

Brain Age Gap Interacts with Plasma pTau217 to Predict Cognitive Decline

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Background:

Why cognitive decline?

- Cognitive decline exists on a spectrum, but progression between stages is highly variable¹
- Predicting who is at greater risk for decline enables more targeted early interventions

Why Brain Age Gap (BAG)?

- BAG is a novel neuroimaging-derived metric to estimate a brain's "age"
- Machine learning models learn the associations between chronological age and morphological changes from healthy individuals' MRI scans to derive a Brain Age estimate²
- BAG = Predicted Brain Age – Chronological Age → individualized marker of accelerated brain aging

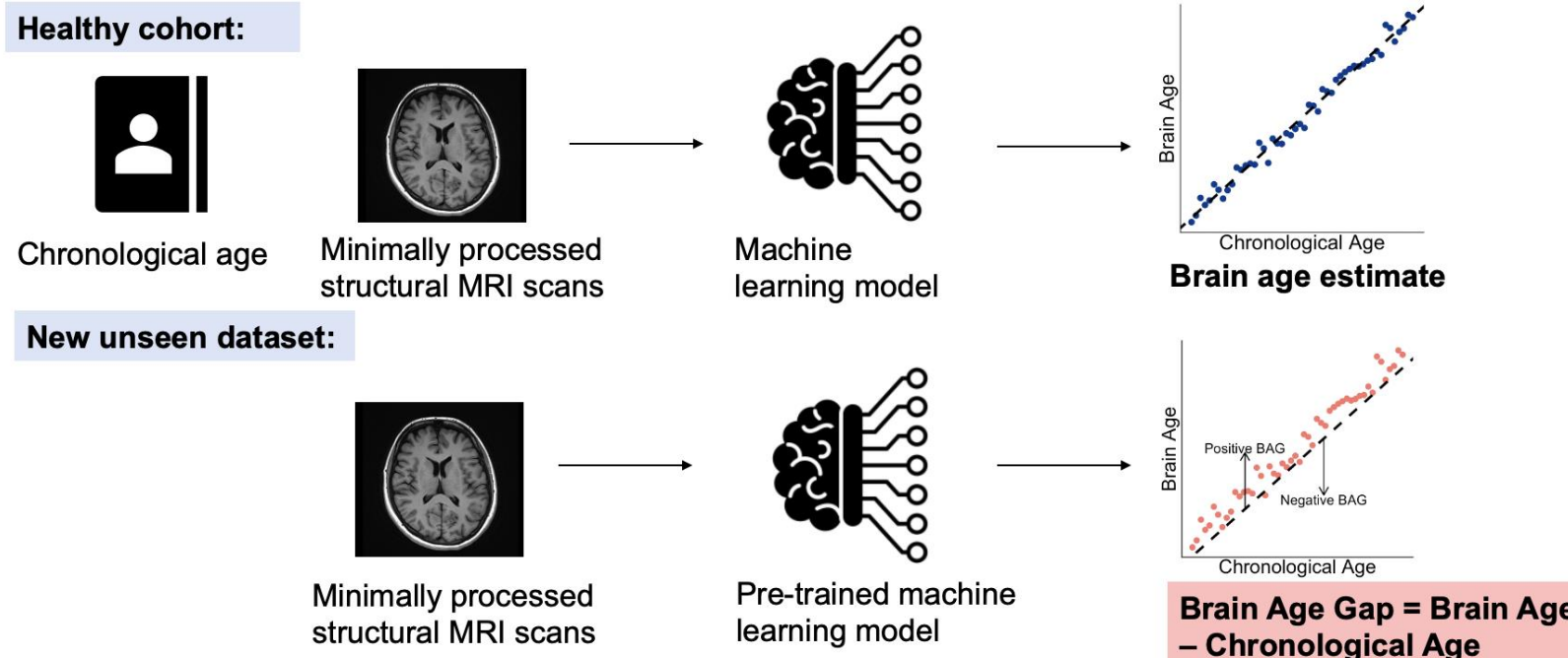


Figure 1. Diagram illustrating the Brain Age model training process

Why plasma pTau217?

- Plasma pTau217 is a recent diagnostic indicator for AD pathology (with growing evidence for its prognostic utility), but reflects distinct underlying neurodegenerative mechanisms from BAG
- The interaction between BAG and plasma pTau217 in improving cognitive decline prediction has not yet been explored

Aims:

- Investigate BAG's utility in predicting cognitive decline generally across the cognitive spectrum
- Explore how BAG may interact with plasma pTau217 levels to predict decline

Methods:

Sample

- 210 NNI memory clinic patients and healthy controls (29 HC, 33 SCI, 108 MCI, 30 AD, 10 FTD) with available longitudinal MMSE data between 2013-2025

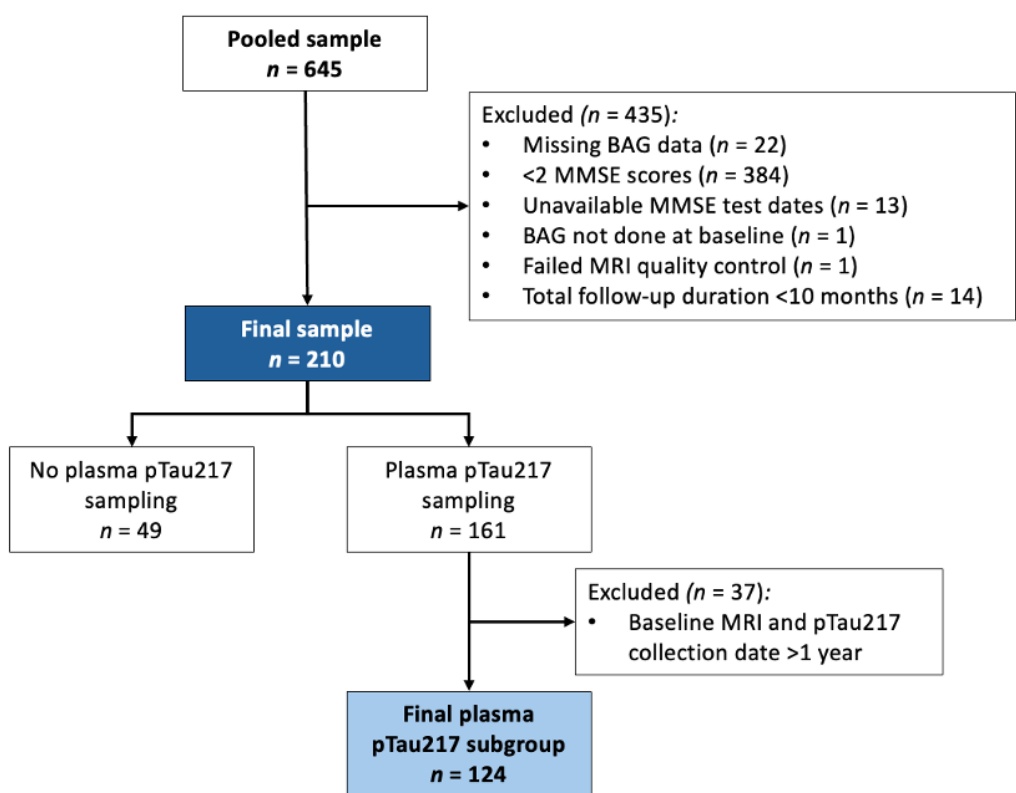


Figure 2. Flow chart of study participants

BAG estimation

- T1-weighted structural MRI scans were acquired using vendor-standard MPRAGE-type structural sequences, minimally preprocessed
- Brain Age estimates were derived via the "pyment" pre-trained simple fully convolutional network³, and corrected by -5.7 years for the local population

Plasma pTau217 sampling

- Plasma pTau217 was measured using ALZpath single molecule array assay in a subset of 124 subjects

Analysis

- Linear mixed models were constructed to investigate the effect of BAG on cognitive decline
 - eTIV, ApoE4 carrier status, age and years of education included as clinical confounders
- Type III ANOVA to investigate the overall significance of the 3-way interaction between BAG, pTau217 and Time on cognitive decline
- Simple slopes analysis to compare the effect of BAG on cognitive decline within each pTau217-stratified group

Results:

BAG at baseline predicts cognitive decline

- BAG at baseline was associated with cognitive decline rates across our cohort ($\beta = -0.077$, $p < .001$)
- The effect remained significant even within MCI patients alone ($\beta = -0.048$, $p = .031$)

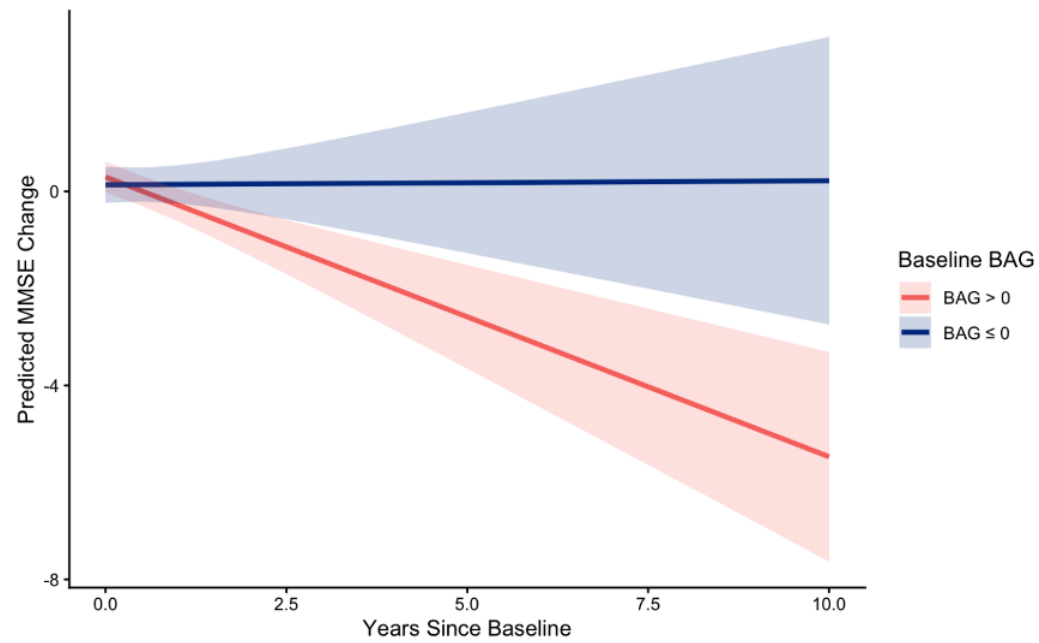


Figure 3. Predicted Cognitive Trajectories in Those Estimated Older (BAG>0) vs Younger (BAG≤0) than Chronological Age

BAG interacts with plasma pTau217 to predict decline

- BAG interacted with plasma pTau217 group to predict cognitive decline rates ($p = .002$)
- The effect of BAG on cognitive decline differed between the AD and non-AD group ($\beta = -0.282$, $p = .002$), but not between the Intermediate Risk and non-AD group ($\beta = 0.108$, $p = .204$)
- Simple slopes analysis showed BAG predicted cognitive decline significantly in the AD group alone ($\beta = -0.294$, $p < .001$)

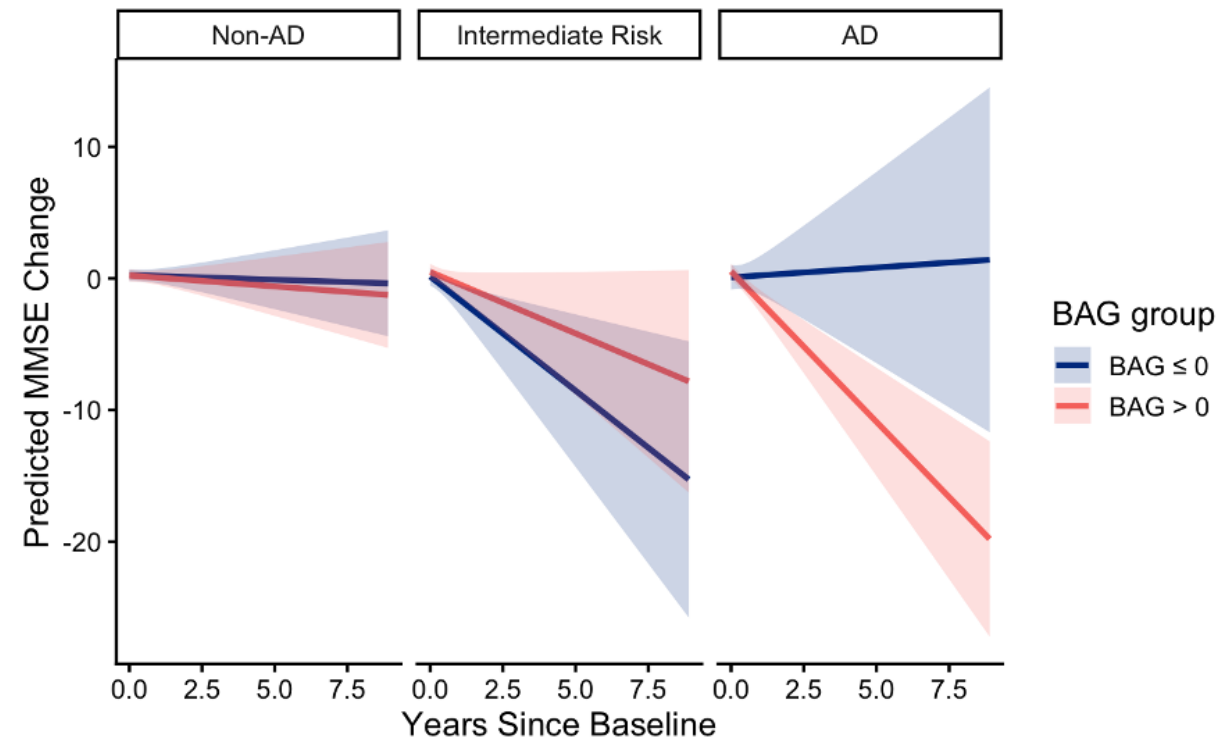


Figure 4. Predicted Cognitive Trajectories in those Estimated Older (BAG>0) vs Younger (BAG≤0) than Chronological Age, stratified by pTau217 group

Discussion:

- BAG is a robust, intuitive imaging marker for faster cognitive decline risk**
 - It shows utility even in earlier MCI stage
- BAG interacts with plasma pTau217 to predict rate of cognitive decline**
 - Suggests that BAG explains additional variance in dementia prognosis not accounted for by pTau217, particularly in those with biological AD

Future work

- Future studies should investigate BAG's role in predicting cognitive decline in the context of non-AD copathologies
- Ongoing studies are increasing peripheral plasma pTau217 sampling and MMSE follow-ups among our local cohort for more robust results

References:

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