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Optical measures of cerebral arterial stiffness are associated with white matter signal abnormalities and cognitive performance in normal aging

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ABSTRACT

Decline in fluid abilities in normal aging is associated with increased white matter lesions, measured on T1-weighted images as white matter signal abnormalities (WMSAs). WMSAs are particularly evident in hypertensive older adults, suggesting vascular involvement. However, because hypertension is assessed systemically, the specific role of cerebral arterial stiffening in WMSAs has yet to be demonstrated. In 93 cognitively normal adults (aged 18–87 years), we used a novel method to measure cerebral arterial elasticity (pulse relaxation function [PReFx]) with diffuse optical tomography (pulse-DOT) and investigated its association with WMSAs, age, and cognition. PReFx was associated with WMSAs, with older adults with low PReFx showing the greatest WMSA burden. PReFx in brain regions perfused by the middle cerebral artery showed the largest associations with WMSAs and partially mediated the relationship between age and WMSAs. Finally, WMSAs partially mediated the relationship between PReFx and fluid but not crystallized abilities scores. Taken together, these findings suggest that loss of cerebral arterial elasticity is associated with cerebral white matter lesions and age-related cognitive decline.

1. Introduction

Normal aging is often accompanied by decreases in cognitive functions (Fabiani, 2012; Park and Reuter-Lorenz, 2009; Salthouse, 2010). Associations have been found between age-related cognitive declines and white matter lesion burden (e.g., DeCarli et al., 1995; Leaper et al., 2001; Rabbitt et al., 2007; Raz et al., 2007). This age-related white matter degradation manifests as white matter signal abnormalities (WMSAs), which appear as hypointensities on T1-weighted magnetic resonance images (MRIs) and hyperintensities on T2-weighted images (Brickman et al., 2011; Debette and Markus, 2010; Wardlaw et al., 2015). Clinical and pathophysiological data suggest that greater WMSA volume is associated with chronic hypoperfusion and/or lacunar lesions (Behrouz et al., 2012; Pantoni and Simoni, 2003; VanDijk et al., 2008), which may be the consequence of age-related arteriosclerosis (i.e., the hardening of arteries, characterized by a loss of their elastic properties).

Studies investigating the relationship between arterial stiffness and WMSAs typically assess pulse pressure (i.e., the difference between systolic and diastolic blood pressure, an index of arteriosclerosis) systemically rather than within the brain (e.g., Kennedy and Raz, 2009; Leritz et al., 2014; Salat et al., 2012). As such, a specific link between white matter degeneration and cerebral arterial elasticity is not yet well established. Although Transcranial Doppler ultrasound methods have been used to quantify

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intracranial cerebrovascular function using pulsatility and resistivity indices (see Keage et al., 2012 for a review), they are typically restricted to the insonation of one, or at most a few large arteries, which limits its field of view. A broad field of view is essential to map elasticity across the cortical mantle and investigate its regional effects. Here we used a newly developed measure of the cerebral arterial pulse relaxation function (PReFx, also referred to as arterial compliance in previous papers) obtained throughout the cortex, based on diffuse optical tomography (pulse-DOT; Fabiani et al., 2014b; Chiarelli et al., 2017, 2019; Tan et al., 2016, 2017) to index cerebral arterial elasticity in cognitively normal adults.

In previous research, PReFx averaged across the whole head was found to be negatively associated with age and positively associated with estimated cardiorespiratory fitness, brain volume (cortical gray and white matter and subcortical gray matter), and cognitive flexibility in healthy older adults (Fabiani et al., 2014b; Tan et al., 2017). Recent methodological improvements now allow for the derivation of tomographic regional PReFx measurements in at least 50 (of 70) cerebral cortical regions obtained from FreeSurfer (Chiarelli et al., 2017).

As evidenced by studies investigating age-related changes in glial (e.g., Duncombe et al., 2017; Hutchison et al., 2013) and vascular function (e.g., Ances et al., 2009; Chen et al., 2014; Mohtasib et al., 2012; Restom et al., 2007), the tight link between neural activity and vascular properties (i.e., neurovascular coupling, see Fabiani et al., 2014a) may play important roles in the hemodynamic changes observed in neurocognitive aging studies. Other studies have also established the role of white matter health on cognition in aging (e.g., Charlton et al., 2009; Coxon et al., 2012; Madden et al., 2012; Salami et al., 2012). As such, the primary goal of the present study was to investigate the relationships between cerebral arterial elasticity (measured with PReFx), macrostructural measures of white matter lesions (WMSAs), and cognitive function in healthy, cognitively normal younger and older adults.

Specifically, we hypothesized that cerebral arterial elasticity (measured with PReFx) should be associated with WMSAs, and that these effects should be particularly evident in older adults with low PReFx. We further investigated whether regional PReFx was associated with WMSAs. Finally, we tested whether PReFx mediated the relationship between age and WMSAs and whether WMSAs mediated the relationship between PReFx and fluid intelligence.

2. Methods

Most of the methods and procedures reported here overlap with those reported by Fabiani et al. (2014b) and Tan et al. (2017), so we are including only an abbreviated methods section, as per journal guidelines. Please note that all analyses reported here are new and not previously published.

2.1. Participants

Ninety-three unique adult participants (age range = 18–87 years, mean age = 58.8, 46 females) were included in the present study. These are the same participants included in the studies by Fabiani et al. (2014b) and Tan et al. (2017), but none of the analyses presented here or the combination of both samples was previously published. Supplementary Figure S1 shows the age distribution of this combined sample. Participants were recruited through a mix of advertisements in local newspapers, gyms, retirement homes, and community centers, in addition to campus-wide emails. Sample demographics are summarized in Table 1. Twenty-one participants reported taking blood pressure medications and 17 reported taking cholesterol medications. Six individuals showed signs of hypertension (i.e., >140/90 mmHg) based on sphygmomanometer blood pressure measurements. Note, however, that PReFx measures are normalized (see Methods) by cerebral peak-systole to peak-diastole amplitude (a measure of cerebral pulse pressure, see Tan et al., 2016, 2017). Thus, pulse pressure and PReFx are substantially independent.

Table 1
Demographic characteristics of the participants

Variable	N = 93 mean (SD)
Age (y)	58.8 (17.9)
Education (y)	16.8 (2.5)
mMMSE	55.5 (1.3)
Beck's Depression Index	2.8 (3.4)
PReFx	0.08 (0.02)
WMSAs (log)	3.1 (0.3)
Systolic blood pressure	133.1 (13.2)
Diastolic blood pressure	78.6 (7.9)

Key: mMMSE, modified Mini–Mental Status Examination; PReFx, pulse relaxation function; WMSAs, white matter signal abnormalities.

All participants reported themselves in good health and were free of depression and dementia, as assessed by the Beck's depression inventory (Beck et al., 1996) and the modified Mini–Mental Status Examination (Mayeux et al., 1981). All procedures were approved by the University of Illinois Institutional Review Board.

2.2. Assessment of cognitive function

Participants underwent a battery of neuropsychological tests (see Fabiani et al., 2014b; Tan et al., 2017). To reduce the number of comparisons, using an approach similar to that of Chan et al. (2014), we sorted the neuropsychological scales into 2 different domains, which we labeled "fluid" and "crystallized" abilities, respectively. The fluid abilities domain included the following tests: Raven's matrices (Raven et al., 2003), forward and backward digit span (Mayeux et al., 1981), Operation-Span (O-Span; Altamura et al., 2007), trail A, trail B, and trail B-A (Corrigan and Hinkeldey, 1987). The crystallized abilities domain included Shipley's vocabulary (Shipley, 1940) and a test of verbal fluency (letters CFL, Benton and Hamsher, 1989). For each test, each participant's scores were standardized, and, when needed, their sign was changed so that positive values always indicated a higher-than-average performance and negative values indicated a lower-than-average performance. Then, for each participant, the standardized values for the tests in each domain were averaged together (effectively giving equal weight to each of them). These yielded 2 scores for each individual, a "fluid abilities" score and a "crystallized abilities" score. These scores were used for all further analyses.

2.3. Electrocardiogram acquisition and processing

A Brain-Vision recorder and a Brain-Vision professional BrainAmp integrated amplifier system (Brain Products GmbH, Germany) were used to record Lead I of the electrocardiogram (EKG) (left wrist referenced to right wrist; impedance <20 kOhm; sampling rate = 1000 Hz). EKG data were used for time-locking the optical pulse data to the R-wave, to ensure that the same pulse cycle was measured at all scalp locations.

2.4. Optical recording and analysis

Optical data were acquired using a multichannel frequency domain oximeter (ISS Imagent, Champaign, Illinois) equipped with 128 laser diodes (64 emitting light at 690 nm and 64 at 830 nm) and 24 photomultiplier tubes at a sampling rate of 39.0625 Hz. Time-division multiplexing was used such that each detector picked up light from 16 different sources at different times within a

multiplexing cycle. The light was transported to the scalp with optic fibers (0.4 mm core) and from the scalp back to the detectors using optic fiber bundles (3 mm diameter). Fibers were securely attached using custom-built helmets of varying sizes. A resting-state paradigm (e.g., Eggebrecht et al., 2014) was used during recording. Optical data were recorded for a total of 8 blocks (6 minutes each) using 4 different optical montages (2 blocks, or 12 minutes recording time per montage), with the sequence of 4 montages counterbalanced across subjects. 384 channels (192 at 830 nm and 192 at 690 nm) were acquired for each montage (total = 1536 channels, encompassing most of the scalp surface; source-detector distances = 15–80 mm). These procedures are similar to what was described in Tan et al. (2017) and Fabiani et al. (2014b), with the exception that data from the study by Fabiani et al. (2014b) were based on 384 channels and 72 seconds of recording time. Comparisons between the PReFx values obtained in the 2 studies revealed no significant difference in mean and standard deviation, when participants with overlapping age ranges were considered, lending strong support to the merging of these 2 data sets.

Direct current (DC) optical intensity data were normalized, movement corrected (Chiarelli et al., 2015), and band-pass filtered between 0.5–5 Hz. As cerebral arterial blood is highly (>95%) oxygen saturated, only the 830 nm light intensity data were used for pulse estimation, as this wavelength is more sensitive to oxygenated hemoglobin (Fabiani et al., 2014b). Optical pulse waveforms for each channel were derived by averaging the DC light intensity time-locked to the peak of the EKG R-wave (signaling the depolarization of the ventricular myocardium). Sensitivity to superficial artifacts was reduced by only using channels with interoptode distance >25 mm. Channels with interoptode distance >70 mm were also excluded to increase the signal-to-noise ratio (as light intensity is too low at those distances to be reliable).

3D reconstruction of the pulse waveform was conducted with a model of light propagation within the head (forward model) and an inverse procedure. A Finite Element Method (FEM) applied to the diffusion equation (Ishimaru, 1989; Paulsen and Jiang, 1995) was used to estimate the forward model. The FEM software NIRFAST (Dehghani et al., 2009; Eggebrecht et al., 2014) was used to model light propagation through heterogeneous head models and to compute Jacobian (sensitivity) matrices of DC light intensity reflecting absorption changes. "Fine" meshes (maximum tetrahedral volume = 2 mm^3) were generated for FEM using the MATLAB software iso2mesh (Fang and Boas, 2009). The heterogeneous head models were based on segmented T1-weighted 3D anatomical images. Segmentation of the skull and scalp, cerebrospinal fluid, white matter, and gray matter was performed using Statistical Parametric Mapping (Friston et al., 1994) functions applied to T1-weighted images (Penny et al., 2011). Baseline optical properties (absorption μ_a, reduced scattering coefficient μ_s' and refraction index η) of tissues at the relevant wavelength were taken from the studies by Tian and Liu (2014) and Chiarelli et al. (2016). The optical values at the wavelength of interest (830 nm) were set to scalp and skull: $\mu_a = 0.014\ mm^{-1}$, $\mu_s' = 0.84\ mm^{-1}$; cerebrospinal fluid: $\mu_a = 0.004\ mm^{-1}$, $\mu_s' = 0.3\ mm^{-1}$; gray matter: $\mu_a = 0.019\ mm^{-1}$, $\mu_s' = 0.673\ mm^{-1}$; white matter: $\mu_a = 0.021\ mm^{-1}$, $\mu_s' = 1.01\ mm^{-1}$. The refraction index was set to be equal for all the media considered, at $\eta = 1.4$. An inverse procedure was used to convert intensity changes on individual channels to absorption changes in voxel space (Chiarelli et al., 2016), which allows for an unbiased localization of absorption fluctuations up to a depth of 30 mm from the scalp.

PReFx (Chiarelli et al., 2017; Fabiani et al., 2014b; Tan et al., 2017) is a measure of the shape of the pulse during the interval between a peak systole and peak diastole. It represents the way in which arteries return to their original size after dilating to accommodate the blood bolus generated by a heart pulsation. If this curve is decelerated, the artery can be considered to be elastic, whereas acceleration of this function is an indication of arterial stiffness. As such, arterial elasticity is computed as the area under the pulse waveform during this interval, after subtracting a triangle corresponding to a linear relaxation. To ensure that this measure of elasticity is independent of peak amplitude (which is related to pulse pressure) and heart rate, the values are normalized (setting the peak systole = 1 and peak diastole = 0 and dividing them by the duration of the systole-diastole interval). PReFx was estimated for each voxel in which sensitivity (measured by the average Jacobian) was greater than 1/1000 (60 dB) of the maximum value. This allowed for the exclusion of voxels too deep to provide useful data (approximately >3 cm from the scalp), as well as voxels beyond the coverage of the optical montages. In addition, only voxels within the cortex (as identified by FreeSurfer) were considered. Regional arterial elasticity was computed for 50 of the 70 FreeSurfer regions (25 per hemisphere) because at least 10% of their volume was sampled by the optical montage. The remaining 20 regions (10 per hemisphere) were either too deep or insufficiently covered by the optical montages, preventing reliable measurements. The 50 usable regions (25 per hemisphere) were averaged to compute a measure of global PReFx for each subject. In addition, we computed 3 composite PReFx scores by averaging regions that were expected to be perfused by the anterior, middle, or posterior cerebral artery.

2.4.1. Optodes coregistration with structural MRI

For each participant, optical sources and detectors' locations on the scalp were digitized using a Polhemus "3Space" FASTRAK 3D digitizer (Polhemus, Colchester, VT), with the nasion and preauricular points as references. The Polhemus digitization points were then coregistered with the MR based on procedures described by Chiarelli et al. (2015; see also Whalen et al., 2008).

2.5. MRI acquisition and WMSA volume estimation

Structural images were collected for each participant using a 3T Siemens Trio full body scanner. No other MRI sequences (e.g., T2/FLAIR), which are commonly used for examining WMSAs, were collected. A high-resolution, 3D MPRAGE protocol was used—flip angle = 9°, TE = 2.32 ms, TR = 1900 ms, inversion time = 900 ms, 192 sagittal slices, voxel size 0.9 × 0.9 × 0.9 mm with a field of view of 172.8 × 230 × 230 mm. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer 6.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/; Fischl and Dale, 2000). Estimated total intracranial volume was also extracted from the structural images derived from the same automated procedures in FreeSurfer (Buckner et al., 2004). WMSAs (appearing as hypointense on T1-weighted images) were labeled automatically based on FreeSurfer 6.0's probabilistic procedure (Fischl et al., 2002), and the automatic segmentation was extensively examined for errors, which were corrected following http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData. Intraclass correlations between T1-weighted WMSAs and manually segmented white matter hyperintensities have also been reported to be as high as $r = 0.91$ (Smith et al., 2011). Here, we focused on the overall WMSA volume as an index of white matter lesions, to avoid overinterpreting the T1-weighted hypointensities. WMSA volumes were log-transformed to reduce the skewing of the distribution (e.g., Atwood et al., 2004; Jefferson et al., 2007) and adjusted for sex and estimated total intracranial volume to obtain the final WMSA scores used in the present study.

2.6. Mediation analysis

In 2 simple mediation analyses, we investigated whether PReFx mediated the relationship between age and WMSA and whether

WMSA mediated the relationships between PReFx and scores in the fluid and crystallized domains of cognition. Mediations were performed by using PROCESS model 4 macro in SPSS (R) based on a series of ordinary least square regression models (Hayes, 2013). This analysis was chosen for its directional path approach, which is the best option here, given the limitations of a cross-sectional study. We tested the indirect effect by using a bias-corrected bootstrapping procedure based on 5000 samples, chosen because it is considered the most trustworthy and provides more power, given our relatively small sample size (Hayes and Scharkow, 2013).

3. Results

3.1. Relationships between global PReFx, WMSA, and age

Higher global PReFx was associated with lower WMSA burden ($\beta = -0.16$, SE = 0.03, $p = 7.90 \times 10^{-7}$, Fig. 1). Post hoc power analysis using R package "pwr" showed that the analysis is powered at 99.9%. The Kolmogorov-Smirnov test indicated that the model residuals were normally distributed ($p > 0.05$). Testing for age-associated differences in this relationship, we found a significant age by PReFx interaction ($\beta = -0.05$, SE = 0.02, $p = 0.04$), with older adults showing a significant association ($\beta = -0.11$, SE = 0.04, $p = 0.01$) but not younger adults ($\beta = -0.01$, SE = 0.04, $p > 0.05$, Fig. 2).

3.2. Relationships between regional PReFx, WMSAs, and age

Higher WMSA burden was associated with lower regional PReFx in 24 of the 25 brain regions (average of left and right) identified on the basis of the FreeSurfer atlas, corrected for multiple comparisons at a false discovery rate <0.05. The only region that did not reach statistical significance was the frontal pole. The largest associations were found in the banks of the superior temporal sulcus, supramarginal gyrus, and postcentral and precentral gyrus (Fig. 3, Supplemental Table S1), all areas that are likely perfused by the middle cerebral artery. None of the interactions between age and regional PReFx on WMSA burden reached statistical significance at false discovery rate <0.05.

3.3. Mediating effects of PReFx and WMSAs

We found that global PReFx did not mediate the relationship between age and WMSAs (95% CI: −0.006 - 0.196). However, the composite PReFx from brain regions supplied by the middle cerebral artery partially mediated the relationship between age and WMSAs (95% CI: 0.01 - 0.22, Fig. 4A), meaning that the direct effect (path c'), although significantly reduced in value, remains significant after accounting for the effects of PReFx. Post hoc power analysis using R package "WebPower" showed that this analysis is powered at 91.5%. PReFx computed from brain regions supplied by the anterior and posterior cerebral arteries, however, did not significantly mediate the age-WMSA relationship. For the cognitive function mediation, we found that WMSAs partially mediated the relationship between global PReFx and fluid abilities (95% CI: 0.045 - 0.258, Fig. 4B) such that the direct effect (path c') is reduced but remains significant after accounting for the effects of WMSAs. A post hoc power analysis showed that this analysis is powered at 90.0%. WMSAs did not significantly mediate the relationship between PReFx and crystallized ability scores (95% CI: −0.2213 - 0.017).

4. Discussion

The results presented here support the presence of an association between reduced cerebral arterial elasticity measured with PReFx pulse-DOT in the cortex and the extent of WMSAs in normally aging adults. This relationship was particularly evident for older participants and was not significant in younger adults. Although correlations between systemic indices of arterial status (such as pulse pressure) and WMSA volume have been reported in the literature (Kennedy and Raz, 2009; Leritz et al., 2014; Salat et al., 2012), our results indicate that WMSA volume is also associated with a more direct assessment of the status of the cerebral vasculature. The regional associations between PReFx and WMSAs also suggest that PReFx in regions in the frontal, temporal, and parietal cortices, which are perfused by the middle cerebral artery, are most indicative of the degree of overall WMSA burden.

That said, it should be noted that the PReFx measures were obtained in cortical regions rather than in deep periventricular

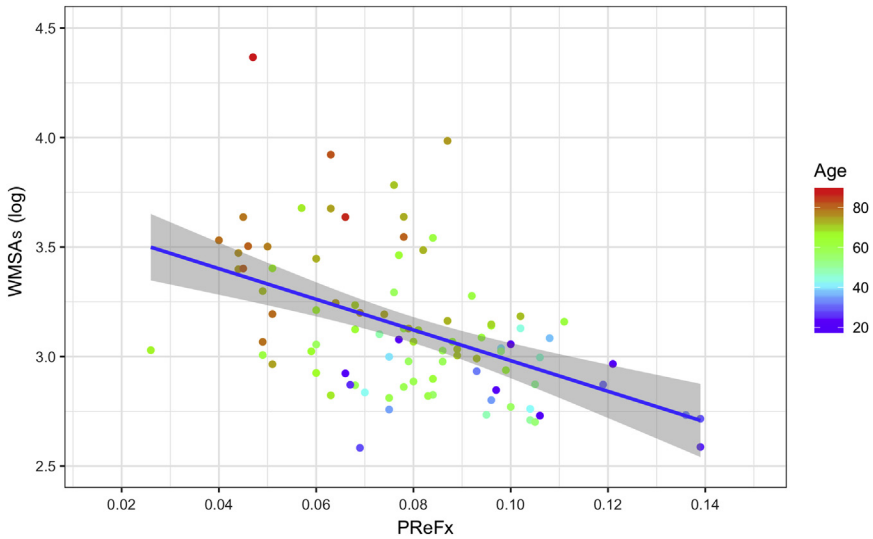

Fig. 1. Scatter plot showing the relationship between arterial elasticity (PReFx, averaged across all cortical regions) and WMSA burden. Color scale reflects the age of the participants. Abbreviations: PReFx, pulse relaxation function; WMSAs, white matter signal abnormalities. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

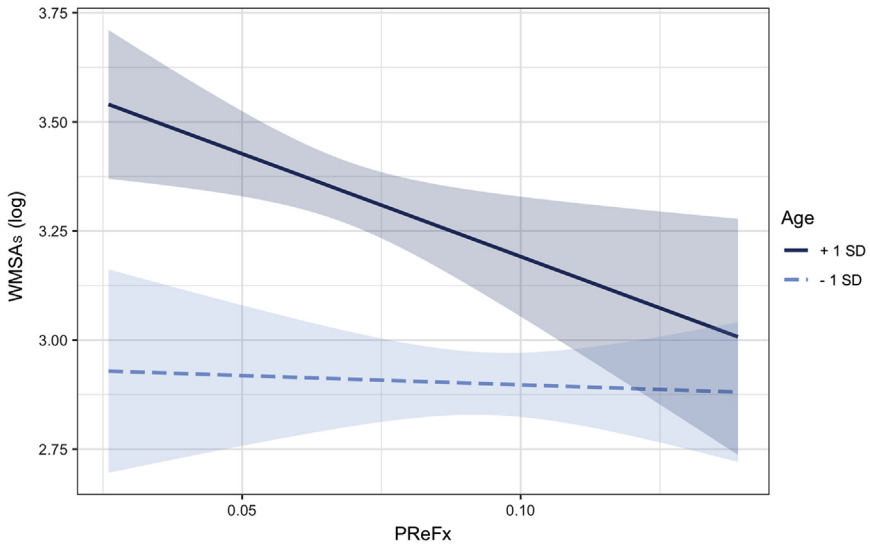

Fig. 2. Interaction between global PReFx and age on WMSAs. Older individuals with low PReFx had the highest amount of WMSA burden. Abbreviations: PReFx, pulse relaxation function; WMSAs, white matter signal abnormalities.

white matter, due to the limited penetration of diffuse optical measures. Although this initial correlational finding would need to be replicated on a much larger sample, to determine the actual sensitivity and specificity of the relationship, the results suggest a strong association between arterial elasticity in the cortex and WMSAs (a possible indication of cerebral small vessel disease [CSVD]; Sachdev et al., 2007; Shi and Wardlaw, 2016). This also suggests that there may be potential value in using pulse-DOT measurements as a screening tool for CSVD. The validity and effectiveness of such screening procedures should be the subject of further larger scale investigations.

The data reported here also suggest that arterial elasticity in regions perfused by the middle cerebral artery likely plays a mediating role in age-related increases in WMSA burden in normal aging. These findings are consistent with the general consensus that the emergence of WMSAs stems from cerebral vascular pathology, which is exacerbated in aging (Salat, 2014), and are also consistent with our regional PReFx results showing that the largest correlations are in temporal and parietal cortices.

We additionally found that WMSA burden partially mediated the relationship between global PReFx and fluid ability but not crystallized ability scores. Although verbal ability, which largely contributes to crystallized intelligence, is relatively preserved in aging, our results suggest that reductions in PReFx may lead to declines in fluid abilities through increases in WMSAs (Baltes and Lindenberger, 1997). Taken together, the mediation analyses suggest that PReFx may reflect a mechanistic chain of events linking arterial dysfunction with white matter damage and cognitive decline. Future research will be needed to further investigate the independent and interacting influences of neural activity and vascular properties on age-related decline in cognitive processing.

The partial mediations found also suggest a role for unexamined variables such as cardiorespiratory fitness, which may influence the effects of both arterial elasticity and WMSA volume (see Cotman, Berchtold & Christie, 2007; Barnes, 2015). These variables could be investigated in larger studies in the future. Future studies may also investigate whether regional PReFx and WMSAs could act as mediators of age-related decline in cognitive function and determine the regional specificity of the mediation results found in the present study.

4.1. Limitations

The findings presented here must be interpreted within the inherently limited depth of penetration of diffuse optical imaging. A

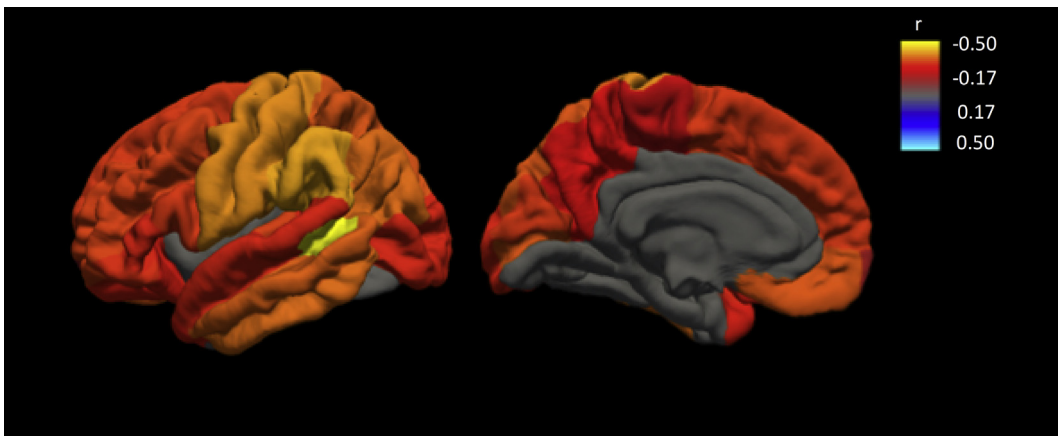

Fig. 3. Associations of regional PReFx with WMSA burden. All associations except the frontal pole were statistically significant after correction for multiple comparisons at FDR <0.05. Abbreviations: FDR, false discovery rate; PReFx, pulse relaxation function; WMSAs, white matter signal abnormalities.

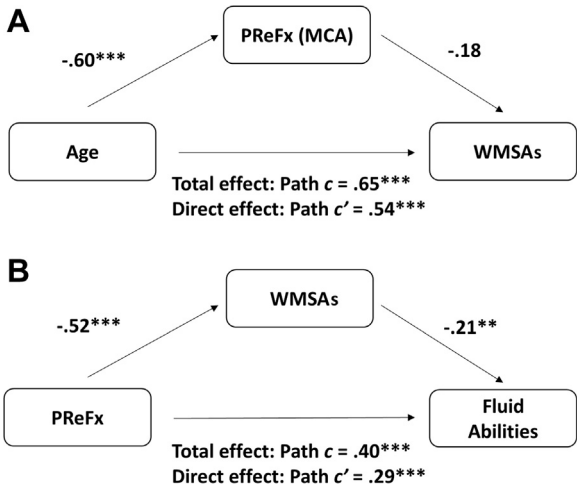

Fig. 4. (A) PReFx from regions perfused by the middle cerebral artery partially mediated the relationship between age and WMSAs. (B) WMSAs partially mediated the relationship between global PReFx and fluid abilities scores. $^{**}p < 0.05$; $^{***}p < 0.01$. Abbreviations: MCA, territory of the middle cerebral artery; PReFx, pulse relaxation function; WMSAs, white matter signal abnormalities.

consequence of this is that the PReFx measures are not taken directly from the periventricular areas where most white matter abnormalities are found. That said, it should be noted that PReFx reflects the speed of propagation of the recoil wave from the periphery (muscular arteries and arterioles providing peripheral resistance) back to the point of measurement (reflected wave, see Izzo and Shykoff, 2001). In other words, PReFx is a measure of arterial function downstream relative to the measurement point, functionally extending the field of view of pulse-DOT. Furthermore, the measurements used in the present study do use recent advancements in 3D reconstruction (Chiarelli et al., 2016), which have increased the effective optical depth penetration to 30–35 mm, and therefore provide the best estimation of cerebral arterial elasticity possible, given the current state of the technology.

The regional measures have limited spatial resolution, which makes it difficult to distinguish the specific arterial collaterals that feed into any specific WMSA cluster. Magnetic resonance angiography may be used to aid the spatial mapping of regional PReFx with the cerebrovasculature. Although newer dynamic arterial spin labeling (ASL) measures for quantifying vascular elasticity, based on changes in cerebral blood volume and arterial pressure, can be extracted from deep structures (Yan et al., 2016), they also suffer from lack of adequate spatial resolution. Furthermore, diffuse optical measures for quantifying arterial elasticity and their association with a host of factors such as age, fitness, and brain volume have been replicated and found to be highly robust (Fabiani et al., 2014b). Whether dynamic ASL methods can serve as a mediator of age-related declines in cognition remains to be tested. In the future, it would be very fruitful to combine ASL, Transcranial Doppler, and/or magnetic resonance angiography with pulse-DOT methods to address some of these spatial specificity issues. There has also not been any systematic study comparing T1-weighted WMSAs with T2/FLAIR white matter hyperintensities, demonstrating that they share the same pathophysiology. Future research using pulse-DOT with both types of measures should explore this issue.

4.2. Summary and conclusions

Despite these limitations, the present study opens up the novel possibility of providing an extensive assessment of global and regional cerebral arterial elasticity, and of using arterial elasticity as a target for intervention. Although vascular risk factors accumulate over the life span, they are amenable to changes by increasing physical activity (e.g., Hawkins et al., 2014) and/or by maintaining healthy dietary practices (e.g., Santos-Parker et al., 2014). A recent review of studies investigating the association between white matter lesions and physical activity concluded that greater physical activity was associated with a lower amount of white matter lesions (Torres et al., 2015; see also; Burzynska et al., 2014; Fletcher et al., 2016; Gordon et al., 2008). This suggests that early interventions may help slow or prevent progressive CSVD from developing and manifesting as WMSAs. This preventive approach is especially important, given the general consensus that lesions in the white matter are nonreversible, although revascularization surgery may help (Komatsu et al., 2016). Therefore, in addition to using WMSAs as an indirect marker of CSVD severity (Sachdev et al., 2007), measures of arterial elasticity may also be useful as an early risk-screening tool in cognitively normal individuals, for selective intervention before the onset of widespread WMSAs.

Disclosure

The authors declare no actual or potential conflicts of interest. The views expressed in this paper are solely those of the authors, and all authors have approved this manuscript.

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Appendix A. Supplementary data

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