

Background

- Brain age gap (predicted brain age – chronological age) reflects accelerated neural aging and can be used to quantify longitudinal neurodegeneration.
- Whether amyloid and tau pathology independently or differentially drive brain age acceleration and whether sex moderates these relationships remains unclear.
- We tested timepoint × tau, timepoint × amyloid, and timepoint × sex interactions on brain age gap across three visits, then examined sex-stratified tau effects.

Methods

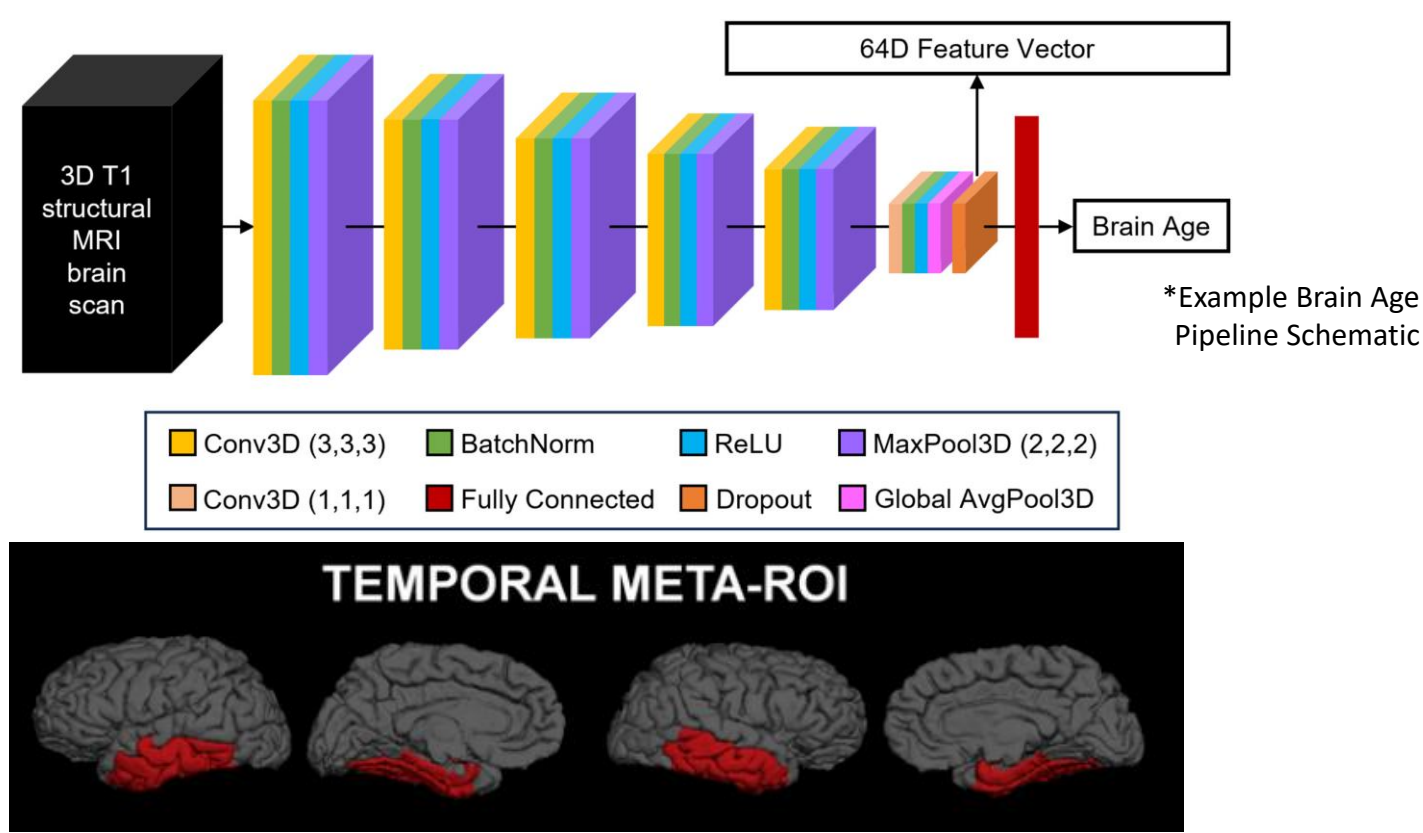
Participants: 55 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (26 male, 29 female; CN=37, MCI=14, Dementia=4), 3 visits (participants only selected if had concurrent amyloid and tau PET within 2 years)

Measures: Amyloid PET (Centiloids), tau PET (meta-temporal SUVR), MRI-derived brain age via the pyment deep neural network (Leonardsen et al., 2022, Neurolmage).

Models: Linear mixed-effects models (random intercept, REML) tested timepoint × tau, timepoint × amyloid, and timepoint × sex interactions. Sex-stratified partial correlations examined tau–brain age gap associations at each visit, controlling for amyloid, age, race, and ethnicity.

Robustness checks: Five influence metrics (leverage, studentized residuals, Cook's D, DFFITS, Mahalanobis distance) identified influential observations; sensitivity analyses re-ran models excluding them. A residual-based partial Spearman correlation (residualize on covariates, then rank) confirmed findings were not driven by non-normality.

Contrasts: Sex × timepoint estimated marginal means (EMMs) computed via the exact fixed-effects covariance matrix (cVc method); df=45 (conservative vs. Kenward-Roger ≈100–110).



Sample Characteristics

	N	Age, yrs (mean±SD)	Diagnosis (CN/MCI/Dem)	Tau SUVR (mean±SD)	Amyloid Centiloids (mean±SD)
Total	55	70.8 ± 6.0	37 / 14 / 4	1.34 ± 0.36	34.0 ± 46.6
Male	26	72.2 ± 5.1	16 / 8 / 2	1.32 ± 0.42	30.3 ± 46.8
Female	29	69.5 ± 6.4	21 / 6 / 2	1.36 ± 0.30	37.3 ± 46.9

CN = cognitively normal; MCI = mild cognitive impairment; Dem = dementia. Tau = meta-temporal SUVR; amyloid = Centiloids, both at Visit 1.

Mixed Model Results

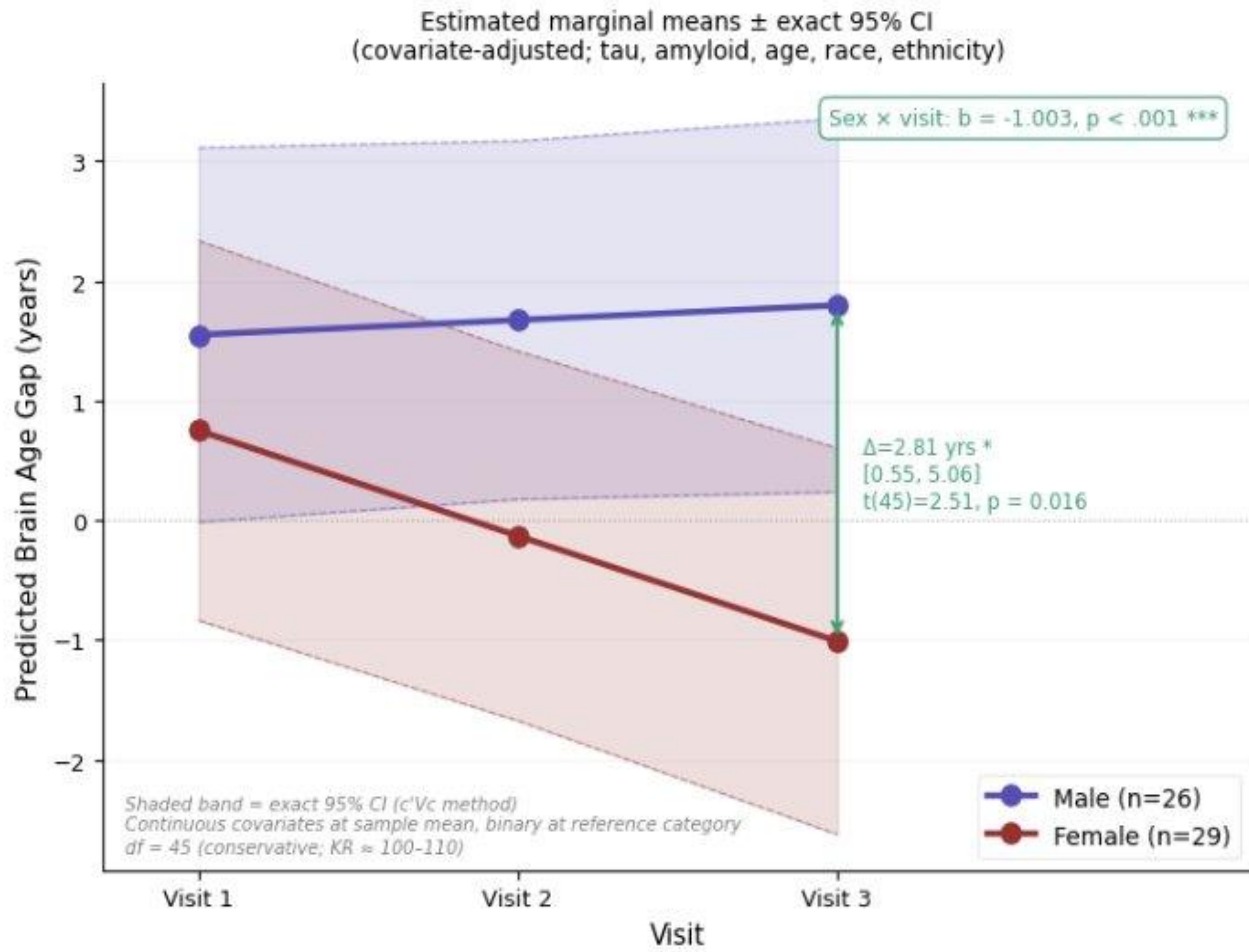
Fixed effect	b	SE	p
Intercept	11.960	6.711	.075 ns
Timepoint	0.194	0.219	.375 ns
Tau	0.559	1.347	.678 ns
Timepoint × Tau	0.742	0.420	.077 ns
Amyloid	0.010	0.010	.314 ns
Timepoint × Amyloid	0.002	0.003	.517 ns
Sex	−0.724	1.110	.514 ns
Timepoint × Sex	−1.057	0.289	<.001 ***
Age	−0.148	0.092	.108 ns
Race (non-White)	−0.970	2.046	.635 ns
Ethnicity (Hispanic)	1.002	4.223	.813 ns

Linear mixed-effects model (random intercept, REML); brainAGEgap as outcome, timepoint × tau, × amyloid, and × sex as fixed-effect interactions, controlling for age, race, and ethnicity.

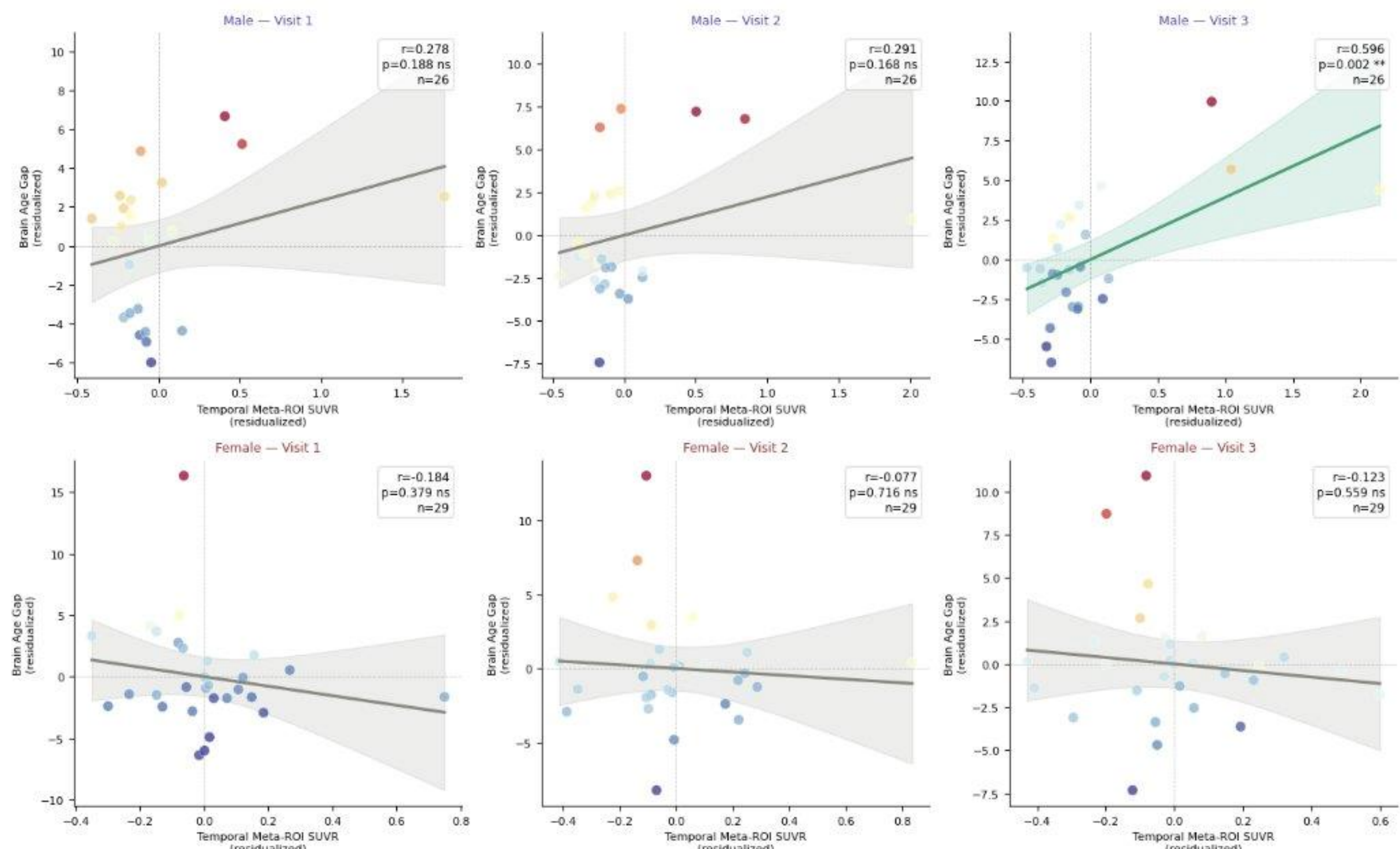
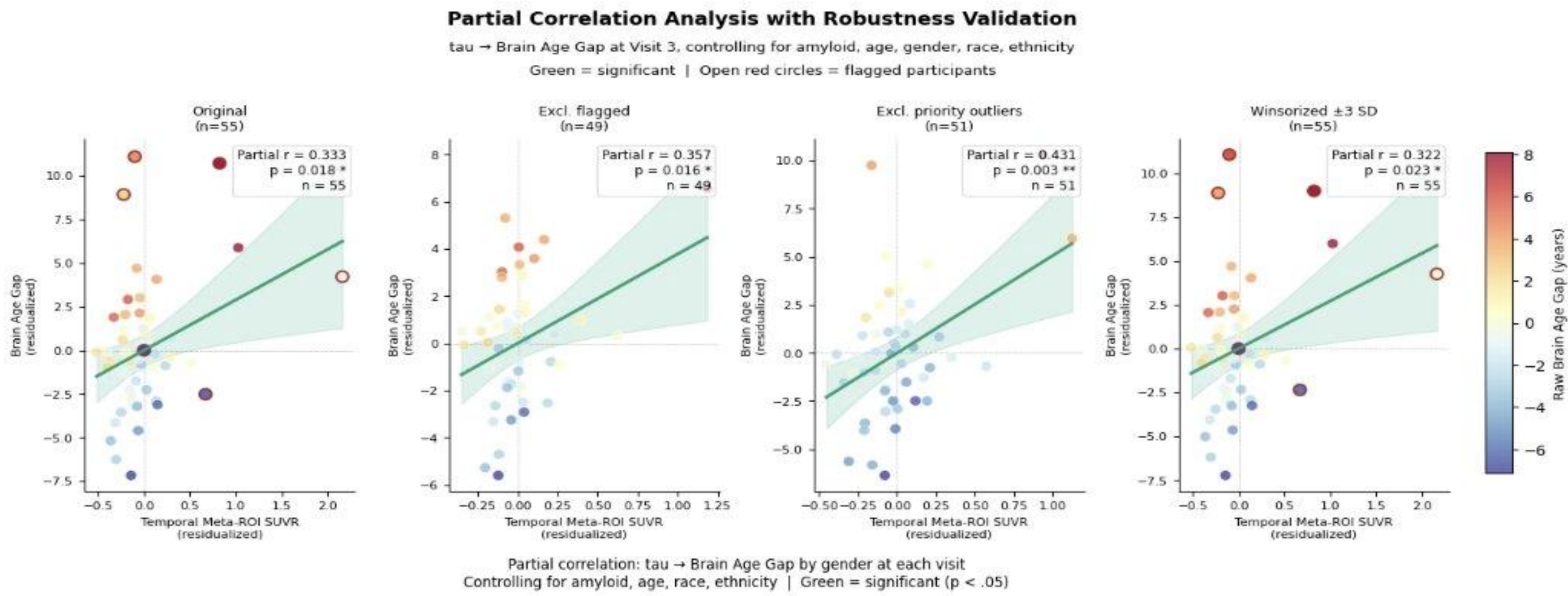
Only the timepoint × sex interaction reached significance (**b=−1.057, p<.001**), indicating male and female brain age gap trajectories diverge over the three visits. Neither timepoint × tau nor timepoint × amyloid reached significance in the pooled sample, motivating the sex-stratified partial correlation analyses presented at right.

Results

Brain age gap trajectories diverge by sex, emerging by Visit 3



Sex × tau × timepoint: tau effect emerges and is male-specific by Visit 3



Sex-Stratified Estimates

Visit	Male EMM	Female EMM	Adj. Δ (M–F)	p
1	1.55	0.75	0.80	ns
2	1.67	−0.13	1.80	ns
3	1.80	−1.01	2.81	*

EMMs in years, covariate-adjusted (tau, amyloid, age, race, ethnicity at reference/mean); exact 95% CI via fixed-effects covariance matrix, df=45.

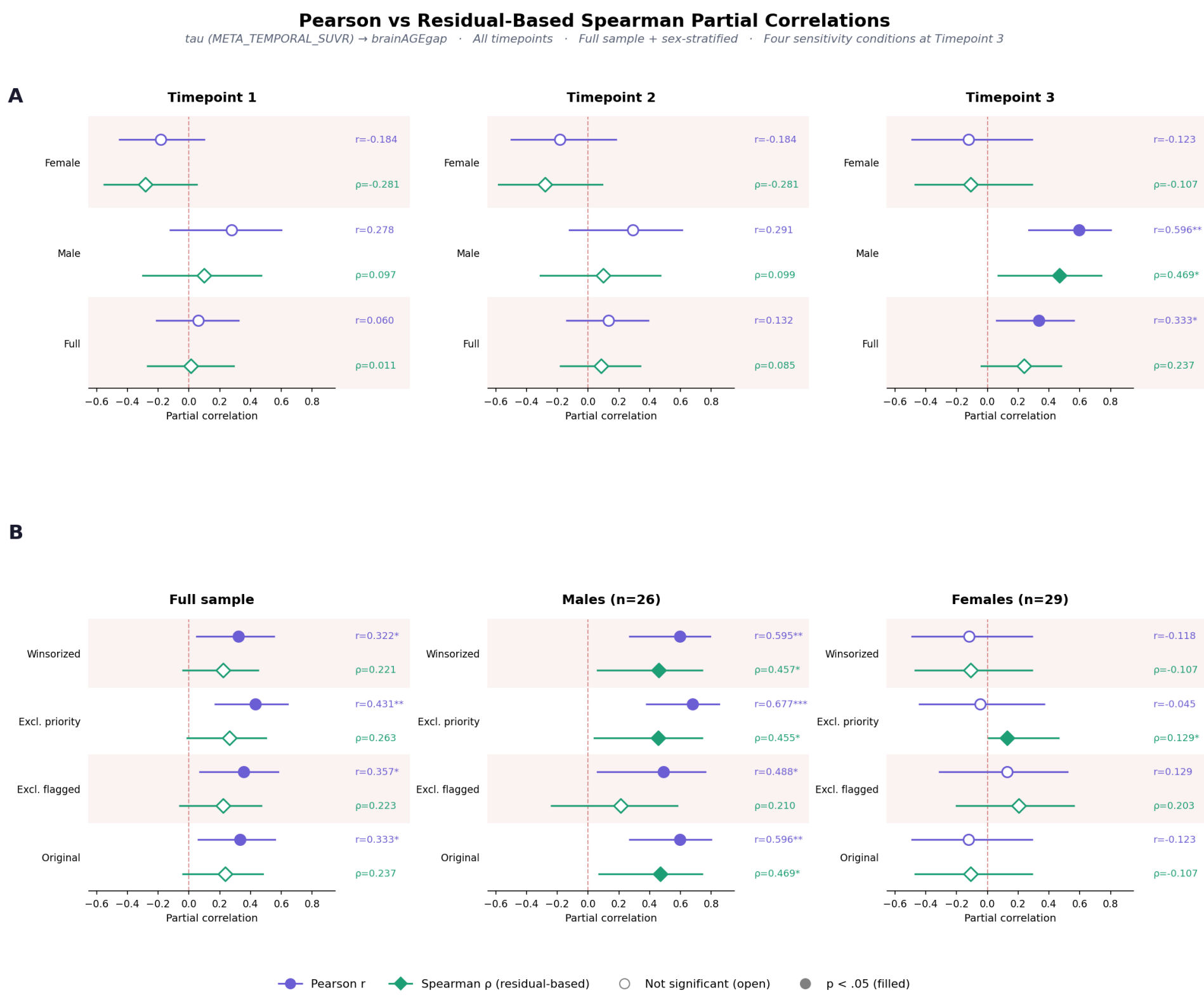
Tau → Brain Age Gap by Sex

Group	Visit 1	Visit 2	Visit 3
Male	r=.28 ns	r=.29 ns	r=.60 **
Female	r=−.18 ns	r=−.08 ns	r=−.12 ns
Full sample	r=.06 ns	r=.13 ns	r=.33 *

Tau × sex interaction at Visit 3: b=−5.42, p=.044. Amyloid was non-significant at all visits (all p>.19).

Robustness in males (n=26):

The Visit-3 tau effect (r=.596) survived five influence-detection methods and all four sensitivity conditions (Pearson r range .488–.677, all p<.05).



Conclusions

- Temporal lobe tau burden is a male-predominant, late timepoint-emergent predictor of accelerated brain aging, independent of amyloid.
- Females show progressive normalization of brain age gap apparently independent of tau load, although larger sample sizes are needed to confirm this.
- The sex divergence is absent at baseline and emerges specifically by Visit 3, consistent with a true longitudinal process.
- Convergent Pearson/Spearman evidence and 5-method outlier sensitivity analyses confirm the male tau effect is statistically robust.
- Tau PET may have differential prognostic value by sex in Alzheimer's disease and other neurodegenerative conditions.

References:

Leonardsen, E. H., Peng, H., Kaufmann, T., Agartz, I., Andreassen, O. A., Celius, E. G., ... & Wang, Y. (2022). Deep neural networks learn general and clinically relevant representations of the ageing brain. *NeuroImage*, 256, 119210.