



BACKGROUND

Alzheimer's disease (AD) exhibits substantial heterogeneity in neurodegeneration, including variability in the timing and regional pattern of brain atrophy.

Earlier estimated age of amyloid PET onset (EAOA) has been associated with earlier downstream pathology and clinical symptoms, yet its relationship with longitudinal brain atrophy remains unclear.

Using longitudinal MRI and amyloid PET data from three cohorts, we examined whether EAOA is associated with regional brain volume trajectories, accounting for sex and APOE-ε4 positivity.

STUDY OBJECTIVES

Investigate whether earlier amyloid onset is associated with regional brain volume trajectories in linear and nonlinear patterns.

Examine regional differences in brain volume trajectories as they relate to amyloid onset across multiple cohorts.

Compare stratified classes of amyloid positivity relative to negative controls while controlling for known risk factors of female sex and APOE-ε4 positivity.

METHODS

Participants

1,843 participants (1,073 ADNI, 333 OASIS, 437 WISC) with ≥3 MRI visits, ≥1 amyloid PET scan, and ≥1 year of follow-up were included.

Methods

EAOA was estimated within-cohort using the Sampled Iterative Local Approximation (SILA; silaR package) algorithm, with amyloid positivity defined as Centiloid >20.

Participants were classified as early-onset A+, late-onset A+, or amyloid-negative controls using the cohort-specific median EAOA.

Gray matter volumes from six ROIs (Medial Temporal, Hippocampus, Temporal Neocortex, AD-vulnerable; Cingulate and Precuneus, Parietal, Frontal, Occipital, Striatum) were derived from structural MRI and normalized by intracranial volume.

Longitudinal volume trajectories were modeled using linear mixed-effects models with random intercepts for participant and imaging site.

Time was parameterized as centered age at appointment with second-order polynomial terms. Fixed effects included sex, APOE-ε4, EAOA group, and their interactions with time.

Models were fit separately for each region and predicted trajectories with 95% confidence intervals estimated.

Higher-order polynomial terms and spline models were considered but failed to yield improved model fit above a second-order polynomial term.

RESULTS

Table 1. Cohort Summaries

	ADNI (N=1073)	OASIS (N=333)	WISC (N=437)	Overall (N=1843)
Baseline MRI Age				
Mean (SD)	72.5 (6.93)	65.4 (9.12)	60.3 (7.10)	68.3 (9.05)
# MRIs				
Median [Min, Max]	6.00 [3.00, 15.0]	4.00 [3.00, 10.0]	4.00 [3.00, 13.0]	5.00 [3.00, 15.0]
Length Follow-Up				
Median [Min, Max]	4.13 [1.00, 15.8]	7.59 [1.78, 15.9]	10.4 [1.21, 18.1]	6.22 [1.00, 18.1]
Female				
N (%)	507 (47.3%)	201 (60.4%)	286 (65.4%)	994 (53.9%)
APOE-ε4+				
N (%)	459 (42.8%)	113 (33.9%)	165 (37.8%)	737 (40.0%)
Missing	0 (0%)	2 (0.6%)	1 (0.2%)	3 (0.2%)
CDR Global at Last Visit				
0	380 (35.4%)	266 (79.9%)	335 (76.7%)	981 (53.2%)
0.5	423 (39.4%)	37 (11.1%)	84 (19.2%)	544 (29.5%)
1	161 (15.0%)	17 (5.1%)	4 (0.9%)	182 (9.9%)
2	82 (7.6%)	12 (3.6%)	4 (0.9%)	98 (5.3%)
3	27 (2.5%)	1 (0.3%)	0 (0%)	28 (1.5%)
Missing	0 (0%)	0 (0%)	10 (2.3%)	10 (0.5%)
PET Tracer				
FBB	122 (11.4%)	0 (0%)	0 (0%)	122 (6.6%)
FBP	951 (88.6%)	29 (8.7%)	0 (0%)	980 (53.2%)
PiB	0 (0%)	304 (91.3%)	437 (100%)	741 (40.2%)
# A+ Cases				
N (%)	616 (57.4%)	126 (37.8%)	143 (32.7%)	885 (48.0%)
Estimated A+ Age				
Mean (SD)	67.2 (9.20)	69.3 (7.88)	63.5 (7.40)	66.9 (8.90)
EAOA Group				
A-	457 (42.6%)	207 (62.2%)	294 (67.3%)	958 (52.0%)
Early	314 (29.3%)	54 (16.2%)	102 (23.3%)	470 (25.5%)
Late	302 (28.1%)	72 (21.6%)	41 (9.4%)	415 (22.5%)

Figure 1. Standardized Volume Changes by ROI

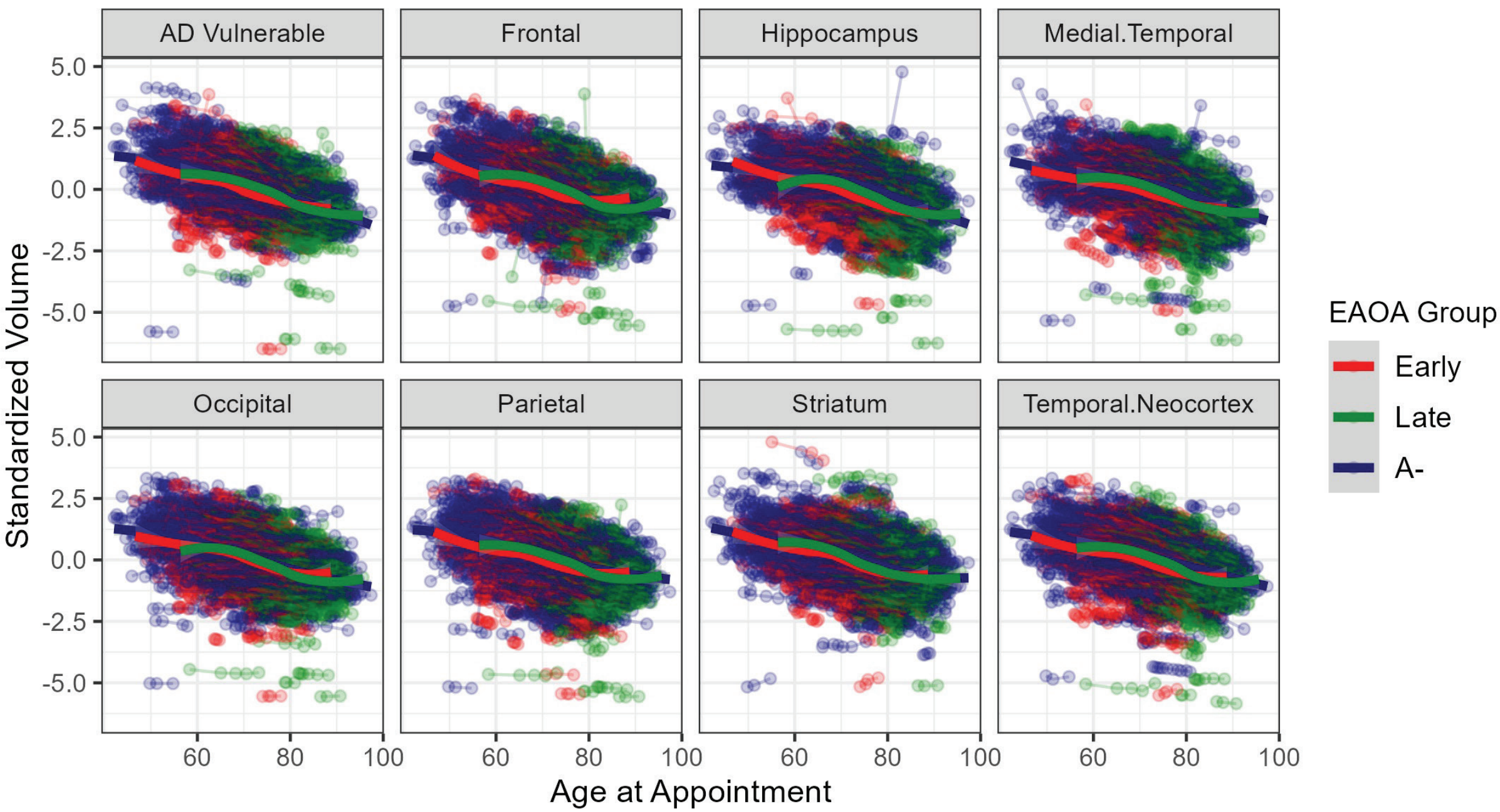


Figure 1: Longitudinal trajectories of standardized brain volume by ROI, colored by EAOA groups, with smoothed LOESS trends overlaid for each EAOA groups

Figure 3. Fixed Effects on Standardized Volume by ROI

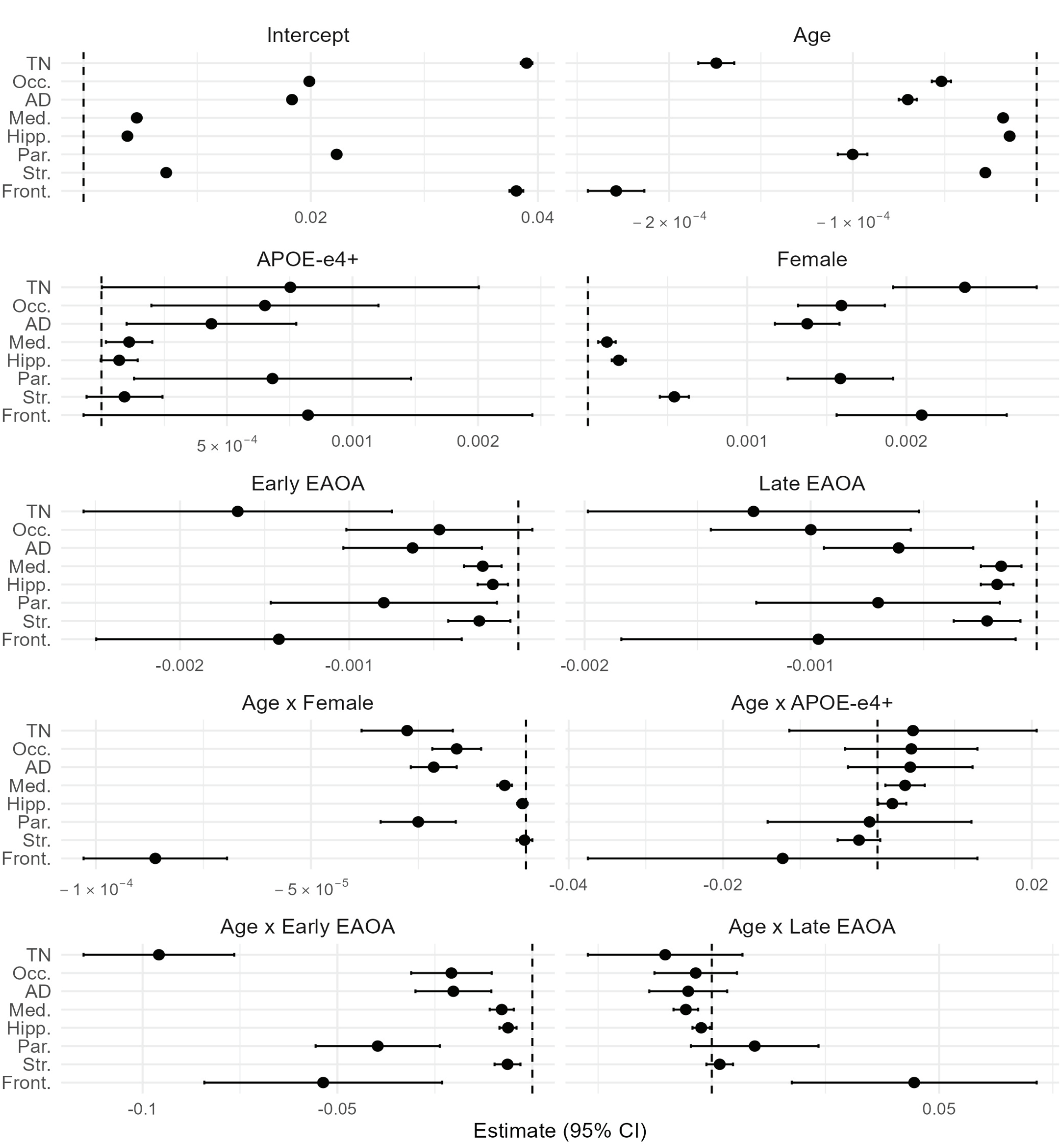


Figure 3: Model estimate values for coefficients with 95% confidence intervals show by horizontal lines; Polynomial terms included in the final models, as well as interactions between APOE-ε4+ and EAOA group but are omitted from the figure above.

Figure 2. Predicted Volume / ICV Trajectories by EAOA Group

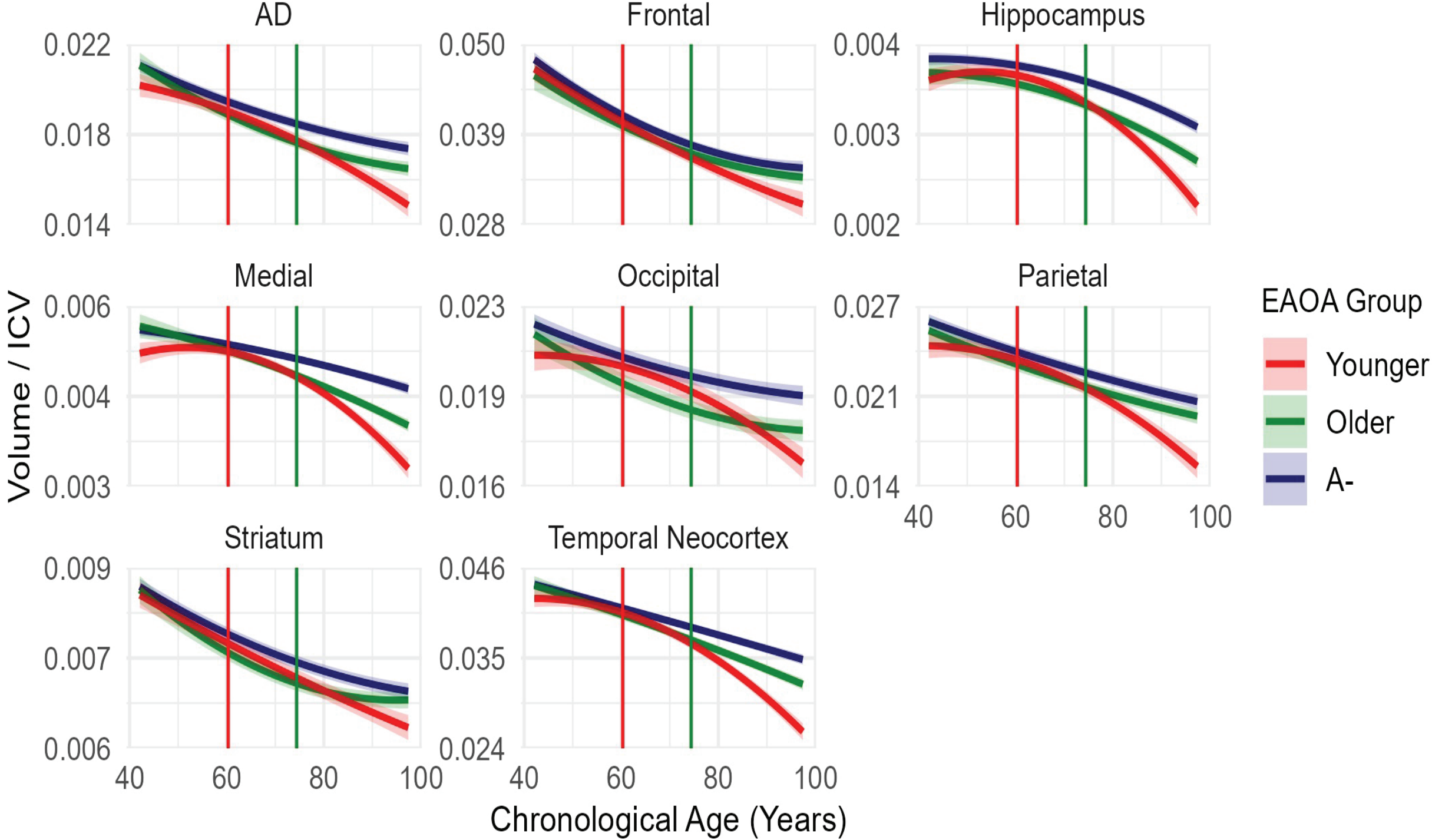


Figure 2: Lines represent model-predicted trajectories accounting for APOE-ε4 and sex. Shaded ribbons indicate 95% confidence intervals. Vertical lines denote mean EAOA for younger (60.3 years; red) and older (74.4; green) A+ groups.

RESULTS SUMMARY

Across all regions, early- and late-onset A+ groups showed significantly lower volumes at baseline MRI compared with amyloid-negative controls (all $p < 0.01$) and significant nonlinear age effects.

Compared to the A- control group, earlier EAOA was associated with steeper age-related decline and greater nonlinearity, particularly in frontal, parietal, and temporal neocortical regions; late-onset A+ showed similar but less pronounced patterns (Figure 2; Figure 3).

Females exhibited higher baseline volumes but steeper age-related decline in most ROIs, except the hippocampus and striatum.

APOE-ε4 positivity was associated with modestly greater age-related volume loss in all but the occipital ROI.

CONCLUSIONS

Earlier EAOA is associated with more aggressive and nonlinear neurodegeneration across multiple regions.

These findings suggest that heterogeneity in amyloid onset reflects distinct longitudinal volumetric trajectories, highlighting the importance of biomarker timing when characterizing AD progression.

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MATLAB SILA



silaR

