Cerebral blood flow, tau imaging, and memory associations in cognitively unimpaired older adults

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ABSTRACT

Objective: Cerebral blood flow (CBF) has been independently linked to cognitive impairment and traditional Alzheimer's disease (AD) pathology (e.g., amyloid-beta [Aβ], tau) in older adults. However, less is known about the possible interactive effects of CBF, Aβ, and tau on memory performance. The present study examined whether CBF moderates the effect of Aβ and tau on objective and subjective memory within cognitively unimpaired (CU) older adults.

Methods: Participants included 54 predominately white CU older adults from the Alzheimer's Disease Neuroimaging Initiative. Multiple linear regression models examined meta-temporal CBF associations with (1) meta-temporal tau PET adjusting for cortical Aβ PET and (2) and cortical Aβ PET adjusting for tau PET. The CBF and tau meta region was an average of 5 distinct temporal lobe regions. CBF interactions with Aβ or tau PET on memory performance were also examined. Covariates for all models included age, sex, education, pulse pressure, APOE-ε4 positivity, and imaging acquisition date differences.

Results: CBF was significantly negatively associated with tau PET ($t = -2.16$, $p = .04$) but not Aβ PET ($t = 0.98$, $p = .33$). Results revealed a CBF by tau PET interaction such that there was a stronger effect of tau PET on objective ($t = 2.51$, $p = .02$) and subjective ($t = -2.67$, $p = .01$) memory outcomes among individuals with lower levels of CBF.

Conclusions: Cerebrovascular and tau pathologies may interact to influence cognitive performance. This study highlights the need for future vascular risk interventions, which could offer a scalable and cost-effective method for AD prevention.

1. Introduction

Research into mechanisms underlying Alzheimer's disease (AD) pathogenesis and progression has identified novel vascular pathways that may operate parallel to and/or synergistically with pathologic changes to amyloid-beta 1–42 (Aβ) and tau [1]. Cerebrovascular risk emerges as an area of great interest for several reasons: (1) the high degree of vascular co-pathology identified postmortem in individuals with AD, particularly among racial/ethnic minorities (i.e., non-white individuals) and women [2–4];(2) increasing incidence of cardiovascular conditions (e.g., diabetes, hypertension) and vascular dementia [5]; and (3) recent evidence suggesting that intensive blood pressure control may mitigate risk for cognitive impairment in late adulthood [6]. A better understanding of whether cerebrovascular pathology, including cerebral blood flow (CBF) changes, interacts with traditional AD pathology (Aβ and tau) to affect cognition is an important step toward identifying scalable and cost-effective methods of AD prevention and intervention.

Although histopathologic studies have identified the co-occurrence of cerebrovascular and traditional AD pathology [4], less is known about the interaction between these pathologies and their potential synergistic effect on AD-related cognitive and clinical outcomes. The "two-hit" vascular hypothesis suggests that AD dementia emerges as the result of (1) vascular damage, including impaired CBF, which in turn leads to (2) tau phosphorylation and Aβ accumulation [7]. Indeed, animal studies have demonstrated that arterial occlusion-induced cerebral hypoperfusion increases both phosphorylated tau and Aβ levels and induces spatial memory impairments [8,9]. Thus, providing evidence for a potential causal role of CBF changes in the promotion AD pathology and cognitive decline.

The development of arterial spin labeling (ASL) magnetic resonance imaging (MRI) has allowed for examination of CBF changes in human participants that support observations in the animal literature [10,11]. Several studies have reported reductions in CBF across AD clinical stages (e.g., mild cognitive impairment [MCI], dementia) [12]. Furthermore, cerebrovascular dysregulation as detected by ASL has been identified as one of the first pathological events that occur in the preclinical phase of the disease, and these reductions in CBF have been shown to predict future cognitive decline and conversion from cognitively unimpaired (CU) to MCI status [13–15]. Additionally, research from the Alzheimer's Disease Neuroimaging Initiative (ADNI) has demonstrated that reduced CBF across temporal and parietal regions is associated with higher global Aβ positron emission tomography (PET) burden [16] and temporal-parietal tau PET levels [17]. However, the moderating effect of CBF on the associations between AD pathology and memory in this cohort has yet to be investigated.

The current study builds upon existing literature on the role of CBF in AD-related outcomes by examining a meta-temporal CBF region of interest (ROI) in terms of (1) its association with cortical Aβ and meta-temporal tau PET and (2) the moderating role of CBF on the association between Aβ or tau PET and memory among CU older adults from the ADNI cohort. We hypothesize that, consistent with prior research, CBF will be associated with both tau and Aβ PET levels. However, we suspect that CBF will interact only with tau PET to influence objective and subjective memory performance, given that prior research has demonstrated a stronger link between tau and cognition relative to Aβ [18–20]. Importantly, demonstrating that CBF not only co-occurs but also interacts with Aβ and tau to affect memory performance prior to overt cognitive impairment will allow us to better understand the contributions of cerebrovascular changes in the preclinical period of AD when prevention and intervention efforts focused on reducing vascular risk may be especially pertinent.

2. Material and methods

2.1. Data availability

This study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which is a public-private partnership that was originally launched in 2003 by the National Institute on Aging, National Institute of Biomedical Imaging and Bioengineering, Food and Drug Administration, private pharmaceutical companies, and various non-profit organizations. The goal of ADNI is to enhance our understanding of the progression of mild cognitive impairment (MCI) and the preclinical stages of Alzheimer's disease (AD) with serial magnetic resonance imaging (MRI), positron emission tomography (PET), and clinical and neuropsychological assessments. Additional information about the ADNI study, sites of data collection, and procedures can found at www.adni-info.org. ADNI participants are recruited from over 50 sites across the United States and Canada. Each ADNI participant provided written informed consent upon enrollment in the study and the ADNI study was approved by Institutional Review Boards (IRB) of all participating sites.

2.2. Inclusion/Exclusion criteria

Enrollment criteria for the ADNI study are described in detail elsewhere [21] but briefly include older adults that are: between 55 and 90 years-old, fluent in English or Spanish, with ≥ 6 years of education, that demonstrated adequate vision and hearing to engage in neuropsychological testing procedures, and did not have significant neurological or psychiatric disorder or history of traumatic brain injury.

2.3. Participants

The present study included a total of 72 ADNI3 participants that had complete data available for download on June 1, 2022 for all of the following variables: arterial spin labeling MRI, tau PET (Flortaucipir), and Aβ PET (Florbetapir or Florbetaben) neuroimaging data; blood pressure measurements; key demographic information (e.g., age, years of education, sex); apolipoprotein E (APOE) genotyping; and neuropsychological data. Of the 72 participants, 15 were determined to have MCI and were thus excluded from the final study sample, bringing the sample to 57 CU participants. Three of these 57 CU participants were subsequently determined to have physiological implausible CBF values and were thus excluded from analyses, resulting in a final sample size of 54 CU participants.

2.4. Cognitively unimpaired status and objective memory performance

Participants were administered a comprehensive neuropsychological battery comprised of measures of general cognition (Mini-Mental Status Examination), attention/executive functioning (Trail Making Test Parts A and B), verbal memory (Immediate and Delayed Recall from Story A of the Weschler Memory Scale-Revised; Delayed Recall and Recognition [hits minus false positives] of the Auditory Verbal Learning Test [AVLT]), and language (Boston Naming Test or Multilingual Naming Test; animal fluency). Raw scores for each cognitive test were converted to z-scores that were based on predicted values from demographically adjusted (age, sex, and education) regression equations based on a "robust" normal control group that remained CU throughout their duration of participation in ADNI [22,23].

Demographically corrected z-scores for 1) AVLT delay recall and recognition trials were averaged to create an AVLT memory composite score and 2) the Logical Memory immediate and delayed z-scores were averaged to create a Logical Memory composite score. The Logical Memory composite did not include a recognition trial given this is not administered in the ADNI cognitive testing protocol. Higher scores across both composited equate to better objective memory performance.

CU classification was based upon actuarial neuropsychological criteria [24] and performance on the previously mentioned test (with the exception of MMSE and WMS Story A). Participants were classified as CU if they did not meet criteria for MCI as defined by (1) impairment ($z < -1$) on at least two scores within one cognitive domain or (2) one impaired score across three separate cognitive domains [24]. Given Story A has been utilized in ADNI conventional MCI criteria, it was intentionally excluded from actuarial diagnostic criteria to ensure independence of the criteria for comparisons purposes in the original investigation [see 22 for a representation of the cognitive measures utilized in the criteria]. Importantly, actuarial neuropsychological criteria has previously been show to improve biomarker associations and MCI/AD progression rates relative to conventional ADNI MCI criteria [23].

2.5. Subjective memory performance

The Everyday Cognition (ECog) questionnaire was used to assess an individual's self-reported ability to perform everyday tasks [25]. The ECog consists of 39 items on a 4-point scale (1 = no change or performs better than 10 years ago; 2 = occasionally performs the task worse than

10 years ago; 3 = consistently performs the task worse than 10 years ago; 4 = performs the task much worse than 10 years ago). These items can be subdivided into seven cognitive subdomains of memory, language, visuospatial abilities, planning, organization, and divided attention. An average memory ECog score across 8 memory-related items was created (range 1–4) to assess subjective memory concerns such that higher scores equate to worse subjective memory.

2.6. Neuroimaging procedures

Comprehensive information about MRI/PET acquisition, processing, and analysis pipelines can be found online at adni.loni.ucsd.edu. Pulsed ASL, T1-weighted 3D MPRAGE MRI, tau PET, and Aβ PET scans were acquired on 3 Tesla Siemens scanners.

2.6.1. ASL acquisition and analysis

Pulsed ASL scans were acquired using QUIPS thin-slice T11 period saturation with echo-planar imaging [26]. ASL sequence parameters included inversion time for arterial spins (T11) = 700 ms, total transit time of spins (T12) = 1900 ms, tag thickness = 100 mm, tag to proximal slice gap = 25.4 mm, repetition time = 3400 ms, echo time = 12 ms, field of view 256 mm, 64×64 matrix, 24 4-mm thick axial slices (52 tag and control image pairs), time lag between slices = 22.5 ms. An automated MATLAB processing pipeline involved motion correction, frame alignment using rigid body transformation, and least squares fitting using SPM 8 (http:/www.fil.ion.ucl.uk/spm). The differences between mean-tagged and mean-untagged ASL data were used to calculate perfusion weighted images and were intensity scaled to account for signal decay and generate physiological units. Geometric distortion was applied using Insight Toolkit libraries, and then ASL images were subsequently aligned to T1 images using FSL (http:/www.fmrid.ox.ac.uk/fsl/). Images were corrected for tissue partial volume effects at the voxel wise level under the assumption that perfusion for each voxel is a combination of gray matter, white matter, and cerebrospinal fluid signal (tissues segmented using SPM8), with the weighting coefficients based on tissue densities and a constant ratio of 2.5 times greater perfusion for gray matter to white matter. Partial volume-corrected perfusion weighted images were normalized by a reference image and converted into physical units of measurement (mL/100 g tissue/min). Quality control consisted of visual inspection of signal uniformity, distortions, gray matter contrast, and the presence of any artifacts. ASL data that passed all these assurances were included. Full processing methods have been previously described [27].

T1-weighted 3D MPRAGE parameters included field of view = 256 mm, repetition time = 23,000 ms, echo time = 2.98 ms, flip angle = 9, and $1.1 \times 1.1 \times 1.2 \text{ mm}^2$ resolution. FreeSurfer (http://surfer.nmr.mgh.harvard.edu/fswiki) was used to skull-strip, segment, and parcellate structural scans. FreeSurfer-derived anatomical regions of interest (ROIs) were applied and used to extract CBF estimates for each participant. Subsequently, a voxel count weighted average of bilateral estimates of CBF in the amygdala, entorhinal cortex, fusiform gyrus, inferior temporal gyrus, and middle temporal gyrus were averaged to create a meta-temporal CBF ROI. Data that pass ADNI FreeSurfer quality control standards were included.

2.6.2. PET acquisition and analysis

PET imaging included Flortaucipir (to quantify tau burden) and Florbetapir or Florbetaben (to quantify Aβ burden) with all acquired PET scans co-registered to T1 images acquired closest in time to the PET scan. FreeSurfer-derived regional standardized uptake values were subsequently intensity normalized using the inferior cerebellar gray matter (tau PET) or whole cerebellum (Aβ PET) to create standardized uptake value ratios (SUVRs) as recommended by ADNI documentation [28–30]. For tau PET, SUVR estimates for the amygdala, entorhinal cortex, fusiform gyrus, inferior temporal gyrus, and middle temporal gyrus were averaged to create a meta-temporal tau ROI to approximate

early-moderate stage tau deposition [31,32]. Note that the hippocampus was not included in this meta-temporal ROI as it is known to be influenced by off-target signal from the adjacent choroid plexus [28]. For Aβ PET, SUVR estimates across frontal, parietal, and temporal regions were used to create a cortical summary metric to capture regions vulnerable to early Aβ deposition given that Aβ plaques first develop across diffuse cortical regions rather than the more circumscribed temporal regions associated with early tau tangle formation [33–35]. Florbetapir and Florbetaben values were converted to a centiloid scale as previously described to standardize across the two tracers [36]. Aβ PET positivity was defined as a centiloid value > 28.8 [37]. The time difference (in months) between acquisition of tau PET and Aβ PET as well as Aβ PET and ASL were included as a covariate in all models. All tau PET and ASL scans were within less than one month of one another and were therefore not included as a covariate.

2.7. Genetics, vascular risk, and psychiatric symptoms

APOE-ε4 positivity was determined by the possession of at least one APOE-ε4 allele. Pulse pressure was determined by subtracting systolic from diastolic blood pressure (BP) measurements and standardizing to systolic blood pressure (systolic BP – diastolic BP/systolic BP). Depression was measured with the Geriatric Depression Scale [38].

2.8. Statistical analyses

All data were checked for normality and outliers. The ECog memory score was log transformed to improve normality. All analyses were performed R version 3.5.0 (https://cran.r-project.org/). Multiple linear regression analyses were used to explore: (1) meta-temporal CBF associations with meta-temporal tau PET SUVR and cortical Aβ PET centiloid; and (2) the moderating effect of meta-temporal CBF on associations between PET values with objective and subjective memory performance. Covariates included age, sex, years of education, pulse pressure, APOE-ε4 positivity, and imaging acquisition date differences. Models including tau PET as the primary predictor additionally adjusted Aβ PET, and models including Aβ PET as the primary predictor additionally adjusted for tau PET to assess the independent effects of these variables in their associations with CBF and memory performance. The unstandardized beta estimates (B) for continuous predictors are reported in the text.

3. Results

Participant demographics and clinical characteristics are presented in Table 1. On average, the sample was approximately 71 years-old, college educated, predominantly white (87%) and consisted of more women relative to men (53%). The average Mini-Mental State Examination (MMSE) score was 29 and the sample endorsed minimal depressive symptoms on the Geriatric Depression Scale.

3.1. Meta-Temporal CBF, meta-temporal tau, and amyloid SUVR associations

Regressions adjusting for age, years of education, sex, pulse pressure, APOE-ε4 positivity, imaging acquisition date differences, and cortical Aβ PET were used to explore meta-temporal CBF associations with meta-temporal tau PET. Results revealed that lower meta-temporal CBF was negatively associated with higher meta-temporal tau PET burden ($B = -0.003$, $t = -2.16$, $p = .04$). See Fig. 1. Regressions adjusting for the same covariates and meta-temporal tau PET burden revealed that meta-temporal CBF was not significantly associated with cortical Aβ PET ($B = 0.71$, $t = 0.98$, $p = .33$).

3.2. Meta-Temporal CBF x tau interactions on memory

Multiple regression analyses adjusting for age, education, sex, APOE-

Table 1

Participant demographics and clinical characteristics.

	Overall($N = 54$)
Age (years)	
Mean (SD)	71.0 (7.48)
Median (SD)	69.5 [56.6, 89.9]
Education (years)	
Mean (SD)	16.5 (2.53)
Median [Min, Max]	17.0 [8.00, 20.0]
Sex	
Males	24 (44.4%)
Female	30 (55.6%)
Race	
American Indian/Alaska Native	1 (1.9%)
Asian	1 (1.9%)
Black/African American	3 (5.6%)
White	47 (87.0%)
More than one race	2 (3.7%)
Ethnicity	
Hispanic/Latino	4 (7.4%)
Not Hispanic/Latino	50 (92.6%)
APOE-e4 Positivity	
e4-	34 (63.0%)
e4+	20 (37.0%)
GDS Total Score	
Mean (SD)	0.870 (1.23)
Median [Min, Max]	0 [0, 5.00]
Pulse Pressure (mmHg)	
Mean (SD)	60.8 (16.5)
Median [Min, Max]	58.5 [26.0, 97.0]
MMSE Total Score	
Mean (SD)	29.2 (1.02)
Median [Min, Max]	29.0 [26.0, 30.0]
Summary SUVR Centiloid	
Mean (SD)	21.9 (34.3)
Median [Min, Max]	8.16 [−9.81, 134]
Meta-Temporal Tau SUVR	
Mean (SD)	1.18 (0.0735)
Median [Min, Max]	1.16 [1.03, 1.40]
Meta-Temporal CBF (mL/100 g/min)	
Mean (SD)	30.2 (7.12)
Median [Min, Max]	29.0 [14.8, 49.7]
AVLT Z-Score Composite	
Mean (SD)	0.254 (1.21)
Median [Min, Max]	0.406 [−2.17, 3.02]
Missing	2 (3.7%)
Logical Memory Z-score Composite	
Mean (SD)	−0.236 (1.54)
Median [Min, Max]	−0.0290 [−4.62, 2.30]
ECog Memory Average	
Mean (SD)	1.73 (0.637)
Median [Min, Max]	1.56 [1.00, 3.88]

Note for Table 1. GDS = Geriatric Depression Scale; MMSE = Mini-Mental Status Examination; SUVR.

standardized uptake value ratio; CBF = cerebral blood flow; ECog = Everday Cognition Questionnaire.

Note for Table 1. GDS = Geriatric Depression Scale; MMSE = Mini-Mental Status Examination; SUVR = standardized uptake value ratio; CBF = cerebral blood flow; ECog = Everday Cognition Questionnaire.

ε4 positivity, pulse pressure, imaging acquisition date differences, Aβ PET, and the simple effects of meta-temporal CBF and meta-temporal tau PET were used to explore meta-temporal CBF x meta-temporal tau PET interactions on objective a memory performance. Results revealed there were significant meta-temporal CBF x meta-temporal tau PET interactions for the Logical Memory composite ($B = 1.16$, $t = 2.51$, $p = .02$). See Table 2. A median split for meta-temporal CBF (28.95 mL/100 g/min) was conducted and participants were divided into those with low ($n = 27$) versus high levels CBF ($n = 27$) to aid in interpretation and graphically depict the association between the three continuous variables. See Fig. 2. Results revealed there were no significant meta-temporal CBF x meta-temporal tau PET interactions for the AVLT composite score ($B = 0.20$, $t = 0.49$, $p = .63$). Furthermore, there were no meta-temporal CBF x cortical Aβ PET interaction on the AVLT ($B = −0.0002$, $t = −0.32$, $p = .75$) or Logical Memory ($B = 0.001$, $t = 1.03$, $p = .31$) composites.

Similar models were conducted to examine the interaction between meta-temporal CBF and meta-temporal tau on subjective memory. Results revealed there were significant meta-temporal CBF x meta-temporal tau PET interactions for ECog memory scores ($B = −0.24$, $t = −2.67$, $p = .01$). See Table 3. A median split for meta-temporal CBF (28.95 mL/100 g/min) was conducted and participants were divided into those with low ($n = 27$) versus high levels CBF ($n = 27$) to aid in interpretation and graphically depict the association between the three continuous variables. See Fig. 3. There were no meta-temporal CBF x cortical Aβ PET interaction on the ECog memory scores ($B = - 0.0002$, $t = −1.02$, $p = .32$).

4. Discussion

The current study demonstrated that, independent of demographic factors, cardiovascular risk, and Aβ PET levels, lower levels of meta-temporal CBF were associated with higher levels of meta-temporal tau PET. The same association was not significant between CBF and Aβ PET adjusting for tau PET levels. Additionally, there was a significant interaction between meta-temporal CBF and meta-temporal tau PET on (objective) Logical Memory performance and (subjective) ECog memory such that, among individuals with lower levels of CBF, there was a stronger effect of tau PET on memory outcomes (i.e., lower Logical Memory, higher ECog memory). These results demonstrate that well-established associations between tau PET and memory performance are moderated by cerebral blood flow even among relatively healthy CU older adults.

There are several possible mechanisms by which CBF and tau may interact to promote neurodegeneration and resultant cognitive dysfunction. These pathologic processes may act in a cumulative manner, such that phosphorylated tau induces neuronal injury through microtubule instability and dysconnectivity [39] while hypoperfusion simultaneously affects neuronal integrity through impaired protein synthesis and diminished oxygen delivery [7]. Per the two-hit hypothesis, impaired CBF may directly initiate phosphorylation of tau by activating protein kinase pathways, promoting neuroinflammatory processes, and altering pH and electrolyte balances [40]. However, there likely exists a bidirectional association between hypoperfusion and tau pathology such that tau may induce blood vessel abnormalities (e.g., spiraling morphologies, reduced diameter) and damage the blood-brain-barrier [41–43]. Additionally, there may be a mediating mechanism by which individuals with low CBF also have greater atherosclerosis and resultant BBB dysfunction that exacerbates the negative effects of tau [44]. While the complex dynamics between cerebrovascular and tau pathologies suggest multiple pathways to neurodegeneration and cognitive dysfunction, our findings add to the robust body of literature by demonstrating that regional CBF and tau PET interact to impact both objective and subjective memory among CU older adults.

Previous research has identified robust associations between tau PET and memory [18–20]. There is considerable inter-individual variability in tau-memory associations, however, such that certain individuals with high levels of tau PET may be more susceptible than others to poorer memory. For example, one prior study demonstrated that the negative association between tau PET and objective memory was exacerbated by the presence of the APOE e4 allele [20]. Our results suggest that elevated cerebrovascular pathology as measured by CBF may also partially explain this variability in tau-memory associations by interacting with high tau PET levels to confer greater difficulty with objective and subjective memory among CU older adults with lower CBF.

Notably, we did not find evidence of an association between CBF and Aβ PET after adjusting for relevant demographic factors, cardiovascular risk, and tau PET levels. Although the two-hit hypothesis suggests that hypoperfusion may alter processing of the amyloid precursor protein
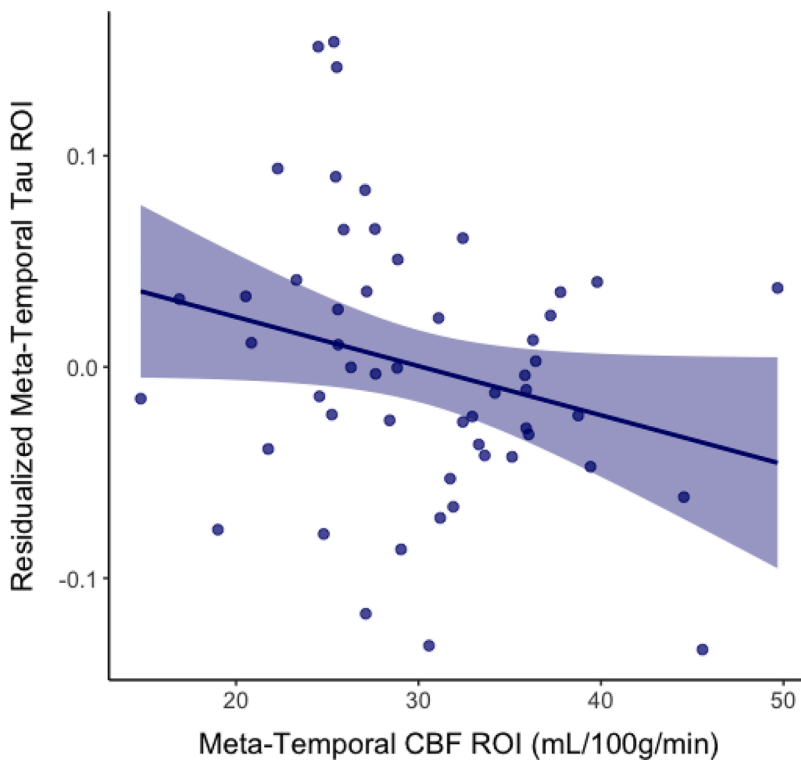
Fig. 1. CBF and tau PET burden associations.
ROI = region of interest. CBF = cerebral blood flow. PET = positron emission tomography. SUVR = standardized uptake value ratio. CBF is depicted on the x-axis. SUVR residualized for age, education, sex, apolipoprotein e4 positivity, pulse pressure, and imaging date differences is depicted on the y-axis. The blue dots and line represent the association between CBF and tau PET burden.

Table 2
Regression Table Output for Logical Memory Composite

Predictors	Logical Memory Z-score Composite			
	B Estimates	CI	t statistic	p
(Intercept)	43.24	10.69 – 75.79	2.68	**0.010**
Age (years)	-0.02	-0.08 – 0.05	-0.56	0.577
Education (years)	0.06	-0.12 – 0.24	0.66	0.511
Sex: Female	0.43	-0.47 – 1.33	0.97	0.340
APOE-e4 Positivity: e4+	0.12	-0.96 – 1.20	0.23	0.822
Tau, Amyloid PET date difference	-0.58	-1.09 – -0.06	-2.24	**0.031**
CBF, Amyloid PET date difference	0.06	-0.40 – 0.53	0.28	0.780
Summary SUVR Centiloid	-0.01	-0.03 – 0.00	-1.49	0.143
Pulse Pressure (mmHg)	-0.01	-0.04 – 0.02	-0.60	0.550
Meta-Temporal CBF (mL/100g/min)	-1.36	-2.44 – -0.28	-2.55	**0.014**
Meta-Temporal Tau SUVR	-36.38	-63.51 – -9.24	-2.71	**0.010**
Meta-Temporal CBF x Meta-Temporal Tau SUVR	1.16	0.23 – 2.08	2.51	**0.016**
Observations	54			
R^2 / R^2 adjusted	0.322/ 0.145			

and promote aggregation of Aβ through similar mechanisms mentioned above [40], human studies have yielded mixed findings. Whereas one study identified an association between temporal-parietal CBF and global Aβ levels [16], another study examining associations between white matter hyperintensities (WMH) – an indicator of chronic small vessel ischemic changes – with Aβ and tau PET identified a link between WMH and tau independent of Aβ levels that was not observed between

WMH and Aβ independent of tau levels [45]. Thus, it's possible that any association between Aβ and cerebrovascular pathology may be largely explained by the degree of tau accumulation rather than a mechanistic link specific to Aβ. Alternatively, the lack of an association observed in the current study may be due to our use of a cortical summary Aβ PET measure, which increases the reliability of Aβ estimates but may mask any regional specificity. Therefore, the discrepancy between those findings and the current findings may be more likely attributable to other differences in methodological approaches including our exclusion of individuals with cognitive impairment or adjustment for cardiovascular risk and tau PET levels.

The current study is significantly limited by the racial/ethnic homogeneity of the ADNI cohort, which limits generalizability of the observed findings beyond white older adults. Importantly, increased incidence of cerebrovascular pathology on autopsy and greater vascular risk burden has been observed among underserved racial/ethnic individuals [2,46]. Thus, differential patterns may be observed in non-white groups, and it is critical to address potential disparities in AD before formulating conclusions and implementing potential interventions that may differentially impact other racial/ethnic groups. Additionally, the ADNI cohort is relatively healthy with low levels of cardiovascular risk and extending these findings to community-based samples with a larger range of health conditions may yield different results. Although our study had a relatively small sample due to the multiple PET and MRI neuroimaging measures, our sample size is comparable to prior research including similar measures [16,47,48]. That said, the sample size may have limited our power to detect significant associations and our analyses should be replicated in future larger samples. Finally, it is important to note performance on the AVLT composite utilized in this study was not independent of cognitive status given the AVLT was used in the actuarial criteria diagnosis of CU. Strengths of the current study include use of a brain-based measure of cerebrovascular pathology, ASL, that is sensitive to early functional ischemic changes; inclusion of both Aβ and tau PET in all statistical models to assess their interactions with CBF independent of the other pathology; and examination of both objective and subjective memory
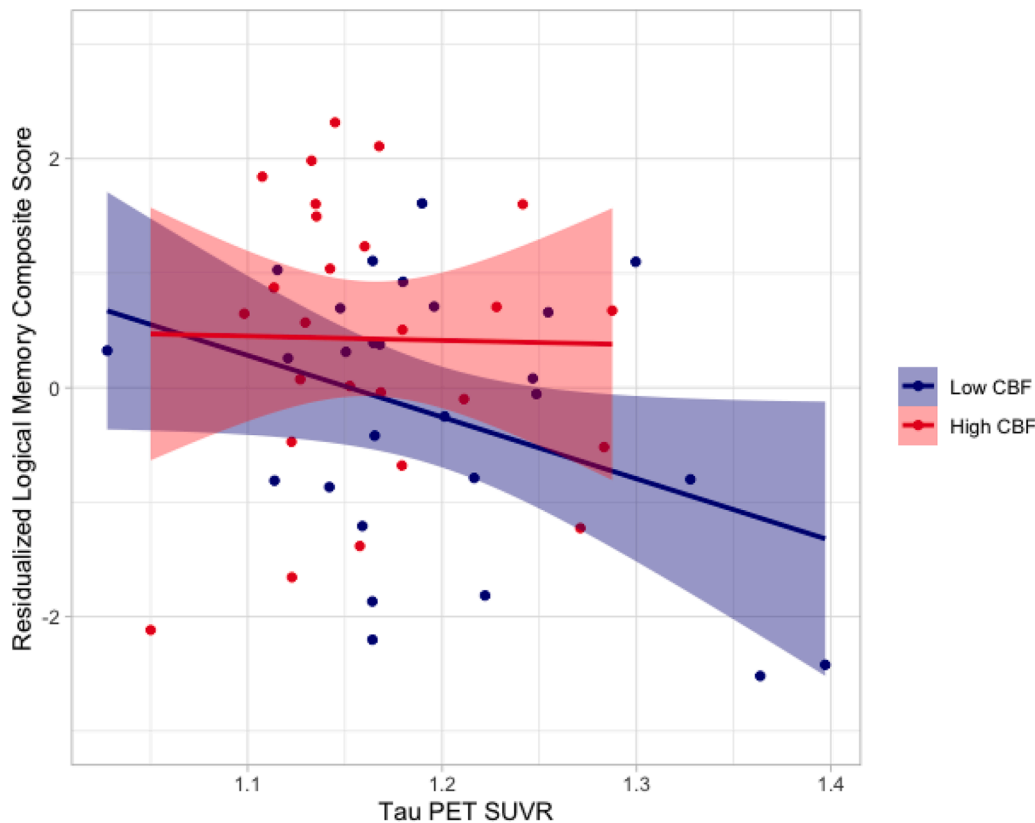
Fig. 2. CBF, tau PET burden, and objective memory associations. CBF = cerebral blood flow. PET = positron emission tomography. SUVR = standardized uptake value ratio. SUVR is depicted on the x-axis. Logical memory scores residualized for age, education, sex, apolipoprotein e4 positivity, pulse pressure, and imaging date differences are depicted on the y-axis. The red dots and line represent the association between tau PET burden and logical memory performance in the high CBF group. The blue dots and line represent the association between tau PET burden and logical memory performance in the low CBF group.

Table 3
Regression Table Output for ECog Memory Scores.

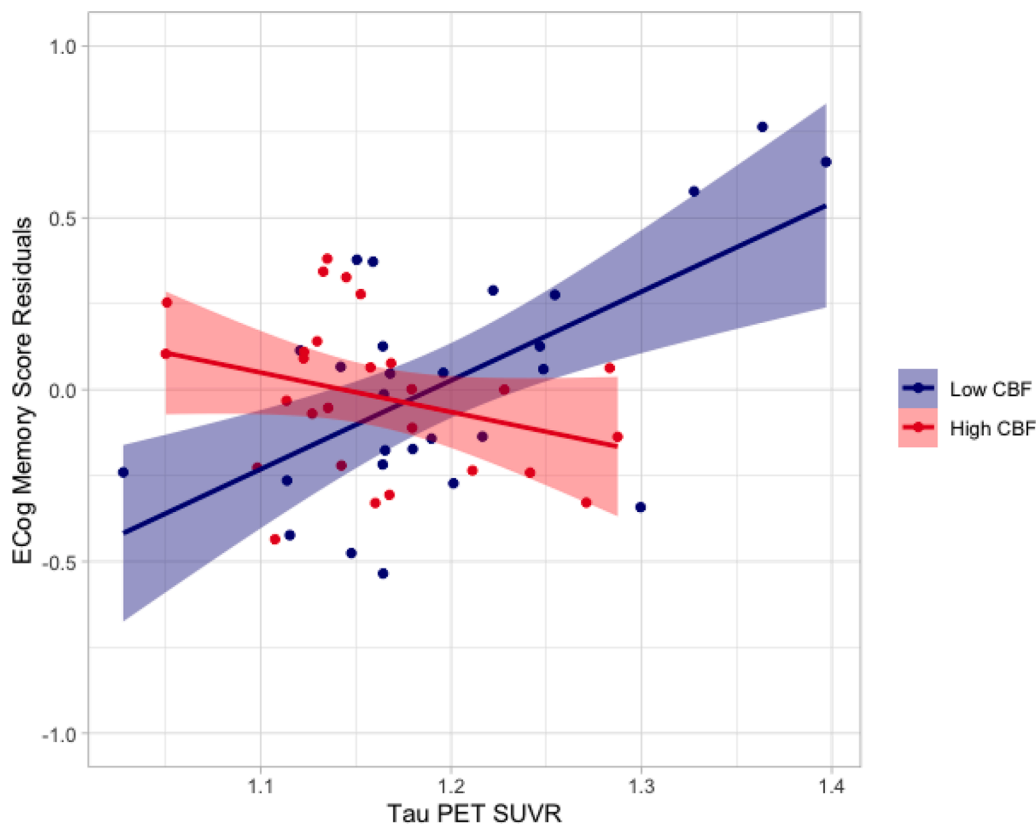| Predictors	ECog Memory Score			
	B Estimates	CI	Statistic	p
(Intercept)	−9.83	−16.17 – −3.49	−3.13	**0.003**
Age (years)	0.01	−0.00 – 0.02	1.62	0.112
Education (years)	−0.03	−0.07 – 0.00	−1.76	0.085
Sex: Female	−0.06	−0.23 – 0.12	−0.64	0.528
APOE-e4 Positivity: e4+	0.11	−0.10 – 0.32	1.06	0.296
Tau, Amyloid PET date difference	0.11	0.01 – 0.21	2.17	**0.035**
CBF, Amyloid PET date difference	0.02	−0.07 – 0.11	0.34	0.733
Summary SUVR Centiloid	0.00	−0.00 – 0.00	0.76	0.451
Pulse Pressure (mmHg)	0.00	−0.01 – 0.01	0.11	0.909
Meta-Temporal CBF (mL/ 100 g/min)	0.28	0.07 – 0.49	2.71	**0.010**
Meta-Temporal Tau SUVR	8.51	3.22 – 13.79	3.25	**0.002**
Meta-Temporal CBF x Meta-Temporal Tau SUVR	−0.24	−0.42 – −0.06	−2.67	**0.011**
Observations	54			
R^2 / R^2 adjusted	0.420 / 0.268			

outcomes.

Conclusions

The current study examined associations between cerebrovascular, Aβ, and tau pathologies and their interactive effects on memory in a sample of CU older adults from ADNI. We identified an association between CBF and tau PET levels that was not present with Aβ PET, as well as a moderating effect of CBF on tau PET associations with both objective and subjective memory. These findings extend prior literature by demonstrating the interactive effects of CBF and tau on cognition, suggesting that these pathologies may act synergistically to promote memory dysfunction typically observed early in the AD clinical continuum. Future studies examining longitudinal cognitive and clinical outcomes may further elucidate whether the combination of reduced CBF and high tau PET in CU individuals contributes to disease progression. Such evidence of CBF as an early pathologic process exacerbating tau-associated memory impairment would have implications for future prevention and intervention efforts targeting vascular risk that may offer a more easily implementable and cost-effective treatment target relative to the Aβ immunotherapies currently under investigation.

Fig. 3. CBF, tau PET burden, and subjective memory associations.
ECog = Everyday Cognition Questionnaire. CBF = cerebral blood flow. PET = positron emission tomography. SUVR = standardized uptake value ratio. SUVR is depicted on the x-axis. ECog memory scores residualized for age, educ ation, sex, apolipoprotein e4 positivity, pulse pressure, and imaging date differences are depicted on the y-axis. The red dots and line represent the association between tau PET burden and ECog memory score in the high CBF group. The blue dots and line represent the association between tau PET burden and ECog memory score in the low CBF group.

Declaration of Competing Interest

The authors have no conflict of interest to report.

Acknowledgments

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