

Astrocyte Reactivity Enhances the Clinical Impact of p-Tau217: Evidence From Longitudinal Biomarkers and Postmortem Brain Tissue

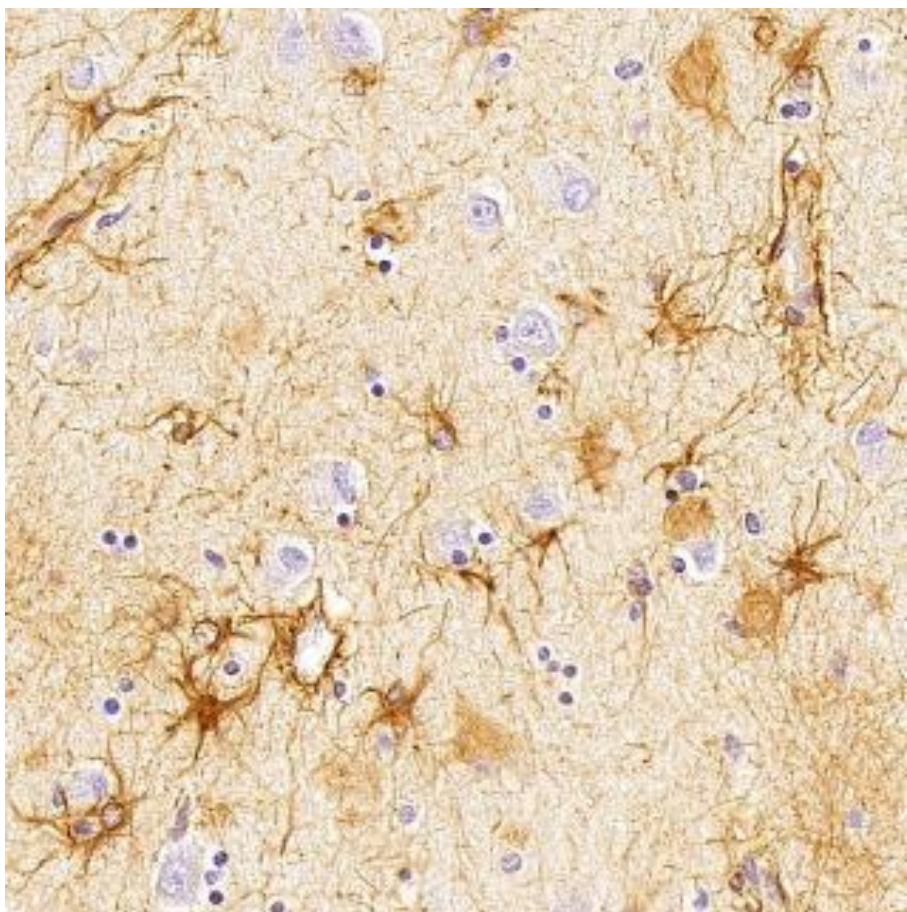
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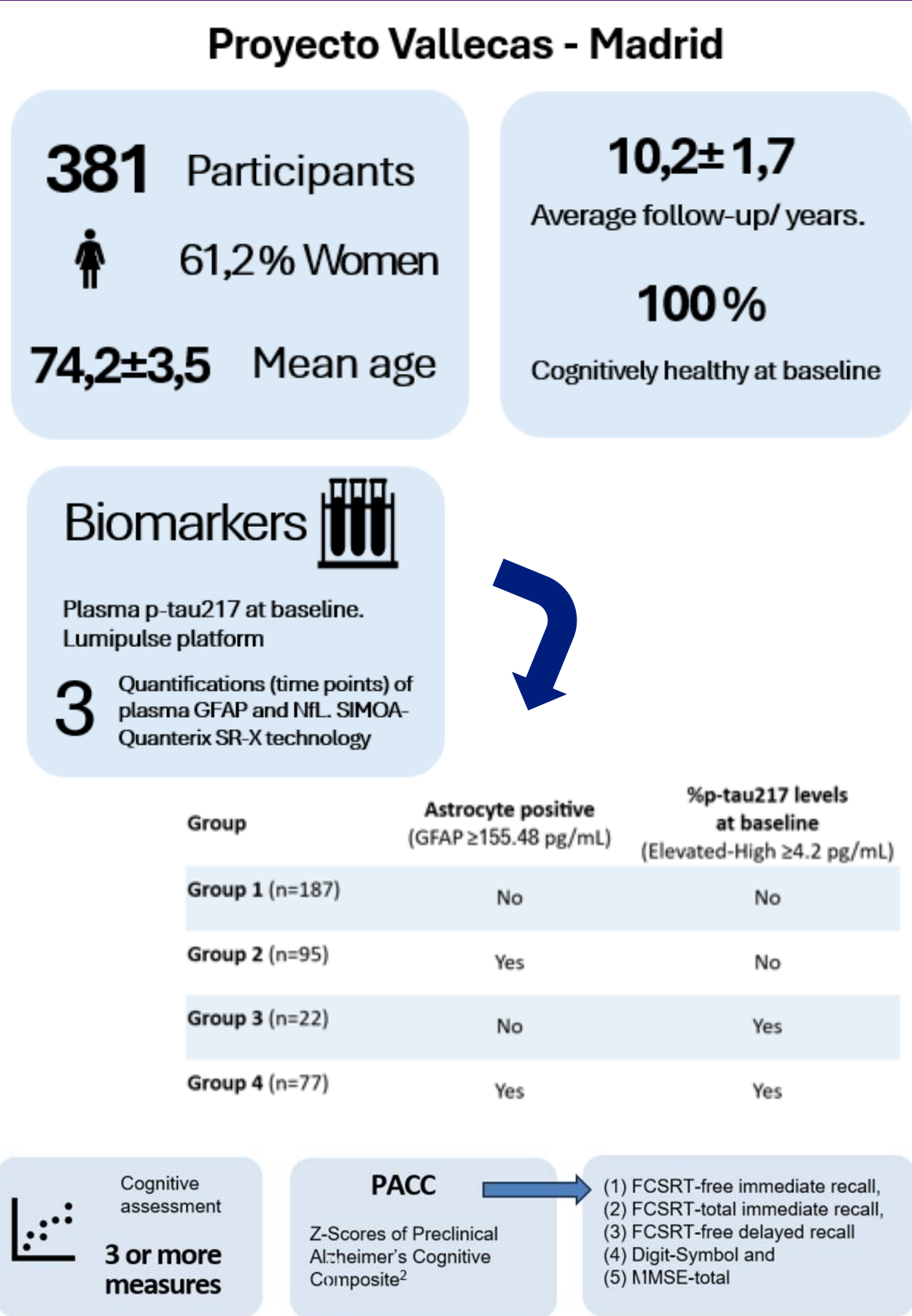
KEY TAKEAWAY: Elevated p-tau217 together with heightened astrocyte reactivity (GFAP) defines a biologically vulnerable preclinical AD phenotype in which astrocytic activation exacerbates tau-related neurodegeneration, driving hippocampal atrophy and cognitive decline. Stable NfL trajectory points to synaptic–glial rather than axonal injury, supported by stronger GFAP–tau coupling in AD-predominant post-mortem brains.

INTRODUCCION

Astroglial reactivity has been proposed as a key amplifier of early tau phosphorylation in preclinical Alzheimer’s disease (Bellaver et al., 2023). Building on this framework, we examined whether the interaction between plasma p-tau217 and GFAP delineates biologically distinct trajectories of cognitive decline, neuroaxonal injury, and hippocampal atrophy. We further assessed whether this astroglial-tau coupling differs across neuropathologically defined groups, AD-predominant, AD+(mixed pathology), and non-AD, to determine its specificity to Alzheimer-type processes.



METHOD



Longitudinal change was modelled with a GAMM for global cognition and for hippocampal volume (ICV-adjusted), and a GAM for plasma NfL, all including smooth time-by-group terms and standard covariates. We analysed a second cohort of 100 brain donors using partial correlations adjusted for age at extraction, estimated symptom-onset age, sex, and Thal stage.

RESULTS

Figure 1. Across all outcomes, the Ast+/p tau+ group (Group 4) showed the most adverse profile. Cognitively, this group exhibited significantly lower baseline performance and a steeper decline ($\beta_{\text{Group4}}=0.41$, $p<0.001$).

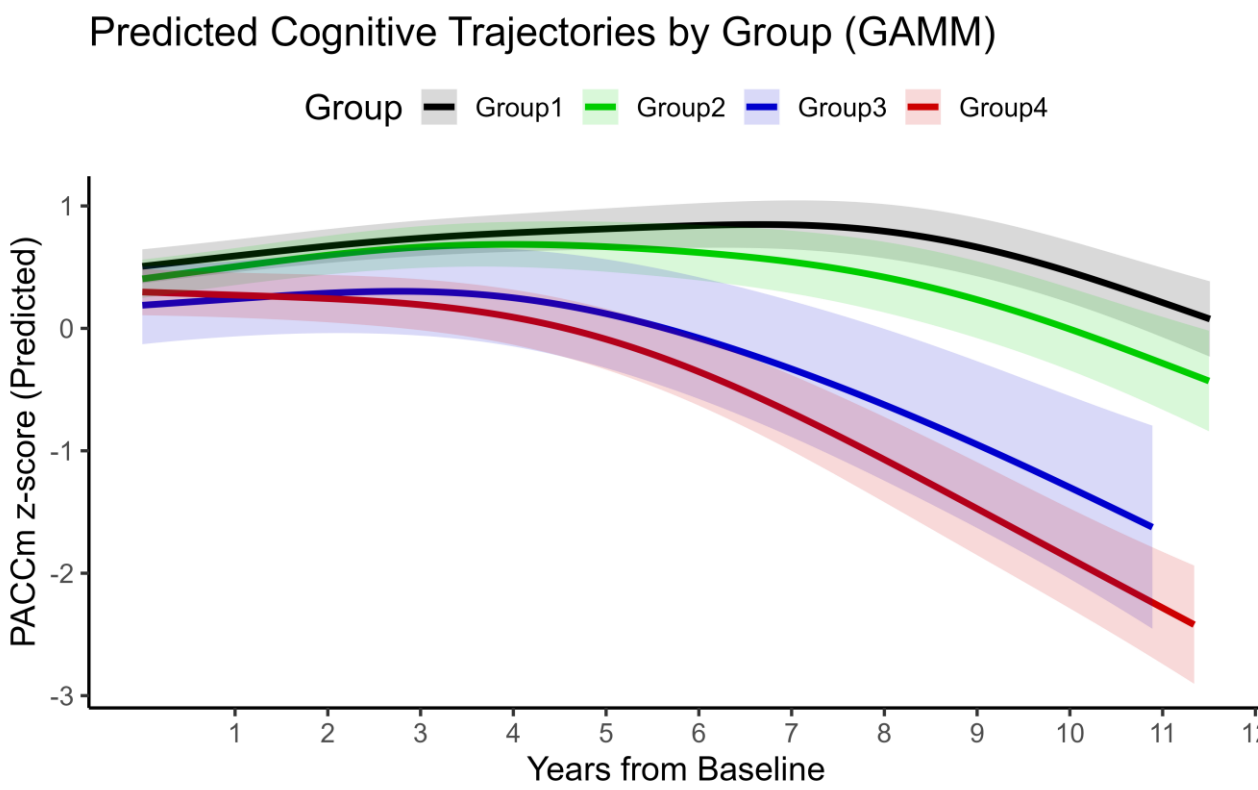


Figure 2. Hippocampal volume was significantly reduced ($\beta_{\text{Group4}}= -76.1 \text{ mm}^3$, $p = 0.031$) and declined faster than in all other groups.

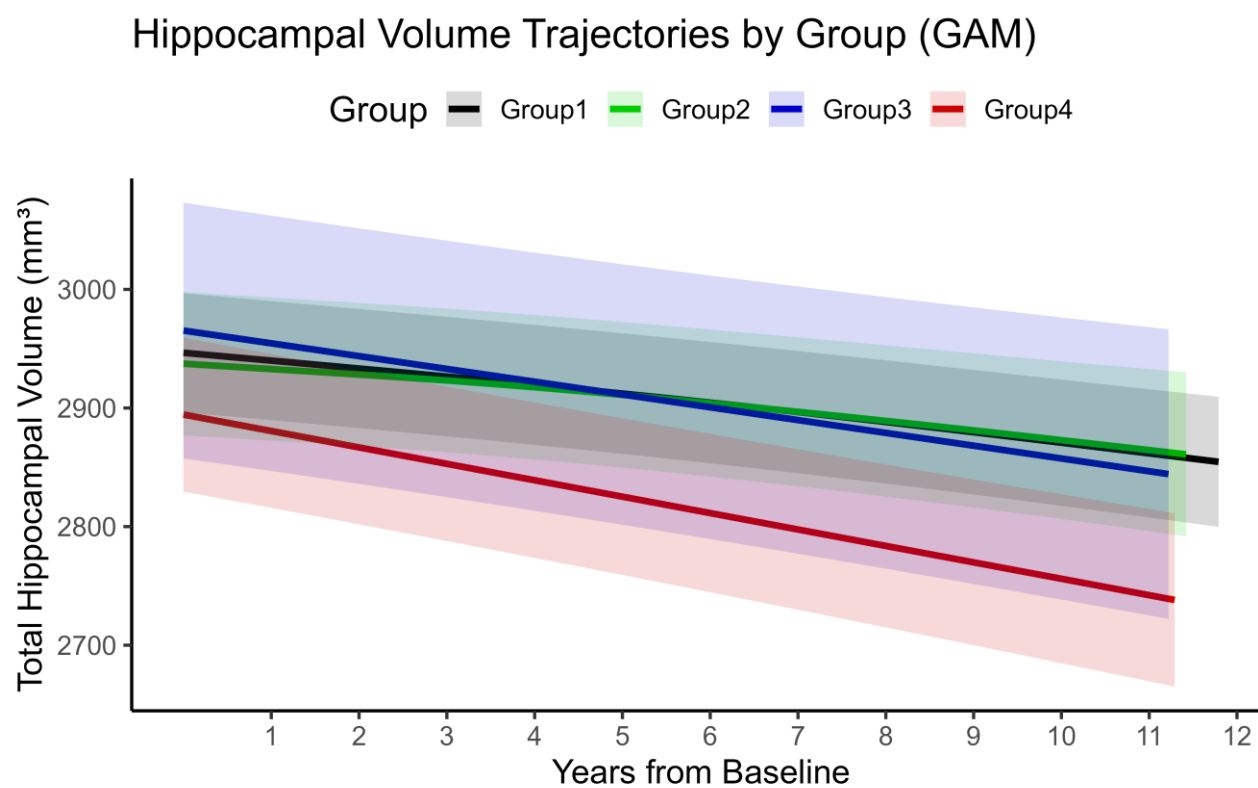


Figure 3. For the Ast+/p tau+ (Group 4) and Ast+/p tau- groups, the NfL levels were higher at baseline and increased more rapidly over time; however, the estimate was not statistically significant.

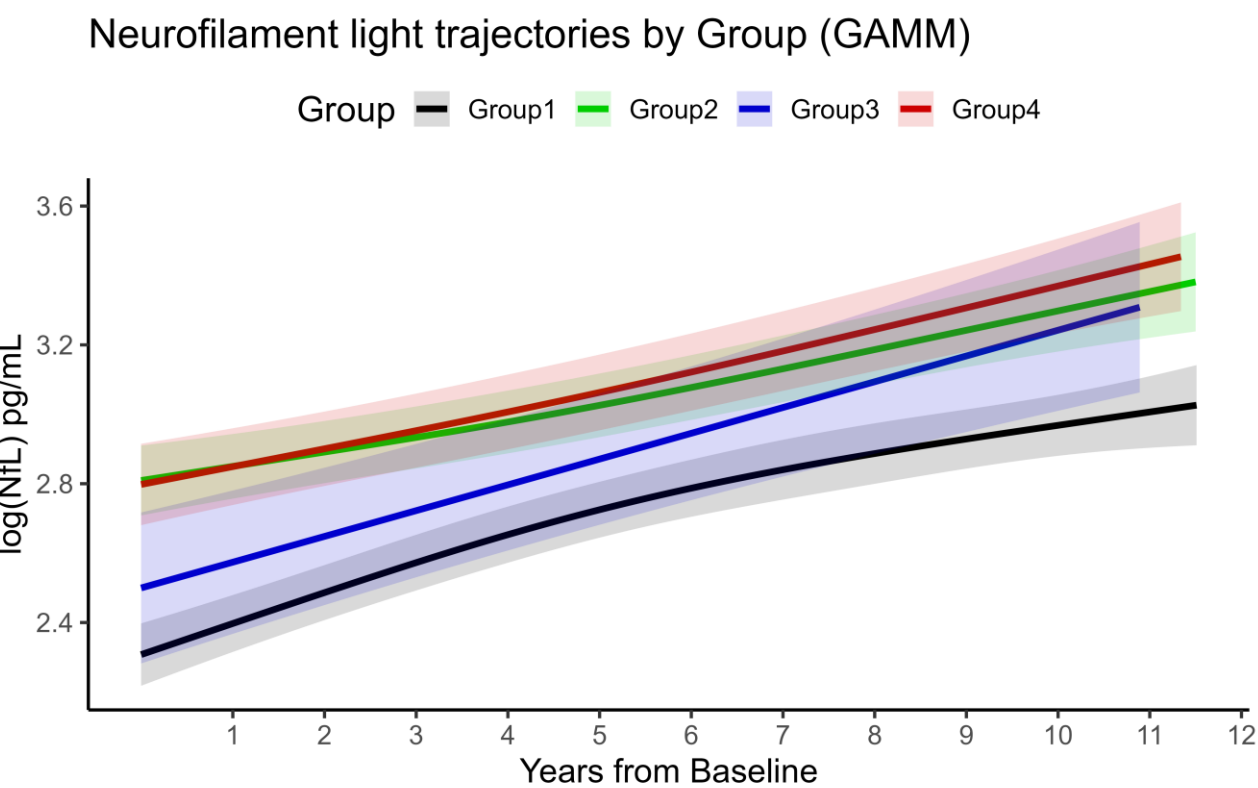
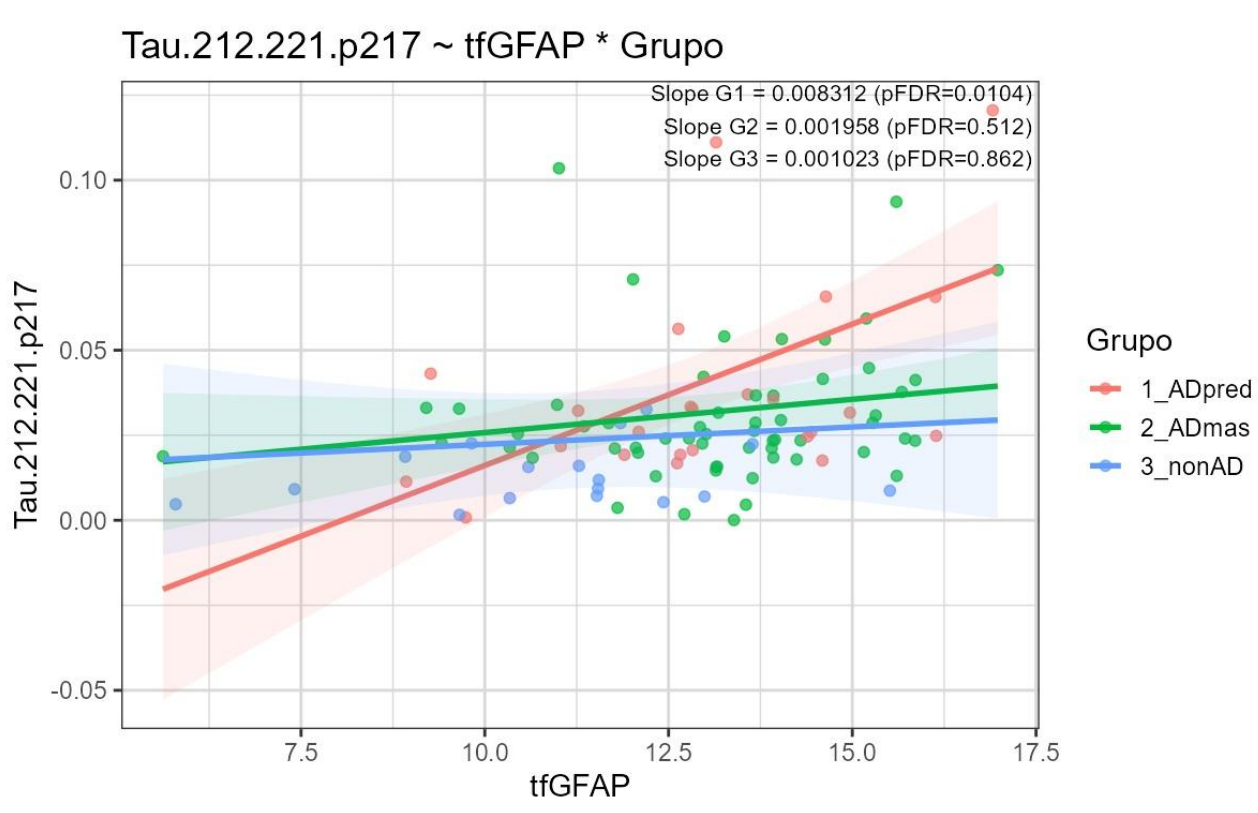


Figure 4. In post-mortem tissue, only the AD group showed a significant GFAP-p-tau217 association ($\beta_{\text{AD}}=0.0083$, $p\text{FDR}=0.010$), whereas AD+ and non-AD groups showed no significant effects.



CONCLUSIONS

- Elevated p-tau217 together with increased astrocyte reactivity (GFAP) defines a biologically vulnerable phenotype in which astrocytic activation amplifies tau-related neurodegeneration, resulting in more pronounced hippocampal atrophy and accelerated cognitive decline.
- The absence of differences in NfL suggests that the injury is not primarily axonal, but rather synaptic–glial.
- Post-mortem analyses reveal a stronger association between GFAP and plasma tau in AD-predominant brains, reinforcing the coherence between plasma biomarkers and underlying neuropathology.

GFAP emerges as a key biomarker for risk stratification, with the potential to identify individuals at a higher likelihood of neurodegenerative progression before the onset of clinical symptoms.

REFERENCES

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