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Association of Medial Temporal Lobe Cerebrovascular Reactivity and Memory Function in Older Adults With and Without Cognitive Impairment

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Abstract

Background and Objectives

Cerebrovascular reactivity (CVR) represents the ability of cerebral blood vessels to regulate blood flow in response to vasoactive stimuli and is related to cognition in cerebrovascular and neurodegenerative conditions. However, few studies have examined CVR in the medial temporal lobe, known to be affected early in Alzheimer disease and to influence memory function. We aimed to examine whether medial temporal CVR is associated with memory function in older adults with and without mild cognitive impairment (MCI).

Methods

In this observational study, independently living older adults free of dementia or stroke were recruited from the community and underwent brain MRI, neuropsychological assessment, and blood draw in an academic research setting. pCASL MRI quantified medial temporal lobe cerebral perfusion during CVR response to hypercapnia. Hypercapnia was induced by visually guided breathing exercises (15 seconds breath holds) during capnographic monitoring. MCI diagnosis and memory performance were assessed through comprehensive neuropsychological assessment. $A\beta42/40$ and pTau181 levels were quantified in blood plasma. Logistic and hierarchical linear regression examined medial temporal CVR in relation to MCI diagnosis and memory function.

Results

In a sample of 144 older adults (mean age = 69.6 years; SD = 7.4%; 34.7% male; mean education = 16.6 years, SD = 2.3), CVR to hypercapnia in the medial temporal lobe was attenuated in individuals with MCI after adjusting for age, sex, education, apolipoprotein ε4 carrier status, $A\beta42/40$ and pTau181 levels, and vascular risk factors (OR = 0.87, 95% CI [0.77–0.97], p = 0.013). Cerebrovascular reactivity to hypercapnia was associated with verbal memory performance for stories (B = 0.33, 95% CI [0.09–0.57], p = 0.009), a word list (B = 0.10, 95% CI [0.001–0.20], p = 0.048), and visual memory (B = 0.33, 95% CI [0.09–0.57], p = 0.008).

Discussion

Deficits in medial temporal CVR are observed in older adults with MCI and are related to worse memory function. Findings suggest that medial temporal cerebrovascular dysfunction is related to cognition and memory before the onset of dementia, independent of changes in Alzheimer pathophysiologic markers. Limitations of the study include the cross-sectional design. Future longitudinal studies are warranted to examine whether early cerebrovascular changes can predict progressive memory decline.

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Glossary

BOLD = blood oxygen level–dependent; **CBF** = cerebral blood flow; **CU** = cognitively unimpaired; **CVR** = cerebrovascular reactivity; **FoV** = field of view; **FWHM** = full-width at half-maximum; **MCI** = mild cognitive impairment; **MPRAGE** = magnetization-prepared rapid acquisition gradient-echo; **MTL** = medial temporal lobe; **RAVLT** = Rey Auditory Verbal Learning Test; **ROI** = region of interest; **TE** = echo time; **TI** = inversion time; **TR** = repetition time.

Introduction

Cerebrovascular dysfunction commonly occurs with advancing age[1] and is associated with increased risk of dementia.[2] Breakdown of the cerebrovasculature is known to independently contribute to the development of cognitive impairment and may augment cognitive impairment that develops during the progression of Alzheimer disease and other neurodegenerative diseases.[3-5] Biomarkers of Alzheimer disease have been extensively studied and targeted to develop disease-modifying interventions, but robust vascular biomarkers are lacking.[6] Identification of vascular biomarkers that may be targeted for treatment before irreversible vascular brain injury would represent a major contribution to preventative and early treatment efforts for Alzheimer disease and Alzheimer disease–related dementias.[7]

Cerebrovascular reactivity (CVR) is a dynamic marker of cerebrovascular function and indicates the ability of cerebral blood vessels to regulate cerebral blood flow (CBF) in response to vasoactive stimuli.[8,9] Previous studies have found deficits in whole-brain CVR in older adults relative to younger adults[10,11] and in patients with mild cognitive impairment (MCI),[12,13] Alzheimer disease,[13-15] cerebral amyloid angiopathy,[16] and hypertension.[14] Fewer studies have examined regional CVR changes, but a longitudinal study suggested that much of the age-related decline in CVR occurs in the temporal lobe,[17] a key region for memory formation that is affected early in the pathophysiology of Alzheimer disease.[18,19] Other studies indicate cerebral microvascular dysfunction, such as increased blood-brain barrier permeability, may occur specifically in medial temporal regions, including the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal gyrus, in patients with cognitive impairment, and those at genetic risk for Alzheimer disease.[5,17,20,21] Some studies have further suggested that medial temporal microvascular dysfunction may contribute to cognitive decline independent of Alzheimer pathophysiologic changes.[5,20] To the best of our knowledge, no study has specifically examined medial temporal CVR in older adults with and without MCI or in relation to memory function.

In this study, we investigated the association between CVR in the medial temporal lobe (MTL) and MCI diagnosis as well as memory across multiple neurocognitive measures before the onset of functional decline. We hypothesized lower CVR in the medial temporal lobe would be a marker of vascular dysfunction that would be associated with cognitive impairment and worse performance across memory measures, independent of Alzheimer disease pathophysiologic and genetic risk factors.

Methods

Participants

All participants were recruited from the Los Angeles County and Orange County community, and all study procedures were conducted as part of the Vascular Senescence and Cognition Study at the University of Southern California (USC) and University of California, Irvine (UCI). Participants were recruited through outreach events, mailing lists, word-of-mouth, online portals, and other modes of community outreach facilitated by the Leonard Davis School of Gerontology at the University of Southern California and the Alzheimer's Disease Research Center at the University of California, Irvine. Inclusion criteria were independently living older adult aged 55 years or older. Exclusion criteria were a history of clinical stroke, dementia, family history of dominantly inherited neurodegenerative disorders, current major neurologic or psychiatric disorder impacting cognition, history of moderate-to-severe traumatic brain injury, current use of medications impairing the CNS, MRI contraindication, current organ failure, or other systemic or neurologic illness that may affect CNS function. Eligibility for the study was determined through a clinical interview with the participant and an informant study partner when available. All participants underwent (1) detailed clinical assessment, (2) brain MRI for evaluation of CBF and CVR, (3) venipuncture to determine *APOE4* ($\varepsilon 4$ allele of the APOE) carrier status and plasma levels of amyloid-$\beta_{42/40}$ peptide ratio ($A\beta_{42/40}$) and phosphorylated tau at threonine-181 (pTau$_{181}$), and (4) neuropsychological testing to determine diagnosis of MCI or cognitively unimpaired (CU) and to characterize verbal and visual memory.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the local Institutional Review Board at USC and UCI. All participants gave written informed consent before participating in the study.

Clinical Assessment

History of vascular risk factors, including hypertension, dyslipidemia, diabetes, smoking, TIA, cardiovascular disease, atrial fibrillation, as well as history of other medical illnesses, and demographic information were obtained by a semistructured clinical interview.

Neuroimaging

All participants underwent brain MRI on a 3T scanner (Siemens MAGNETOM Prisma System). The following sequences were examined for the current analysis: 3D T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) to examine brain structure and identify any abnormalities (scan parameters were as follows: repetition time [TR] = 2,300 ms; echo time [TE] = 2.98 ms; inversion time [TI] = 900 ms; flip angle = 9 deg; field of view [FOV] = 256 mm; resolution = $1.0 \times 1.0 \times 1.2$ mm^3; scan time = 9 minutes), and fluid-attenuated inversion recovery for white matter hyperintensity lesion segmentation (scan parameters: TR = 10,000 ms; TE = 91.0 ms; flip angle = 150 deg; FOV = 220 mm; resolution = $0.0.9 \times 0.9 \times 5.0$ mm^3; echo spacing = 8.31 ms; echo trains per slice = 8; scan time = 4.5 minutes). In addition, CBF was determined using 3D gradient and spin-echo pseudocontinuous arterial spin labeling (pCASL; scan parameters were as follows: TR = 5,000 ms; TE at USC = 36.3 ms; TE at UCI = 37.46 ms; FOV = 240 mm; resolution = $2.5 \times 2.5 \times 3.4$ mm^3; slice thickness = 3.42 mm; number of slices = 24; labeling duration = 1,517 ms; postlabeling delay = 2000 ms; 32 acquisitions = 1 M0 image + 1 dummy image + 30 alternating tag and control images (yielding 15 tag-control pair images); scan time = 5 minutes 25 seconds).

Cerebral Blood Flow

Following the protocol as described by Yew et al. (2022), the pCASL scans were preprocessed using the ASLtbx pipeline, implemented in SPM12 within MATLAB.[10,22-24] Preprocessing steps for pCASL scans included motion correction, coregistration to individual subject's structural T1-weighted image, spatial smoothing with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel, and tag-control subtraction resulting in 15 tag-control pairs for each subject with values for absolute CBF (mL/100 g tissue/min). All CBF images were thresholded below 10 or above 150 mL/100 g/min to exclude CBF outside the expected physiologic range of gray matter.[25,26] Tag-control pairs were warped to Montreal Neurological Institute space and averaged to create mean CBF maps for each subject. Resulting mean CBF maps were visually inspected for quality and gross abnormalities (i.e., large signal dropout). Partial volume correction was performed by applying subject-specific gray matter masks derived from the gray matter tissue class segmentation of T1-weighted structural images.[27] Segmented gray matter maps were thresholded at 0.3, binarized, and multiplied by the mean CBF maps to ensure CBF was limited to gray matter.

CO$_2$ Manipulation and Capnography

Hypercapnia was induced using a visually guided breathing paradigm during pCASL-MRI with capnographic monitoring, described in detail elsewhere.[10,24,28] Briefly, visual stimuli-guided patient breathing during the pCASL scan. Interval breath hold (15 seconds) was used to induce hypercapnia. If participants could not adhere to breathing instructions, they were excluded from analyses. End tidal CO$_2$ ($_{ET}CO_2$) was monitored by capnography during hypercapnia and hypocapnia manipulations and MRI acquisition using an M3015A sidestream CO$_2$ extension module (Philips Medical Systems) connected to a nasal cannula into which participants breathed. To correct for sampling tube latency, $_{ET}CO_2$ time series were shifted by a precalibrated duration of time (i.e., 10 seconds in our set-up). Additional details of the protocol and extraction of $_{ET}CO_2$ have previously been described in detail.[10] To determine increases in $_{ET}CO_2$ induced by breath hold (hypercapnia), maximum $_{ET}CO_2$ was extracted for each tag-control pair (i.e., maximum positive peak across the acquisition interval for each tag-control pair).

Cerebrovascular Reactivity

A modified version of CVR measure described elsewhere was applied in this study.[10] CVR was defined as percent change in CBF per unit change in $_{ET}CO_2$ (% $\Delta CBF/\Delta mm$ Hg $_{ET}CO_2$) as follows:

$$CVR\left(\%\frac{\Delta CBF}{\Delta mmHg\ _{ET}CO_2}\right)$$
$$= \frac{100 \times (CBF_{maximum} - CBF_{minimum})/CBF_{minimum}}{_{ET}CO_{2\ maximum} - \ _{ET}CO_{2\ minimum}}$$

CVR was calculated for 3 breathing cycles, and average CVR across breathing cycles was used in the current analysis. Quality control assessment identified 5 participants demonstrating large variability in CVR values between the 3 breathing cycles who were excluded from the current analysis. Regional mean CVR values were extracted for our region of interest (ROI), the medial temporal lobe, which included Brodmann areas 27 (rostral parahippocampal gyrus), 28 (ventral entorhinal cortex), 34 (dorsal entorhinal cortex), and 35 and 36 (perirhinal cortex) concatenated based on the Wake Forest University PickAtlas.[29]

White Matter Hyperintensity Lesion Segmentation and Brain Volumetrics

White matter lesions were segmented with the lesion growth algorithm implemented in the Lesion Segmentation Tool toolbox version 3.0.0[30] for SPM12 (Wellcome Department of Cognitive Neurology, London, UK30). Initial threshold was set at 0.2, and visual inspection was conducted to determine optimal threshold for each individual; manual quality control check ensured no gross overestimation or underestimation.

To determine intracranial volume and hippocampal volume, postprocessing of MPRAGE scans included FreeSurfer semiautomated segmentation and parcellation algorithm for quantification of bilateral hippocampal and intracranial volume (FreeSurfer 6.0). After automated segmentation, each individual participant was checked for any inaccuracies or misclassifications; manual corrections were made as needed with FreeSurfer's built-in editing tools. Postprocessing was conducted using SPM12 and CAT12 to index brain regional volume by voxel-based morphometry analysis. Gray and white matter tissue classes were segmented on T1-weighted images using the SPM12's unified segmentation procedure, which included spatial normalization, and smoothing with an 8 mm FWHM isotropic Gaussian kernel. The resulting gray matter

images were examined for sample homogeneity to identify any potential outliers.

APOE Genotyping

Genotyping was conducted on the blood cell pellet fraction obtained from plasma separation, as previously described.[31] Genomic DNA was extracted using the PureLink Genomic DNA Mini Kit (Thermo). Using a NanoDrop One (Thermo), the isolated DNA concentration was determined. DNA was then stored at − 80°C. Before PCR, isolated DNA was first diluted to a concentration of 10 mg/μL. PCR reactions were performed in a final volume of 25 μL containing 25 ng DNA, 0.5 μM of forward (ACGGCTGTCCAAGGAGCTG) and reverse (CCCCGGCCTGGTACACTG) primers, and 1× SYBR Green Master Mix (Qiagen) diluted in H_2O. T100 Thermal Cycler (BioRad) was used for the amplification, with the following settings: 95°C for 10 minutes; 32 cycles of 94°C for 20 seconds, 64°C for 20 seconds, and 72°C for 40 seconds; followed by 72°C for 3 minutes. Fifteen microliter of the DNA PCR product was digested with Hhal-fast enzyme at 37°C for 15 minutes. For gel electrophoresis, the digested PCR product was added to a 3% agarose gel in 1× borax buffer. The gel was run at 175 V for 25 minutes and then visualized on ChemiDoc (BioRad) with a GelRed 10,000× gel dye.

$A\beta_{42/40}$ and $pTau_{181}$ Quantification

Plasma levels of $A\beta_{40}$ and $A\beta_{42}$ were determined, and the $A\beta_{42/A\beta40}$ ratio was calculated for all analyses as an index of cerebral amyloid retention.[32] Plasma levels of $A\beta_{40}$ and $A\beta_{42}$ were obtained by digital immunoassay, Simoa Neurology 3-Plex A Advantage Kit (Quanterix), following the manufacturer's protocol. Accepted ranges were as follows: $A\beta40 = 0–560$ pg/mL, $A\beta_{42} = 0–240$ pg/mL. Plasma $pTau_{181}$ levels were obtained by the Simoa $pTau_{181}$ Advantage V2.0 and 2.1 Assay (Quanterix), following the manufacturer's protocol. Accepted ranges were 8–1,280 pg/mL.

Neuropsychological Assessment

All participants underwent comprehensive neuropsychological assessment that included tests of global cognition (Dementia Rating Scale), verbal and visual memory (Rey Auditory Verbal Learning Test [RAVLT] word list learning and memory, Logical Memory I and II, Craft Story 21, Consortium to Establish a Registry for Alzheimer's Disease Word List, California Verbal Learning Test), attention/executive function (Trail Making A and B, Golden Stroop, DKEFS Color-Word Interference, Number Span: Backwards), and language abilities (Animal Fluency, D-KEFS Letter Fluency, Boston Naming Test, Multilingual Naming Test). For the purpose of this analysis, only diagnosis of MCI and measures of memory with a sufficient sample size were examined.

MCI Diagnosis

Using scores on 9 neuropsychological tests (3 memory, 3 attention/executive, and 3 language), cognitive status was determined as CU or impaired using the Bondi et al.[33] (2014) neuropsychological criteria for MCI. All diagnostic classifications were actuarial but also underwent quality control by multiple blinded investigators including a licensed clinical neuropsychologist (D.A.N.). Briefly, based on these criteria, MCI is operationalized as scores >1 SD below demographically corrected normative mean values on two or more tests within a single-cognitive domain *or* 1 or more tests score across each of the 3 included domains (i.e., memory, attention/executive function, and language). These neuropsychological criteria for MCI have been extensively validated and are widely used.[5,33,34]

Memory Assessment

The neuropsychological battery assessed verbal memory for a word list from the RAVLT and for a story from the Wechsler Memory Scale—Revised Logical Memory,[35,36] and visual memory for designs from the Wechsler Memory Scale—IV Visual Reproduction.[36] The delayed free recall scores from all 3 tests were studied specifically to index underlying memory ability.

Statistical Analyses

All analyses were performed using R Version 3.6.1 and IBM SPSS Statistics 28. Data visualization was performed in GraphPad Prism version 10.2.2. Demographic variables were computed to characterize the sample and compared between individuals with and without MCI using two-tailed t tests and χ^2 tests. When the Levene test for equality of variances suggested significant heterogeneity of variance, equal variances were not assumed. The relationship between CVR to hypercapnia in the medial temporal lobe (independent predictor) and MCI diagnosis (dependent outcome) was examined using logistic regression, adjusting for age, sex, education, APOE4 carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors (0–1 vs ≥2). In addition, we examined the association between medial temporal lobe CVR to hypercapnia (independent predictor) and memory measures (dependent outcome) using hierarchical linear regression. Step 1 included age, sex, and education as predictors of memory performance. In step 2, APOE4 carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors (0–1 vs ≥2) were added. Finally, in step 3, CVR was included into the model. The hierarchical linear regression was conducted for memory ability on the following specific measures (dependent outcomes): Logical Memory II long delay free recall for a story, RAVLT long delay free recall for a word list, and Visual Reproduction II long delay free recall for designs. For all models, multicollinearity was assessed, with a variance inflation factor above 4 indicating significant multicollinearity. Significance threshold was set at $p < 0.05$. The false discovery rate (FDR) was set at $p < 0.05$.[37]

Data Availability

Data will be made available through reasonable request to the authors and based on the conditions outlined by the Data Availability Policy and Statement.

Results

A total of 144 participants were included in the current analysis (eFigure 1). Age of study participants ranged from 55

Table 1 Participant Characteristics, Vascular Risk Factors, and Cognitive Scores

	All N = 144	Mild cognitive impairment N = 24	Cognitively unimpaired N = 120	p Value
Age (y), M (SD)	69.6 (7.4)	68.6 (5.5)	69.8 (7.7)	0.488
Sex (male), n (%)	50 (34.7)	10 (41.7)	40 (33.3)	0.434
Education (y), M (SD)	16.6 (2.3)	15.7 (2.3)	16.7 (2.2)	0.033
Vascular risk factors, n (%)				
Hypertension[a]	50 (35.7)	11 (45.8)	39 (33.6)	0.256
Dyslipidemia[b]	68 (49.3)	12 (52.2)	56 (48.7)	0.761
Diabetes[a]	18 (12.9)	5 (20.8)	13 (11.2)	0.200
Smoking history[a]	44 (31.4)	10 (41.7)	34 (29.3)	0.235
Transient ischemic attack[c]	4 (2.9)	1 (4.2)	3 (2.6)	0.678
Cardiovascular disease[c]	12 (8.6)	2 (8.3)	10 (8.7)	0.954
Atrial fibrillation[a]	10 (7.1)	3 (12.5)	7 (6.0)	0.263
Handedness, n (%)				0.835
Right-handed	122 (84.7)	21 (87.5)	101 (84.2)	
Left-handed	17 (11.8)	2 (8.3)	15 (12.5)	
Ambidextrous	5 (3.5)	1 (4.2)	4 (3.3)	
Race, n (%)				0.843
White	114 (79.2)	19 (79.2)	95 (79.2)	
Black or African American	3 (2.1)	1 (4.2)	2 (1.7)	
American Indian or Alaska Native	2 (1.4)	0 (0.0)	2 (1.7)	
Asian	23 (16.0)	4 (16.7)	19 (15.8)	
Other	2 (1.4)	0 (0.0)	2 (1.7)	
Aβ42/40 ratio, M (SD)[d]	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.317
pTau181 (pg/mL), M (SD)[e]	24.4 (11.5)	26.8 (13.0)	23.8 (11.1)	0.321
APOE4 status (carrier), n (%)[f]	58 (46.0)	6 (30.0)	52 (49.1)	0.117
ε4/4	4 (3.2)	1 (5.0)	3 (2.8)	0.182
ε3/4	54 (42.9)	5 (25.0)	49 (46.2)	
ε3/3	63 (50.0)	14 (70.0)	49 (46.2)	
ε2/3	5 (4.0)	0 (0.0)	5 (4.7)	
Logical Memory II Score, M (SD)[g]	22.4 (8.0)	15.9 (6.9)	23.5 (7.6)	<0.001
RAVLT Delayed Recall Score, M (SD)[h]	11.2 (3.3)	8.6 (4.1)	11.6 (2.9)	0.004
Visual Reproduction II Score, M (S)[g]	24.4 (8.9)	18.2 (8.3)	25.5 (8.6)	0.001
Medial temporal CVR hypercapnia (%ΔCBF/Δmm Hg $_{ET}CO_2$), M (SD)	4.4 (6.9)	0.1 (4.5)	5.2 (7.1)	<0.001

Abbreviations: CBF = cerebral blood flow; CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2; M = mean; RAVLT = Rey Auditory Verbal Learning Test.
p Values reported are based on two-tailed *t* tests and χ^2 tests.
[a] Missing for 4 participants (0 participants with MCI).
[b] Missing for 6 participants (1 MCI).
[c] Missing for 5 participants (0 MCI).
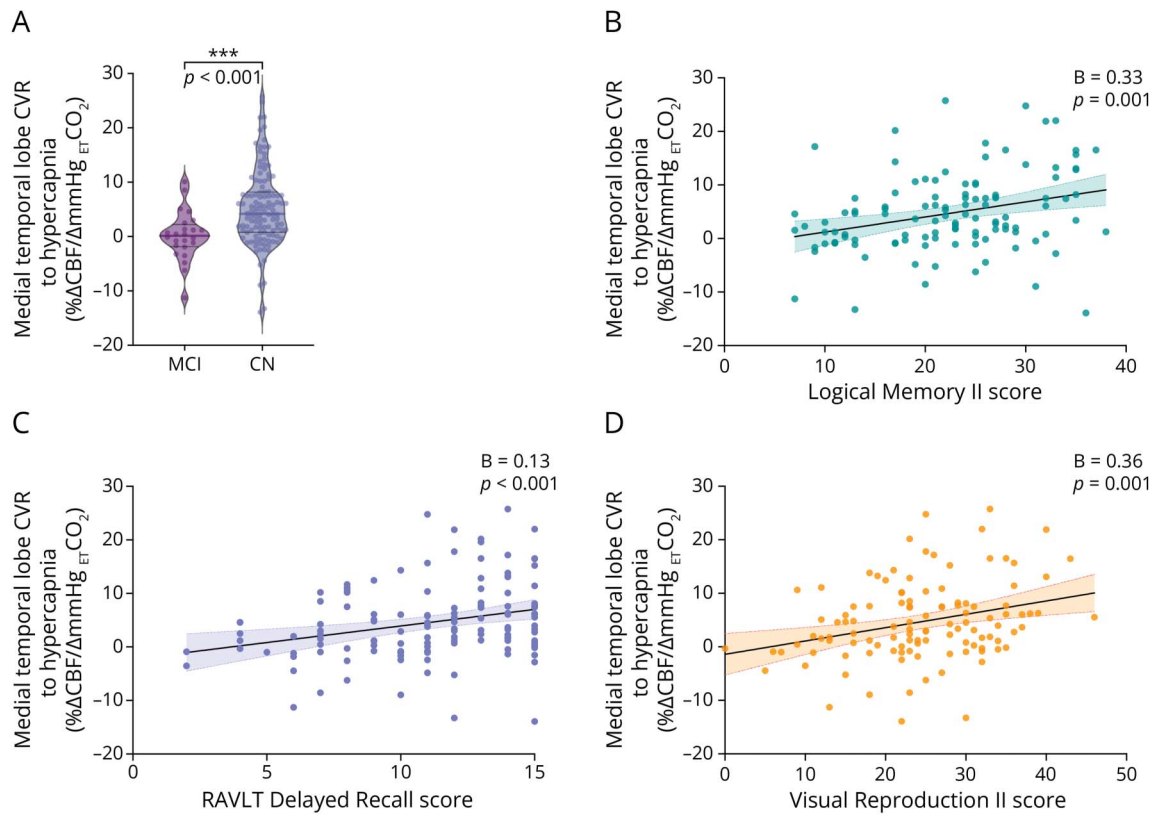[d] Missing for 25 participants (4 MCI).
[e] Missing for 50 participants (6 MCI).
[f] Missing for 18 participants (4 MCI).
[g] Missing for 31 participants (7 MCI).
[h] Missing for 12 participants (4 MCI).

Figure 1 Medial Temporal CVR to Hypercapnia in MCI and Memory Performance

Medial temporal lobe CVR to hypercapnia was significantly higher among cognitively unimpaired compared with those with MCI. (A) Higher medial temporal lobe CVR to hypercapnia was associated with higher scores on (B) Logical Memory II, (C) RAVLT delayed recall, and (D) Visual Reproduction II. B = unstandardized beta coefficient; CBF = cerebral blood flow; CU = cognitively unimpaired; CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2; MCI = mild cognitive impairment; RAVLT = Rey Auditory Verbal Learning Test.

to 90 years and years of education ranged from 12 to 20. Participant characteristics and scores on memory measures are reported in Table 1. Twenty-four (16.7%) of participants met criteria for MCI. Demographic variables did not differ between individuals with or without MCI, with the exception of education (Table 1). Among participants who had difficulty adhering to the breathing instructions and were excluded from analyses, 3 of 9 (33.3%) met criteria for MCI, which was not statistically significantly different from the proportion of MCI participants who were compliant with the breathing protocol (16.7% met criteria for MCI; χ^2 (1, N = 153) = 1.62, $p = 0.203$).

Medial Temporal Lobe CVR to Hypercapnia and MCI

Lower medial temporal CVR was observed in MCI compared with those who were CU (Table 1, Figures 1A and 2). The CVR map of randomly selected participant with MCI and CU participant is depicted in Figure 2. In logistic regression analyses, higher medial temporal lobe CVR to hypercapnia was a predictor of lower likelihood of MCI diagnosis (OR = 0.87, 95% CI [0.77–0.97], $p = 0.013$; N = 88; 17 participants with MCI), adjusting for age, sex, education, *APOE4* carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors

(Table 2). The association persisted even after white matter hyperintensity volume (OR = 0.89, 95% CI [0.79–0.99], $p = 0.039$) or hippocampal volume (OR = 0.86, 95% CI [0.76–0.97], $p = 0.015$) were added to the model and adjusted for intracranial volume.

Whole-brain CVR was not associated with MCI diagnosis, after adjusting for covariates. We further added whole-brain CVR and MTL CVR to the model with all covariates, which revealed that MTL CVR remained the strongest predictor of MCI diagnosis (OR = 0.76, 95% CI [0.63–0.91], $p = 0.003$).

Medial Temporal Lobe CVR to Hypercapnia and Verbal Memory

In univariate regression analyses, greater medial temporal lobe CVR to hypercapnia was associated with higher scores on Logical Memory II (B = 0.33, 95% CI [0.13–0.52], $p = 0.001$; Figure 1B). In hierarchical linear regression modeling, greater medial temporal lobe CVR to hypercapnia predicted higher scores on Logical Memory II (B = 0.33, 95% CI [0.09–0.57], $p = 0.009$; N = 69), adjusting for age, sex, education, *APOE4* carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors (Table 3). The final model explained 27% of the observed variation in Logical Memory II scores ($R^2 = 0.27$, Adj. $R^2 = 0.17$,

Figure 2 CVR Map of Medial Temporal CVR to Hypercapnia in an Individual With MCI vs Cognitively Unimpaired Individual
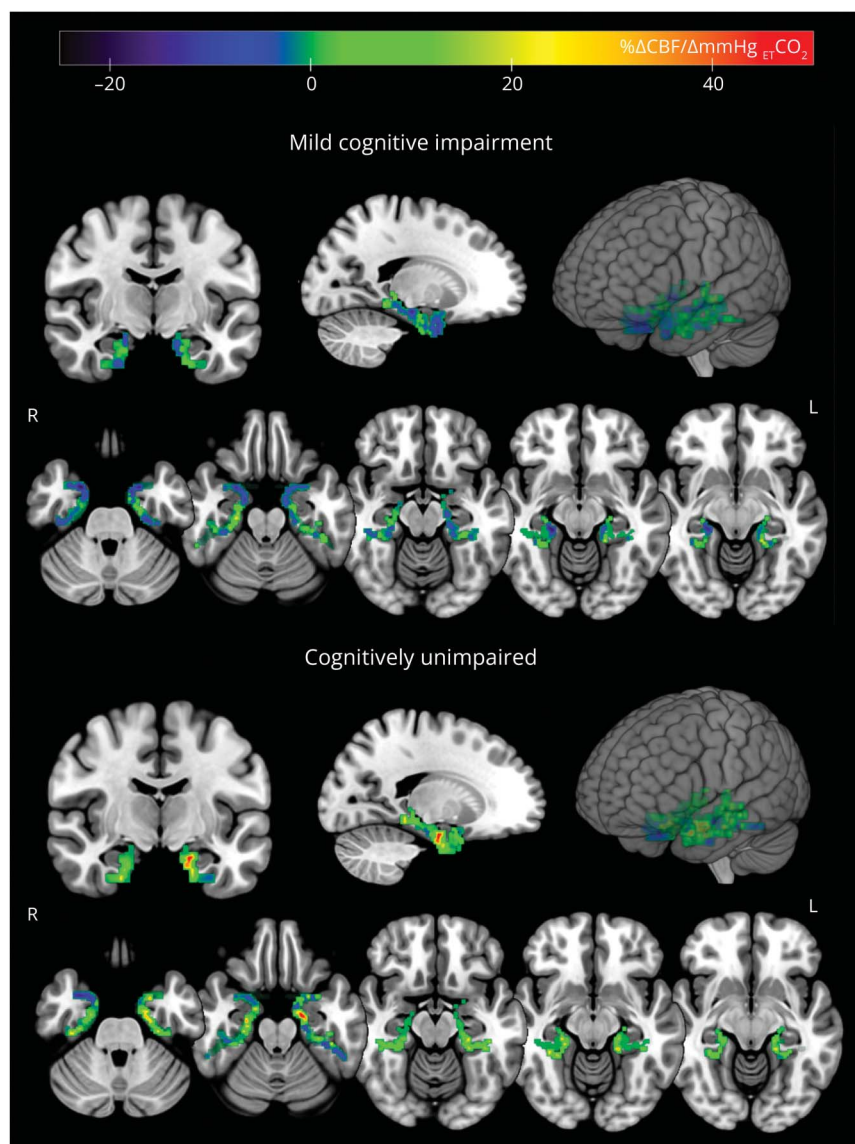
Warmer colors indicate higher CVR values (greater average percent change in cerebral blood flow per mm Hg change in $_{ET}CO_2$), while darker colors show lower CVR values. CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2; MCI = mild cognitive impairment.

$F [8, 68] = 2.73$, $p = 0.012$). Adding CVR to hypercapnia as a predictor of Logical Memory II scores improved the proportion of variation explained in Logical Memory II scores ($\Delta R^2 = 0.09$, $\Delta F [1, 60] = 7.36$, p for $\Delta R^2 = 0.009$).

Similarly, a univariate association was observed between medial temporal lobe CVR to hypercapnia and scores on RAVLT Delayed Recall (B = 0.13, 95% CI [0.06–0.21], $p < 0.001$; Figure 1C). In hierarchical linear regression modeling, greater medial temporal lobe CVR to hypercapnia predicted higher scores on RAVLT Delayed Recall (B = 0.10, 95% CI [0.001–0.20], $p = 0.048$; N = 78), adjusting for age, sex, education, *APOE4* carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors (0–1 vs ≥2; Table 4). The final model explained 24% of the observed variation in RAVLT Delayed Recall scores ($R^2 = 0.24$, Adj. $R^2 = 0.15$, $F [8, 77] = 2.75$, $p = 0.011$). Adding CVR to hypercapnia as a predictor of RAVLT

Delayed Recall scores improved the proportion of variation explained in RAVLT Delayed Recall scores ($\Delta R^2 = 0.04$, $\Delta F [1, 69] = 4.04$, p for $\Delta R^2 = 0.048$).

Medial Temporal Lobe CVR to Hypercapnia and Visual Memory

Medial temporal lobe CVR to hypercapnia was also associated with a measure of visual memory, Visual Reproduction II (B = 0.36, 95% CI [0.14–0.57], $p = 0.001$; Figure 1D). In hierarchical linear regression modeling, greater medial temporal lobe CVR to hypercapnia predicted higher scores on Visual Reproduction II (B = 0.33, 95% CI [0.09–0.57], $p = 0.008$; N = 69), adjusting for age, sex, education, *APOE4* carrier status, $A\beta_{42/40}$ and $pTau_{181}$ levels, and vascular risk factors (0–1 vs ≥2; Table 5). The final model explained 41% of the observed variation in Visual Reproduction II scores ($R^2 = 0.41$, Adj. $R^2 = 0.33$, $F [8, 68] = 5.20$, $p < 0.001$). Adding CVR to hypercapnia as a predictor of Visual

Table 2 Association Between Medial Temporal CVR to Hypercapnia and Mild Cognitive Impairment

Variable	Unstandardized coefficients		OR	Sig.	95% CI for B	
	B	Std. Error			Lower bound	Upper bound
Age (y)	−0.047	0.046	0.954	0.306	0.872	1.044
Sex (male)	−0.223	0.674	0.800	0.740	0.213	2.997
Education (y)	−0.161	0.153	0.851	0.294	0.630	1.150
Aβ42/40 ratio	11.757	27.426	1.2×10^5	0.668	0.000	2.8×10^{28}
pTau181 (pg/mL)	0.074	0.032	1.077	0.020	1.012	1.146
APOE4 carrier status (carrier)	−0.980	0.686	0.375	0.153	0.098	1.441
Vascular risk factors (0–1 vs ≥2)	0.247	0.626	1.281	0.692	0.376	4.366
Medial temporal CVR hypercapnia (%ΔCBF/Δmm Hg $_{ET}CO_2$)	−0.143	0.058	0.867	0.013	0.774	0.970

Abbreviations: CBF = cerebral blood flow; CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2; OR = odds ratio.
Dependent variable: MCI. N for the full model = 88.

Reproduction II scores improved the proportion of variation explained in Visual Reproduction II scores ($\Delta R^2 = 0.08$, $\Delta F[1, 60] = 7.61$, p for $\Delta R^2 = 0.008$). All associations between medial temporal lobe CVR and cognitive outcomes remained significant after FDR correction and after adjusting for study site.

Table 3 Association Between Medial Temporal CVR to Hypercapnia and Logical Memory

Step	Variable	Unstandardized coefficients		t	p Value	95% CI for B		Standardized B coefficient	R^2
		B	Std. error			Lower bound	Upper bound		
1	Age (y)	−0.297	0.123	−2.409	0.019	−0.543	−0.051	−0.283	0.141
	Sex (male)	−2.952	1.919	−1.538	0.129	−6.785	0.881	−0.181	
	Education (y)	0.877	0.411	2.135	0.037	0.057	1.697	0.255	
2	Age (y)	−0.300	0.128	−2.340	0.023	−0.557	−0.044	−0.287	0.177
	Sex (male)	−3.585	2.034	−1.763	0.083	−7.652	0.481	−0.220	
	Education (y)	0.912	0.423	2.159	0.035	0.067	1.757	0.265	
	Aβ42/40 ratio	110.470	74.218	1.488	0.142	−37.939	258.879	0.188	
	pTau181 (pg/mL)	0.069	0.091	0.762	0.449	−0.113	0.251	0.100	
	APOE4 carrier status (carrier)	0.595	1.806	0.329	0.743	−3.016	4.206	0.039	
	Vascular risk factors (0–1 vs ≥2)	1.374	1.873	0.733	0.466	−2.372	5.119	0.088	
3	Age (y)	−0.238	0.124	−1.914	0.060	−0.487	0.011	−0.227	0.267
	Sex (male)	−2.553	1.972	−1.294	0.200	−6.499	1.392	−0.156	
	Education (y)	0.852	0.403	2.116	0.039	0.046	1.658	0.248	
	Aβ42/40 ratio	136.788	71.293	1.919	0.060	−5.820	279.396	0.232	
	pTau181 (pg/mL)	0.041	0.087	0.471	0.639	−0.133	0.216	0.059	
	APOE4 carrier status (carrier)	0.271	1.723	0.157	0.875	−3.175	3.717	0.018	
	Vascular risk factors (0–1 vs ≥2)	1.895	1.793	1.057	0.295	−1.691	5.481	0.122	
	Medial temporal CVR hypercapnia (%ΔCBF/Δmm Hg $_{ET}CO_2$)	0.326	0.120	2.712	0.009	0.086	0.566	0.320	

Abbreviations: CBF = cerebral blood flow; CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2.
Dependent variable: Logical Memory II Score. N for the full model = 69.

Table 4 Association Between Medial Temporal CVR to Hypercapnia and RAVLT

Step	Variable	Unstandardized coefficients				95% CI for B		Standardized B coefficient	R²
		B	Std. error	t	p Value	Lower bound	Upper bound		
1	Age (y)	−0.137	0.050	−2.770	0.007	−0.236	−0.039	−0.303	0.165
	Sex (male)	−1.742	0.765	−2.277	0.026	−3.266	−0.218	−0.249	
	Education (y)	0.143	0.167	0.859	0.393	−0.189	0.475	0.095	
2	Age (y)	−0.145	0.052	−2.774	0.007	−0.249	−0.041	−0.320	0.197
	Sex (male)	−2.029	0.810	−2.505	0.015	−3.644	−0.414	−0.290	
	Education (y)	0.149	0.171	0.873	0.386	−0.191	0.489	0.099	
	Aβ42/40 ratio	5.470	30.526	0.179	0.858	−55.413	66.353	0.021	
	pTau181 (pg/mL)	0.006	0.036	0.173	0.863	−0.066	0.078	0.021	
	APOE4 carrier status (carrier)	−0.564	0.727	−0.775	0.441	−2.015	0.887	−0.085	
	Vascular risk factors (0–1 vs ≥2)	1.088	0.754	1.443	0.154	−0.416	2.592	0.163	
3	Age (y)	−0.129	0.052	−2.491	0.015	−0.232	−0.026	−0.285	0.242
	Sex (male)	−1.813	0.800	−2.266	0.027	−3.408	−0.217	−0.259	
	Education (y)	0.140	0.167	0.840	0.404	−0.193	0.473	0.093	
	Aβ42/40 ratio	15.651	30.309	0.516	0.607	−44.815	76.116	0.060	
	pTau181 (pg/mL)	−0.002	0.036	−0.068	0.946	−0.073	0.069	−0.008	
	APOE4 carrier status (carrier)	−0.652	0.713	−0.914	0.364	−2.076	0.771	−0.099	
	Vascular risk factors (0–1 vs ≥2)	1.198	0.740	1.618	0.110	−0.279	2.674	0.179	
	Medial temporal CVR hypercapnia (%ΔCBF/Δmm Hg $_{ET}CO_2$)	0.100	0.050	2.011	0.048	0.001	0.199	0.223	

Abbreviations: CBF = cerebral blood flow; CVR = cerebrovascular reactivity; $_{ET}CO_2$ = end tidal CO_2; RAVLT = Rey Auditory Verbal Learning Test.
Dependent Variable: RAVLT Delayed Recall Score. N for the full model = 78.

Discussion

Cerebrovascular dysfunction is a known, yet understudied, contributor to cognitive impairment and dementia that frequently occurs in both the presence and absence of Alzheimer disease and Alzheimer disease-related dementias.[6] CVR to hypercapnia is a measure of vasodilatory capacity which can capture cerebrovascular dysfunction and may represent a useful marker of vascular contributions to cognitive impairment and dementia.[10,24,28,38] Previous studies have examined the relation between CVR and cognition[13,39]; however, this study has specifically examined the association between CVR to hypercapnia in the medial temporal lobe and its association with MCI diagnosis or memory ability. In a sample of older adults with no history of dementia or stroke, we observed deficient medial temporal CVR response to hypercapnia in MCI and in relation to worse verbal and visual memory ability. Moreover, the association between medial temporal lobe CVR and cognitive performance persists even after controlling for demographic factors and Alzheimer disease pathophysiologic markers and genetic risk factors. Previous studies have examined the relation between CVR and cerebrovascular disease,[24,38] and have illustrated that cerebrovascular disease contributes to MCI.[2,3] However, we

observed that CVR is an important contributor to MCI above and beyond observable cerebrovascular lesions on brain MRI. These findings suggest that CVR, as a measure of cerebrovascular dysfunction, may be a unique and independent marker for cognitive impairment and an important factor to consider in older adults experiencing memory decline.

Our finding that medial temporal lobe CVR predicted diagnosis of MCI, after accounting for demographic, Alzheimer disease, and vascular risk factors, is consistent with previous studies evaluating that whole-brain CVR is related to MCI diagnosis.[39] Individuals meeting criteria for MCI in this study could be experiencing deficits in single or multiple cognitive domains due to numerous possible etiologies. Our findings, therefore, suggest that CVR may be an important predictor of cognition in older adults, across etiologies, including Alzheimer disease. Alzheimer disease and vascular disease are known to be highly comorbid, and these findings highlight the need to examine the role of vascular dysfunction across dementias.[40]

No previous study has specifically examined whether CVR in the medial temporal lobe is associated with memory function across a range of measures. Structures within the medial

Table 5 Association Between Medial Temporal CVR to Hypercapnia and Visual Reproduction

Step	Variable	Unstandardized coefficients		t	p Value	95% CI for B		Standardized B coefficient	R²
		B	Std. error			Lower bound	Upper bound		
1	Age (y)	−0.603	0.126	−4.787	<0.001	−0.855	−0.352	−0.518	0.271
	Sex (male)	2.256	1.964	1.148	0.255	−1.667	6.179	0.124	
	Education (y)	0.616	0.420	1.464	0.148	−0.224	1.455	0.161	
2	Age (y)	−0.595	0.128	−4.639	<0.001	−0.851	−0.339	−0.511	0.335
	Sex (male)	2.255	2.032	1.110	0.272	−1.809	6.318	0.124	
	Education (y)	0.660	0.422	1.562	0.123	−0.185	1.504	0.172	
	Aβ42/40 ratio	117.448	74.157	1.584	0.118	−30.837	265.733	0.179	
	pTau181 (pg/mL)	0.023	0.091	0.248	0.805	−0.159	0.204	0.029	
	APOE4 carrier status (carrier)	2.691	1.804	1.491	0.141	−0.917	6.299	0.159	
	Vascular risk factors (0–1 vs ≥2)	−1.944	1.872	−1.039	0.303	−5.687	1.798	−0.112	
3	Age (y)	−0.532	0.124	−4.289	<0.001	−0.780	−0.284	−0.457	0.409
	Sex (male)	3.302	1.967	1.679	0.098	−0.633	7.237	0.182	
	Education (y)	0.598	0.402	1.490	0.141	−0.205	1.402	0.156	
	Aβ42/40 ratio	144.143	71.100	2.027	0.047	1.921	286.364	0.220	
	pTau181 (pg/mL)	−0.006	0.087	−0.071	0.944	−0.180	0.168	−0.008	
	APOE4 carrier status (carrier)	2.362	1.718	1.375	0.174	−1.074	5.799	0.140	
	Vascular risk factors (0–1 vs ≥2)	−1.416	1.788	−0.792	0.432	−4.992	2.161	−0.082	
	Medial temporal CVR hypercapnia (%ΔCBF/Δmm Hg $_{ET}CO_2$)	0.330	0.120	2.758	0.008	0.091	0.570	0.292	

Abbreviations: CBF = cerebral blood flow; CVR = cerebrovascular reactivity.
Dependent variable: Visual Reproduction II Score. N for the full model = 69.

temporal lobe, including the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal gyrus, are vital for encoding, storage, and retrieval of information, which underlies episodic memory.[41,42] The temporal lobe seems to be most vulnerable to age-related decline in CVR, and changes in CVR in the temporal lobe have been found to predict change in episodic memory.[17] Our study further extends these findings by specifically examining the medial temporal lobe and including measures of rote verbal memory, narrative episodic memory, and visual memory. By examining a target ROI and including multiple measures of memory function, the study allowed us to methodically explore this relationship.

Moreover, given that cerebrovascular dysfunction is strongly implicated in the pathophysiology of Alzheimer disease[43] and episodic memory dysfunction is a prominent feature of Alzheimer disease,[44,45] we specifically accounted for the influence of *APOE4* and pathophysiologic biomarkers, $Aβ_{42/40}$ and $pTau_{181}$ levels, on the relationship between medial temporal lobe CVR and MCI as well as memory function. Previous studies have illustrated that *APOE4* carriers display breakdown of the blood-brain barrier in the hippocampus and medial temporal lobe, which contributes to cognitive decline, independent of amyloid-β or tau pathology.[20,21] Similarly, amyloid and tau may independently, synergistically, or additively influence cognition, in the presence of cerebrovascular dysfunction.[46,47] By accounting for both *APOE4* carrier status and levels of $Aβ_{42/40}$ and $pTau_{181}$ in hierarchical linear modeling, our findings reveal that CVR in the medial temporal lobe contributes to memory function above and beyond Alzheimer disease-related factors.

Finally, although biomarker research in Alzheimer disease and other dementias has focused primarily on proteinopathy,[48] the findings of our study and the mounting literature on the role of vascular dysfunction in a range of cognitive disorders suggest a need to further examine vascular biomarkers.[6] CVR, which is a dynamic marker of cerebrovascular function and represents the ability of blood vessels to respond to changes in CBF, remains a potential candidate for a valuable biomarker which could be incorporated into research frameworks to address the need for vascular markers.[39]

This study has numerous limitations that warrant consideration in future studies. First, this was a cross-sectional study,

which precludes us from establishing causality. Future studies with longitudinal designs may elucidate whether medial temporal lobe CVR can predict memory decline or dementia, beyond established biomarkers, such as amyloid-β or tau. This would provide further evidence for the prognostic value of CVR as a vascular biomarker. Second, this study used pCASL as opposed to blood oxygen level–dependent (BOLD) MRI, which is both a strength and weakness.[10] BOLD-CVR provides higher temporal resolution and signal-to-noise ratio; however, the BOLD signal encompasses the complex interplay between cerebral blood volume, blood flow, and metabolic rate of oxygen,[49] which makes it challenging to delineate its' physiologic basis. By contrast, pCASL-CVR allows changes in blood flow in response to CO_2 levels to be captured more directly. In addition, although we excluded participants who were not able to adhere to the breathing protocol, these participants were not significantly more likely to meet criteria for MCI. Our protocol was well-tolerated and showed good adherence even in participants with MCI, requiring only 5 minutes of training and 3 breath holds of 15 seconds duration to quantify CVR. Another limitation is that missing data affected our sample size for our hierarchical regression models, which may have introduced bias. However, we observed similar effects across the 3 models, suggesting a robust effect of MTL CVR on memory measures, after accounting for covariates. In addition, the proportion of individuals with MCI in our sample was small (16.7%), leading to unequal sample sizes between groups. Although equality of variances between groups was formally tested in this study and such differences in group sizes are common in observational studies, this is a limitation of our sample. Finally, we used plasma levels of $A\beta_{42/40}$ and $pTau_{181}$ in our analysis, which may be a limitation. Plasma levels of these biomarkers can be obtained relatively noninvasively, but amyloid-β is also present peripherally, and therefore, we may be capturing both cerebral and peripheral levels of these proteins. Nonetheless, previous studies have established that plasma levels of these markers correlated with cortical deposition of these proteins and are related to cerebrovascular pathologies,[50,51] suggesting levels of these proteins in plasma reflect cortical changes.

Overall, the study demonstrates that decreased CVR in the medial temporal lobe is associated with MCI diagnosis and worse memory function in older adults before the onset of functional decline. CVR is therefore a sensitive vascular measure that contributes to memory function above and beyond pathophysiologic markers of Alzheimer disease, which is particularly characterized by memory changes. Future longitudinal studies are warranted to establish whether CVR changes can predict long-term development of Alzheimer disease and other dementias to evaluate the value of CVR as a vascular biomarker and treatment target for neurodegenerative and neurocognitive disorders.

Author contributions

A. Kapoor: 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. S. Dutt: 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. A.C. Engstrom: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.P.M. Alitin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Lohman: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I.J. Sible: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Marshall: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Shenasa: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Gaubert: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.R. Bradford: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Sordo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. X. Shao: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Rodgers: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Head: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.J. Wang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.A. Nation: 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.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

References

1. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease—systematic review and meta-analysis. Neurobiol Aging. 2009;30(3):337-352. doi:10.1016/j.neurobiolaging.2007.07.015

2. Bos D, Wolters FJ, Darweesh SKL, et al. Cerebral small vessel disease and the risk of dementia: a systematic review and meta-analysis of population-based evidence. *Alzheimers Dement*. 2018;14(11):1482-1492. doi:10.1016/j.jalz.2018.04.007

3. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. *Alzheimers Dement*. 2015;11(6):710-717. doi:10.1016/j.jalz.2014.10.008

4. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol*. 2003;2:89-98. doi:10.1016/s1474-4422(03)00305-3

5. Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*. 2019;25(2):270-276. doi:10.1038/s41591-018-0297-y

6. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease. *Alzheimers Dement*. 2019;15(1):158-167. doi:10.1016/j.jalz.2018.07.222

7. Juul Rasmussen I, Frikke-Schmidt R. Modifiable cardiovascular risk factors and genetics for targeted prevention of dementia. *Eur Heart J*. 2023;44(28):2526-2543. doi:10.1093/eurheartj/ehad293

8. Liu P, De Vis JB, Lu H. Cerebrovascular reactivity (CVR) MRI with CO2 challenge: a technical review. *Neuroimage*. 2019;187:104-115. doi:10.1016/j.neuroimage.2018.03.047

9. Urback AL, MacIntosh BJ, Goldstein BI. Cerebrovascular reactivity measured by functional magnetic resonance imaging during breath-hold challenge: a systematic review. *Neurosci Biobehav Rev*. 2017;79:27-47. doi:10.1016/j.neubiorev.2017.05.003

10. Yew B, Jang JY, Dutt S, et al. Cerebrovascular reactivity deficits in cognitively unimpaired older adults: vasodilatory versus vasoconstrictive responses. *Neurobiol Aging*. 2022;113:55-62. doi:10.1016/j.neurobiolaging.2022.02.006

11. Suri S, Mackay CE, Kelly ME, et al. Reduced cerebrovascular reactivity in young adults carrying the APOE ε4 allele. *Alzheimers Dement*. 2015;11(6):648-657.e1. doi:10.1016/j.jalz.2014.05.1755

12. Glass Umfleet L, Pommy J, Cohen AD, et al. Decreased cerebrovascular reactivity in mild cognitive impairment phenotypes. *J Alzheimers Dis*. 2023;94(4):1503-1513. doi:10.3233/jad-221156

13. Catchlove SJ, Pipingas A, Hughes ME, Macpherson H. Magnetic resonance imaging for assessment of cerebrovascular reactivity and its relationship to cognition: a systematic review. *BMC Neurosci*. 2018;19(1):21. doi:10.1186/s12868-018-0421-4

14. Aslanyan V, Mack WJ, Ortega NE, et al. Cerebrovascular reactivity in Alzheimer's disease signature regions is associated with mild cognitive impairment in adults with hypertension. *Alzheimers Dement*. 2024;20(3):1784-1796. doi:10.1002/alz.13572

15. Marchena-Romero K-J, Ji X, Sommer R, et al. Examining temporal features of BOLD-based cerebrovascular reactivity in clinical populations. *Front Neurol*. 2023;14:1199805. doi:10.3389/fneur.2023.1199805

16. Beaudin AE, McCreary CR, Mazerolle EL, et al. Cerebrovascular reactivity across the entire brain in cerebral amyloid angiopathy. *Neurology*. 2022;98(17):e1716-e1728. doi:10.1212/WNL.0000000000200136

17. Peng S-L, Chen X, Li Y, Rodrigue KM, Park DC, Lu H. Age-related changes in cerebrovascular reactivity and their relationship to cognition: a four-year longitudinal study. *Neuroimage*. 2018;174:257-262. doi:10.1016/j.neuroimage.2018.03.033

18. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Eur Arch Psychiatry Clin Neurosci*. 1999;249(s3):S14-S22. doi:10.1007/pl00014168

19. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55(10):967-972. doi:10.1136/jnnp.55.10.967

20. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71-76. doi:10.1038/s41586-020-2247-3

21. Moon W-J, Lim C, Ha IH, et al. Hippocampal blood–brain barrier permeability is related to the APOE4 mutation status of elderly individuals without dementia. *J Cereb Blood Flow Metab*. 2021;41(6):1351-1361. doi:10.1177/0271678X20952012

22. Wang Z. Improving cerebral blood flow quantification for arterial spin labeled perfusion MRI by removing residual motion artifacts and global signal fluctuations. *Magn Reson Imaging*. 2012;30(10):1409-1415. doi:10.1016/j.mri.2012.05.004

23. Wang Z, Aguirre GK, Rao H, et al. Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. *Magn Reson Imaging*. 2008;26(2):261-269. doi:10.1016/j.mri.2007.07.003

24. Kapoor A, Yew B, Jang JY, et al. Older adults with perivascular spaces exhibit cerebrovascular reactivity deficits. *Neuroimage*. 2022;264:119746. doi:10.1016/j.neuroimage.2022.119746

25. Clark AL, Weigand AJ, Bangen KJ, Merritt VC, Bondi MW, Delano-Wood L. Repetitive mTBI is associated with age-related reductions in cerebral blood flow but not cortical thickness. *J Cereb Blood Flow Metab*. 2021;41(2):431-444. doi:10.1177/0271678X19897443

26. Nation DA, Wierenga CE, Clark LR, et al. Cortical and subcortical cerebrovascular resistance index in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*. 2013;36(4):689-698. doi:10.3233/JAD-130086

27. Petr J, Mutsaerts HJMM, De Vita E, et al. Effects of systematic partial volume errors on the estimation of gray matter cerebral blood flow with arterial spin labeling MRI. *MAGMA*. 2018;31(6):725-734. doi:10.1007/s10334-018-0691-y

28. Sible IJ, Jang JY, Dutt S, et al. Older adults with higher blood pressure variability exhibit cerebrovascular reactivity deficits. *Am J Hypertens*. 2023;36(1):63-68. doi:10.1093/ajh/hpac108

29. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19(3):1233-1239. doi:10.1016/s1053-8119(03)00169-1

30. Schmidt P, Gaser C, Arsic M, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. *Neuroimage*. 2012;59(4):3774-3783. doi:10.1016/j.neuroimage.2011.11.032

31. Sible IJ, Yew B, Jang JY, et al. Blood pressure variability and plasma Alzheimer's disease biomarkers in older adults. *Sci Rep*. 2022;12(1):17197. doi:10.1038/s41598-022-20627-4

32. Doecke JD, Pérez-Grijalba V, Fandos N, et al. Total $A\beta_{42}/A\beta_{40}$ ratio in plasma predicts amyloid-PET status, independent of clinical AD diagnosis. *Neurology*. 2020;94(15):e1580-e1591. doi:10.1212/WNL.0000000000009240

33. Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis*. 2014;42(1):275-289. doi:10.3233/JAD-140276

34. Clark LR, Delano-Wood L, Libon DJ, et al. Are empirically-derived subtypes of mild cognitive impairment consistent with conventional subtypes? *J Int Neuropsychol Soc*. 2013;19(6):635-645. doi:10.1017/S1355617713000313

35. Bean J. Rey auditory verbal learning test, Rey AVLT. *Encyclopedia of Clinical Neuropsychology*. Springer New York; 2011:2174-2175.

36. Chlebowski C. Wechsler Memory Scale. *Encyclopedia of Clinical Neuropsychology*. Springer New York; 2011:2688-2690.

37. Benjamini Y, Hochsberg Y. Controlling the false Discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57(1):289-300. doi:10.1111/j.2517-6161.1995.tb02031.x

38. Kapoor A, Dutt S, Alitin JPM, et al. Older adults with reduced cerebrovascular reactivity exhibit high white matter hyperintensity burden. *Neurobiol Aging*. 2024;139:5-10. doi:10.1016/j.neurobiolaging.2024.03.006

39. Sur S, Lin Z, Li Y, et al. Association of cerebrovascular reactivity and Alzheimer pathologic markers with cognitive performance. *Neurology*. 2020;95(8):e962-e972. doi:10.1212/WNL.0000000000010133

40. Khan A, Kalaria RN, Corbett A, Ballard C. Update on vascular dementia. *J Geriatr Psychiatry Neurol*. 2016;29(5):281-301. doi:10.1177/0891988716654987

41. Raslau FD, Mark IT, Klein AP, Ulmer JL, Mathews V, Mark LP. Memory part 2: the role of the medial temporal lobe. *AJNR Am J Neuroradiol*. 2015;36(5):846-849. doi:10.3174/ajnr.A4169

42. Squire LR, Stark CEL, Clark RE. The medial temporal lobe. *Annu Rev Neurosci*. 2004;27:279-306. doi:10.1146/annurev.neuro.27.070203.144130

43. Iadecola C, Gottesman RF. Cerebrovascular alterations in Alzheimer disease. *Circ Res*. 2018;123(4):406-408. doi:10.1161/CIRCRESAHA.118.313400

44. Schwindt GC, Black SE. Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. *Neuroimage*. 2009;45(1):181-190. doi:10.1016/j.neuroimage.2008.11.024

45. Economou A, Routsis C, Papageorgiou SG. Episodic memory in Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies/Parkinson disease dementia: disentangling retrieval from consolidation. *Alzheimer Dis Assoc Disord*. 2016;30(1):47-52. doi:10.1097/WAD.0000000000000089

46. Liu W, Wong A, Law ACK, Mok VCT. Cerebrovascular disease, amyloid plaques, and dementia. *Stroke*. 2015;46(5):1402-1407. doi:10.1161/STROKEAHA.114.006571

47. Weigand AJ, Hamlin AM, Breton J, Clark AL. Cerebral blood flow, tau imaging, and memory associations in cognitively unimpaired older adults. *Cereb Circ Cogn Behav*. 2022;3:100153. doi:10.1016/j.cccb.2022.100153

48. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

49. Bhogal AA, Siero JCW, Fisher JA, et al. Investigating the non-linearity of the BOLD cerebrovascular reactivity response to targeted hypo/hypercapnia at 7T. *Neuroimage*. 2014;98:296-305. doi:10.1016/j.neuroimage.2014.05.006

50. Fandos N, Pérez-Grijalba V, Pesini P, et al. Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals. *Alzheimers Dement (Amst)* 2017;8:179-187. doi:10.1016/j.dadm.2017.07.004

51. Kapoor A, Gaubert A, Yew B, et al. Enlarged perivascular spaces and plasma Aβ42/Aβ40 ratio in older adults without dementia. *Neurobiol Aging*. 2023;128:43-48. doi:10.1016/j.neurobiolaging.2023.04.004