

A Blood–Brain–Memory Pathway: CA1 Mediates Plasma NfL and pTau217 Associations With Memory in Older Adults at Risk for Alzheimer’s Disease

Nicole Espinosa^{1,2,3}, Rachael Yu^{1,2,3}, Johannes C. Michaelian^{1,2,3}, Marshall A. Dalton², Kimberly Bassett^{1,2}, Sharon L. Naismith^{1,2,3}

¹Healthy Brain Ageing Program, Brain and Mind Centre, ²School of Psychology, Faculty of Science, ³Charles Perkins Centre, University of Sydney, Camperdown, NSW 2050, Australia

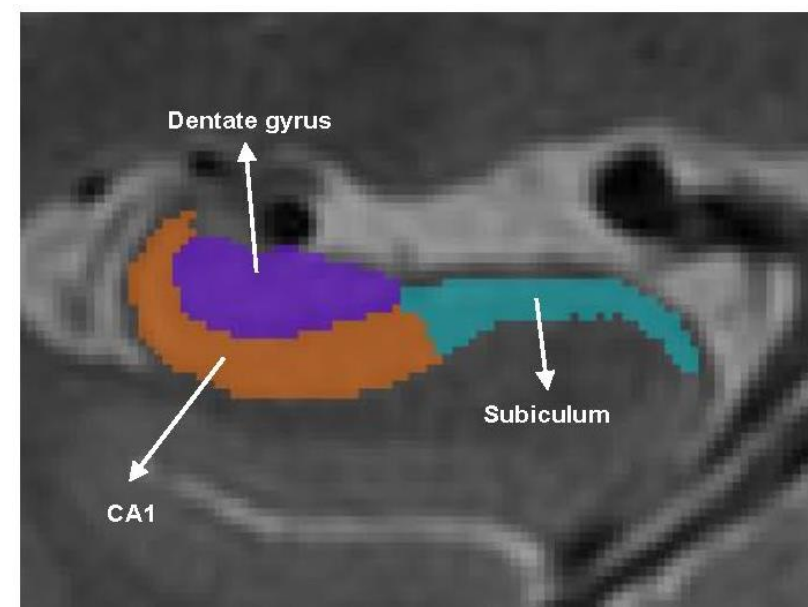
Email: nicole.espinosa@sydney.edu.au

Background

- Memory loss commonly reflects hippocampal compromise and may rise from neurodegeneration, neuroinflammation and Alzheimer’s disease (AD) pathology.
- Blood-based biomarkers now enable the detection of these processes non-invasively.
- However, the pathways linking these biomarkers to memory impairment and hippocampal integrity remain unclear, particularly in at-risk populations.

Methods

- 263 older adults at-risk for AD aged >50 years recruited from a specialist brain health and memory clinic.
- All participants underwent fasting blood collection, MRI scanning, and comprehensive neuropsychological assessment.
- Volumes of CA1, subiculum, and dentate gyrus were extracted from structural MRI scans.
- Plasma phosphorylated tau 217 (pTau217), amyloid- β (A β) 42/40, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL) and serum YKL-40 were measured.
- Mediation analyses, adjusted for age, sex, BMI, and APOE ϵ 4, were conducted.



Aims

To examine whether:

- Hippocampal subfields mediate associations between blood-based biomarkers and verbal memory performance in older adults at-risk for AD.
- These associations differed between individuals with subjective cognitive impairment (SCI) and mild cognitive impairment (MCI).

Results

- Key demographics (n = 263):**

Age (median)	68.79
Female (%)	71%
BMI (median)	48.67
MCI (%)	49%
APOE ϵ 4 (%)	36%

- Hippocampal subfields & blood-based biomarkers:** CA1 and subiculum were associated with NfL, GFAP, and pTau217 in the total sample and MCI. No associations for dentate gyrus; In SCI, dentate gyrus was associated with GFAP only (see Figure 1).

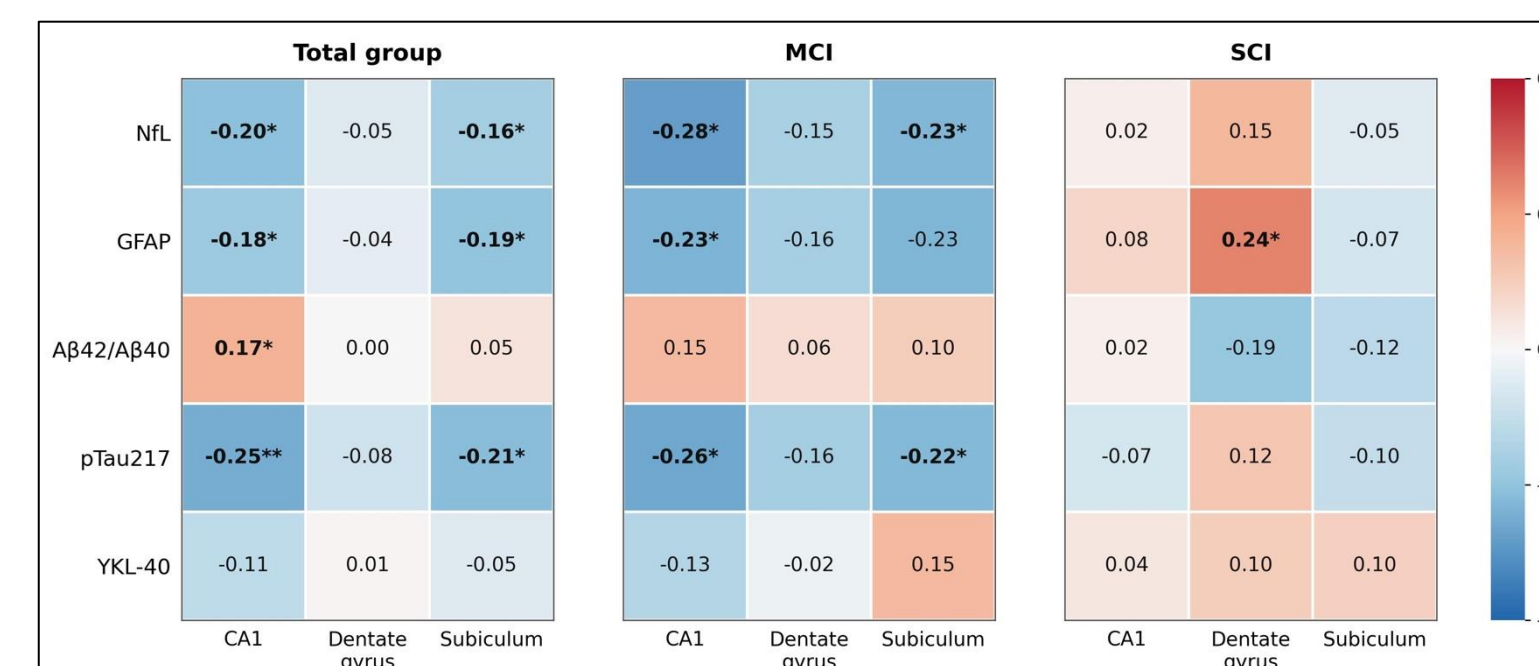


Figure 1. Relationships between hippocampal subfield volumes and blood-based biomarkers in the total group and separately for MCI and SCI. Note. * $p < .05$; ** $p < .01$. All analyses were Spearman's correlations. p-values were corrected for false discovery rate.

- Associations with verbal memory:** Smaller hippocampal subfield volumes, and higher NfL, GFAP, pTau217 and lower A β 42/A β 40 were associated with poorer verbal memory in the total sample. Hippocampal and pTau217 associations were maintained in MCI. No associations in SCI (see Figure 2).

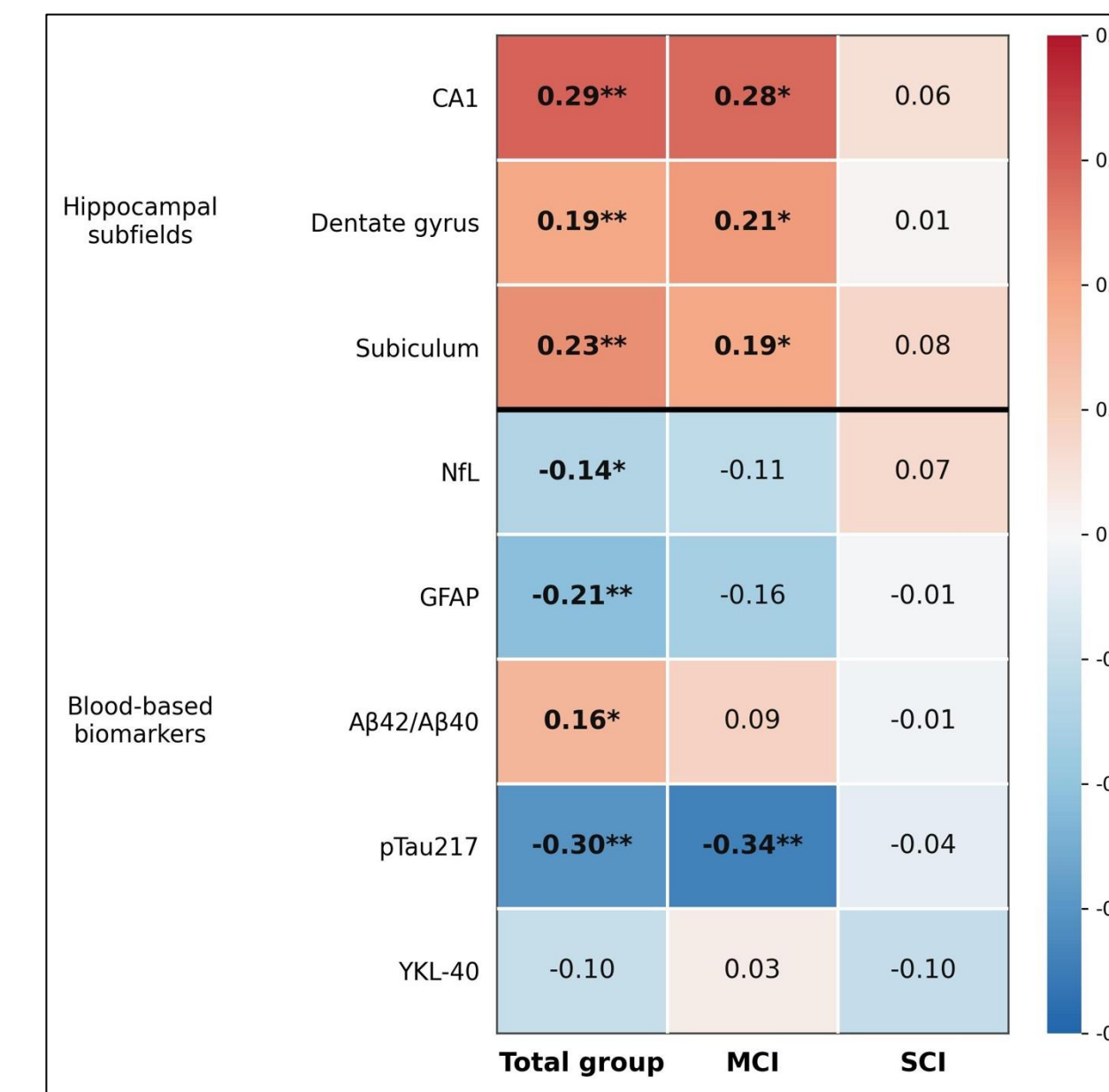
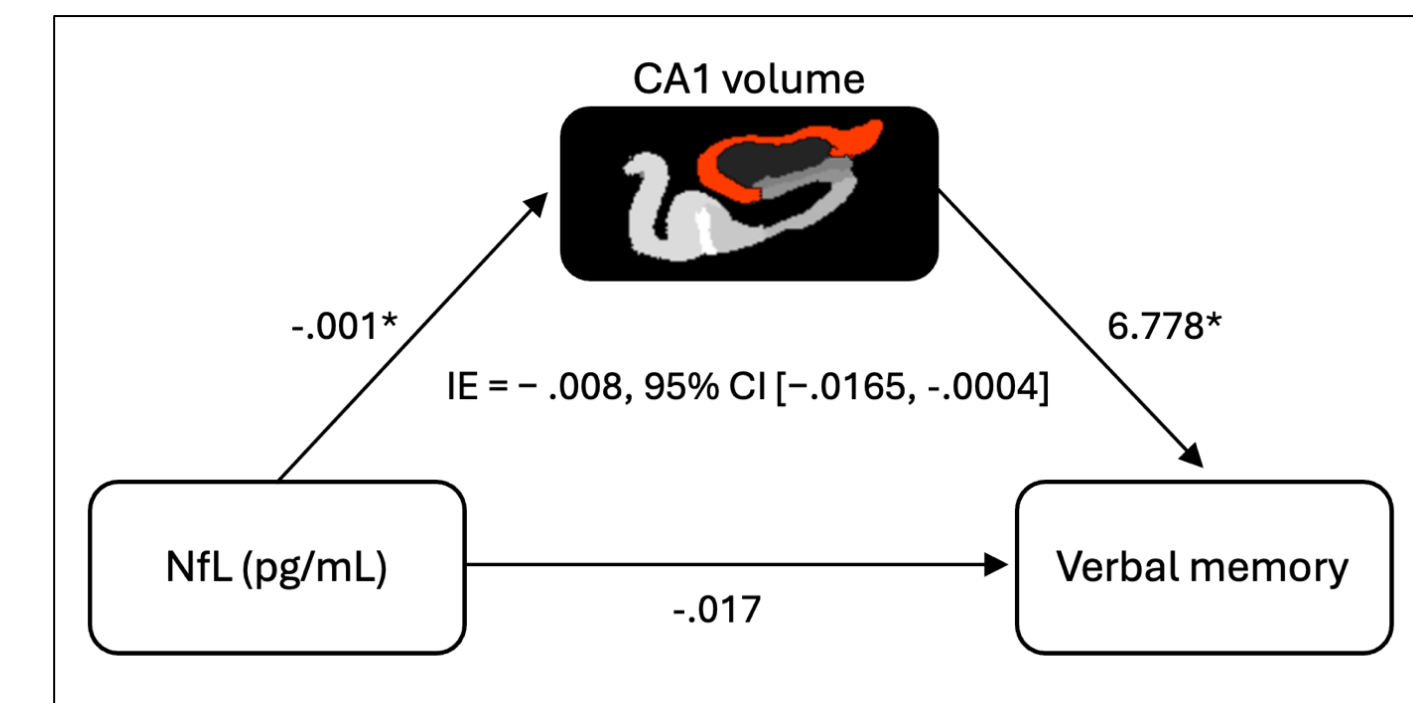
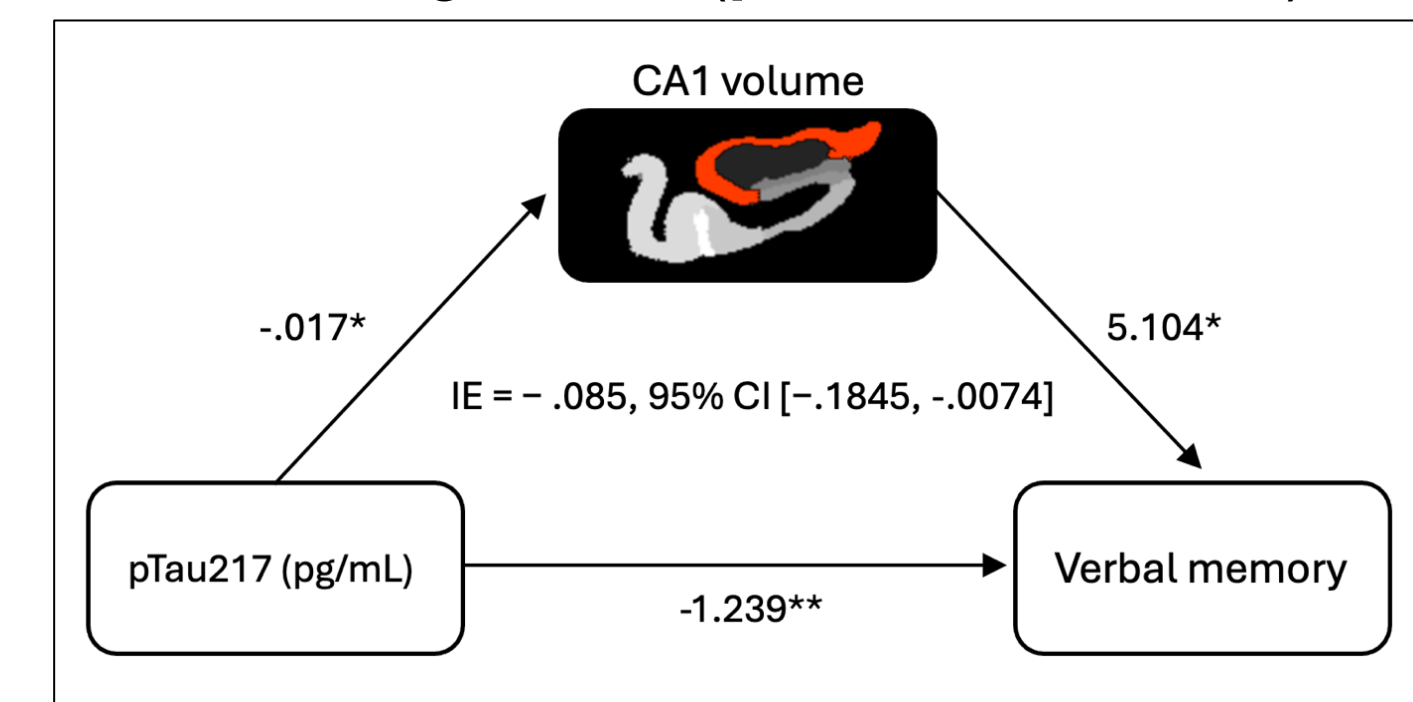


Figure 2. Relationships between hippocampal subfield volumes and blood-based biomarkers with verbal memory performance in the total group and separately for MCI and SCI. Note. * $p < .05$; ** $p < .01$. All analyses were Spearman's correlations. p-values were corrected for false discovery rate.

- Mediation — NfL $\rightarrow$ CA1 $\rightarrow$ Memory:** CA1 fully mediated NfL–memory. The direct effect of NfL was non-significant (**full mediation**).



- Mediation — pTau217 $\rightarrow$ CA1 $\rightarrow$ Memory:** CA1 partially mediated pTau217–memory. The direct effect of pTau217 remained significant (**partial mediation**).



Conclusions

These findings suggest that **CA1 volume mediates key biomarker–memory relationships in older adults at-risk for AD**. CA1 acted as a structural pathway linking NfL to memory decline, while pTau217 showed both hippocampal and extra-hippocampal effects. Although mediation effects did not reach significance in the MCI group, the direction and magnitude were consistent with the full sample, likely reflecting reduced statistical power, rather than a true absence of effect. Together, these results underscore the value of combining blood-based and imaging markers for early risk prediction and point to CA1 as a key target for monitoring neurodegeneration in at-risk populations.