

Cell type-specific adaptive brain aging associated with cognitive resilience despite amyloid and tau pathology in Alzheimer's disease



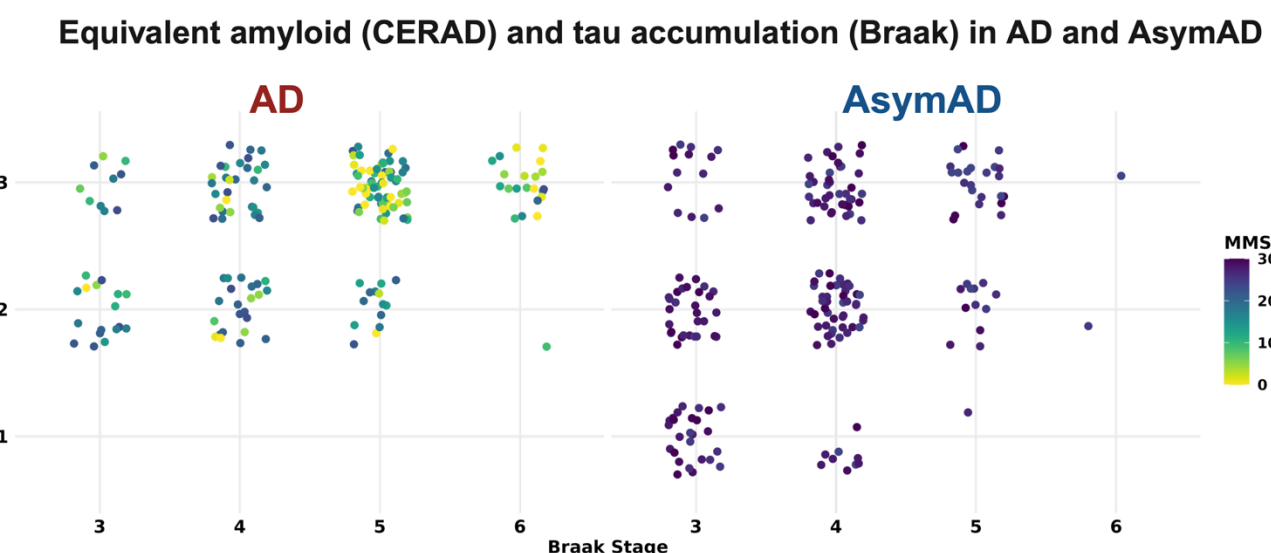
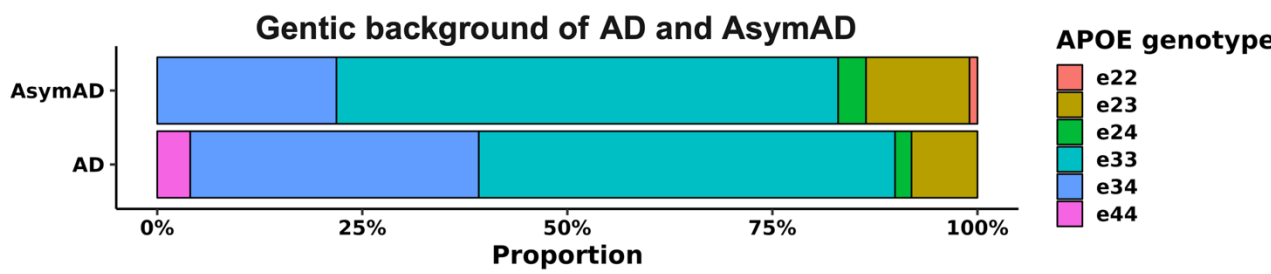
Purba Mandal, Priyanka Baloni

School of Health Sciences, Purdue University, West Lafayette, IN 47907, USA

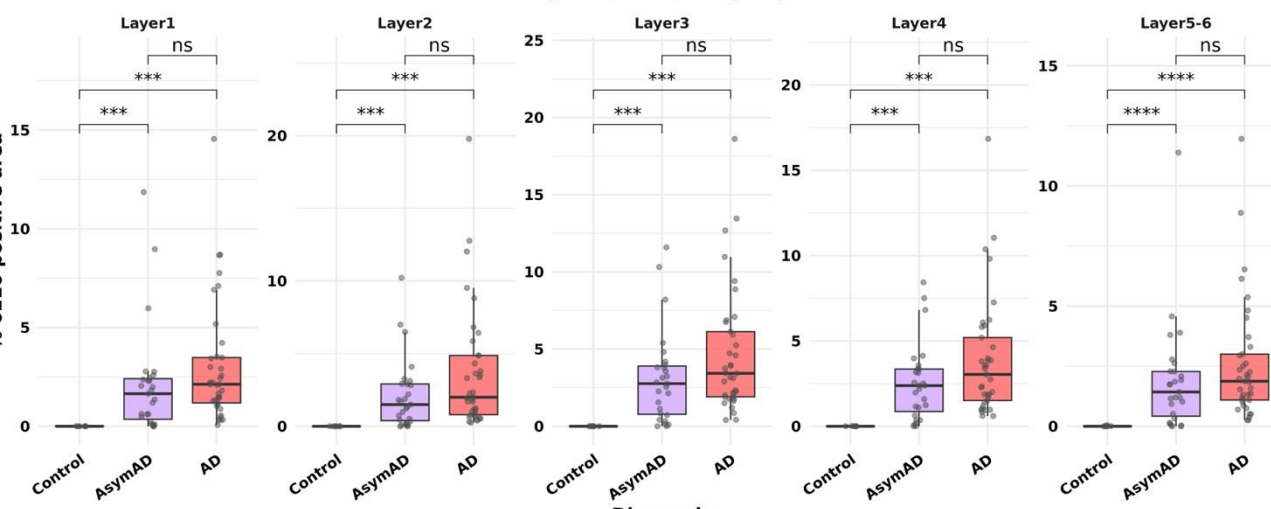
Cognitive resilience in the presence of amyloid- β and tau in Alzheimer's disease is driven by active, cell type-specific programs preserving mitochondrial energy, proteostasis, and neurotransmission while avoiding excitotoxicity and metabolic failure.

INTRODUCTION

- Alzheimer's disease affects around 7 million Americans making it the 6th largest cause of death in the USA (CDC 2025)
- Large scale human studies like ROSMAP have identified individuals with equivalent levels of amyloid- β and tau pathology in brain, and having normal cognition known as Asymptomatic AD (AsymAD)¹⁻³



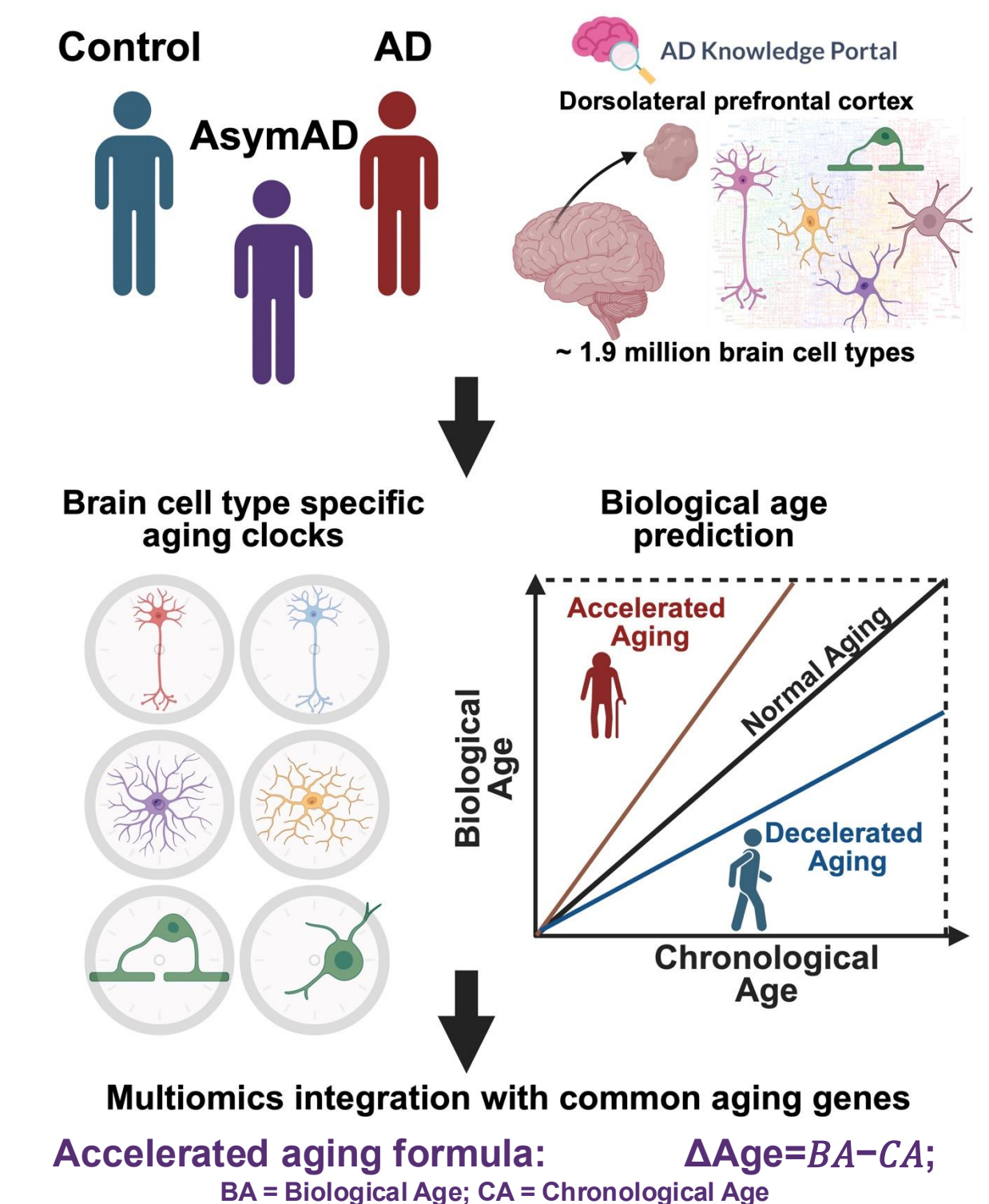
- Seattle AD (SEA-AD) shows increased accumulation of Amyloid beta in neuronal layers in AsymAD and AD compared to Cognitive normals^{4,5}



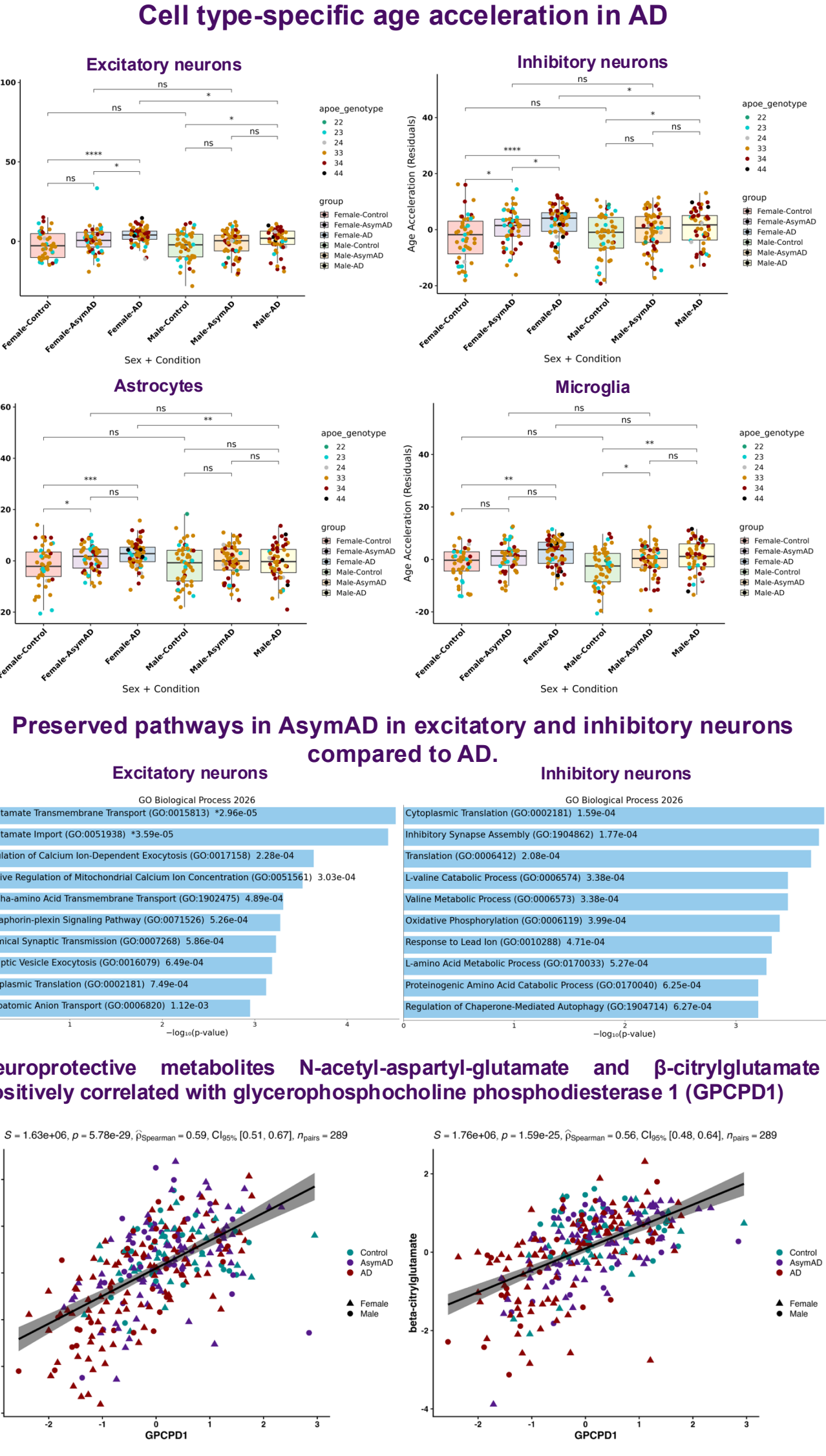
Amyloid beta	Tau tangles	Cognition
CERAD Score	Braak Stage	MMSE: Mini Mental State Examination
0: No neuritic plaques	0: No neurofibrillary tangles	MMSE score >= 24 = No dementia
1: Sparse neuritic plaques	1-2: NFT confined mainly to the entorhinal region of the brain	MMSE score < 24 = Dementia
2: Moderate neuritic plaques	3-4: NFT in limbic regions such as hippocampus	
3: Frequent neuritic plaques	5-6: Moderate to severe NFT in neocortical regions	

METHODS

- We leveraged six published transcriptomic aging clocks trained on human cell type-specific single-nucleus RNA-sequencing data, where regression models predicted chronological age across excitatory and inhibitory neurons, oligodendrocytes, OPCs, microglia, and astrocytes⁶.
- Using ~1.9 million nuclei from the dorsolateral prefrontal cortex (BA9) of 345 ROSMAP donors (100 Control, 120 AsymAD, 125 AD), we applied these models to estimate biological age and assess age acceleration in AD versus AsymAD.
- Unique aging-associated genes were identified in AsymAD and were validated using proteomics with additional integration of metabolomics



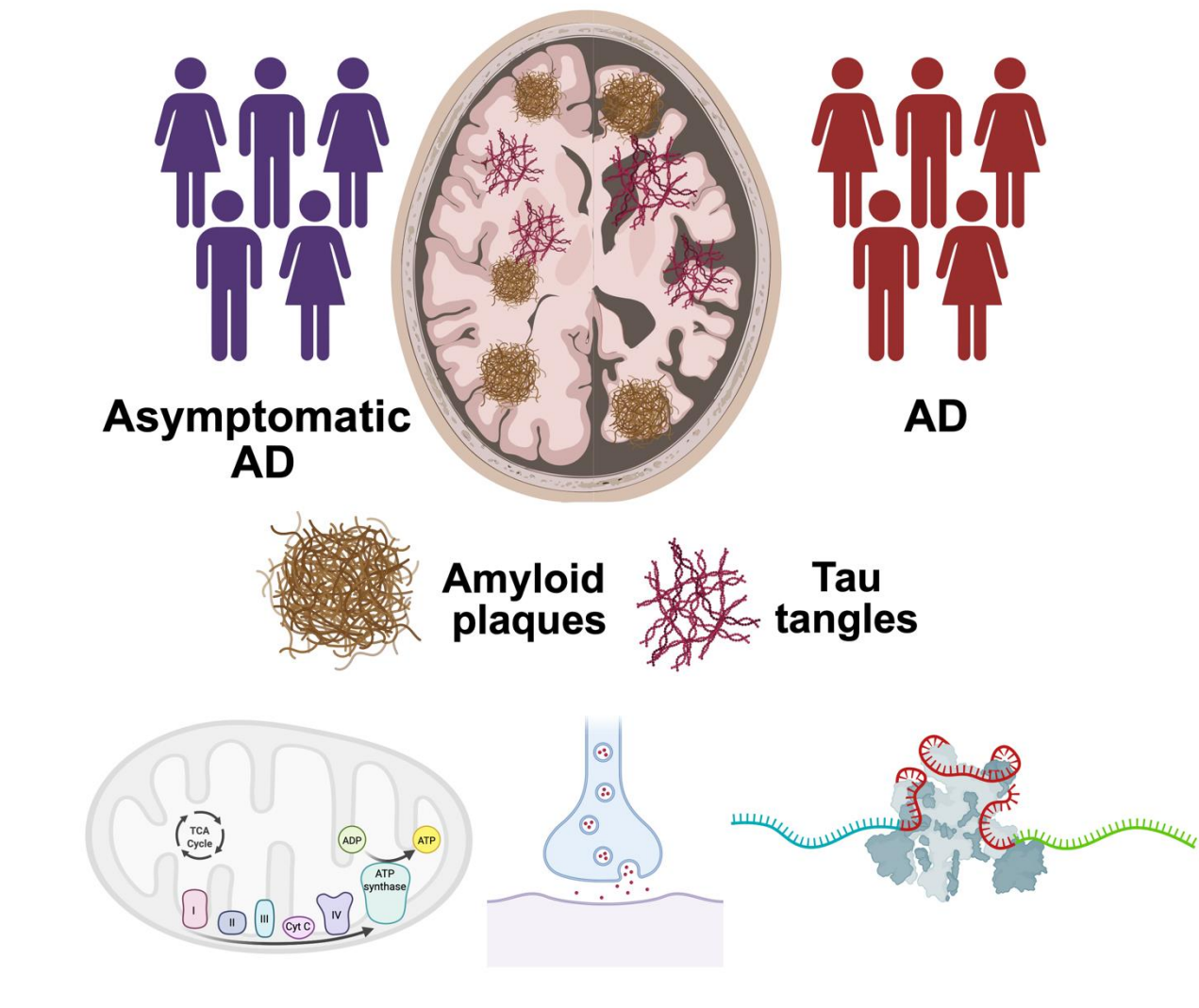
RESULTS



CONCLUSIONS

- Excitatory neurons, inhibitory neurons, and microglia showed significant biological age acceleration in AD compared to AsymAD, with female neurons, astrocytes, and oligodendrocytes aging faster than males.
- AsymAD preserved pathways linked to mitochondrial electron transport, oxidative phosphorylation, cytoplasmic translation, enhanced regulation of L-glutamate transport and calcium-dependent signaling, consistent with protection from excitotoxic stress.
- Neuroprotective metabolites including N-acetyl-aspartyl-glutamate and β -citrylglutamate were positively correlated with glycerophosphocholine phosphodiesterase 1 GPCPD1 indicating coordinated phospholipid turnover and energy metabolism.

Our analyses demonstrate that cognitive resilience in the presence of amyloid- β and tau is driven by active, cell-type specific programs preserving mitochondrial energy, proteostasis, and neurotransmission while avoiding excitotoxicity and metabolic failure. These cell-resolved markers offer a framework for targeting resilience mechanisms rather than pathology in future therapies.



REFERENCES

- Mandal P, Trushina E, Arnold M, Kaddurah-Daouk R, Baloni P. Mitochondrial bioenergetic signatures differentiate asymptomatic from symptomatic Alzheimer's disease. *Commun Biol.* 2026 Jun 10. doi: 10.1038/s42003-026-10474-8. Epub ahead of print. PMID: 42270947.
- Neuner, Sarah M et al. "Translational approaches to understanding resilience to Alzheimer's disease." *Trends in neurosciences* , 2022
- Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimer's Dement.* 2023;19:658–670.
- Kapasi, Alifiya et al. "High-throughput digital quantification of Alzheimer disease pathology and associated infrastructure in large autopsy studies." *Journal of neuropathology and experimental neurology* vol. 82,12 (2023)
- Gabitto, M.I., Travaglini, K.J., Rachleff, V.M. *et al.* Integrated multimodal cell atlas of Alzheimer's disease. *Nat Neurosci* 27, 2366–2383 (2024).
- C. Muralidharan, E. Zakar-Polyák, A. Adami, et al. "Human Brain Cell-Type-Specific Aging Clocks Based on Single-Nuclei Transcriptomics." *Adv. Sci.*12, no. 43 (2025): e06109.

CONTACT



Graduate student:
Purba Mandal;
mandal11@purdue.edu
PI/corresponding author:
Dr. Priyanka Baloni;
pbaloni@purdue.edu

