

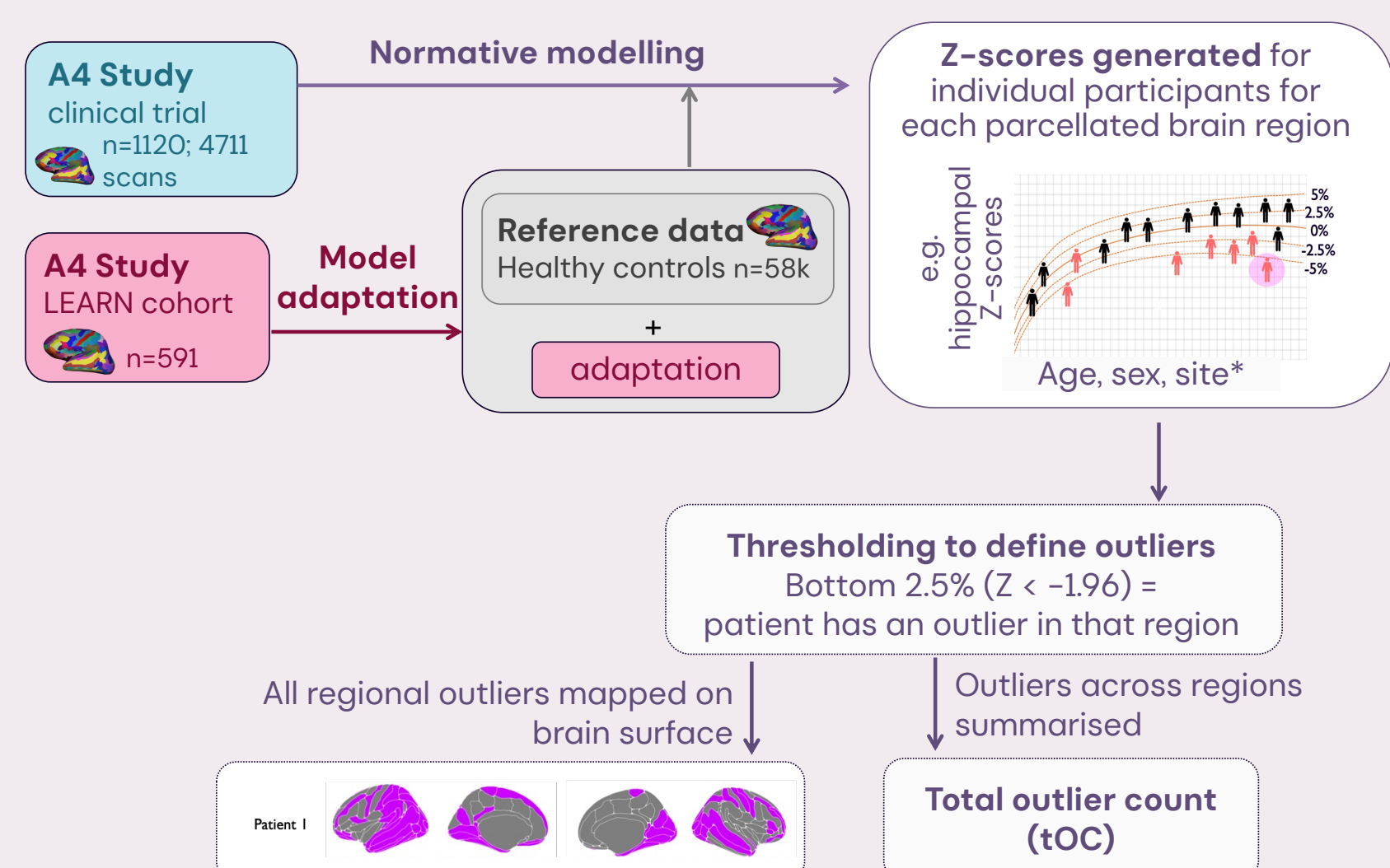
Individualised measures of neuroanatomical heterogeneity (derived from normative modelling) may have utility for participant stratification and outcome assessment in Alzheimer's disease clinical trials.

INTRODUCTION

- Alzheimer's disease is highly heterogeneous in both clinical presentation and neurobiology (Verdi *et al.*, 2021).
- Group-average trial analyses may overlook treatment-responsive individuals.
- Neuroanatomical normative modelling reveals substantial individual variability in Alzheimer's disease (Verdi *et al.*, 2023; Verdi *et al.*, 2024).
- We apply this framework to a preclinical Alzheimer's disease trial cohort to assess whether neuroanatomical heterogeneity may have influenced trial outcomes.

METHODS

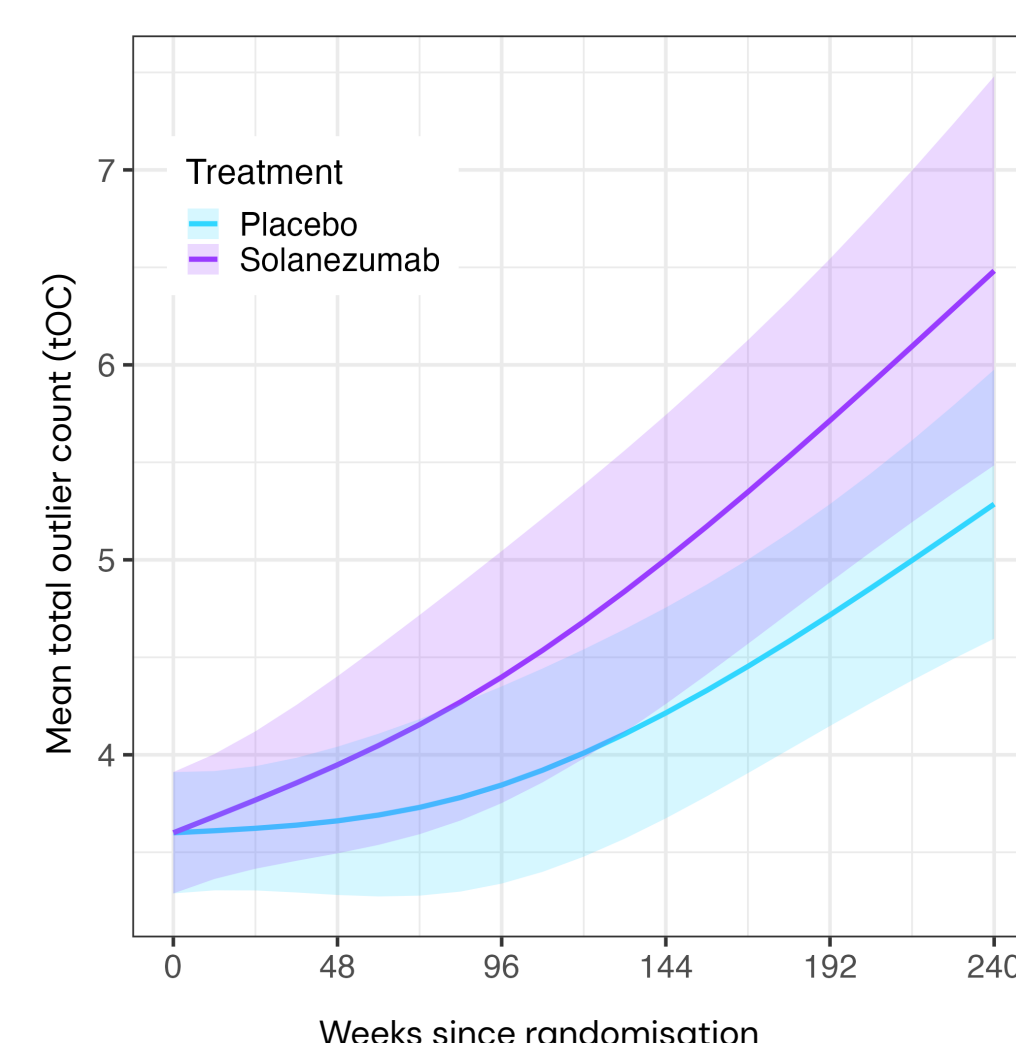
- A4 Study: 1,120 cognitively unimpaired, amyloid-positive adults (65–85 years) randomised to solanezumab or placebo.
- Serial 3T T1-weighted MRI scans acquired over 240wks. **Cortical thickness and subcortical volumes** extracted using FreeSurfer.
- Normative models** were trained on ~58k healthy controls using warped Bayesian regression, accounting for age, sex, & site.
- Individual regional Z-scores were generated for 4,711 MRI scans.
- Regions with $Z < -1.96$ were classified as **outliers** and summarised as **total outlier count (tOC)**.
- Longitudinal trajectories of cognition (PACC), total outlier count (tOC), and Hamming dissimilarity were assessed using mixed-effects models with nonlinear time effects, adjusting for demographic and disease-related covariates.



RESULTS

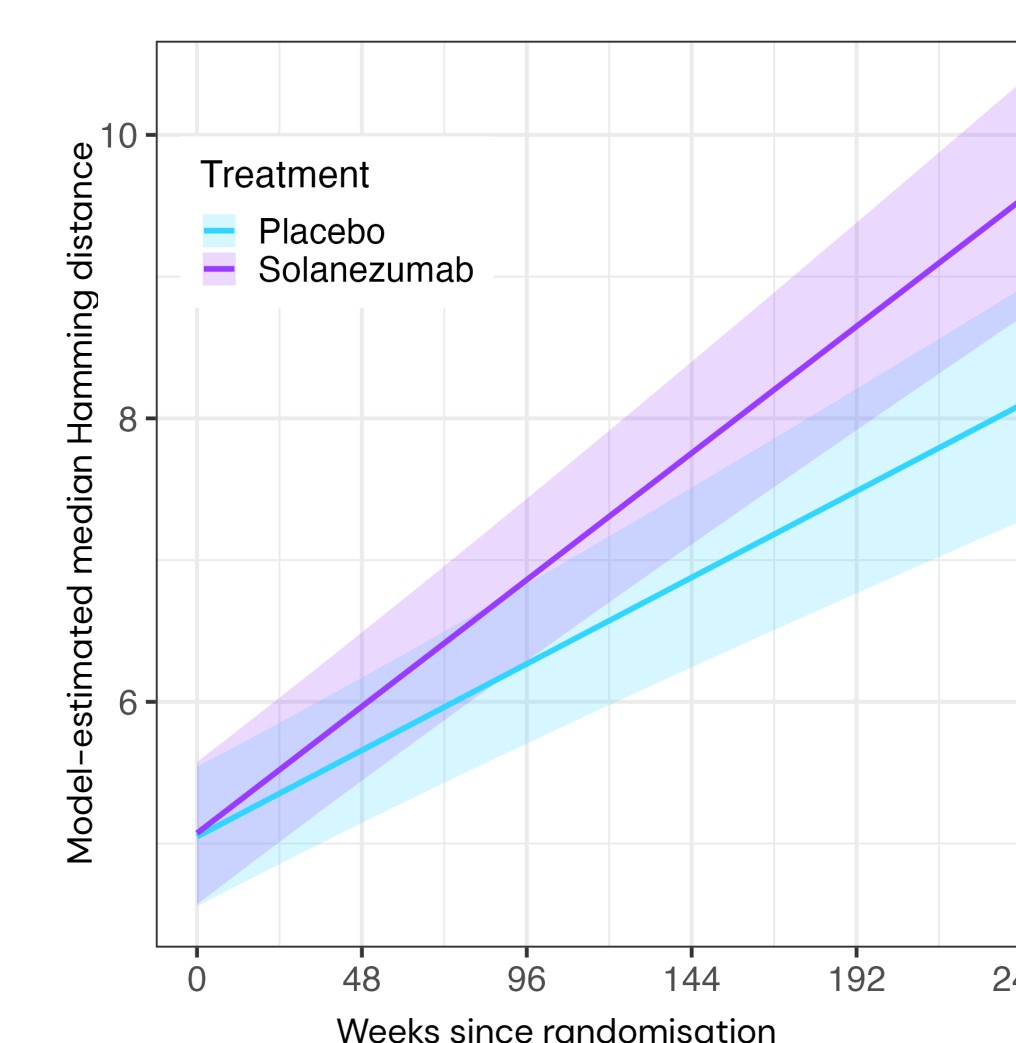
	Placebo	Solanezumab	Statistical differences
N	562	558	-
Age, years	72.1 (5.0)	72.1 (4.6)	p= 0.921, d = -0.01 [-0.12, 0.11]
Age range, years	65 – 86	65 – 86	-
Female, n (%)	343 (61.0%)	324 (58.1%)	p= 0.312, V = 0.00 [0.00, 1.00]
Male, n (%)	219 (39.0%)	234 (41.9%)	-
Education, years	16.6 (2.9)	16.6 (2.7)	p= 0.972, d = -0.00 [-0.12, 0.12]
APOE4 carrier, n (%)	329 (58.5%)	332 (59.5%)	p= 0.745, V = 0.00 [0.00, 1.00]
Baseline florbetapir SUVR	1.33 (0.17)	1.33 (0.18)	p = 0.774, d = -0.02 [-0.13, 0.10]
Baseline PACC	-1.2 (2.4)	-1.2 (2.5)	p= 0.66, d = 0.03 [-0.09, 0.14]
Baseline tOC	3.48 (5.14)	3.74 (6.03)	-
Baseline tOC, median (IQR)	2.0 (5.0)	2.0 (4.0)	p= 0.964, r = 0.00 [-0.07, 0.07]
Any baseline tOC (tOC > 0), n (%)	391 (69.6%)	397 (71.1%)	p= 0.564, V = 0.00 [0.00, 1.00]

A) Differences in neuroanatomical heterogeneity between treatment arms during trial course



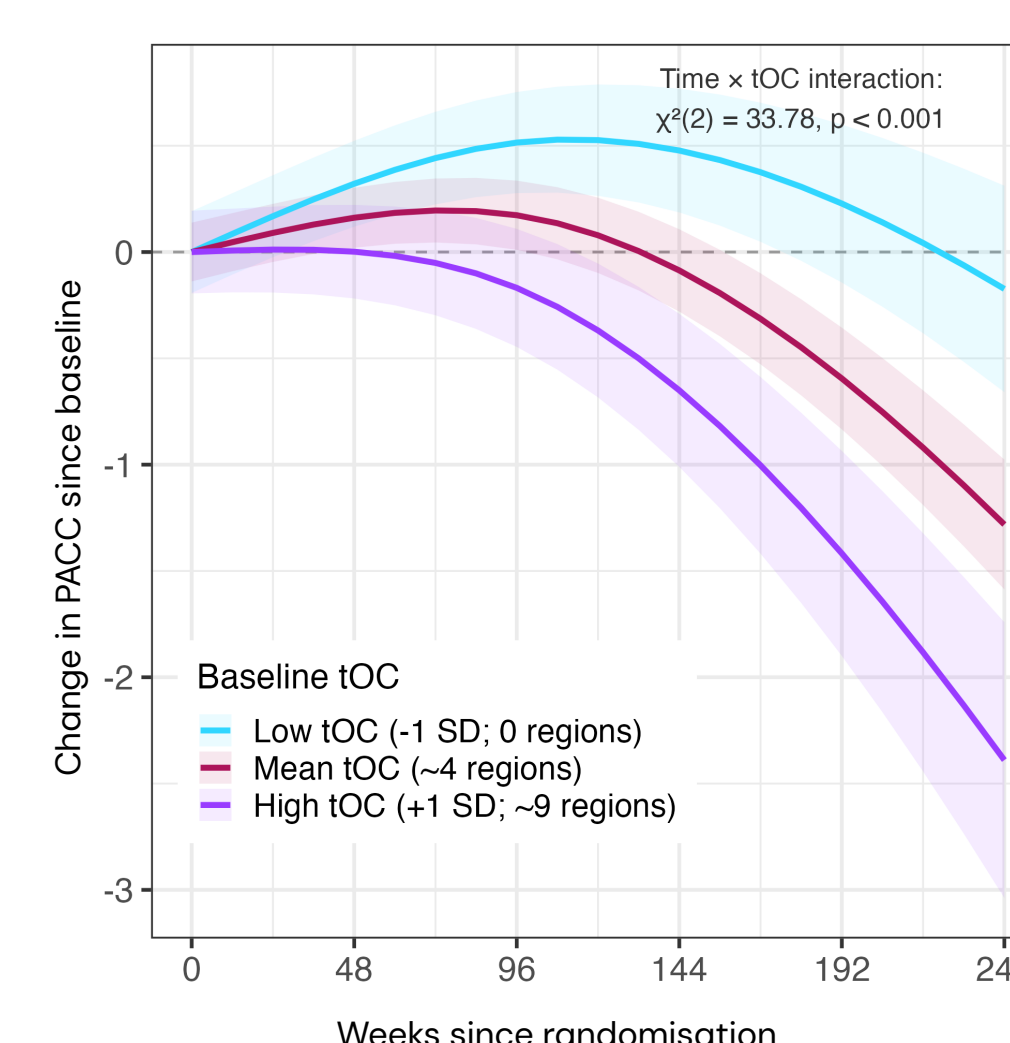
tOC increased in both treatment groups ($p < 0.001$), with higher model-estimated tOC in the solanezumab arm at week 240 ($\Delta = 1.20$, 95%CI 0.01–2.39, $p = 0.049$).

B) Individual neuroanatomical outlier dissimilarity in treatment arms during trial course



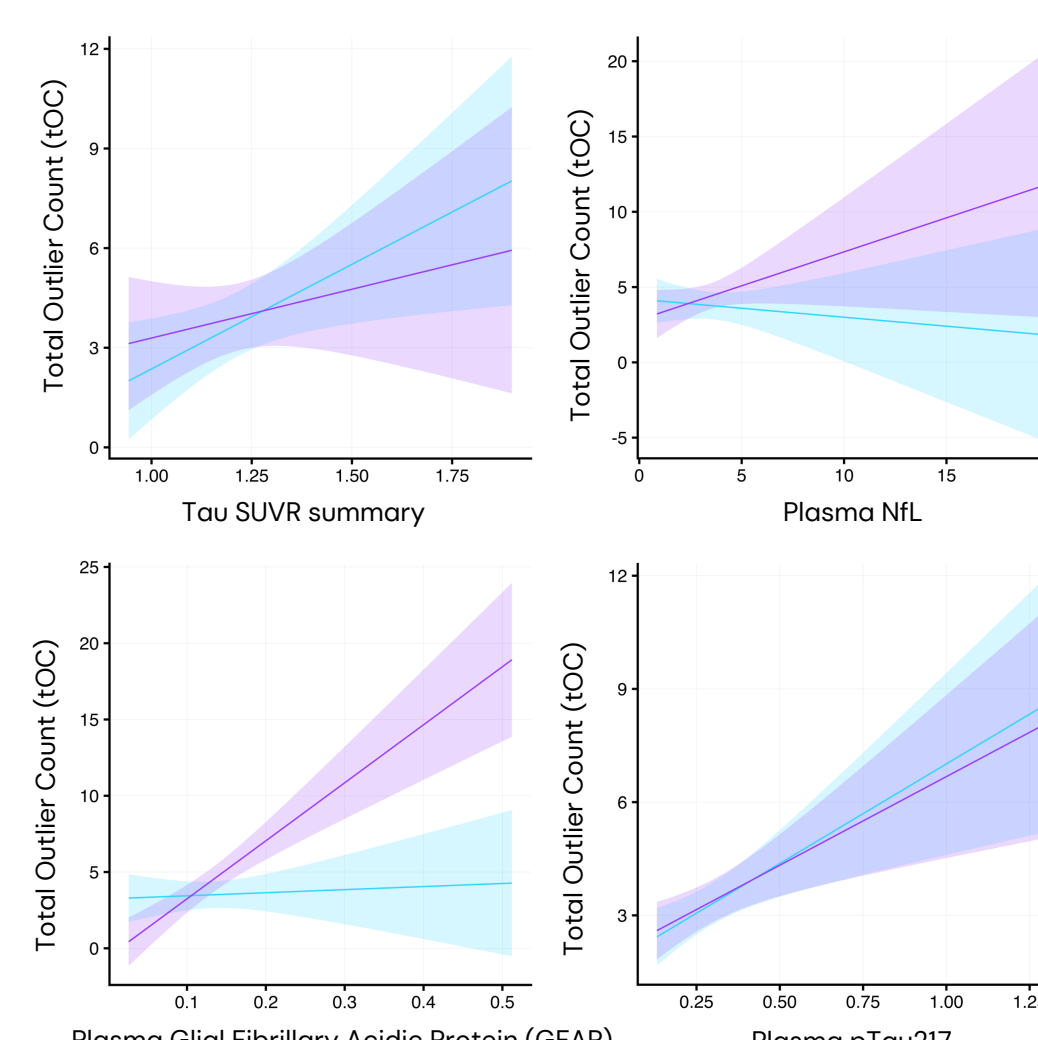
Hamming dissimilarity increased over follow-up ($\beta = 0.013$, $p < 0.001$) and more rapidly in the solanezumab group than placebo (time $\times$ treatment: $\beta = 0.006$, $p = 0.002$).

C) Greater neuroanatomical heterogeneity at baseline associate with cognitive decline



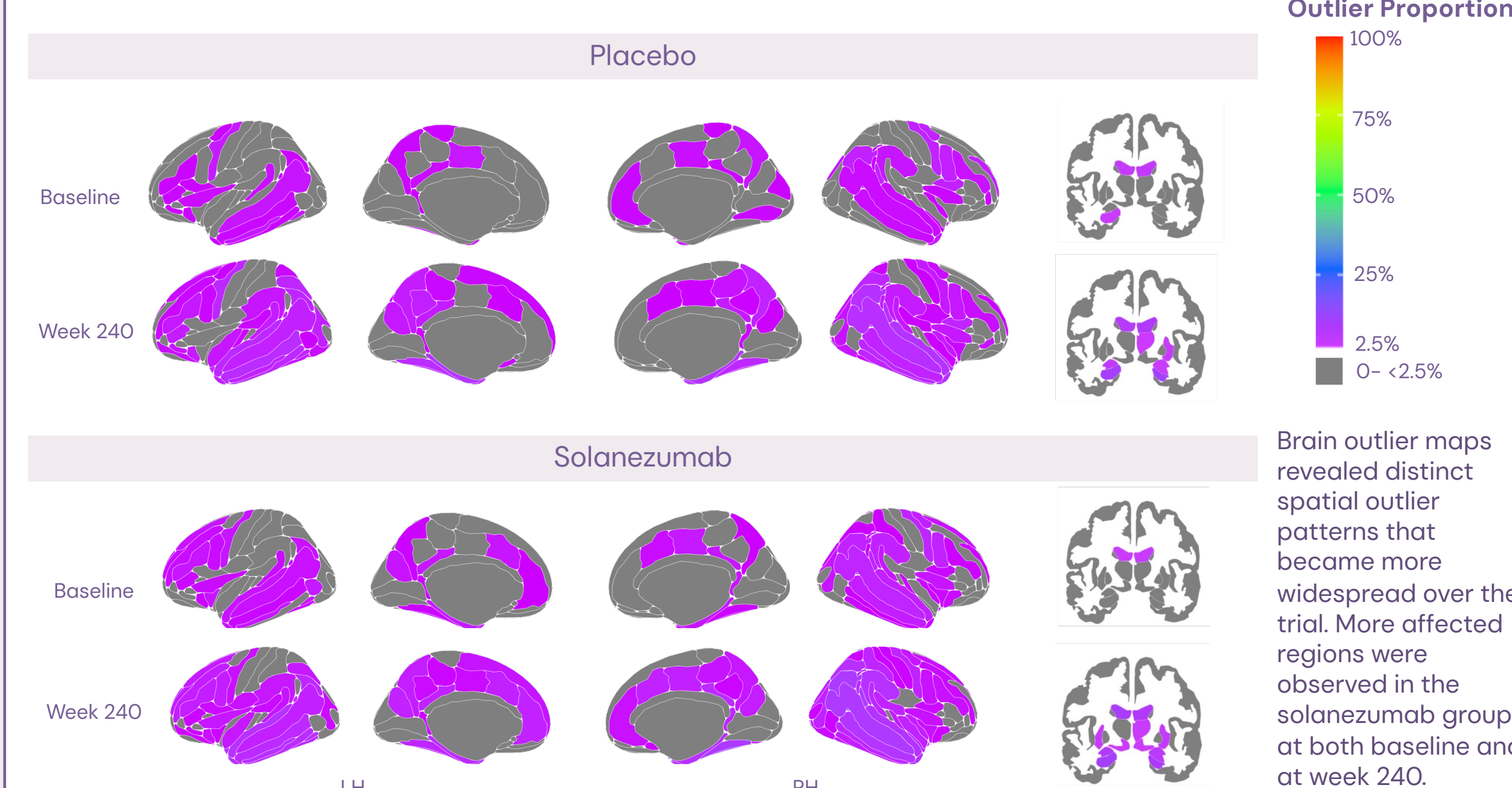
Model-estimated cognitive trajectories diverged according to baseline tOC, with greater decline observed in participants with higher baseline tOC (time $\times$ tOC: $\chi^2(2) = 33.78$, $p < 0.001$).

D) Greater neuroanatomical heterogeneity is associated with markers of AD pathology at baseline



Baseline tOC associated with tau PET SUVR ($\beta = 6.30$, $p = 0.020$) and CSF pTau217 ($\beta = 5.27$, $p = 0.002$), but not plasma NfL or GFAP. GFAP and baseline tOC differed by treatment group (GFAP $\times$ treatment interaction: $\beta = 36.02$, $p < 0.001$).

E) Brain outlier maps by treatment arm assignment



Brain outlier maps revealed distinct spatial outlier patterns that became more widespread over the trial. More affected regions were observed in the solanezumab group at both baseline and at week 240.



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