Physiological fluctuations in white matter are increased in Alzheimer's disease and correlate with neuroimaging and cognitive biomarkers

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Abstract

The objective of this study was to determine whether physiological fluctuations in white matter (PFwm) on resting state functional magnetic resonance images (rs-fMRI) could be used as an index of neurodegeneration and Alzheimer's disease (AD). Using rs-fMRI data from participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI), PFwm was compared across cohorts: cognitively healthy, mild cognitive impairment (MCI), or probable AD. Secondary regression analyses were conducted between PFwm and neuroimaging, cognitive and cerebrospinal fluid (CSF) biomarkers. There was an effect of cohort on PFwm ($t=5.08$, $df=424$, $p<5.7e-7$), after accounting for nuisance effects from head displacement and global signal ($t>6.16$). From the neuroimaging data, PFwm was associated with glucose metabolism ($t=-2.93$, $df=96$, $p=0.004$), but not ventricular volume ($p<0.49$) or hippocampal volume ($p>0.44$). From the cognitive data, PFwm was associated with composite memory ($t=-3.24$ [$df=149$], $p=0.0015$) but not executive function ($p>0.21$). PFwm was not associated with CSF biomarkers. In one final omnibus model to explain PFwm ($N=124$), glucose metabolism ($p=0.04$) and cohort ($p=0.008$) remained significant, as were global and head motion RMS terms, whereas memory was not ($p=0.64$). PFwm likely reflects end-arteriole intracranial pulsatility effects that may provide additional diagnostic potential in the context of AD neurodegeneration.

Keywords: Alzheimer's disease; neurodegeneration; physiological noise; pulsatility; resting state functional MRI; white matter.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized by progressive cognitive dysfunction that interferes with daily activities and results in significant morbidity. Mild cognitive impairment (MCI) is considered the prodromal stage of Alzheimer's dementia that can predate AD by several years ^{1,2}. Although the MCI period provides a potential intervention window, there are no established treatments. Furthermore the MCI classification is increasingly viewed as heterogeneous since not all MCI individuals convert to AD ^{3,4}.

AD-related progression is influenced by multiple pathophysiological changes, notably amyloid deposition ^{5,6} cerebral amyloid angiopathy⁷, and new evidence of AD pathogenesis within pericytes ⁸. Increasingly, cerebrovascular techniques are used to characterize small vessel disease phenomena that contribute to neurodegeneration ⁹. Central and cerebral hemodynamic measures, such as arterial stiffening, carotid artery stiffening and cerebral blood flow are predictors of cognitive performance¹⁰, cognitive decline¹¹ and AD diagnosis^{12,13}. Work by others provides support for the theory of mechanical factors of arterial aging ¹⁴, which leads to excessive intracranial pulsatility (described as windkessel dysfunction) in normal and demented older adult cohorts ^{15,16}.

In the current study we use a summary measure of physiological noise in white matter, which we reported on previously in a group with small vessel disease ¹⁷, to serve as a proxy index of cerebrovascular dysfunction, whereby elevated arterial pulsatility contributes to increased image temporal variance observed in white matter on resting state functional MRI (rs-fMRI). Rs-fMRI has traditionally been used in AD to study grey matter functional connectivity, such as reported decreased co-activation of default mode network ¹⁸. Whereas white matter rs-fMRI signals are viewed as nuisance variables in grey matter connectivity analyses ^{19,20}, they

also provide non-neuronal physiological contrast, due to: cardiac pulsatility^{17,21,22}, vasomotion in ischemia²³, and cerebrovascular impairment²⁴. To date there are but a few rs-fMRI studies that specifically investigate white matter^{17,25}, therefore our primary objective is to compare PFwm among normal older controls, MCI and AD groups. We hypothesize that there will be an effect of group on PFwm from among other factors that can influence this rs-fMRI summary measure. Our secondary objective was to determine whether PFwm was associated with any established markers of AD pathology and/or neurodegeneration. For this secondary objective, neuroimaging, cognitive and cerebrospinal fluid (CSF) data are considered. For neuroimaging markers, we used glucose metabolism, ventricular volume and hippocampal volume. The former reflects altered bioenergetics reported in AD²⁶, whereas the latter two are structural markers of neurodegeneration and AD^{27,28}. For the cognitive measures, composite scores of memory and executive function, developed from ADNI, were considered²⁹. Lastly, the following AD pathological markers were also considered from CSF: amyloid-beta 1 to 42 peptide, tau and phosphorylated tau protein levels³⁰. Secondary analyses were conducted in this manner (i.e. separately) to capture the largest sub-sample size for each of the association tests.

2. Methods

2.1 ADNI dataset

Data were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical/neuropsychological assessment can be combined to

measure the progression of MCI and early AD. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the U.S. and Canada.

2.2 Ethics statement

Participants gave written informed consent at the time of enrollment and completed questionnaires approved by each participating site's Institutional Review Board (IRB).

2.3 Participants

Only data from ADNI-2 and ADNI-GO were used since ADNI-1 did not include rs-fMRI.

Participants with rs-fMRI within the first year of participation in the study were selected, which amounted to 437 rs-fMRI datasets for the primary objective. First-year data were selected to minimize potential retention bias from repeat scans. Available rs-fMRI and corresponding structural T1 images were acquired between June 30 2010 and May 12 2014 (downloaded in June 2014). Sample sizes for the secondary objectives were smaller due to the inclusion of rs-fMRI with other measures (i.e. matched samples with neuroimaging, cognitive, or CSF data).

2.3.1 Normal Controls, MCI and AD criteria

Participants were enrolled if they were between 55-90 years old, spoke English or Spanish as the first language, completed at least 6 years of schooling. Diagnostic classification was made by ADNI investigators using established criteria³¹⁻³³, albeit early and late MCI group were combined into a single MCI group. Controls had mini-mental status examination (MMSE)³⁴ scores between 24-30 and no significant memory concerns. MCI adults had: MMSE scores between 24-30; memory complaint; objective memory loss as quantified by the Wechsler Memory Scale Logical Memory II test³⁵; a Clinical Dementia Rating (CDR)³⁶ score of 0.5; lack of cognitive impairment in other domains such as executive function, visuospatial function and

language; relative sparing of activities of daily living; and absence of frank dementia.

Participants in the AD cohort fulfilled the NINCDS-ADRA criteria for probable AD.

2.4 MRI acquisition

MR images were collected on 3 Tesla Philips MRI systems (Philips, Amsterdam, Netherlands) from a total of 13 sites using a standardized protocol ³⁷. Data from 3 Tesla MRI systems were considered (and not 1.5 T) because physiological sources in fMRI are field-strength dependent ³⁸. T1 images were acquired with an echo time (TE) of 3ms, a repetition time (TR) of 7 ms, flip angle of 9°, slice thickness of 1.2mm and a matrix size of 256x256x170. Rs-fMRI echo planar images were acquired with a TE of 30ms, TR of 3000ms, flip angle of 80°, slice thickness of 3.3mm and a matrix size of 64x64x48 (note: <5% of rs-fMRI data were collected with a TR of 2250ms).

2.5 MRI preprocessing

Preprocessing of the structural T1 images involved bias field correction using a histogram peak-sharpening algorithm (N3) ³⁹. Echo planar rs-fMRI were corrected for head motion using mcflirt, a tool that is part of the FMRIB Software Library (FSL) ⁴⁰. Next, the mean relative root mean squared (RMS) head displacement (mm) was determined from FSL's mcflirt and used as a nuisance regressor. In addition, a global rs-fMRI signal from within-skull voxels (i.e. brain parenchyma and ventricles) was also used as a second nuisance regressor, extracted from the global signal time series. Global RMS in units of signal intensity was then calculated on the demeaned global time series. The rs-fMRI preprocessing steps were chosen based on the following rationale: 1) white matter signals tend to be spatially consistent and robust in rs-fMRI ⁴¹, hence the appeal of a PFwm summary measure, 2) the use of voxel-wise regression of motion traces may not be indicated for this application as it may introduce spatially non-uniform effects across the white matter ⁴² and 3) both global RMS and head displacement

RMS can be viewed as confound effects that could each contribute to PFwm, of which case the latter is reported as strongly related to frame-to-frame change in signal ^{42,43}. Head displacement and global RMS regressors were included in the group-level model for all analyses (see Statistics below).

Previously we have shown that PFwm correlates with cardiac pulsatility in white matter. We confirmed our findings by comparing conventional rs-fMRI and high temporal resolution rs-fMRI (TR of 250 ms) in young and older adults, demonstrating that aliasing of the cardiac signal in conventional fMRI data did not significantly influence this outcome ¹⁷. In the current study, PFwm was calculated in native rs-fMRI space using a similar method to the previous report ¹⁷. Step 1: isolate per voxel (i.e. x,y,z) physiological fluctuations in the rs-fMRI time series by computing the following equation:

$$PF_{x,y,z} = \sqrt{\sigma_{x,y,z}^2 - \sigma_{thermal}^2}$$

Thermal noise variance ($\sigma_{thermal}^2$) was determined as the average variance in a user-defined region of interest (ROI) placed outside the brain in a corner of each resting-state image. The placement of the background ROI was chosen to minimize contribution from EPI ghosting artefact and evaluated by histogram inspection. Step 2: the physiological noise from step 1 was normalized by the mean signal intensity in each voxel, producing a fractional blood oxygenation level dependent (BOLD) change map (see examples in Figure 1). Step 3: PFwm was calculated as the mean physiological noise across WM voxels and used as a summary metric (see below on PFwm adjustment for head motion). To facilitate quality control by visual inspection, PFwm white matter maps were registered to a common template space, by affine transformation and by using the T1 structural image as an intermediate transformation. The common template was created by randomly selecting 15 participants from each cohort (45 in

total) and co-registering the T1 images to a common template using Advanced Normalization Tools. T1 images were brain-extracted and segmented into CSF, grey matter and WM tissue classes. White matter masks were eroded using a 3mm Gaussian kernel. The medulla, pons, midbrain and cerebellum were removed from rs-fMRI to focus the analysis on white matter found in the telencephalon.

2.6. Secondary analyses on biomarker measures

Ventricular volume, hippocampal volume and FDG glucose metabolism were used as neuroimaging biomarkers. Composite scores of memory and executive function and protein levels in CSF were ascertained from the ADNI database. ADNI ventricular volumes were calculated as described by Nestor and colleagues ²⁷. Both ventricular volume and hippocampal volume were normalized by total intracranial volume. For the FDG glucose metabolism intensity normalized images, a composite grey matter region of interest mask was used to generate a single glucose metabolism value from five regions identified by Landau et al. ²⁶ (i.e. left and right angular gyri, left and right inferior temporal gyri and bilateral posterior cingulate cortex). Cognitive composite scores for executive function and memory were computed by Crane et al. ²⁹ using factor analysis. CSF protein concentrations (pg/mL) were calculated by the University of Pennsylvania ADNI Biomarker Laboratory, as described in the work of Shaw and colleagues ³⁰.

2.7 Statistics

Primary and secondary analyses were conducted using R (version 3.1.2 from RStudio Inc). The primary analysis used a univariate linear model (ANOVA, type III) and included the following independent variables: cohort, age, visit, WM volume, head displacement RMS, global RMS and site, of which case cohort was the primary variable of interest. For secondary analyses involving sub-samples, PFwm (adjusted for global and head RMS terms) was

compared against ventricular volume, hippocampal volume and glucose metabolism.

Adjusted PFwm was also compared with composite measures of memory and executive function. Adjusted PFwm was compared with protein levels in CSF. The final regression test was performed using all variables that were found to correlate with PFwm, with specific interest in the effect of cohort on PFwm.

3. Results

Characteristics of the sample drawn from ADNI are summarized in Table 1. There were cohort differences that included: MMSE scores ($p < 0.001$), age (ANOVA, $p < 0.05$, controls were older on average), but no differences in gender (Chi Squared, $p = 0.70$), years of education ($p = 0.42$, ANOVA), or age at onset of symptoms for MCI and AD cohorts ($p = 0.79$, t-test).

PFwm was significantly associated with cohort (Figure 2; $t = 5.08$, $df = 424$, $p = 5.6e-7$), head motion RMS ($t = 12.65$, $df = 424$, $p = 2e-16$) and global RMS ($t = 6.16$, $df = 424$, $p = 1.68e-9$), whereas age ($p = 0.075$) and site ($p = 0.062$) were associated with non-significant trends. The effects of visit ($p = 0.51$) and WM volume ($p = 0.31$) were not significant.

Adjusted PFwm was associated with regional glucose metabolism (Figure 3A; $t = -2.93$, $df = 96$, $p = 0.0042$) but not ventricular volume ($p = 0.49$) nor hippocampal volume ($p = 0.44$). Note these data were extracted from samples that had all of these neuroimaging measures available to permit a direct comparisons with PFwm. Adjusted PFwm was not associated with any of the CSF biomarkers ($p > 0.73$ with $df = 63$). For the cognitive composite scores, adjusted PFwm was correlated with composite memory (Figure 3B; $t = -2.69$, $df = 148$, $p = 0.0079$) but not composite executive function ($t = -0.97$, $df = 148$, $p = 0.34$). In the final regression model that included cohort, glucose metabolism, composite memory and head and global RMS

variables, cohort and glucose metabolism were significant ($t=2.71$, $p=0.0078$, and $t=-2.07$, $p=0.040$, respectively for $df=117$), as were head displacement RMS and global RMS ($t=11.23$, $p=2e-16$, and $t=6.97$, $p=2e-10$, respectively for $df=117$), while composite memory was not ($p=0.63$).

4. Discussion

Resting state fMRI data from ADNI were used to investigate physiological fluctuations in white matter as a source of cerebrovascular contrast in three cognitive groups. We found support for our primary hypothesis: PFwm was significantly increased in AD compared to the MCI and control groups. Secondary regression analyses were conducted on subsets of ADNI participants to support the relevance of PFwm to established biomarkers. PFwm was inversely correlated with regional grey matter glucose metabolism from the neuroimaging data, and inversely correlated with the memory from the cognitive composite score data. Glucose metabolism and cohort remained as significantly associated with PFwm, whereas memory was not, when each of these variables were included in one omnibus model.

Multiple pathophysiological sources could contribute to our findings of increased PFwm in AD. Amyloid angiopathy and tortuous arterioles in white matter are reported in AD and this could explain why PFwm was increased in the current sample of AD participants⁴⁴. Mechanistically, altered cerebrovascular compliance⁴⁵ and/or increased transmission of arterial pulsatility effects into white matter could explain elevated PFwm^{17,21}, which is consistent with previous findings on intracranial pulsatility^{15,16}. While these physiological phenomena may not be purely AD etiology, mixed AD and cerebrovascular disease is recognized as the most common clinical dementia and raises questions about the role of cerebrovascular dysfunction in cognitive decline. Indeed, Scuteri et al. reported that systemic arterial stiffness was a strong

predictor of cognitive decline among older adults with memory problems ¹¹. Microvascular aberrations such as thickening of the basement membrane, luminal narrowing and endothelial compression decrease vascular compliance ⁴⁶, which would contribute to propagation of higher pulsatility down the vascular system and into tissue. A future direction for the current study is to consider PFwm in the context of diffusion tensor imaging (DTI), however, both DTI and rs-fMRI are unfortunately not available for the same participants in ADNI. Such an analysis would speak to white matter changes, such as demyelination, axonal and tissue volume changes that occur in AD and could influence rs-fMRI white matter signals ⁴⁵.

Results of our secondary analyses suggest that PFwm may have merit as a new and complimentary imaging biomarker to study neurodegeneration. Although intracranial pulsatility is reported to be associated with increased ventricular volume ¹⁵, we failed to detect a significant association of PFwm with ventricular or with hippocampal volume. Whereas, we did find that PFwm was negatively associated with glucose metabolism in the Landau ROI ²⁶, which are regions that continue to be implicated in AD ⁴⁷. Both the correlation analysis of adjusted PFwm with the biomarkers and the full model stepwise backward regression demonstrate that adjusted PFwm provide unique information with respect to cohort. We believe this was the case because PFwm provides physiological information that is not captured by the four biomarkers that were tested in this study, hence the between cohort differences in PFwm may reflect underlying differences in cerebrovascular health. Furthermore, brain pulsatility can be characterized by various means and has demonstrated diagnostic merit in neurodegenerative research ^{11,15,16}.

It is important to discuss limitations of the current study. First, we have previously shown that it is ideal to isolate cardiac pulsatility effects on rs-fMRI, particularly among adults with diffuse white matter hyperintensities ¹⁷, however this requires high temporal resolution rs-fMRI to

sample the cardiac signals that was not part of the ADNI rs-fMRI. Second, despite our previous findings ¹⁷, we did not include white matter hyperintensity (WMH) lesion volume in the current study. Although WMH small vessel disease has been linked to vascular pulsatility measures ¹⁰, at the time of this study the ADNI sample appears to exhibit low WMH burden levels ⁴⁸, thus future considerations are warranted. Third, cardiac monitoring by pulse oximetry was also not part of the ADNI rs-fMRI data collection. This limits our ability to characterise PFwm in relation to heart rate during rs-fMRI. Similarly, it remains to be seen whether the respiratory cycle influences PFwm. Fourth, while the sample size for our primary objective was large, our secondary analyses were performed on subsets of participants because of the need for multiple datasets (e.g. samples with rs-fMRI and FDG PET). This also speaks to the challenges of considering longitudinal analysis of the ADNI data since at the time of this study there were insufficient rs-fMRI scans beyond one year. It would be useful to replicate our findings from the secondary analysis as ADNI data accumulates. Furthermore, it would be useful to consider rs-fMRI data beyond one year in ADNI, which was an inclusion criteria by necessity because of the smaller number of samples and the need to address retention bias, specifically in the AD cohort.

In summary, this study demonstrates that physiological fluctuations can be extracted from white matter regions in rs-fMRI data and used to study neurodegeneration. PFwm was robustly different between the cognitive cohorts and was associated with established neuroimaging and cognitive biomarkers of AD. PFwm may therefore be useful in characterising the vascular complications associated with AD.

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Table 1

	Controls	MCI	AD	P value
Participants	53	102	34	
Total rs-fMRI datasets	117	246	74	
Average visits per participant	2.2	2.1	2.2	
Age at baseline (years, mean $\pm$ sd)	75.5 $\pm$ 6.7	71.9 $\pm$ 7.7	72.5 $\pm$ 7.1	<0.05
Gender (M/F)	32/21	49/53	16/18	0.70
Education (years $\pm$ sd)	16.5 $\pm$ 2.2	16.1 $\pm$ 2.6	15.8 $\pm$ 2.9	0.42
Onset of symptoms (years $\pm$ sd)	–	67.5 $\pm$ 8.1	67.1 $\pm$ 8.0	0.79
MMSE (mean of all time points $\pm$ sd)	28.9 $\pm$ 1.5	27.4 $\pm$ 2.2	21.5 $\pm$ 3.5	<0.001
Clinical Dementia Rating (median)	0	0.5	1	<0.001
Functional Assessment Questionnaire (FAQ) (mean $\pm$ sd)	0.5 $\pm$ 2.4	3.6 $\pm$ 5.0	16.0 $\pm$ 7.1	<0.001
Cerebrospinal Fluid (sub-sample size)	16	47	5	
Amyloid-beta level (mean $\pm$ sd)	174.8 $\pm$ 45.0	173.8 $\pm$ 58.2	126.9 $\pm$ 13.9	0.23
Tau level (mean $\pm$ sd)	71.2 $\pm$ 37.4	94.0 $\pm$ 60.1	130.4 $\pm$ 70.2	0.04
Phosphorylated tau level (mean $\pm$ sd)	33.4 $\pm$ 11.9	45.0 $\pm$ 25.2	62.0 $\pm$ 22.5	0.01

Table 1. Sample characteristics.

Figure Captions

Figure 1. PFwm colour maps in axial view for three representative participants in each cohort and overlaid on a group template T1-weighted image. Top row: controls, middle row: MCI, bottom row: AD. The right column shows the average physiological fluctuation maps by cohort.

Figure 2. PFwm boxplots are plotted by cohort and visit (within Year 1). Controls (blue), MCI (green) and AD (red) are shown by different colour bars. PFwm values are in units of % BOLD signal change and are adjusted for head displacement and global signal root-mean square BOLD signal (global RMS). Visits were centered at baseline, 3 and 6 months using k-means clustering. Cohort was a significant predictor of adjusted PFwm ($t=5.08$, $df=424$, $p=6 \times 10^{-7}$).

Figure 3. Scatterplots were used to visualise regression results from single visit data. PFwm (adjusted for head displacement and global RMS) is plotted against A) FDG glucose metabolism ($t=-2.93$, $df=96$, $p=0.004$, intensity normalization FDG) and B) the composite memory score ($t=-2.69$, $df=148$, $p=0.008$).