Defining Neurodegenerative Disease Through Precision Biology

Multimodal profiling and statistical machine learning in Alzheimer's disease

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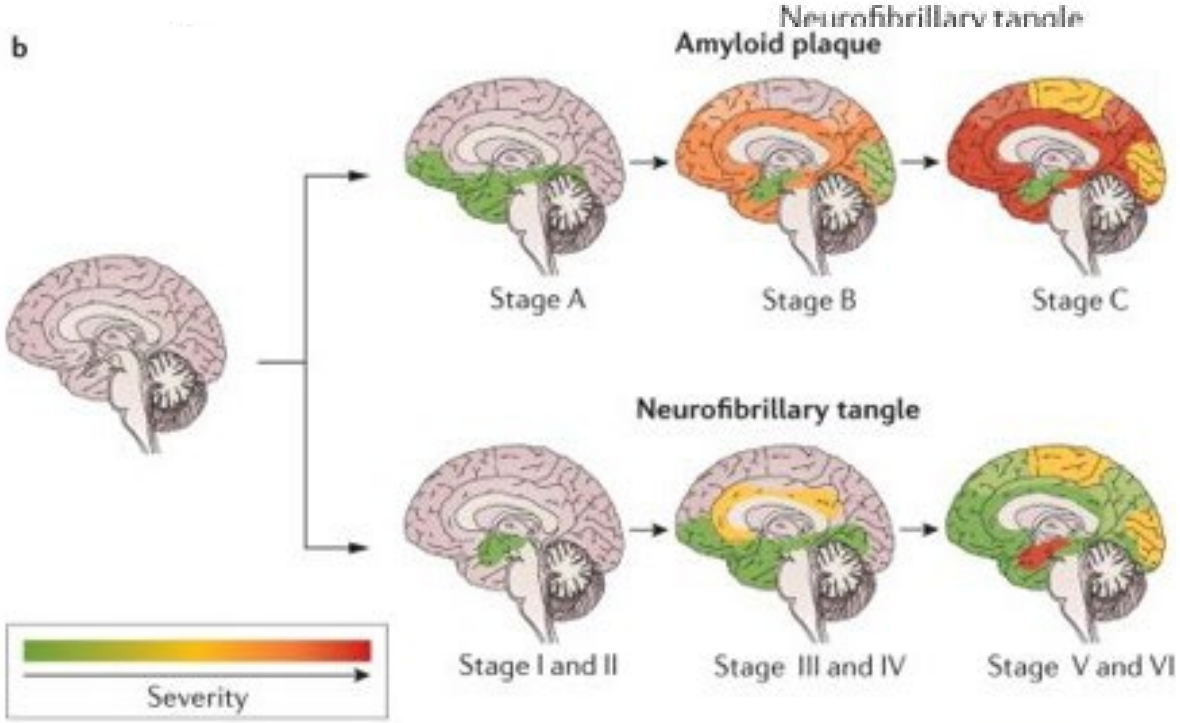
Alzheimer's Disease (AD) a Biologically Grounded and Progressive Brain Disease

AD is the most common form of dementia, affecting +6M adults in the US alone over the age of 65.



Disease progression follows **stereotypical spatiotemporal** trajectories across the brain

SEA-AD: A Multidisciplinary Platform for Defining AD Biology

UW Medicine

ALLEN INSTITUTE for BRAIN SCIENCE

KAISER PERMANENTE

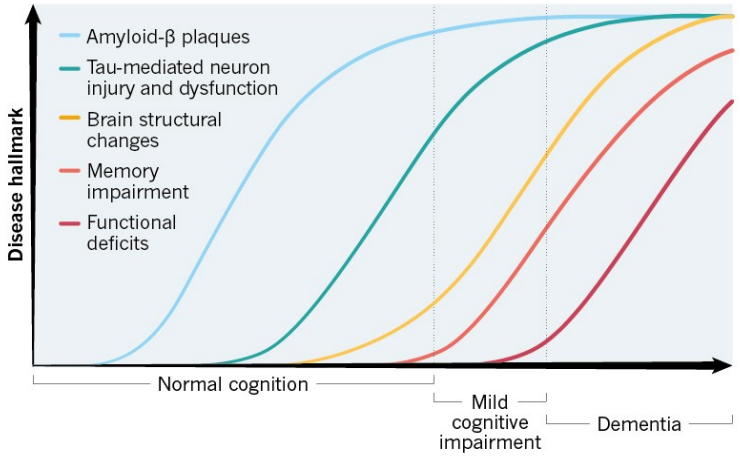
Kaiser Permanente Washington Health Research Institute

ADRC Alzheimer's Disease Research Center

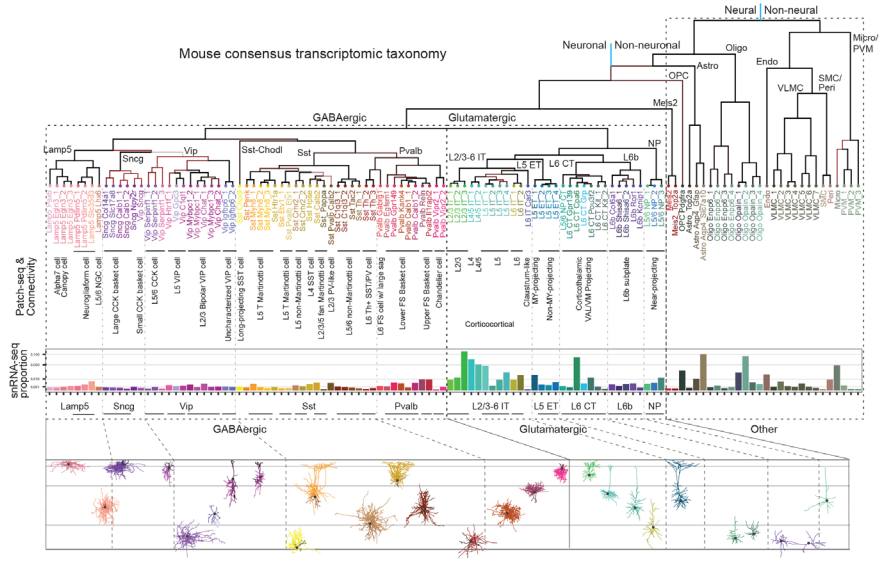
NIH National Institute on Aging

Neuropathology – Genomics – Clinical Phenotyping – Computational Modeling

SEA-AD Aspiration: Defining Alzheimer's Through Precision Cellular Biology



Drew L. (2018) *Nature*



BICCN (2021) *Nature*

Strategy

Deep, multimodal profiling of human brain tissue using state-of-the-art tissue preservation that enabled single-cell genomics and neuropathology, combined with clinical phenotyping and computational modeling.

Core Questions

- **Are specific cell types selectively vulnerable or resilient?**
- **Does AD progression represent an abnormal aging trajectory?**
- **Which molecular pathways are perturbed, in which cells, and when?**
- **Can this cellular resolution reveal actionable therapeutic targets?**

We aim to move from descriptive pathology to mechanistic cellular definition.

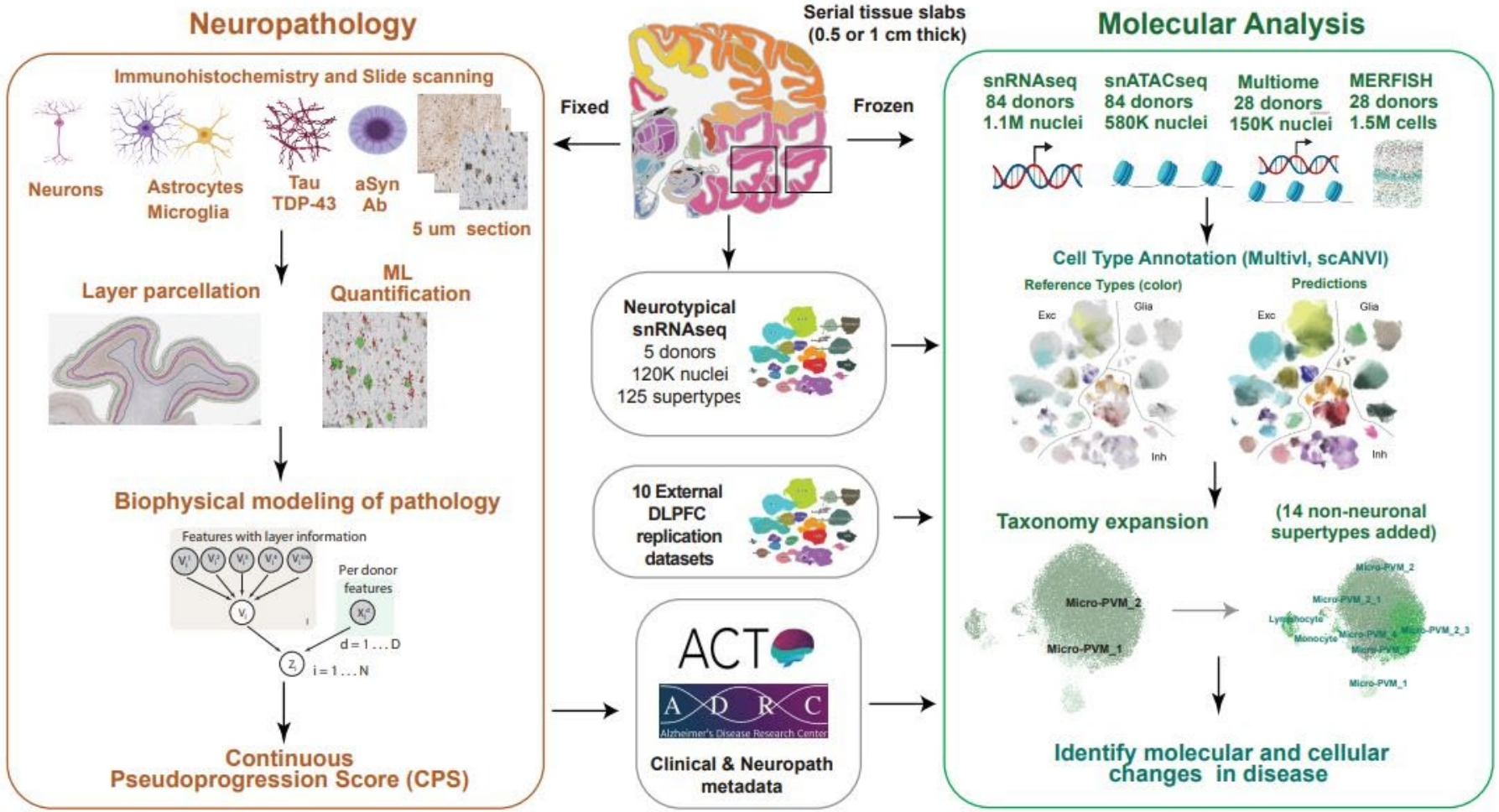
SEA-AD : Building a Reference-Scale Multimodal Atlas of AD

Integrated multimodal experimental paradigm

Profile

Middle Temporal Gyrus (MTG)

~100 Brain Donors

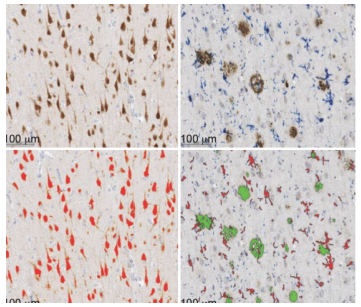


Gabitto*, Travaglini* et al. (2024) *Nature Neuroscience*

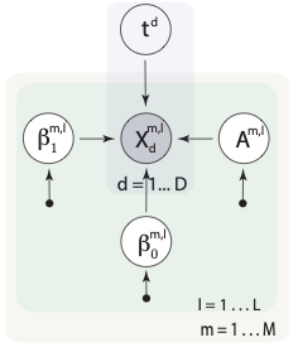
Modeling Alzheimer's Disease Across Scales

Donor-level severity modeling and single-cell generative representations

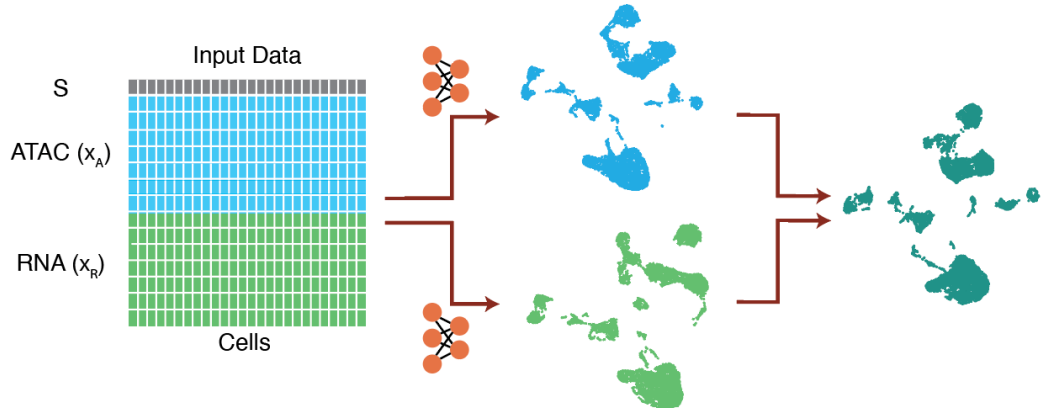
Quantitative** Description of **Brain Pathology.



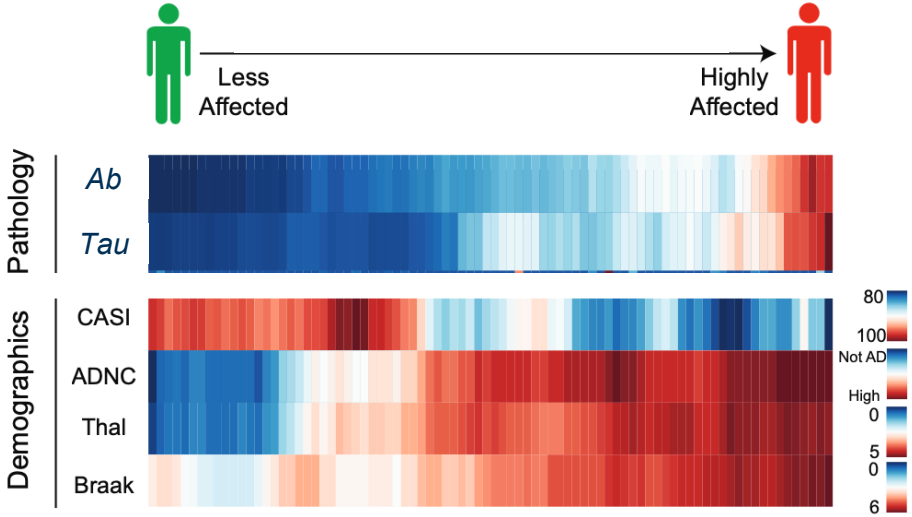
Biophysically-Inspired Hierarchical Bayesian Model



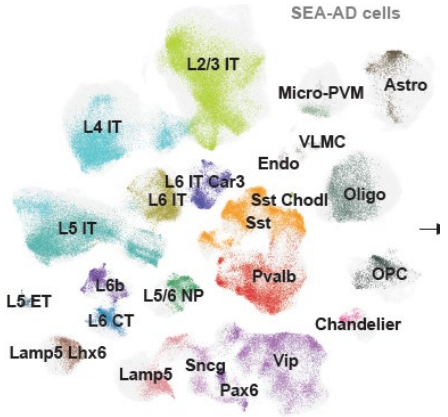
ML Deep Generative Models to describe single cells

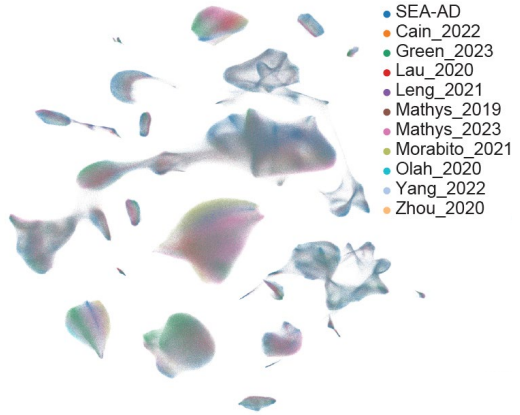


*Created a per-Brain donor **Scale of Disease Severity***



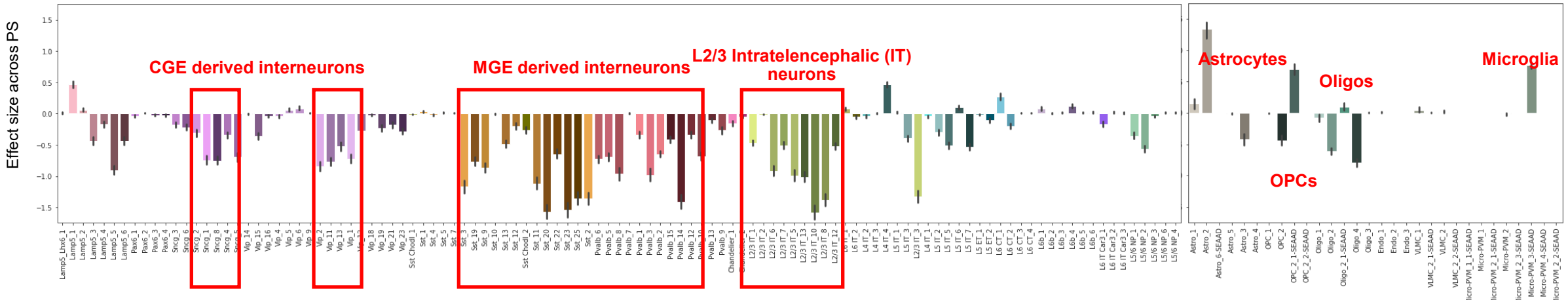
Multimodal AD-disease Reference taxonomy + Integration of publicly datasets ~700 donors





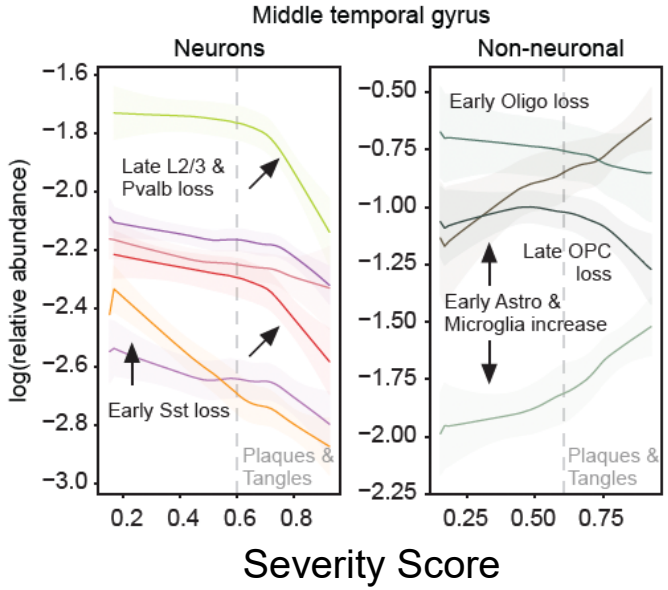
Agrawal et al. (2025) *Annals of Applied Statistics*

Selective Cellular Vulnerability Reveals Early Circuit Disruption in AD



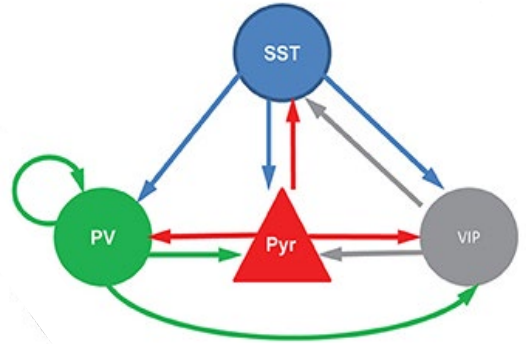
Donor Proportions ~ CPS + Age at death + Sex + Race + 10x Chemistry

Cell Type Trajectories Across Disease Progression



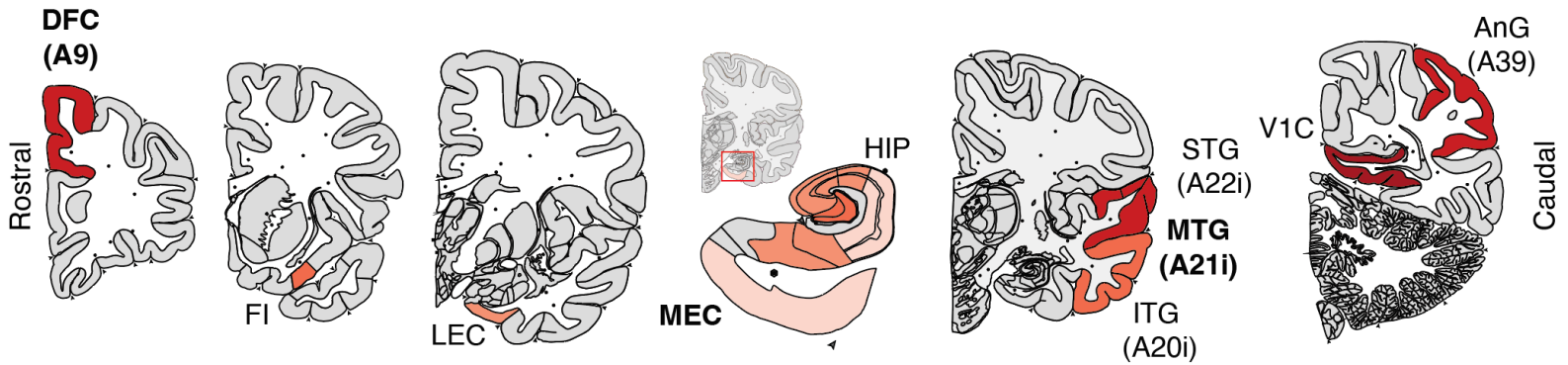
Earliest Vulnerable Neurons

SST Inhibitory Interneurons



Early disruption of SST interneurons may destabilize cortical excitation–inhibition balance at the onset of disease.

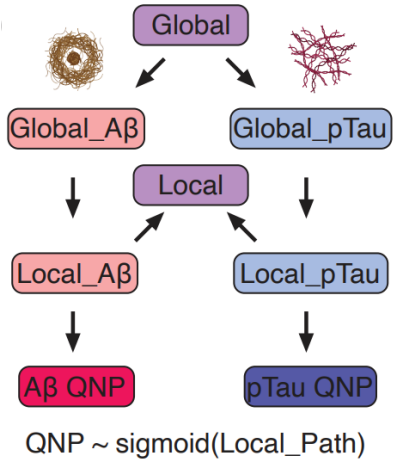
A Multiregional, Hierarchical Model of AD Progression



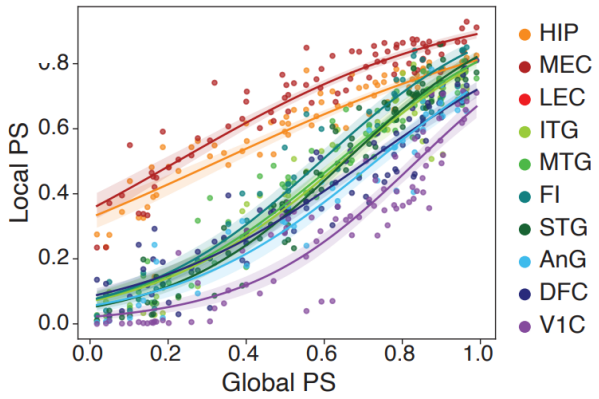
Braak I/II: MEC, CA1 (HIP) Braak III: Sub (HIP), CA2-3 (HIP), LEC Braak IV: CA4 (HIP), ITG, MTG, FI

Braak V: STG, DFC, AnG Braak VI: V1C AD spectrum only (n=43) / **AD spectrum and co-morbidities (n=84)**

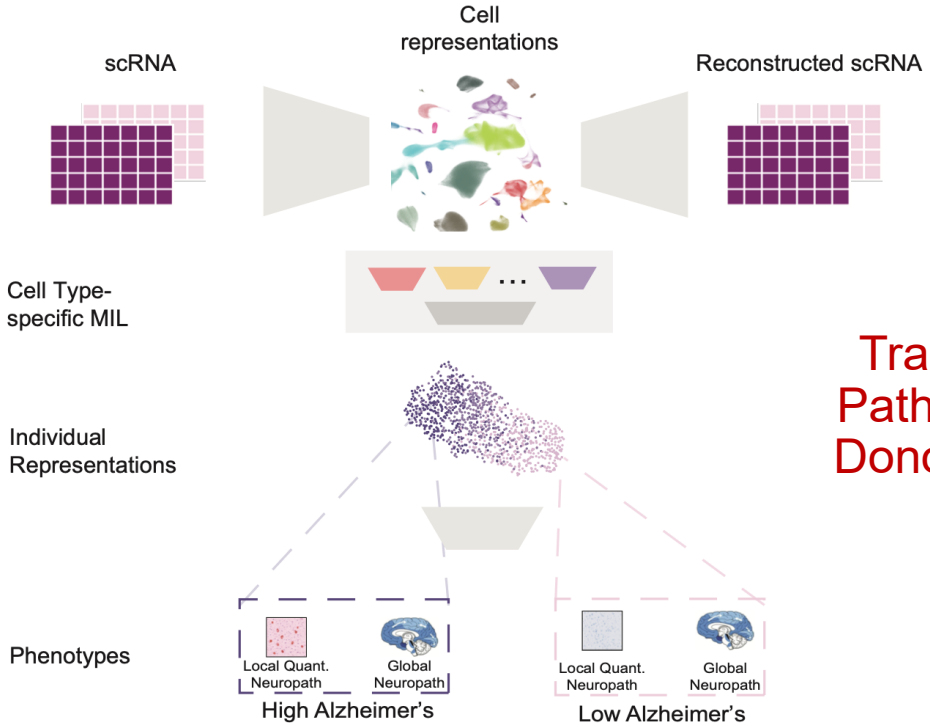
Multiregional Brain Profiling



QNP ~ sigmoid(Local_Path)

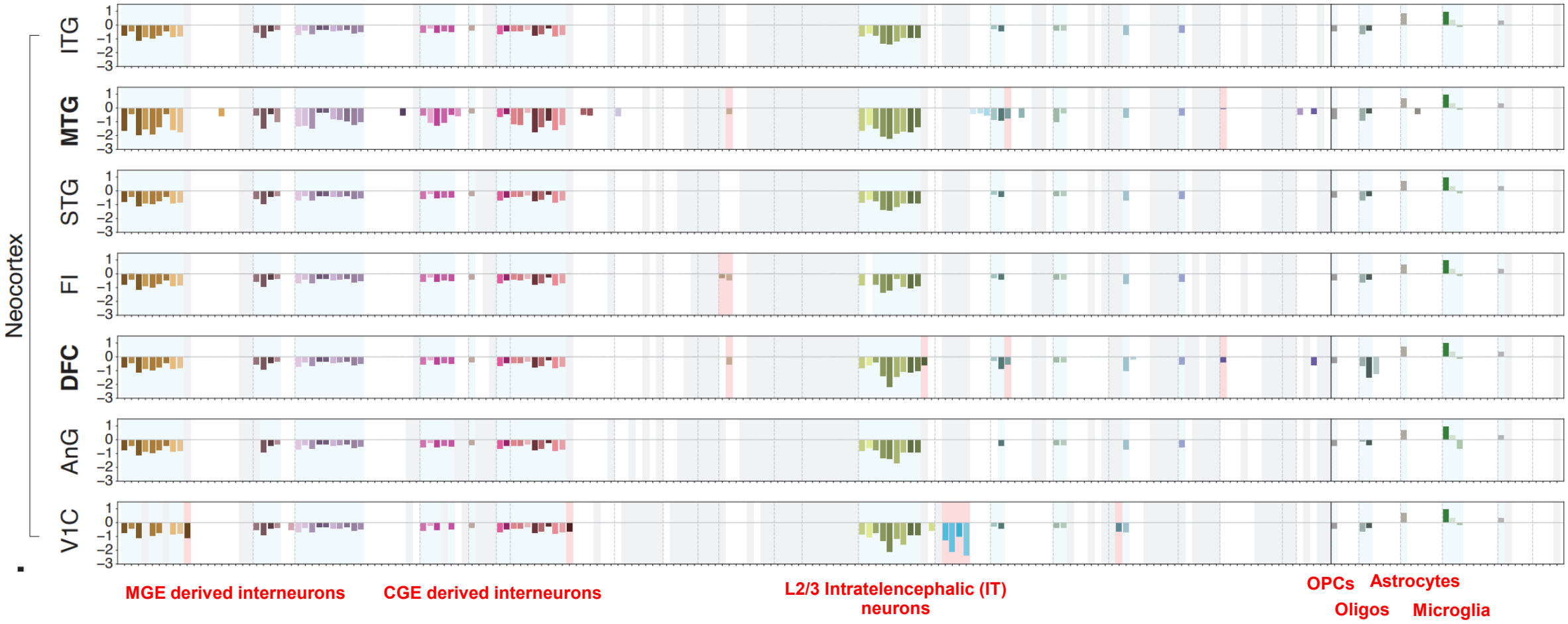


Hierarchical Bayesian Modeling of Global and region-specific Disease Time



Transcriptomic+ Pathology-derived Donor Trajectories

A Conserved Motif of Cellular Vulnerability Across the Cerebral Cortex



*Across independent cortical regions, the same **canonical motif of cellular vulnerability** emerges.*

*This shifts the focus **from cataloging pathological aggregates to** identifying the **cellular substrates** that mediate disease vulnerability.*

Redefining Disease Through Precision Biology

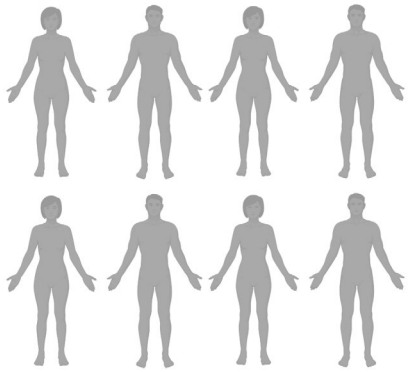
Neurodegenerative Diseases are not binary labels

They are structured, multiscale biological trajectories that unfold over decades

Precision requires integration across pathology, cell types, brain regions, and individuals

Evidence becomes actionable when it reshapes how we define and stage disease

How Do We Get There? Designing the Next Generation of Precision Cohorts



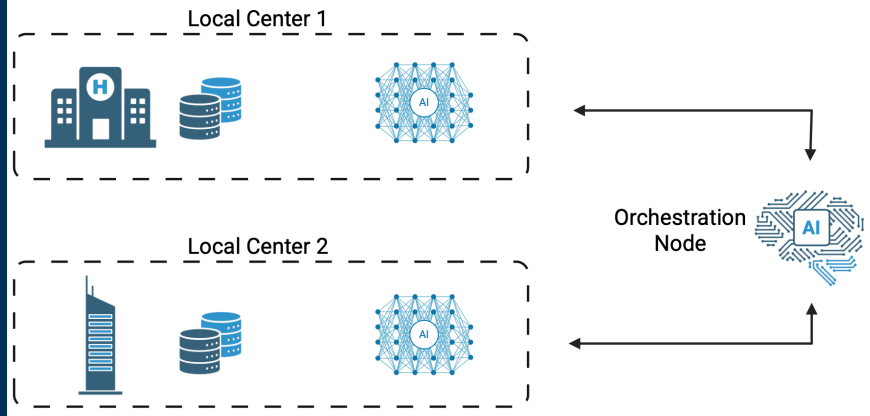
The cohort of the Future

Designing Precision-Ready Cohorts

Longitudinal, multimodal **IN VIVO** + **Post-Mortem** Brain Collection

Neurodegenerative Diseases don't occur in isolation.
Monitor Communities + Epidemiology to Capture the Spectrum of Disease

Cohorts must be designed for integration, not just association.



Federated Infrastructure for Learning at Scale

Orders-of-magnitude growth in multimodal data

Privacy-preserving, federated computation across institutions

Foundation models that learn across cohorts without central data

Precision at scale, requires learning across data sets without copying that data.