

Introduction

- Plasma phosphorylated tau 217 (p-tau217) is increasingly used as a surrogate for Alzheimer's disease (AD) pathology, given its strong associations with amyloid-β (Aβ) and tau positron emission tomography (PET).
- However, the biological interpretation of a p-tau217 result may differ by age and cognitive status, and how these factors map p-tau217 onto the underlying amyloid–tau (A/T) profile remains unclear.
- Characterizing the frequency of plasma phosphorylated tau 217 (p-tau217) positivity across age and the Alzheimer's disease (AD) continuum is relevant for screening for AD pathology and for clarifying the disease's natural history.

Aim: to investigate whether the underlying A/T profiles associated with plasma p-tau217 differ between cognitively unimpaired (CU) and impaired (CI) individuals across the age spectrum.

Methods

Study Sample

Multicohort
A4, ADNI, BICWALZS, HABS-HD, MYHAT, and WRAP

Cross-sectional

Aβ PET (Centiloid), plasma p-tau217, and CDR

n = 4,372

CU: n = 3,053; CI: n = 1,319

Definitions

CU: CDR global = 0; CI: CDR global > 0;
Aβ PET positivity: Centiloid > 20;
Tau PET+: ≥ 2 SD above the reference group mean;
p-tau217+: ≥ 2 SD above the reference group mean;
Reference group (cohort/assay-specific):
Centiloid < 12, CDR global = 0, aged 60–70;

Statistical Analyses

Subgroup with tau PET (Braak I–II)

n = 2,133 (CU = 1,571 · CI = 562)

Binary logistic regressions

- p-tau217+ ~ age + covariates;

Multinomial logistic regression

- Joint A/T–p-tau217 classes ~ age + covariates

All models adjusted for Aβ status, sex and cohort when applicable and segregated by cognitive status.

Results

Figure 1.

Frequency of p-tau217 positivity as a function of age.

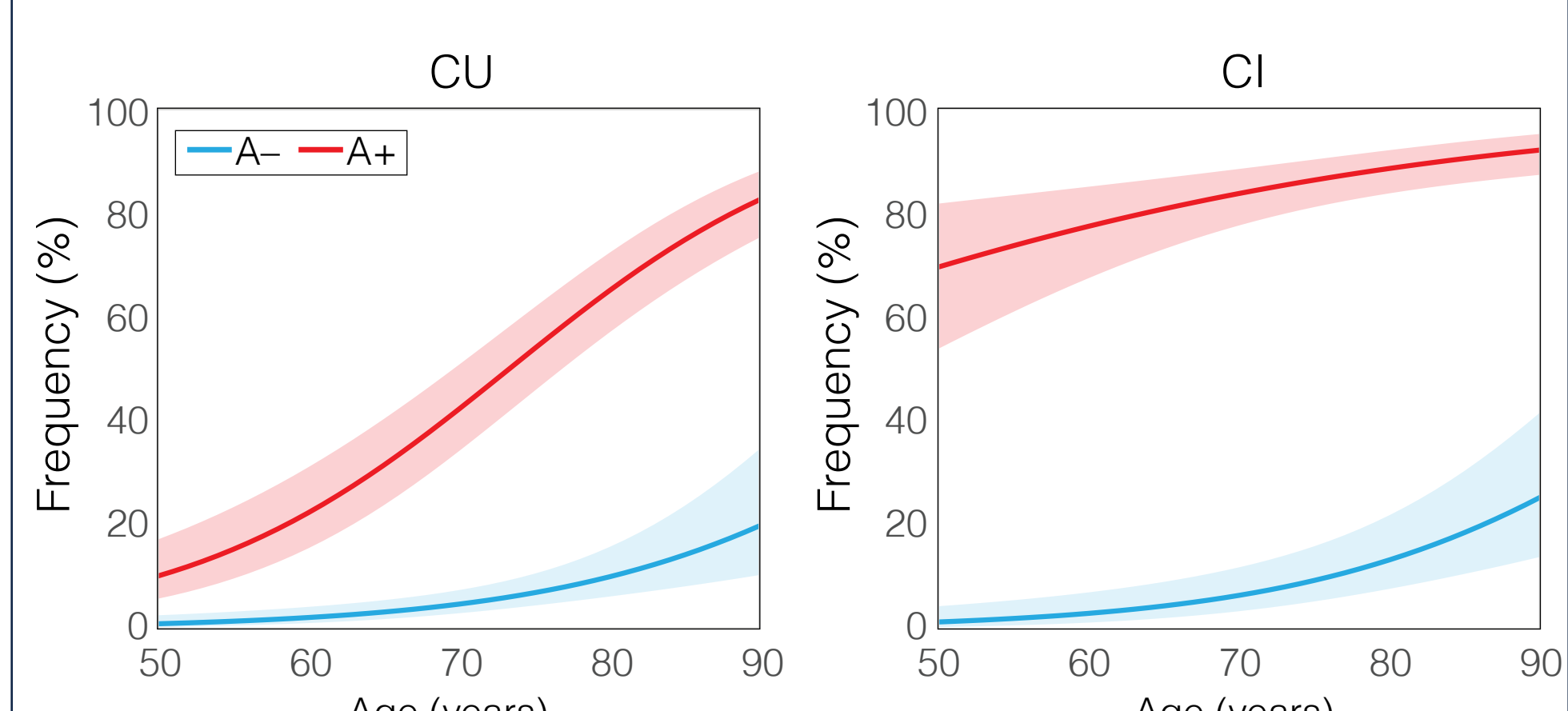


Figure 2A.

Frequency of joint A/T class and p-tau217 status as a function of age.

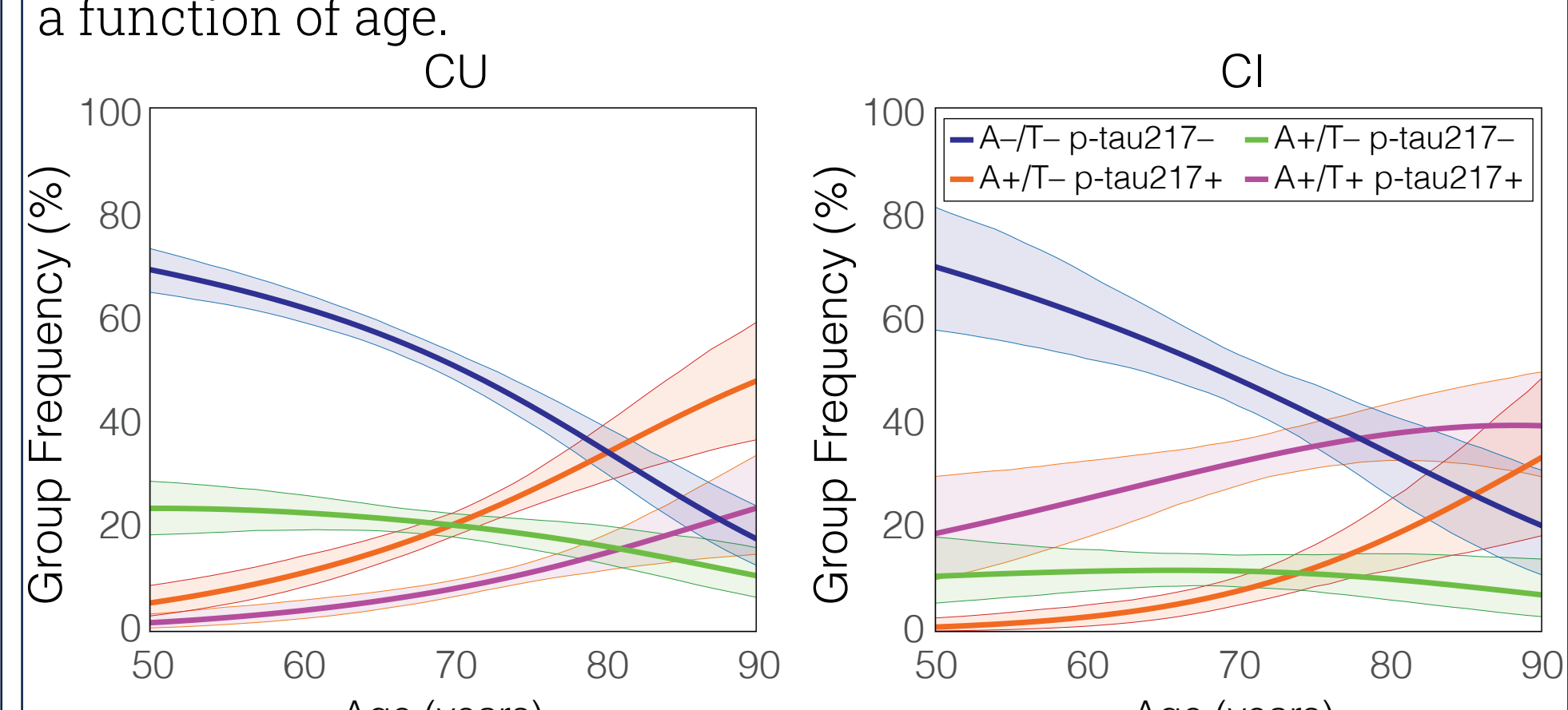


Table 1.

Characteristics of the study sample.

	Overall (n = 4,372)	CU (n = 3,053)	CI (n = 1,319)
Age, mean (SD)	69.90 (8.47)	69.31 (8.16)	71.25 (9.01)
Sex (Female), No. (%)	2,624 (60%)	1,886 (62%)	738 (56%)
Education (years), mean (SD)	14.82 (4.13)	15.71 (3.40)	12.75 (4.87)
A+, No. (%)	2,286 / 4,372 (52%)	1,612 / 3,053 (53%)	674 / 1,319 (51%)
Centiloids, mean (SD)	38.22 (40.27)	36.08 (37.62)	43.19 (45.45)
p-tau217+, No. (%)	1,661 / 4,372 (38%)	1,150 / 3,053 (38%)	511 / 1,319 (39%)
T+, No. (%)	450 / 2,133 (21%)	231 / 1,571 (15%)	219 / 562 (39%)
CDR Global, median (range)	0 (0–3) / 4,196	0 / 2,883	0.5 (0.5–3) / 1,313
MMSE, mean (SD)	27.63 (3.28) / 4,367	28.72 (1.56) / 3,050	25.11 (4.59) / 1,317
Dementia, No. (%)	225 (5%)	0 (0%)	225 (17%)

Values are mean (SD) or n/N (%) with variable-specific denominators (non-missing N).
Abbreviations: A+, amyloid-β PET positive; CDR, Clinical Dementia Rating; CI, cognitively impaired; CU, cognitively unimpaired; MMSE, Mini-Mental State Examination; No., number; PET, positron emission tomography; p-tau217, plasma phosphorylated tau 217; SD, standard deviation; T+, tau PET positive.

Conclusion

- The biological interpretation of p-tau217 positivity differs by cognitive status and age. This supports p-tau217 positivity, rather than serving merely as a proxy for Aβ or tau PET, as marking an intermediate biomarker stage between the onset of Aβ PET abnormality and subsequent tau PET positivity in the AD continuum.
- Together, p-tau217, cognitive status, and age can estimate the likely A/T biological profile, placing patients on a clinically interpretable AD risk map.

Acknowledgments

Contact information



ORCID

alvaro_franco@pitt.edu
Alvaro de Oliveira Franco, MD



X: @labpascoal



pascoal lab.org



University of Pittsburgh



CAPES



ADNI



UFRGS



ALZHEIMER'S ASSOCIATION
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Get to know our lab



The A4 Study
NOW IS THE TIME



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Attendance at this conference was supported by an AAIC 2026 Conference Fellowship.