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Brain tissue pulsatility is related to clinical features of Parkinson's disease

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ABSTRACT

Introduction: This study investigated whether brain tissue pulsatility is associated with features of disease severity in Parkinson's disease (PD).

Methods: Data were extracted from the Parkinson's Progression Markers Initiative among 81 adults with PD (confirmed with DATSCAN™). Brain tissue pulsatility was computed using resting state blood oxygenation level dependent (BOLD) MRI in white matter (WM), referred to as $BOLD_{TP}$. Motor impairment was assessed using the Movement Disorders Society unified Parkinson's disease rating scale. Factor analysis generated composite scores for cognition and vascular risk burden. A linear regression model examined the association of $BOLD_{TP}$ with age, sex, motor impairment, cognition, vascular risk burden and PD duration. In addition, we investigated whether $BOLD_{TP}$ relates to WM hyperintensity (WMH) volume, WM fractional anisotropy (WM-FA) and striatal binding ratio (SBR) of dopamine transporter.

Results: Motor impairment ($t = 2.3$, $p = .02$), vascular burden ($t = 2.4$, $p = .02$) and male sex ($t = 3.0$, $p = .003$) were independently associated with $BOLD_{TP}$ ($r^2 = 0.40$, $p < .001$). $BOLD_{TP}$ was correlated with WMH volume ($r = 0.22$, $p = .05$) but not WM-FA nor SBR ($p > .1$). In addition, $BOLD_{TP}$ ($t = 2.76$, $p = .008$) and SBR ($t = -2.04$, $p = .04$) were independently related to motor impairment ($r^2 = 0.18$, $p = .006$).

Conclusion: Our findings show that brain tissue pulsatility from BOLD images in WM is related to neurological and vascular features in PD. $BOLD_{TP}$ may be useful in PD to study small vessel alterations that appear distinct from WM structural changes.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that imposes a significant burden on individuals, their families and healthcare systems (Schapira and Tolosa, 2010). While classic motor symptoms of tremor, rigidity and bradykinesia are responsive to dopamine replacement therapies, other features including postural instability/gait difficulty (PIGD) (Stebbins et al., 2013) and cognitive impairment, are typically less responsive (Antonini et al., 2012). The severity of these predominantly non-dopaminergic features vary among people with PD, especially in early stages of the disease (Adler et al., 2014). These features tend to predominate as PD progresses and markedly reduce quality of life (Lin and Wu, 2015).

Studies have shown that cerebral small vessel disease (CSVD), manifesting as white matter hyperintensity (WMH) on magnetic resonance images (MRI), is associated with motor deficits (Baezner et al., 2008) and cognitive impairment (Gunning-Dixon and Raz, 2000) in older adults. In addition, there is evidence of subcortical arteriosclerosis as well as microinfarcts pathologies at autopsy in adults with motor impairment, a finding that is independent of age, sex, atherosclerosis and dementia diagnosis, suggesting microvascular pathology involvement in motor deficits (Buchman et al., 2013).

Comorbid CSVD in PD is thought to contribute to symptom severity, given the overlap between their clinical features e.g., motor and cognitive impairment (Bohnen and Albin, 2011). A recent study in > 800 people with PD found that WMH and the number of cardiovascular risk factors are related to motor (especially PIGD) and cognitive impairment (Malek et al., 2016). Other studies have shown that WMH increases in

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PIGD dominant PD patients compared to the tremor dominant patients (Lee et al., 2009), and is related to elevated risk of developing dementia (Alves et al., 2006).

By the time CSVD is manifest in a patient, however, it may be late to alter the prognosis (Jolly et al., 2013). Therefore, it is imperative to develop novel neuroimaging strategies that identify those at risk of developing CSVD. Recent findings support the theory that increased arterial pulsatility contributes to CSVD (Maillard et al., 2017; Mitchell et al., 2011). Mechanistically, increased arterial stiffness results in the transmission of higher pulse energy into the downstream cerebral microcirculation; this leads to elevated microvascular pulsatility and likely causes small vessel damage in tissue (O'Rourke and Hashimoto, 2007). Therefore, characterizing brain tissue pulsatility is of interest, yet not well studied in PD perhaps due to the limits of observing small-scale hemodynamic features.

Our group has developed a method to non-invasively quantify pulsatility from blood oxygenation level dependent (BOLD) MRI (Makedonov et al., 2013). Resting state BOLD images are traditionally used to investigate grey matter functional connectivity whereas white matter (WM) signal are discarded. BOLD signal in WM is of interest because it provides physiological information that is not related to neurovascular BOLD signals and index small vessel related features since few large arteries reside in WM. We define the temporal physiological fluctuations of the BOLD signal within WM as the BOLD tissue pulsatility ($BOLD_{TP}$) (Makedonov et al., 2013). We found that $BOLD_{TP}$ was elevated in people with Alzheimer's disease, associating directly with memory impairment and inversely with glucose uptake in the brain (Makedonov et al., 2016).

The current study used data from the Parkinson's Progression Markers Initiative (PPMI) to test whether $BOLD_{TP}$ can explain between-participant differences in PD symptoms. We hypothesized that $BOLD_{TP}$ would be related to neurological symptoms of PD in addition to vascular risk burden. To further develop the utility of $BOLD_{TP}$, we examined $BOLD_{TP}$ relative to WMH volume, WM fractional anisotropy (WM-FA) from diffusion tensor imaging and striatal binding ratio (SBR) of the dopamine transporter (DATSCAN™).

2. Material and methods

2.1. Participants

Data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data). PPMI study was approved by the institutional review board of all participating sites and written informed consent was obtained from all participants before study enrolment. For up-to-date information, visit www.ppmi-info.org. Patients with idiopathic PD, confirmed by DATSCAN™, and available resting state BOLD images were included in this study. Data were collected between 2011 and 2015 and accessed in June 2017.

2.2. Clinical assessments

Motor performance was assessed using the Movement Disorders Society, unified Parkinson's disease rating scale part3 (MDS-UPDRS3). We also calculated PIGD and tremor subscores from MDS-UPDRS using a previously established method (Stebbins et al., 2013) as a means of studying motor phenotypes. Cognitive performance was assessed by neuropsychological testing that included a revised Hopkins verbal learning test, Benton judgment of line orientation, semantic fluency, letter number sequencing and symbol digit modalities. Clinical characteristics of interest included body mass index, supine pulse pressure and the following cardiovascular risk factors: hypertension, hypercholesterolemia, hyperglycemia/diabetes mellitus and prior cardiovascular disease. We extracted SBR from the processed DATSCAN™ data and calculated mean striatum SBR (i.e., mean of bilateral caudate and bilateral putamen). Details on PPMI DATSCAN™ may be accessed at http://www.ppmi-info.org/wp-content/uploads/2017/06/PPMI-TOM-V8_09-March-2017.pdf. SBR analysis was restricted to individuals who completed BOLD MRI and DATSCAN™ acquisitions on the same visit.

2.3. MRI acquisition

MRI were acquired on Siemens 3.0 T scanners (Siemens Healthcare, Malvern, PA, USA) from 8 sites using a standardized protocol included: 1) T1-weighted images: TE = 3 ms, TR = 2300 ms, TI = 900 ms, flip angle = 9° and voxel size = $1\times1\times1mm^3$; 2) resting state BOLD images: TE = 25 ms, TR = 2400 ms, flip angle = 80°, voxel size = $3.25\times3.25\times3.25mm^3$ and number of volumes = 212; 3) interleaved proton density and T2-weighted images: TE = 11 ms and 101 ms, TR = 3270 ms and voxel size = $0.9\times0.9\times3mm^3$; and 4) diffusion tensor images: TE = 88 ms, TR = 900 ms, voxel size = $2\times2\times2mm^3$, number of directions = 64, b = $1000s/mm^2$ and one b0 image.

2.4. MRI processing

We performed BOLD image processing using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) (MATLAB2015 and SPM12) and in-house tools based on FSL5 (Jenkinson et al., 2012). Image processing included: 1) motion correction of BOLD images, 2) bias field correction and tissue segmentation of T1-weighted images, and 3) co-registration of BOLD images to Montreal Neurological Institute (MNI152) template space using T1-weighted images as intermediates. The CONN toolbox provides a composite estimate of scan-to-scan movement that is calculated as the maximum movement across 6 control points placed on the image (Whitfield-Gabrieli and Nieto-Castanon, 2012). We then calculated the root mean square of these scan-to-scan movements to index the global head motion for each individual. To mitigate issues regarding excessive head motion cases, individuals with global head motion that exceeded 2 mm were excluded from further analyses (Seto et al., 2001).

We generated a temporal coefficient of variation image from the BOLD time series (i.e., a temporal standard deviation image divided by temporal mean image, expressed as a percentage). We computed thermal noise from non-brain voxels and subtracted this estimate from the temporal coefficient of variation image to isolate physiological sources (Makedonov et al., 2013). $BOLD_{TP}$ was calculated as the average BOLD physiological signal in normal appearing WM from the cerebrum. The segmented WM map was masked by a probability threshold of 0.9 and considered a volume of twenty consecutive 2-mm axial slices (inferior-superior range in MNI152 template space was 8-48 mm; Fig. 1A).

We segmented WMH using an in-house semi-automated tool based on T1-weighted, proton density and T2-weighted images (Ramirez et al., 2014). Diffusion tensor image processing included: 1) correction for head motion and eddy current, 2) co-registration to MNI152 template space using structural images and 3) computation of FA map. More details can be accessed at http://www.ppmi-info.org/study-design/research-documents-and-sops. We calculated mean FA in WM (WM-FA) as a global measure using the previously described WM mask (Fig. 1A).

2.5. Statistical assessments

We performed statistical assessments in R (R 3.2.2 GUI 1.66) with $p < .05$ observed as significant. We used two separate factor analyses to encapsulate: 1) a composite cognitive score and 2) a vascular risk burden. The cognitive model included: sum of correct words from the three Hopkins verbal learning acquisition trials, the number of correct items from the Benton test, the number of correct unique animal, vegetable and fruit names from the semantic fluency test, the sum of the scores from the seven trials of the letter number sequencing test and the number of correct responses from symbol digit test. The vascular