow the same acquisition protocol as ADNI. The quality of the registrations and segmentations was visually assessed and cases that did not pass this quality control were discarded (n = 43). WMHL was defined as the volume (in cm^3) of all segmented WMH voxels in the standard space, i.e. the WMH volumes were corrected for total intracranial volume (ICV). All MRI processing and segmentation steps were blinded to clinical outcomes.

For voxel-wise analysis of WMHs, the WMH probability maps generated by the segmentation tool were nonlinearly transformed to the template space at $2 \times 2 \times 2\,mm^3$ resolution and blurred with a 3D Gaussian kernel with full width at half maximum of 5 mm to compensate for the variability caused by differences in voxel sizes in the native FLAIR and T2-weighted images. Rates of cognitive decline were calculated for subjects that had at least one-year follow-up information as the change of the score per year (N_{PD} = 365, N_{HC} = 174), using a linear regression between time and the score values at different time points along with an intercept term.

Only subjects with T1-weighted 3 T MRI data at both initial/baseline visit and at a one-year follow-up MRI were included for cortical thickness analysis (N_{Total} = 155, see Table 1). Cortical models were generated using the CIVET 2.1 preprocessing pipeline (Ad-Dab'bagh et al., 2006), registered to MNI-ICBM-152 template, and analyzed using the SurfStat software package (http://www.math.mcgill.ca/keith/surfstat/)(Yau et al., 2018). Distances between inner and outer cortical surfaces were evaluated to provide a measure of cortical thickness at each vertex. Changes in cortical thickness were calculated by subtracting the values ($\Delta t = t_1 - t_2$) at the one-year follow-up (t_2) from the baseline (t_1). The average time between the baseline and follow-up visits was 1.05 ± 0.11 and 1.05 ± 0.09 years for the PD and control subjects, respectively.

2.3. Statistical analysis

We tested two major hypotheses: 1. greater WMHL will lead to more extensive and faster decline in cognition of the PD patients, and 2. patients with a higher WMHL will show more cortical thinning in their follow-up visit after one year.

Survival analysis was used to investigate the relationship between WMH burden and decline in cognition. It has been previously shown that a threshold of WMHs should be present before cognitive deficits are observed (Price et al., 2012; Boone et al., 1992). The question of