

BrainAge moderates associations between AD biomarkers and cognitive decline: findings from A4/LEARN and the Harvard Aging Brain Study

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Abstract

Background: BrainAge models estimate biological brain age based on neuroimaging data, providing a measure of brain health. This metric is particularly relevant in Alzheimer's disease (AD), where accelerated brain aging is exacerbated by β -amyloid ($A\beta$) and tau accumulation. We investigated the extent to which BrainAge moderates associations between AD biomarkers and longitudinal cognitive decline across two independent cohorts.

Methods: We examined 1690 participants from A4/LEARN and 349 from HABS (Table 1). Using the Open-Source tool *AgeML* within each cohort, we built a BrainAge linear regressor model with 5-fold cross validation using MRI-T1 volumetric and FreeSurfer cortical thickness ROIs. We compared predicted ages with chronological age to create a BrainAge_{delta}. To avoid regressing out sex and *APOE* ϵ 4 variance, separate male/female models were built with data from *APOE* ϵ 4 non-carriers and applied to each cohort. We examined BrainAge_{delta} as a moderator of global neocortical $A\beta$ -PET burden, temporal lobe Tau PET composite and *p*-tau₂₁₇ associations with longitudinal PACC using linear mixed effects models. We adjusted for random intercepts and slopes, and baseline age, sex, years of education and *APOE* ϵ 4. In A4/LEARN we additionally adjusted for cumulative dose and treatment group using a spline model.

Results: Higher levels of $A\beta$ -PET, Tau-PET and *p*-tau₂₁₇ at baseline was significantly correlated with higher BrainAge_{delta} (worse) (Figure 1). BrainAge_{delta} was directly associated with PACC trajectories in both cohorts. It also moderated the association

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between $A\beta$ and Tau-PET and PACC trajectories such that higher $\text{BrainAge}_{\text{delta}}$ was associated with faster cognitive decline with increasing levels of each biomarker. We found the same pattern of effects in $p\text{-tau}_{217}$ limited only to the A4/LEARN sample but was trend-level in HABS (Figure 2).

Conclusions: $\text{BrainAge}_{\text{delta}}$ is significantly associated with $A\beta$ and tau burden and moderates their association with cognitive decline, supporting previous literature suggesting that BrainAge is a robust marker of brain health. Prioritizing individuals with worse BrainAge for clinical trials could not only effectively reduce screen fails (estimates forthcoming) but is a potentially feasible approach given that it can be calculated from a single T1-weighted MRI scan. These findings also highlight the importance of age-independent neurodegeneration patterns to contribute unique signal in models of brain health and pathological progression.

Table 1 Cohort Demographics

Characteristic	A4/LEARN		HABS	
	A β - N = 530 ¹	A β + N = 1,160 ¹	A β - N = 233 ¹	A β + N = 112 ¹
Age	70.53 (4.33)	71.94 (4.83)	69.97 (8.02)	74.73 (6.68)
Sex				
Female	326 (61.51%)	688 (59.31%)	146 (62.66%)	63 (56.25%)
Male	204 (38.49%)	472 (40.69%)	87 (37.34%)	49 (43.75%)
Education (Years)	16.78 (2.63)	16.57 (2.80)	15.72 (3.01)	16.20 (2.94)
APOE				
ϵ 4-	408 (76.98%)	475 (40.95%)	189 (81.82%)	59 (52.68%)
ϵ 4+	122 (23.02%)	685 (59.05%)	42 (18.18%)	53 (47.32%)
Aβ-PET SUVR	0.99 (0.07)	1.33 (0.18)	1.13 (0.06)	1.64 (0.25)
Tau-PET SUVR	1.26 (0.09)	1.42 (0.23)	1.30 (0.13)	1.49 (0.22)
p-tau₂₁₇ (U/ml)	NA (NA)	0.29 (0.15)	3.54 (3.24)	6.66 (3.71)
PACC at Baseline	-0.61 (2.20)	-1.19 (2.45)	0.08 (0.69)	0.00 (0.69)
Follow-up Time (Years)	5.52 (2.22)	5.55 (2.35)	8.61 (3.74)	7.97 (3.82)

¹Mean (SD); n (%)

Figure 1. Correlation of BrainAge_{delta} with composite measure of (A) A β -PET, (B) Tau PET and (C) p-tau₂₁₇ at baseline for each cohort.

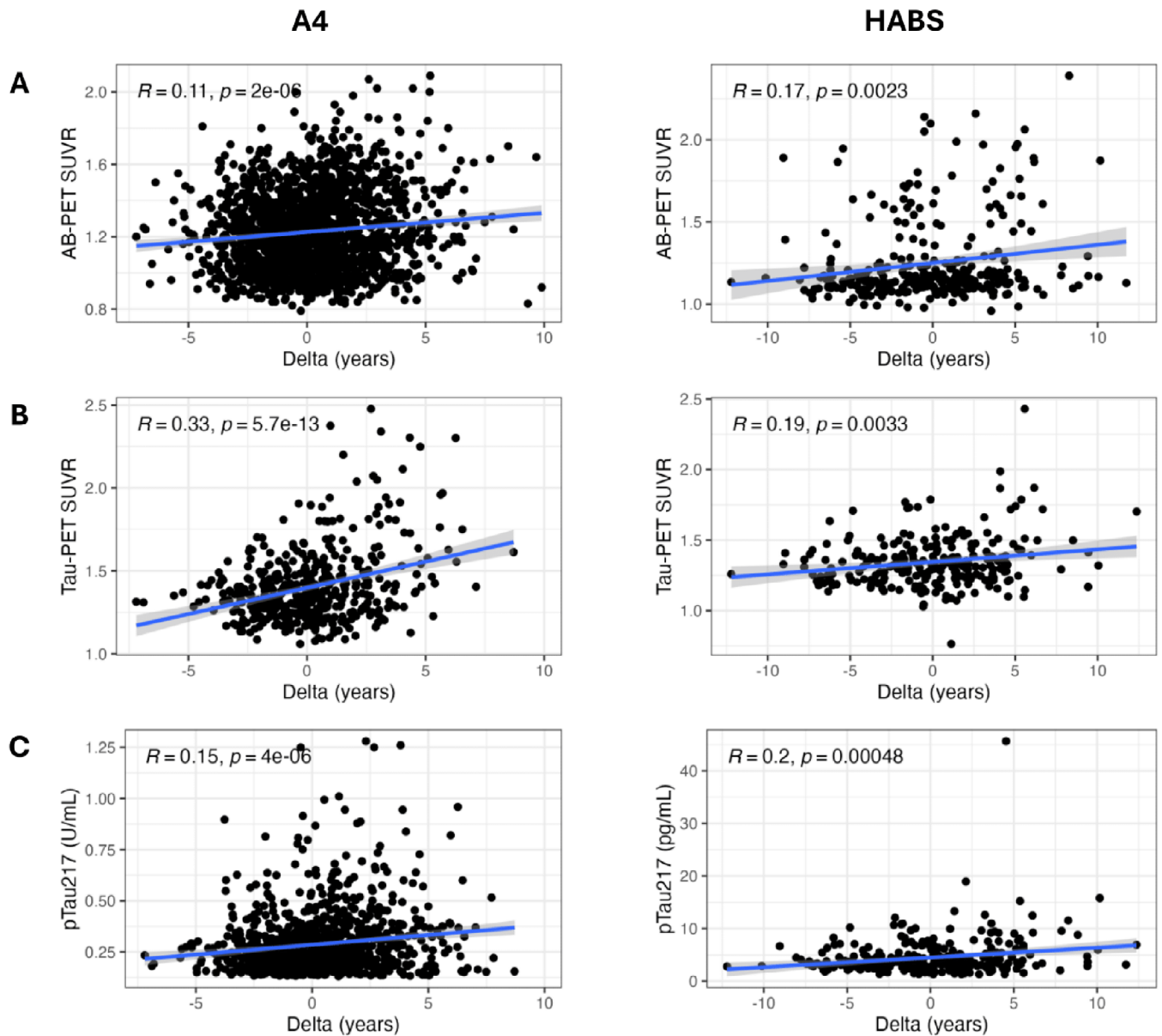


Figure 2. BrainAge_{delta} association with PACC Longitudinal trajectories. **(A)** BrainAge_{delta} and PACC **(B)** BrainAge_{delta}, Aβ-PET and PACC **(C)** BrainAge_{delta}, Tau-PET and PACC **(D)** BrainAge_{delta}, p-tau₂₁₇ and PACC. Red line shows -1 SD, blue line shows mean and green line shows +1SD for BrainAge_{delta}. Similarly, in **(B, C, D)** each column shows -1SD, mean and +1SD. PACC trajectories are more pronounced in A4 than HABS.

