

α -Synuclein Positivity and Brain Microstructural Decline in the Alzheimer's Disease Spectrum

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BACKGROUND

- α -Synuclein co-pathology occurs in up to 50% of Alzheimer's disease (AD) cases and may contribute to clinical heterogeneity.
- α -synuclein seed amplification assay (SAA) enables sensitive, specific *in vivo* detection of Lewy body pathology from CSF.
- Diffusion tensor imaging (DTI; FA, MD) captures white and gray matter microstructural integrity, but how α -synuclein shapes microstructure, independent of and interacting with AD pathology, is still unknown.

OBJECTIVES

- Determine whether SAA+ status is associated with microstructural change, cross-sectionally and longitudinally.
- Assess whether α -synuclein effects persist after accounting for and interacting with AD biomarker burden.

METHODS

- ADNI participants with CSF α -synuclein SAA, diffusion MRI, and AD biomarkers (SAA+ n=115, SAA- n=453).

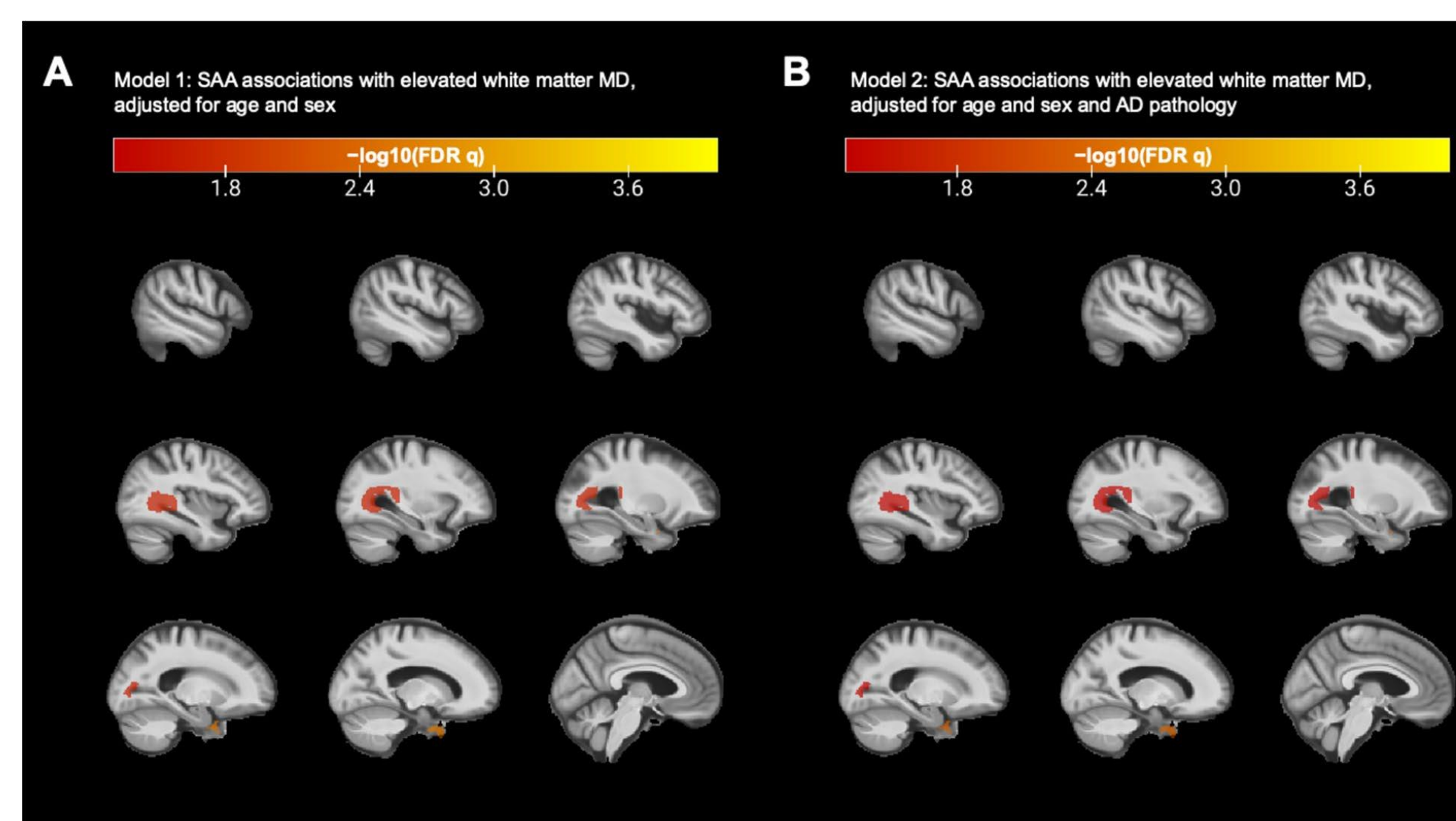
Characteristic	Cognitively unimpaired			Cognitively impaired		
	SAA-	SAA+	p	SAA-	SAA+	p
Age, yrs	72.6 (6.7)	76.1 (6.1)	0.001	73.4 (8.1)	74.5 (7.6)	0.3
Female, n (%)	149 (65%)	21 (47%)	0.02	88 (40%)	30 (43%)	0.6
Education, yrs	16.8 (2.2)	17.1 (2.3)	0.5	15.9 (2.6)	16.0 (2.5)	0.8
MMSE	29.1 (1.1)	29.2 (1.1)	0.5	26.2 (3.9)	24.4 (4.2)	0.001
CDR-SB	0.1 (0.3)	0.1 (0.3)	0.4	2.5 (2.4)	3.6 (2.7)	<0.001

- FA and MD extracted from white matter (JHU, 39 ROIs) and gray matter (MCALT, 51 ROIs), harmonized via ComBat.
- Analyses: linear regression models and LME models with random intercepts, both adjusted for age, sex, AD pathology (CSF p-tau181/A β 42).
- FDR correction (q<0.05) applied across ROIs; results were visualized using ggeffects and brain overlays.

RESULTS

CROSS-SECTIONAL FINDINGS

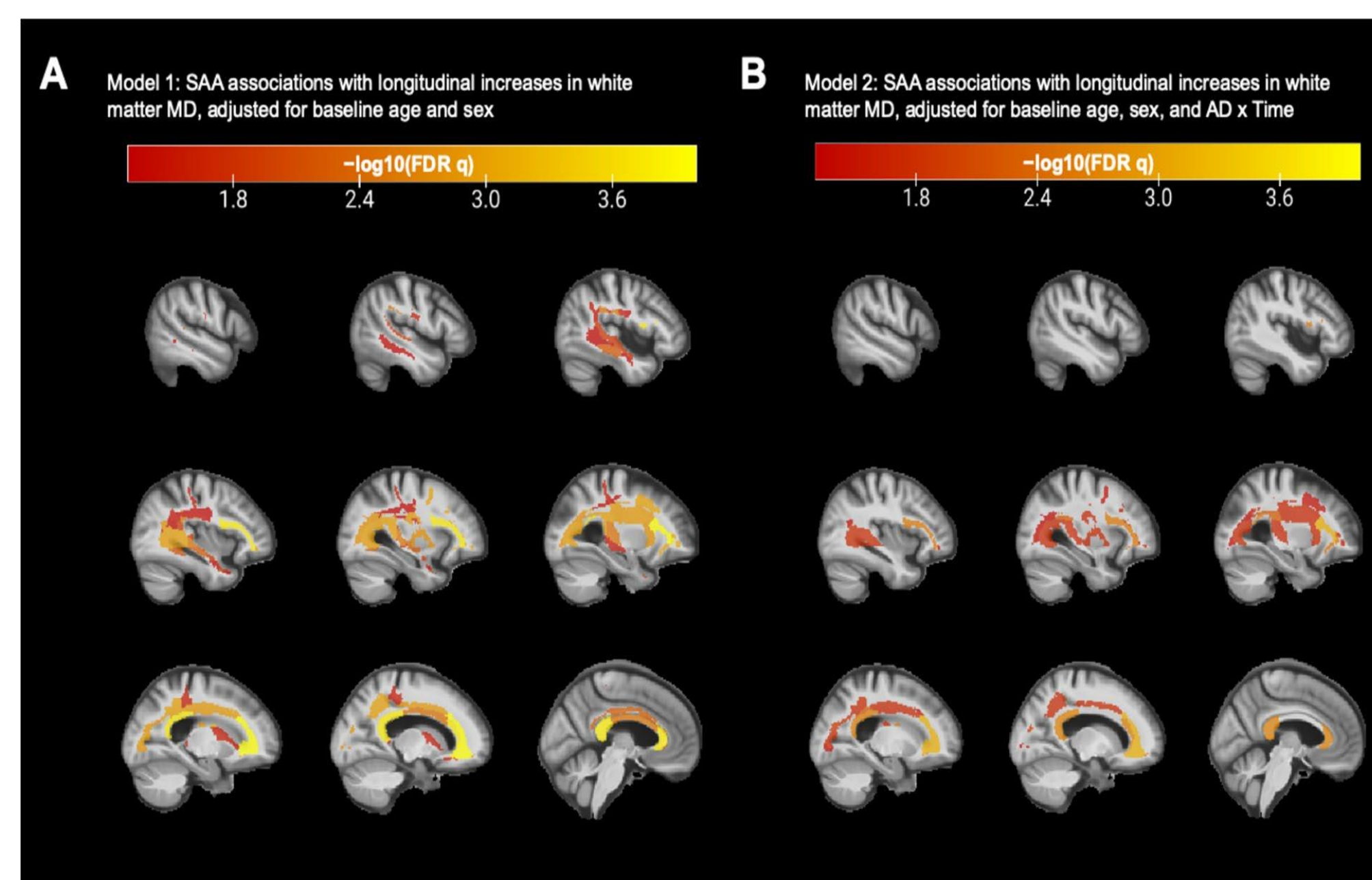
- SAA+ CI participants showed higher white matter MD in entorhinal white matter and posterior thalamic radiation vs SAA- (FDR q<0.05). Effects persisted after adjusting for AD pathology (CSF p-tau181/A β 42).
- No significant FA differences detected in CI and CU.



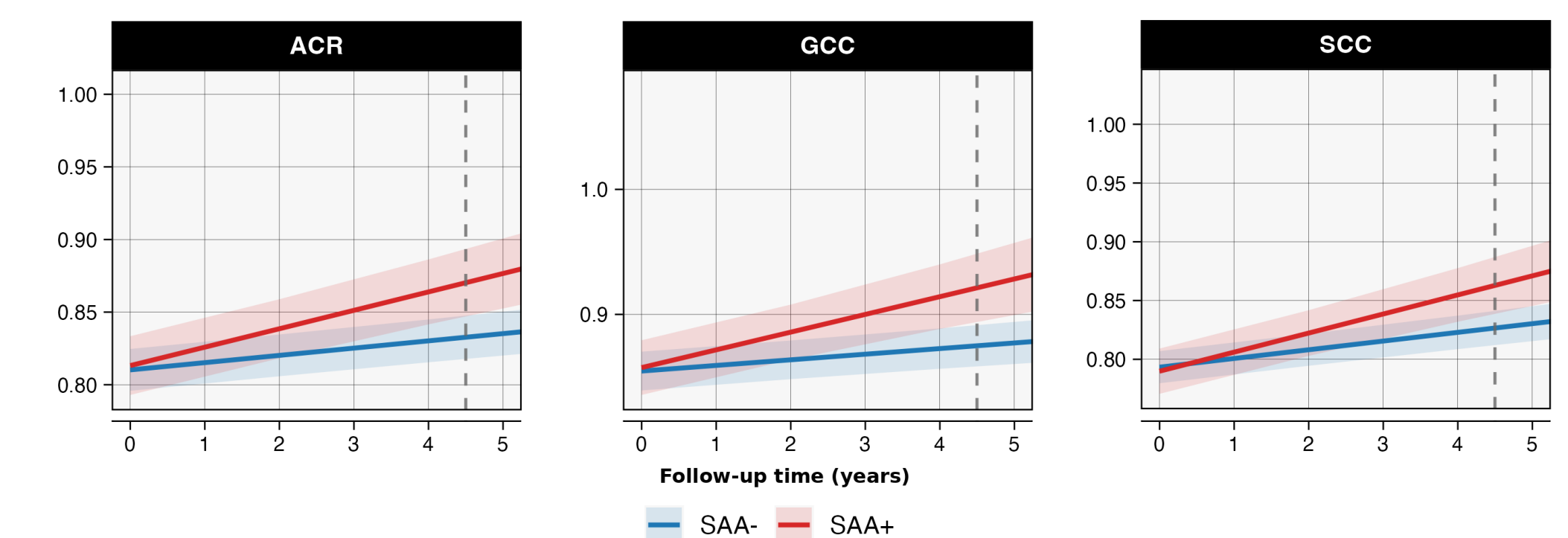
Brain overlays of regional white matter MD associations with SAA status in the CI group (FDR q< 0.05).

LONGITUDINAL FINDINGS

- SAA+ CI: accelerated MD increases across 27/39 tracts (69.2%), strongest in genu/splenium of corpus callosum and anterior corona radiata. After AD pathology adjustment, effects remained in 15/39 tracts (38.5%).



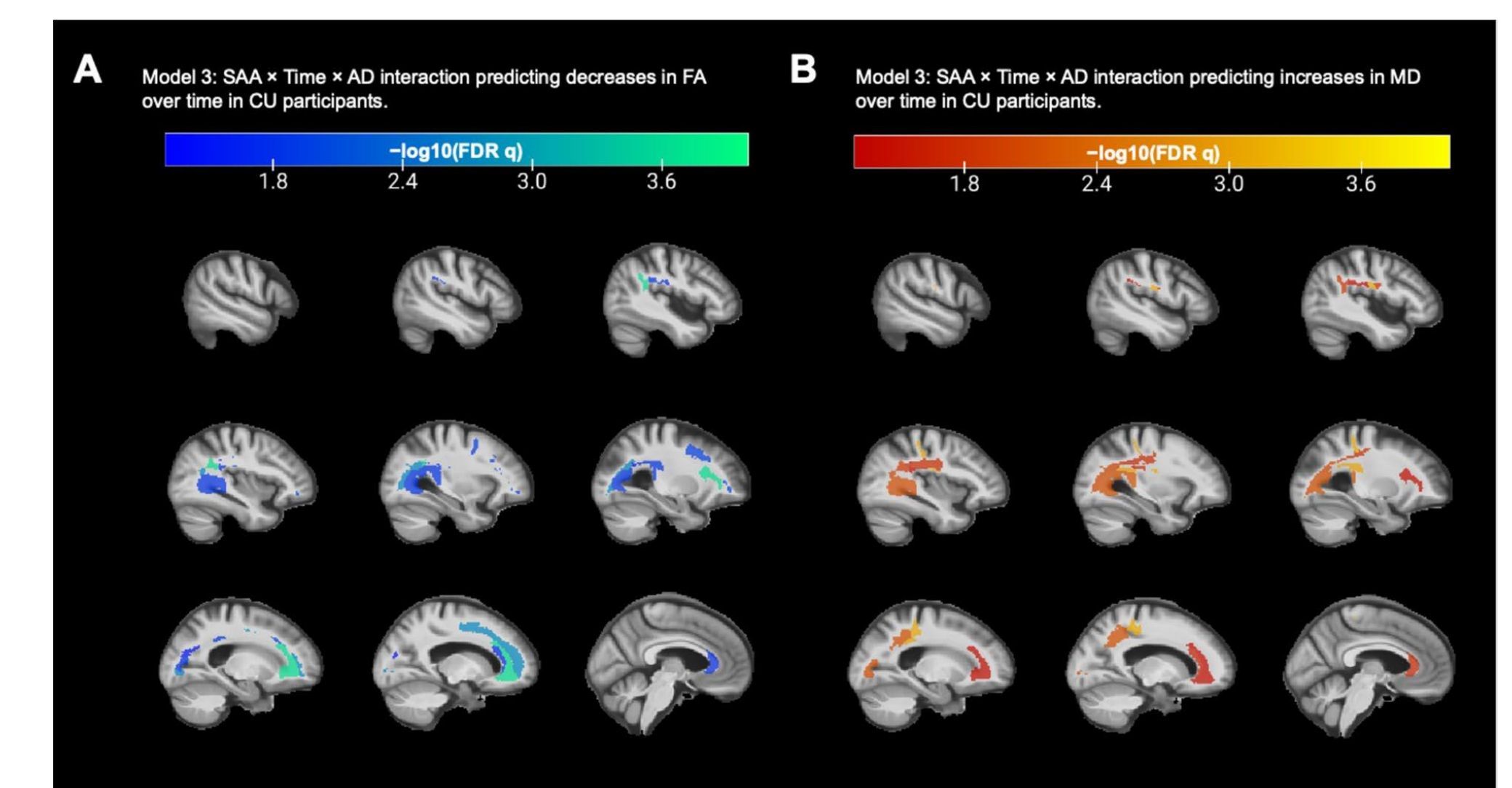
Brain overlays showing that CI SAA+ had increased white matter MD over time relative to SAA- (FDR q<0.05).



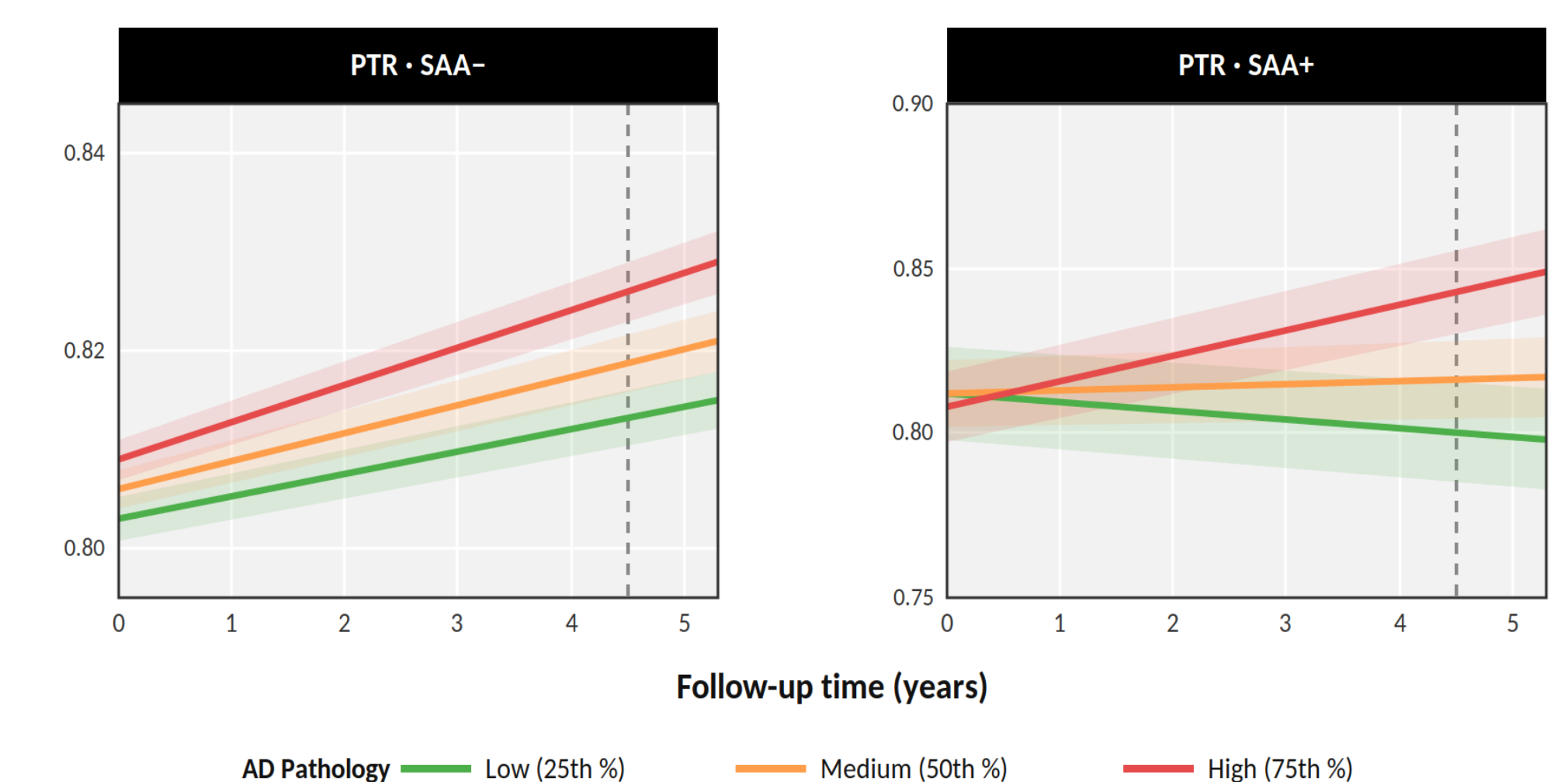
Predicted longitudinal MD trajectories in SAA- and SAA+ for the three ROIs showing significant group $\times$ time interactions (FDR q<0.05).

A-SYNUCLEIN SAA $\times$ AD $\times$ TIME

- Higher baseline AD pathology (CSF p-tau181/A β 42) accelerated white matter FA decline and MD increase over time, but this was only in SAA+ individuals.
- SAA- individuals showed stable trajectories regardless of AD pathology levels.



Brain overlays of the SAA $\times$ AD pathology $\times$ time interaction on white matter changes in the CU group (FDR q<0.05).



Predicted longitudinal MD trajectories in the posterior thalamic radiation by AD pathology tertile (low/medium/high) in SAA- and SAA+.

α -Synuclein SAA positivity is associated with progressive white matter decline in cognitively impaired individuals and may influence AD-related WM decline in cognitively unimpaired individuals, suggesting that α -synuclein acts as a modifier of disease progression across the AD spectrum.