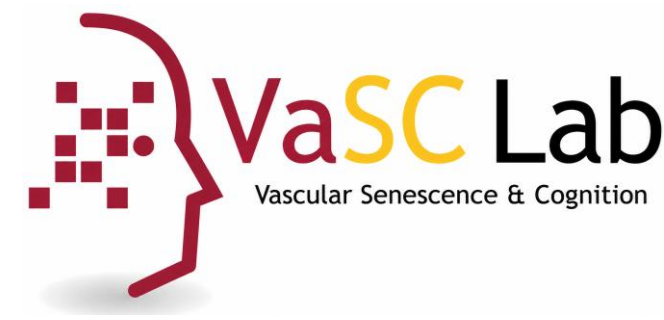


Cerebral Blood Flow as a Marker of Resilience in Cognitively Unimpaired *APOE4* Carriers



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INTRODUCTION

- Cerebrovascular dysfunction emerges early in Alzheimer's disease (AD).
- APOE4* increases risk for AD and contributes to cerebrovascular dysfunction independently of amyloid- β and tau.
- Cognitively unimpaired *APOE4* carriers often exhibit elevated cerebral blood flow (CBF) in medial temporal lobe (MTL) regions.
- It is unclear whether hyperperfusion in *APOE4* carriers is a marker of cognitive resilience or dysfunction. Prior studies report mixed findings, but do not account for underlying AD pathophysiological changes.
- Aim:** Examine whether associations between MTL CBF and cognition differ by *APOE* genotype and plasma pTau₂₁₇ status.

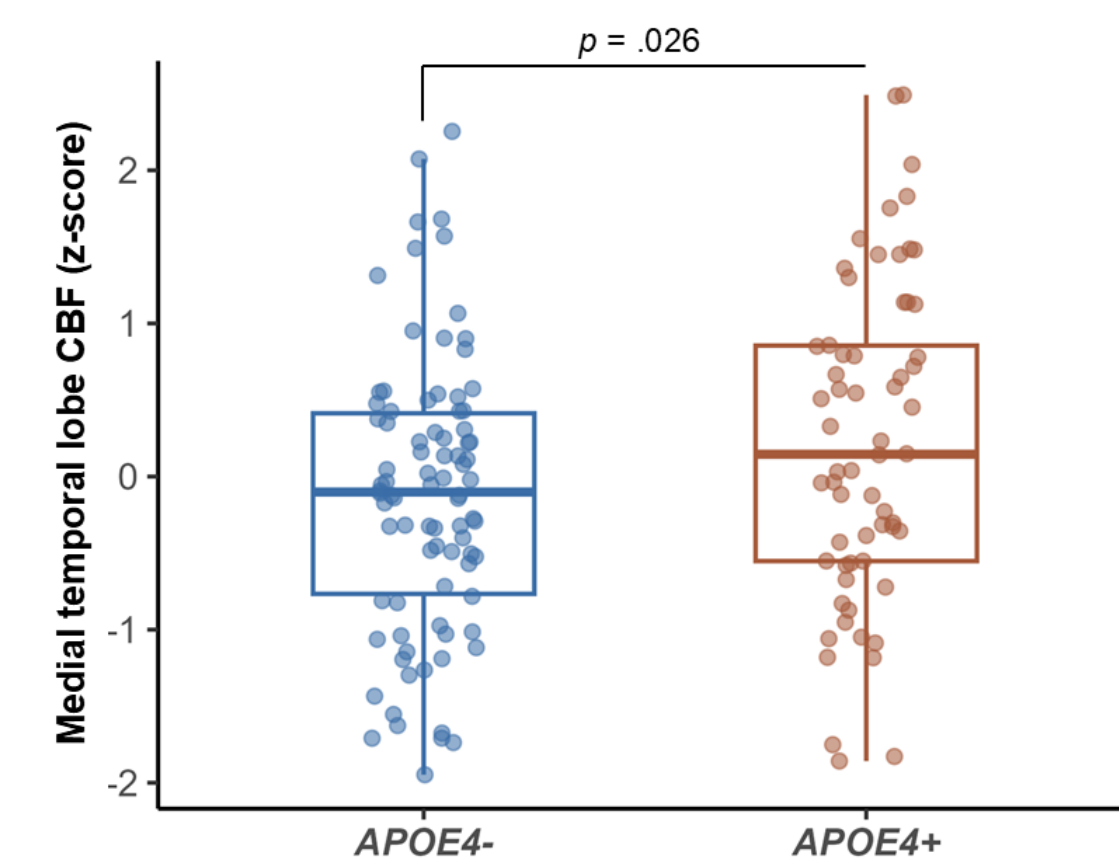
METHOD

Participants (aged 55–89) from the Vascular Senescence and Cognition observational study received clinical and neuropsychological evaluation, underwent brain MRI, and provided a blood sample. The present study included **148 cognitively unimpaired older adults**, including 62 *APOE4* carriers and 86 noncarriers. A subset of 126 participants had valid plasma pTau₂₁₇ data, including 35 pTau₂₁₇-positive and 91 pTau₂₁₇-negative individuals.

- Mean **medial temporal lobe cerebral blood flow (MTL CBF)** was quantified (mL/100 g tissue/min) from a ~5-minute resting state pseudo-continuous arterial spin labeling (pCASL) MRI scan.
- Plasma pTau₂₁₇** concentrations were analyzed using the Simoa ALZpath p-Tau217 Advantage Plus assay kit. An established cut-point optimized for A β PET positivity (≥ 0.42 pg/mL) was applied to classify participants as pTau₂₁₇ positive or negative.
- Demographically adjusted test scores were used to calculate a **memory composite score** (delayed story recall, verbal list-learning delayed recall, and recognition memory) and an **executive function composite score** (processing speed, set shifting, and either inhibitory control or working memory).
- Vascular risk factor burden** was categorized as low (0–1 risk factors) or high (≥ 2 risk factors).

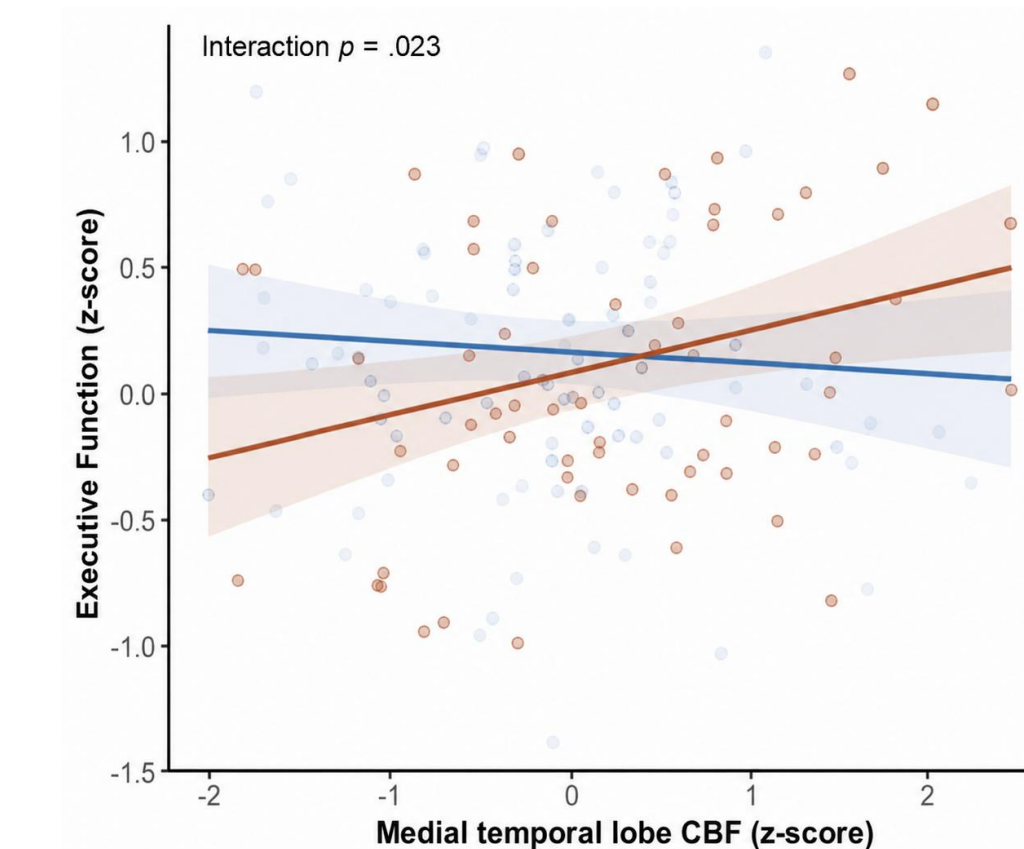
Statistical Analyses: Differences in MTL CBF between *APOE4* carriers and noncarriers were tested with analysis of covariance (ANCOVA), adjusted for age, sex, education, and vascular risk factor burden. MTL CBF x *APOE4* interactions on memory or executive function were examined using linear regression models adjusted for vascular risk factor burden. Stratified analyses examined whether associations differ by plasma pTau₂₁₇ status. Significant interactions were decomposed with simple slopes tests. Sensitivity analyses adjusted for hippocampal volume, entorhinal cortical thickness, or white matter hyperintensity volume in separate models.

RESULTS



$F(1, 142) = 5.1$, partial $\eta^2 = .04$

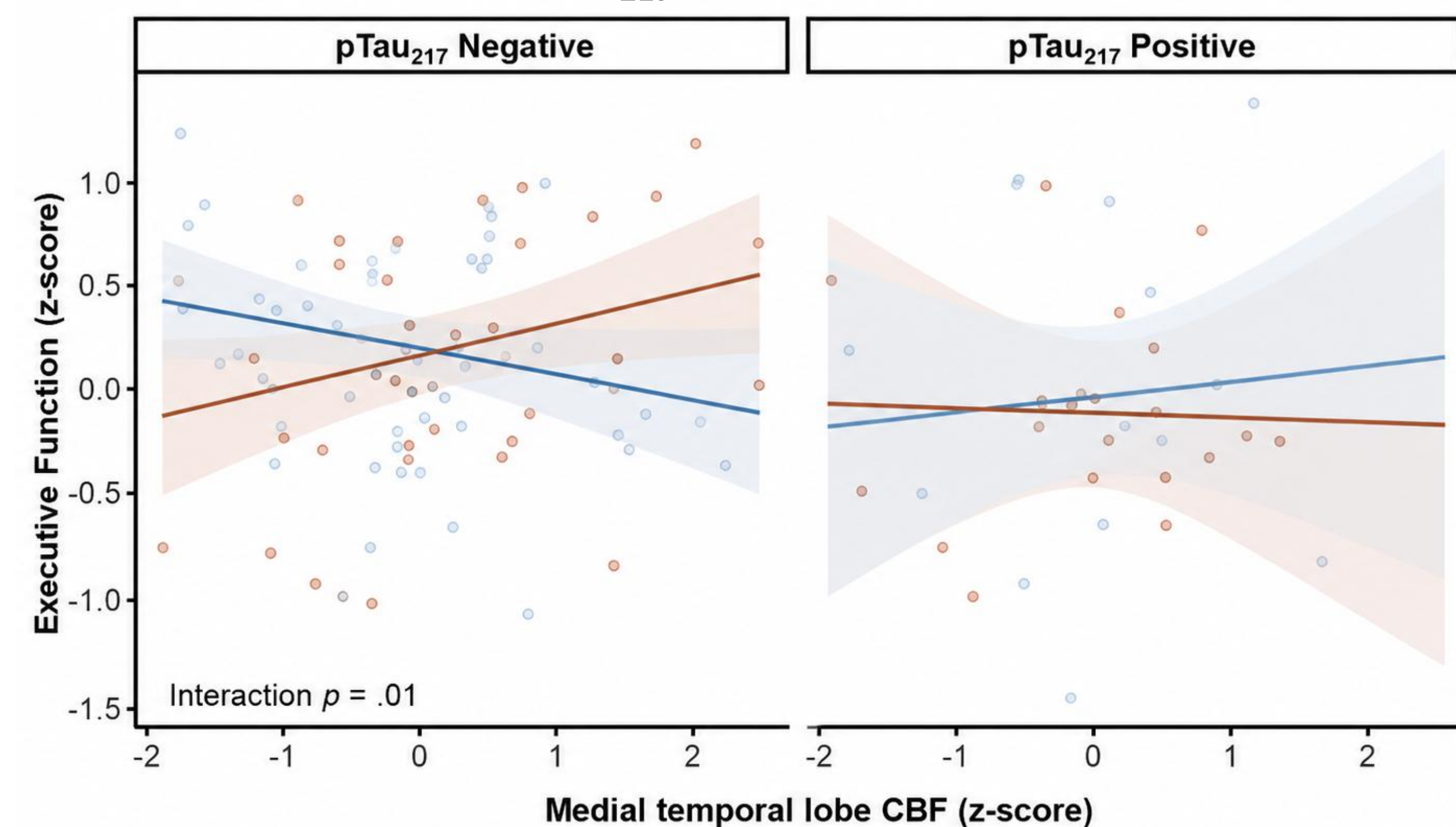
APOE4 carriers show higher MTL CBF than noncarriers



APOE4 carriers with elevated MTL CBF exhibit better executive function scores

APOE4 carriers: $b = 0.17$, 95% CI [0.04, 0.30], $p = .01$

Higher MTL CBF is associated with better executive function only in pTau₂₁₇-negative *APOE4* carriers



pTau₂₁₇-negative *APOE4* carriers: $b = 0.16$, 95% CI [0.01, 0.31], $p = .04$

DISCUSSION

- Cerebral hyperperfusion may be a biomarker of cognitive resilience in *APOE4* carriers well before cognitive decline, but this resilience wanes as the cerebrovascular effects of *APOE4* combine with AD pathogenic protein accumulation.
- This resilience is specific to executive function and is not observed for memory, possibly reflecting MTL connections to broader executive control systems, the malleable nature of executive functioning, or its vulnerability to cerebrovascular dysfunction. Effects remain significant after controlling for white matter hyperintensity volume, implicating microvascular mechanisms independent of overt white matter injury.
- Longitudinal studies are needed to determine when CBF increases occur relative to AD biomarker changes and cognitive decline, and will improve understanding of early risk and resilience markers in *APOE4* carriers.

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