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Introduction

- Astrocyte reactivity is increasingly recognized as a critical modulator linking amyloid- β (A β) burden to downstream tau pathology, offering a mechanistic explanation for why amyloid deposition alone is insufficient to induce Alzheimer's disease (AD)-related neurodegeneration in many individuals.
- Moreover, tau pathology is frequently observed within early Braak regions even in the absence of detectable A β , suggesting the presence of A β -independent pathways of tau accumulation.
- We therefore hypothesized that astrocyte reactivity contributes to AD-related tau phosphorylation independently of amyloid deposition.

Objective

In the present study, we aimed to investigate if plasma GFAP, a proxy for astrocyte reactivity, is associated with p-tau217 in A β -negative individuals or not.

Method

- All 2194 participants were assessed for plasma GFAP, plasma ptau217, A β PET.
- Linear regression models adjusted for age, sex, and cohort was applied between z-scored values of GFAP and p-tau217 in A β -negative individuals (All other cohorts: Centiloid < 12; SPIN cohort: CSF A β 42/40 > 0.6).
- For neuropathological validation, brain tissue from three AD and three non-AD donors (FTD and CBD) spanning early and late Braak regions were examined by GFAP and p-tau217 immunohistochemistry.

Results

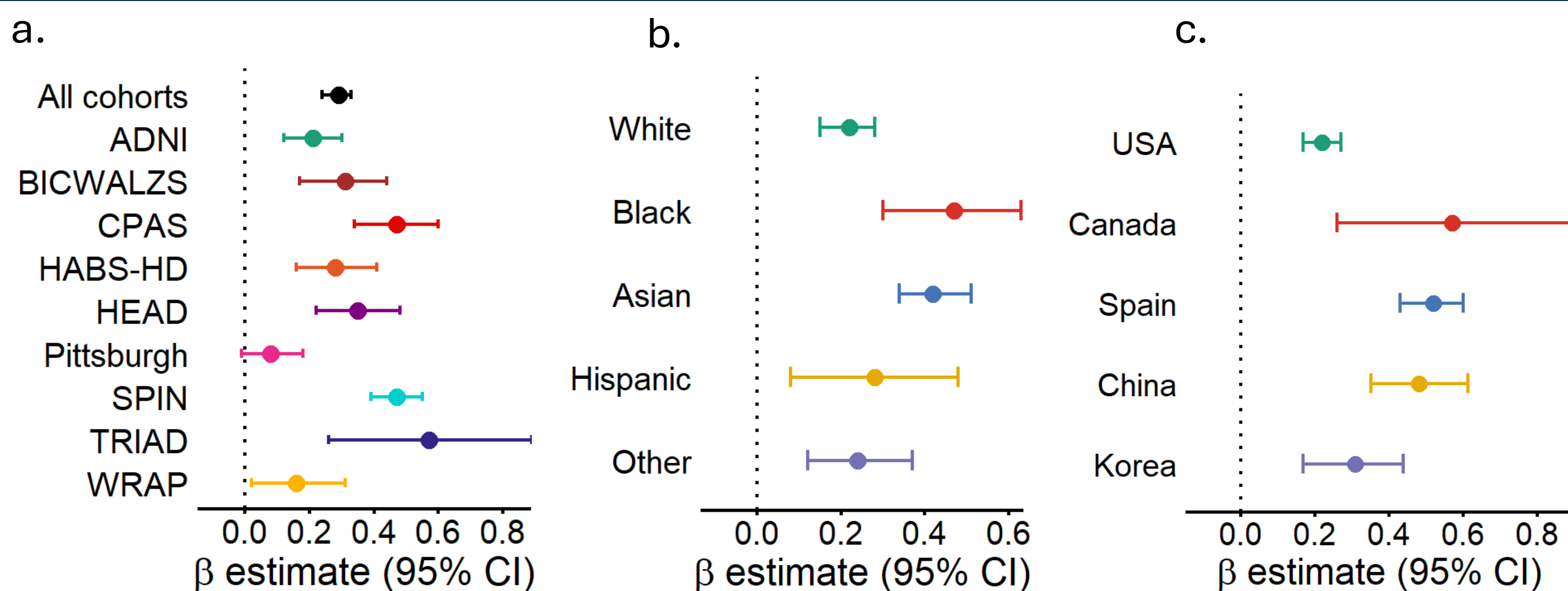


Figure1: **a**, Forest plot is showing the β estimates of age and sex adjusted linear regression analyses for association between plasma GFAP and plasma p-tau217 within each cohort. Significant positive associations were observed in ADNI, BICWALZS, CPAS, HABS-HD, HEAD, SPIN, TRIAD, and WRAP, with a nearly significant trend in the Pittsburgh cohort. **b**, β estimates in the forest plot is showing the regression analyses stratified by race/ethnicity demonstrating consistent GFAP-p-tau217 associations across White, Black, Asian, Hispanic, and Other groups. **c**, Country-stratified analyses showing robust positive associations across participants from the USA, Canada, Spain, China, and South Korea.

Study Design

Participants: 2,194 [mean age 69.7 $\pm$ 9.6 years; (**CU:** 1426, **CI:** 768)] A β -PET negative individuals from ADNI(n=569), BICWALZS(n=209), CPAS(n=205), HABS-HD(n=348), HEAD(n=375), Pittsburgh(n=204), SPIN(n=310), TRIAD(n=95), and WRAP(n=189)

Available measures: Plasma GFAP, Plasma p-tau217, A β -PET

Neuropathological Validation: 3AD and 3Non-AD (1FTD & 2 CBD) from TRIAD cohort were subjected to immunohistochemistry with GFAP and p-tau217 antibodies

Results

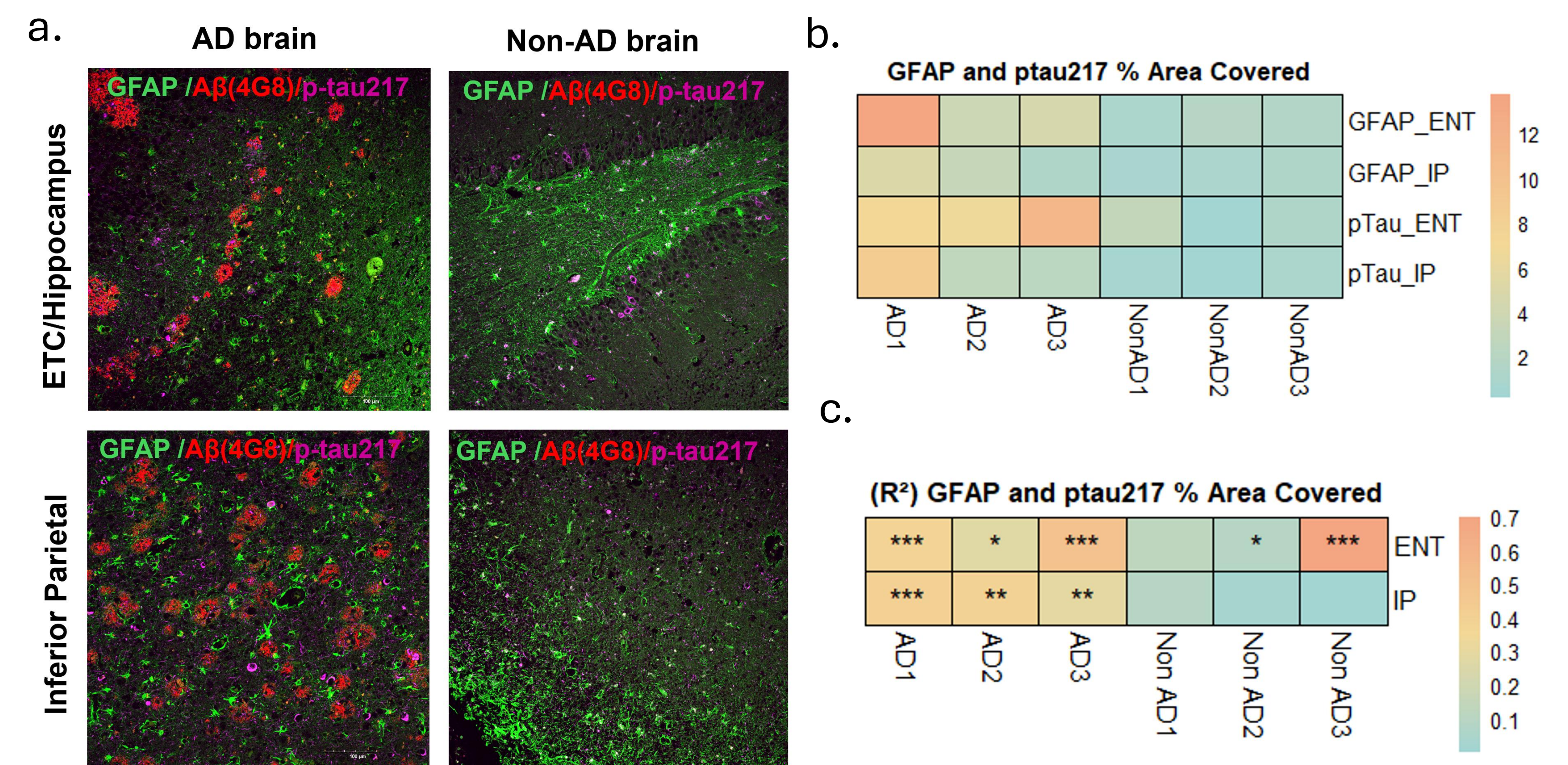


Figure2: **a**, Representative images of immunohistochemical staining of reactive astrocyte by GFAP (green), A β senile plaques by 4G8 (red) and p-tau217 (magenta) in AD and Non-AD human brain sections. Upper panel is showing early Braak regions (entorhinal cortex/hippocampus) and the lower panel is showing late Braak regions (inferior parietal). Images were taken at 20X magnification under Olympus FV3000 confocal microscope. Non-AD brains that do not have any A β plaque, showing reactive astrocytes and p-tau217+ cells are co-existing. **b**, Heatmap is showing quantitative analyses of GFAP and p-tau217 % area covered in 3 AD and 3 non-AD brains in entorhinal cortex/hippocampus and Inferior parietal regions. **c**, Heatmap is indicating the Pearson's correlation coefficient (R^2) of GFAP and p-tau217 % area covered in entorhinal cortex/hippocampus and Inferior parietal region. A significant correlation is being marked with asterisks.

Conclusions

- Our study provides a robust evidence of plasma p-tau217 association with plasma GFAP independently of A β pathology across multiple cohorts, race and countries.
- The neuropathological study further validates the co-occurrence of reactive astrocytes with p-tau217 positive cells in early and late Braak regions in Non-AD brains that do not have A β senile plaques.

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