



Slowed Temporal and Parietal Cerebrovascular Response in Patients with Alzheimer's Disease

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ABSTRACT: Background: Recent investigations now suggest that cerebrovascular reactivity (CVR) is impaired in Alzheimer's disease (AD) and may underpin part of the disease's neurovascular component. However, our understanding of the relationship between the magnitude of CVR, the speed of cerebrovascular response, and the progression of AD is still limited. This is especially true in patients with mild cognitive impairment (MCI), which is recognized as an intermediate stage between normal aging and dementia. The purpose of this study was to investigate AD and MCI patients by mapping repeatable and accurate measures of cerebrovascular function, namely the magnitude and speed of cerebrovascular response (τ) to a vasoactive stimulus in key predilection sites for vascular dysfunction in AD. **Methods:** Thirty-three subjects (age range: 52–83 years, 20 males) were prospectively recruited. CVR and τ were assessed using blood oxygen level-dependent MRI during a standardized carbon dioxide stimulus. Temporal and parietal cortical regions of interest (ROIs) were generated from anatomical images using the FreeSurfer image analysis suite. **Results:** Of 33 subjects recruited, 3 individuals were excluded, leaving 30 subjects for analysis, consisting of 6 individuals with early AD, 11 individuals with MCI, and 13 older healthy controls (HCs). τ was found to be significantly higher in the AD group compared to the HC group in both the temporal ($p = 0.03$) and parietal cortex ($p = 0.01$) following a one-way ANCOVA correcting for age and microangiopathy scoring and a Bonferroni *post-hoc* correction. **Conclusion:** The study findings suggest that AD is associated with a slowing of the cerebrovascular response in the temporal and parietal cortices.

RÉSUMÉ : Ralentissement de la réponse cérébrovasculaire dans le lobe temporal et le cortex pariétal chez des patients atteints de la maladie d'Alzheimer. **Contexte :** Des travaux de recherche récents suggèrent désormais que la réactivité cérébrovasculaire (RCV), en plus d'être altérée dans le cas de patients atteints de la maladie d'Alzheimer (MA), pourrait renforcer la composante neurovasculaire de cette maladie. Il n'empêche que notre compréhension des liens entre l'ampleur de la RCV, la rapidité d'une réponse cérébrovasculaire et la progression de la MA demeure limitée. Cela est particulièrement vrai dans le cas de patients aux prises avec des troubles cognitifs légers (TCL), lesquels sont reconnus comme étant des affections intermédiaires entre le vieillissement normal et la démence. L'objectif de cette étude est donc de se pencher sur les cas de patients atteints de MA et de TCL en établissant des mesures répétables et précises de la fonction cérébrovasculaire, à savoir l'ampleur et la rapidité de la réponse cérébrovasculaire (τ) à une stimulation vasoactive dans les principales régions de dysfonctionnement vasculaire associées à la MA. **Méthodes :** Au total, 33 sujets âgés de 52 à 83 ans, 20 étant des hommes, ont été recrutés de façon prospective. La RCV et la réponse cérébrovasculaire (τ) ont été évaluées au moyen d'IRM détectant le signal BOLD (*blood oxygen level-dependent*) à l'occasion d'une stimulation standardisée de dioxyde de carbone. Des résultats se rapportant à deux régions d'intérêt (lobe temporal et cortex pariétal) ont été obtenus à partir d'images anatomiques et du logiciel d'imagerie FreeSurfer. **Résultats :** Sur ces 33 sujets recrutés, 3 d'entre eux ont fini par être exclus. Sur ces 30 sujets, 6 étaient atteints d'une forme précoce de MA, 11 étaient aux prises avec des TCL alors que 13 autres ont intégré notre groupe de témoins en santé. À la suite d'une analyse correctrice de covariance à sens unique pour l'âge et pour des scores évaluant la sévérité de cas de microangiopathie et d'une correction de Bonferroni *a posteriori*, la réponse cérébrovasculaire (τ) s'est avérée sensiblement plus élevée dans le groupe de patients atteints de la MA en comparaison avec nos témoins en santé, et ce, qu'il s'agisse du lobe temporal ($p = 0,03$) et du cortex pariétal ($p = 0,01$).

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RECEIVED AUGUST 22, 2019. FINAL REVISIONS SUBMITTED JANUARY 18, 2020. DATE OF ACCEPTANCE FEBRUARY 5, 2020.

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Conclusion : Les résultats de cette étude suggèrent en somme que la MA est associée à un ralentissement de la réponse cérébrovasculaire dans le lobe temporal et dans le cortex pariétal.

Keywords: Alzheimer's disease, Magnetic resonance imaging, Cerebrovascular reactivity, Cerebral blood flow regulation

doi:10.1017/cjn.2020.30

Can J Neurol Sci. 2020; 47: 366–373

INTRODUCTION

Alzheimer's disease (AD) is the most common contributing cause of dementia in the world, accounting for 60%–80% of the estimated 30–40 million cases worldwide.^{1,2} The presence of cerebrovascular disease (CVD) was originally used to demarcate AD and vascular dementia (VaD); however, converging evidence now supports a major vascular component in AD. CVD and AD share numerous risk factors including obesity and hypertension during midlife, hypercholesterolemia, hyperhomocysteinemia, diabetes mellitus, and smoking.^{3–5} Additionally, atherosclerosis ratings in AD patients significantly correlate with neuritic plaque, neurofibrillary tangles, and cerebral amyloid angiopathy.^{6,7}

Cerebral hypoperfusion has been repeatedly observed in AD patients, with the temporal and parietal cortices found to be the most consistently affected.^{8–13} Moreover, reduced cerebral blood flow (CBF) is demonstrable several years before the diagnosis of clinical AD,¹⁴ suggesting that vascular dysfunction may play an important role early in the disease.

Building on basal perfusion studies, there is now a growing body of evidence that cerebrovascular reactivity (CVR) in response to CO₂ may be impaired in AD.¹⁵ Simply defined, CVR is the change in CBF in response to a given vasoactive stimulus that occurs during reductions in systemic blood pressure, hypercapnia, or during increases in neural activity. Initial studies using PET imaging techniques reported no differences in CVR between AD patients and elderly controls.^{16,17} However, early studies using alternative imaging modalities found CVR to be significantly impaired in AD.^{18,19} Since then, investigations using transcranial Doppler have more reliably demonstrated CVR impairment in AD patients.^{20,21} Most recently, studies utilizing blood oxygen level-dependent (BOLD) MRI and fixed inspired CO₂ have found diminished CVR in both AD^{22,23} and mild cognitive impairment (MCI)²³, which is recognized as an intermediate stage between normal aging and dementia. These findings indicate that CVR deficits may occur early in the disease and could contribute to progression, though the spatial location of CVR deficits remains to be elucidated.

Beyond measuring CVR magnitude, assessing the speed of cerebrovascular response may also be of interest as it is an indicator of vascular compliance²⁴ and may impact the important temporal linkage between neural activity and the resultant change in CBF. Richiardi and colleagues investigated the speed of cerebrovascular response to vasoactive stimuli in AD and MCI patients using BOLD MRI and a fixed inspired CO₂ stimulus.²⁵ They reported that both MCI and AD patients demonstrated a slowed vascular response globally when compared to healthy controls (HCs). However, further studies were needed to corroborate their findings.

Therefore, we applied an accurate, repeatable, and reproducible CVR methodology for measuring the magnitude and speed of the cerebrovascular response to CO₂ in key predilection sites

of AD in patients with MCI and early AD. The method uses BOLD MRI as a surrogate for CBF during precision control of end-tidal tensions of carbon dioxide (P_{ET}CO₂) and oxygen (P_{ET}O₂) thus providing a standardized and repeatable vasoactive stimulus. We hypothesized that reduced CVR and slowed vascular reactivity would occur in the temporal and parietal cortices of subjects with MCI and AD when compared to older HCs.

METHODS

Participants

This study was approved by the Research Ethics Board at the University Hospital Network. Subjects were recruited through the memory clinic located at Toronto Western Hospital, where both written and informed consent were provided. Thirty-three subjects were recruited to participate in the study, consisting of 7 individuals with early AD, 12 individuals with MCI, and 14 older (HCs (age range: 52–83 years, 20 males). Diagnosis of MCI and AD patients was performed by a neurologist according to the 2011 guidelines set out by the National Institute on Aging and Alzheimer's Association consensus panels.^{26,27} Older HC was also recruited and screened according to the outlined inclusion and exclusion criteria. Subjects were asked to refrain from heavy exercise or caffeine intake on the day of the scan.

Inclusion criteria for this study were as follows: (i) a diagnosis of MCI (amnestic subtype) or early dementia due to AD; (ii) over 50 years of age; and (iii) deemed fit for investigation by the referring neurologist. Exclusion criteria for this study were as follows: (i) medical contraindications to controlled hypercapnia; (ii) incompatibility with 3-Tesla MRI; (iii) mixed AD and VaD; (iv) history of stroke, transient ischemic attack (TIA), or hemodynamically significant carotid stenosis; (v) uncontrolled hypertension, dyslipidemia, or diabetes; (vi) history of unrelated neurological disease; (vii) pulmonary disease; and (viii) medications known to interfere with CVR measurements.

Image Acquisition

All studies were performed at the Toronto Western Hospital on a 3-Tesla GE MRI system (Signa HDx platform, GE Healthcare, Milwaukee, WI, USA) using an eight-channel phased array head coil. A third generation RespirActTM gas blender was employed for control of P_{ET}CO₂ during the BOLD CVR sequence. All patients underwent T1-weighted structural imaging, followed by a T2*-weighted axial single-shot BOLD CVR image, 2D FLAIR image, and a proton density/T2-weighted sequence. Full imaging parameters are included in Supplement 1.

Vasodilatory Stimulus

Assessing CVR requires the delivery of a vasoactive stimulus. In this study, a standardized hypercapnic breathing stimulus was delivered to each patient during BOLD MRI to fulfill this

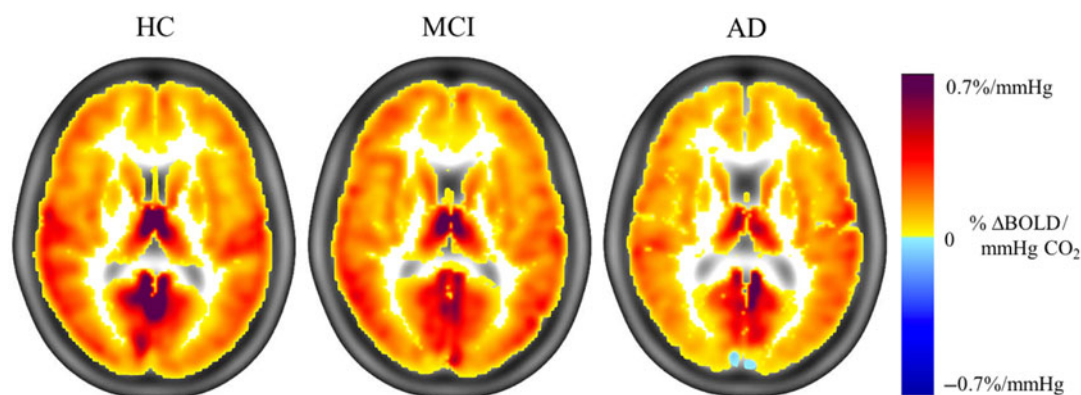


Figure 1: Maps of mean CVR in cortical GM in each group. Color-coded map of mean CVR in cortical GM for each group superimposed on a T1-weighted anatomical map in standard space. Purple/red/orange/yellow indicate a graded positive CVR response, while blues indicate a reduction in blood flow to the vasodilatory stimulus (steal physiology).

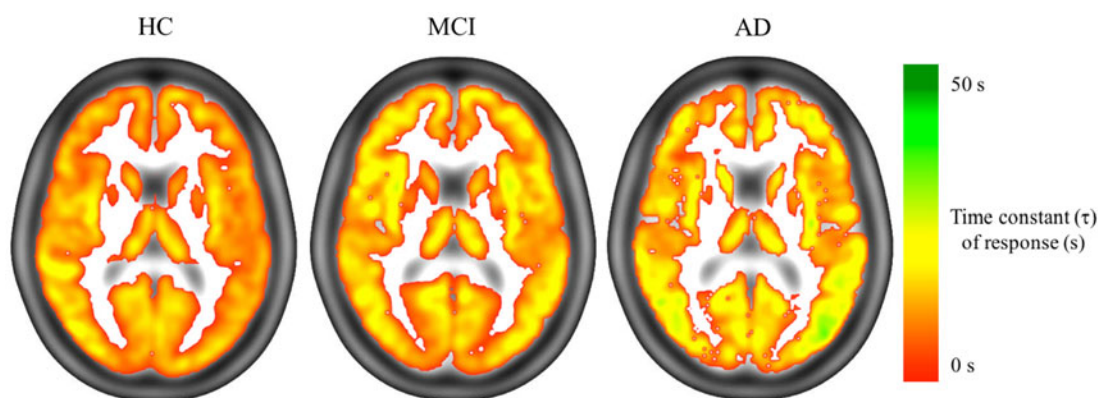


Figure 2: Maps of mean time constant (τ) of the cerebrovascular response in cortical GM in each group. Color-coded map of mean τ value in cortical GM for each group superimposed on a T1-weighted anatomical map in standard space. Reds and oranges indicate smaller τ values and a faster cerebrovascular response to hypercapnia, while greens indicate larger τ values and a slower cerebrovascular response.

requirement. Control of $P_{ET}CO_2$ was achieved, enabling control of alveolar ventilation, using the RespirAct™ system (Thornhill Medical Inc., Toronto, Canada). For this study, a standardized CO_2 inspiratory stimulus was implemented, consisting of the following: baseline for 120 s at subject's resting $P_{ET}CO_2$, a hypercapnic step of 10 mmHg above resting for 120 s (rise time = two breaths), baseline for 150 s, a hypocapnic step of 10 mmHg below resting followed immediately by a gradual ramp up to 15 mmHg above resting lasting 270 s, and a final baseline for 120 s, all during normoxia.

Calculating CVR and Speed of Cerebrovascular Reactivity

After initial processing of raw BOLD images, scans with greater than 2 mm of motion were discarded. CVR was then calculated as the regression coefficient of a linear, least-squares fit of the BOLD signal to the $P_{ET}CO_2$ time series on a per voxel basis.²⁸ CVR is expressed as the percent change in BOLD signal per mmHg change in $P_{ET}CO_2$. For visualization purposes, the CVR value in each voxel can be assigned a color and superimposed on the corresponding voxel of the anatomical images (using real-time linear interpolation) to produce a color-coded CVR map (Figure 1).

Calculating the speed of the cerebrovascular response has been previously described.²⁴ In short, the BOLD response to the hypercapnic step change in CO_2 was modeled by convolving the $P_{ET}CO_2$ time series with a hemodynamic response function in the form of an exponential decay function, $\exp(-t/\tau)$ where t is time and τ is the time constant of the cerebrovascular response. Pearson correlation testing was then used to identify the τ value most correlated with the observed BOLD response to the vasodilatory stimulus. This τ value represents the speed of response expressed in seconds. Therefore, smaller τ values reflect a faster cerebrovascular response, while larger τ values reflect a slower response. The τ value in each voxel is then assigned a color and superimposed on the corresponding voxel of the anatomical images (using real-time linear interpolation) to produce a color-coded τ map (Figure 2). Further details regarding BOLD signal processing and calculation of both CVR and speed of cerebrovascular response are included in Supplement 1.

Partial Volume Correction

Progressive cortical atrophy is a cardinal feature of AD and may cause a partial volume effect in imaging data. To address this potential confound, the analysis was confined to cortical gray

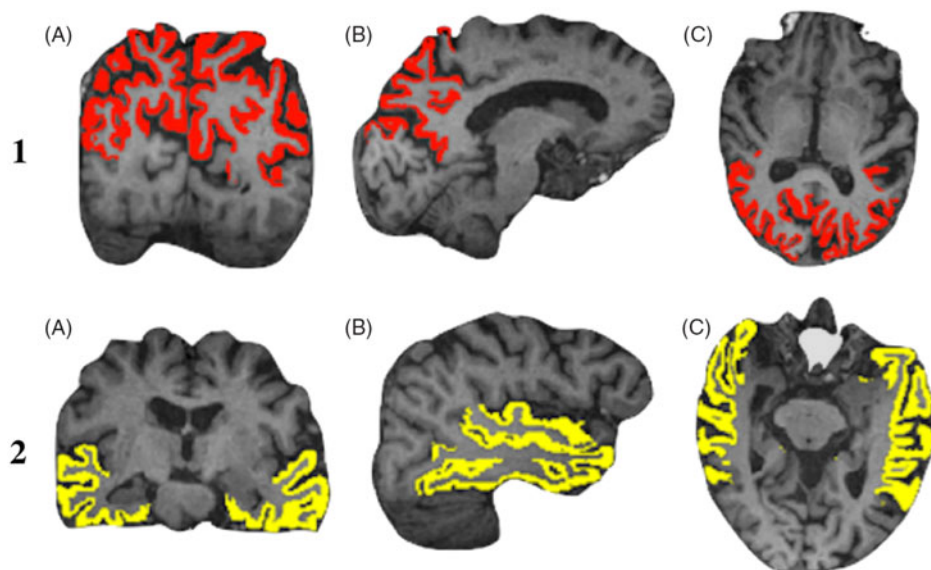


Figure 3: ROIs in an example subject. Panel 1 shows the (A) coronal, (B) sagittal, and (C) axial views of the parietal cortex ROI (red), whereas panel 2 shows the (A) coronal, (B) and sagittal, (C) axial views of the temporal cortex ROI (yellow).

matter (GM) and a correction was applied to both the CVR and τ values in each voxel to account for variability in the proportion of GM and WM within the voxel. This correction is further described in Supplement 1.

Generation of ROIs

Two ROIs were included in the analysis, namely the temporal and parietal cortices. These two regions were selected due to their established selective vulnerability in AD. The ROIs were generated from the T1-weighted anatomical images using the FreeSurfer image analysis suite. First, anatomical images underwent a bias field correction and GM/WM segmentation. Then, cortical surface models of the GM/WM boundary and pial surface were reconstructed, followed by parcellation and labeling of the cortical surface. Whole-lobe cortical ROIs were then constructed for the temporal and parietal cortex for each subject and visually inspected for quality (Figure 3).

Assessment of White Matter Hyperintensity (WMH) Burden

To ensure that any group differences in CVR or the speed of cerebrovascular response were not the result of group differences in small vessel disease, the WMH burden was scored for each patient as a surrogate measure of microvascular disease and added to subsequent statistical analyses as a covariate of no interest. To accomplish this, WMH burden was scored by an experienced neuroradiologist (DJM), blinded to group membership, for each patient according to the Fazekas scale using proton density/T2-weighted images and 2D FLAIR images.²⁹

Statistical Analyses

All statistical analyses were completed using IBM SPSS Statistics (IBM SPSS Statistics for Macintosh, Version 21.0, Armonk, NY, USA). To assess differences in CVR and speed of cerebrovascular response (τ) among AD, MCI, and HC groups, a one-way ANCOVA was carried out for both measures, CVR

and τ , in both ROIs, while correcting for age and Fazekas score. Also, the assumptions of homogeneity of variances and normality of residuals were tested using Levene's test and the Shapiro–Wilk test, respectively. In the event of a statistically significant finding, Bonferroni-corrected *post-hoc* testing assessed pairwise comparisons.

RESULTS

Among the 33 subjects recruited to participate in this study, 3 individuals were excluded due to: (i) incomplete imaging protocol due to study drop-out ($n = 1$), (ii) poor/unsatisfactory acquisition quality ($n = 1$), and (iii) scanner-related image artifact ($n = 1$). Altogether, 30 subjects remained for analysis, consisting of 6 AD subjects, 11 MCI, and 13 older HCs. Table 1 summarizes all demographic data for each group.

Descriptive statistics for CVR in each ROI in each group are summarized in Table 2 and visualized in Figure 4. Group maps of mean CVR in cortical GM are presented in Figure 1. The assumptions of homogeneity of variances and normality of residuals were found to be satisfactory. In the temporal cortex, mean CVR was greatest in the MCI group (measured as $\% \Delta \text{BOLD}/\text{mmHg}$ with standard deviations in Table 2) at 0.527 and lowest in the HC group at 0.515, with AD possessing an intermediate mean CVR value of 0.519. In the parietal cortex, mean CVR was greatest in the MCI group at 0.410 and lowest in the AD group at 0.365, with HC possessing an intermediate mean CVR value of 0.384. The between-groups ANCOVA found no significant main effect in either the temporal cortex, $F(2,29) = 0.38$, $p = 0.69$, or the parietal cortex, $F(2,29) = 1.32$, $p = 0.29$.

Descriptive statistics for speed of cerebrovascular response in each ROI in each group are summarized in Table 3 and visualized in Figure 5. Group maps of the time constant (τ) of the cerebrovascular response in cortical GM are presented in Figure 2. The assumptions of homogeneity of variances and normality of residuals were found to be satisfactory. In both the temporal and

Table 1: Patient demographics

		HC (n = 13)	MCI (n = 11)	AD (n = 6)
Age		63.9 ± 10.2	73.1 ± 5.7	70.5 ± 5.8
Gender	Female	4	4	2
	Male	9	7	4
Vascular risk factors	Hypertension	1	2	2
	Dyslipidemia	1	2	3
	Diabetes mellitus	0	0	1
	Smoking	0	1	0
Medications	AChE inhibitor	0	0	1
	Antidepressant	1	1	2
	Antihypertensive	1	2	2
	Statin	1	1	1
	Beta-blocker	0	1	2
	Platelet drug	0	0	2
	Insulin/Metformin	0	0	1
Fazekas score		0.69 ± 0.75	1.64 ± 0.81	1.00 ± 0.63
MoCA		n/a	23.4 ± 1.99	18.3 ± 1.71

For MoCA testing, $n = 7$ for MCI and $n = 4$ for AD.

Table 2: CVR in temporal and parietal ROIs across HC, MCI, and AD groups

Cortical ROI	Group	Mean CVR (%/mmHg)	Std. Deviation	Est. Marg. Mean
Temporal	HC	0.515	0.064	0.504
	MCI	0.527	0.136	0.544
	AD	0.519	0.094	0.512
Parietal	HC	0.384	0.060	0.365
	MCI	0.410	0.118	0.429
	AD	0.365	0.073	0.368

parietal cortices, mean τ of the cerebrovascular response was greatest in the AD group at 44.5 and 48.3 s, respectively. It was lowest in the HC group at 26.4 and 23.7 s, respectively, with MCI possessing intermediate mean τ values of 34.2 and 34.3 s, respectively. This indicates that the mean speed of cerebrovascular response was fastest in the HC group and slowest in the AD group in both ROIs. The between-groups ANCOVAs found significant effects in both the temporal and parietal cortices (temporal: $F(2,29) = 3.93$, $p = 0.03$; parietal: $F(2,29) = 5.05$, $p = 0.01$). Bonferroni-corrected *post-hoc* testing revealed significantly increased τ in the AD group compared to the HC group in both the temporal ($p = 0.03$) and parietal cortex ($p = 0.01$); however, the MCI group was not significantly different from either group.

DISCUSSION

Impaired cerebral vasoreactivity is now increasingly recognized as a potential contributor to AD.³⁰ This study aimed to

evaluate both CVR and speed of cerebrovascular response to CO₂ in amnesic MCI and AD patients using a repeatable and reproducible methodology. This was achieved with a gas blending apparatus that enabled tight control of arterial pCO₂. This allowed delivery of a hypercapnic stimulus optimized for measuring both CVR and speed of cerebrovascular response. The initial abrupt pCO₂ step change is ideal for assessing speed of response as gradual increases in P_aCO₂ will make it difficult to resolve vascular responses with a time course shorter than that of the stimulus. On the other hand, the ramp component is delay insensitive, allowing for the CVR to be assessed with minimal confound due to delayed responses. In comparison, previous studies have generally used a fixed inspired CO₂ challenge, which results in a biexponential rise in P_aCO₂ that is influenced by minute ventilation and cannot be accurately quantified by measuring P_{ET}CO₂.³¹ Ultimately, we found that development of AD is associated with a slowing of the cerebrovascular response, and that this deficit cannot be explained by differences in age or microangiopathy. However, we were unable to detect any CVR impairment in either the MCI or AD groups. Nevertheless, our findings support the hypothesis that abnormal vascular responses may play a meaningful role in the pathophysiology of AD.

Failing to detect CVR impairment in either the temporal or parietal cortex was not entirely unexpected given the inconsistency of recent reports investigating CVR in AD, especially with respect to these two cortical regions. Our CVR findings are generally consistent with Yezhuvath and colleagues, who used BOLD MRI and fixed inspired CO₂ to examine CVR in 17 AD patients and 17 age-matched controls.²² Despite observing a resting CBF reduction in posterior cortical structures, the authors observed no significant CVR impairment in the temporal or parietal cortex. Conversely, our CVR results conflict with the findings of Cantin and colleagues, who reported a widespread CVR deficit in both AD ($n = 9$) and MCI ($n = 7$) groups that was statistically significant in both the temporal and parietal cortices of both MCI and AD groups.²³ Altogether, our findings refute the notion that CVR deficits occur in the temporal or parietal cortex in AD patients. This may be due to the study design that was employed that enabled precise control of the vasodilatory stimulus as well as the aggressive approach used to control partial volume averaging errors that can arise from brain atrophy. Nonetheless, CVR deficits may be present elsewhere in the brain. If that were the case, it would be unlikely that they are related to the characteristic hypoperfusion found in AD, which typically predominates in the temporal and parietal cortices.

Our findings of slowed vasoreactivity in both the temporal and parietal cortex are consistent with the current body of work on the subject. Richiardi and colleagues reported a global slowing of the cerebrovascular response to inhaled CO₂ in both AD and MCI patients when compared with older HCs;²⁵ in particular, a delayed response was found in the temporal and parietal cortices in the AD group. Cantin and colleagues also observed a different slope to the BOLD response to hypercapnia in MCI and AD groups compared to controls, suggesting that the temporal dynamics of CVR may be altered by the disease.²³ Moreover, AD and MCI patients have been shown to elicit delayed BOLD responses to visual encoding tasks.³² An inference can be drawn that slowing of the vasodilatory vascular response may be due to a decrease in vascular compliance. Furthermore, it is tempting to link this loss of compliance with recent work in a rodent model of

Table 3: Time constant (τ) of the cerebrovascular response to CO₂ across HC, MCI, and AD groups

Cortical ROI	Group	Mean τ (s)	Std. Deviation	Est. Marg. Mean (s)
Temporal	HC	26.4	11.5	27.6
	MCI	34.2	12.9	32.7
	AD	44.5	7.8	44.6
Parietal	HC	23.7	12.9	25.1
	MCI	34.3	16.5	32.5
	AD	48.3	11.6	48.6

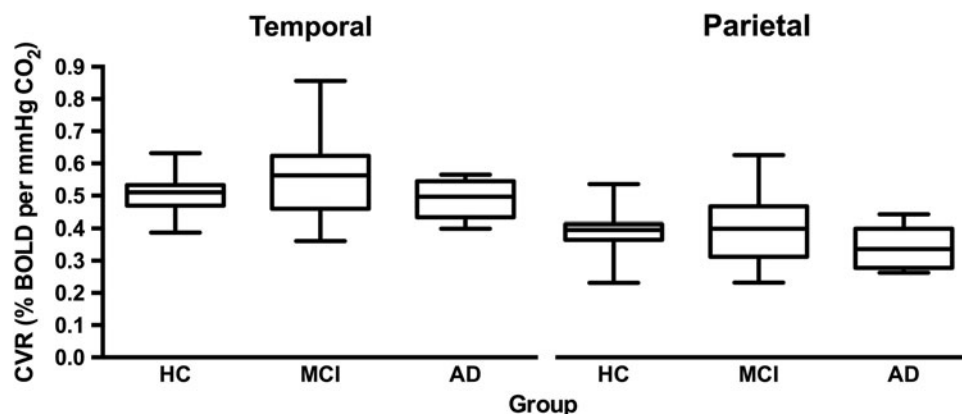


Figure 4: CVR in the temporal and parietal cortex across groups. CVR values are reported as % change in BOLD per mmHg change on $P_{ET}CO_2$. Bars indicate minimum and maximum, boxes indicate the interquartile range, and the middle line denotes the median. No significant group differences were found in CVR in either cortical ROI.

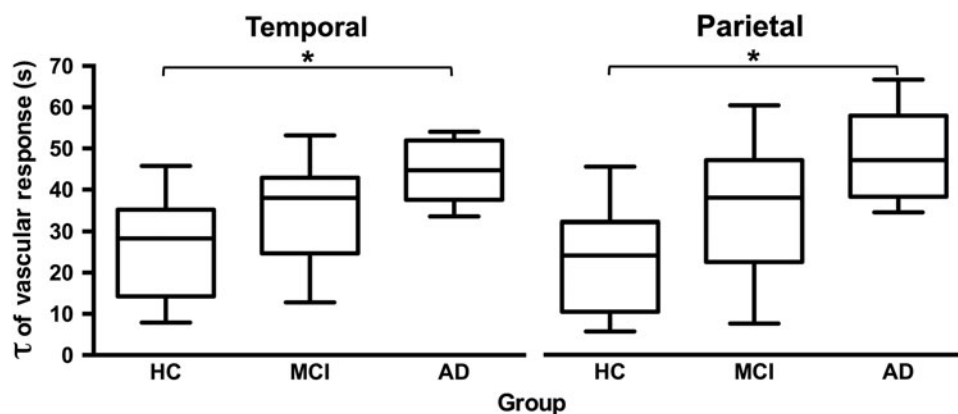


Figure 5: Time constant (τ) of the cerebrovascular response to CO₂ in temporal and parietal cortex across groups. τ values are reported in seconds. Bars indicate minimum and maximum, boxes indicate the interquartile range, and the middle line denotes the median value. Higher values indicate a slower speed of response. * denotes significance compared to HC ($p < 0.05$). ANCOVA testing yielded a significant group effect on τ for both the temporal ($p = 0.03$) and parietal ($p = 0.01$) cortex, and Bonferroni-corrected *post-hoc* testing determined that τ was significantly greater in the AD group than the HC group in both cortical ROIs ($p = 0.03$ and 0.01 , respectively).

AD showing radial bands of amyloid protein deposition separating endothelial cells from glial foot processes in the cerebral microvessels.³³

A slowed vascular response may directly confer an ischemic burden present in AD by adding a significant delay between neural activity and the resultant increase in CBF to support it.

While the associated vascular deficit would be temporary, it may give rise to short ischemic ‘events’ during neuronal signaling activity. Due to the protracted disease latency of AD, the relatively small burden of these events may gradually accumulate over years or even decades, contributing to the total ischemic burden in AD in a meaningful way. In addition, as an indicator of

poor vascular compliance, reduced speed of response in cerebral vessels may partially explain findings of impaired cerebral autoregulation in AD.³⁴ Lastly, reduced speed of the cerebrovascular response may also reflect a mechanism for impaired glymphatic flow in AD. A recent study by Peng and colleagues found that in a mouse model of AD, glymphatic transport was significantly reduced compared to wild-type.³⁵ The driving force of glymphatic transport is still not fully understood, but recent evidence indicates that smooth muscle pulsation may drive CSF into the interstitial compartment.^{36,37} Slowed vasoreactivity may indicate impaired arteriolar pulsatility and, potentially, poor clearance of amyloid- β and other waste products. Together, these represent three plausible mechanisms by which reduced speed of the cerebrovascular response could contribute to the vascular component of AD.

Limitations

The main limitation of this study relates to sample size. Given the modest sample, our study may be underpowered to detect alterations in CVR. Also, this sample does suffer somewhat from a discrepancy in ages and prevalence of vascular risk factors between the groups. Theoretically, age may alter CVR or speed of vascular response. Additionally, vascular risk factors may reflect a greater burden of cerebrovascular disease, which can impair vascular responses. These potential confounders were mitigated by adding age and Fazekas score as a surrogate for cerebral microvascular disease to the statistical analyses as covariates of no interest.

The use of BOLD MRI as a surrogate measure of CBF may represent another potential limitation of this study as BOLD MRI does not directly measure changes in CBF. Instead, BOLD is sensitive to changes in the voxel concentration of deoxyhemoglobin (dHb). Changes in CBF will influence dHb concentration; however, changes in the cerebral metabolic rate of O₂ (CMRO₂) and cerebral blood volume can also impact dHb concentration and, by extension, may create a nonlinearity effect in the BOLD signal or create a between-subject CVR scaling effect due to variable concentrations of dHb at rest. However, it is thought that CMRO₂ is unaffected and changes in blood volume are negligible during a hypercapnic stimulus, though this cannot be definitively ruled out in this study.

CONCLUSION

Our findings indicate that AD is associated with a slowing of the cerebrovascular response in the temporal and parietal cortex. This preliminary work may provide new insights into the role of vascular dysregulation in the pathogenesis and progression of AD. Further evaluation of the relationship between speed of the cerebrovascular response and relevant cognitive measures may identify specific contributions of hemodynamic impairment to the functional progression of AD, and thus may be of interest for future studies. Finally, early detection of future AD may be possible at the MCI stage of the disease by comparing the speed of response of MCI subjects against normal control atlases using an as yet to be determined threshold defined by the number of standard deviations below normal responses. If this could be validated in a larger sample size, it could represent a valuable clinical predictor of AD. With disease-modifying therapies on the horizon, this may prove clinically useful in identifying candidates for therapy.

ACKNOWLEDGMENTS

We are grateful to the Toronto Western Hospital, including research coordinator Abby Skanda, and MR imaging technologists Keith Ta and Eugen Hlasny.

STATEMENT OF AUTHORSHIP

KRH was involved in all aspects of the research including research design, acquisition of data, image processing, statistical analysis, and manuscript generation. DTW and MCT assessed and selected subjects for study inclusion. KS, LM, OS, JD, JAF, JP, and APC assisted in implementation of breathing protocol, image acquisition and post-processing methodology. MC provided neuropsychological protocol, data collection, and analysis. BW was involved in development of external funding proposal and advised on implementation of research protocol. SEB and DJM were members of KRH's MSc program advisory committee and supervised all aspects of this research. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

KRH and DM received financial support for this work from the Canadian Institutes of Health Research. DM received a grant from the American Society of Neuroradiology during the conduct of this study. JF and JD are senior scientists at Thornhill Research Inc. (TRI), a spin-off company affiliated with the University Health Network that developed the RespirAct™, a non-commercial research tool assembled by TRI to enable cerebrovascular reactivity studies. JF and DM hold a patent related to the RespirAct™. Also, DM is a shareholder in TRI and reports non-financial support from TRI. OS is a part time employee of TRI. Outside of the submitted work, SEB reports institutional grants from GE Healthcare, Eli Lilly, Biogen, Novartis, Genentech, Optina, Roche, and personal fees from Novartis, Roche, and Eli Lilly. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <https://doi.org/10.1017/cjn.2020.30>.

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