

A Proteomic Signature Of Cognitive Resilience Reveals Synaptic Preservation Against Amyloid And Tau Clocks

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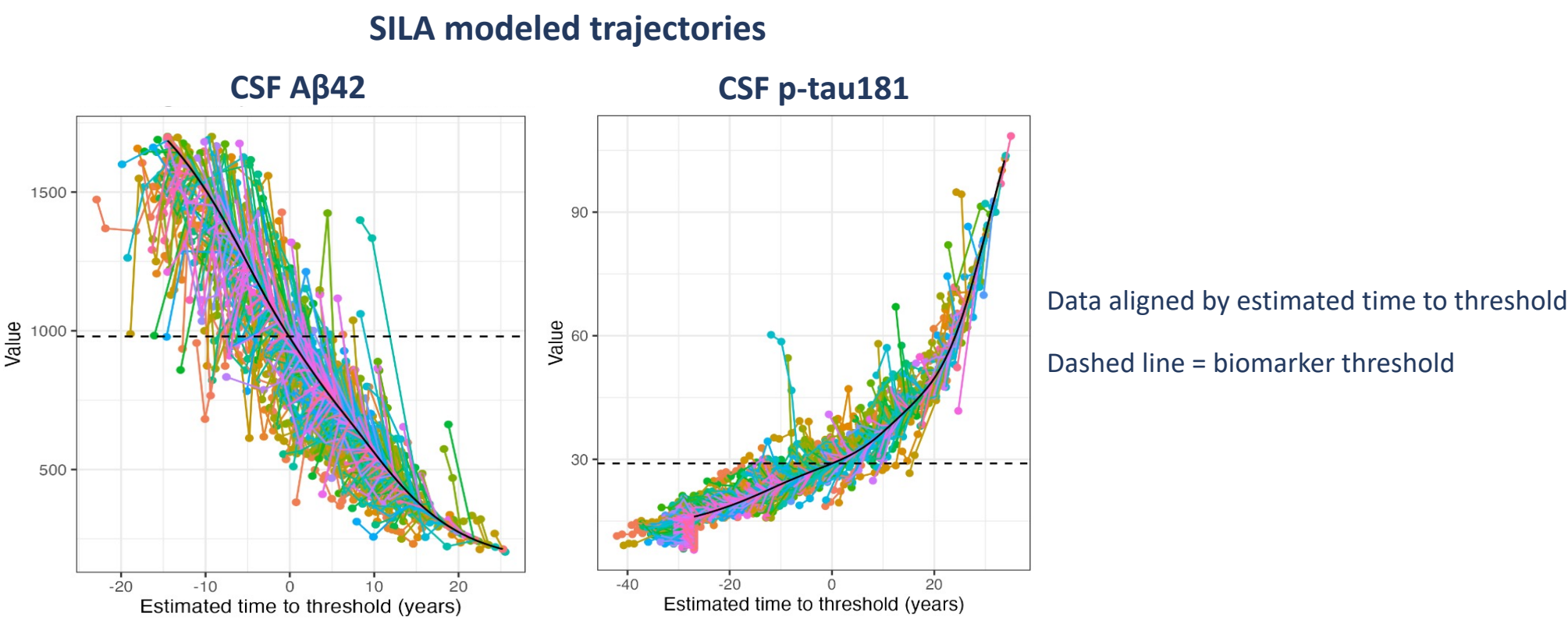
Background

- Cognitive resilience (CR) in Alzheimer’s disease (AD) refers to maintaining cognitive performance relatively well considering the level of brain pathologies such as amyloid- β (A β) and tau.
- Amyloid and tau disease clocks provide individualized estimates of disease progression, enabling CR to be quantified as better- or worse-than-expected cognition for a given stage of pathology.
- CSF proteomics enables the identification of pathways associated with CR by capturing proteins that reflect ongoing biological processes.
- Aim: Identify a CSF proteomic signature and the biological pathways underlying CR in AD.

Sampled Iterative Local Approximation (SILA)

Longitudinal CSF A β 42 and p-Tau181 changes were modeled using SILA to reconstruct biomarker trajectories against time. Years from the time point of reaching abnormal levels of CSF A β 42 and p-Tau181 can be estimated, yielding indices of pathology chronicity and estimated age of onset of abnormal biomarker status.

Pathology chronicity (disease clock): current age – estimated age of biomarker abnormality



Sample Characteristics

CSF A β ⁺ individuals from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (discovery) and Emory’s Goizueta Alzheimer’s Disease Research Center (GADRC) (validation) were selected for this study.

	Discovery sample		Validation sample	
	CN	MCI	CN	AD
n	96	282	39	218
Age, mean (SD) in years	74.80 (5.45)	73.50 (7.18)	64.07 (8.28)	67.98 (8.91)
Sex:male (%)	34 (35.4)	172 (61.0)	8 (20.5)	90 (41.3)
Education, mean (SD) (years)	16.39 (2.56)	16.01 (2.58)	-	-
APOE4 status:positive (%)	59 (61.5)	199 (70.6)	21 (53.8)	157 (72.0)
ADAS-cog total score, mean (SD)	9.44 (4.69)	18.53 (6.68)	-	-
MoCA score, mean (SD)	-	-	26.28 (2.50)	14.68 (6.81)
CSF p-tau181 (z-scored), mean (SD)	-	-	-0.85 (0.36)	0.57 (0.96)
CSF Aβ42 (z-scored), mean (SD)	-	-	-0.40 (0.26)	-0.86 (0.34)
CSF p-tau181 chronicity, mean (SD)	-5.01 (13.62)	2.18 (14.57)	-	-
CSF Aβ42 chronicity, mean (SD)	6.78 (4.38)	8.08 (4.63)	-	-
Cortical thickness: Braak I, mean (SD)	2.51 (0.32)	2.39 (0.33)	-	-
Cortical thickness: Braak III-IV, mean (SD)	2.51 (0.12)	2.44 (0.14)	-	-
Cortical thickness: Braak V-VI mean (SD)	2.36 (0.13)	2.31 (0.12)	-	-

Methods

Cognitive Resilience

- CR was estimated as the standardized residuals from a linear regression model predicting ADAS-Cog13 from A β 42 chronicity, p-Tau181 chronicity, diagnosis, age, sex, and education.
- Residuals represent the difference between observed and expected cognitive performance at a given stage of AD pathology.

Cortical Thickness

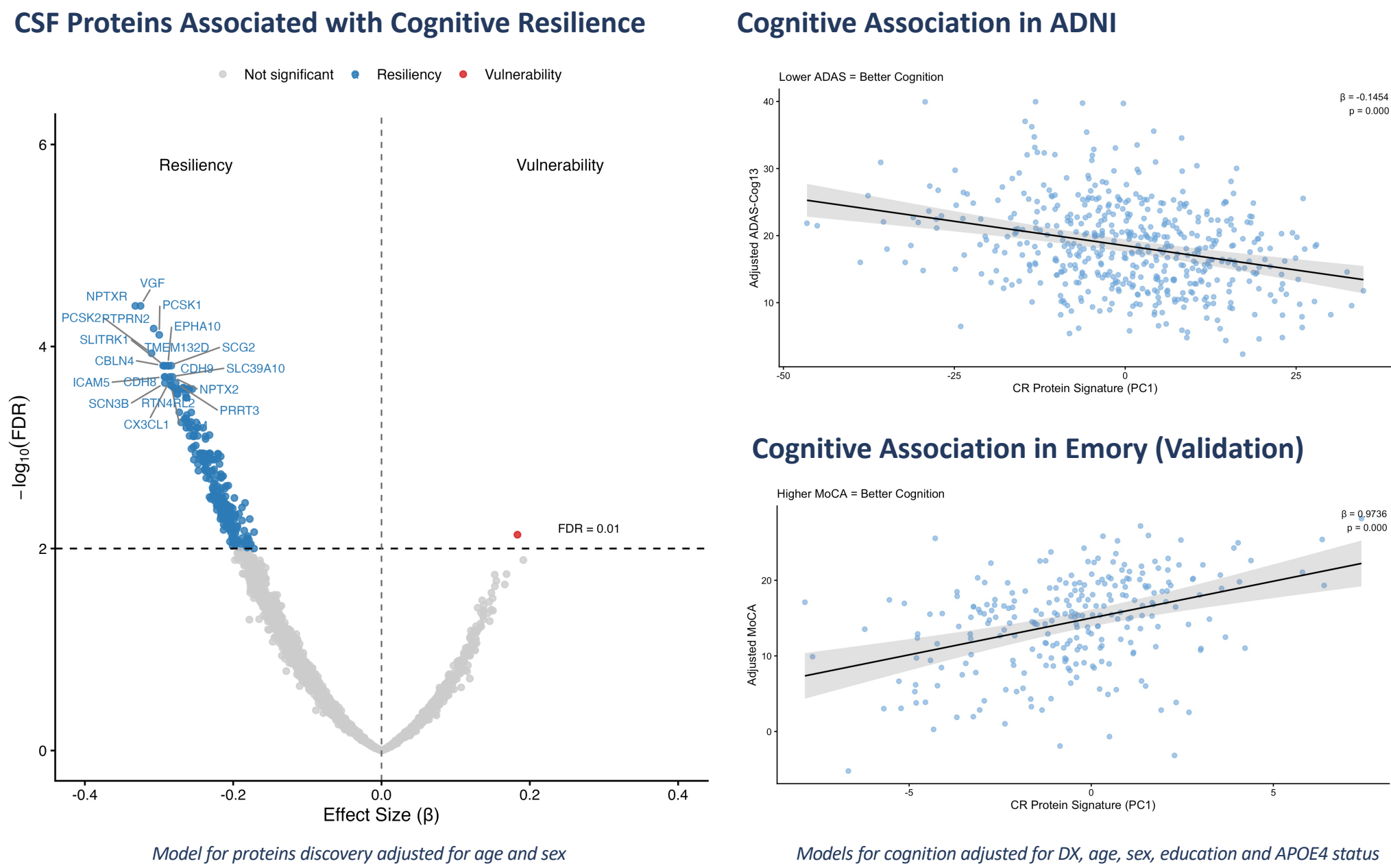
- Cortical thickness was estimated from T1-weighted MRI using CAT12. Regional cortical thickness measures were extracted using the Desikan–Killiany–Tourville (DKT) atlas and mapped to Braak stage regions.

Proteomics Characteristics

CSF tandem mass tag-based mass spectrometry (TMT-MS) proteomics was analyzed in ADNI and Emory. Following quality control and normalization, 2,250 proteins were included in the ADNI discovery analysis. Among the 265 resilience-associated proteins identified, 260 (98.1%) were also measured in Emory. Principal component analysis was applied to the identified resilience-associated proteins, and the first PC was used as the proteomic signature of CR.

Results

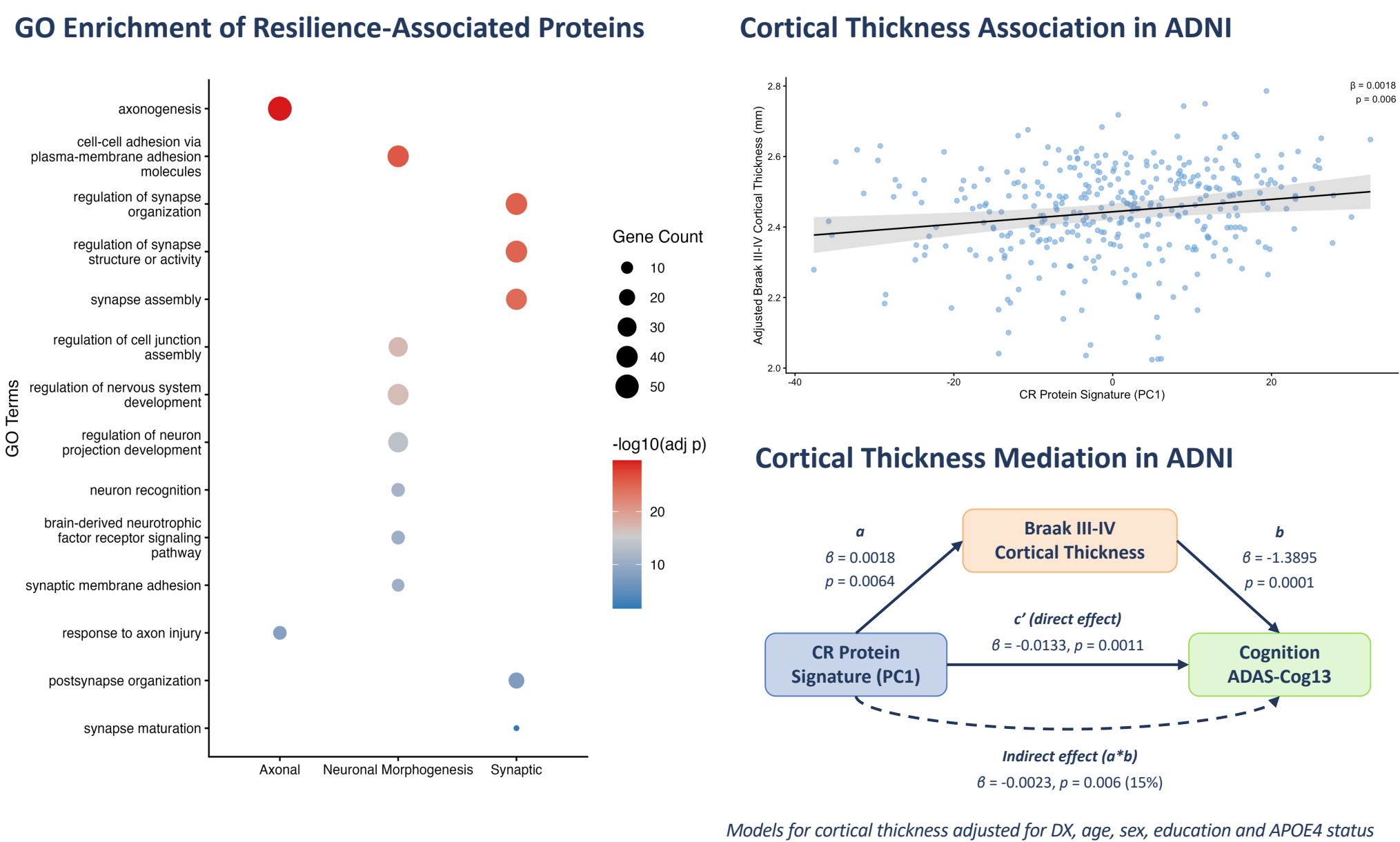
Identification and validation of a CSF proteomic signature of cognitive resilience



265 proteins associated with cognitive resilience were identified in the discovery cohort (ADNI) and summarized into a composite principal component (PC1) proteomic signature. Higher PC1 values were consistently associated with better cognitive performance in both the ADNI discovery cohort (including all DX groups: CN, MCI, Dementia) and the independent Emory validation cohort.

Results

Biological characterization of the cognitive resilience proteomic signature



Functional enrichment revealed that the cognitive resilience proteomic signature is predominantly associated with synaptic and neuronal biological processes. Consistent with these findings, higher resilience signature scores were associated with greater Braak III–IV cortical thickness in ADNI (including all DX groups: CN, MCI, Dementia), which partially mediated the relationship between the proteomic signature and cognitive performance, suggesting that maintenance of cortical integrity is one mechanism linking the resilience-associated proteome to preserved cognition.

Conclusions

- The proteomic signature of CR was enriched for synaptic, axonal and adhesion-related cell processes, where higher protein levels mitigated the cognitive decline relative to amyloid and tau chronicity.
- The CR proteome signature was associated with higher cortical thickness in AD-vulnerable regions (Braak III–IV)
- Cortical thickness partially mediated the association between the proteomic signature and cognitive resilience, suggesting that preservation of brain structure is one mechanism underlying resilient cognition.

References:

- [1] Oh, H.SH., Urey, D.Y., Karlsson, L. et al. A cerebrospinal fluid synaptic protein biomarker for prediction of cognitive resilience versus decline in Alzheimer’s disease. Nat Med 31, 1592–1603 (2025).
- [2] Brown CA, Mundada NS, Cousins KAQ, et al. Evaluation of Copathology and Clinical Trajectories in Individuals With Tau-Clinical Mismatch. JAMA Neurol. 2026;83(2):126–136.