



Resilient Synaptic Proteomic Profiles Reveal Preserved Signaling and Reduced Glial Responses

BSHAIER ALLEHYANY^{1,2}TATIANA GEORGIADIS^{1,2}, JESSICA GRIFFITHS³, PATRICIO OPAZO³, HARRY WHITWELL⁴, YU YE^{1,2}, JOHANNA S. JACKSON^{1,2}. ¹DEPARTMENT OF BRAIN SCIENCES AT IMPERIAL, ²UK DRI AT IMPERIAL, ³UK DRI AT EDINBURGH, ⁴NATIONAL PHENOME CENTRE

Correspondence: b.allehyany21@imperial.ac.uk

WHAT MAKES SYNAPSES RESILIENT?

Synaptic loss is the strongest correlate of cognitive decline in Alzheimer's disease (AD). The synaptic proteomic signature underlying resilience to AD, and whether it is younger-like remain poorly characterized in the human synaptic proteome.

Hypothesis

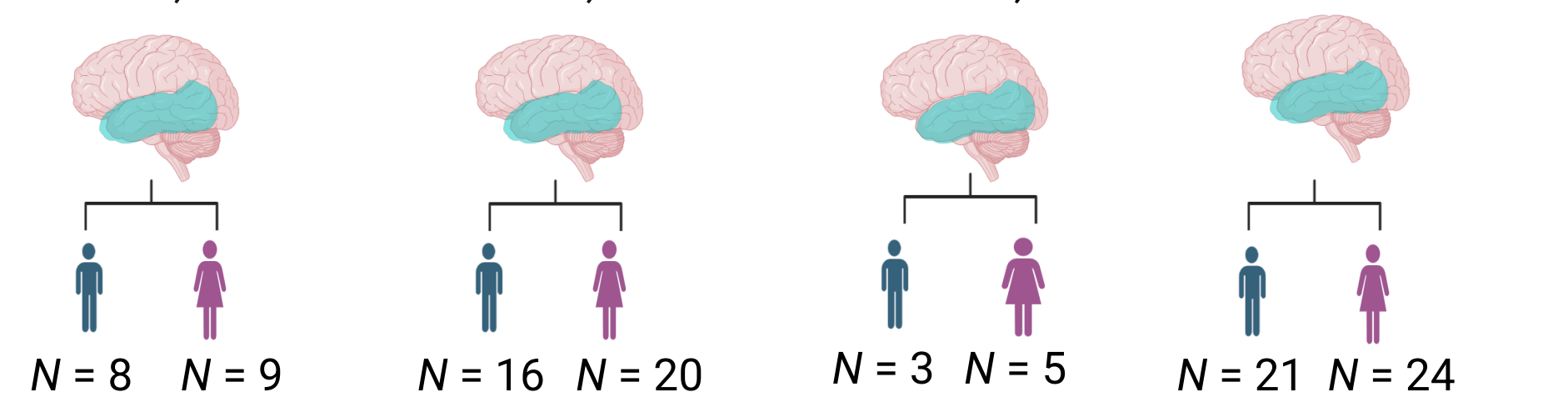
Cognitive resilience is associated with preserved, younger-like synaptic proteins that are disrupted in AD and other neurodegenerative conditions.

Aims

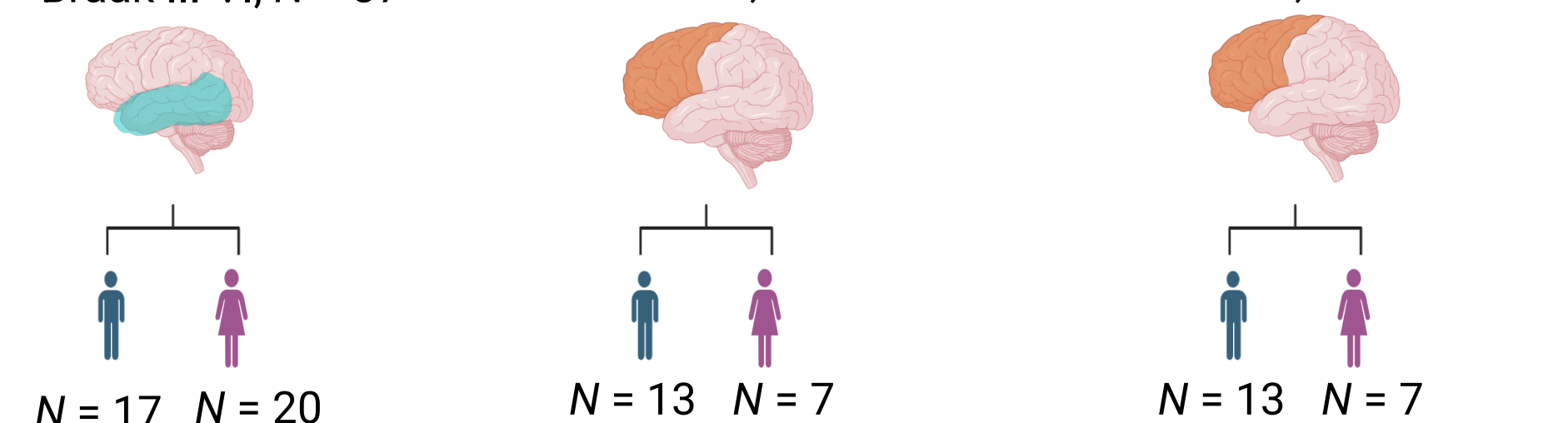
Determine how age, AD, and resilience to AD shape the synaptic proteome, and how this differs from other neurodegenerative conditions.

Human tissue cohort

Younger-aged 41.5 years Braak 0, N = 17
Controls (CN) 84.1 years Braak 0-II, N = 36
Resilient (RES) 86.9 years Braak III-VI, N = 8
AD 83.3 years Braak III-VI, N = 45

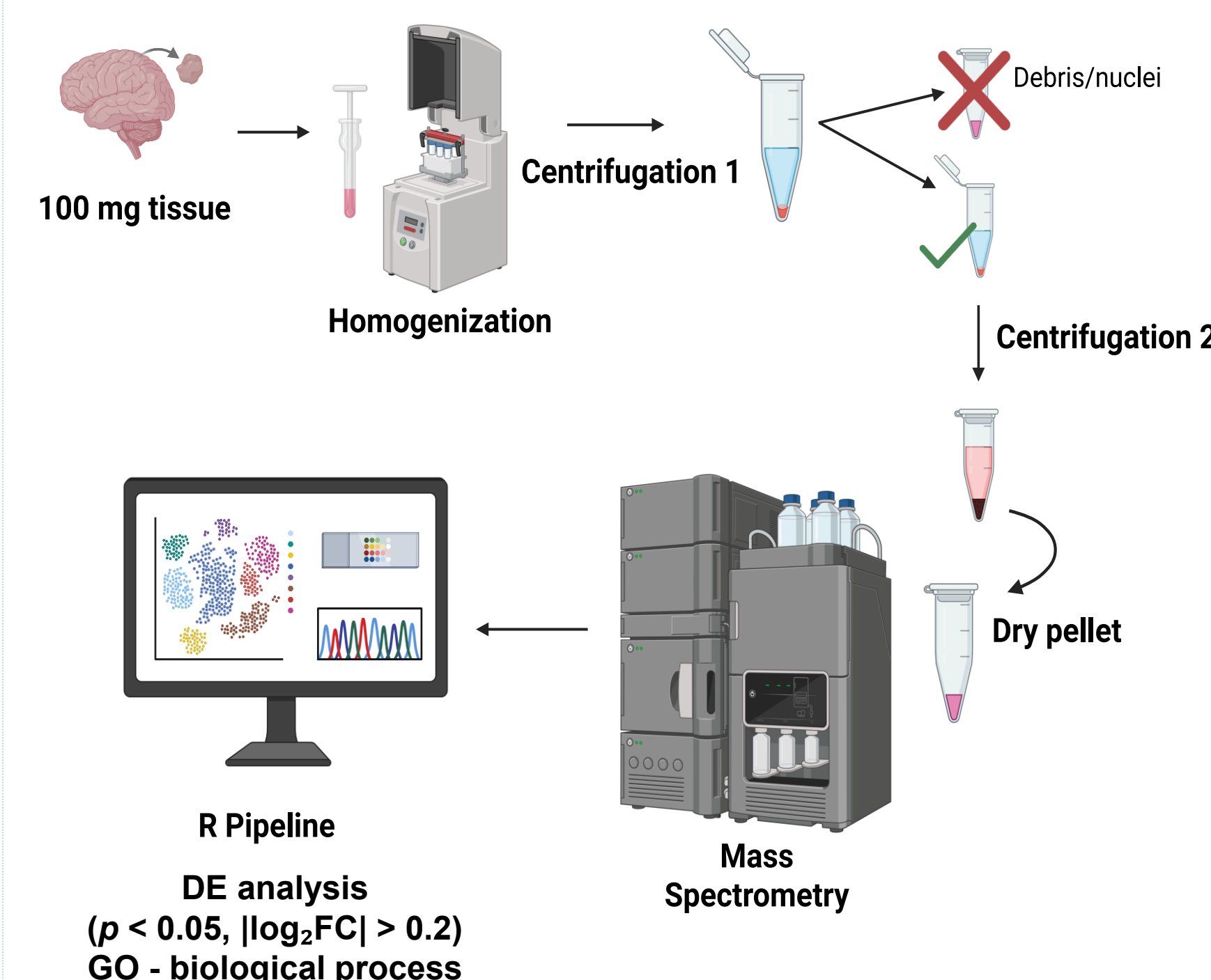


AD pathology-only (PO) 88.3 years Braak III-VI, N = 37
Parkinson's disease 77.8 years Braak 0-II, N = 20
Parkinson's disease dementia 78.6 years Braak 0-II, N = 20



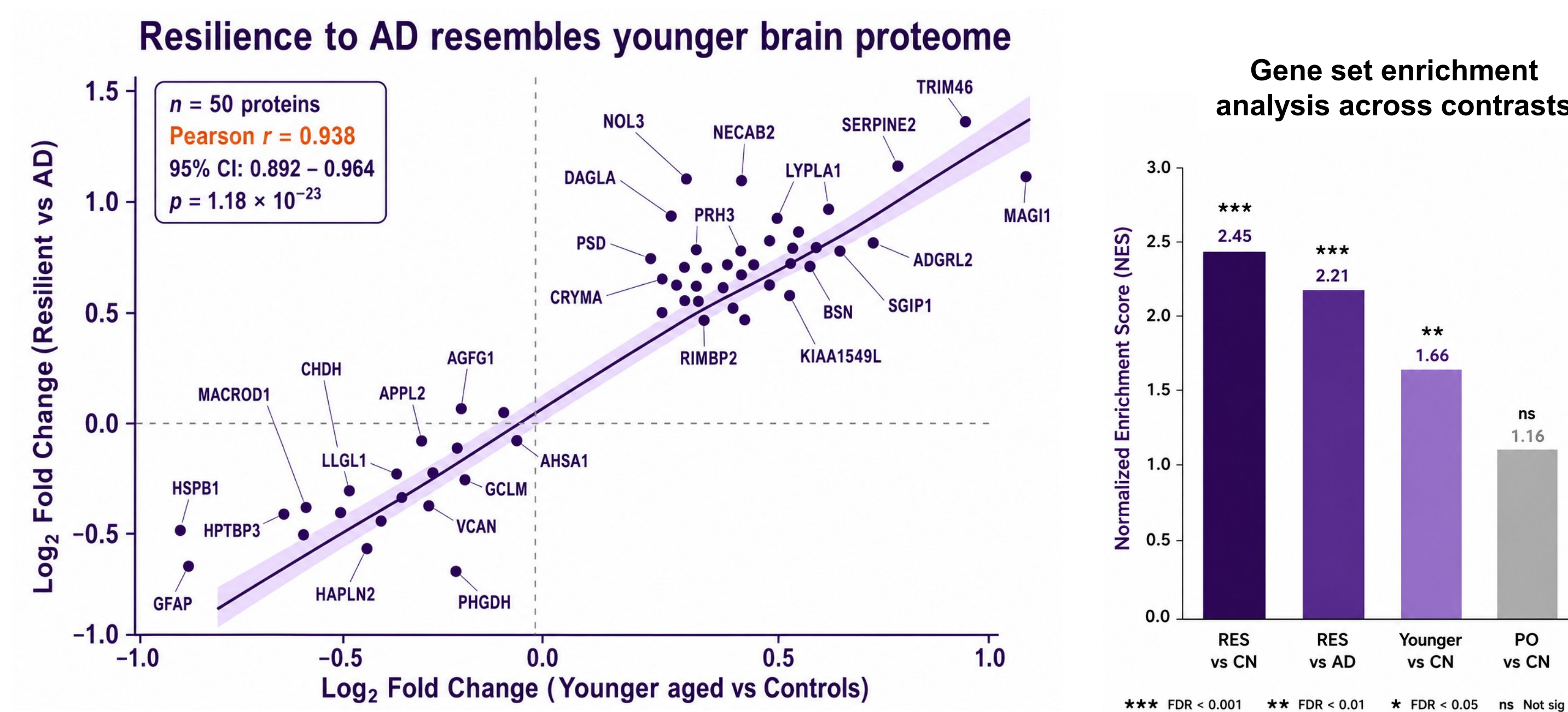
Case distribution of postmortem human middle-temporal gyrus and prefrontal cortex tissue

Experimental workflow



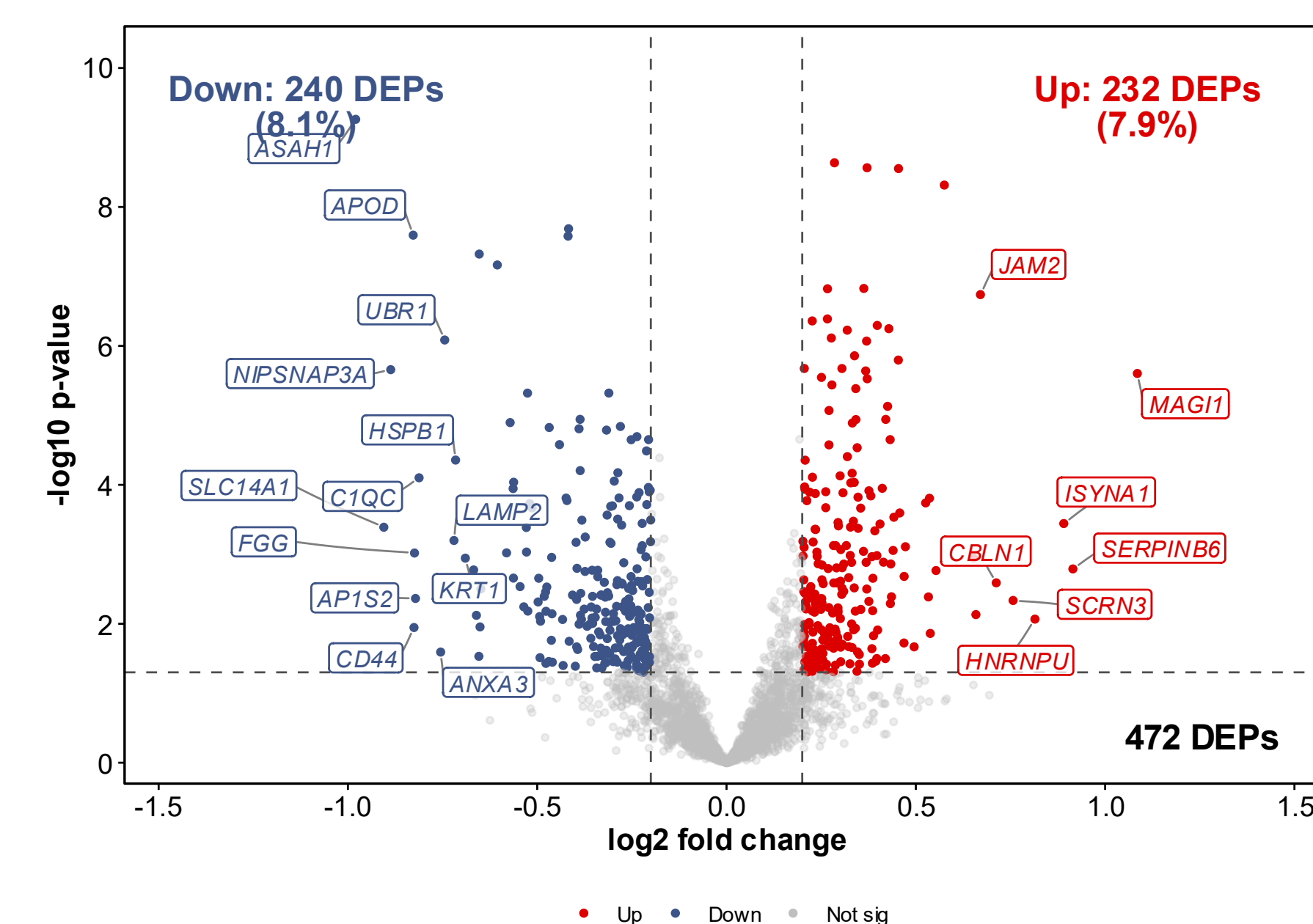
Overview of synaptoneurosome extraction protocol

RESILIENT SYNAPSES RETAIN A YOUNGER PROTEOME

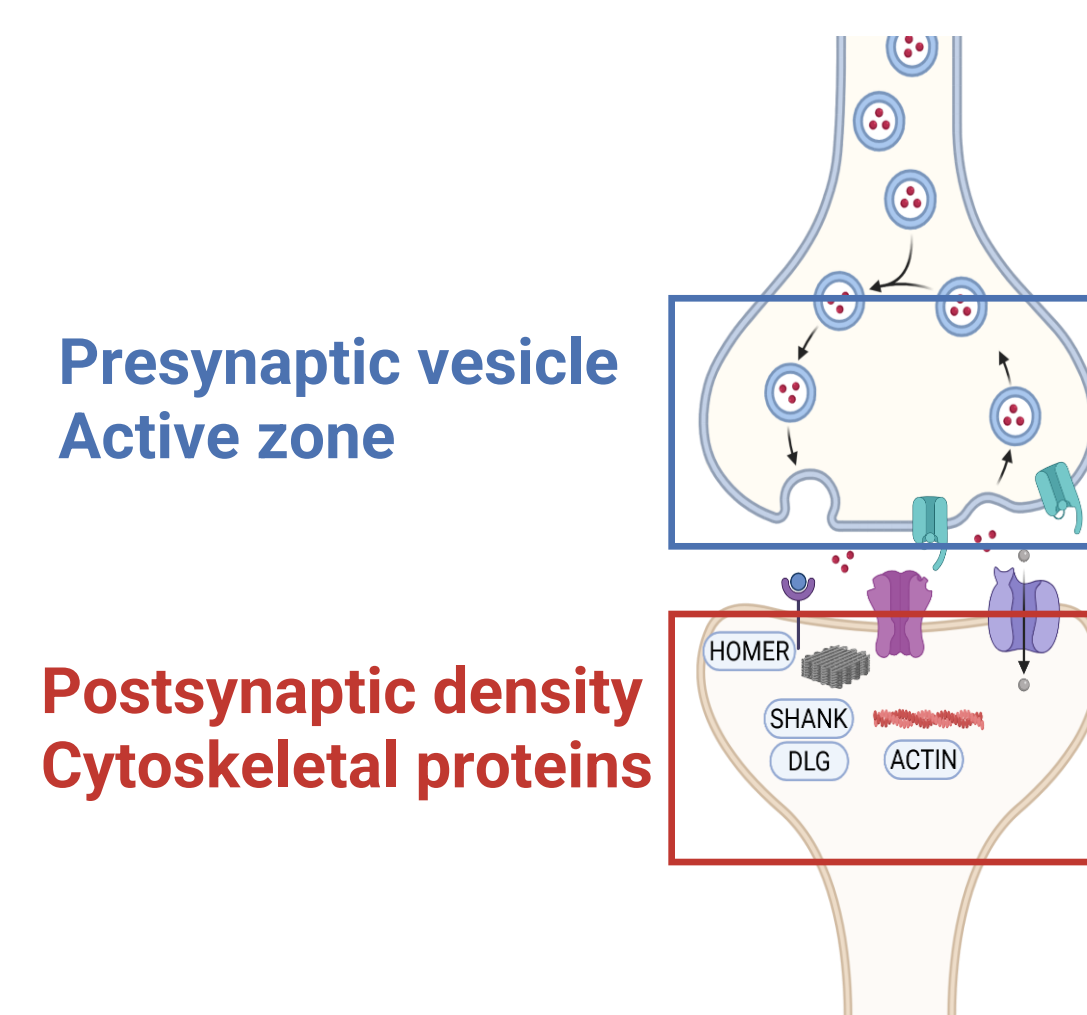


A younger-like synaptic proteomic signature is preserved in resilient synapses and is enriched in resilience (RES vs CN and RES vs AD), whereas enrichment is absent in AD pathology-only synapses (PO)

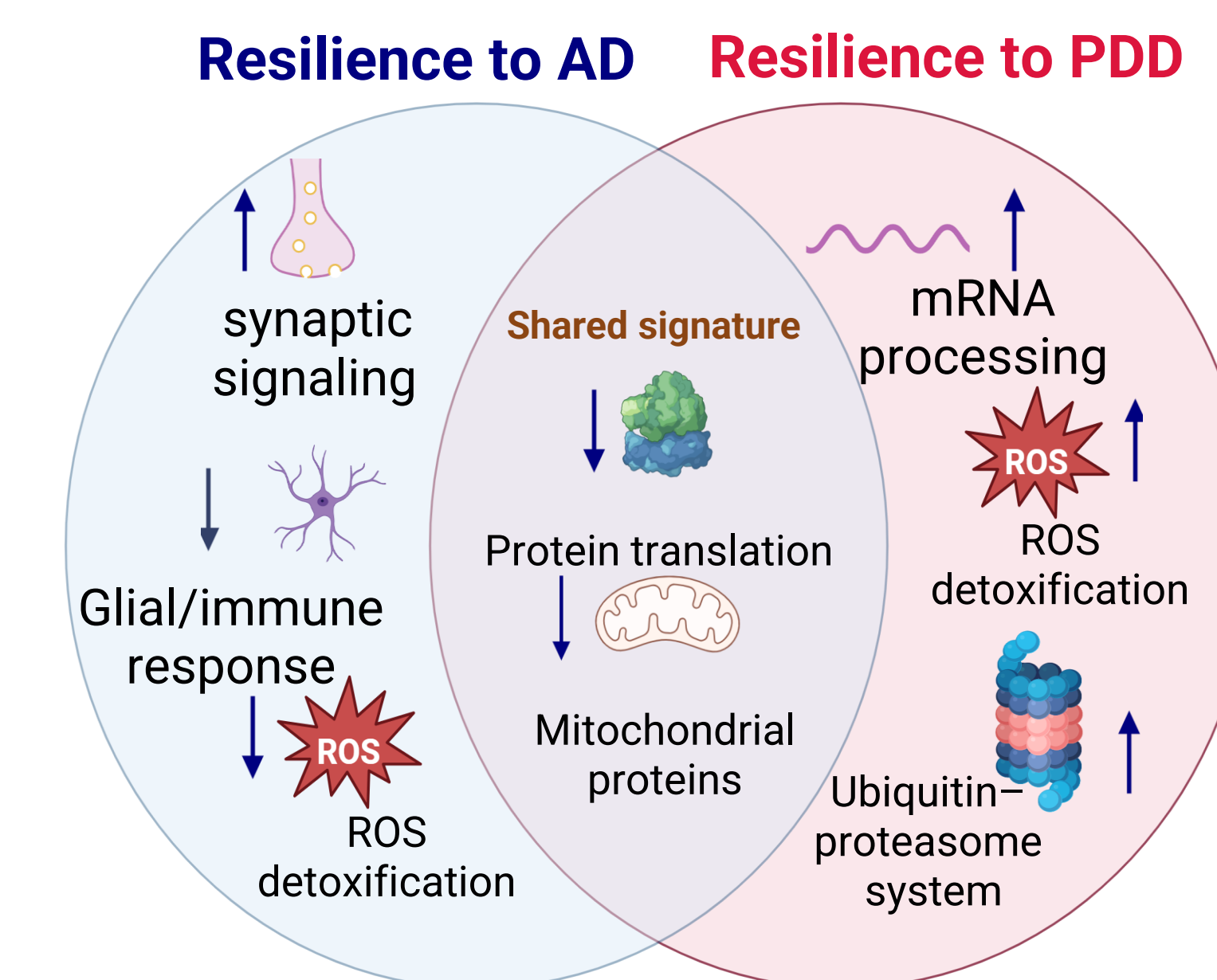
YOUNGER SYNAPSES PRESERVE SYNAPTIC ORGANIZATION PROTEINS



Top upregulated differentially expressed proteins in younger age compared with controls are cytoskeletal and synaptic signalling proteins



YOUNGER-LIKE SYNAPTIC SIGNATURE IS AD-SPECIFIC



Younger-like synaptic proteomic signature is not observed in resilience to PDD

Conclusions

1. Resilient synapses preserve a younger-like synaptic proteome
2. Resilience to AD signature strongly correlates with the younger aged synaptic proteome
3. The younger-like signature is not preserved in other neurodegenerative conditions