

Amyloid-Beta Progression and Cognitive Performance in Marmosets with Autosomal Dominant Alzheimer's Disease PSEN1 mutations

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INTRODUCTION

Fundamental questions remain about the key mechanisms that initiate Alzheimer's disease (AD), the factors that promote its progression, and the relationship with cognitive impairment.

Therapeutic interventions that are successful at clearing amyloid plaque accumulation, fail to rescue and prevent cognitive decline.

To understand the association between amyloid burden and cognitive decline, we are studying marmosets that carry a C410Y point mutation in the presenilin-1 (PSEN1) gene that confers early onset AD in human carriers, and the association of cognitive function with amyloid progression measured by fluid and neuroimaging biomarkers.

METHODS

N=17 male and female marmosets carrying the C410Y mutation in the PSEN1 gene (F1 and F2 generation) and their age-and sex-matched non-carrier (WT) controls are studied longitudinally from birth throughout their lifespan as part of the NIA-funded MARMO-AD consortium (*Homanics, Park, Bailey et al., 2024*).

Beginning at 6-weeks of age and at 6-month intervals, plasma biomarkers of Aβ₁₋₄₀, Aβ₁₋₄₂, total tau, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) are analyzed using MesoScale Discovery multiplex ELISAs.

Marmosets were trained on a cognitive testing battery that was adapted from CANTAB using a touchscreen mounted to their homepage (Lafayette Instruments; see *Murai & Bailey et al 2024*) in daily 20-30 min testing sessions that included tests of spatial working memory and reversal learning (delayed-match and delayed-non-match-to-position), visual recognition memory (trial unique match to sample), and attention (serial reaction time task).

Amyloid uptake was measured longitudinally with ¹¹C-PiB-PET. Animals were fasted and anesthetized prior to ligand injection and scan start. Animals received an average dose of 18.5 MBq of ¹¹C-Pittsburgh Compound B (PiB) via catheter in either the lateral tail vein or saphenous vein. Acquisitions were acquired for 90 minutes post-injection using a Bruker SI-78 PET/CT scanner. Reconstructed datasets were analyzed using PMOD v.4.5. (for detailed PiB protocol information contact Leila Letica: LEL97@pitt.edu)

SUMMARY

PSEN1-C410Y mutation carriers show significantly elevated plasma Aβ₄₂:Aβ₄₀ ratios relative to age-matched non-carriers as early as 1.5 months of age, which is in line with human PSEN1 mutation carriers in adolescence.

There were no differences in plasma GFAP, NfL, or total tau levels up to 3.5 years of age, which corresponds to a 30-year-old human. We have begun observing aging-dependent increases in GFAP and NfL in marmosets >5 years of age and longitudinal studies are in progress as subjects continue to age.

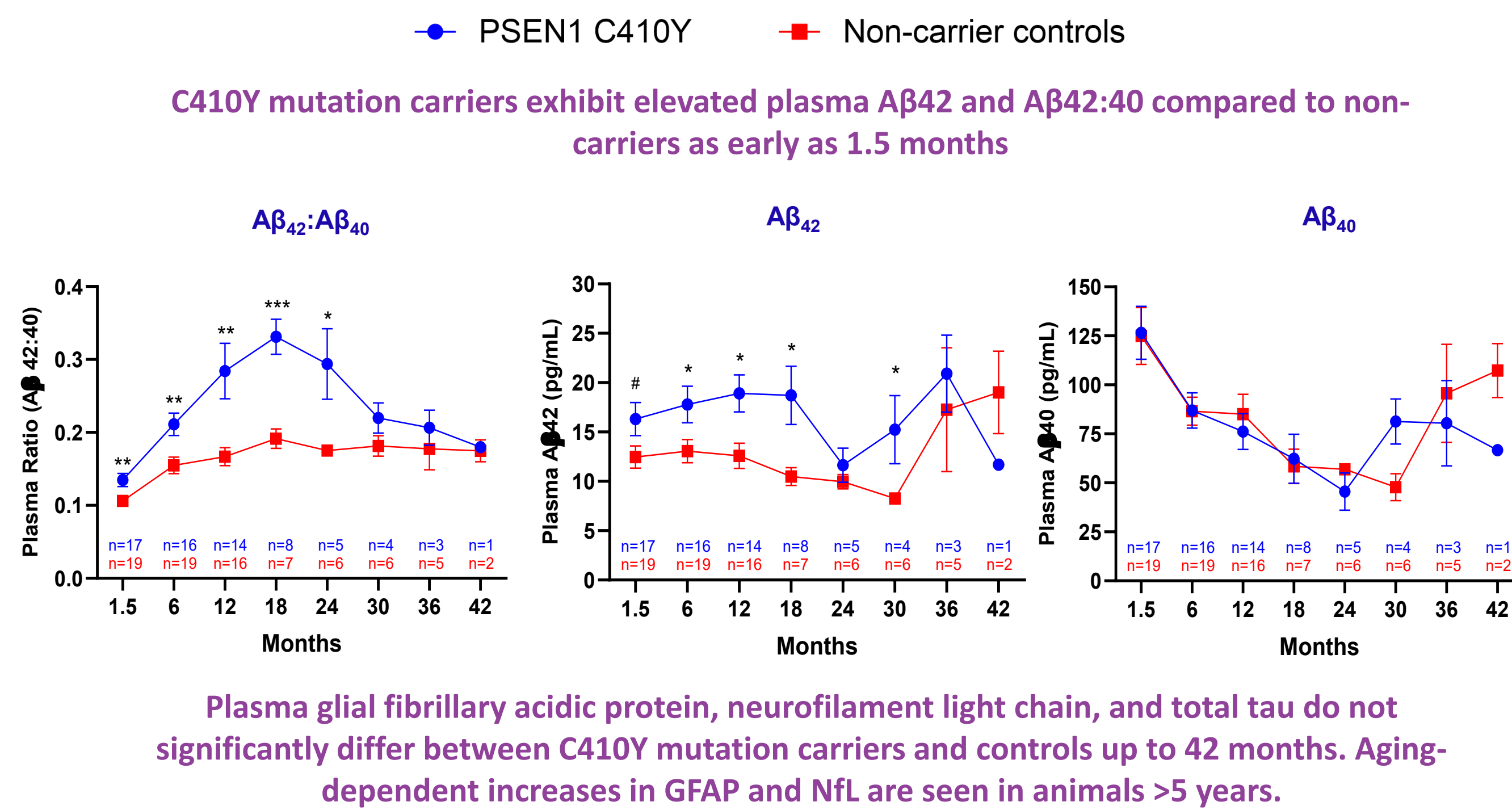
PSEN1-C410Y mutation carriers exhibit an age-dependent increase in ¹¹C-PiB retention, indicating greater Aβ accumulation. Regional analysis of the overall delta change in ligand binding shows that areas associated with AD pathology, such as the PFC and Hippocampal Formation, experience increased ligand uptake in F1 generation compared to age-matched controls.

PSEN1-C410Y and age-matched control animals exhibit similar performance across cognitive tests, despite significantly elevated plasma Aβ₄₂:Aβ₄₀ ratios. No significant correlations were observed between plasma Aβ₄₂:Aβ₄₀ ratios, or measures of learning (task acquisition), cognitive flexibility, working memory capacity, or attention.

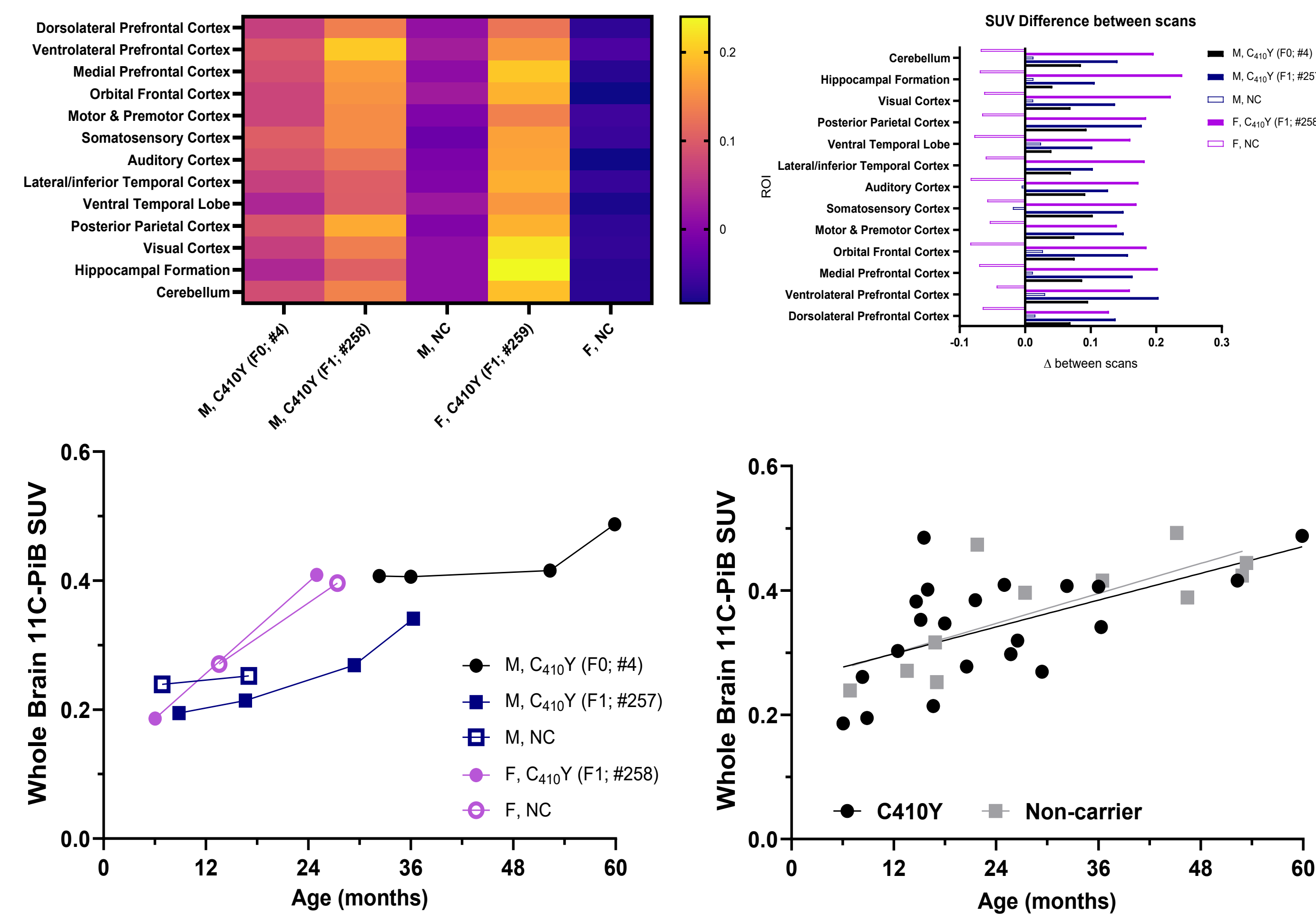
These studies highlight the importance of studying PSEN1 mutation carriers before disease onset. These findings demonstrate disease-relevant amyloid trajectories and post-mortem plaque pathology in the absence of cognitive impairment, modeling early AD-related pathology prior to cognitive decline.

RESULTS

Plasma Biomarker Trajectories of PSEN1-C410Y Mutation Carriers and Non-Carrier Controls from Infancy through Adulthood



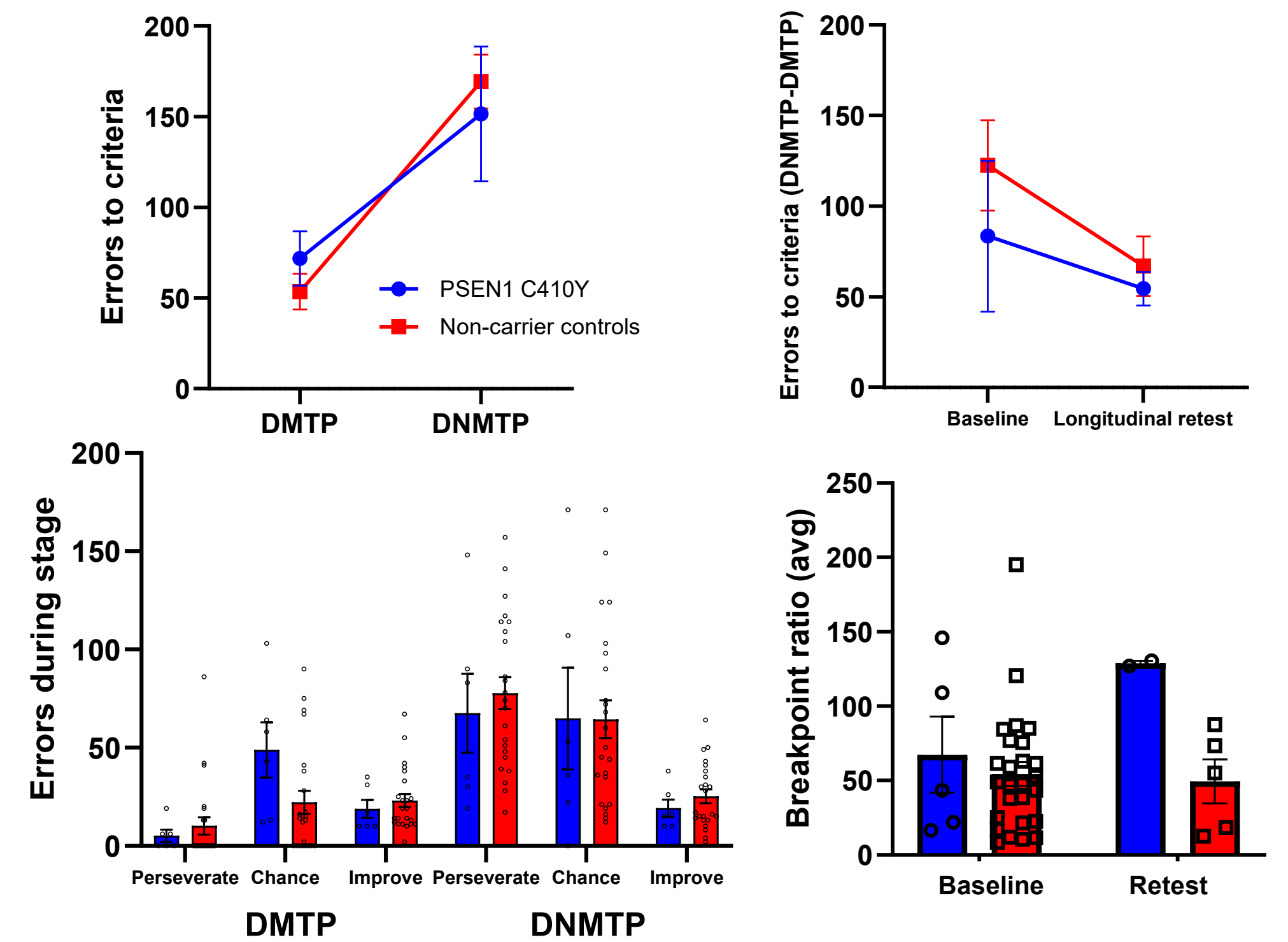
Amyloid Uptake Measured by ¹¹C-PiB-PET



Touchscreen Testing Battery for Marmosets

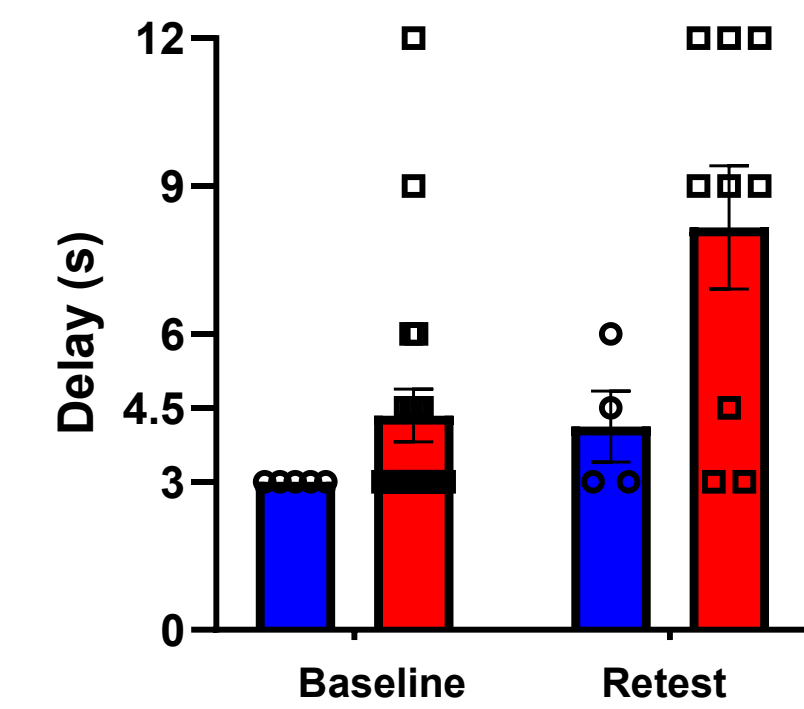


No significant differences in errors to criteria of DMTP/DNMTP reversal in C410Y mutation carriers relative to non-carriers across baseline and annual longitudinal retest, with no difference in progressive ratio motivation

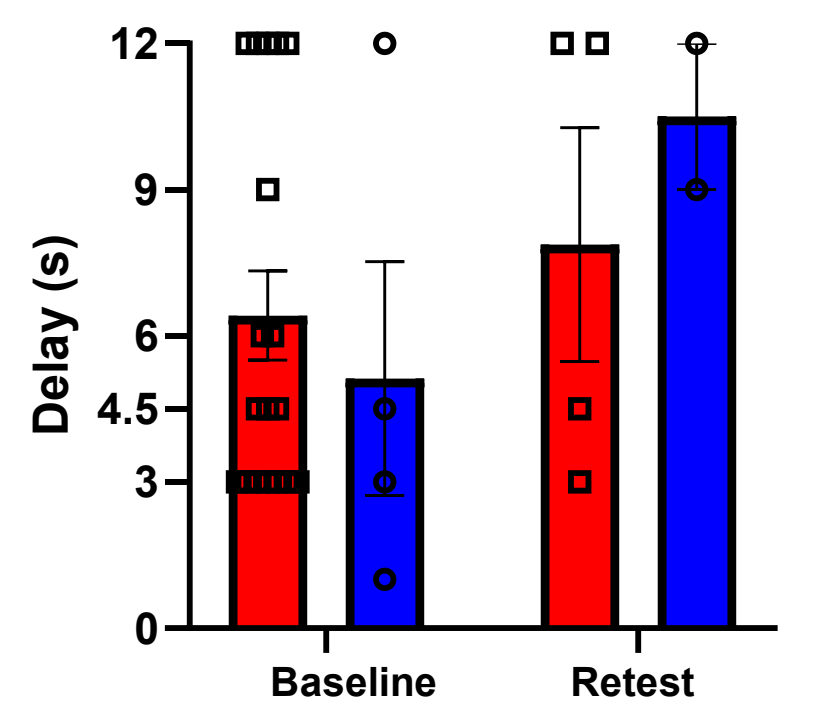


C410Y mutation carriers show similar spatial working (DNMTP) and visual recognition (TUMS) memory thresholds relative to non-carriers up to 3.5 years of age

Spatial Working Memory Threshold



Visual Recognition Memory Threshold



Stimulus duration dependent reductions in accuracy with increased omissions is comparable in C410Y mutation carriers and non-carriers as measured in the 4-choice serial reaction time task

