

Plasma Proteomic Signatures of Alzheimer's Neuropathology: Insights from Bio-Hermes Study

P1-08



Hanjun Zhao^{1,2}, Taiyu Zhu^{1,3}, Buddhprabha Erabadda¹, Rashmi Maurya¹, Ganna Leonenko⁴, Valentina Escott-Price⁴, Ivan Koychev¹, Shisong Jiang², Alejo J Nevado-Holgado¹, and Laura Winchester¹

¹ Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JX , UK

² Department of Oncology, University of Oxford, Oxford

³ Department of Biostatistics & Health Informatics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London

⁴ Dementia Research Institute, School of Medicine, Cardiff University, Cardiff, United Kingdom



Introduction and Background

- Large-scale plasma proteomics can capture molecular changes across different stages of the AD continuum and deepen insights into pathological mechanisms in AD.
- We analysed the Bio-Hermes proteomics cohort (n=988) enrolled across 17 sites. Participants were stratified by both clinical status and amyloid PET scan-based Core1 biomarker positivity (CN Core1-, CN Core1+, MCI Core1+ and AD Core1+).
- Plasma proteins were quantified with SomaScan (7,289 aptamers mapping to 6,402 unique proteins).

Methods

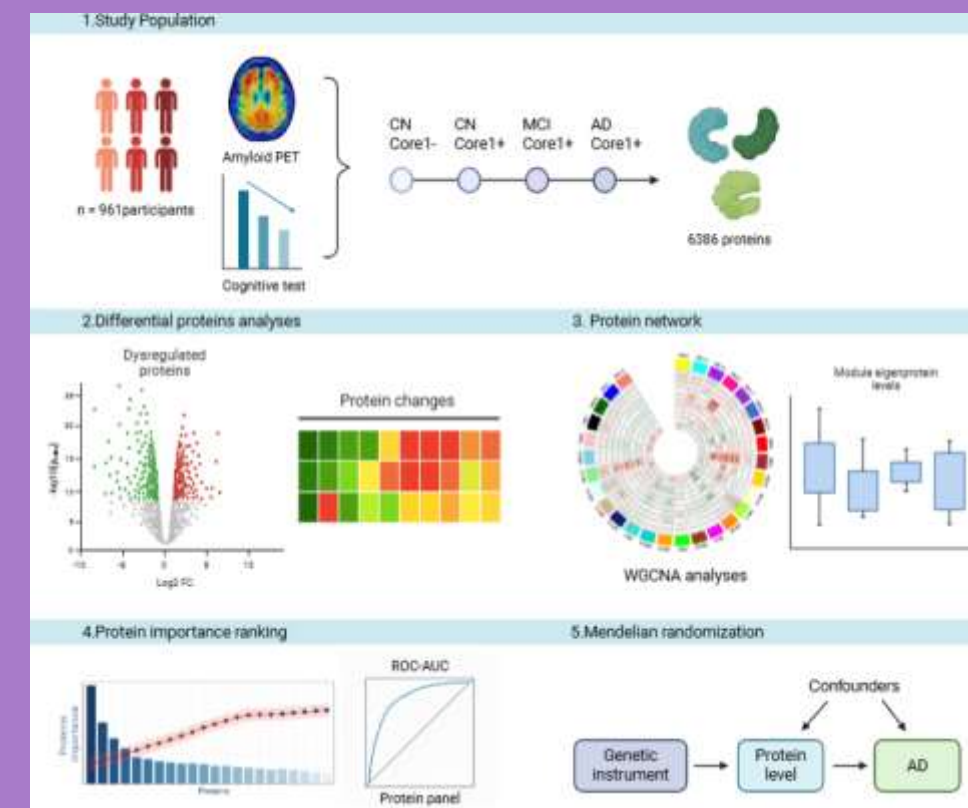


Figure 1. Study design overview.

Conclusions

- Plasma proteomics delineated a stage-spanning core signature alongside the AD continuum. Eight core proteins, including LRRN1, SPC25, TBCA, S100A13, BCDIN3D, ST8SIA1, FOXO1 and NEFL, were consistently dysregulated from preclinical through prodromal and dementia phases.
- WGCNA network and cell-type enrichments revealed microglia-linked module implicated in disease progression.
- LightGBM identified high-performance protein panels to distinguish biologically defined AD (CN Core1+, MCI Core1+ and AD Core1+), with implications for prioritizing therapeutic targets across diverse pathological mechanisms.
- Mendelian randomization supported a significant genetic link between plasma ACHE abundance and AD risk.

Results

Plasma proteomic differences across AD continuum in the Bio-Hermes Study

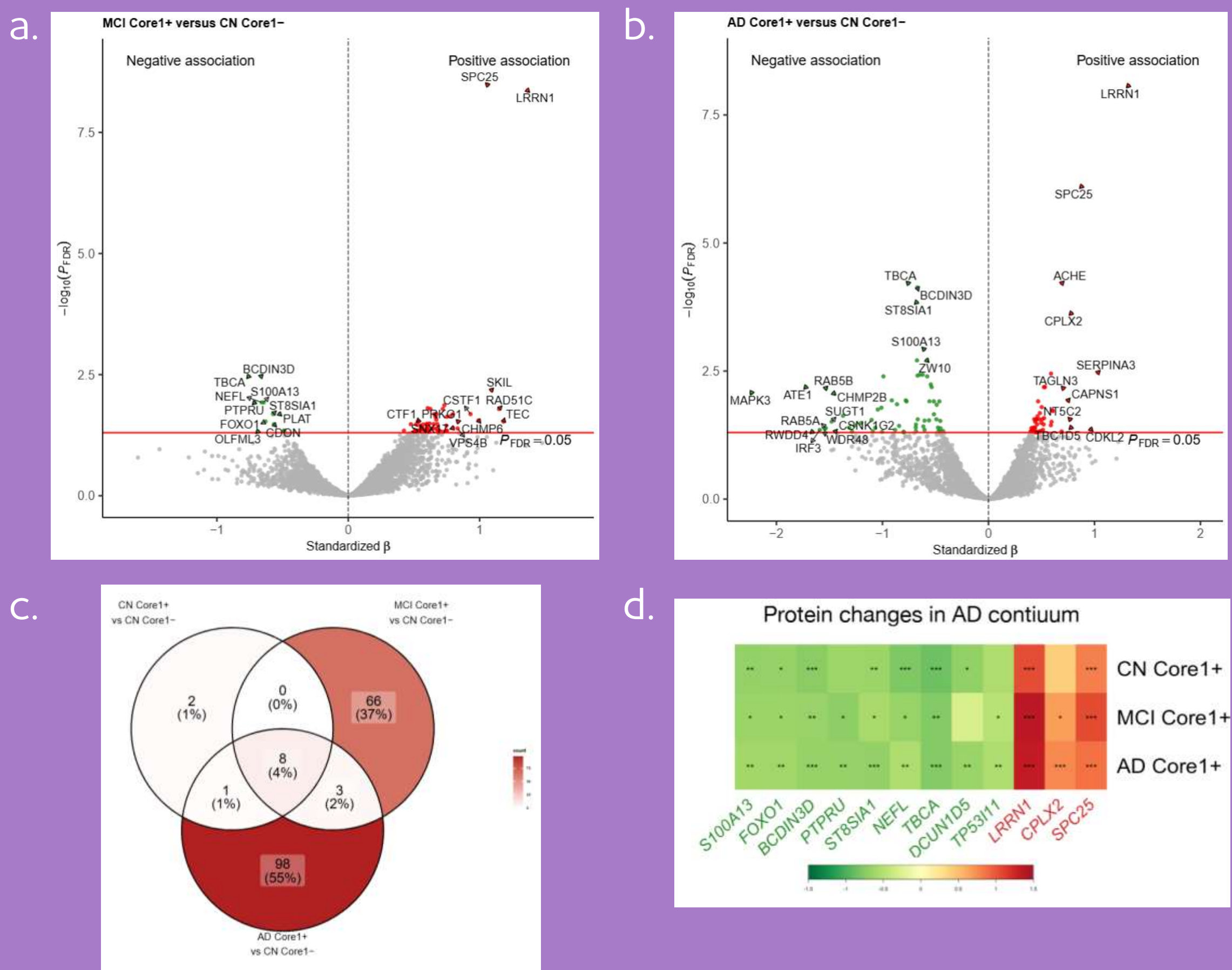


Figure 2. Differential analyses were performed in the Bio-Hermes Study for plasma proteomics across AD continuum using multiple linear regression adjusted for age, sex and PC 1-2. a, b. Volcano plots showing the standardised beta (x axis) and $-\log_{10}(P_{FDR})$ (y axis) for MCI Core1+ versus CN Core1- (a) and AD dementia Core1+ versus CN Core1- (b). c. A venn diagram showing overlap number in significant dysregulated proteins from CN Core1+, MCI Core1+, and AD dementia Core1+. d. A heat map showing changes in overlapping dysregulated proteins across the AD continuum. Colours represent standardised beta and asterisks indicate statistical significance after Benjamini-Hochberg FDR correction.

Protein co-expression network revealing modules linked to AD endophenotypes and stages

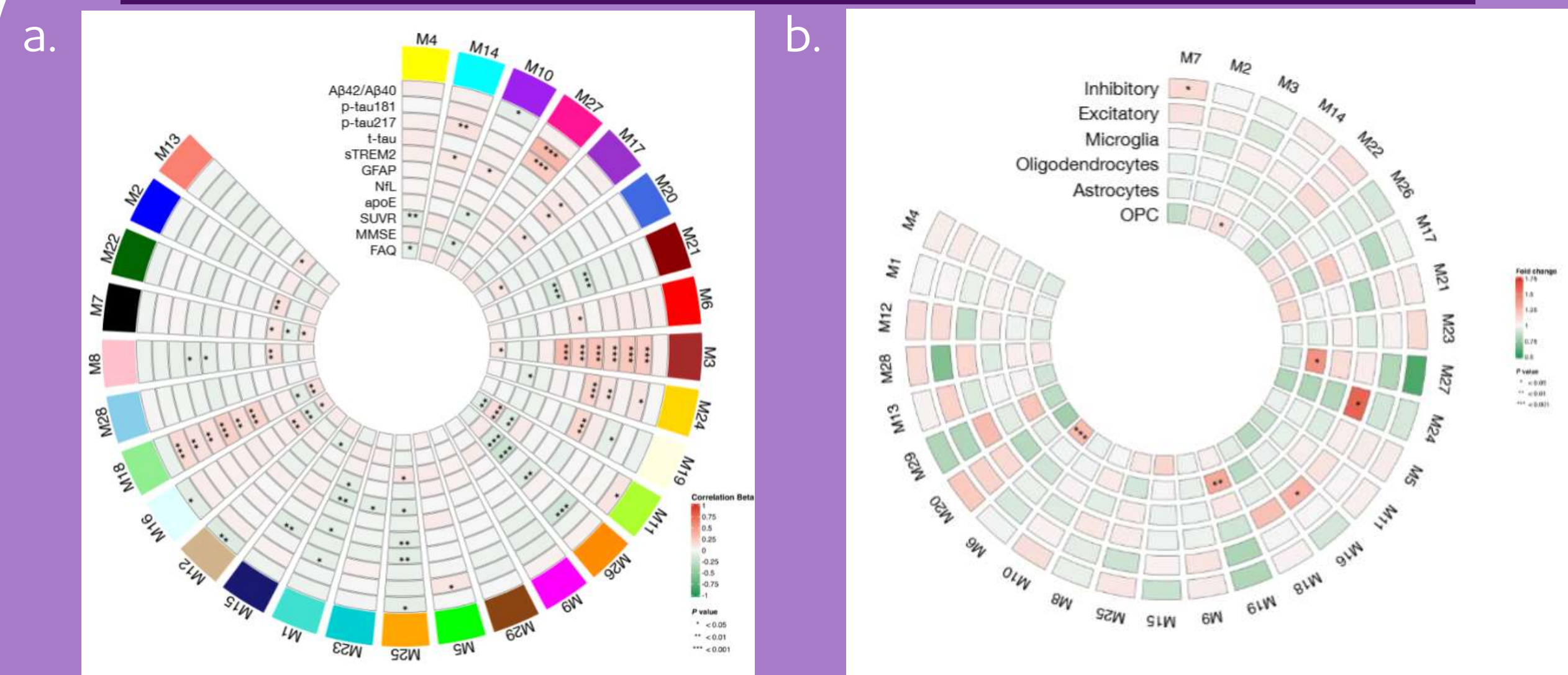
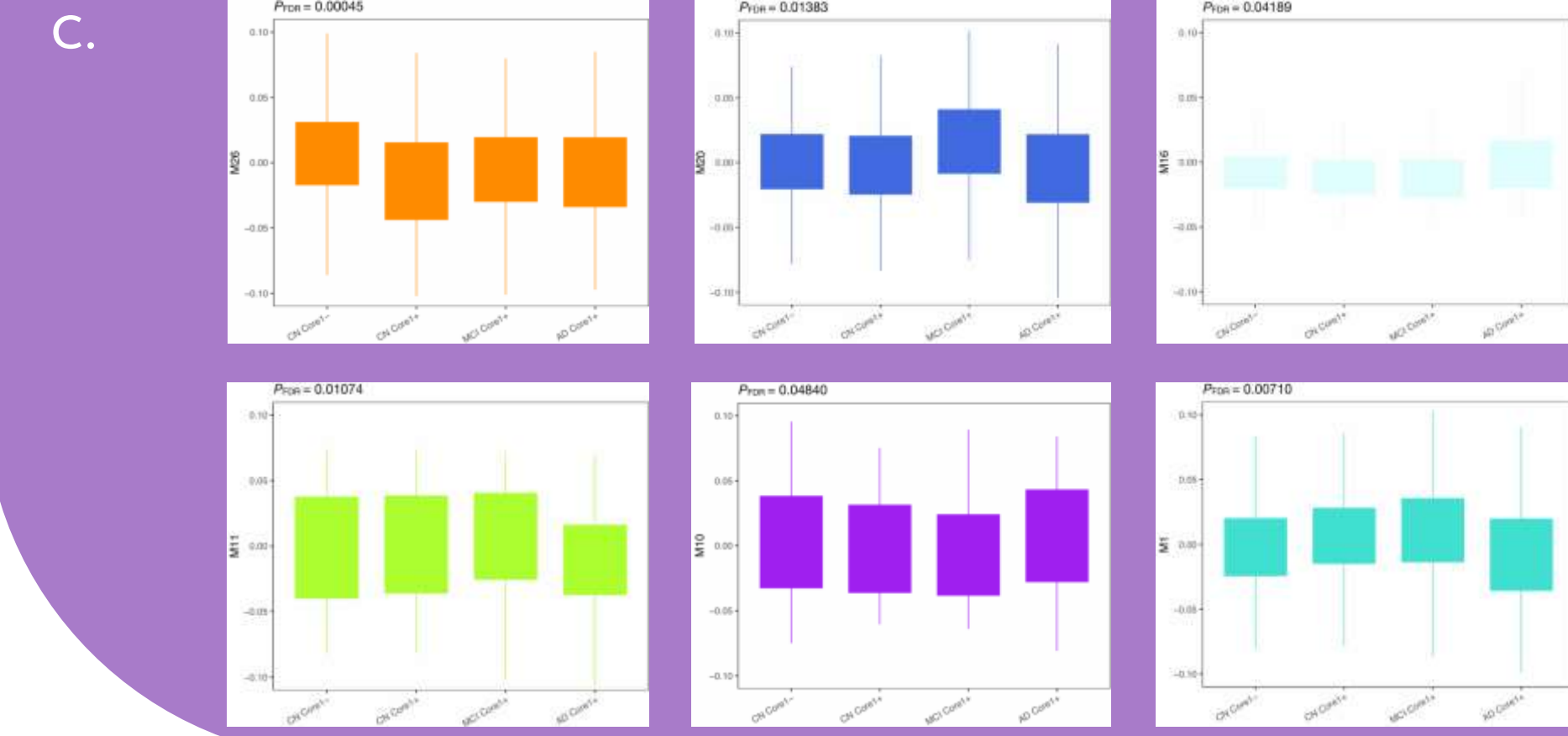


Figure 3. A protein co-expression network was built using WGCNA and comprised 29 co-expression modules. Module eigenproteins were correlated with blood-based neuropathological, cognitive, and imaging traits present in the Bio-Hermes Study. a. A heatmap showing the correlations between the 29 modules and clinical feature. b. Cell-type enrichment analyses based on single-cell transcriptomics data from the middle temporal gyrus using proteins for 29 co-expression network modules. Red indicates positive correlation; blue indicates negative correlation. Colour intensities represent Pearson correlation coefficients and asterisks indicate statistical significance after Benjamini-Hochberg FDR correction.



c. Module eigenprotein levels by AD continuum for the six significantly associated modules. Groups were ordered from CN Core1- and CN Core1+ through MCI Core1+ to AD dementia Core1+. Differences in module eigenprotein levels among groups were evaluated using the Kruskal-Wallis rank-sum tests.

Protein importance ranking and Genetic links

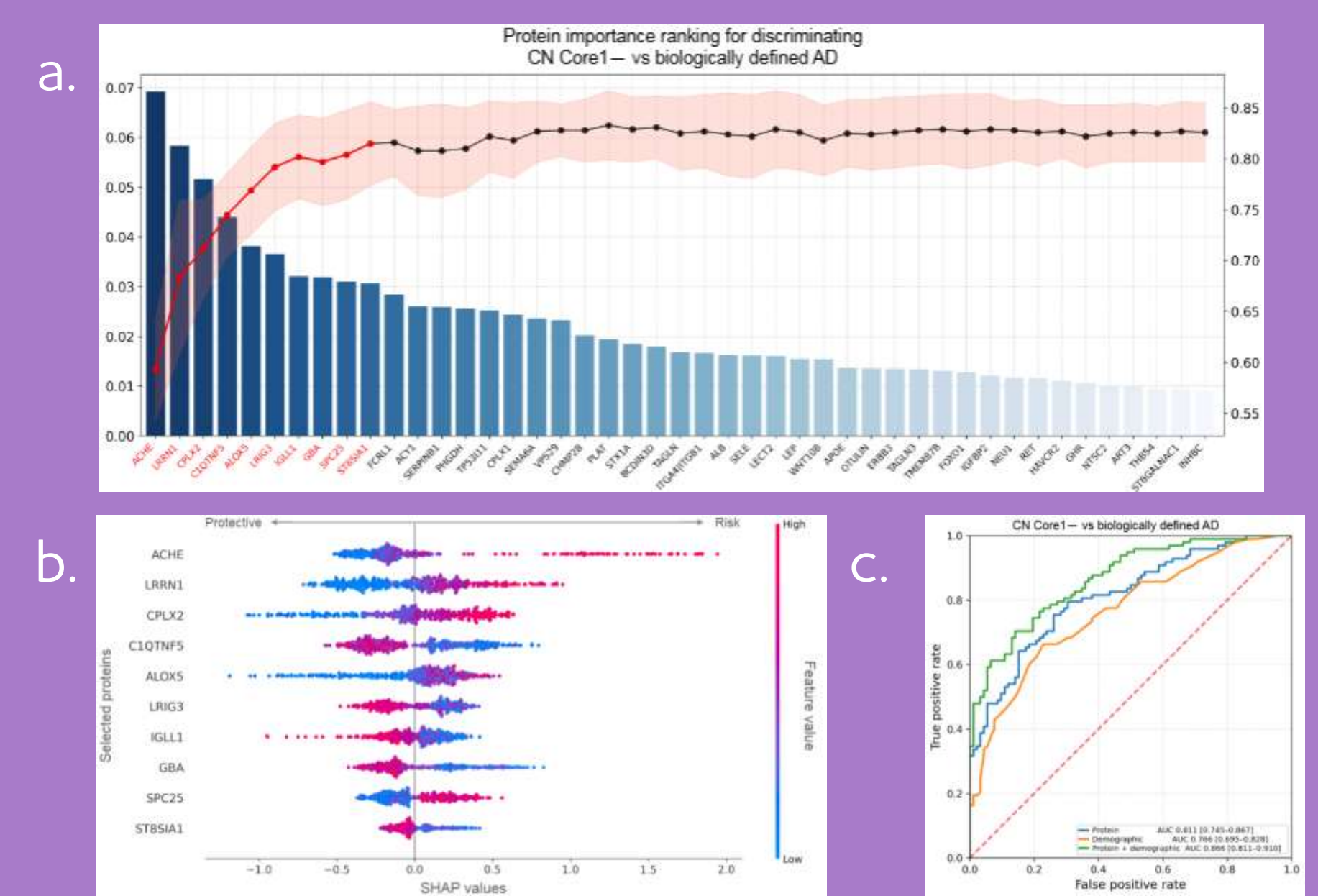


Figure 4. a. Protein panel selection in the derivation set. The bar plot demonstrates ranked importance of proteins according to contribution to distinguishing CN Core1- from biologically defined AD, assessed by information gain. b. SHAP plot illustrating the contributions of selected proteins to model predictions. c. ROC curves derived in the replication cohort showing discriminatory performance (AUC with 95% CIs) of the selected protein panel alone and combined with demographic variables (age and sex) for distinguishing CN Core1- from biologically defined AD.

Forward MR (proteins → AD)			
Protein	No. SNPs	Slope (95% CI)	p value
ACHE	1	0.394 (0.154–0.634)	0.0013
FCRL1	1	-0.321 (-0.603– -0.039)	0.0256
LRIG3	2	-0.706 (-1.345– -0.067)	0.0303

Table 1. Mendelian randomization associations between proteins and AD.

Reference

1. Mohs R C, Beaugard D, Dwyer J, et al. The Bio-Hermes Study: Biomarker Database Developed to Investigate Blood-based and Digital Biomarkers in Community-based, Diverse Populations Clinically Screened for Alzheimer's Disease., 2024, 20[J]. DOI: <https://doi.org/10.1002/alz.13722>: 2752-2765.