

Molecular Mechanisms of Resilience in the Brain

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Overview of the Resilience World – State of Science
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Rush Alzheimer's Disease Center

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Study Participants:

Religious Orders Study

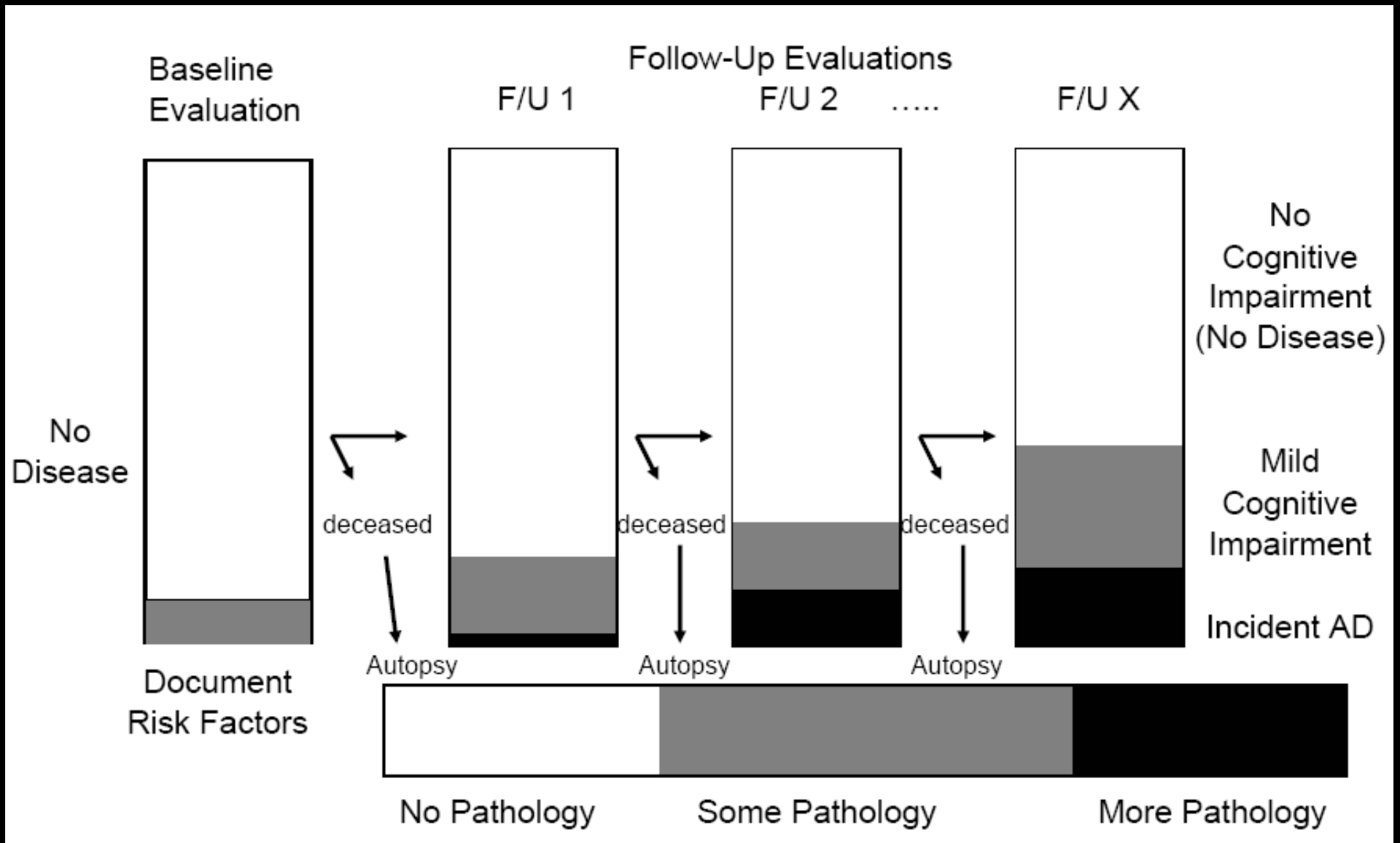
Rush Memory and Aging Project

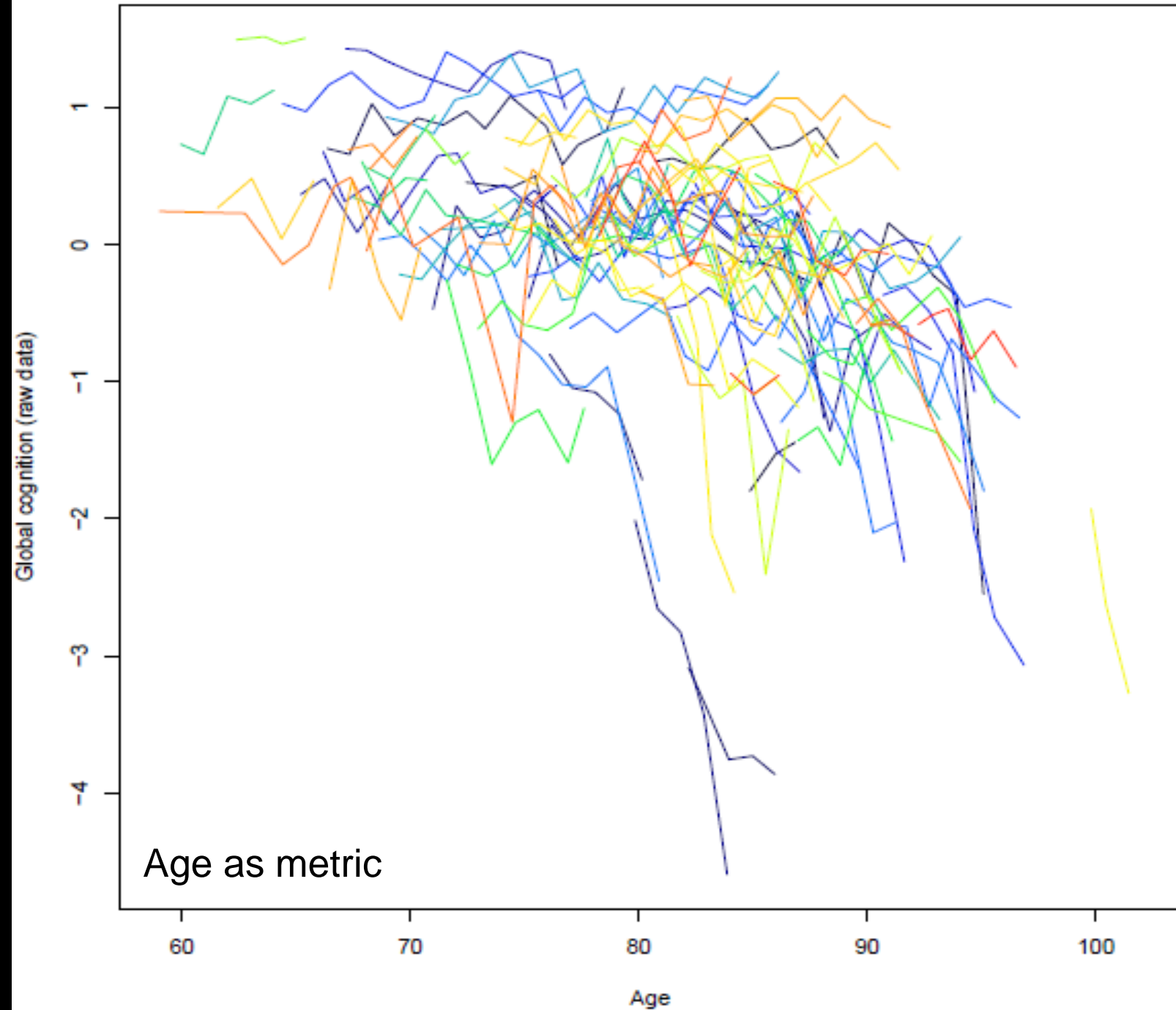
No Relevant Disclosures

The Religious Orders Study Rush Memory and Aging Project

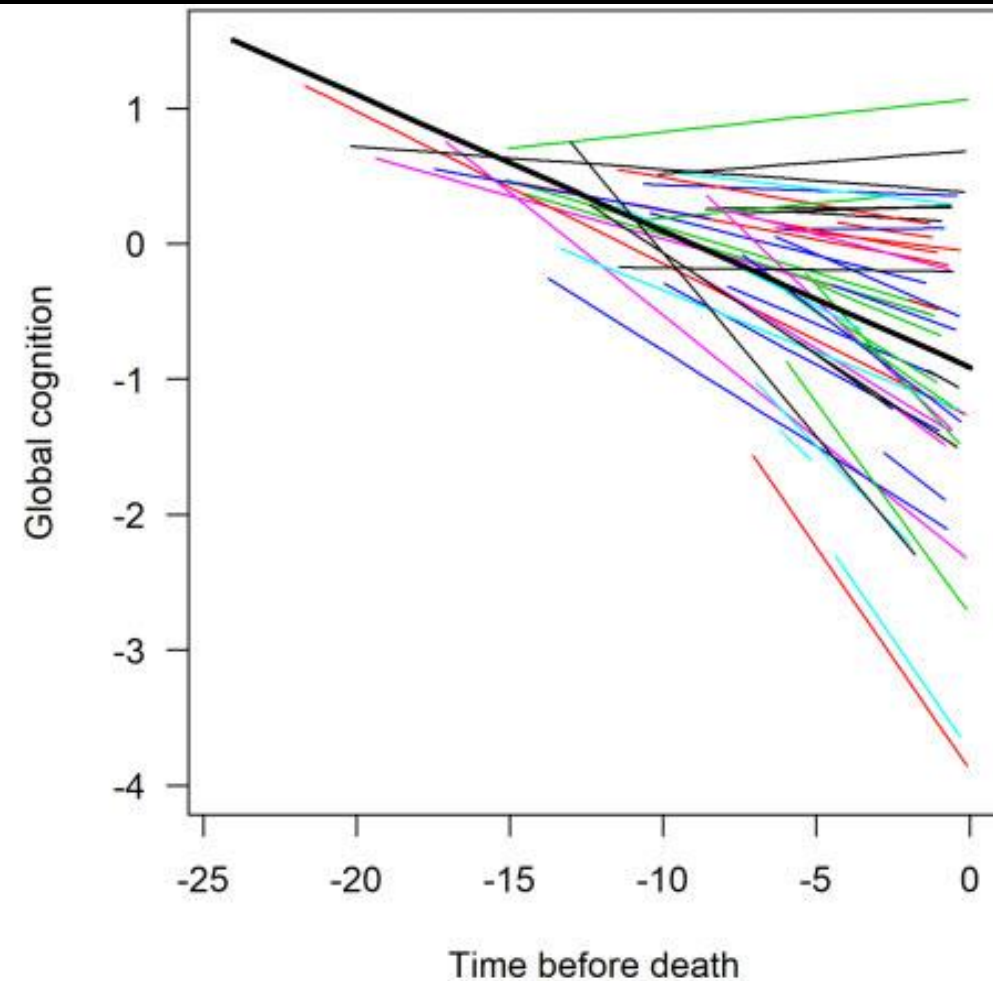
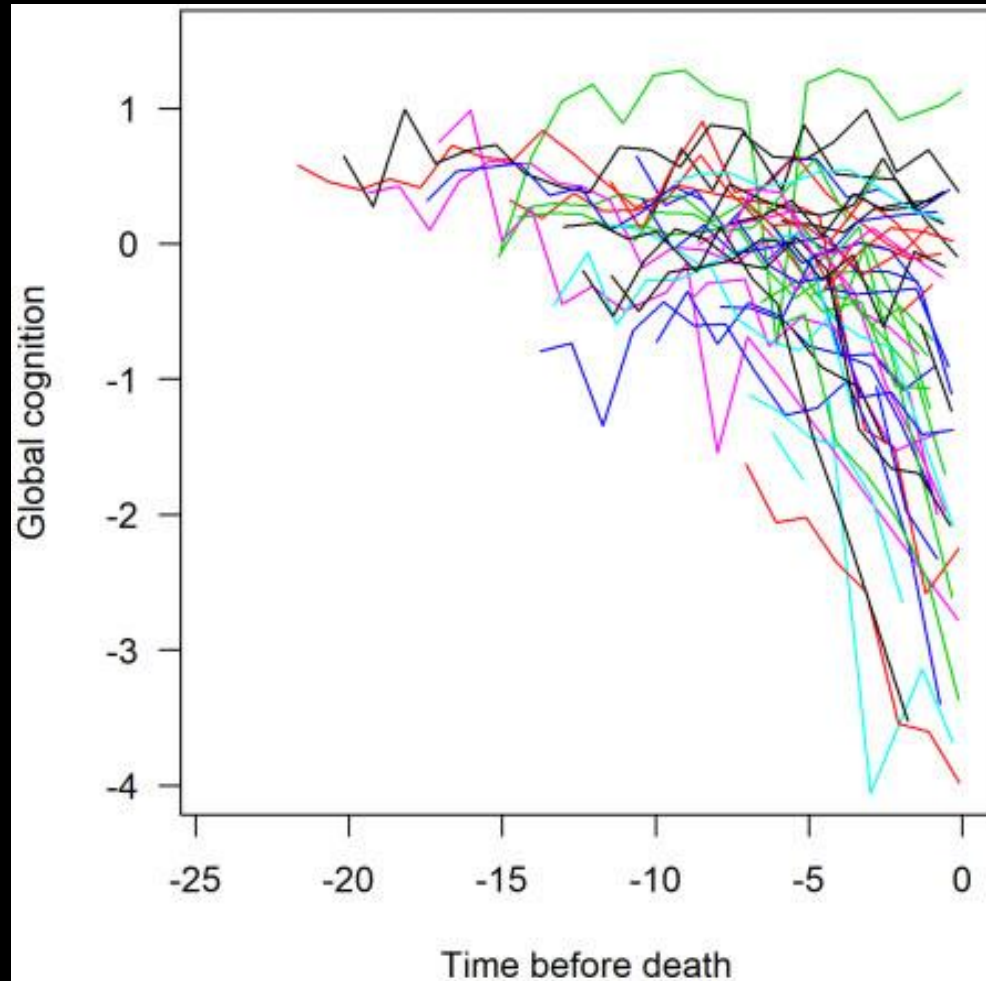
- Began in 1993 and 1997
- > 3,800 older persons without known dementia from across the U.S.
- All agreed to annual clinical evaluation
- All agreed to organ donation
- > 750 have developed dementia
- > 1200 have developed MCI
- > 1800 brain autopsies

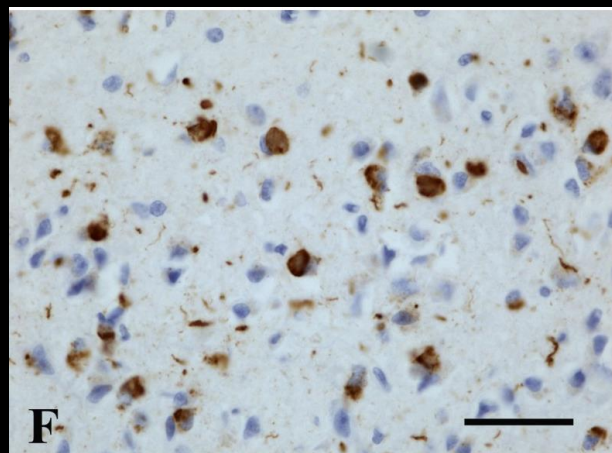
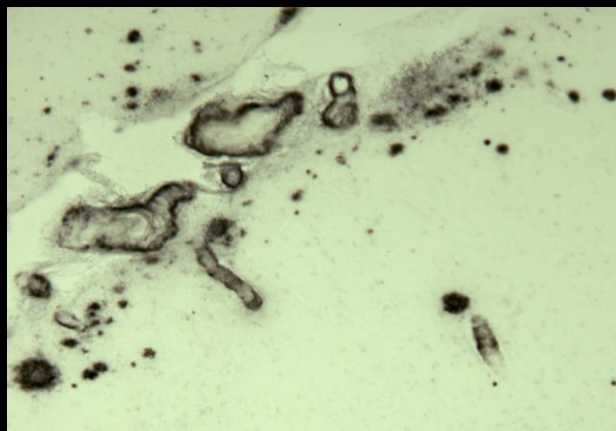
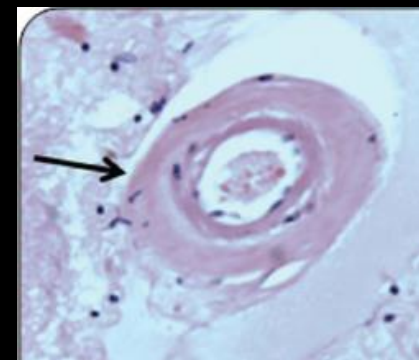
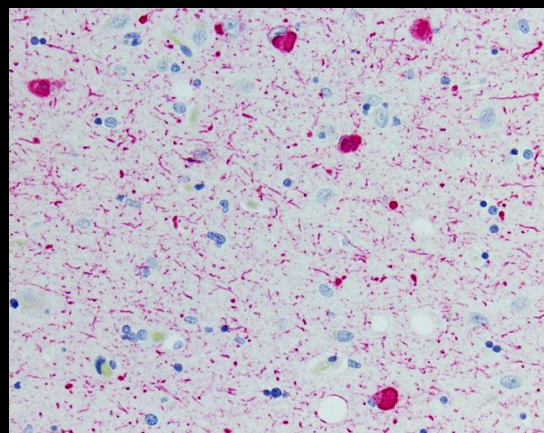
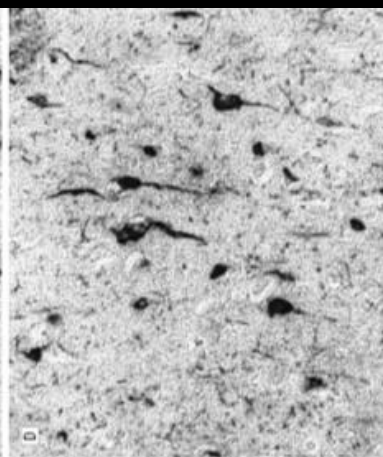
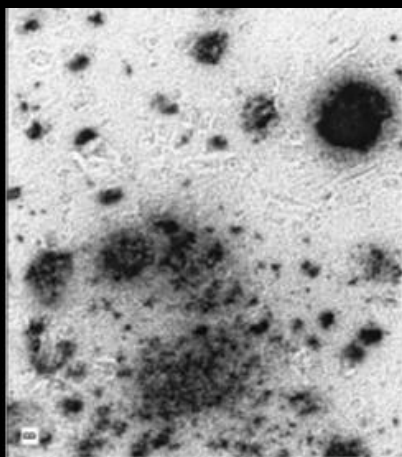
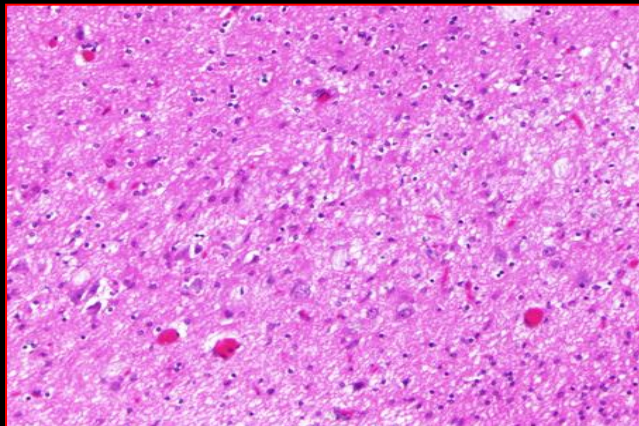
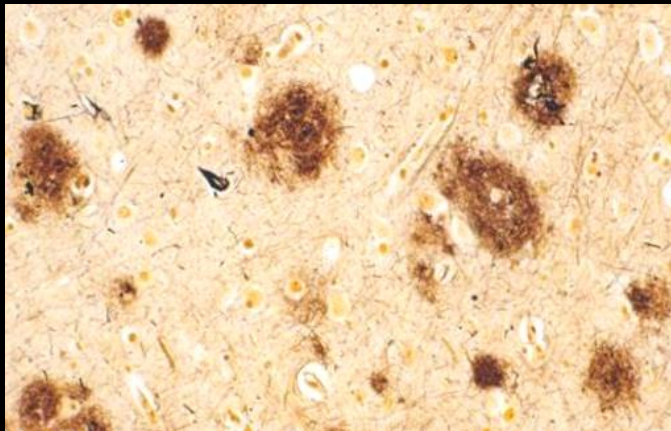
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort



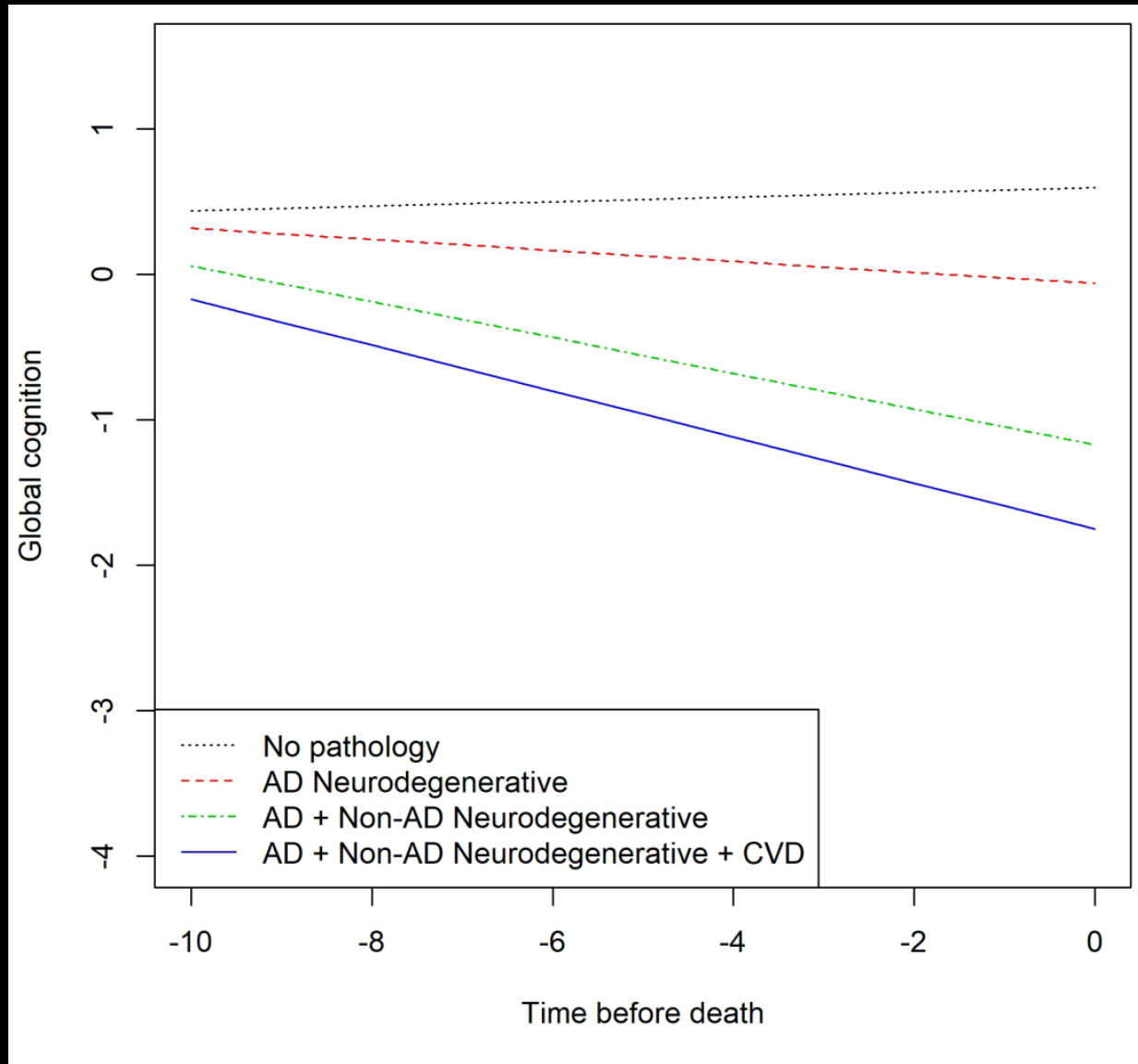


To what degree is late life cognitive decline driven by age-related neuropathologies?



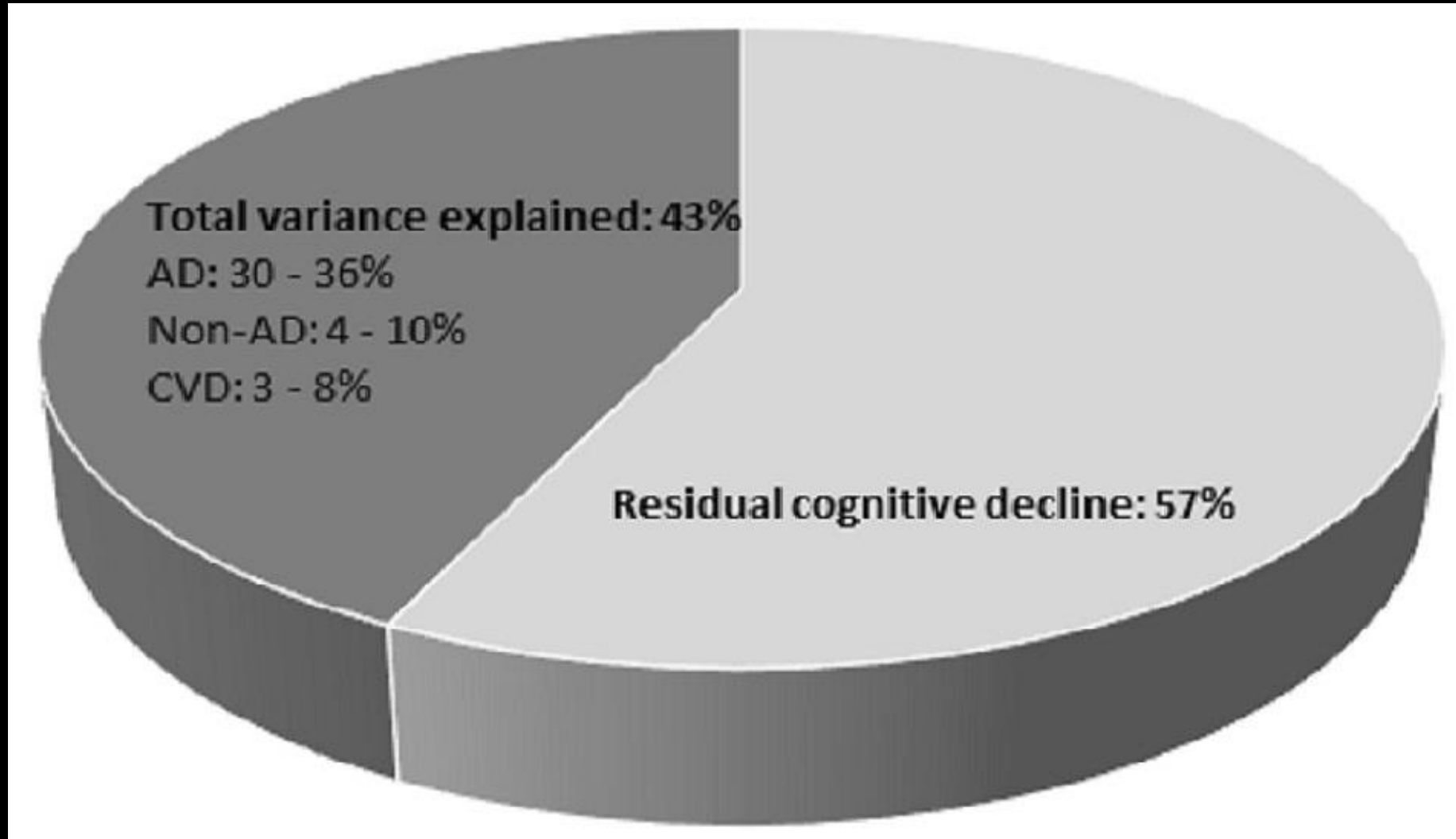


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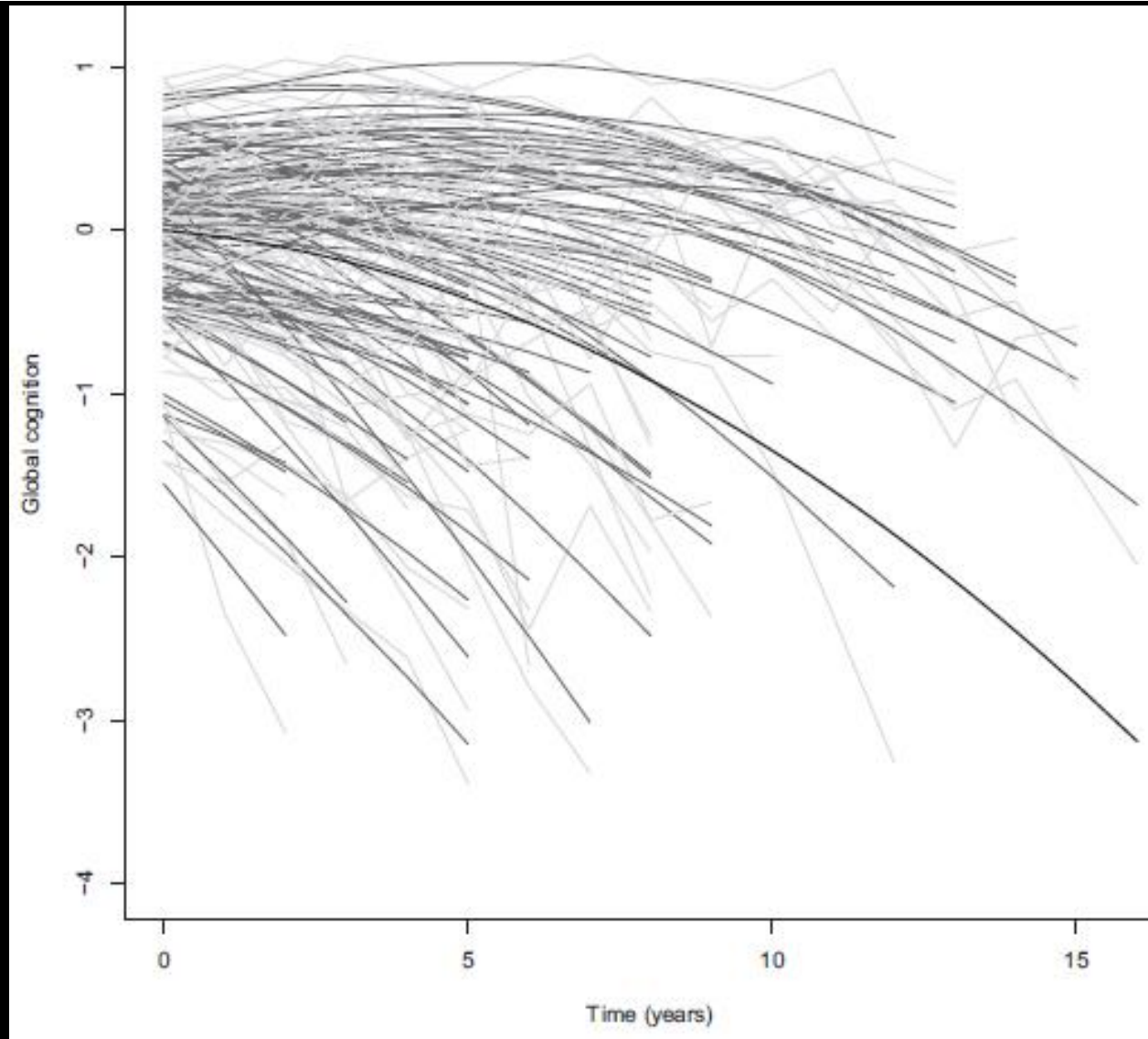


Boyle PA, et al. *Brain*.
2021;ep144:2166-75.

To what degree is late life cognitive decline driven by age-related neuropathologies?

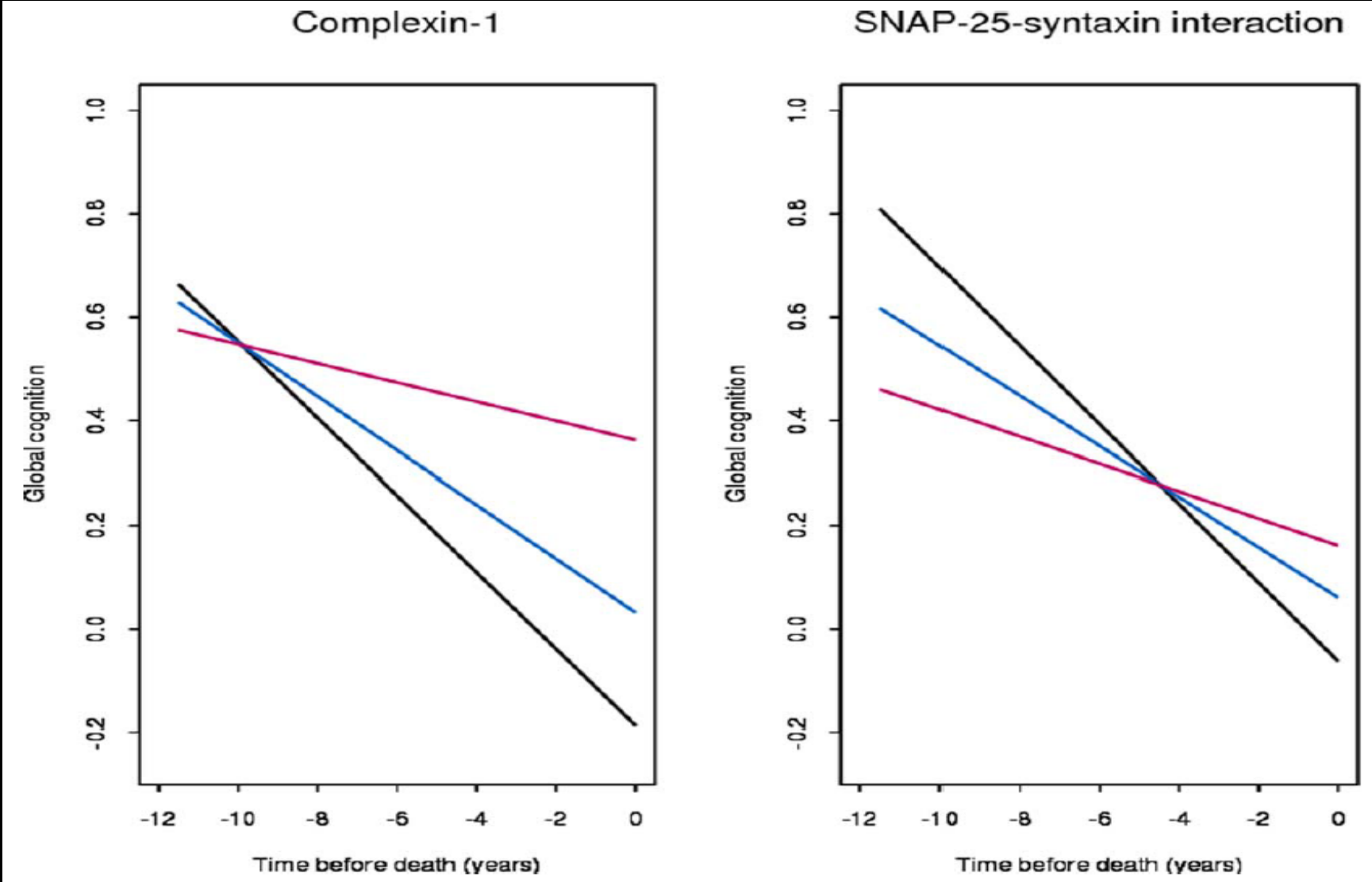


Residual Decline in Cognition After Adjustment for Common Neuropathologic Conditions

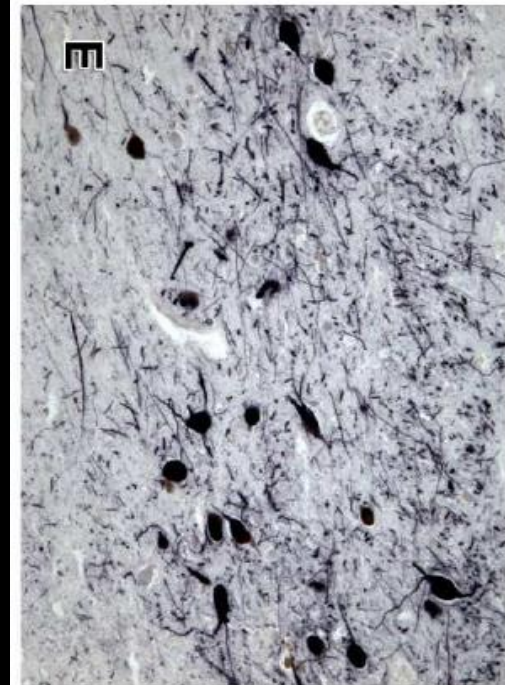
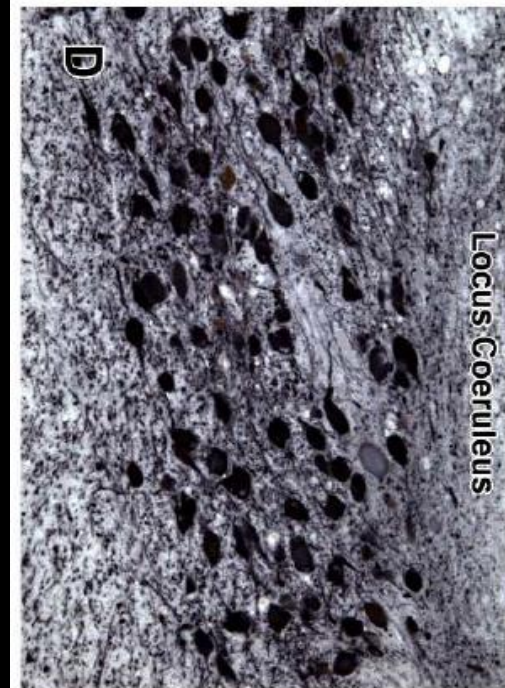
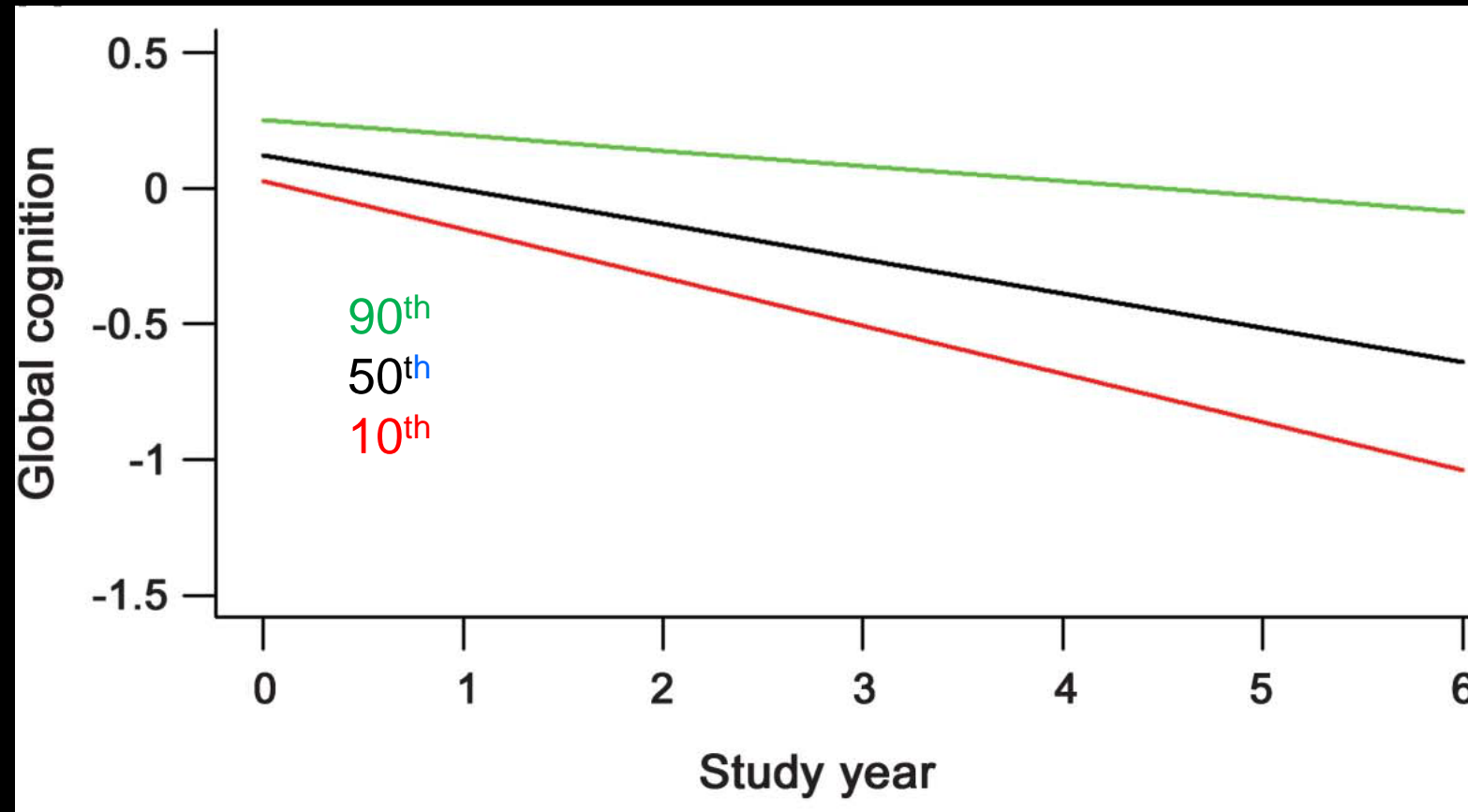


Yu L, et al. *Neuropsychology*. 2014;29:335-43.

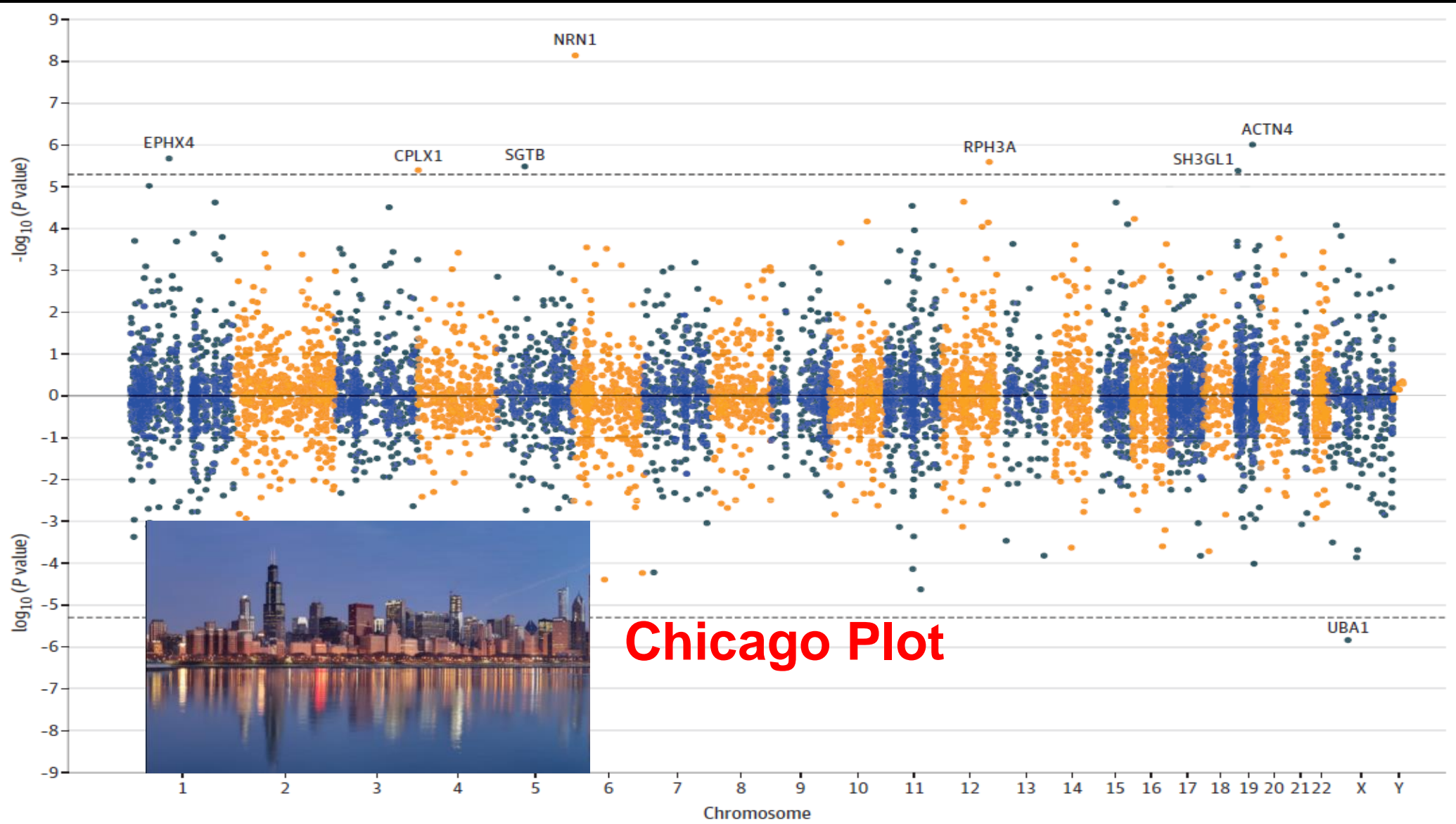
Much of Late Life Cognitive Decline
Is Not due to Common
Neurodegenerative Pathologies



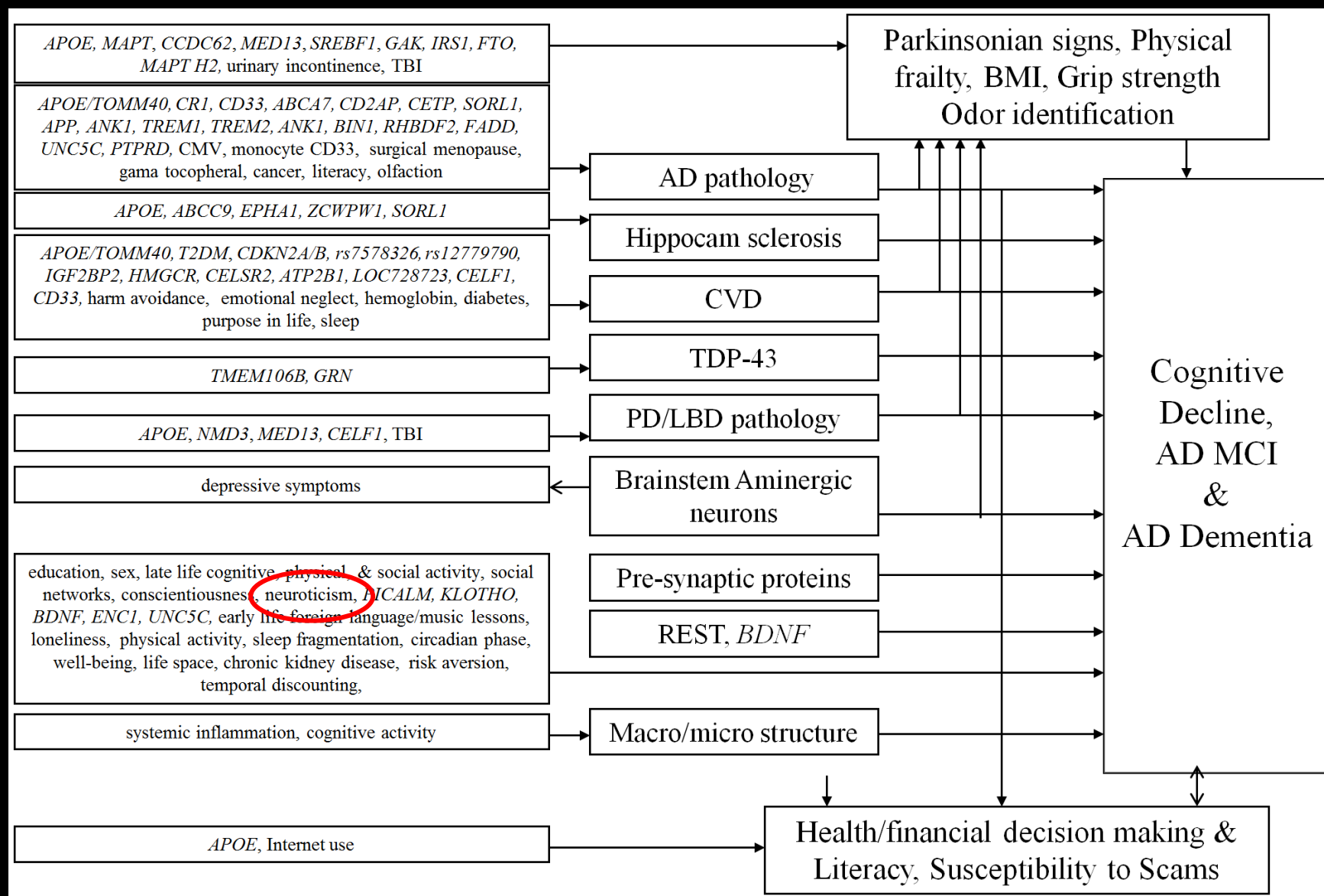
Neural reserve, neuronal density in the locus coeruleus, and cognitive decline



Cortical Proteins Associated With Cognitive Resilience in Community-Dwelling Older Persons

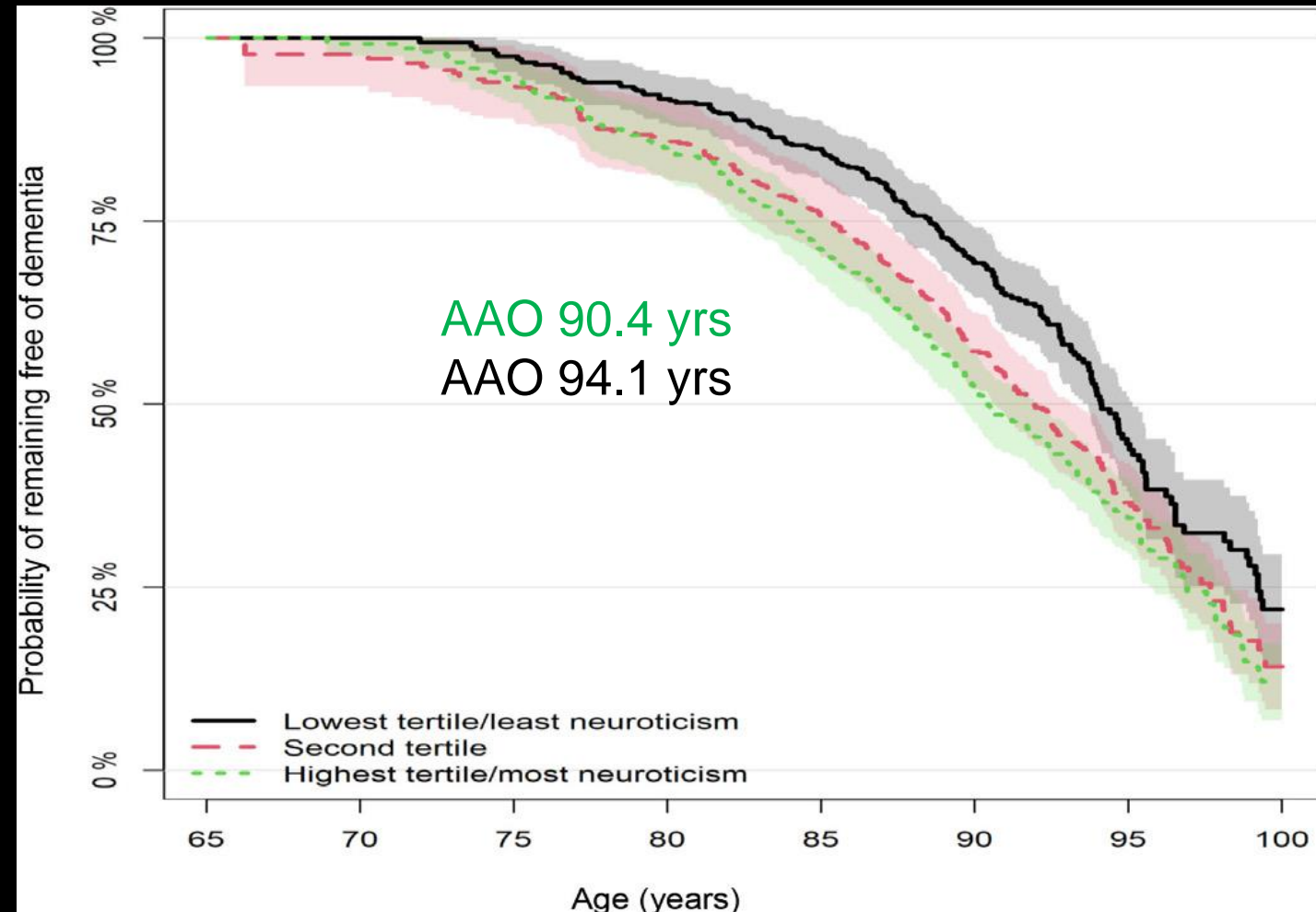


Religious Orders Study and Rush Memory and Aging Project

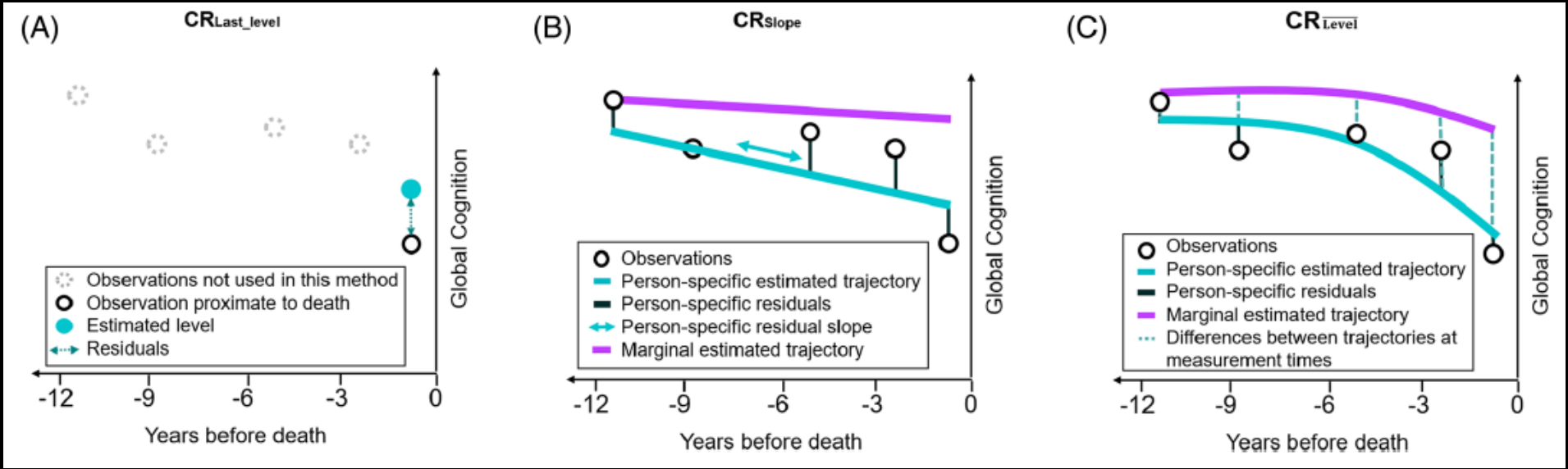


Modifiable psychosocial risk factors and delayed onset of dementia in older populations: analysis of two prospective US cohorts

Neuroticism (NEO) refers to the disposition to experience psychological distress (e.g., I am not a worrier; I often feel tense and jittery; I often get angry at the way people treat me; I often feel helpless and want someone else to solve my problems).



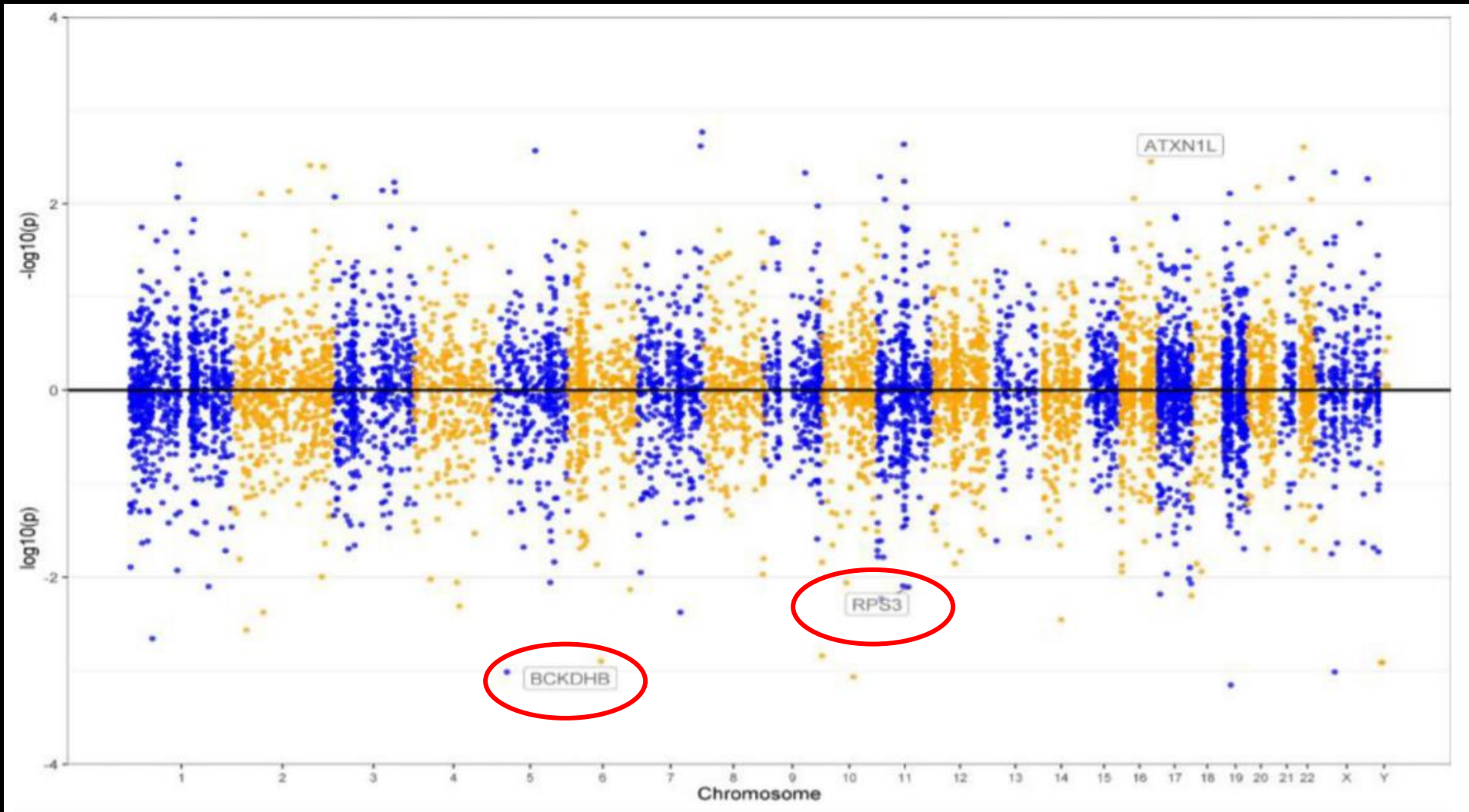
Quantifying longitudinal cognitive resilience to Alzheimer's disease and other neuropathologies



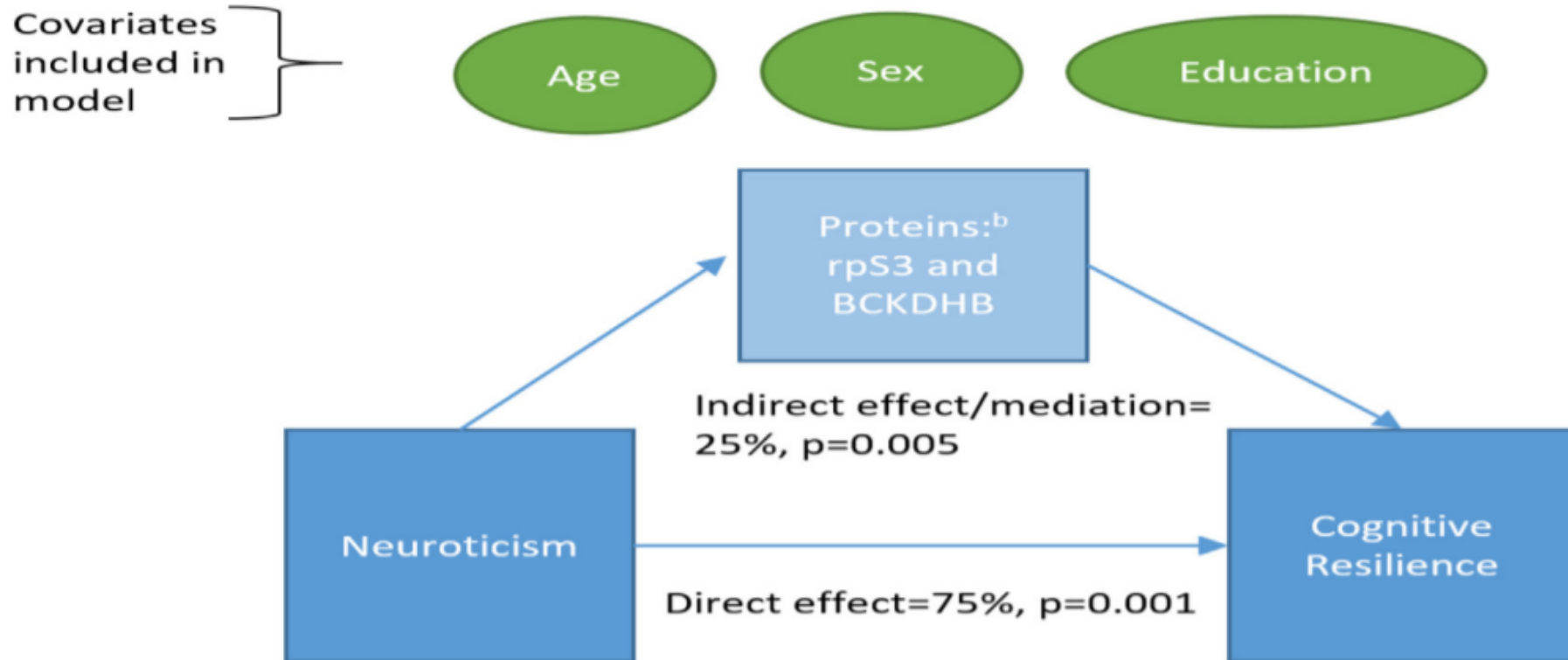
	CR_{Last_level}			CR_{Slope}			CR_{Level}		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Late-life cognitive activity, score ^b	0.167	(0.099; 0.236)	$<2 \times 10^{-6}$	0.041	(-0.028; 0.110)	.244	0.243	(0.175; 0.311)	$<3 \times 10^{-12}$
Education, years	0.029	(0.013; 0.044)	.0002	-0.002	(-0.017; 0.014)	.844	0.059	(0.044; 0.074)	$<3 \times 10^{-14}$
Neuroticism, score	-0.025	(-0.035; -0.016)	$<2 \times 10^{-7}$	-0.012	(-0.022; -0.003)	.012	-0.031	(-0.040; -0.022)	$<5 \times 10^{-11}$
Nb. of depressive symptoms	-0.081	(-0.117; -0.045)	$<2 \times 10^{-5}$	-0.079	(-0.115; -0.042)	$<3 \times 10^{-5}$	-0.094	(-0.131; -0.058)	$<4 \times 10^{-7}$

Exploring cortical proteins underlying the relation of neuroticism to cognitive resilience

Chicago Plot showing direction of association



Exploring cortical proteins underlying the relation of neuroticism to cognitive resilience

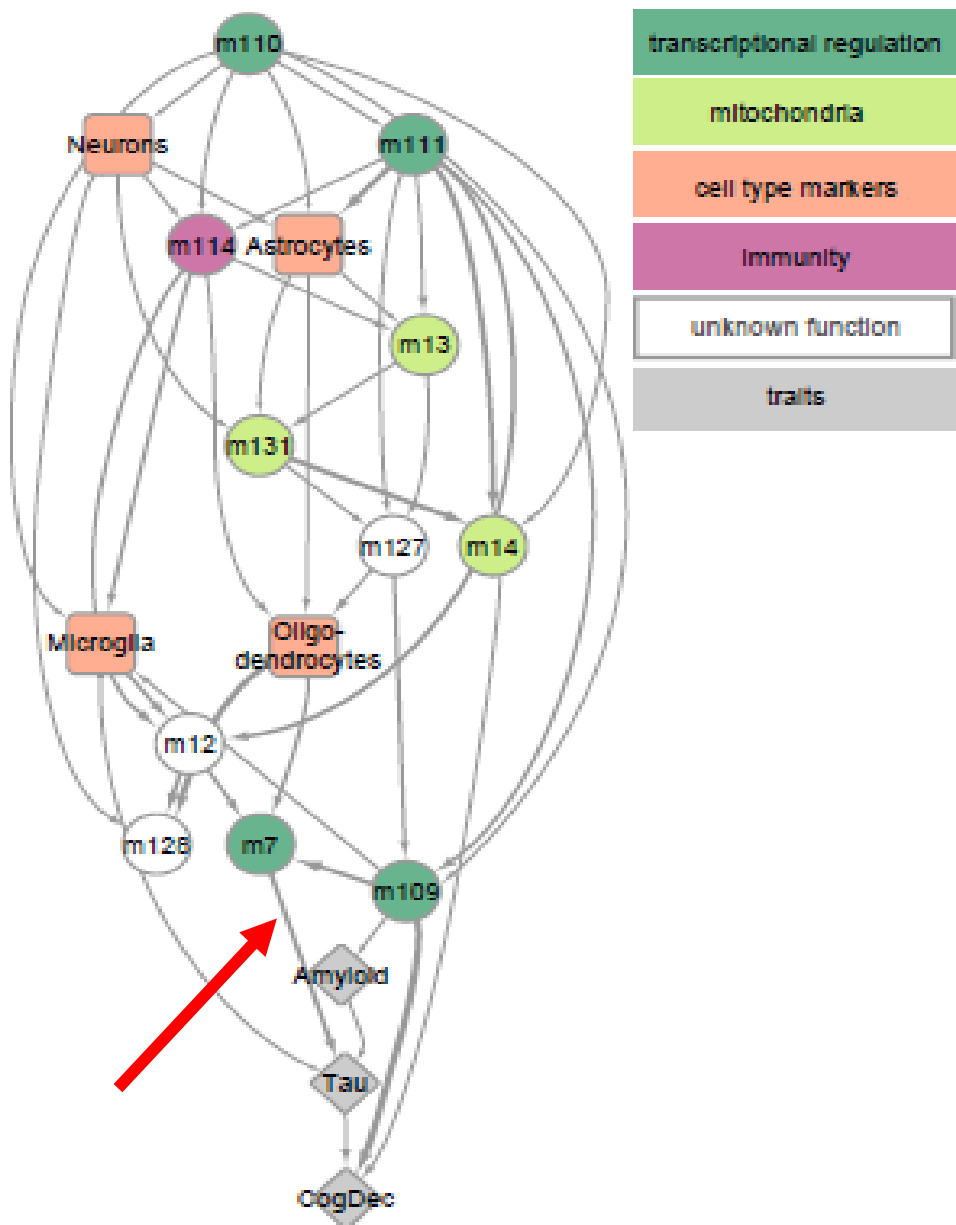


Total effect of neuroticism on Cognitive Resilience: $\beta = -0.167$, $p=0.001$

Indirect effect of proteins on relation of neuroticism to Resilience: $\beta = -0.042$, $p=0.005$

A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease

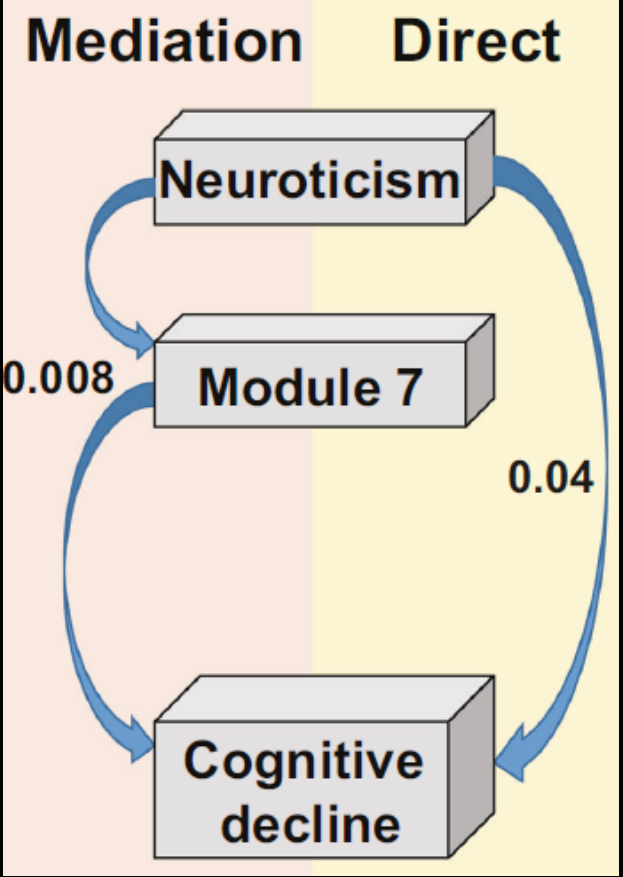
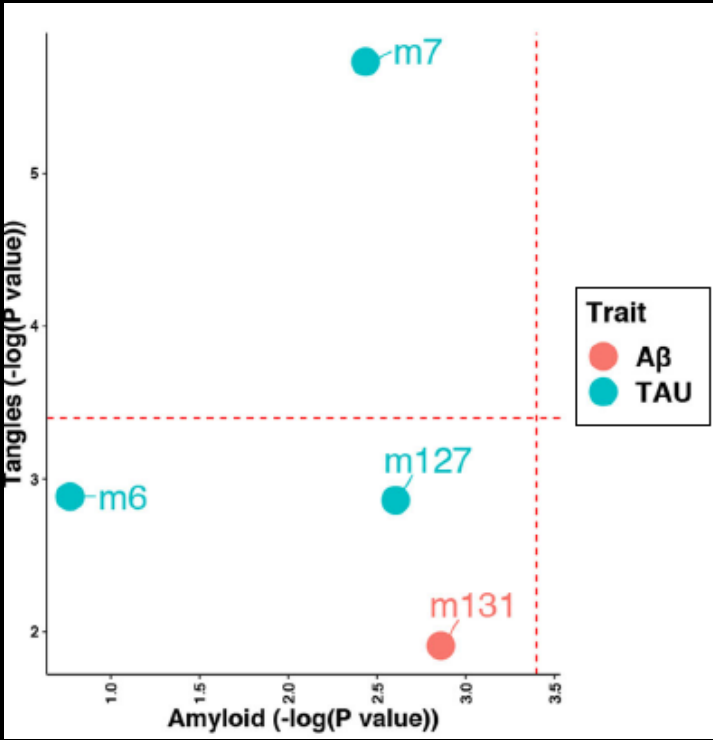
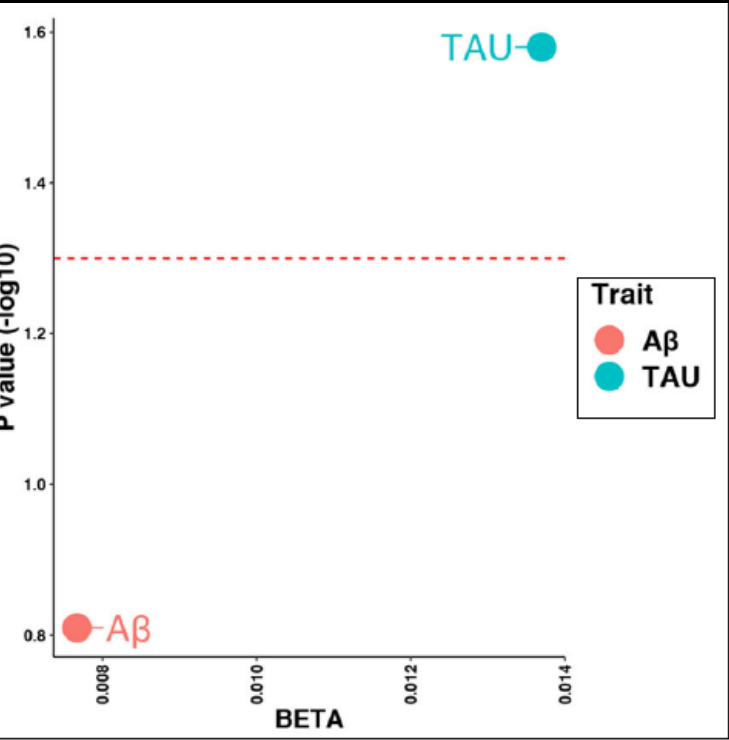
47 co-expression networks
53 ADRD phenotypes



Neuroticism alters the transcriptome of the frontal cortex to contribute to the cognitive decline and onset of Alzheimer's disease

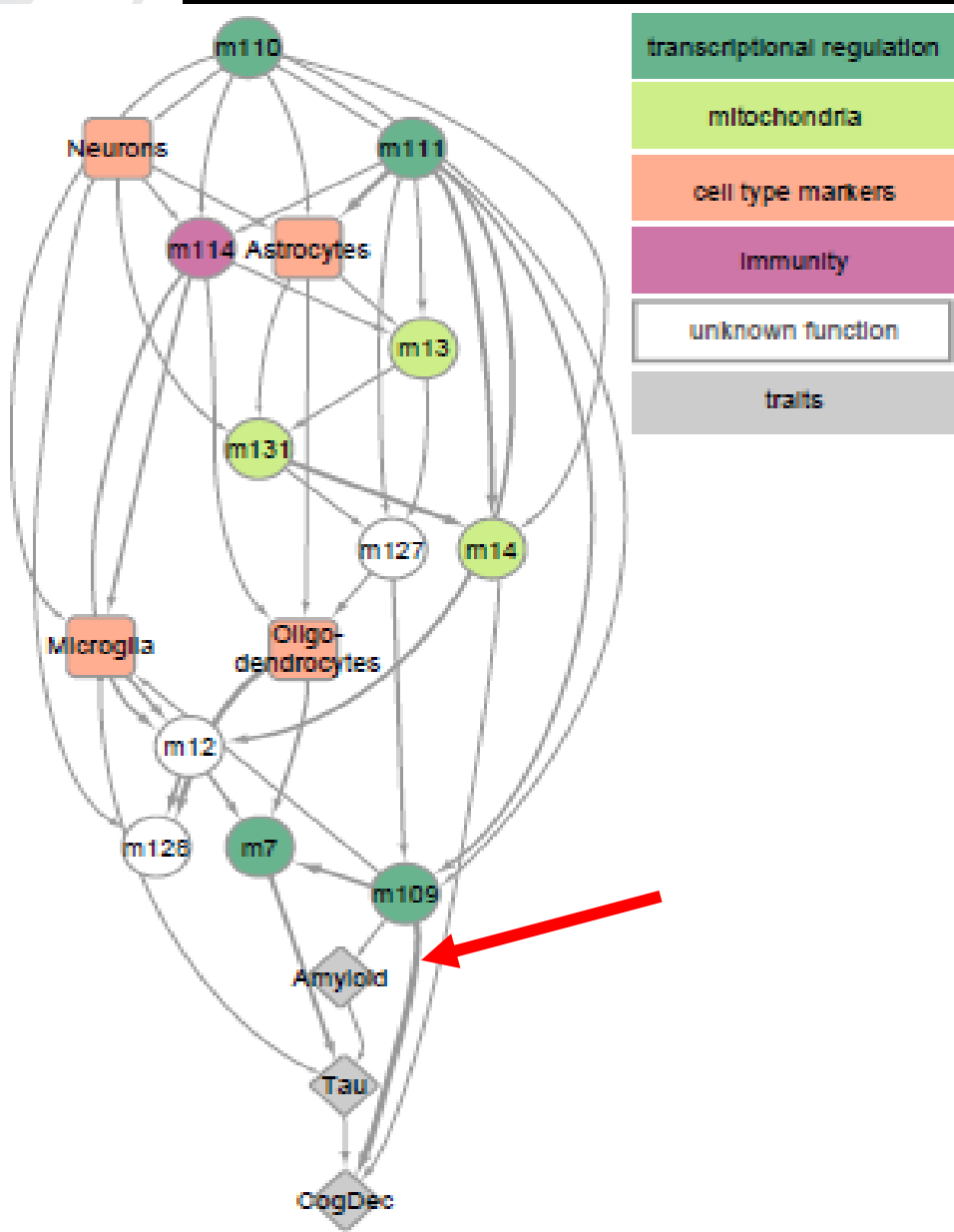
M7 mediates association of neuroticism with cognitive decline

Neuroticism a/w tau pathology m7 a/w tau pathology

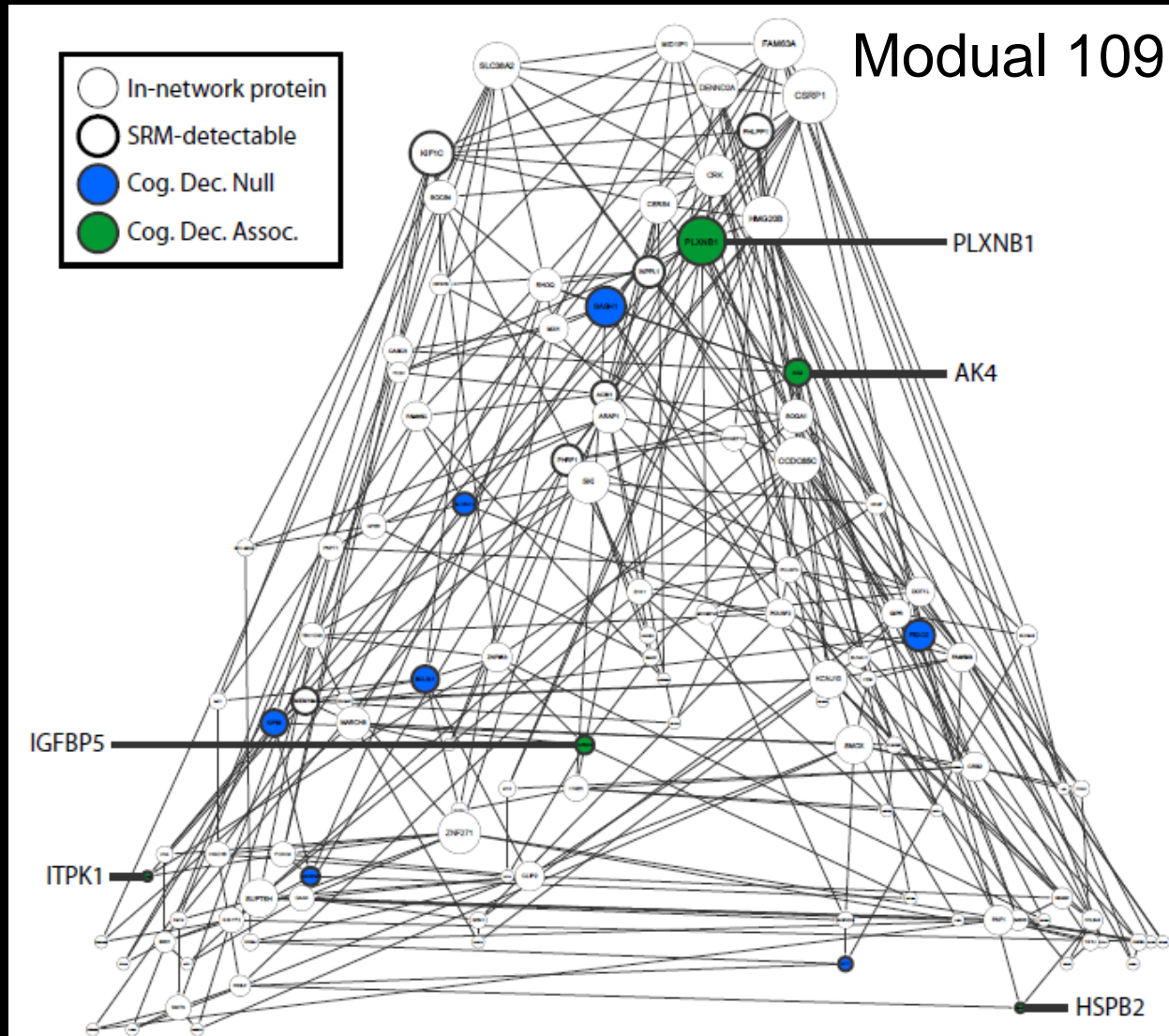


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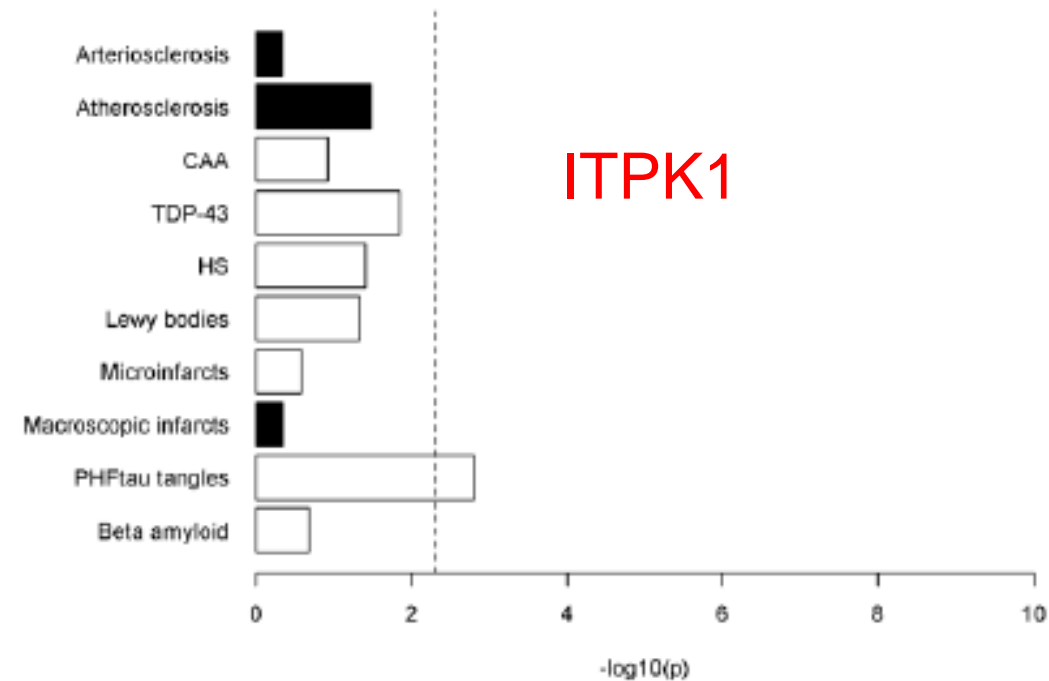
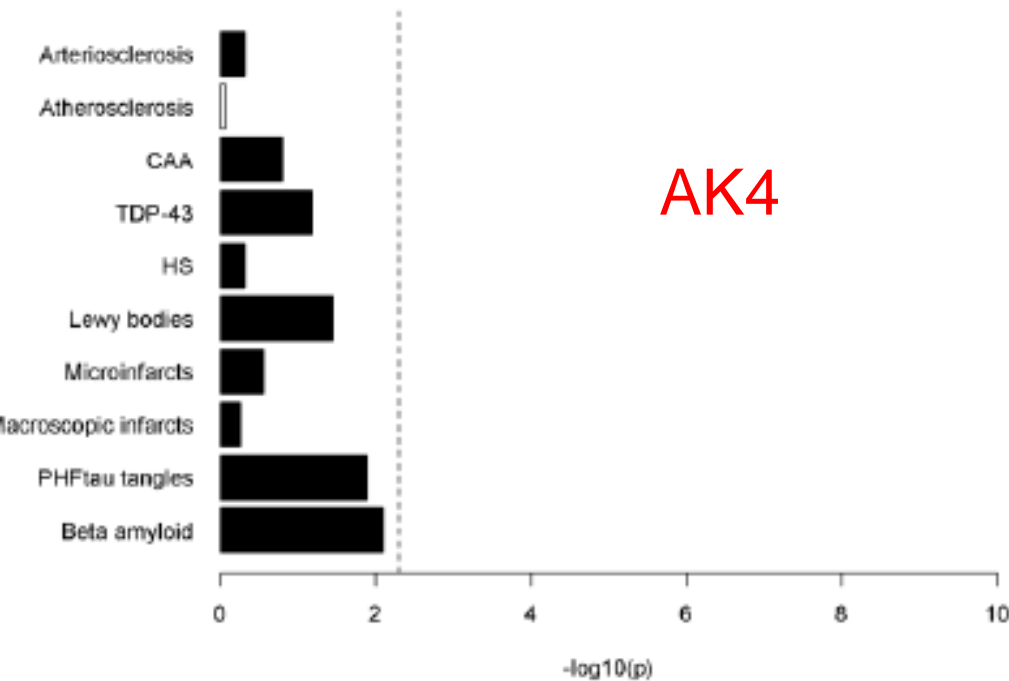
Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia



Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia

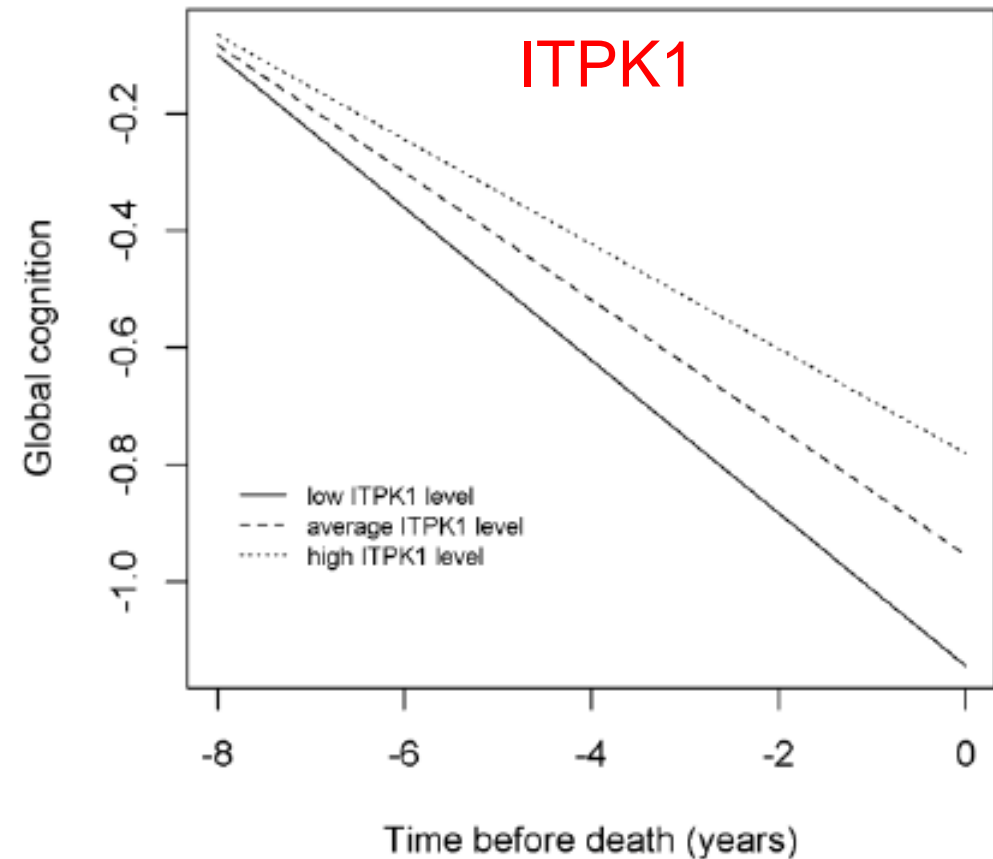
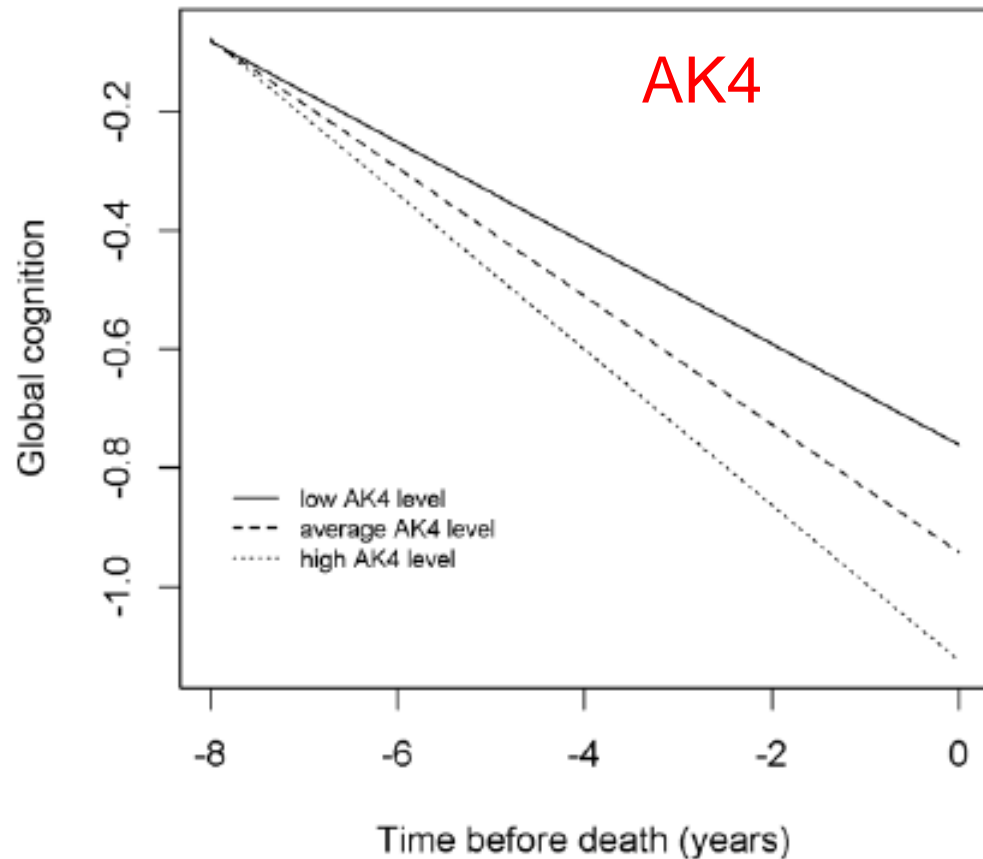
Protein	Cog Decline Est	P value
AK4	-0.090	7.3×10^{-6}
ANKRD40	-0.0009	0.922
BCL2L1	-0.012	0.576
FBXO2	-0.023	0.033
HSPB2	-0.048	7.4×10^{-6}
IGFBP5	-0.063	1.2×10^{-16}
ITPK1	0.056	7.8×10^{-5}
KIF5B	0.006	0.606
SASH1	0.006	0.512
SLC6A12	-0.034	0.006
VAT1	-0.023	0.017

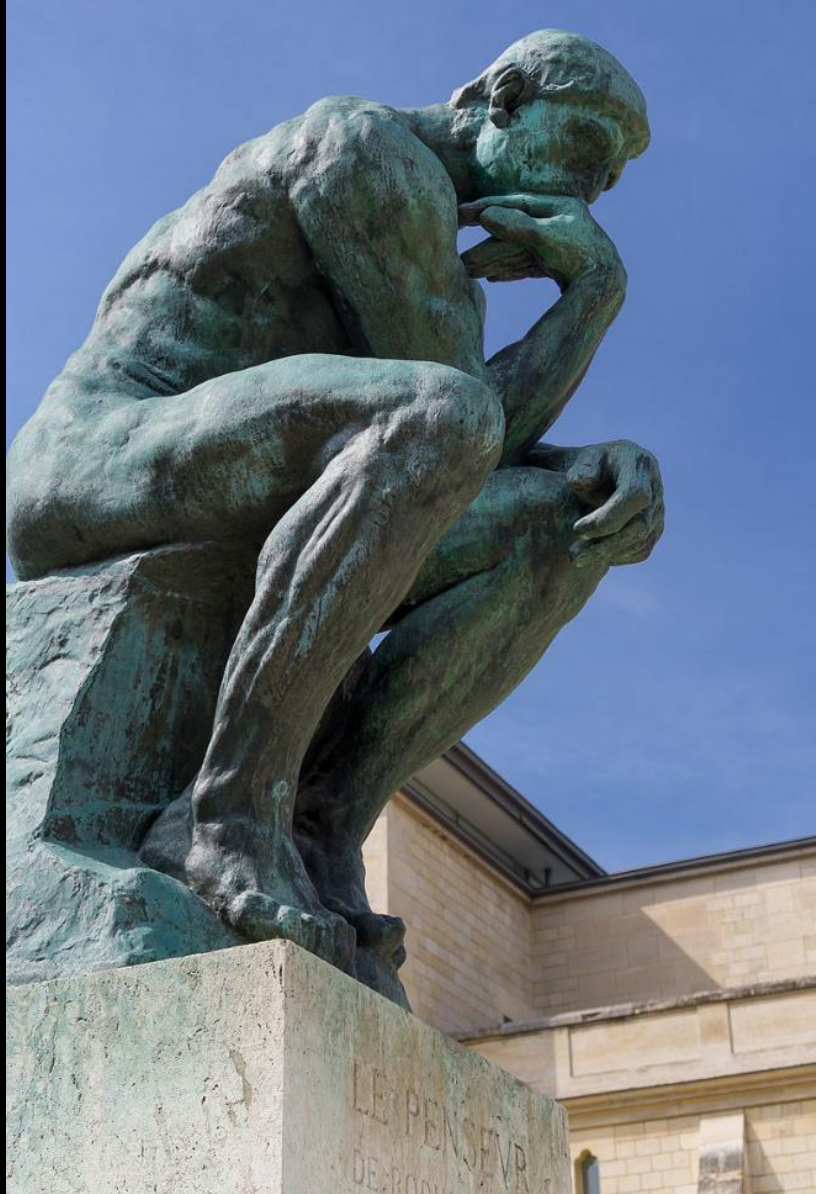
Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia



Black is positive and white is negative association

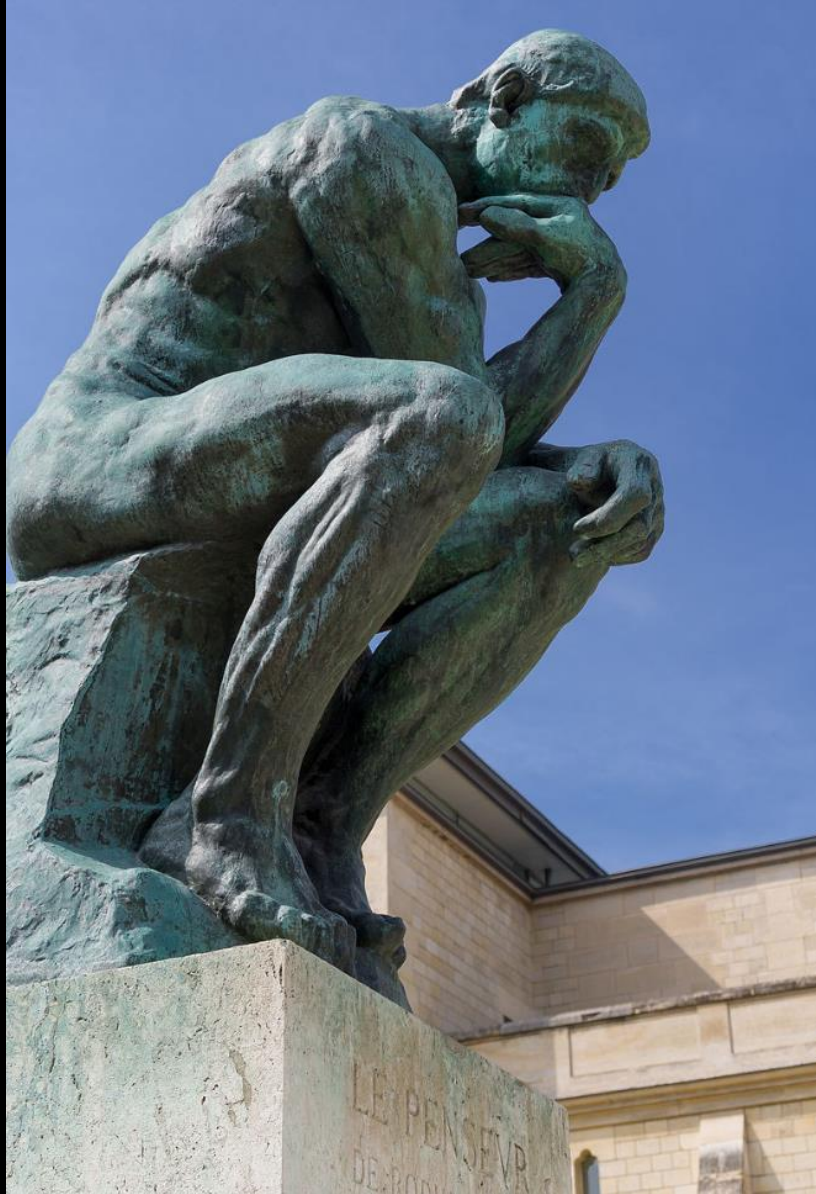
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Path to AD/ADRD Personalized Medicine

For complex diseases that cannot
be biopsied and interrogated in a
dish like cancer...
what is the path to AD/ADRD
personalized medicine?



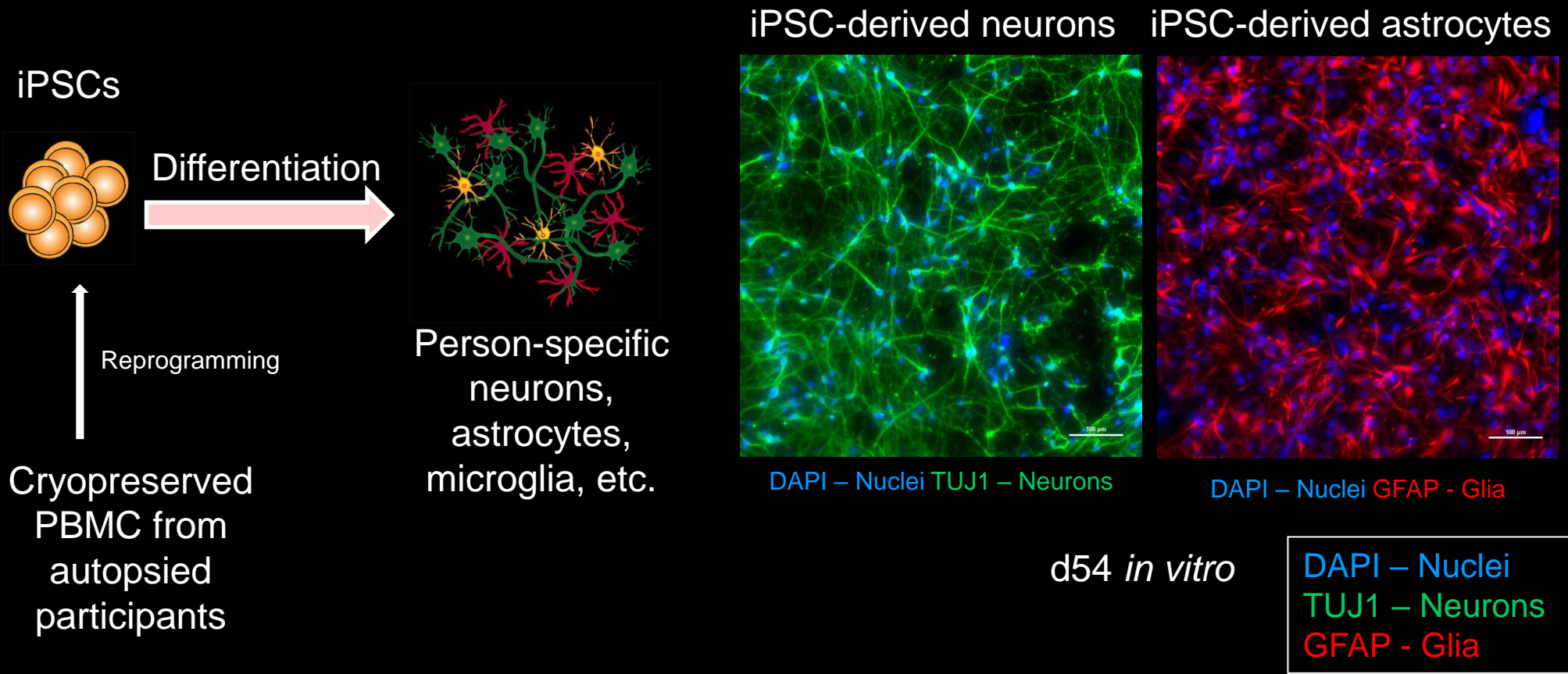
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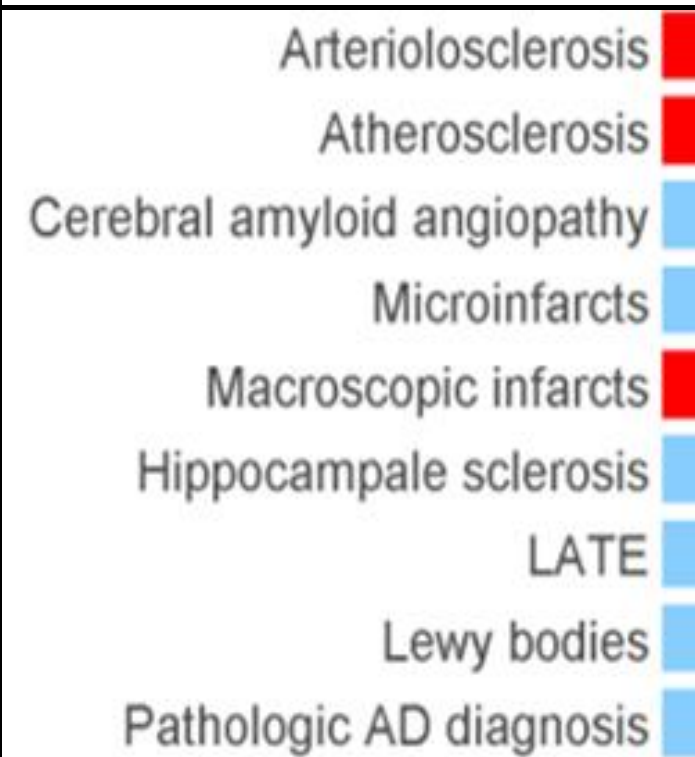
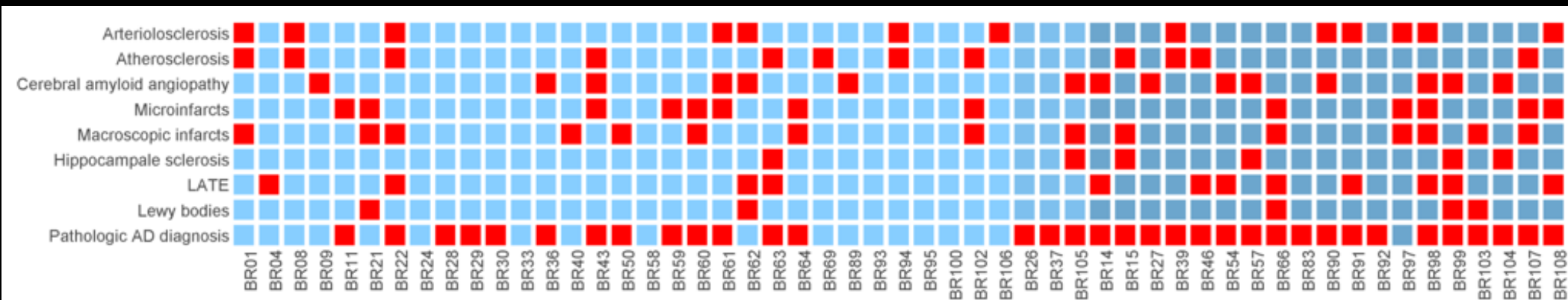
Need to study “person-specific”
differences in a “group” of human
brains... in a dish!

An approach that combines
epidemiologic study design with
human cell modeling

Neurons/Astrocytes Derived from ROSMAP iPSCs



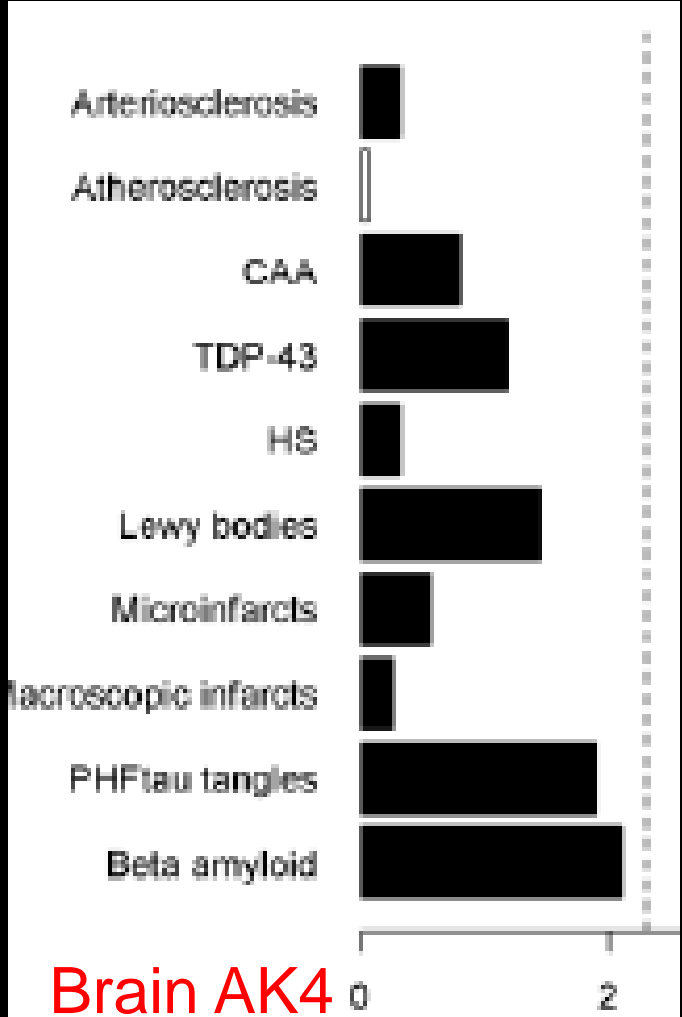
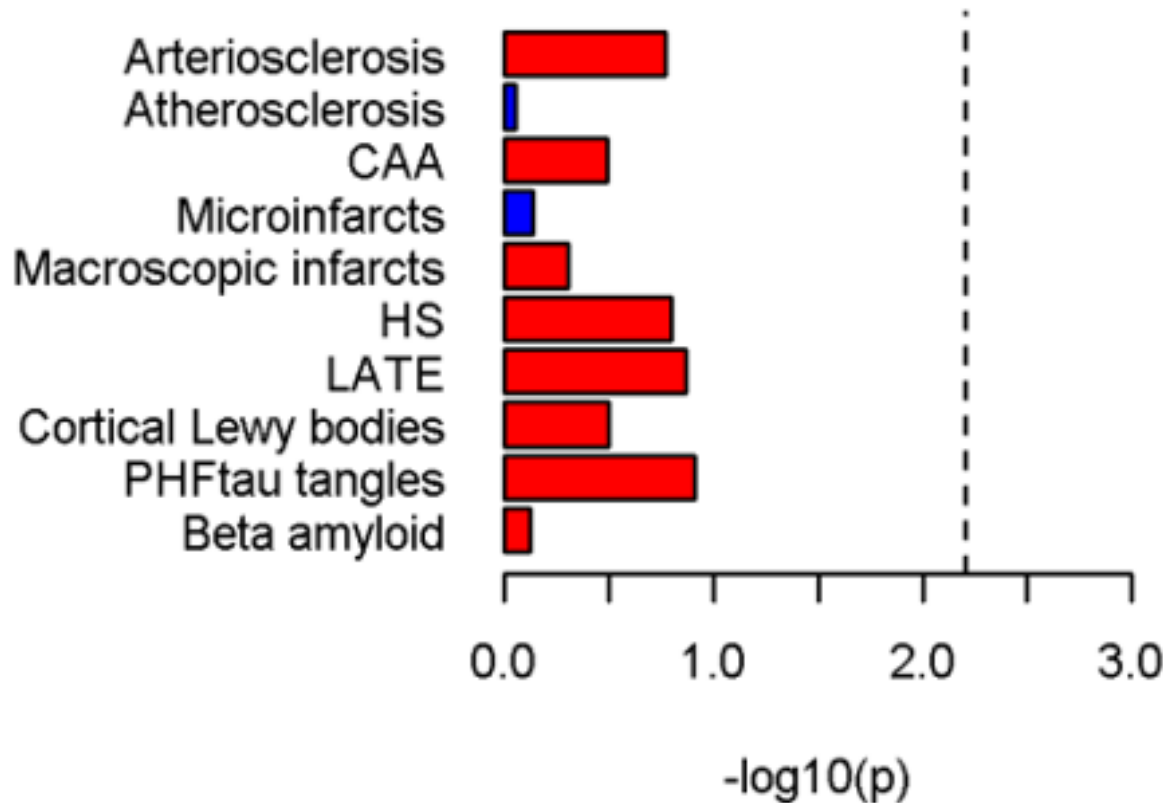
Association of AK4 protein from stem cell-derived neurons with cognitive reserve in human donors



Association of AK4 protein from stem cell-derived neurons with cognitive reserve in human donors

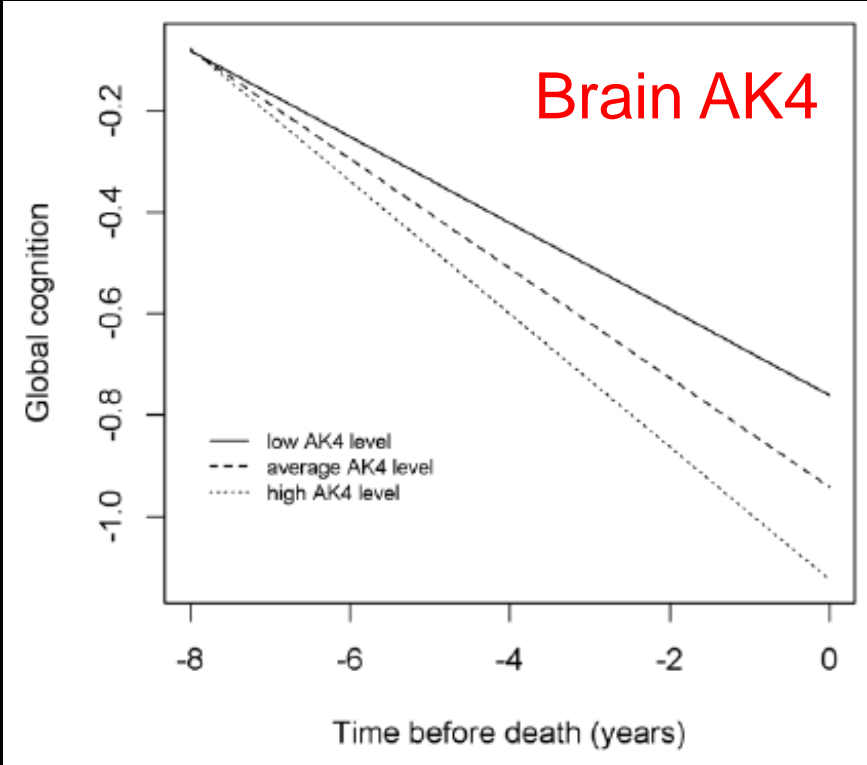
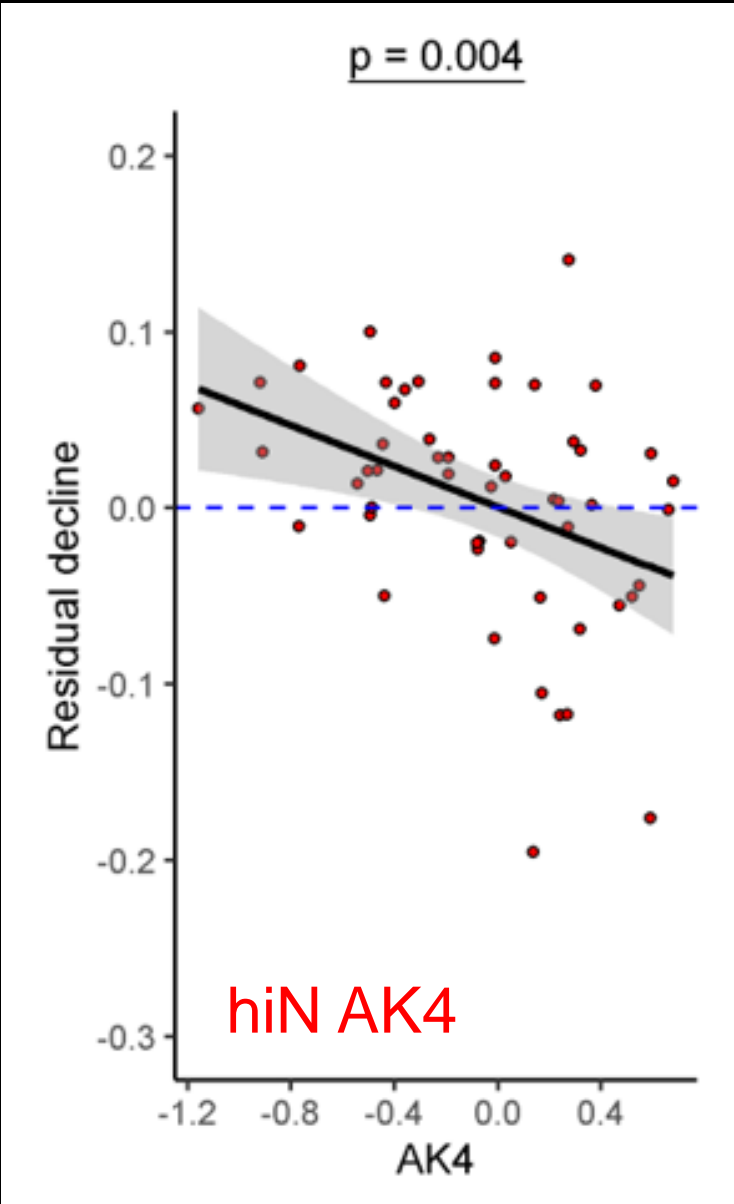
hiN AK4

AK4|P27144



Brain AK4

Association of AK4 protein from stem cell-derived neurons with cognitive reserve in human donors



Summary

- Resilience, here defined as residual cognitive decline, accounts for about half of person-specific change in cognition at the end of life
- A variety of cellular and molecular mechanisms contribute to more or less resilience:
 - presynaptic proteins, cell loss in the locus coeruleus, EPHX4, CPLX1, SGTB, NRN1, RPH3A, SH3GL1, ACTN4, UBA1, rpS3, BCKDHB, m7, m109, AK4, ITPK1
- AK4 generated by hiPSC lines are associated with residual cognitive decline, possibly leading to a path towards personalized medicine

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