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NEUROIMAGING

Validation of Amyloid Chronicity in Autosomal Dominant Alzheimer Disease

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Abstract

Background: Alzheimer Disease (AD) pathology evolves over decades, and understanding this progression is critical to the understanding of the disease and timing therapeutic interventions. Since individuals with Autosomal Dominant AD (ADAD) develop symptoms around the same age as their parent, it is possible to predict symptom onset and stage individuals by their estimated years to symptom onset (EYO). This approach does not generalize to other forms of AD, thus there is a pressing need for the timecourse of ADAD to be defined in broadly relevant terms.

The objective of this project is to validate the Sampled Iterative Local Approximation (SILA) algorithm in a cohort with a known disease timecourse. SILA generates an estimate of time from amyloid positivity (A_{time}) based on longitudinal PET data.

Method: We evaluated A_{time} in a longitudinal ADAD sample (N = 316) with PET PiB data in three ways. First, we compared predicted age at amyloid positive (A+) to observed age at A+ for individuals who became A+ during enrollment. Next, using linear regression, we compared estimated age at A+ to estimated age at symptom

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onset (EYO=0). Finally, we used generalized additive models to compare the amount of variance in concurrent cognitive performance explained both A_{time} and EYO.

Result: We observed a mean average error of 1.15 years between actual age at A+ ($N = 26$) and the SILA-predicted A_{time}. Across all participants, SILA-estimated age at A+ explained 39% of the variance in estimated age at symptom onset ($\beta = 0.918$, $p < 0.0001$). Finally, we observed a nonlinear association between cognition and both A_{time} and EYO. A_{time} explained 19% of the variance in the general cognitive composite while EYO explained 43% of the variance.

Conclusion: SILA produces a valid estimate of time-from-amyloid positivity in ADAD. This work allows for disease stage in ADAD to be compared to staging for broad forms of AD, which was not previously possible using EYO. However, this work also illustrates that there is a high degree of heterogeneity in preclinical disease duration that is not explained by amyloid alone.

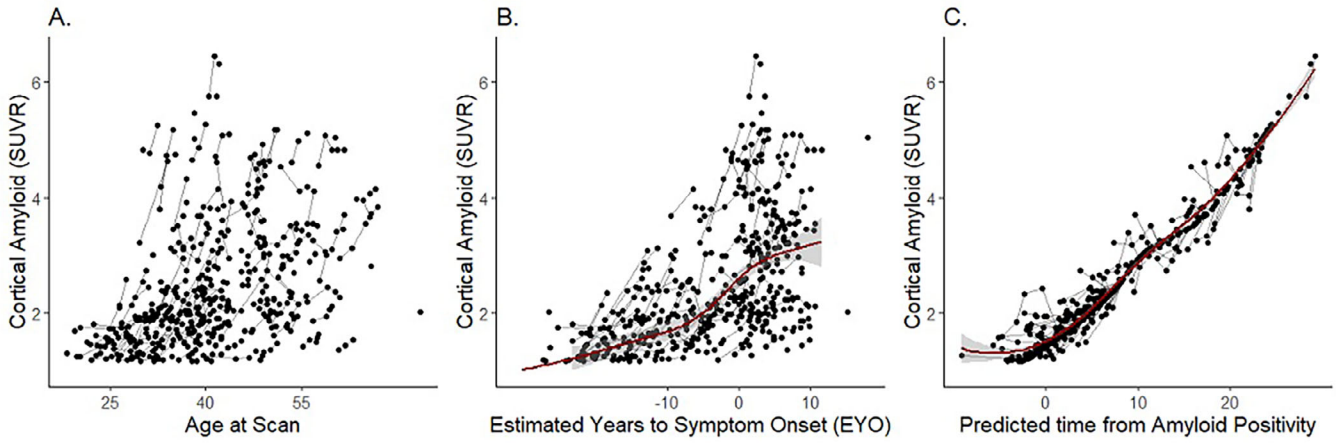

Figure 1. Cortical amyloid burden increases across the lifespan for individuals with Autosomal Dominant Alzheimer Disease (ADAD) (A). This pathological accumulation occurs prior to symptom onset (B), and can be translated into a chronological estimate of time from amyloid positivity using the Sampled Iterative Local Approximation (SILA) algorithm (C).

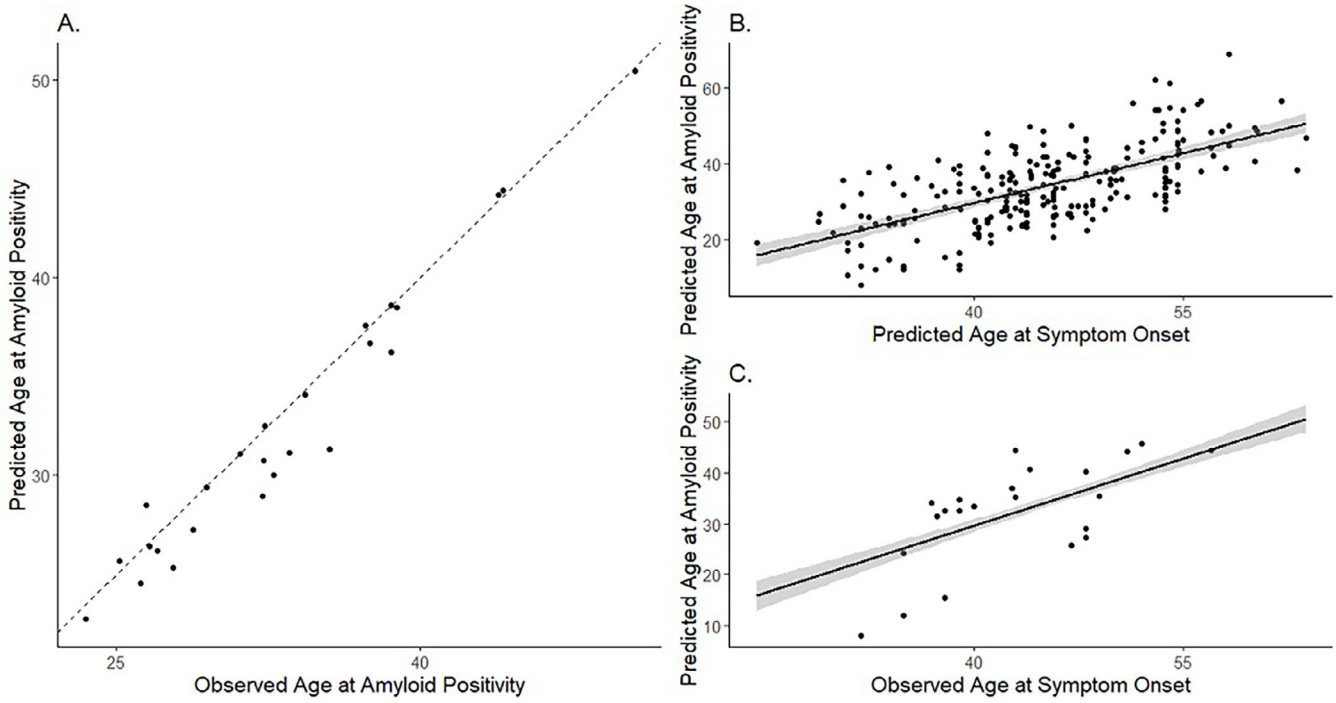

Figure 2. In individuals who convert from amyloid negative to amyloid positive during study enrollment (N = 28) we observe a mean average error in model prediction of 1.15 years (A). Across the study cohort, using the predicted conversion to symptomatic Alzheimer Disease (AD) age, we find that the model predicted age at amyloid positivity explains 39% of the variance in symptom onset (B); however, when we limit to cohort to only include participants who convert from asymptomatic to symptomatic AD during study enrollment, we observe a high correspondance between age at amyloid positive and age at symptom onset, with a roughly 10 years elapsing between when individuals become amyloid positive and when they become symptomatic (C).

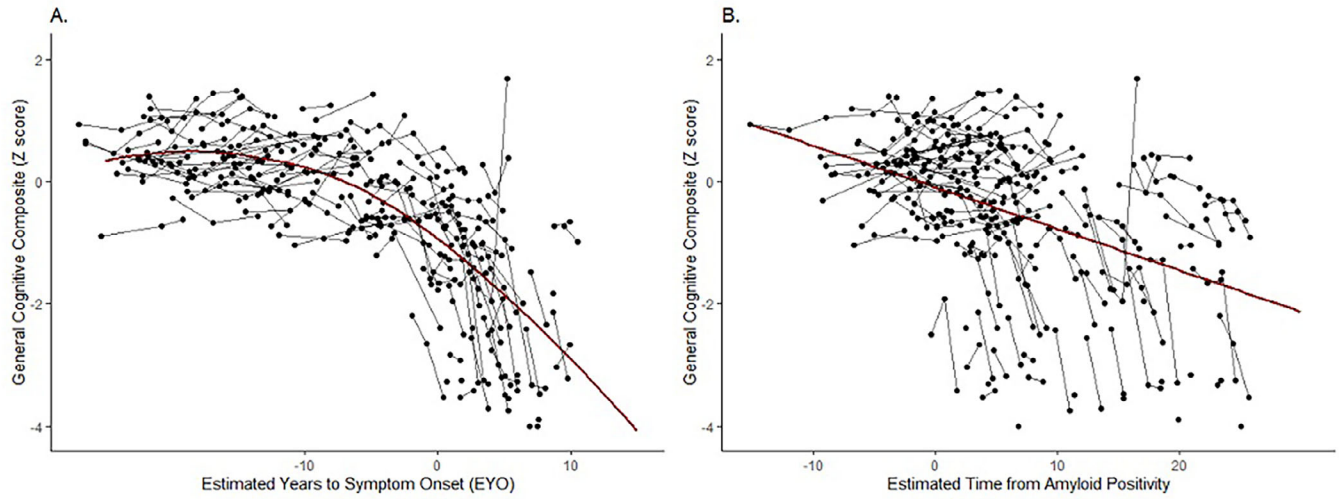

Figure 3. Performance on a general cognitive composite reliable declines around the time of symptom onset in individuals with Autosomal Dominant Alzheimer Disease (A). Cognitive performance does decline after individuals have converted to amyloid positive; however, there is a greater degree of heterogeneity (B).