



Age Related Changes in Cerebrovascular Reactivity and Its Relationship to Global Brain Structure

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GDW and CS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author GGC provided image analysis support. Author TSA provided the dual echo pulse sequence. Author ADM provided clinical reporting of all scans. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: There is growing evidence to suggest that vascular and CSF haemodynamic effects are related to structural changes in the ageing brain. We investigated these effects in a sample of healthy participants by measuring changes in cerebrovascular reactivity induced by hypercapnia and comparing these to global and ROI based cerebral volume measures.

Methods: Forty five participants aged 21 to 58 years (23 female) were recruited. Cerebrovascular reactivity was determined from hypercapnia induced BOLD signal change during two 3-minute intervals of breathing 6% CO₂, interleaved with three 2-minute intervals of breathing room air. Parametric maps of reactivity were calculated as the ratio of % BOLD signal change to end-tidal CO₂ (mmHg). High resolution 3D T1-weighted images were segmented and lateral ventricle volume and white matter hypointensity volume determined.

Results: Significant negative correlations between both grey matter ($p = .042$) and white matter ($p = .021$) reactivity and age were found and significant negative correlations between grey matter

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($p = .013$) and white matter ($p = .004$) reactivity and lateral ventricle volume were also found while correcting for age and total intracranial volume. A significant negative correlation between white matter reactivity and white matter hypointensity volume was found ($p = .049$) after correcting for age.

Conclusion: These results support the hypothesis that cerebrovascular haemodynamics influence structural brain changes that occur during normal ageing that are independent of the age of the individual.

Keywords: MRI; hypercapnia; dual echo; cerebrovascular reactivity; volume; white matter hypointensity.

1. INTRODUCTION

The ability of the cerebral vasculature to adapt rapidly to changes in arterial blood pressure or metabolic demand is essential to maintain normal brain function. Cerebrovascular reactivity (CVR) to a vasoactive stimulus (such as hypercapnia) is a well-established marker of cerebral hemodynamic integrity. In a Transcranial Doppler study of CVR to hypercapnia, a significant reduction has been reported in both AD and Vascular Dementia (VaD) patients compared to controls [1]. A recent MRI study in ageing rodents has shown that lower hypercapnia-derived CVR predicts mild cognitive impairment [2] and may therefore provide supporting evidence to the search for the causes of dementia.

The current global prevalence of dementia is > 30 million and this is expected to treble over the next 40 years [3]. The UK prevalence is about 800,000 with estimated cost to the UK economy exceeding £23 billion. Brain changes associated with dementing illnesses, the most common of which is Alzheimer's disease (AD), impose a significant burden even before clinical symptoms are present. Understanding how the brain changes in late life and the impact of such changes on mental (cognitive) ability is not only crucial to understanding dementia but also for developing preventative and therapeutic strategies.

In a recent magnetic resonance imaging (MRI) study in normal, non-demented old people, we have shown that structural brain changes predict future dementia and death [4]. With age, the brain undergoes structural and functional changes which are thought to be responsible for cognitive decline [5-7]. Cerebral compliance, a property of the brain that describes its deformability or ability to expand

and contract as blood is pumped from the heart, has been shown to be reduced in individuals with AD [8]. Hydrodynamic theory predicts that a reduction in arterial tree compliance (age related increased arterial stiffness) will lead to a reduction in conversion of the pulse pressure within the arterial tree to pulsatile flow. Essentially, this reduces the ability of the arterial tree to dampen the pulse pressure and results in a greater transmission of pulsation to the brain. This may cause enlarged perivascular spaces and via choroid plexus pulsation, cause ventricular dilation and elevated CSF pulsatility [9].

With age, there is also an increase in brain white matter hyperintensities (WMH). High WMH loads, i.e. total volume of white matter hyperintensities, are associated with reduced cognitive ability [11-13] and with vascular risk factors such as hypertension [14]. However, their interaction with other measurable brain abnormalities in cognitive ageing, such as atrophy, is less well understood.

Although it has been shown that there are components of both subject demographics [15] and of brain structure, such as WMH lesion load and brain volume that contribute to variations in cognitive decline, there is still a significant unknown component. Evidence is beginning to emerge that points to a possible role for changes in the cerebrovasculature in the aetiology of age-related cognitive decline. In an initial attempt to disambiguate some of those "unknown components", we employed a dual gradient/spin-echo sequence to investigate the interaction of both the cerebral microvasculature (with spin-echo images) and cerebral macrovasculature (with gradient-echo images) on brain structure. The aim of this study, therefore, was to test the hypothesis that there is an age related decline in cerebrovascular reactivity and an associated relationship between both lateral ventricle volume and white matter microstructural damage and reactivity.

2. METHODS

2.1 Participants

Forty five healthy volunteers with no history of trauma or neurological disease were recruited (23 females; age range 21-58 years, 39.56 ± 11.2 years) for this study. Informed and written consent was obtained from all participants and the protocol was approved by the College of Life Sciences and Medicine Ethics Review Board (CERB) of the University of Aberdeen.

Participants were positioned supine on the scanner table and wore an anaesthetics facemask (Quadrilite, Intersurgical, Wokingham, UK). A specially designed unidirectional breathing circuit (Intersurgical, Wokingham, UK; product code 2013014) was used to deliver either room air or a room air/6% CO₂ mix. An MRI-compatible patient monitor (Schiller MAGLIFE Serenity, SCHILLER AG, Baar, Switzerland) was used to continuously monitor physiological and respiratory parameters including heart rate, respiration rate, blood oxygenation, end-tidal O₂ (EtO₂) and end-tidal CO₂ (EtCO₂); parameters were sampled rate of 1Hz and stored in a text file on a remote PC.

Blood pressure was measured, supine, before and after the reactivity imaging sequence, Table 1.

2.2 MR Imaging

MRI data were acquired on a Philips 3 T Achieva scanner (Philips Medical Systems, Best, The Netherlands) using the manufacturer's 32-channel phased-array head coil.

2.2.1 Structural imaging

High-resolution structural images were acquired using a T1-weighted TFE sequence (TR=8.2ms; TE= 3.8 ms; flip angle=8°; matrix size=240x240x160; field of view=240x240x160 mm³; voxel size=1.0x1.0x1.0 mm³; and total acquisition time=5 min 35s). These images were subsequently processed with the Freesurfer software package (<http://surfer.nmr.mgh.harvard.edu>) to measure cortical thickness and regional and global volumes.

2.2.2 Hypercapnia imaging

The signal response of gradient echo and spin echo sequences are different depending on the

vasculature of the tissue, with gradient echo signals being sensitive to changes in the venous macrovasculature (venous vessel radius > 50 μm) and spin echo signals being sensitive to changes in the venous microvasculature (venous vessel radius < 10 μm) [16]. A single-shot dual-echo EPI sequence was therefore used for simultaneous acquisition of gradient-echo (GE) and spin-echo (SE) images [17]. Imaging parameters were TR=3.5s; TE_{GE}/TE_{SE}=30/80 ms; flip angle=90°; matrix size=68x67; field of view=200x200 mm²; and in plane resolution 3x3 mm²). 28 oblique transverse slices (slice thickness=3.0 mm; inter-slice gap=1.0 mm) were acquired to cover the whole brain. Reactivity was calculated separately for both SE and GE images. Two 3-minute blocks of hypercapnia (breathing a room air/6% CO₂ mix) were interleaved with three 2-minute blocks of breathing room air, giving a total acquisition time of 12 minutes. Parametric maps of the cerebrovascular reactivity were calculated according to $\Delta\text{BOLD}/\Delta\text{EtCO}_2$, where ΔBOLD denotes the change in GE or SE signal intensity between hypercapnia and normocapnia and ΔEtCO_2 denotes the change in EtCO₂ between hypercapnia and normocapnia.

2.3 Image Analysis

2.3.1 Structural scan analysis

For each participant, T1 images were first intensity normalised, then the boundaries between the grey matter and the white matter and the outer surface of the cortex (the pial surface) were determined. The cortical surface was then divided into 34 different anatomical regions per hemisphere including fusiform, inferior temporal and parahippocampal. The mean thickness of these regions was calculated on the basis of the boundary of the GM and WM and the outline of pial surface, respectively. In addition to cortical thickness a number of regional volume measurements were determined automatically by the Freesurfer software including lateral ventricle volume and white matter hypointensity volume. The segmentation process was manually validated and corrected as necessary.

2.3.2 Hypercapnia image analysis

It has been shown that there is a time lag between the BOLD signal and the EtCO₂ concentration change induced by switching from the room air to CO₂/room air mix. To determine this lag on a subject by subject basis a

preliminary region of interest analysis was performed. The mean BOLD signal within an ROI defining the bilateral thalamus, determined from the Wake Forrest University PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>), was correlated with the EtCO₂ time course using the Matlab “cov” function. The shift at which the EtCO₂ time course provided the maximum cross-correlation coefficient with the BOLD signal was defined as the time lag. This time lag was used to correct the EtCO₂ time courses for all subsequent analysis, **Error! Reference source not found.**

GE and SE BOLD images were pre-processed separately using Matlab (MATLAB 7.14, The Math Works Inc., Natick, MA, 2000) and the SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm>). First, each volume was realigned to match the spatial location of the first volume, and a mean image generated from all of the realigned images. The realigned GE and SEBOLD volumes were then co-registered with the high resolution structural scan.

Spatial normalisation parameters were determined by the SPM image segmentation routine and applied to the co-registered GE BOLD volumes. These parameters transformed the BOLD GE and SE volumes into Montreal Neurological Institute (MNI) standard space. These volumes were re-sampled to a resolution of 2mm isotropic and smoothed with an 8 mm full width at half maximum isotropic Gaussian spatial smoothing kernel.

To determine Cerebrovascular Reactivity (CVR), the shifted EtCO₂ time courses were correlated with the smoothed, spatially normalised GE and SE BOLD volumes on a voxel by voxel basis using a general linear model procedure, Fig. 2. Microvascular reactivity was calculated in a subset of participants.

2.4 Statistical Analysis

Voxel based data analysis was performed using the General Linear Model as implemented by SPM8. Analysis of demographic and ROI based data was performed using R (<http://www.r-project.org> version 3.0.0). A Tukey Honest Significances Difference test was used to identify differences between age decades for structural and haemodynamic measures while correcting

for multiple comparisons. Pearson correlation was used to investigate whether linear relationships existed between age and structural and haemodynamic measures. Sex differences in structural and haemodynamic measures were investigated using a two sample *t* test. Results were expressed as mean±SD. Correction of probability thresholds for multiple comparisons was implemented using the Holm [18] method implemented in the R software package (i.e., *p.adjust* function with the “Holm” option). A result with a corrected *p*< .05 was considered statistically significant.

3. RESULTS

Of the 45 participants who volunteered who took part in the study, 41 completed the scanning session. Of the 4 who did not, 2 were claustrophobic, 1 had a metal plate in their neck and 1 had an incidental finding that required clinical follow-up. Of the remaining 41 participants, 3 reactivity data sets could not be analysed. This was due to an ill fitting mask in 1 participant and corrupt log files in 2 others. No participants who completed the scanning session reported any discomfort either during or after the session. Table 1 summarises the physiological parameters for each decade, as well as the sample as a whole.

3.1 Physiological Measures

Significant differences in Diastolic BP between the 30s and 40s and the 30s and 50s groups (*p*=.037 and *p*=.044 respectively) were found. No significant age related differences were found in any other measures (i.e. Systolic BP, Room air EtCO₂ and hypercapnia EtCO₂). However, as expected, a significant increase in EtCO₂ was found when breathing room air mixed with 6% CO₂ (hypercapnia) when compared to breathing room air alone (Δ EtCO₂ = 10.72±2.29%/ mmHg, *p*<.001). Regrouping the cohort by sex, we found a trend towards significantly higher diastolic BP in males than in females (*p*=.09), and a significantly higher systolic BP in males than in females (*p*=.05), with a significant difference in EtCO₂ when breathing room air between males and females (*p*=.0006) and a significant difference in EtCO₂ when breathing 6% CO₂ mixed with room air between males and females (*p*=.04), Table 2.

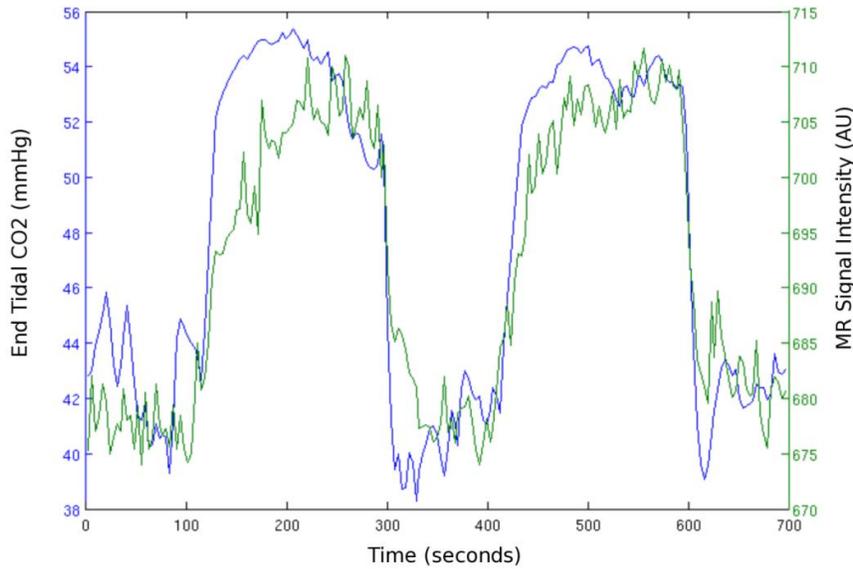


Fig. 1. GE BOLD signal intensity AU (green) and EtCO2 mmHg (blue) time courses

Table 1. Physiological parameters during room air and CO₂ breathing

| Age group | Age (Years) | Systolic BP (mmHg) | Diastolic BP (mmHg)* | End Tidal CO ₂ (mmHg) | End Tidal CO ₂ (mmHg) |
|---------------|-------------|--------------------|----------------------|----------------------------------|----------------------------------|
| | | | | Room Air | 6% CO ₂ |
| 20-29 (N=10) | 25.48±2.7 | 116.3±7.02 | 71.44±8.02 | 40.07±4.24 | 51.08±2.56 |
| 30-39 (N=11) | 34.16±3.17 | 112.6±10.1 | 67.22±10.4 | 41.71±2.43 | 51.62±2.68 |
| 40-49 (N=8) | 45.28±3.41 | 120.2±13.5 | 79.22±10.9 | 40.31±2.52 | 51.55±3.02 |
| 50-59 (N=9) | 54.29±2.96 | 123.5±8.86 | 79.25±4.80 | 40.33±1.69 | 51.21±3.11 |
| Sample (N=38) | 38.98±11.4 | 118.0±10.6 | 74.14±10.0 | 40.65±3.29 | 51.36±2.73 |

3.2 Haemodynamic Measures

When investigating the age dependence of global reactivity in the microvasculature (Table 3) (determined from gradient echo BOLD signal changes) significant negative correlations between age of participant and GM global reactivity ($R^2 = .084$, $p = .043$) and between age of participant and WM global reactivity were found ($R^2 = .114$, $p = .022$), as illustrated in Fig. 3. No significant relationship was found when investigating the global reactivity in the microvasculature (determined from spin echo BOLD signal changes) in either grey matter or white matter.

3.3 Global Structural Measures

When investigating age related changes in global structural measures (see Table 4), we found a significant increase in lateral ventricle volume for the 50s group ($p=.015$ compared to the 40s

group), as shown in Fig. 4a. We also found a significant negative correlation between Age and Mean Cortical Thickness ($R^2 = .45$, $p < .001$) and a related negative correlation between Age and Total Grey Volume ($R^2 = .21$, $p = .002$), as illustrated in Fig. 4b.

3.4 Comparison of Haemodynamic Measures and Global Structural Volumes

We found a significant negative correlation between both grey matter ($R^2 = .127$, $p = .013$) and white matter ($R^2 = .221$, $p = .004$) macrovascular reactivity and total lateral ventricle volume while correcting for age and total intracranial volume, as shown in Fig. 5. We also found a significant negative correlation between white matter macrovascular reactivity and white matter hypointensity volume ($R^2 = .185$, $p = .049$) after correcting for age (see Fig. 6). No such correlation was found for grey matter

macrovascular reactivity or either grey or white microvascular reactivity. No correlation was found between either grey matter volume or white matter volume and either grey or white matter reactivity, while correcting for total intracranial volume.

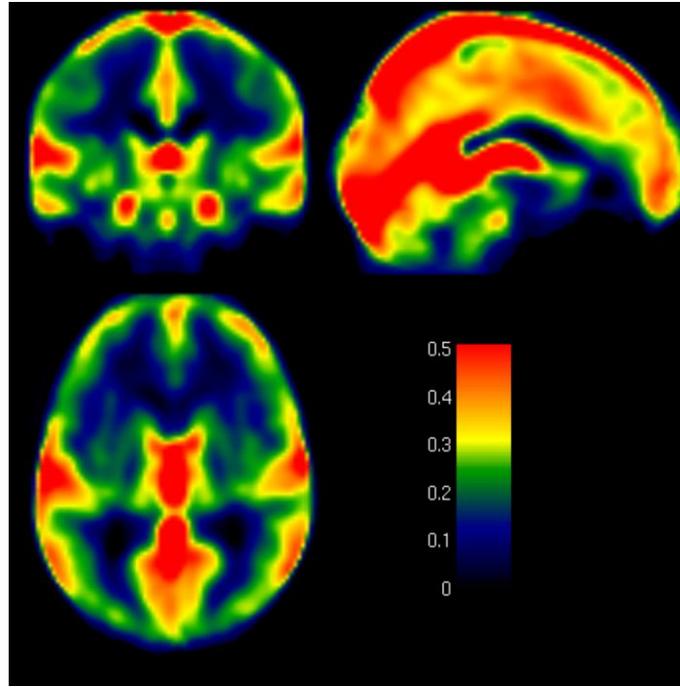


Fig. 2. Three plane view of mean cerebrovascular Reactivity (%BOLD/mmHg) determined from gradient echo signal changes for the sample as a whole

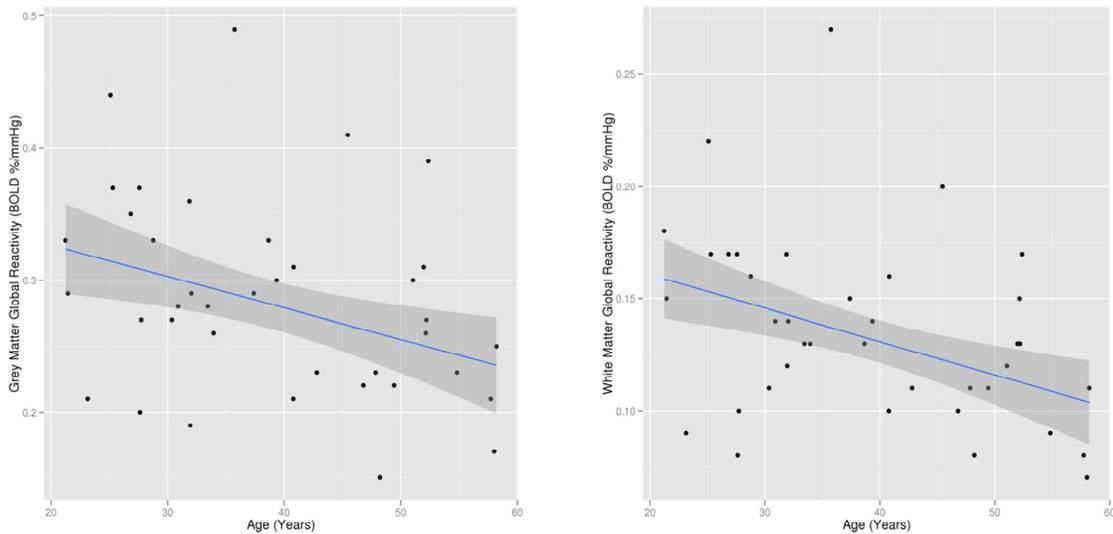


Fig. 3. Correlation of age and global reactivity (calculated from gradient echo signal changes) for grey matter (A) and white matter (B). The blue line represents the best linear fit and the shaded area shows the 95% confidence limits of the fit

Table 2. Sex differences in physiological parameters during room air and 6% CO₂ breathing

| Gender | Age (Years) | Systolic BP (mmHg) | Diastolic BP (mmHg) | End Tidal CO ₂ (mmHg) | |
|---------------|-------------|--------------------|---------------------|----------------------------------|--------------------|
| | | | | Room Air | 6% CO ₂ |
| Male (N=18) | 37.80±10.3 | 120.3±9.33 | 76.76±10.6 | 42.19±2.32 | 52.0±2.78 |
| Female (N=20) | 40.05±12.0 | 116.0±10.8 | 70.81±8.74 | 39.17±2.69 | 50.50±2.44 |

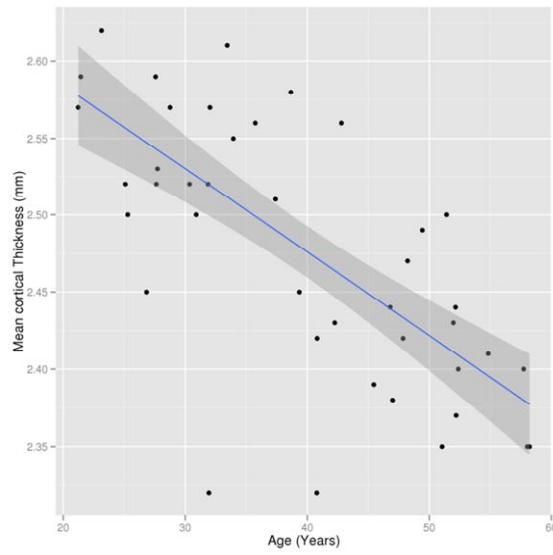


Fig. 4. Age related changes in mean cortical thickness (line represents a linear fit to the data, shaded area shows the 95% confidence limits of the fit)

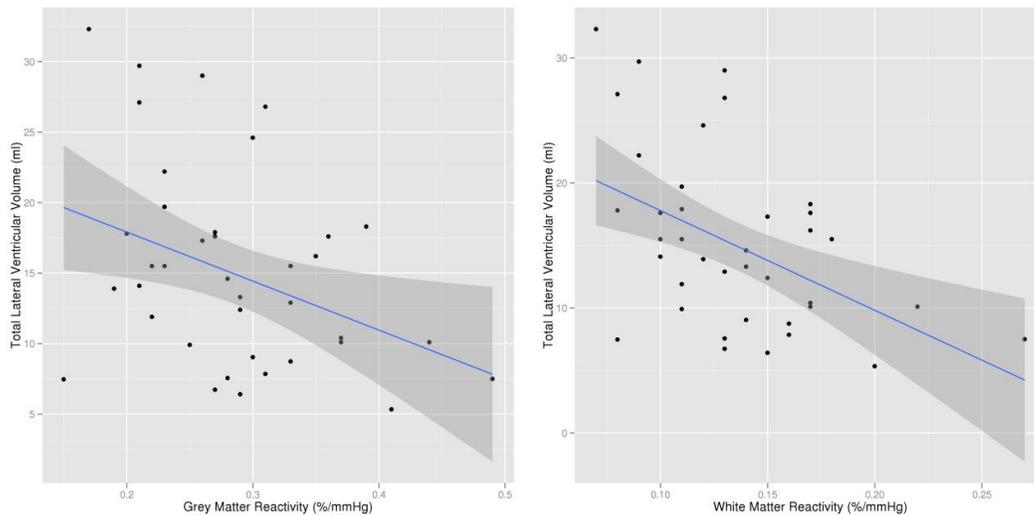


Fig. 5. Correlation of age and global macrovascular reactivity for grey matter (A) and white matter (B). The blue line represents the best linear fit and the shaded area shows the 95% confidence limits of the fit

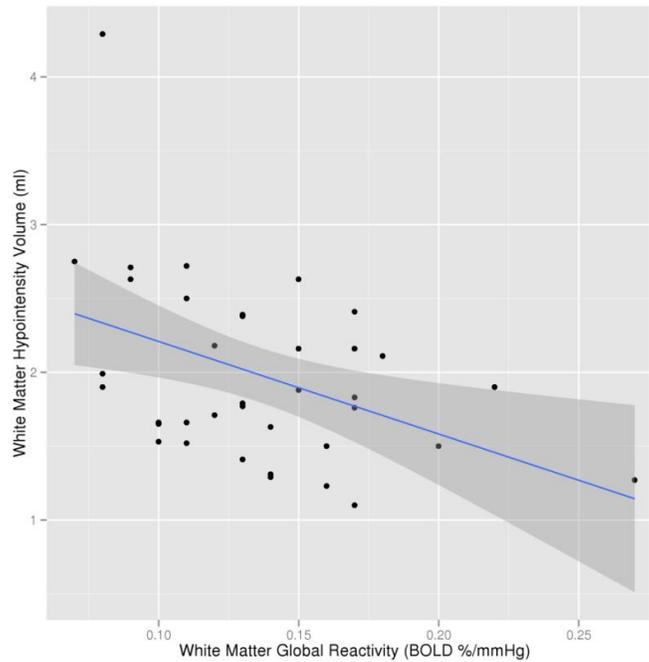


Fig. 6. Significant negative correlation between white matter hypointensity volume and white matter macrovascular reactivity after correcting for age. The blue line represents the best linear fit and the shaded area shows the 95% confidence limits of the fit

Table 3. Age related differences in grey matter (GM) and white matter (WM) cerebrovascular reactivity. The number in each group are given in Table 1

| Age group | GM global reactivity | WM global reactivity | GM global reactivity | WM global reactivity |
|-----------|----------------------|----------------------|----------------------|----------------------|
| | (%/mmHg) | (%/mmHg) | (%/mmHg) | (%/mmHg) |
| | Gradient Echo BOLD | | Spin Echo BOLD | |
| 20-29 | .312±.074 | .149±.044 | .444±.140 | .244±.105 |
| 30-39 | .306±.078 | .148±.043 | .525±.149 | .275±.086 |
| 40-49 | .247±.078 | .121±.039 | .416±.135 | .223±.073 |
| 50-59 | .265±.063 | .117±.032 | .447±.102 | .220±.049 |
| Cohort | .280±.075 | .135±.042 | .462±.135 | .242±.082 |

Table 4. Age differences in global structural volume measures. The numbers in each group are given in Table 1

| Age group | Lateral ventricle volume (ml) | Total grey volume (ml) | Brain volume (ml) | Intra-cranial volume (ml) | Brain volume fraction | Mean cortical thickness (mm) |
|-----------|-------------------------------|------------------------|-------------------|---------------------------|-----------------------|------------------------------|
| 20-29 | 14.26±6.74 | 693±36.7 | 1422±82.8 | 1569±157 | .912±.079 | 2.54±.051 |
| 30-39 | 14.15±6.05 | 650±61.5 | 1351±113 | 1441±156 | .941±.065 | 2.51±.079 |
| 40-49 | 12.17±4.93 | 612±32.9 | 1292±56.6 | 1409±65.3 | .918±.045 | 2.44±.071 |
| 50-59 | 20.58±8.36 | 613±72.9 | 1338±116 | 1440±197 | .933±.069 | 2.39±.035 |
| Cohort | 15.28±7.09 | 644±66.4 | 1354±117 | 1473±159 | .927±.065 | 2.48±.087 |

4. DISCUSSION AND CONCLUSION

In this study, we used 6% CO₂ inhalation and a dual echo “BOLD sensitive” imaging sequence to

investigate age related changes in both micro- and macrovascular cerebral reactivity. We found a significant negative correlation between age and macrovascular cerebral reactivity,

determined from hypercapnia induced gradient echo BOLD signal change, in both cerebral grey and white matter and a significant negative correlation between macrovascular reactivity in white matter and white matter hypointensity volume, that is independent of age.

The calculated macrovascular cerebral reactivity values found here are similar, although slightly lower, than those previously reported in the literature [19,20]. Neither Zande et al. [19] nor Yezhuvath et al. [20] investigated the age dependence of cerebrovascular reactivity. This is probably due to their sample sizes being considerably smaller (11 and 13) compared to the size of the current study (41). Yezhuvath et al. [21] found significant reductions in frontal lobe cerebrovascular reactivity in patients with Alzheimer's disease compared with age matched controls and also showed that white matter hyperintensity volume correlated with the total volume of low reactivity brain regions in the AD group. This agrees in part with our findings which show that the T1 estimated white matter hypointensity volume negatively correlates with global reactivity. In other words both studies show that low cerebrovascular reactivity is associated with increased white matter damage and, as we show, this is evident in otherwise healthy individuals.

Murray et al. [13] showed that brain white matter hyperintensity burden has a significant negative effect on life-long cognitive decline and demonstrated that the negative effect of hypertension on late life ability is all mediated by white matter hyperintensity burden.

Alzheimer's disease, the most common cause of dementia, involves a progressive decline in memory and cognition that correlates with synaptic and neuronal dysfunction and loss [22]. Alzheimer's disease is associated with cerebrovascular changes that precede clinical symptoms of the disease, worsen over the course of degeneration, and exacerbate cognitive decline. This is shown by impaired vascular tone, resting hypoperfusion and reduced haemodynamic responses to stimulation [23-26]. Post-mortem histology has shown various changes in blood vessel morphology in the Alzheimer's disease brain: Decreased vascular density, increased vessel curvature [27], degeneration of smooth muscle cells, vascular endothelium alterations [28], capillary fragmentation and abnormal blood-brain barrier permeability [29]. Whether such vascular

changes are fundamental to Alzheimer's disease or represent co-existing vascular pathology, which makes the clinical expression of dementia more likely remains a topic of discussion [30]. It may be that these changes in blood vessel morphology can be assessed via cerebrovascular reactivity, providing an objective measure of microvascular pathology and vulnerability to dementia.

Alzheimer's disease is not the only dementia that has links to microvascular pathology. Vascular dementia, considered to be the second most common cause of dementia, has several different causes, but the two most common types are dementia resulting from multiple small or large strokes [31,32] and dementia related to ischemic white-matter lesions (WMLs) [33]. Cerebrovascular reactivity may provide a way to investigate the differences, if any, between Alzheimer's and vascular dementia.

Decline in cognitive ability typically begins in late mid-life, although it may manifest at any time from the late 40's onwards. To provide an estimate of the early trajectory of age related changes in cerebral reactivity we chose to investigate a group in the early to middle aged range. By investigating this age group we hoped to determine the effects of cerebral reactivity in an age range where cognitive decline is unlikely to be present, or if present, to have progressed to a level not currently measureable using current instruments.

There are limitations to this study. By using the thalamus as a region of interest to determine BOLD signal-EtCO₂ time delay [20] we are assuming that this time delay is constant across the brain. A voxel by voxel determination of the off-set would eliminate this potential issue; however it may be that noise levels at the voxel level would significantly compromise the correlation analysis. It may be that there are age related differences in this off-set and this should be investigated in the future. No correlation was found between white matter micro-vascular reactivity, as determined by spin-echo imaging, and age or white matter hypointensity volume. Spin-echo (SE) images are sensitive to susceptibility changes from the venous microvasculature (vessel radii < 50µm) where as gradient-echo (GE) images are sensitive to susceptibility changes in the venous macrovasculature (vessel radii > 50µm). This suggests that the cerebrovascular reactivity in the venous microvasculature in both grey and

white matter has relatively lower age dependence. However, the signal and therefore the signal to noise ratio (SNR) of the SE images is much lower than that of the GE images. This may explain why no correlation with microvascular reactivity was demonstrated.

Blood pressure is closely related to perfusion pressure which is the driving force for blood flow. An increase in blood pressure during hypercapnia can contribute to an increase in blood flow. However, we did not find an increase in blood pressure during CO₂ breathing and suggest that changes in cerebrovascular reactivity found here are not due to blood pressure induced increases in blood flow that would cause changes in susceptibility related signal change.

In studies investigating the effects of white matter lesion load on cognitive ability, white matter lesion extent is typically assessed using either a T2-weighted or fluid attenuated inversion recovery (FLAIR) weighted image with visual assessment using a grading scale. The current study determined white matter hypointensity volume from an automated segmentation method applied to T1-weighted images, as implemented by the Free surfer software package, which also provided cortical thickness and ventricle volumes. We looked at a relatively young population with a relatively small range of white matter hypointensity volumes. In adults with relatively few white matter hypo/hyperintensities the increased signal to noise afforded by the T1-weighted images may be more accurate. White matter hypointensities determined from T1-weighted images have been used extensively to investigate white matter damage in multiple sclerosis [34] where they may reflect varying degrees of demyelination, with increasing lesion hypointensity corresponding to more breakdown in the structure. A larger sample, that includes participants with a larger range of white matter hypointensity volume, imaged with both T1-weighted and FLAIR imaging, would be required to determine if the linear relationship between white matter hyper/hypointensity volume and cerebrovascular reactivity is valid and continues beyond age 60.

In conclusion, we believe that cerebrovascular reactivity is a component of brain pathophysiology that is age dependent and that there is a strong correlation between cerebrovascular reactivity and white matter hypointensity that is, in turn, independent of age.

These results support the hypothesis that cerebrovascular haemodynamics influence structural brain changes that occur during normal ageing that are independent of the age of the individual.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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