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Cerebrovascular Reactivity Across the Entire Brain in Cerebral Amyloid Angiopathy

Andrew E. Beaudin, PhD, Cheryl R. McCreary, PhD, Erin L. Mazerolle, PhD, Myrlene Gee, PhD, Breni Sharma, MSc, Arsenije Subotic, MSc, Angela M. Zwiers, MSc, Emily Cox, BSc, Krista Nelles, BSc, Anna Charlton, BSc, Richard Frayne, PhD, Zahinoor Ismail, MD, Christian Beaulieu, PhD, Glen C. Jickling, MD, Richard M. Camicioli, MD, G. Bruce Pike, PhD, and Eric E. Smith, MD, MPH

Correspondence
Dr. Beaudin
abeaudin@ucalgary.ca

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Abstract

Background and Objectives

Reduced cerebrovascular reactivity is proposed to be a feature of cerebral amyloid angiopathy (CAA) but has not been measured directly. Employing a global vasodilatory stimulus (hypercapnia), this study assessed the relationships between cerebrovascular reactivity and MRI markers of CAA and cognitive function.

Methods

In a cross-sectional study, individuals with probable CAA, mild cognitive impairment, or dementia due to Alzheimer disease and healthy controls underwent neuropsychological testing and an MRI that included a 5% carbon dioxide challenge. Cerebrovascular reactivity was compared across groups controlling for age, sex, and the presence of hypertension, and its associations with MRI markers of CAA in participants with CAA and with cognition across all participants were determined using multivariable linear regression adjusting for group, age, sex, education, and the presence of hypertension.

Results

Cerebrovascular reactivity data (mean ± SD) were available for 26 participants with CAA (9 female; 74.4 ± 7.7 years), 19 participants with mild cognitive impairment (5 female; 72.1 ± 8.5 years), 12 participants with dementia due to Alzheimer disease (4 female; 69.4 ± 6.6 years), and 39 healthy controls (30 female; 68.8 ± 5.4 years). Gray and whiter matter reactivity averaged across the entire brain was lower in participants with CAA and Alzheimer disease dementia compared to healthy controls, with a predominantly posterior distribution of lower reactivity in both groups. Higher white matter hyperintensity volume was associated with lower white matter reactivity (standardized coefficient [β], 95% CI −0.48, −0.90 to −0.01). Higher gray matter reactivity was associated with better global cognitive function (β 0.19, 0.03–0.36), memory (β 0.21, 0.07–0.36), executive function (β 0.20, 0.02–0.39), and processing speed (β 0.27, 0.10–0.45) and higher white matter reactivity was associated with higher memory (β 0.22, 0.08–0.36) and processing speed (β 0.23, 0.06–0.40).

Conclusions

Reduced cerebrovascular reactivity is a core feature of CAA and its assessment may provide an additional biomarker for disease severity and cognitive impairment.

From the Department of Clinical Neurosciences (A.E.B., C.R.M., B.S., A.S., A.M.Z., E.C., A.C., R.F., Z.I., G.B.P., E.E.S.), Hotchkiss Brain Institute (A.E.B., C.R.M., E.L.M., B.S., A.S., A.M.Z., E.C., A.C., R.F., Z.I., G.B.P., E.E.S.), Department of Radiology (C.R.M., E.L.M., R.F., G.B.P., E.E.S.), Department of Psychiatry (Z.I.), and Mathison Centre for Mental Health Research & Education (Z.I.), University of Calgary; Seaman Family MR Research Centre, Foothills Medical Centre (C.R.M., R.F., G.B.P., E.E.S.), Alberta Health Services, Calgary; Department of Psychology (E.L.M.), St. Francis Xavier University, Antigonish; and Division of Neurology and Department of Medicine (M.G., K.N., G.C.J., R.C.), Department of Biomedical Engineering (C.B.), and Neuroscience and Mental Health Institute (R.C.), University of Alberta, Edmonton, Canada.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **BOLD** = blood oxygen level–dependent; **BVMT-R** = Brief Visuospatial Memory Test–Revised; **CAA** = cerebral amyloid angiopathy; **CDR** = Clinical Dementia Rating; **CMB** = cerebral microbleed; **cSS** = cortical superficial siderosis; **CVR** = cerebrovascular reactivity; **DSC** = Digit–Symbol Coding subtest of the Wechsler Adult Intelligence Scale, 3rd Edition; **FLAIR** = fluid-attenuated inversion recovery; **GM** = gray matter; **GRE** = gradient recalled echo; **HC** = healthy control; **IADL** = Instrumental Activities of Daily Living; **ICH** = intracerebral hemorrhage; **MAD** = median absolute deviation; **MCI** = mild cognitive impairment; **MoCA** = Montreal Cognitive Assessment total score; **PSMD** = peak width of skeletonized mean diffusivity; **PVE** = partial volume estimate; **RAVLT** = Rey Auditory Verbal Learning Test; **SVD** = small vessel disease; **TFNE** = transient focal neurologic event; **TMT** = Trail Making Test; **VFT** = Verbal Fluency Test; **WM** = white matter.

Cerebral amyloid angiopathy (CAA) is a small vessel disease (SVD) caused by deposition of β-amyloid (Aβ) in the media and adventitia of small blood vessels of the brain and leptomeninges.[1] It causes 5%–20% of intracerebral hemorrhages (ICH)[2] and is a recognized cause of cerebral microbleeds (CMBs), white matter lesions of presumed vascular origin, cortical superficial siderosis (cSS), dilated perivascular spaces, and microinfarcts.[3] CAA is also associated with cognitive decline and causes ~7% of dementia cases.[4,5]

In patients with CAA, a greater burden of hemorrhagic (ICH, CMBs, and cSS) and ischemic (white matter lesion and microinfarcts) consequences is associated with cognitive impairment.[6] Another potential mechanism is reduced cerebrovascular reactivity (CVR), which limits the ability of brain regions to receive higher blood flow when needed. Reduced CVR has been observed in transgenic mouse models of CAA[7] and patients with CAA,[8-11] but its relationship with neuroimaging markers of CAA and cognitive function in CAA is poorly characterized. Furthermore, lower CVR in patients with CAA has only been observed as a reduced blood flow response through the posterior cerebral artery in response to a visual task,[12] reduced increase in blood flow through the posterior and middle cerebral arteries during a standardized breath hold test,[13] and a lower response amplitude in blood oxygen level–dependent (BOLD) functional MRI during a visual task.[8-11] There are no data regarding the distribution of reduced CVR over the entire brain or how gray and white matter CVR may relate to the hemorrhagic, ischemic, and cognitive consequences of CAA.

Alzheimer disease (AD) shares many pathophysiologic links with CAA.[14] Both are characterized by accumulation of Aβ, and AD pathology may coexist with CAA pathology on a spectrum from only vascular Aβ deposition characteristic of pure CAA to only parenchymal Aβ deposition characteristic of pure AD.[15] Some studies suggest that patients with AD have lower CVR compared to healthy controls.[16] Therefore, concurrent AD pathology must be considered to potentially contribute to the reduced CVR and cognitive impairment observed in CAA.

The objectives of the current study were to assess CVR across the entire brain in patients with CAA using a hypercapnic gas challenge; compare CVR between individuals with CAA, mild cognitive impairment (MCI), or AD and healthy controls; and investigate the relationship between CVR and MRI markers of CAA and cognitive function.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was performed according to the tenets of the Declaration of Helsinki and approved by the Conjoint Health Research Ethics Board of the University of Calgary (REB15-0601) and the Health Research Ethics Board of the University of Alberta (Pro00067006). Participants were informed of study requirements prior to providing written informed consent.

Study Population

Individuals ≥55 years of age without neurologic or psychiatric disorders or contraindications for MRI at 3T were recruited. Participants meeting the modified Boston criteria for probable CAA[17] were recruited through stroke prevention and cognitive clinics in Calgary and Edmonton, Canada. Participants presented with ICH, transient focal neurologic events (TFNE), or MCI. Acute effects of ICH were avoided by excluding participants with recent (<90 days) symptomatic stroke. Participants with CAA-related inflammation were studied during remission when there was no evidence of cerebral edema on fluid-attenuated inversion recovery (FLAIR) MRI. Participants without CAA with MCI were recruited from memory clinics and community advertisements and reported concern regarding a change in cognition; had a Clinical Dementia Rating (CDR) score ≤0.5; ≥1 of Logical Memory II (Delayed Recall) score <9 (16 years of education), <5 (8–15 years of education), or <3 (0–7 years of education), Consortium to Establish a Registry for Alzheimer's Disease Word List Recall <6, Montreal Cognitive Assessment (MoCA) score ≤24, and global CDR >0; and maintained activities of daily living (Lawton-Brody Instrumental Activities of Daily Living [IADL] ≥15). Participants were considered to have non–CAA-related MCI if they lacked multiple cortical or cortical–subcortical hemorrhages or the combination of a single lobar, cortical, or cortical–subcortical

hemorrhage and cSS and MRI features consistent with the modified Boston criteria for probable CAA.[17] Participants with a prior diagnosis of AD with dementia ("AD dementia") were recruited from memory clinics. Diagnosis was based on the National Institute on Aging and the Alzheimer's Association clinical criteria for mild dementia due to AD[18] and confirmed using the following criteria from the Canada-wide Comprehensive Assessment of Neurodegeneration and Dementia study[19]: a gradual decline in memory or other cognitive functions over >6 months, ≥1 of the cognitive impairments listed for MCI, reported changes in personality/behavior, and impaired activities of daily living (Lawton-Brody IADL <15). Participants with AD dementia were included if they lacked MRI features indicative of probable CAA, similar to participants with MCI.[17] Healthy controls (HCs) were recruited through community posters and newsletters and were screened by medical history and neuropsychological testing for the absence of stroke, MCI, or dementia.

Study Protocol

All participants underwent a comprehensive neuropsychological examination by qualified personnel and an MRI that included a hypercapnic gas challenge to assess CVR across the entire brain.

Neuropsychological tests included the MoCA, Delis–Kaplan Executive Function System Verbal Fluency Test (VFT), Reitan Trail Making Test (TMT), Brief Visuospatial Memory Test–Revised (BVMT-R), the Rey Auditory Verbal Learning Test (RAVLT), and the Digit–Symbol Coding subtest of the Wechsler Adult Intelligence Scale, 3rd Edition (DSC). Raw test scores were converted into *z* scores using normative data provided in test manuals and published literature.[20,21] A memory *z* score was derived by averaging the BVMT-R and RAVLT delayed recall *z* scores; an executive function *z* score was calculated as the mean of the TMT Part B and the VFT letter fluency *z* scores; and a processing speed *z* score was the mean of TMT Part A and DSC *z* scores.

In Calgary, MRI was performed on a 3T Discovery 750 (GE Healthcare) using a 32-channel receive-only coil (Nova Medical). In Edmonton, imaging was performed on a 3T Prisma using a 64- or 20-channel receive-only coil (Siemens Healthcare). Imaging at both centers included a 3D T1-weighted anatomical image, T2-weighted FLAIR, T2* gradient recalled echo (GRE), 30-direction diffusion-weighted echoplanar imaging (EPI), and either a dual-echo pseudo-continuous arterial spin labeling sequence with a 2D EPI readout[22] or a BOLD 2D EPI acquisition for the hypercapnic challenge. For the dual-echo sequence, BOLD images from echo 2 were used to quantify CVR to hypercapnia. MRI acquisition parameters are provided in eTable 1, links.lww.com/WNL/B835.

The hypercapnic challenge consisted of breathing medical air for 6 minutes, a normoxic-hypercapnic gas mixture (5% CO_2, 21% O_2, balance N_2) for 2 minutes, and then medical air for a final 2 minutes. Gases were delivered continuously at 20 L/min using an automated gas delivery system.[22] The participant wore an anesthetic face mask (Quadralite; Intersurgical Ltd.) connected to a nonrebreathing circuit with a gas reservoir open to room air on the gas delivery side. Respiratory gases were sampled continuously from a port ~2 cm from the participant's mouth and analyzed for the fraction of CO_2 and O_2 via fast responding gas analyzers (CO2100C and O2100C; BIOPAC Systems Inc.).

To compare CVR measures between sites, 2 healthy individuals (one woman, 50 years of age; and one man, 41 years of age) were scanned at both sites with ~3 weeks between scans.

Radiologic Review

A single experienced neuroradiologist performed all radiologic reviews without knowledge of participant group assignment. The presence of CMBs, cSS, and enlarged perivascular spaces was assessed on T2* GRE images and WMH burden was rated according to the Fazekas scale.[23] A total CAA-related SVD burden score (maximum 6) was calculated based on lobar CMBs (2–4 = 1 point; ≥5 = 2 points), cSS (focal = 1 point; disseminated = 2 points), enlarged perivascular spaces within the centrum semiovale (>20 = 1 point), and moderate WMH burden (Fazekas ≥2 = 1 point).[24] WMH volume was quantified on FLAIR images by qualified readers using a semiautomated seed-based 3D region growing algorithm (Cerebra-Lesion-Extractor v1.1.2, CIPAC, University of Calgary).

MRI Processing

Whole brain microstructural disruption of white matter was quantified via the peak width of skeletonized mean diffusivity (PSMD) calculated from diffusion-weighted images[25] and tools from the FMRIB Software Library (FSL v6.0.0).[26] Higher PSMD indicates greater white matter mean diffusivity variability, a measure reflecting greater disruption of white matter microarchitecture.[6] Cortical thickness was measured from T1-weighted images with FreeSurfer (v6.0).[27]

BOLD 4D images were cropped so that CVR was quantified using the final 6 minutes of the hypercapnic challenge (2 minutes air–2 minutes hypercapnia–2 minutes air). Images were motion-corrected and smoothed with a 5-mm full width at half maximum gaussian kernel (SPM12, Wellcome Trust Centre for Neuroimaging) and skull-stripped using FSL's Brain Extraction Tool.[28] The voxel-wise BOLD time course was modeled using the FSL Expert Analysis Tool (FEAT)[29] by convolving the 6 minutes hypercapnia stimulus paradigm with a gamma function (mean lag: 30 seconds; SD: 15 seconds). The model also included a temporal derivative regressor to account for temporal delays in BOLD signal during the on- and off-hypercapnia transitions and a linear drift nuisance regressor. For images acquired with the dual-echo sequence, the model also included an ASL tag-control nuisance regressor. Voxel-wise BOLD percent signal change maps were created by dividing the modeled hypercapnic effect

size by the estimated constant (baseline) term.[22] Voxels with a signal increase ≥10% were removed as this magnitude of change is indicative of cerebral veins rather than parenchyma.[30] Next, CVR maps were created by dividing the BOLD percent signal change maps by the change in partial pressure of end-tidal CO_2 (P_{ETco2}) from the 2 minutes air-breathing baseline to the last minute of hypercapnia. Thus, CVR was expressed as a % Δ BOLD/mm Hg increase in P_{ETco2}.

Subcortical structures (putamen, caudate, globus pallidus, nucleus accumbens, thalamus, amygdala, hippocampus, amygdala, cerebellum, and brainstem) were removed from CVR maps using an exclusion mask modified from the FSL Brain Intensity Abnormality Classification Algorithm tool.[31] Areas of ICH were removed using ICH masks created from FLAIR images registered to BOLD space.

To calculate gray matter (GM) and white matter (WM) CVR, T1-weighted images were skull-stripped and segmented into GM and WM using the FSL FMRIB Automated Segmentation Tool (FAST). Resultant tissue partial volume estimate (PVE) maps were moved into the low-resolution BOLD space and, to account for partial volume effects, voxels with a PVE indicating <50% GM or WM were removed.[32] Maps were then binarized to produce GM and WM masks, which were merged to produce a global brain mask. Cortical GM, supratentorial WM, and global CVR were quantified by multiplying whole brain CVR maps by the respective tissue mask and averaging all nonzero voxels within the resulting CVR maps.

CVR within the primary visual cortex (V1) and the middle temporal gyrus, posterior cingulate, precuneus, and angular gyrus (principal regions affected by AD[33]) were quantified by creating a mask of each region in Montreal Neurological Institute 152 space using the Juelich Histologic Atlas (V1) or the Harvard-Oxford cortical structure atlas (principal regions affected by AD) in FSL. Masks were registered to participant low-resolution BOLD space and CVR was calculated by multiplying participant whole brain CVR maps by each region of interest mask and averaging all nonzero voxels within the resultant CVR maps. CVR within the middle temporal gyrus, posterior cingulate, precuneus, and angular gyrus were averaged to create an AD region-specific CVR ($AD_{regions}$).

Statistical Analyses

Sample size was determined a priori based upon a 2-tailed independent *t* test comparison of CVR between patients with CAA and HC participants. Twenty patients with CAA and 26 HCs were determined to provide ~90% power to detect a similar standardized difference of 1.0 (Cohen *d*) previously observed in vascular reactivity within V1 (percent increase in BOLD signal during visual task) between patients with CAA and HC participants.[9] This sample size was increased to 30 patients with CAA and 40 HCs to provide ~80% power to detect more moderate-sized differences (Cohen *d* 0.7) between patients with CAA and HCs vs patients with either MCI or AD dementia and for greater power to detect associations between CVR and cognition.

Participant characteristics were compared using χ^2 goodness-of-fit tests for categorical variables, 1-way analyses of variance for continuous, normally distributed variables, and Kruskal-Wallis tests for continuous, non-normally distributed variables. Post hoc group comparisons were corrected for multiple comparisons using the Dwass–Steel–Critchlow-Fligner analysis or a Tukey-Kramer correction, respectively.

Detection of CVR outliers was performed using the median absolute deviation (MAD) and all participant data. Participants were removed completely from analyses if their mean MAD score across all 5 CVR measures was >3[34]; otherwise, participants were removed from individual comparisons if their MAD score was >3 for a specific CVR measure. CVR measures were compared between participants with CAA with and without ICH and across groups using analyses of covariance controlling for age, sex, and the presence of hypertension, incorporating a Tukey-Kramer correction for multiple comparisons. Spatial differences in CVR between groups were determined on supratentorial CVR maps using nonparametric permutation-based threshold-free cluster enhancement analyses adjusted for age, sex, and the presence of hypertension with 10,000 permutations via the FSL Permutation Analysis of Linear Models controlling the false discovery rate and familywise error rate across all possible 1-tailed group comparisons (n = 12).[35] Associations between MRI markers of CAA (CMBs, WMH volume, and CAA SVD score), PSMD, and cortical thickness and CVR were assessed within participants with CAA using multivariable linear regression controlling for age, sex, and the presence of hypertension. Lastly, relationships between cognitive scores and CVR were quantified using multivariable linear regression controlling for age, sex, education, and the presence of hypertension. Statistical analyses were performed using Statistical Analysis System (SAS v9.4) and an $\alpha \leq 0.05$ was considered significant.

Data Availability

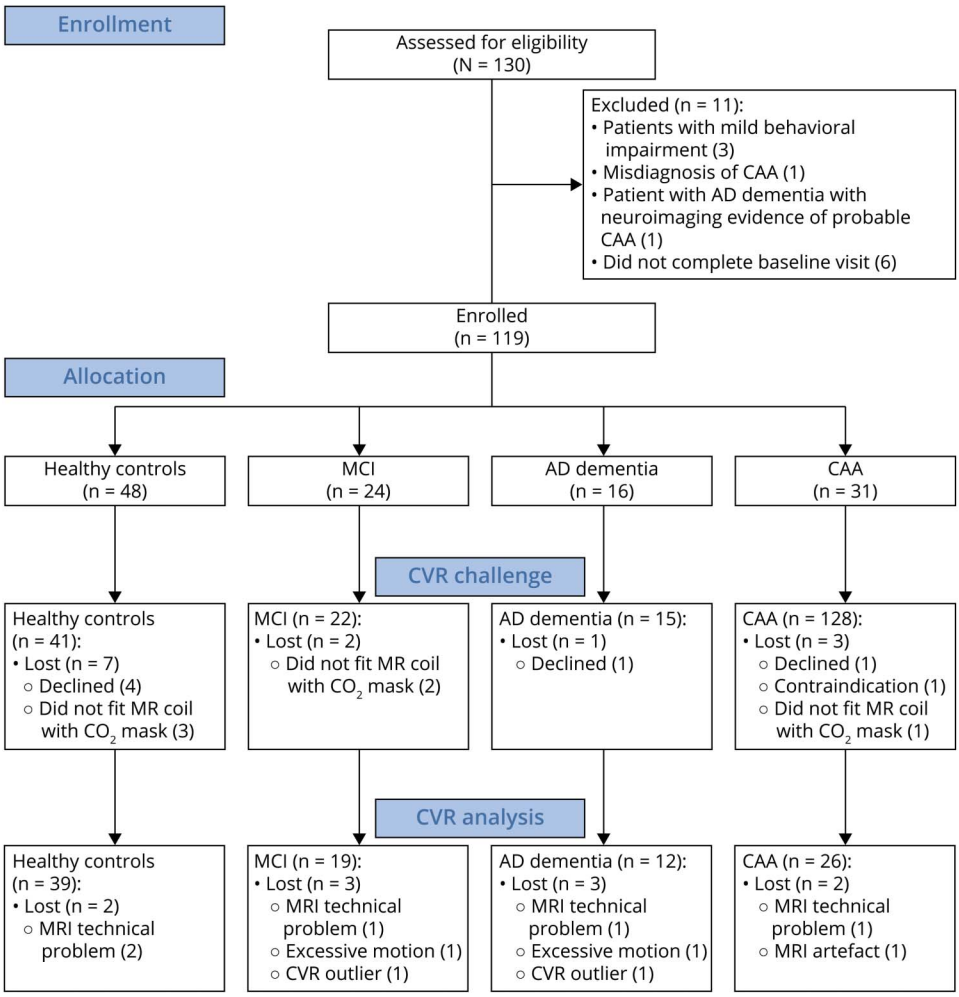
Anonymized data will be made available to other qualified researchers on request to the senior author (E.E.S.).

Results

A total of 130 individuals were assessed for eligibility (Figure 1). Of these, CVR data were available for 96–39 HCs, 19 patients with MCI (18 for V1), 12 patients with AD dementia, and 26 participants with CAA.

Participant characteristics are shown in Table 1. Of the 26 participants with CAA with CVR data, 21 were recruited from stroke clinics and 5 were recruited from memory clinics, 11 presented with ICH, 10 with TFNE, and 5 with MCI. Participants with CAA were older and more likely to be male than

Figure 1 Participant Flow Through Study



A total of 130 individuals were assessed for eligibility. Of those, 119 were enrolled: 48 healthy controls (HC), 24 patients with mild cognitive impairment (MCI), 16 patients with Alzheimer disease (AD) dementia, and 31 patients with cerebral amyloid angiopathy (CAA). Six participants (4 HC, 1 AD, 1 CAA) declined the hypercapnic challenge, 1 participant with CAA was excluded due to a medical contraindication (coronary angioplasty), and 6 participants could not fit the MRI head coil with the CO_2 mask (3 HC, 2 MCI, 1 CAA). All remaining participants who underwent a hypercapnic cerebrovascular reactivity (CVR) challenge completed the entire protocol. Data from 10 participants were excluded (7 were excluded due to technical problems [n = 5: 2 HC, 1 MCI, 1 AD, 1 CAA] or excessive motion [n = 2: 1 MCI, 1 AD]; 1 participant with CAA was excluded due to an artefact on all MRIs; and 2 additional participants [1 MCI, 1 AD] were removed completely from CVR analyses because their mean median absolute deviation values across all CVR metrics were 3.6 and 4.5, respectively).

HCs and to have been diagnosed with hypertension. Cortical thickness was lower in participants with AD dementia and participants with CAA compared to HCs, while all 3 patient groups performed worse on cognitive tests compared to HCs.

There were no differences in CVR across sites (GM, WM, global, and $AD_{regions}$: $p \geq 0.076$; V1: $p = 0.382$) and the between-site coefficient of variation across GM, WM, global, V1, and $AD_{regions}$ CVR for the traveling phantoms was 12.9 ± 12.3% (mean ± SD). There were no differences in GM (estimated mean difference, 95% CI −0.01, −0.07 to 0.05), WM (−0.01, −0.03 to 0.04), global (0.001, −0.05 to 0.05), V1 (−0.02, −0.10 to 0.05), and $AD_{regions}$ (0.0002, −0.06 to 0.06) CVR between participants with CAA who presented with ICH and those who did not ($p \geq 0.536$ for all comparisons adjusted for age, sex, and the presence of hypertension). Therefore, remaining group comparisons did not include site as a covariate and included all 26 participants with CAA.

CVR for each group is shown in Figure 2. Although there was overlap between groups, differences were observed in all CVR measures (GM, $p = 0.003$; WM, $p = 0.010$; global, $p = 0.003$; V1, $p = 0.019$; $AD_{regions}$, $p = 0.001$), with participants with AD dementia and participants with CAA having lower GM, WM, global, and $AD_{regions}$ CVR compared to HCs. For V1, only participants with CAA had a lower CVR compared to HCs.

Figure 3 shows the distribution of brain regions where CVR was lower in patients with CAA or AD dementia compared to HCs. For patients with CAA and patients with AD dementia, there was a predominantly posterior distribution of lower CVR compared to HCs that included the posterior cingulate, precuneus, temporooccipital portion of the middle temporal gyrus, and superior lateral occipital cortex. There were no regional differences in CVR between patients with MCI and HCs.

Associations between CMB count, WMH volume, CAA SVD score, PSMD, and cortical thickness with GM, WM, global, and V1 CVR in participants with CAA are shown in Table 2. Greater WMH volume was associated with lower WM ($p = 0.024$) and global ($p = 0.045$) CVR while increased cortical

Table 1 Participant Characteristics

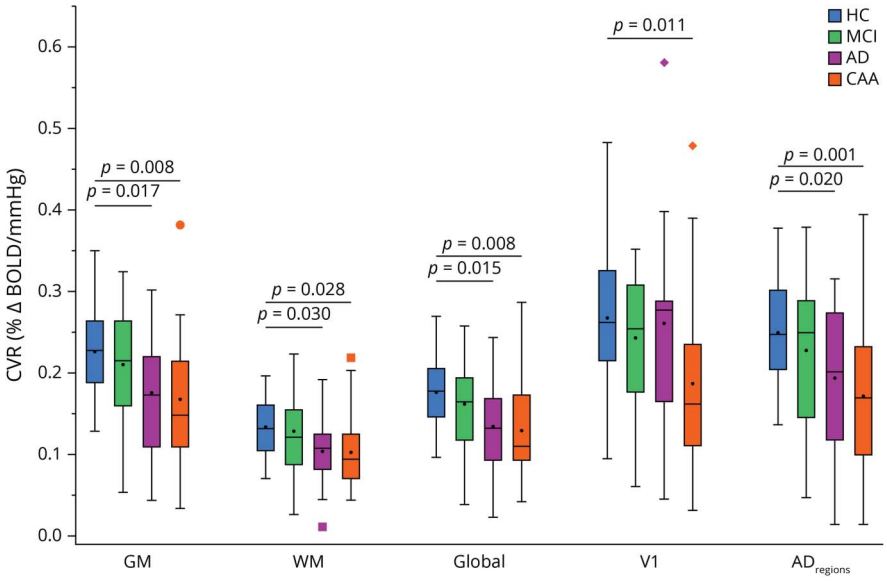
Characteristic	HC	MCI	AD dementia	CAA	*p* Value
N	39	19	12	26	
Female	30 (76.9)	6 (31.6)	4 (33.3)	9 (34.6)	<0.001
Age, y	68.8 ± 5.4	72.1 ± 8.5	69.4 ± 6.6	74.4 ± 7.7[a]	0.013
Education, y	15.8 ± 3.1	15.7 ± 4.3	16.0 ± 3.5	14.1 ± 2.7	0.202
Comorbidities					
Current smoker	0 (0.0); n = 38	0 (0.0)	0 (0.0)	0 (0.0); n = 25	0.638
Past smoker	15 (39.5)	6 (31.6)	5 (41.7)	12 (48.0)	0.745
Never smoked	23 (60.5)	13 (68.4)	7 (58.3)	13 (52.0)	0.745
Hypertension	9 (23.1)	5 (26.3)	4 (33.3)	17 (65.4)	0.004
Hypercholesterolemia	16 (41.0)	11 (57.9)	3 (25.0)	10 (38.5)	0.241
Diabetes	3 (7.7)	3 (15.8)	1 (8.3)	1 (3.8)	0.856
History of ICH	—	—	—	11 (42.3)	—
MRI markers of CAA					
Microbleeds	5 (12.8)	6 (31.6)	0 (0.0)	24 (92.3)	<0.001
CMBs[a]	0 (0–0)	0 (0–1)	0 (0–0)	15 (3–64)[a,b,c]	<0.001
cSS	0 (0)	0 (0.0)	1 (8.3)	17 (65.4)	<0.001
WMH volume, mL	2.9 (1.0–8.0)	5.4 (1.3–14.8)	6.6 (2.6–8.8)	21.7 (10.4–32.9)[a,b,c]	<0.001
WMH volume, % ICV	0.23 (0.06–0.54)	0.33 (0.10–1.05)	0.44 (0.18–0.53)	1.33 (0.95–2.27)[a,b,c]	<0.001
CAA SVD score	0 (0–1)	0 (0–1)	0 (0–1)	4 (3–5)[a,b,c]	<0.001
Additional MRI findings					
PSMD (× 10^{-4} mm^2/s)	2.51 ± 0.46	3.03 ± 0.99	2.90 ± 0.64	4.51 ± 1.34[a,b,c] (n = 25)	<0.001
Lacunes, basal ganglia	2 (5.1)	0 (0.0)	0 (0.0)	2 (7.7)	0.523
Lacunes, centrum semiovale	5 (12.8)	1 (5.3)	2 (16.7)	3 (11.5)	0.774
Cortical thickness, mm	2.45 ± 0.09	2.38 ± 0.09	2.26 ± 0.19[a]	2.28 ± 0.15[a,b] (n = 24)	<0.001
Cognitive scores					
MoCA	27.2 ± 1.6	23.4 ± 2.8[a,c]	18.1 ± 4.1[a,b]	21.2 ± 5.5[a,c]	<0.001
Memory (*z* score)	0.69 ± 0.90	−1.00 ± 1.16[a]	−2.52 ± 0.72[a,b]	−1.56 ± 1.11[a]	<0.001
Executive function (*z* score)	0.50 ± 0.91	−0.72 ± 1.19[a]	−1.58 ± 1.02 [a] (n = 11)	−1.31 ± 1.20[a]	<0.001
Processing speed (*z* score)	0.86 ± 0.79	−0.20 ± 1.08[a]	−1.55 ± 1.24[a,b]	−0.67 ± 1.09 (n = 25)[a]	<0.001

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; cSS = cortical superficial siderosis; HC = healthy control; ICH = intracerebral hemorrhage; ICV = intracranial volume; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment total score; PSMD = peak width of skeletonized mean diffusivity; SVD = small vessel disease; WMH = white matter hyperintensities.
Number (%), categorical variables (*p* value = χ2); mean ± SD, normally distributed continuous variables (*p* value = *t* test); median (interquartile range), non-normally distributed continuous variables (*p* value = Mann-Whitney U).
[a] $p \leq 0.05$ vs HC.
[b] $p \leq 0.05$ vs MCI.
[c] $p \leq 0.05$ vs AD; corrected using a Tukey-Kramer correction or Dwass–Steel–Critchlow-Fligner analysis.

thickness was associated with higher GM ($p = 0.047$), WM ($p = 0.042$), and global ($p = 0.031$) CVR.

For multivariable linear regression analyses of cognitive scores and CVR, there was no interaction between participant group with GM and WM CVR for all cognitive scores (eTable 2, links.lww.com/WNL/B835). Therefore, associations between cognitive scores and CVR were quantified using all participants but controlling for group, age, sex, education (excluding MoCA), and the presence of hypertension.

Figure 2 Cerebrovascular Reactivity to Hypercapnia Across Groups



Boxplots of gray matter (GM), white matter (WM), global (GM + WM), and primary visual cortex (V1) cerebrovascular reactivity (CVR) and the mean CVR within principal brain regions affected by Alzheimer disease (middle temporal gyrus, posterior cingulate, precuneus, and angular gyrus; $AD_{regions}$) for heathy controls (HC; n = 39), patients with mild cognitive impairment (MCI; n = 19 except for V1 where n = 18), patients with Alzheimer disease dementia (AD; n = 12), and patients with cerebral amyloid angiopathy (CAA; n = 26). Post hoc group comparison *p* values adjusted using the Tukey-Kramer correction for multiple comparisons. BOLD = blood oxygen level–dependent.

Figure 4 shows that a higher MoCA total score was associated with higher GM CVR (β, 95% CI 0.19, 0.03–0.36, $p = 0.019$) and there was a trend for a similar association with higher WM CVR (β, 95% CI 0.15, −0.01 to 0.31, $p = 0.059$). Figure 5 shows there were positive associations between GM CVR and memory (β, 95% CI 0.21, 0.07–0.36, $p = 0.004$), executive function (β, 95% CI 0.20, 0.02–0.39, $p = 0.032$), and processing speed (β, 95% CI 0.27, 0.10–0.45, $p = 0.002$), while higher WM CVR was associated with better memory (β, 95% CI 0.22, 0.08–0.36, $p = 0.003$) and processing speed scores (β, 95% CI 0.23, 0.06–0.40, $p = 0.010$).

Discussion

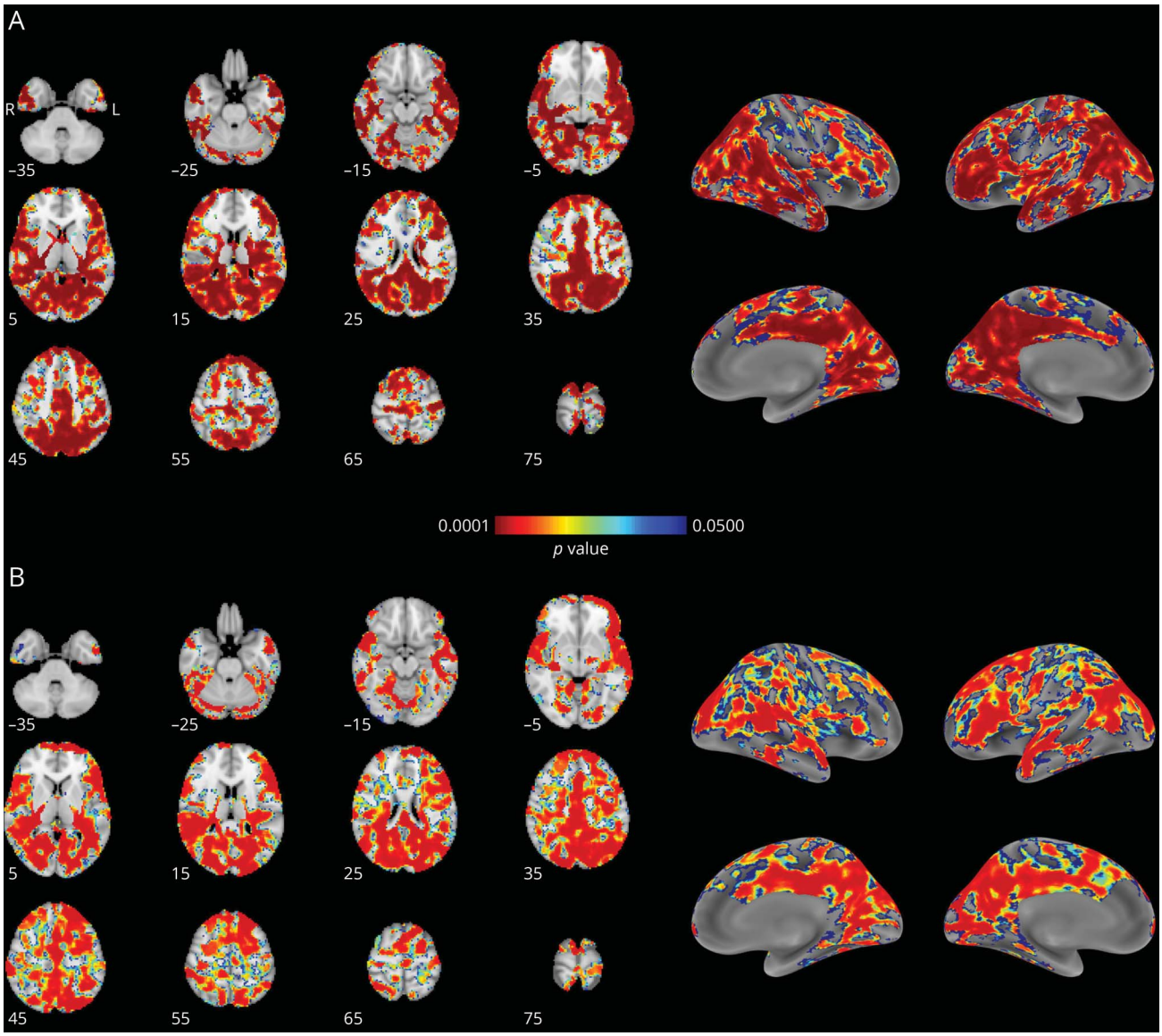
This study investigated whole brain CVR in CAA, AD dementia, and MCI and its association with MRI markers of CAA and cognitive function. The main findings were as follows: (1) GM, WM, global, and $AD_{regions}$ CVR was lower in patients with CAA and patients with AD dementia compared to HCs, whereas only participants with CAA had a lower CVR within the primary visual cortex; (2) greater WMH volume was associated with lower WM CVR among participants with CAA; and (3) MoCA, memory, executive function, and processing speed were positively associated with GM CVR, while memory and processing speed were positively associated with WM CVR.

Mounting evidence implicates reduced CVR as a core feature of CAA. Studies using functional transcranial Doppler ultrasound have reported that patients with CAA have a lower visual-evoked blood flow response within the posterior cerebral artery in response to a flashing checkerboard[12] and a smaller increase in middle cerebral artery blood velocity during a standardized breath hold challenge.[13] Patients with CAA also have a reduced BOLD response amplitude during a visual task compared to HCs,[8-11] with similar occipital visually evoked electrical potential amplitudes.[9,11] Provided that visually evoked electrical potentials reflect cortical metabolism,[36] this finding provided indirect evidence that the lower BOLD response amplitude observed resulted from impaired vasodilation within V1. In contrast, the current study using a hypercapnic stimulus provides direct evidence that there is lower CVR in CAA and that it is not limited to V1 as it was also seen in the GM, WM, and $AD_{regions}$. However, voxelwise comparisons revealed a predominantly posterior distribution of lower CVR (Figure 3), which is consistent with neuropathologic evidence of the distribution of vascular amyloid in the brain.[1] Unlike in AD dementia, CVR in V1 was lower in patients with CAA compared to HCs, likely due to the greater posterior vascular amyloid burden in CAA reported via autopsy[1] and amyloid PET imaging[37] compared to AD dementia.

CVR to hypercapnia in MCI has been explored previously and has been found to be comparable to[38] or lower than[39,40] that in HCs. However, unlike the current study, these prior studies did not exclude participants whose MCI was associated with MRI evidence of CAA. Therefore, the similar CVR between our participants with MCI and HCs may reflect the comparable degree of cerebrovascular disease between these participant cohorts (Table 1).

Whether CVR is reduced in AD is uncertain, with prior studies reporting either similar[39,41] or lower[42,43] CVR to hypercapnia compared to HCs. In contrast to this study, the prior ones did not screen participants with AD for comorbid

Figure 3 Areas of Lower Cerebrovascular Reactivity to CO_2 in CAA and AD Dementia



Statistical maps showing brain regions within gray matter and white matter (left) and on the cortical surface (right) where cerebrovascular reactivity is lower in participants with cerebral amyloid angiopathy (CAA) (A) or Alzheimer disease (AD) dementia (B) compared to healthy controls. Clusters were determined by voxel-wise group comparisons performed using nonparametric permutation-based threshold-free cluster enhancement analyses controlling for age, sex, and the presence of hypertension with 10,000 permutations controlling the false discovery rate and familywise error rate across 12 preplanned 1-tailed group comparisons.

CAA, which is present in 20%–30% of patients with AD[44] and would affect CVR independent of the amount of AD pathology. In this study, we observed lower CVR in the participants with AD dementia who did not have any MRI features indicative of probable CAA, suggesting that AD pathology may contribute to lower CVR even when the burden of vascular amyloid is minimal or absent.

In the current study, lower WM CVR was associated with higher WMH volume. This suggests CVR may decrease as CAA becomes more severe and is consistent with prior studies using functional hyperemia as a surrogate measure for CVR. Specifically, Smith et al.[12] found that greater WMH volume was associated with smaller visual-evoked increases in blood flow through the posterior cerebral artery in response to a flashing checkerboard while Peca et al.[9] and Switzer et al.[11] found similar relationships between WMH volume and the BOLD response amplitude to a visual task. In contrast to prior studies,[9,11] but consistent with this study, Dumas et al.[8] found no relationship between CMB count and BOLD response amplitude.[8] Rather, they found that greater WMH volume was associated with a longer time-to-peak BOLD response, thus still implicating vascular dysfunction in the pathogenesis of CAA-related WM changes. A reduced BOLD response amplitude to a visual task has also been reported in both symptomatic and presymptomatic individuals with hereditary

Table 2 Standardized Parameter Estimates for Linear Associations Between MR Markers of CAA With GM, WM, and Global and Primary Visual Cortex Cerebrovascular Reactivity to CO_2 Adjusted for Age, Sex, and Hypertension in Patients With CAA

Dependent variable	GM	*p* Value	WM	*p* Value	Global	*p* Value	V1	*p* Value
Log CMB, n	−0.46 (−0.93 to 0.02)	0.057	−0.35 (−0.86 to 0.16)	0.170	−0.40 (−0.89 to 0.09)	0.101	−0.39 (−0.88 to 0.10)	0.114
Log WMH, % ICV	−0.34 (−0.76 to 0.08)	0.110	−0.48 (−0.90 to −0.01)	0.024	−0.42 (−0.83 to −0.01)	0.045	−0.34 (−0.77 to 0.09)	0.110
CAA SVD score	−0.40 (−0.86 to 0.06)	0.084	−0.46 (−0.93 to 0.004)	0.052	−0.43 (−0.89 to 0.03)	0.065	−0.12 (−0.62 to 0.38)	0.616
PSMD ($\times 10^{-4}$ mm^2/s)	0.06 (−0.45 to 0.57)	0.815	0.00 (−0.54 to 0.54)	0.999	0.01 (−0.51 to 0.54)	0.961	−0.02 (−0.54 to 0.49)	0.923
Cortical thickness, mm	0.44 (0.01 to 0.87)	0.047	0.46 (0.02 to 0.90)	0.042	0.47 (0.05 to 0.90)	0.031	0.30 (−0.15 to 0.76)	0.176

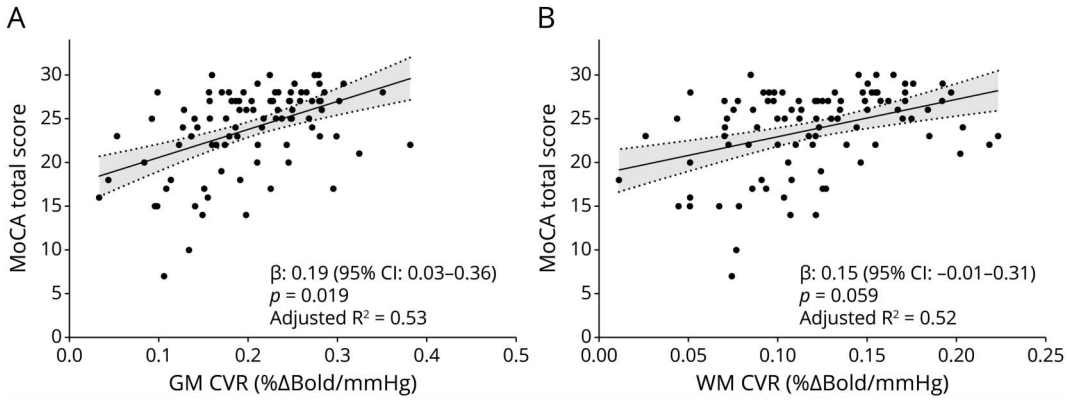
Abbreviations: CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; GM = gray matter; ICV = intracranial volume; MR = magnetic resonance; PSMD = peak width of skeletonized mean diffusivity; SVD = small vessel disease; WM = white matter; WMH = white matter hyperintensity.
Values are β (95% CI).

CAA.[10] Thus, the finding of a negative relationship between WMH volume and WM CVR in the current study, which used a vasodilatory stimulus independent of neuronal activation that acts directly upon the vascular endothelium and smooth muscle cells, suggests that CAA-related reduced WM CVR may contribute to the formation of WMH, which are a common feature of CAA.

Reduced CVR has been hypothesized to contribute to cognitive impairment by reducing oxygen and nutrient delivery to the brain when needed. Associations between CVR and cognitive function have been predominantly investigated in cohorts of HCs, patients with MCI, or patients with AD with no reports in participants with CAA. Our finding of a positive relationship between MoCA scores and GM CVR is comparable to that of Sur et al.,[45] who also found higher MoCA scores were associated with higher BOLD CVR responses to a 5% CO_2 challenge in a cohort of HCs, patients with MCI, and patients with AD. Although we also observed a positive relationship between MoCA scores and WM CVR, in line with Sur et al.,[45] it did not reach statistical significance (Figure 4B).

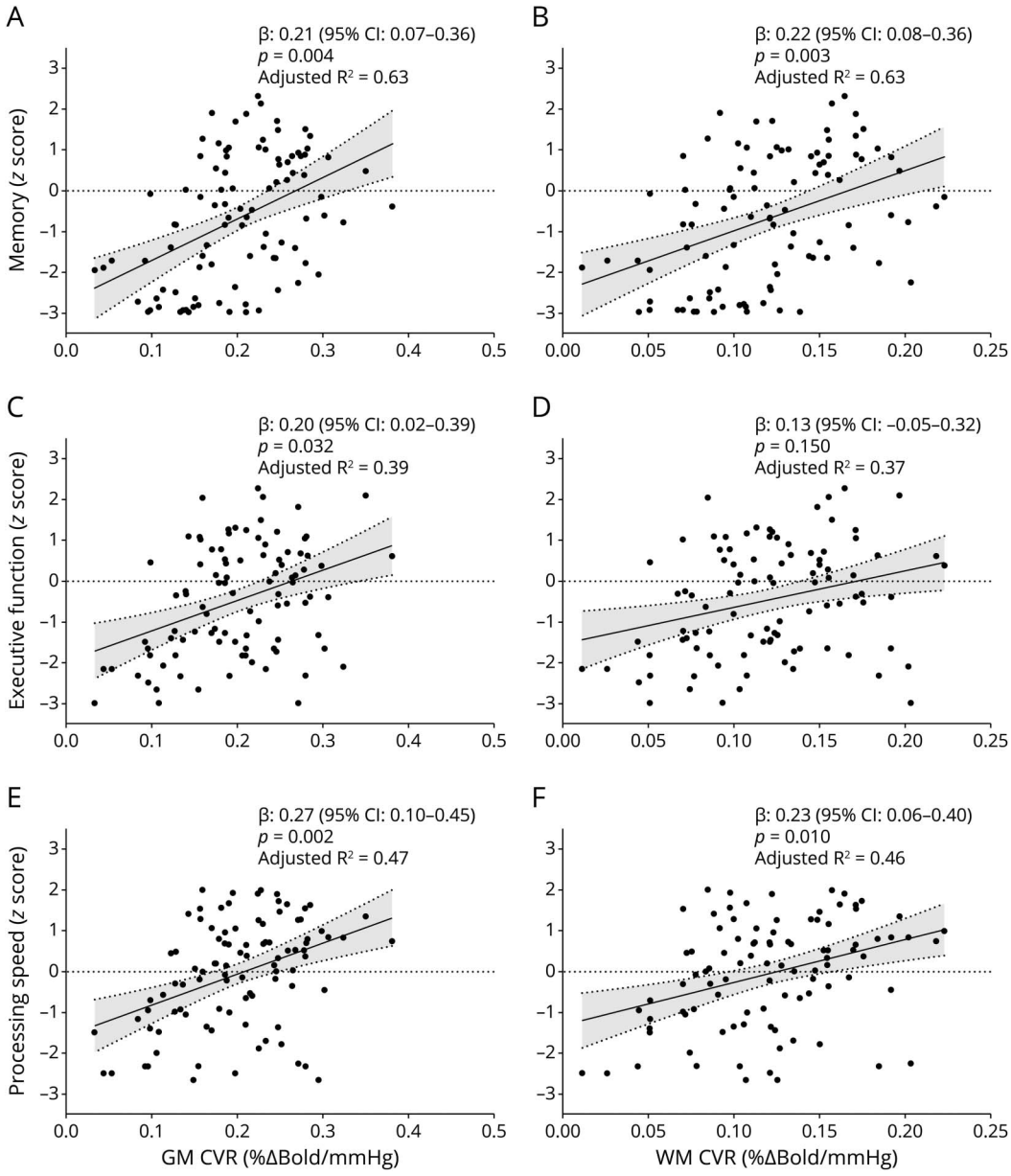
Few studies have investigated the relationships between individual cognitive domains and CVR using MRI in comparable patient groups. Sur et al.[45] examined the relationship between GM, WM, and global hypercapnic BOLD CVR with memory, executive function, and processing speed within their cohort of HCs, patients with MCI, and patients with AD and found no relationship between CVR and these cognitive domains. This contrasts with our findings of positive associations between memory, executive function, and processing speed with GM CVR, and memory and processing speed with WM CVR. One potential reason for these differences is that the composite cognitive domain scores were created from different individual cognitive tests. The association of WM CVR with memory impairment was somewhat unexpected but may reflect dysfunction in white matter tracts involved in episodic memory. We assessed the associations between cognitive function and CVR using data from all participants,

Figure 4 Associations Between MoCA Total Score and Cerebrovascular Reactivity to CO_2



(A) Higher Montreal Cognitive Assessment (MoCA) total scores were associated with higher gray matter (GM) cerebrovascular reactivity (CVR). (B) Higher MoCA total scores were not associated with white matter (WM) CVR. Standardized parameter estimates (β) and 95% CI provided in plots reflect the relationships between MoCA total score and GM (A) and WM (B) CVR adjusting for group, age, sex, and the presence of hypertension.

Figure 5 Associations Between Cognitive Domains With GM and WM Cerebrovascular Reactivity to CO_2



(A, B) Better memory was associated with higher gray matter (GM) and white matter (WM) cerebrovascular reactivity (CVR). (C, D) Better executive function was associated with higher GM, but not WM CVR. (E, F) Better processing speed was associated with higher GM and WM CVR. Standardized parameter estimates (β) and 95% CI provided in plots reflect the relationships between cognitive scores and GM (A, C, E) and WM (A, C, E) CVR adjusted for group, age, sex, education, and the presence of hypertension.

because there were no significant group-by-CVR measure interactions (eTable 2, links.lww.com/WNL/B835), indicating the relationships between each cognitive score and CVR measure were similar within each group, including participants with CAA.

In our analysis, we chose not to adjust for WMH volume or cortical thickness because we considered them to be mediating variables, not confounders. WMH are of presumed vascular origin[46] and a reduced CVR to hypercapnia precedes the development of WMH.[47] Thus, our analyses were based on the hypothesis that CAA causes lower CVR, which damages WM and GM, leading to WMH and cortical thinning.

Another limitation of this study is the small sample size of participants with AD dementia. However, due to the robustness of the hypercapnic challenge used to quantify CVR, a difference in CVR between patients with AD dementia and HCs was still observed, although confirmation of these findings in a larger sample size would be beneficial. A third limitation is that clinical criteria were used to define non–CAA-related MCI and AD dementia rather than using CSF or PET

Aβ and tau biomarkers. This recruitment strategy was employed because CSF Aβ is also altered in CAA[11] and amyloid-PET tracers have limited diagnostic utility in differentiating between CAA and AD as they are nonspecific for cerebrovascular or parenchyma amyloid.[48] However, tau pathology is not expected in CAA and its presence would have indicated greater AD pathology. Therefore, future studies should examine associations between CVR and Aβ and tau brain deposits in both CAA and AD. In addition, MCI is a heterogenous syndrome with multiple causes of which AD is only one, and larger studies are required to distinguish differences in CVR between distinct MCI subtypes. Fourth, CVR was quantified using BOLD imaging and a fixed inspired fraction of CO_2, which imposes some limitations on the measurement accuracy and its interpretation. Although BOLD imaging is the most widely used MRI acquisition for quantifying CVR, its signal represents a complex interaction of brain activity, cerebral oxygen metabolism, and neurovascular factors that requires careful interpretation.[49] Breathing a fixed inspired fraction of CO_2 (e.g., 5%) does not produce the same increase in $P_{ET_{CO2}}$ across all individuals, which can introduce greater variation in CVR across participant groups. Notwithstanding this greater variation and the overlap in CVR between groups (Figure 2), this study found clear differences between patients with CAA and patients with AD dementia and HCs. Nevertheless, more precise and accurate control of $P_{ET_{CO2}}$[50] may have identified greater group differences and stronger associations between CVR and markers of CAA and cognition. Fifth, analyses assessing associations between CVR and MRI markers of CAA and cognition were considered exploratory, and the precision of some estimates was low, resulting in wide CIs. Therefore, the Type I error rate was not controlled for across the multivariable linear regression analyses and associations need to be confirmed by additional studies. Finally, this was a cross-sectional study and causal inferences between cognitive function and CVR cannot be made from our results.

In conclusion, a reduced CVR appears to be a core feature of CAA with areas of greater impairment mapping onto the posterior distribution of CAA-related pathology. While lower WM CVR was associated with greater WMH burden in participants with CAA and a lower CVR was associated with worse cognitive function, the contribution of impaired CVR to these 2 sequalae remains to be investigated longitudinally. Assessment of CVR may prove to be a useful biomarker for the severity of CAA and its effects on cognition.

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Appendix Authors

Name	Location	Contribution
Andrew E. Beaudin, PhD	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; other
Cheryl R. McCreary, PhD	University of Calgary; Alberta Health Services, Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; other
Erin L. Mazerolle, PhD	University of Calgary; St. Francis Xavier University, Antigonish, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; other

Appendix *(continued)*

Name	Location	Contribution
Myrlene Gee, PhD	University of Alberta, Edmonton, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; other
Breni Sharma, MSc	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Arsenije Subotic, MSc	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Angela M. Zwiers, MSc	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Emily Cox, BSc	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Krista Nelles, BSc	University of Alberta, Edmonton, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Anna Charlton, BSc	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; other
Richard Frayne, PhD	University of Calgary; Alberta Health Services, Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Zahinoor Ismail, MD	University of Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Christian Beaulieu, PhD	University of Alberta, Edmonton, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Glen Jickling, MD	University of Alberta, Edmonton, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Richard M. Camicioli, MD	University of Alberta, Edmonton, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
G. Bruce Pike, PhD	University of Calgary; Alberta Health Services, Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Eric Smith, MD, MPH	University of Calgary; Alberta Health Services, Calgary, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or intepretation of data; other

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