



Ji-Hyeon Lee, BS¹, Yeong-Hun Song, BS^{1,2}, Joon-Kyung Seong, PhD^{1,2}, for the Alzheimer's Disease Neuroimaging Initiative*

¹ Department of Artificial Intelligence, Korea University, Seoul, Republic of Korea

²NeuroXT, Research and Development Department, Seoul, Republic of Korea

BACKGROUND

Individuals with a comparable tau burden show several-fold variation in atrophy and clinical decline. Resilience is commonly quantified as a tau–cognition (TC) mismatch that uses cognition as the dependent variable of the residual, and this signal appears attenuated in the cognitively unimpaired, amyloid-positive preclinical stage where baseline cognition is compressed by a floor effect. Here we quantify resilience from neuroimaging as a tau-to-neurodegeneration (TN) mismatch, and examine whether this anatomy-anchored axis separates prospective clinical trajectories in the preclinical cohort where the cognition-based axis weakens.

METHOD

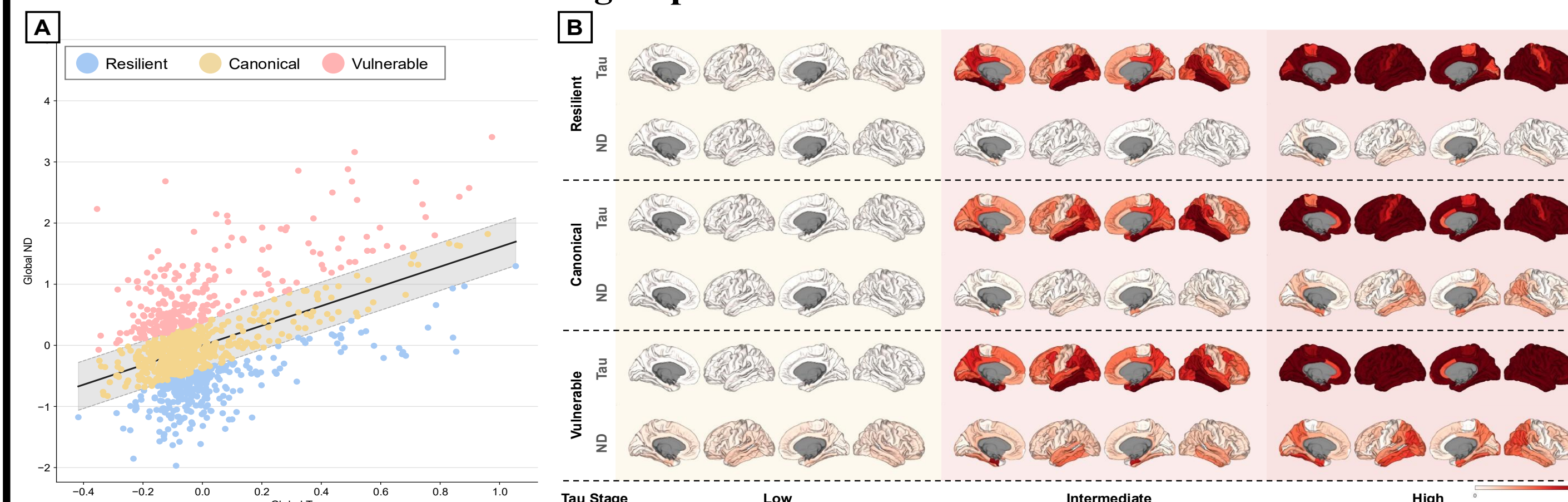
- The discovery cohort comprised 1,019 ADNI and ADNI4 participants (1,637 baseline visits). Each had paired [¹⁸F]flortaucipir tau-PET and 3-tesla T1-weighted MRI. The preclinical cohort comprised 376 cognitively unimpaired, amyloid-positive A4-trial participants (4,674 PACC visits, follow-up up to ≈8.5 years).
- Global tau burden (T) was the volume-weighted mean SUVR across a bilateral temporal-meta region of six structures. Global neurodegeneration (N) was the z-standardized, sign-inverted mean cortical-atrophy measure across nine AD-signature temporo-limbic and parietal regions.
- Global ND was regressed on global T by ordinary least squares, adjusting for age, sex, and education. The standardized residual was partitioned at a ±0.6 SD cutoff. This yielded Resilient (< −0.6 SD), Canonical (±0.6 SD), and Vulnerable (> +0.6 SD) groups.
- Longitudinal CDR-SB, MMSE, and PACC were modeled with linear mixed-effects models including a group-by-time interaction. Progression-free survival was assessed by Cox proportional-hazards and Kaplan–Meier estimation. Two milestones were defined: incident mild cognitive impairment (CDR-SB → 1.0) and progression to dementia (CDR-SB → 2.0).
- For the A4 cohort, the same regression specification and ±0.6 SD cutoff were re-derived internally on its baseline visits.

ACKNOWLEDGEMENT

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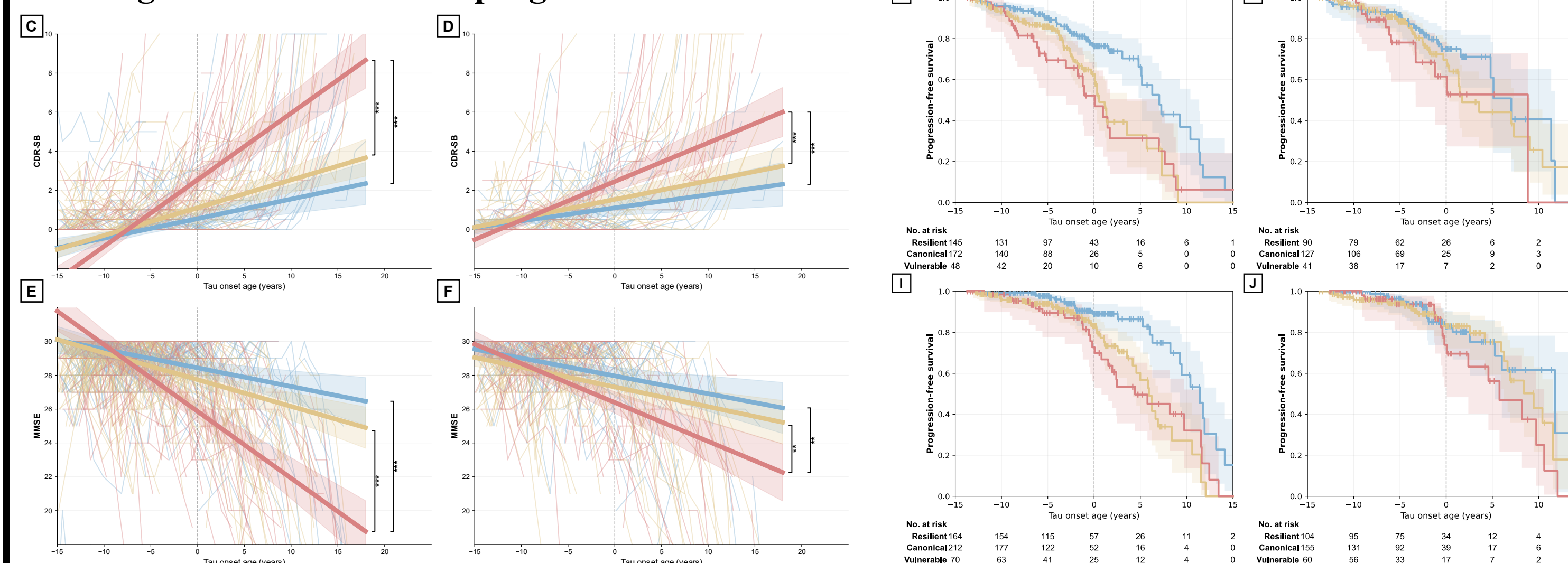
RESULT

S1. Definition of the TN-resilience groups

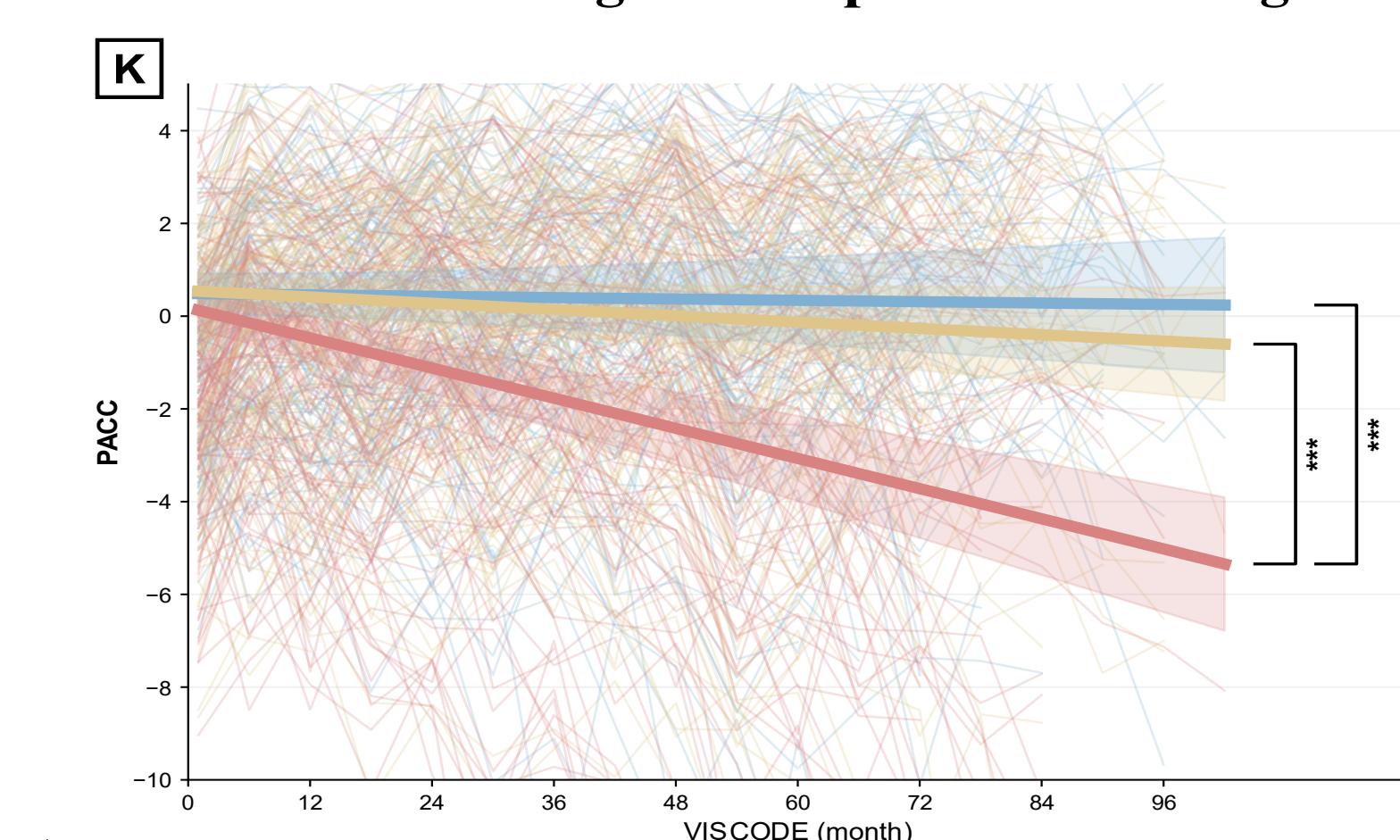


- The tau–neurodegeneration regression was strong ($\beta = +1.61$; $R^2 = 0.365$; $P = 1.6 \times 10^{-98}$), partitioning the cohort into Resilient (28.5%), Canonical (46.6%), and Vulnerable (24.9%) (A). Groups did not differ in age, sex, education, or APOE $\epsilon 4$ (all $P \geq 0.27$).
- At matched tau burden, regional atrophy diverged Vulnerable > Canonical > Resilient across all 62 Desikan–Killiany regions ($q < 0.05$) (B).

S2. Longitudinal decline and progression-free survival



S3. Preclinical divergence despite matched cognition



- The Resilient-versus-Vulnerable slope difference was significant on both CDR-SB and MMSE (both $P < 0.001$) (C, E).
- On progression-free survival, Resilient participants had a lower risk than Canonical for incident mild cognitive impairment (HR 0.49; 95% CI, 0.30–0.78) (G) and for dementia (HR 0.30; 95% CI, 0.17–0.54; $P < 0.001$) (I).
- The Vulnerable-versus-Resilient hazard for dementia was elevated at every ± 0.3 – ± 1.0 SD cutoff (HR, 2.96–15.01; all $P < 10^{-4}$).
- In the preclinical cohort, the three groups did not differ on any baseline measure of cognition or amyloid (all pairwise $P \geq 0.05$).
- The annualized PACC slope nonetheless steepened across groups (Resilient $-0.0024/\text{yr}$, Canonical $-0.0113/\text{yr}$, Vulnerable $-0.0542/\text{yr}$), with Vulnerable steeper than Resilient ($P < 10^{-7}$) (K).

CONCLUSION

- An anatomy-anchored TN-resilience axis, quantified from neuroimaging, carries regional atrophy divergence and separates prospective cognitive trajectories and progression risk, with the Vulnerable and Resilient extremes diverging most strongly.
- In contrast to the cognition-based axis, the TN axis remained informative in the cognitively unimpaired, amyloid-positive preclinical cohort, where groups with indistinguishable baseline cognition diverged on future decline.
- These findings suggest the TN axis may contribute a biology-aware baseline stratifier for prognostic assessment and preclinical trial enrichment.