



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

Zahra Shirzadi^{a,b,*}, Andrew D. Robertson^b, Arron W. Metcalfe^b, Sarah Duff-Canning^c,
Connie Marras^c, Anthony E. Lang^c, Mario Masellis^{b,d}, Bradley J. MacIntosh^{a,b}

^a Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

^b Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

^c Morton and Gloria Shulman Movement Disorders Centre and the Edmond J Safra Program in Parkinson's disease, Toronto western Hospital, University of Toronto, Toronto, Ontario, Canada

^d Division of Neurology, University of Toronto, Toronto, Ontario, Canada



ARTICLE INFO

Keywords:

Brain tissue pulsatility
Parkinson's disease
White matter
Vascular risk factors
Blood oxygenation level dependent MRI

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

* Corresponding author at: Department of Medical Biophysics, University of Toronto, Sunnybrook Research Institute, 2075 Bayview Avenue, M6-168 Toronto, ON, Canada.

E-mail address: zahra.shirzadi@mail.utoronto.ca (Z. Shirzadi).

<https://doi.org/10.1016/j.nicl.2018.07.017>

Received 8 February 2018; Received in revised form 5 June 2018; Accepted 21 July 2018

Available online 23 July 2018

2213-1582/ © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 enrollment. 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 × 1 × 1 mm³; 2) resting state BOLD images: TE = 25 ms, TR = 2400 ms, flip angle = 80°, voxel size = 3.25 × 3.25 × 3.25 mm³ 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 × 0.9 × 3 mm³; and 4) diffusion tensor images: TE = 88 ms, TR = 900 ms, voxel size = 2 × 2 × 2 mm³, number of directions = 64, b = 1000 s/mm² 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

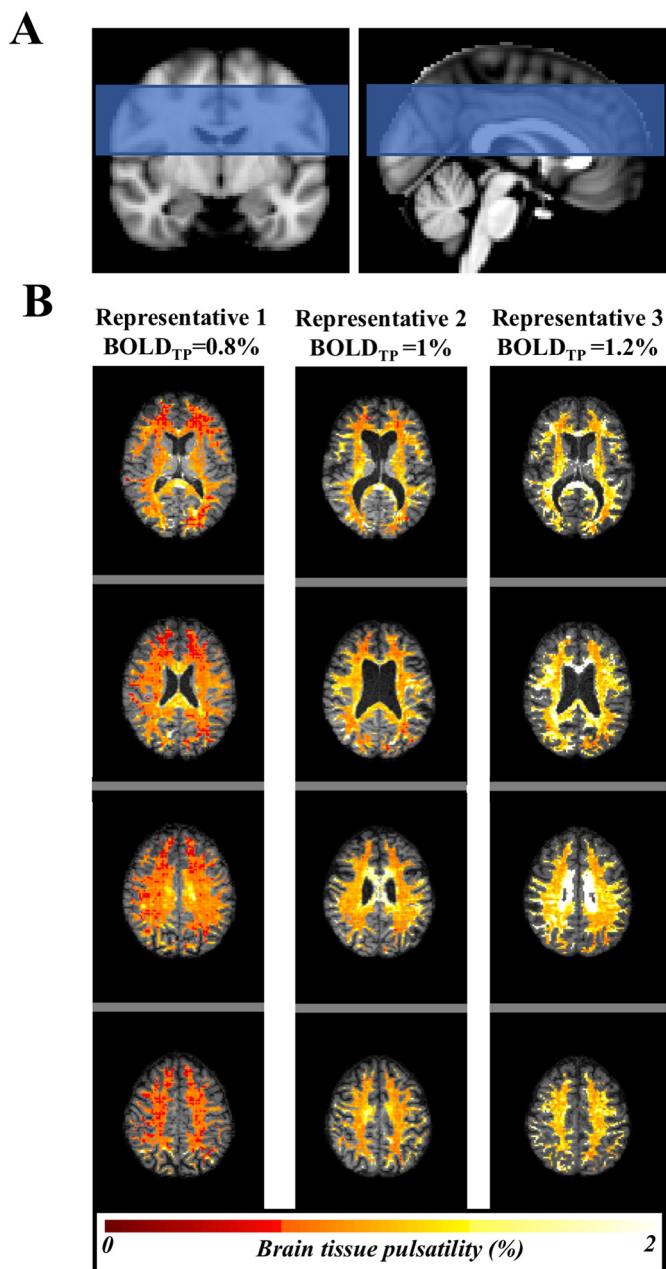


Fig. 1. A) Coronal and sagittal views to demonstrate the white matter volume of interest in Montreal Neurological Institute template space (MNI152; 2 mm). B) Representative brain tissue pulsatility maps. BOLD_{TP} is indicated in each case.

burden model consisted of: body mass index, supine pulse pressure and the diagnosis of cardiovascular risk factors indicated above. Factor analysis (R library: nFactors) extracted latent factors of cognitive and vascular features in two separate models. Scree tests determined the number of factors to retain. Linear regression model assessed the relationship between BOLD_{TP} as the dependent variable and age, sex, MDS-UPDRS3, composite cognitive score, vascular risk burden, PD duration and global head motion as independent variables. To test the effect of brain volume on BOLD_{TP}, we added brain volume to the above-mentioned model secondarily. We also used bivariate correlation to examine whether motor impairment is related to more severe head motion. To investigate different motor phenotypes of PD, we assessed the association of BOLD_{TP} with PIGD and tremor subscores using bivariate correlations.

We performed bivariate correlations between each of the following

variables: BOLD_{TP}, WMH volume and WM-FA. In a subgroup of individuals that also underwent DATSCAN™ at the same visit as MRI, we performed bivariate correlations between SBR and WM measures (BOLD_{TP}, WMH volume, WM-FA). Linear regression examined the relationship of PD neurological symptoms (dependent variable) with BOLD_{TP} and SBR (independent variables).

3. Results

BOLD data were available for 86 people with PD. Five participants were excluded due to excessive global head motion (> 2 mm). Therefore, 81 adults with PD were included in this analysis. Age ranged from 38 to 78 years (mean = 61; SD = 10.6), the sample was predominantly male (56 out of 81 participants) and disease duration ranged from 1 to 50 months (mean = 20; SD = 11.5). Montreal Cognitive Assessment scores (MoCA) ranged from 15 to 30 (mean = 26.7; SD = 2.9). MDS-UPDRS3 ranged from 6 to 51 (mean = 20.3; SD = 10.8), the PIGD subscore ranged from 0 to 1.2 (mean = 0.27; SD = 0.23) and the tremor subscore ranged from 0 to 2.2 (mean = 0.57; SD = 0.46). Approximately 50% of participants had at least one cardiovascular risk factor (42 out of 81). The BOLD_{TP} values ranged from 0.8 to 1.47 (mean = 1.04; SD = 0.13). Fig. 1B shows representative BOLD_{TP} maps from three individuals. Global head motion estimates ranged from 0.2 to 1.9 mm (mean = 0.81; SD = 0.45). Brain volume ranged from 1809 to 2378 cm³ (mean = 2130; SD = 91.5).

The Scree test revealed one factor was sufficient to describe the latent cognitive state. This factor explained 43% of the overall variance (Table 1). One factor was also sufficient for the vascular risk model, which explained 21% of the overall variance (Table 2). The regression model revealed that MDS-UPDRS3 ($t = 2.3$; $p = .02$), vascular risk burden (2.4 ; $p = .02$), male sex ($t = 3.0$; $p = .003$) and global head motion ($t = 3.2$, $p = .001$), but not age, cognition and PD duration ($p > .7$) were associated with BOLD_{TP} (model $r^2 = 0.4$, $p < .0001$). Including brain volume in this model did not change the relationship of BOLD_{TP} with MDS-UPDRS3, vascular risk burden, sex nor head motion, as each of these independent variables remained significant ($p < .05$), while brain volume parameter estimate was not ($p > .1$). We did not observe significant correlation between MDS-UPDRS3 and global head motion ($N = 81$; $p > .14$). Supplementary Fig. 1 shows the scatter plot of global head motion vs. MDS-UPDRS3 for the whole sample. However, we observed a significant correlation between BOLD_{TP} and PIGD ($r = 0.21$, $p = .05$), while there was no correlation between BOLD_{TP} and tremor subscore ($p = .4$), meaning that people with higher postural instability and gait difficulty had elevated BOLD_{TP}.

WMH volumes ranged from 0.016 to 2.12 cm³ (mean = 0.32; SD = 0.37). WMH volume was log-transformed to reduce skewness. BOLD_{TP} and WMH volume was significantly correlated ($r = 0.22$, $p = .05$; Table 3). WM-FA ranged from 0.42 to 0.55 (mean = 0.48; SD = 0.02) and was correlated with WMH volume ($r = -0.35$; $p = .002$) but not BOLD_{TP} (Table 3).

In the subgroup of 52 people with corresponding DATSCAN™, SBR values ranged from 0.17 to 1.95 (mean = 1.2; SD = 0.38). SBR was not correlated with BOLD_{TP}, WMH volume or WM-FA (Table 3; $p > .3$). Linear regression showed that BOLD_{TP} ($t = 2.76$, $p = .008$) and SBR ($t = -2.04$, $p = .04$) independently contributed to between subject

Table 1
Correlation of composite cognitive score and individual cognitive tests.

	Correlation coefficients
Hopkins verbal learning test	0.72 _*
Benton judgment of line orientation	0.28 _*
Semantic fluency	0.63 _*
Letter number sequencing	0.72 _*
Symbol digit modalities	0.97 _*

* $p < .01$.

Table 2
Correlation of vascular risk burden with individual clinical variables.

	Correlation coefficients
Body mass index	0.69 _z
Pulse pressure	0.42 _z
Hypertension	0.45 _z
Hypercholesterolemia	0.69 _z
Hyperglycemia/Diabetes	0.68 _z
Prior cardiovascular disease	0.46 _z

* $p < .01$.

Table 3
Bivariate correlation coefficients among WM metrics and SBR.

	WMH	WM-FA	SBR [#]
BOLD _{TP}	0.22*	−0.18	0.07
WMH	–	−0.35*	−0.14
WM-FA		–	0.11

BOLD_{TP}: BOLD tissue pulsatility / WMH: white matter hyperintensity volume / WM-FA: white matter fractional anisotropy / SBR: striatal binding ratio.

* $p < .05$.

[#] $n = 52$.

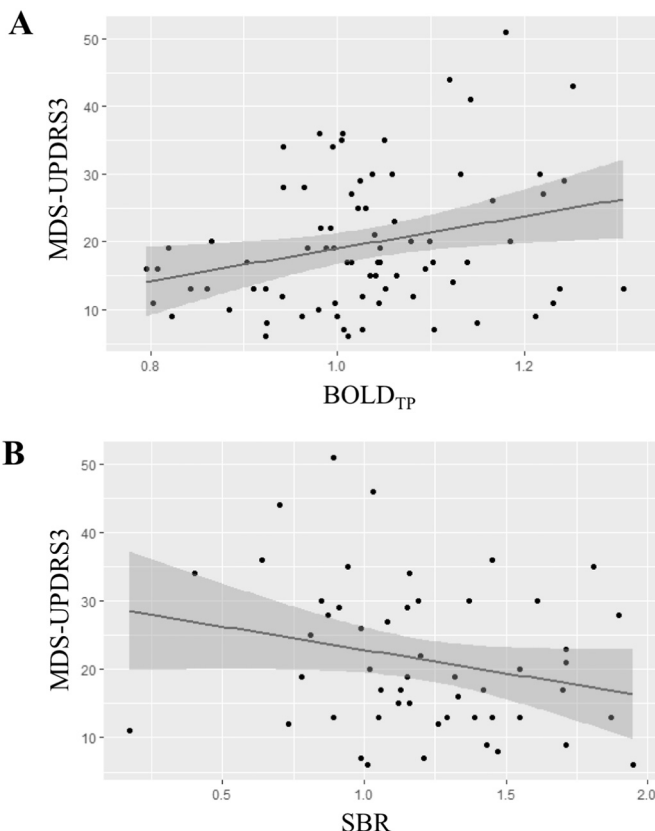


Fig. 2. Motor performance (MDS-UPDRS3) with respect to A) brain tissue pulsatility (BOLD_{TP}) ($t = 2.76$, $p = .008$) and B) striatal binding ratio (SBR) ($t = -2.04$, $p = .04$).

differences in MDS-UPDRS3 (model $r^2 = 0.18$, $p = .006$). Fig. 2A and B illustrate MDS-UPDRS3 with respect to BOLD_{TP} and SBR, respectively.

4. Discussion

This study demonstrates that brain tissue pulsatility, extracted from dynamic BOLD signal in WM, is related to neurological and vascular features in PD. In support of the primary hypothesis, BOLD_{TP} was

directly related to MDS-UPDRS3 and PIGD. Interestingly, BOLD_{TP} was not directly related to SBR, yet both measures independently contributed to motor dysfunction, reinforcing the comorbid influence of CSVD in PD.

BOLD_{TP}, independent of SBR, was related to motor performance which is in agreement with a previous study that showed microvascular damage is related to motor dysfunction (Buchman et al., 2013). Microvascular pulsatility contributes to motor dysfunction through the following possible mechanisms: 1) small vessel damage within sub-cortical substantia nigra and/or striatal regions that may lead to more severe parkinsonism; and 2) disruption of small vessel function involving the WM may disrupt the corticostriatal–thalamocortical loops and interhemispheric connections of corpus callosum which are essential for motor functions (Bohnen and Albin, 2011). In contrast to the association with motor dysfunction, BOLD_{TP} was not related to global cognition. This lack of association may be due to a relatively preserved cognitive function for this group, as reflected by the narrow range of MoCA scores and is consistent with the early stages of PD (Lin and Wu, 2015).

BOLD_{TP} was associated with vascular risk burden, in agreement with previous reports of the impact of vascular risk factors on cerebral hemodynamics (MacIntosh et al., 2015; Cooper and Mitchell, 2016). Since vascular risk burden was strongly correlated with vascular health measures, we conclude that BOLD_{TP} was associated with pulse pressure, body mass index and the presence of vascular risk factors e.g., hypertension. These results are in line with studies that show vascular risk factors are associated with higher risk of CSVD (Wardlaw et al., 2014). Previous researchers showed that increased aortic stiffness and morphological changes to small vessels are associated with CSVD (Webb et al., 2012; Pantoni, 2010). Arterial stiffness increases pulsatile energy transmitted into cerebral circulation. The increased vascular rigidity and higher resistance are thought to develop in response to increased pulsatility (Raignault et al., 2017), thus making the surrounding tissue more susceptible to ischemic lesions (Cooper et al., 2016). Deep brain structures such as WM and basal ganglia are more susceptible to this phenomenon since they are perfused by short, penetrating arterioles with minimal damping ability to dampen the high input pressure (Bohnen and Albin, 2011).

Previously, we found that BOLD_{TP} was lower within the WMH compared to normal appearing WM (Makedonov et al., 2013) which might relate to reduced vascular density as reported in (Brown et al., 2007); however, BOLD_{TP}, i.e., pulsatility in normal appearing WM, was related to WMH volume suggesting that people with higher burden of CSVD have higher BOLD_{TP} (Makedonov et al., 2013) and the direction of this association is consistent with the findings in the current study. Others have also reported on the association between WMH volume and WM-FA (Jolly et al., 2013; Maillard et al., 2017), suggesting the presence of pathological processes involving demyelination and axonal loss in WMH (Wardlaw et al., 2015). Previous studies showed that WM-FA is associated with arterial pulsatility (Jolly et al., 2013) and aortic stiffness (Maillard et al., 2017). We, however, did not find an association between WM-FA and BOLD_{TP}. One possible reason is that BOLD_{TP} represents microvascular pulsatility while these studies measured pulsatility of large vessels. Further research is needed to examine BOLD_{TP} in relation to large vessel pulsatility, such as using transcranial Doppler ultrasound to study intracranial arteries as conduits for pulsatility or other MRI techniques like multi-shell diffusion tensor imaging that attempt to separate bulk water from WM signals (Baykara et al., 2016).

This study has some limitations. First is the absence of a control group; therefore, we are unable to comment on whether BOLD_{TP} is increased in PD relative to healthy controls. To date, there are insufficient PPMI controls ($n = 17$) to warrant such analysis. Second, the BOLD acquisition had a temporal resolution of 2400 ms. Consequently, it is not possible to resolve cardiac from respiratory physiological sources and a proportion of BOLD_{TP} variance may be due to respiratory signals (Bright et al., 2014). Recording these physiological traces would

allow the separation of these sources during post-processing (Theyers et al., 2018), but these data were not available. Third, the vascular risk factor explained only a modest amount of variance for the vascular model, but this factor nonetheless was highly correlated with the model variables and found to increase in direct association with BOLD_{TP}, which was in line with our hypothesis.

Finally, in addition to physiological sources, there are other sources of temporal variability in BOLD signal, namely thermal noise and head motion, which we attempted to account for in the BOLD_{TP} analyses. Although BOLD_{TP} was related to global head motion as we observed before (Makedonov et al., 2016), we did not find a significant relationship between motor impairment and head motion, suggesting that the relationship of BOLD_{TP} and motor impairment was not contaminated by head motion. We also excluded excessive head motion individuals from the outset of the analysis, which is in line with fMRI convention. As illustrated in Supplementary Fig. 1, however, excessive head motion was not related to motor symptom severity in this cohort.

In summary, this study demonstrated that BOLD based brain tissue pulsatility explains PD symptom heterogeneity, independent of dopaminergic deficits. BOLD_{TP} was not only related to vascular risk burden but also was associated with neurological features of PD, notably motor dysfunction. BOLD_{TP} may be an adjunctive neuroimaging measure that can explain PD symptoms, in particular features that relate to small vessel alterations.

Financial disclosure/conflict of interest

We do not have any conflict of interest related to the subject of this study.

Funding sources for study

This study is supported by the Parkinson's Society of Canada and the University of Toronto. The funding sources had no involvement in the study design, data analysis and interpretation or writing of this manuscript.

Acknowledgment

We would like to acknowledge PPMI – a public-private partnership – which is funded by the Michael J. Fox Foundation for Parkinson's Research funding partners: Abbvie, Avid Radiopharmaceuticals, Biogen Idec, BioLegend, Bristol-Myers Squibb, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale Discovery, Piramal, Pfizer, Sanofi Genzyme, Servier, Takeda, Teva, and UCB.

We also want to thank Melissa Holmes, Christopher Scott and Dr. Joel Ramirez for their help in white matter hyperintensity segmentation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.07.017>.

References

- Adler, C.H., Beach, T.G., Hentz, J.G., Shill, H.A., Caviness, J.N., Driver-Dunckley, E., Sabbagh, M.N., Sue, L.I., Jacobson, S.A., Belden, C.M., Dugger, B.N., 2014. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. *Neurology* 83, 406–412. <https://doi.org/10.1212/WNL.0000000000000641>.
- Alves, G., Larsen, J.P., Emre, M., Wentzel-Larsen, T., Aarsland, D., 2006. Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Mov. Disord.* 21, 1123–1130. <https://doi.org/10.1002/mds.20897>.
- Antonini, A., Barone, P., Marconi, R., Morgante, L., Zappulla, S., Pontieri, F.E., Ramat, S., Ceravolo, M.G., Meo, G., Ciccarelli, G., Pederzoli, M., Manfredi, M., Ceravolo, R., Mucchiut, M., Volpe, G., Abbruzese, G., Bottacchi, E., Bartolomei, L., Ciacci, G., Cannas, A., Randisi, M.G., Petrone, A., Baratti, M., Toni, V., Cossu, G., Del Dotto, P., Bentivoglio, A.R., Abrignani, M., Scala, R., Pennisi, F., Quatrate, R., Gaglio, R.M., Nicoletti, A., Perini, M., Avarello, T., Pisani, A., Scaglioni, A., Martinelli, P.E., Iemolo, F., Ferigo, L., Simone, P., Soliveri, P., Troianiello, B., Consioli, D., Mauro, A., Lopiano, L., Nastasi, G., Colosimo, C., 2012. The progression of non-motor symptoms in Parkinson's disease and their contribution to motor disability and quality of life. *J. Neurol.* 259, 2621–2631. <https://doi.org/10.1007/s00415-012-6557-8>.
- Baezner, H., Blahak, C., Poggesi, A., Pantoni, L., Inzitari, D., Chabriat, H., Erkinjuntti, T., Fazekas, F., Ferro, J.M., Langhorne, P., O'Brien, J., Scheltens, P., Visser, M.C., Wahlund, L.O., Waldemar, G., Wallin, A., Hennerici, M.G., LADIS Study Group, 2008. Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology* 70, 935–942. <https://doi.org/10.1212/01.wnl.0000305959.46197.e6>.
- Baykara, E., Gesierich, B., Adam, R., Tuladhar, A.M., Biesbroek, J.M., Koek, H.L., Ropele, S., Jouvent, E., Chabriat, H., Ertl-Wagner, B., Ewers, M., Schmidt, R., de Leeuw, F.-E., Biessels, G.J., Dichgans, M., Duering, M., Duering, M., 2016. A novel imaging marker for small vessel disease based on Skeletonization of white matter tracts and diffusion histograms. *Ann. Neurol.* 80, 581–592. <https://doi.org/10.1002/ana.24758>.
- Bohnen, N.I., Albin, R.L., 2011. White matter lesions in Parkinson disease. *Nat. Rev. Neurol.* 7, 229–236. <https://doi.org/10.1038/nrneuro.2011.21>.
- Bright, M.G., Bianciardi, M., de Zwart, J.A., Murphy, K., Duyn, J.H., 2014. Early anti-correlated BOLD signal changes of physiologic origin. *NeuroImage* 87, 287–296. <https://doi.org/10.1016/j.neuroimage.2013.10.055>.
- Brown, W.R., Moody, D.M., Thore, C.R., Challa, V.R., Anstrom, J.A., 2007. Vascular dementia in leukoaraiosis may be a consequence of capillary loss not only in the lesions, but in normal-appearing white matter and cortex as well. *J. Neurol. Sci.* 257, 62–66. <https://doi.org/10.1016/j.jns.2007.01.015>.
- Buchman, A.S., Yu, L., Boyle, P.A., Levine, S.R., Nag, S., Schneider, J.A., Bennett, D.A., 2013. Microvascular brain pathology and late-life motor impairment. *Neurology* 80, 712–718. <https://doi.org/10.1212/WNL.0b013e3182825116>.
- Cooper, L.L., Mitchell, G.F., 2016. Aortic stiffness, cerebrovascular dysfunction, and memory. *Pulse* 4, 69–77. <https://doi.org/10.1159/000448176>.
- Cooper, L.L., Woodard, T., Sigurdsson, S., van Buchem, M.A., Torjesen, A.A., Inker, L.A., Aspelund, T., Eiriksdottir, G., Harris, T.B., Gudnason, V., Launer, L.J., Mitchell, G.F., 2016. Cerebrovascular damage mediates relations between aortic stiffness and MemoryNovelty and significance. *Hypertension* 67, 176–182. <https://doi.org/10.1161/HYPERTENSIONAHA.115.06398>.
- Gunning-Dixon, F.M., Raz, N., 2000. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology* 14, 224–232. <http://www.ncbi.nlm.nih.gov/pubmed/10791862>.
- M. Jenkinson, C.F. Beckmann, T.E.J. Behrens, M.W. Woolrich, S.M. Smith, FSL, *NeuroImage*. 62 (2012) 782–790. doi:<https://doi.org/10.1016/j.neuroimage.2011.09.015>.
- Jolly, T.A.D., Bateman, G.A., Levi, C.R., Parsons, M.W., Michie, P.T., Karayanidis, F., 2013. Early detection of microstructural white matter changes associated with arterial pulsatility. *Front. Hum. Neurosci.* 7, 782. <https://doi.org/10.3389/fnhum.2013.00782>.
- Lee, S.-J., Kim, J.-S., Lee, K.-S., An, J.-Y., Kim, W., Kim, Y.-I., Kim, B.-S., Jung, S.-L., 2009. The severity of leukoaraiosis correlates with the clinical phenotype of Parkinson's disease. *Arch. Gerontol. Geriatr.* 49, 255–259. <https://doi.org/10.1016/j.archger.2008.09.005>.
- Lin, C.-H., Wu, R.-M., 2015. Biomarkers of cognitive decline in Parkinson's disease. *Parkinsonism Relat. Disord.* 21, 431–443. <https://doi.org/10.1016/j.parkreldis.2015.02.010>.
- MacIntosh, B.J., Swardfager, W., Robertson, A.D., Tchistiakova, E., Saleem, M., Oh, P.I., Herrmann, N., Stefanovic, B., Lanctot, K.L., 2015. Regional Cerebral Arterial Transit Time Hemodynamics Correlate with Vascular Risk Factors and Cognitive Function in Men with Coronary Artery Disease. pp. 1–7.
- Maillard, P., Mitchell, G.F., Himali, J.J., Beiser, A., Fletcher, E., Tsao, C.W., Pase, M.P., Satizabal, C.L., Vasan, R.S., Seshadri, S., Decarli, C., 2017. Aortic stiffness, increased white matter free water, and altered microstructural integrity. *Stroke* 48, 1567–1573. <https://doi.org/10.1161/STROKEAHA.116.016321>.
- Makedonov, I., Black, S.E., MacIntosh, B.J., 2013. BOLD fMRI in the white matter as a marker of aging and small vessel disease. *PLoS One* 8, 1–9. <https://doi.org/10.1371/journal.pone.0067652>.
- Makedonov, I., Chen, J.J., Masellis, M., MacIntosh, B.J., 2016. Alzheimer's disease neuroimaging initiative, physiological fluctuations in white matter are increased in Alzheimer's disease and correlate with neuroimaging and cognitive biomarkers. *Neurobiol. Aging* 37, 12–18. <https://doi.org/10.1016/j.neurobiolaging.2015.09.010>.
- Malek, N., Lawton, M.A., Swallow, D.M.A., Grosset, K.A., Marrinan, S.L., Bajaj, N., Barker, R.A., Burn, D.J., Hardy, J., Morris, H.R., Williams, N.M., Wood, N., Ben-Shlomo, Y., Grosset, D.G., 2016. PROBaND clinical consortium, vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease. *Mov. Disord.* 31, 1518–1526. <https://doi.org/10.1002/mds.26698>.
- Mitchell, G.F., van Buchem, M.A., Sigurdsson, S., Gotlib, I.H., Jonsdottir, M.K., Kjartansson, O., Garcia, M., Aspelund, T., Harris, T.B., Gudnason, V., Launer, L.J., 2011. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the age, gene/environment susceptibility – Reykjavik study. *Brain* 134, 3398–3407. <https://doi.org/10.1093/brain/awr253>.
- O'Rourke, M.F., Hashimoto, J., 2007. Mechanical factors in arterial aging. A clinical perspective. *J. Am. Coll. Cardiol.* 50, 1–13. <https://doi.org/10.1016/j.jacc.2006.12.050>.
- Pantoni, L., 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* 9, 689–701. [https://doi.org/10.1016/S1474-4422\(10\)70104-6](https://doi.org/10.1016/S1474-4422(10)70104-6).
- Raignault, A., Bolduc, V., Lesage, F., Thorin, E., 2017. Pulse pressure-dependent cerebrovascular eNOS regulation in mice. *J. Cereb. Blood Flow Metab.* 37, 413–424.

- <https://doi.org/10.1177/0271678X16629155>.
- Ramirez, J., Scott, C.J.M., McNeely, A.A., Berezuk, C., Gao, F., Szilagyi, G.M., Black, S.E., 2014. Lesion Explorer: a video-guided, standardized protocol for accurate and reliable MRI-derived volumetrics in Alzheimer's disease and normal elderly. *J. Vis. Exp.* <https://doi.org/10.3791/50887>.
- Schapira, A.H.V., Tolosa, E., 2010. Molecular and clinical prodrome of Parkinson disease: implications for treatment. *Nat. Rev. Neurol.* 6, 309–317. <https://doi.org/10.1038/nrneurol.2010.52>.
- Seto, E., Sela, G., McIlroy, W.E., Black, S.E., Staines, W.R., Bronskill, M.J., McIntosh, A.R., Graham, S.J., 2001. Quantifying head motion associated with motor tasks used in fMRI. *NeuroImage* 14, 284–297. <https://doi.org/10.1006/nimg.2001.0829>.
- Stebbins, G.T., Goetz, C.G., Burn, D.J., Jankovic, J., Khoo, T.K., Tilley, B.C., 2013. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov. Disord.* 28, 668–670. <https://doi.org/10.1002/mds.25383>.
- Theyers, A.E., Goldstein, B.I., Metcalfe, A.W., Robertson, A.D., MacIntosh, B.J., 2018. Cerebrovascular blood oxygenation level dependent pulsatility at baseline and following acute exercise among healthy adolescents. *J. Cereb. Blood Flow Metab.* <https://doi.org/10.1177/0271678X18766771>. 271678X18766771.
- J.M. Wardlaw, M. Allerhand, F.N. Doubal, Z. Morris, A.J. Gow, M.E. Bastin, J.M. Starr, M. S. Dennis, Vascular risk factors, large-artery atheroma, and brain white matter hyperintensities, *Neurology* 82 (2014) 1331–1338. doi:<https://doi.org/10.1212/WNL.0000000000000312>.
- Wardlaw, J.M., Valdés Hernández, M.C., Muñoz-Maniega, S., 2015. What are white matter Hyperintensities made of? Relevance to vascular cognitive impairment. *J. Am. Heart Assoc.* 4, e001140. <https://doi.org/10.1161/JAHA.114.001140>.
- Webb, A.J.S., Simoni, M., Mazzucco, S., Kuker, W., Schulz, U., Rothwell, P.M., 2012. Increased cerebral arterial Pulsatility in patients with Leukoaraiosis: arterial stiffness enhances transmission of aortic Pulsatility. *Stroke* 43, 2631–2636. <https://doi.org/10.1161/STROKEAHA.112.655837>.
- Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and Anticorrelated brain networks. *Brain Connect.* 2, 125–141. <https://doi.org/10.1089/brain.2012.0073>.