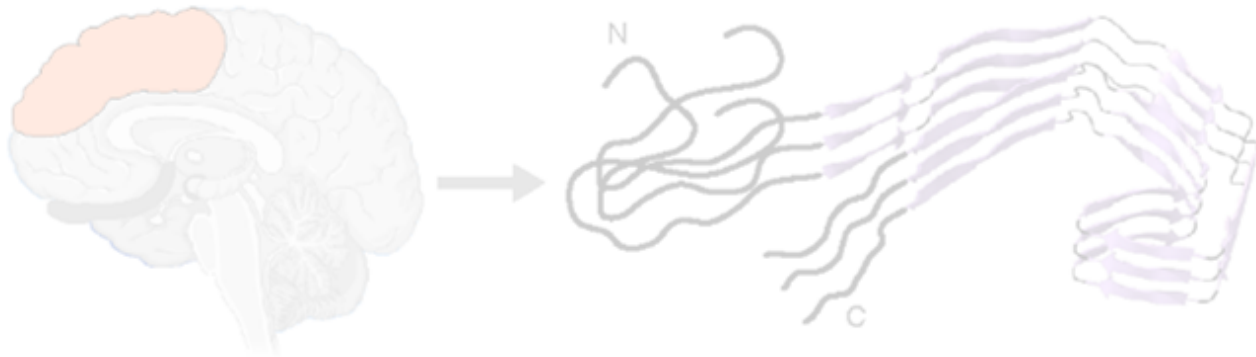




The top diagram shows a sagittal view of a human brain with a red highlight in the hippocampal region. An arrow points to a detailed illustration of a tau protein molecule, showing its N-terminal and C-terminal domains and several microtubule-binding repeats. The N-terminal is labeled 'N' and the C-terminal is labeled 'C'.

Profiling tau seeds in aging and across mixed proteinopathies in neurodegenerative diseases



Allison Kraus, PhD

Associate Professor, Department of Pathology

Associate Director, National Prion Disease Pathology Surveillance Center

Case Western Reserve University School of Medicine

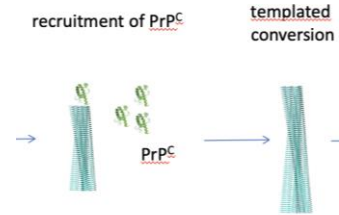
Amyloids

Can assemble into large multimeric deposits (amyloid plaque, NFTs)

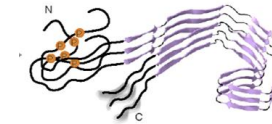
Auxiliary associated (co)factors

Can co-occur proximal to other amyloids

Protein based templated propagation (seeding)

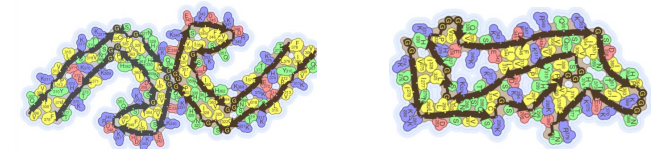


Characteristic 3D architectures



Harbor characteristic post-translational modifications

Structural basis of disease



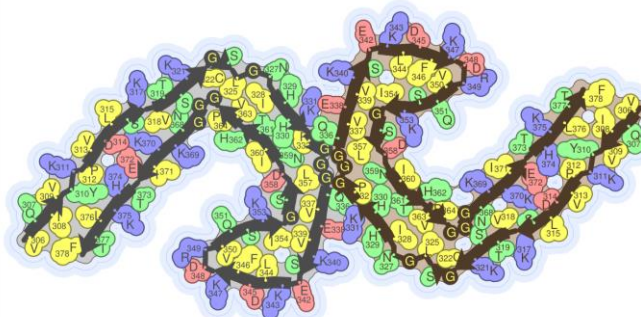
A structural basis for neurodegenerative diseases

Tau

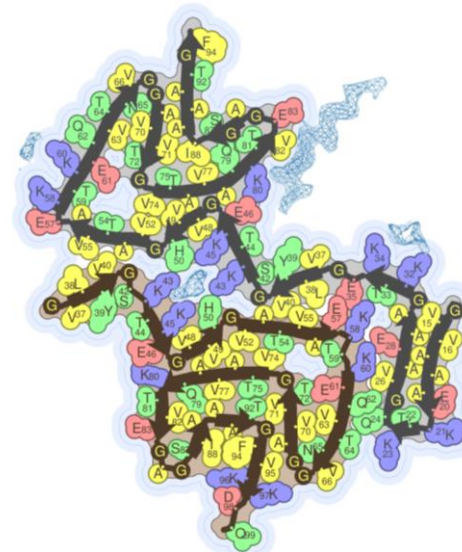
α -Syn

Prion

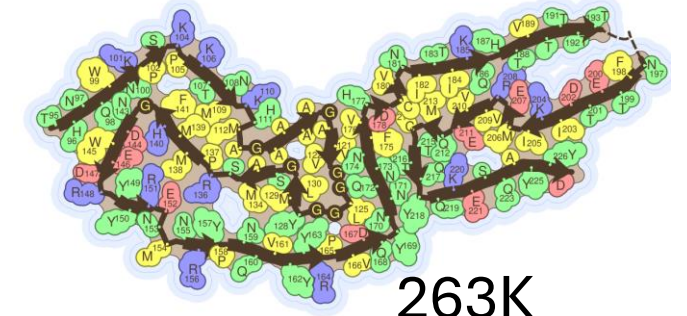
(infectious mammalian)



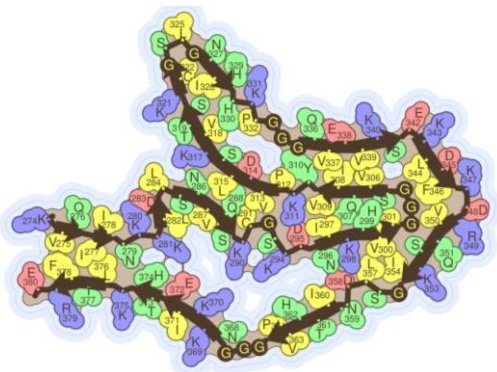
AD (3R/4R)



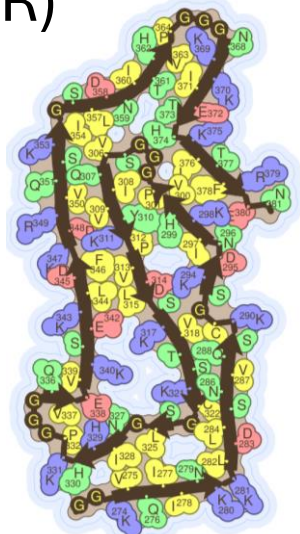
MSA



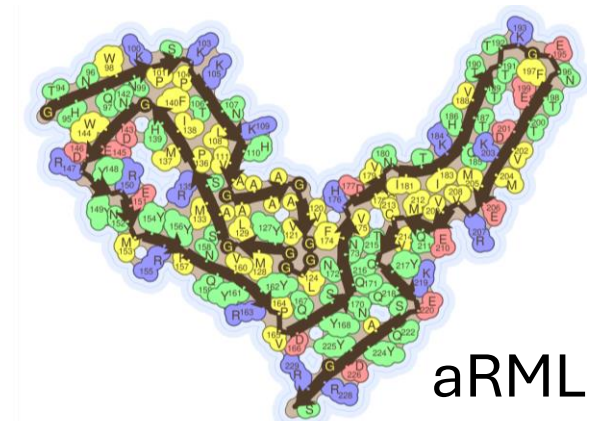
263K



CBD (4R)



PSP(4R)



aRML

Illustrations from Amyloid Atlas

The amyloid spectrum in health and disease

Functional amyloids

Transmissible,
Pathogenic amyloids

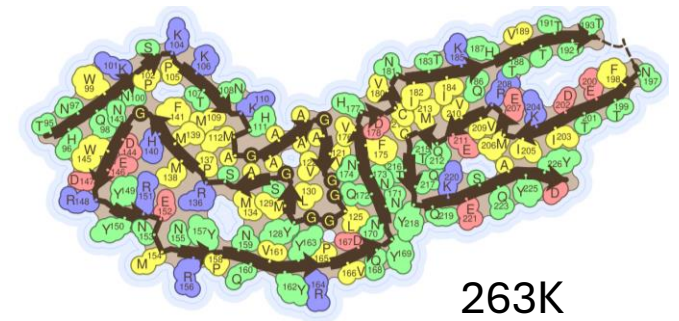
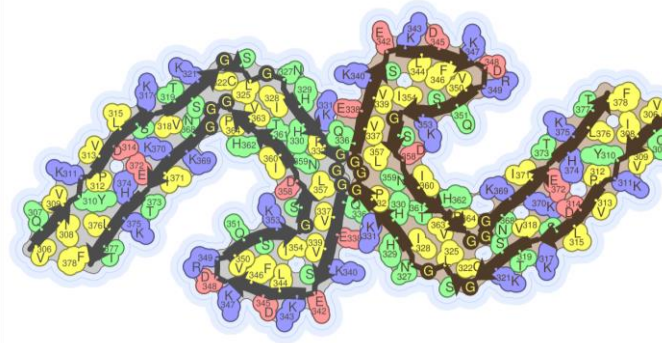
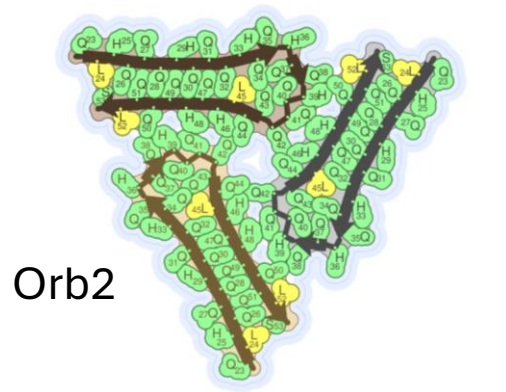


Innate immune signaling

Prions

Bacterial biofilms

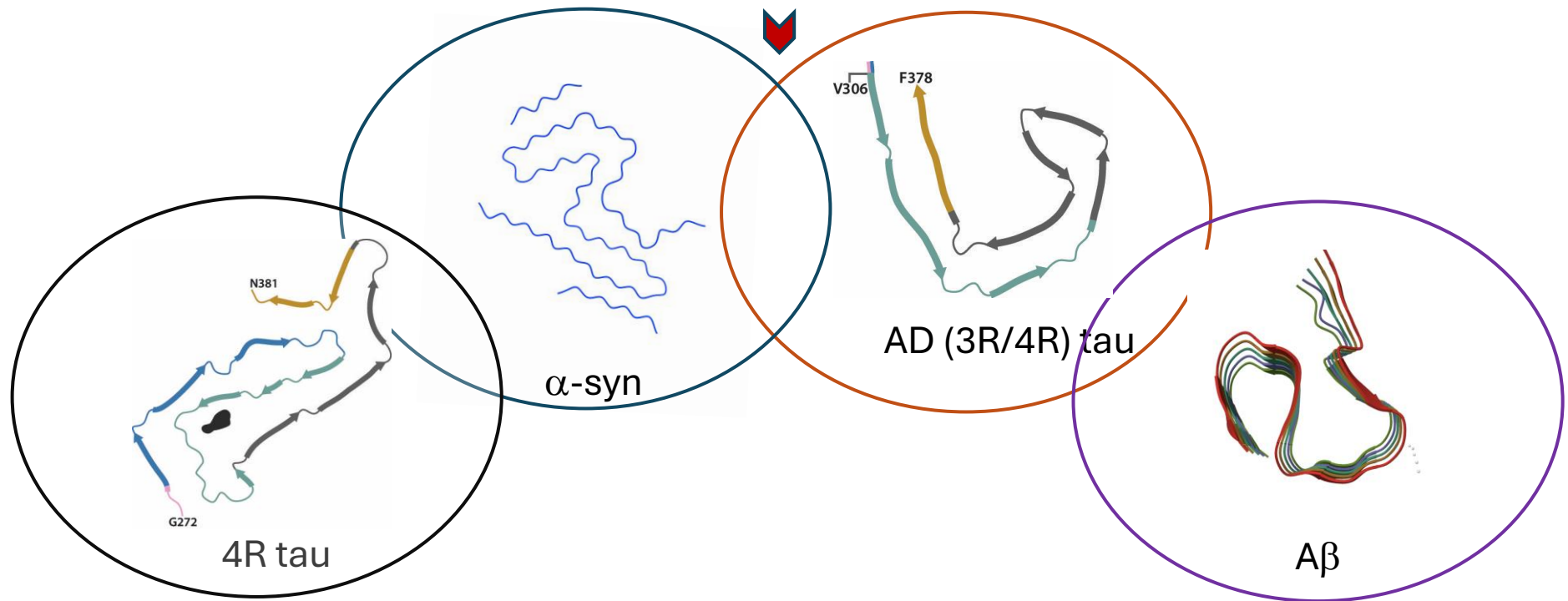
Tau filaments of AD



Orb2

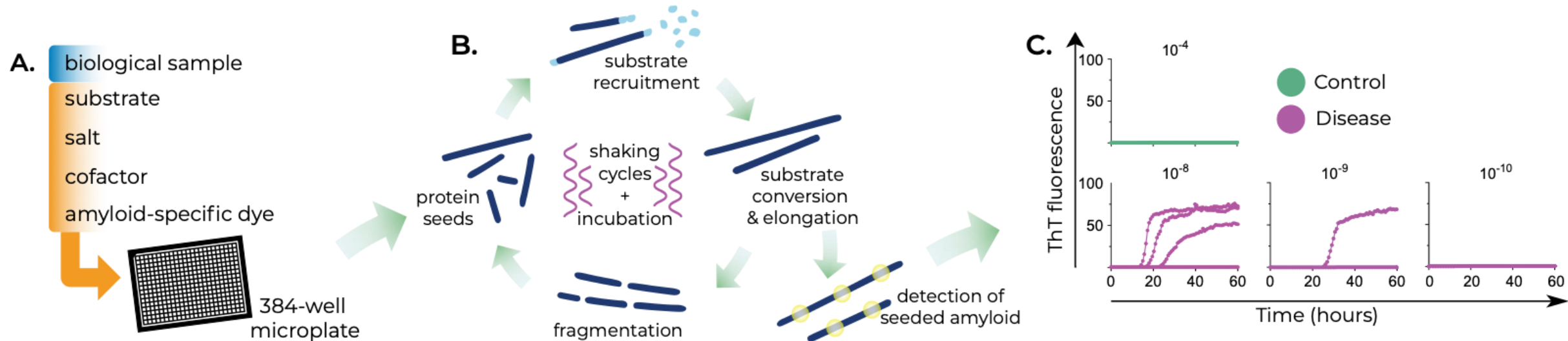
Infectious misfolded proteins

The amyloid spectrum in health and disease



How do co-occurring protein seed pathologies correspond with and/or contribute to neuropathological and clinical outcomes??

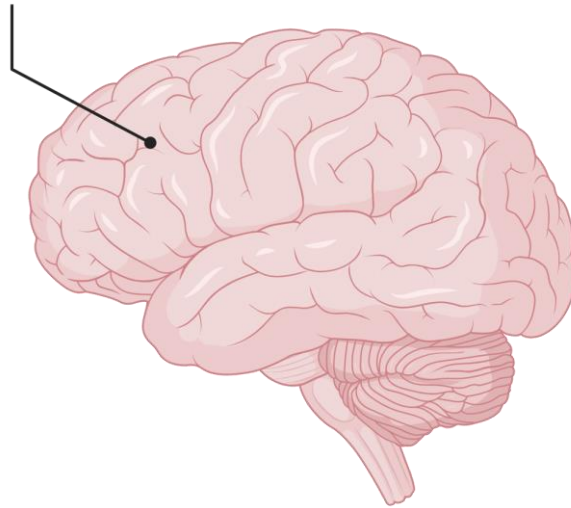
Evaluating seeding activities using real-time quaking-induced conversion (RT-QuIC)



Endpoint dilution analysis
to calculate seeding doses

Evaluating 3R/4R, 4R tau and α -synuclein seeds in the frontal lobe in AD and non-AD cases across different Braak stages

mid frontal lobe



Alzheimer's disease (n=16)

Lewy body disease (DLB) (n=13)

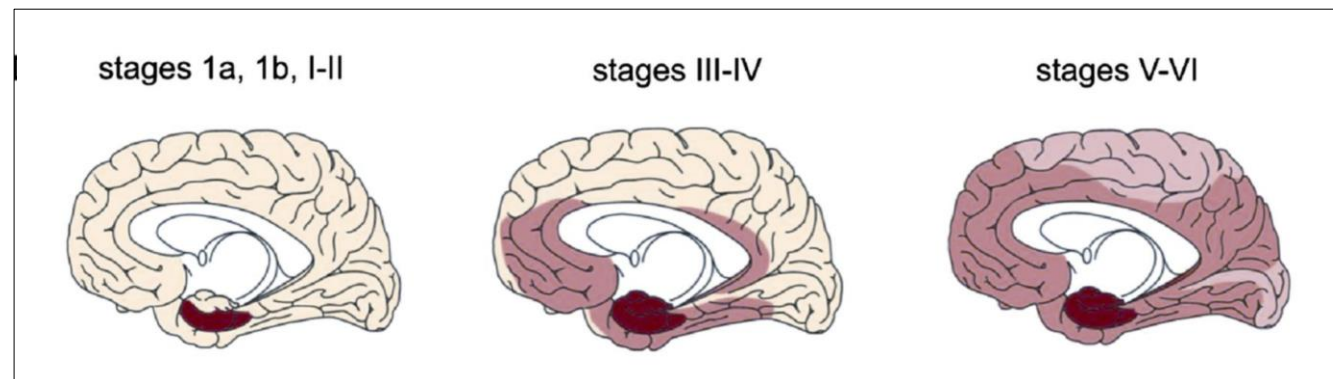
Lewy body disease (PD) (n=8)

Multiple System Atrophy (n=6)

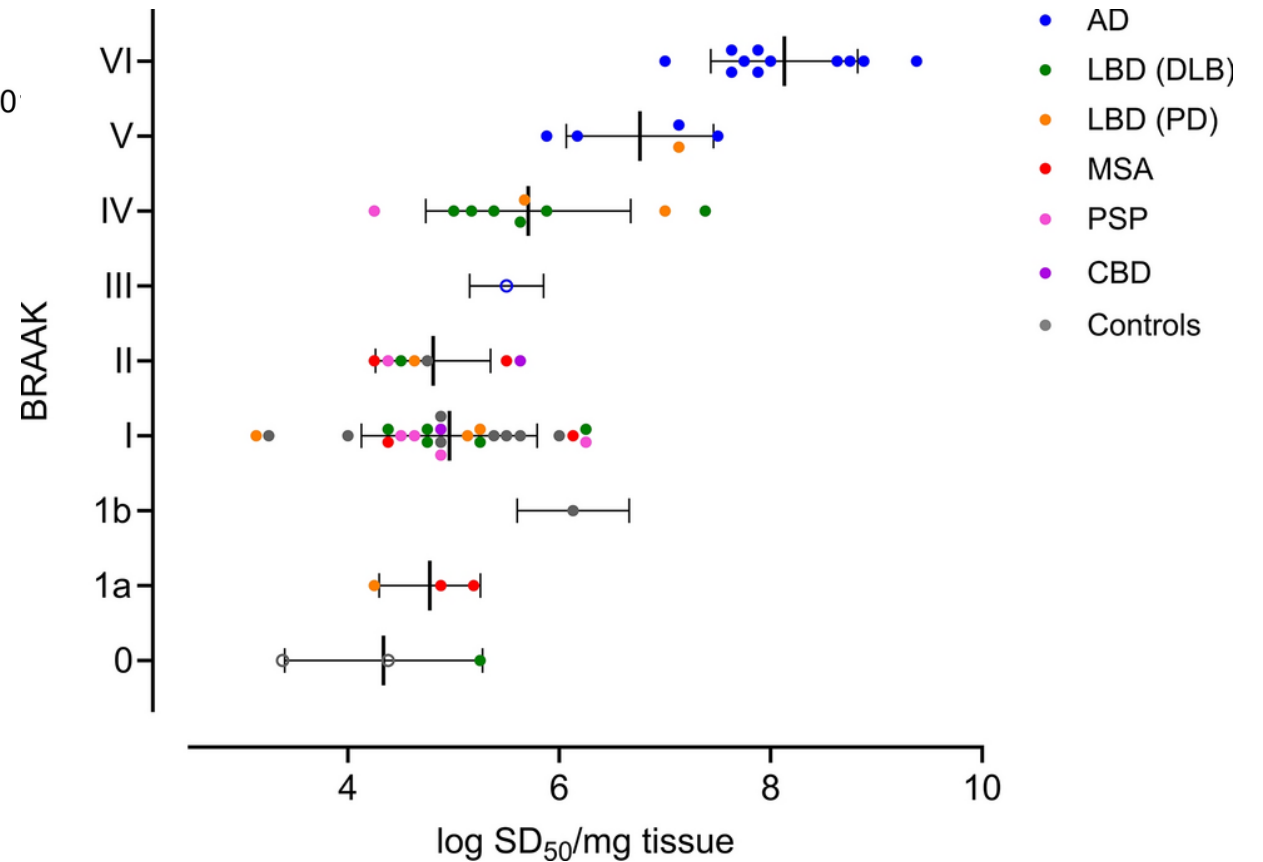
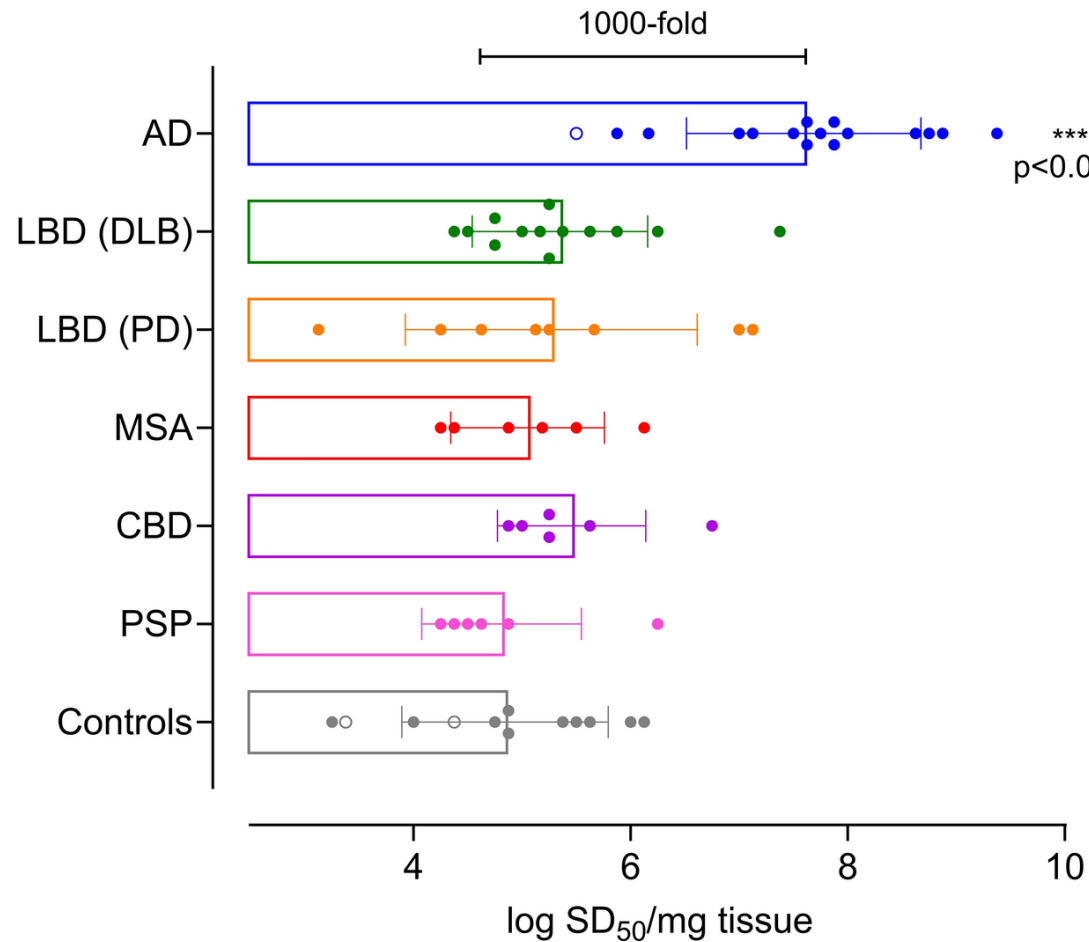
Corticobasal degeneration (n=6)

Progressive supranuclear palsy (n=6)

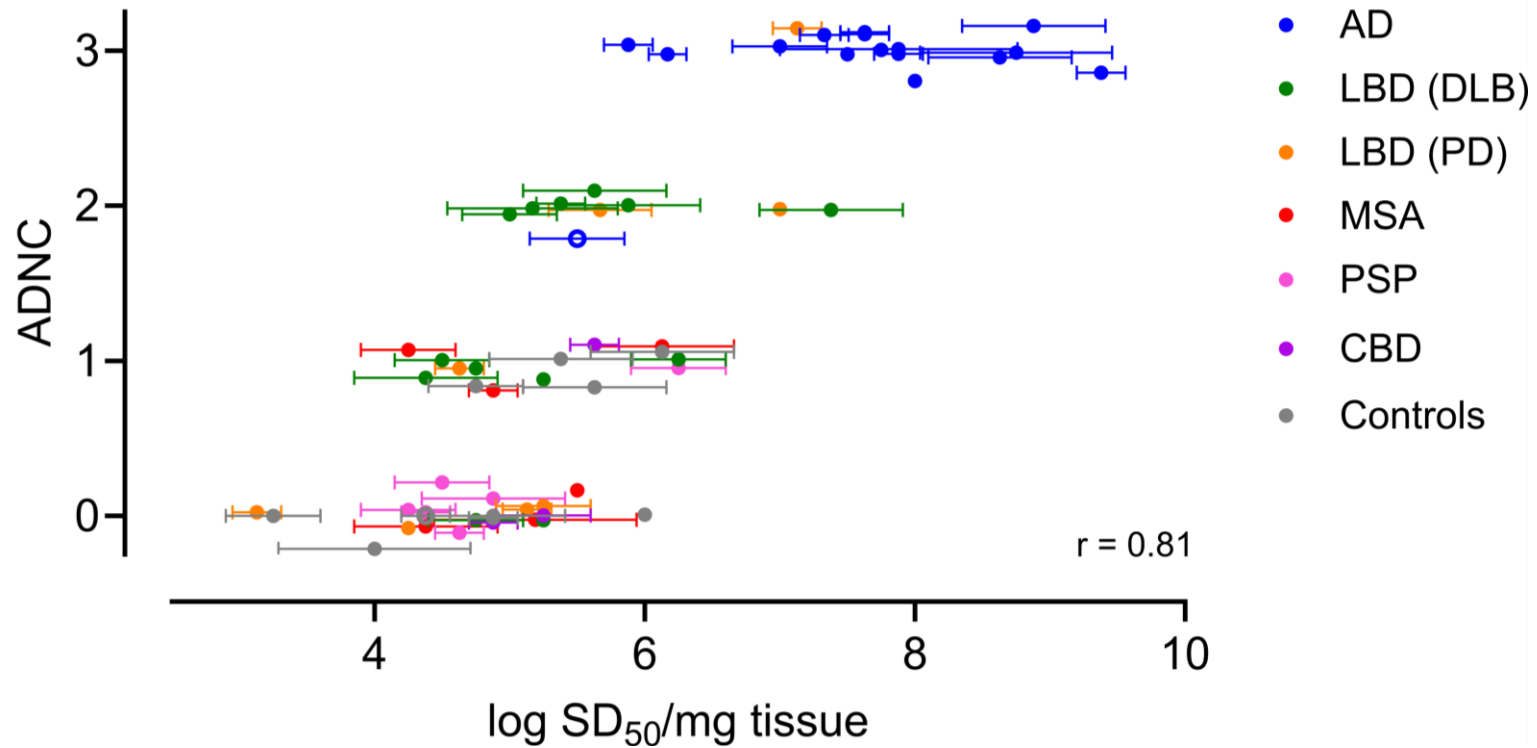
Controls (Braak 0-II) (n=12)



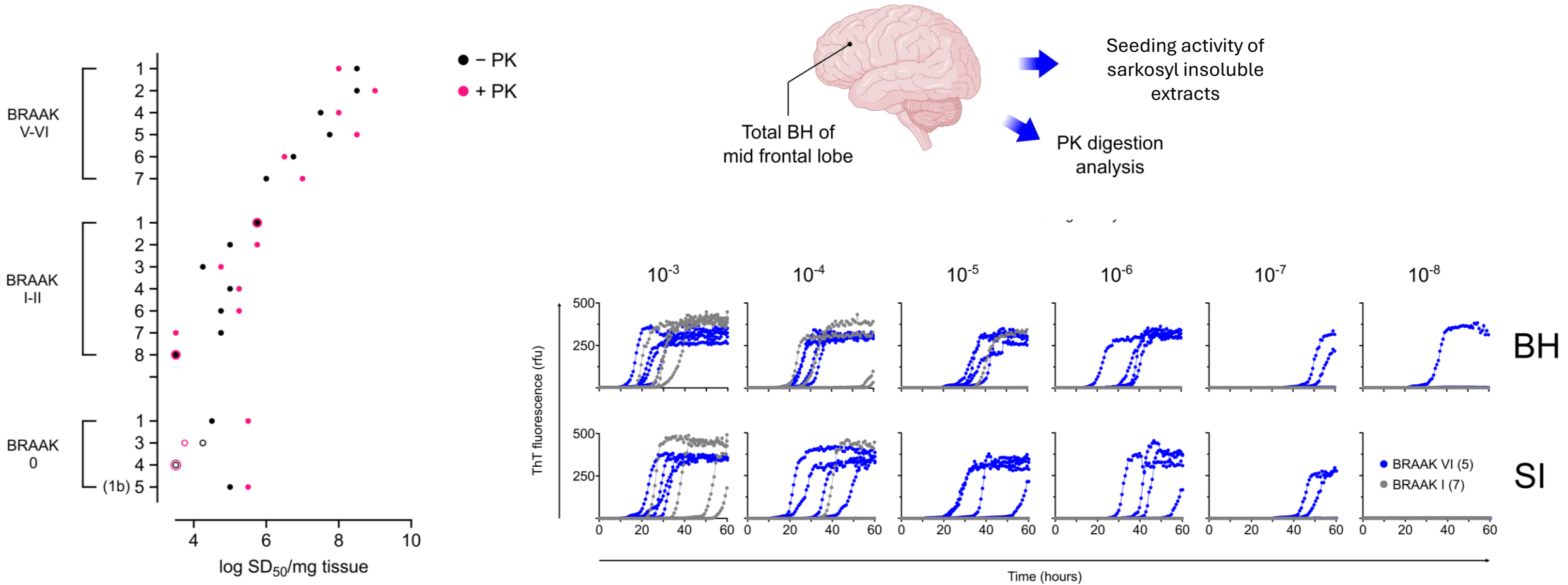
3R/4R tau seeding activities are prevalent in LBD and other neurodegenerative diseases and correspond with overall Braak stage



3R/4R tau seeding activities correspond with overall AD neuropathologic change



Tau seeds that occur at both early and late stages of accumulation are largely protease resistant and sarkosyl insoluble



The amyloid spectrum in health and disease



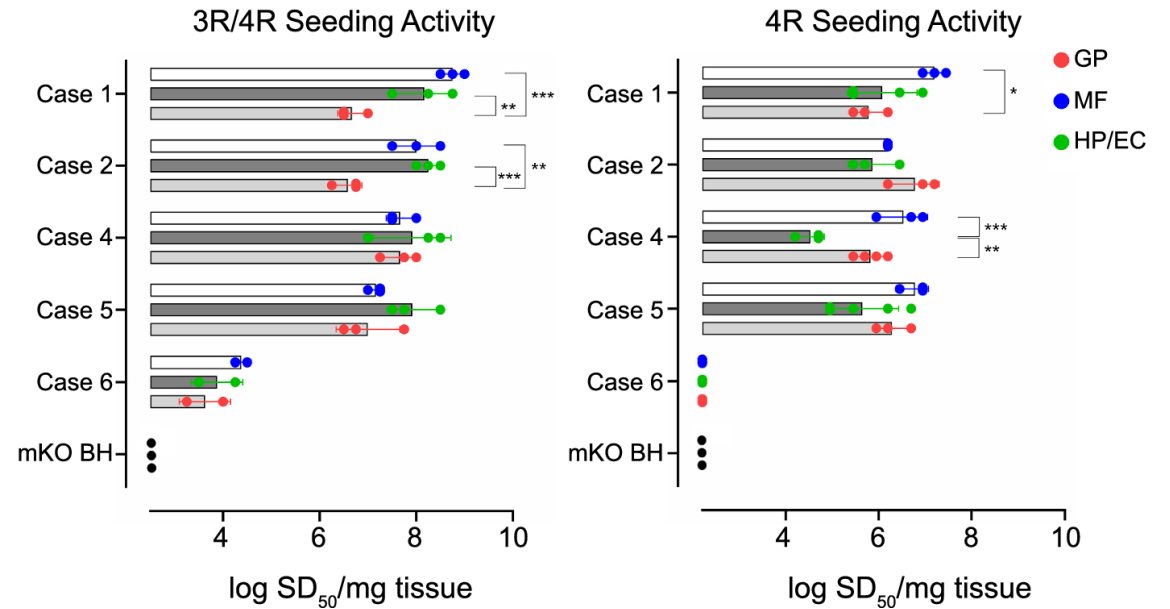
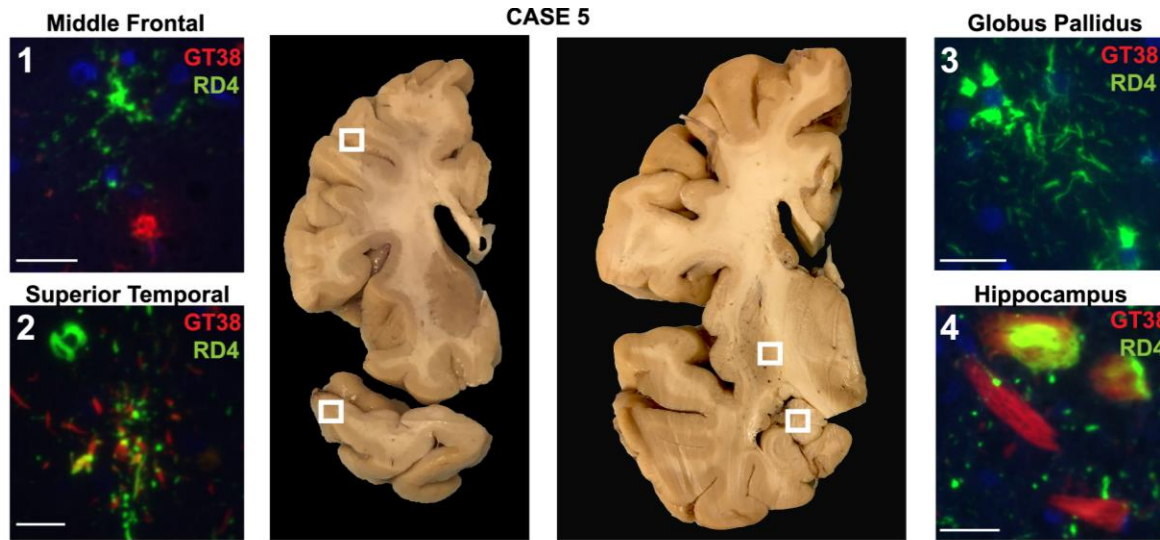
Where do distinct protein seeds (tau, α -syn) and protein seed networks intersect?

How does this relate to neuropathology and disease?

Features of seeds found at prodromal stages?

Clinical outcome?

Isoform-selective tau seeding assays to define neuroanatomic distribution of AD versus PSP tau seeds

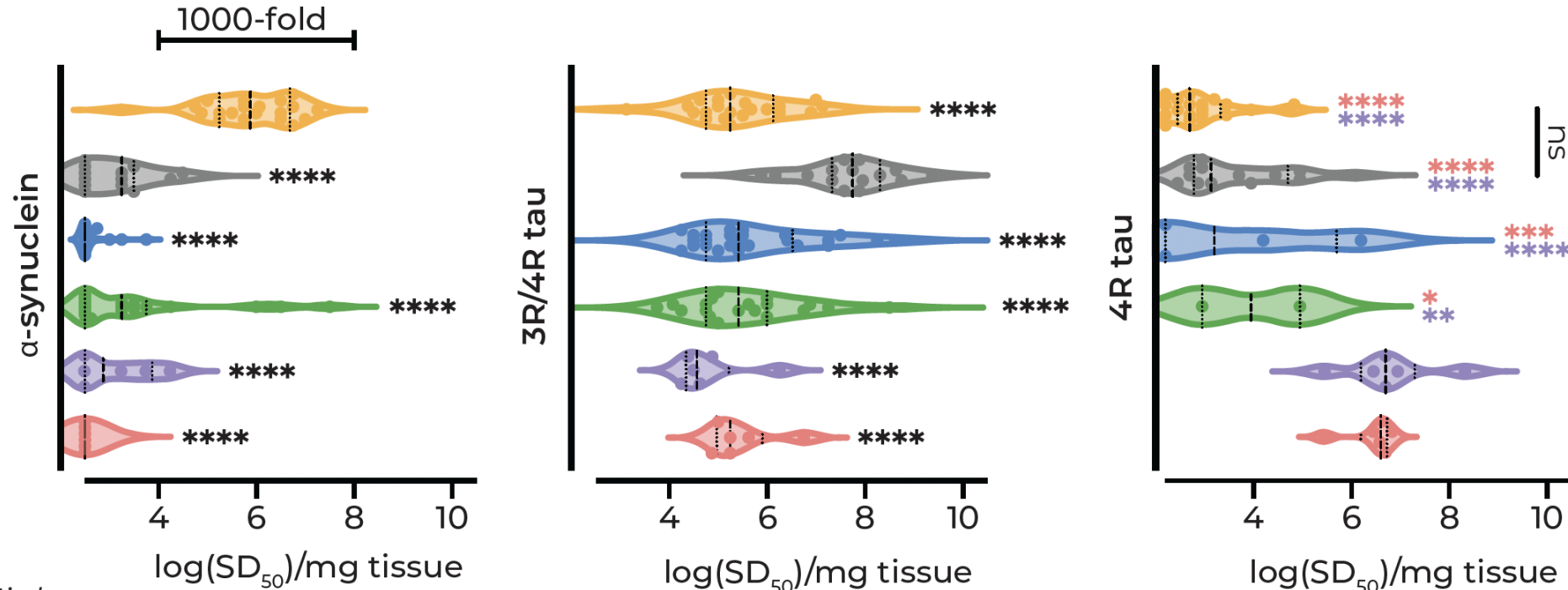


3R/4R - 4R Seeding
Difference (log SD₅₀/mg tissue)

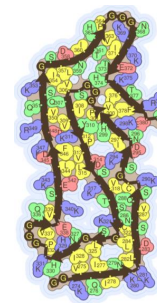
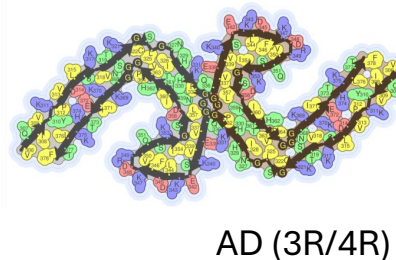
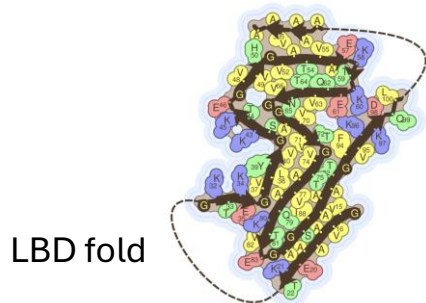
Case	GP	MF	HP
1			
2			
4			
5			



RT-QuIC supports highly sensitive and selective detection of co-occurring α -synuclein and tau seeds & strains in the brain



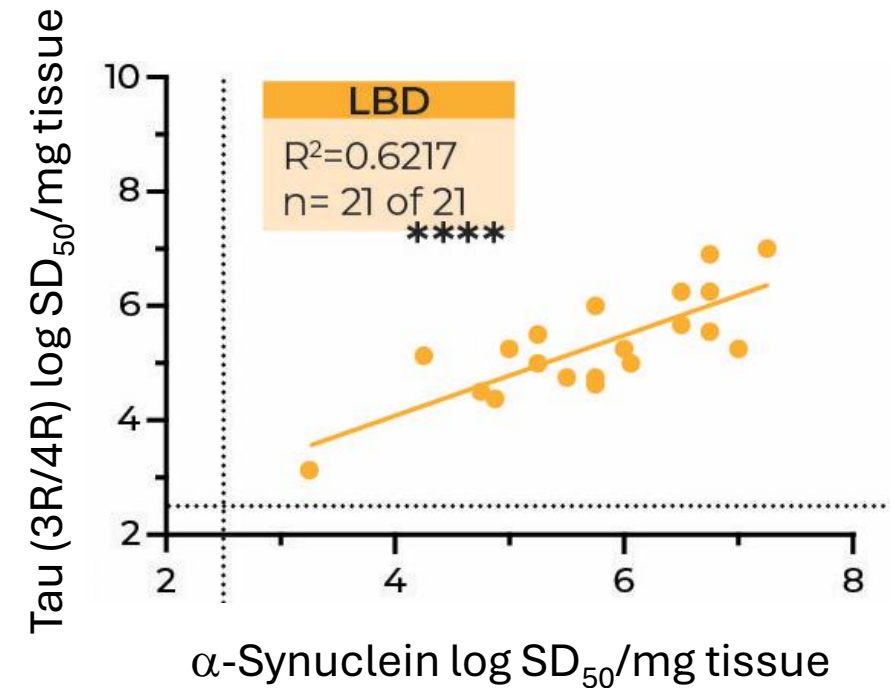
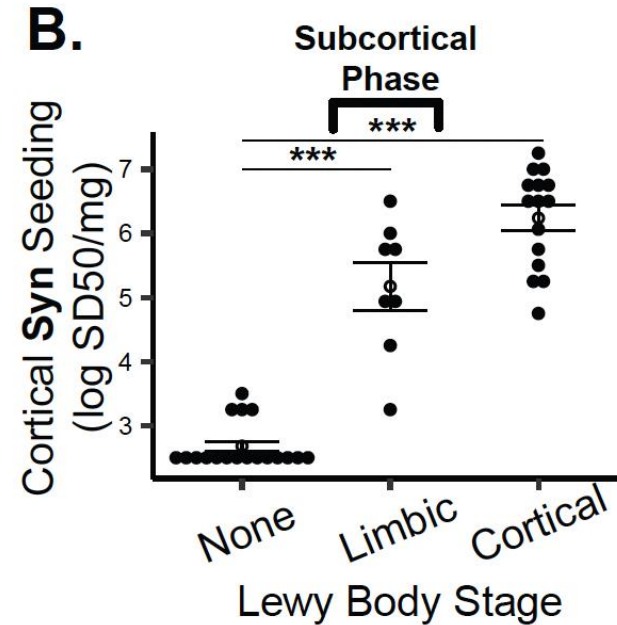
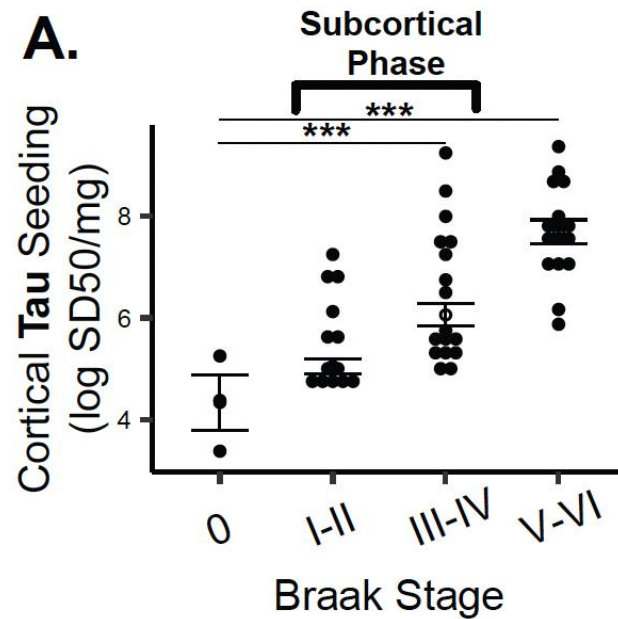
- LBD
- ADNC High
- ADNC Low
- PART
- PSP
- CBD



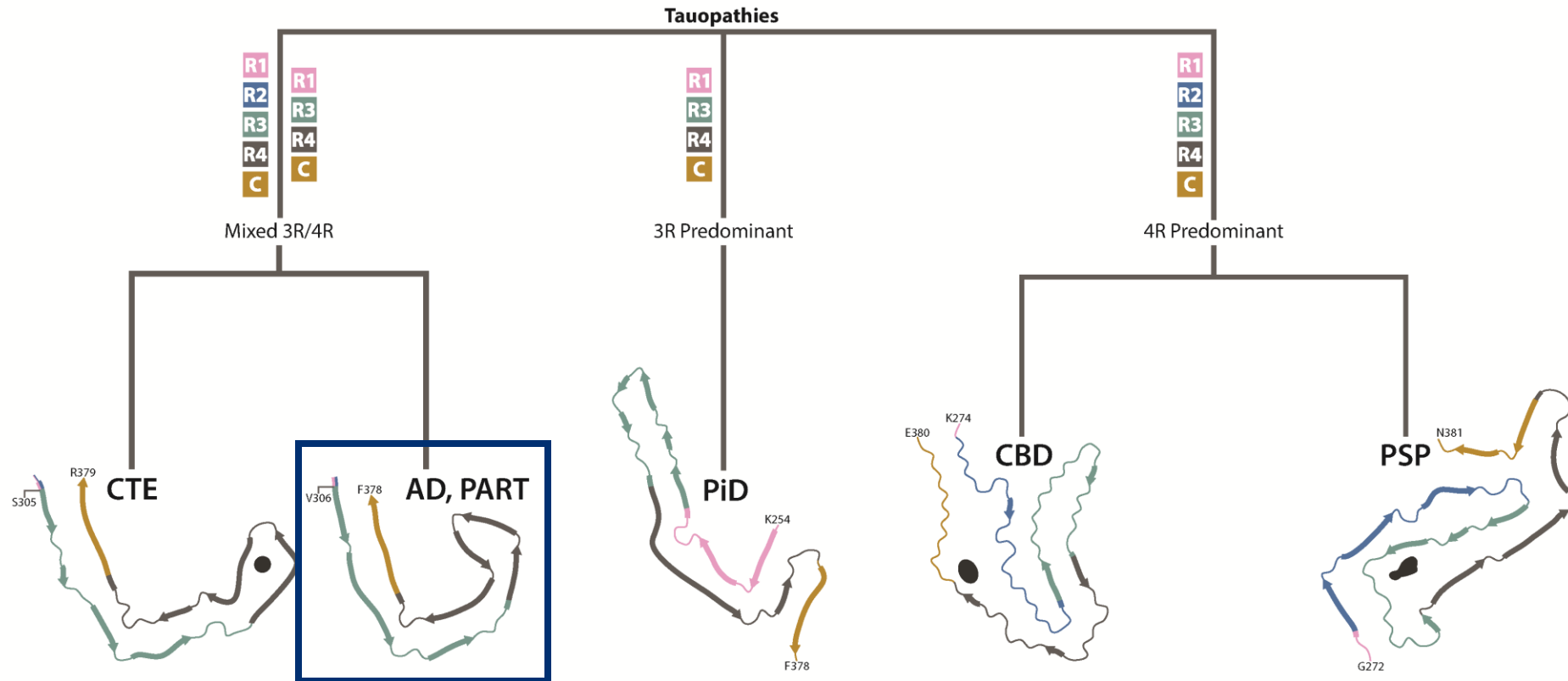
PSP(4R)

Manca, Standke *et al.*, *Acta Neuropath 2023 and unpublished*
 David Coughlin, Annie Hiniker,
 Douglas Galasko

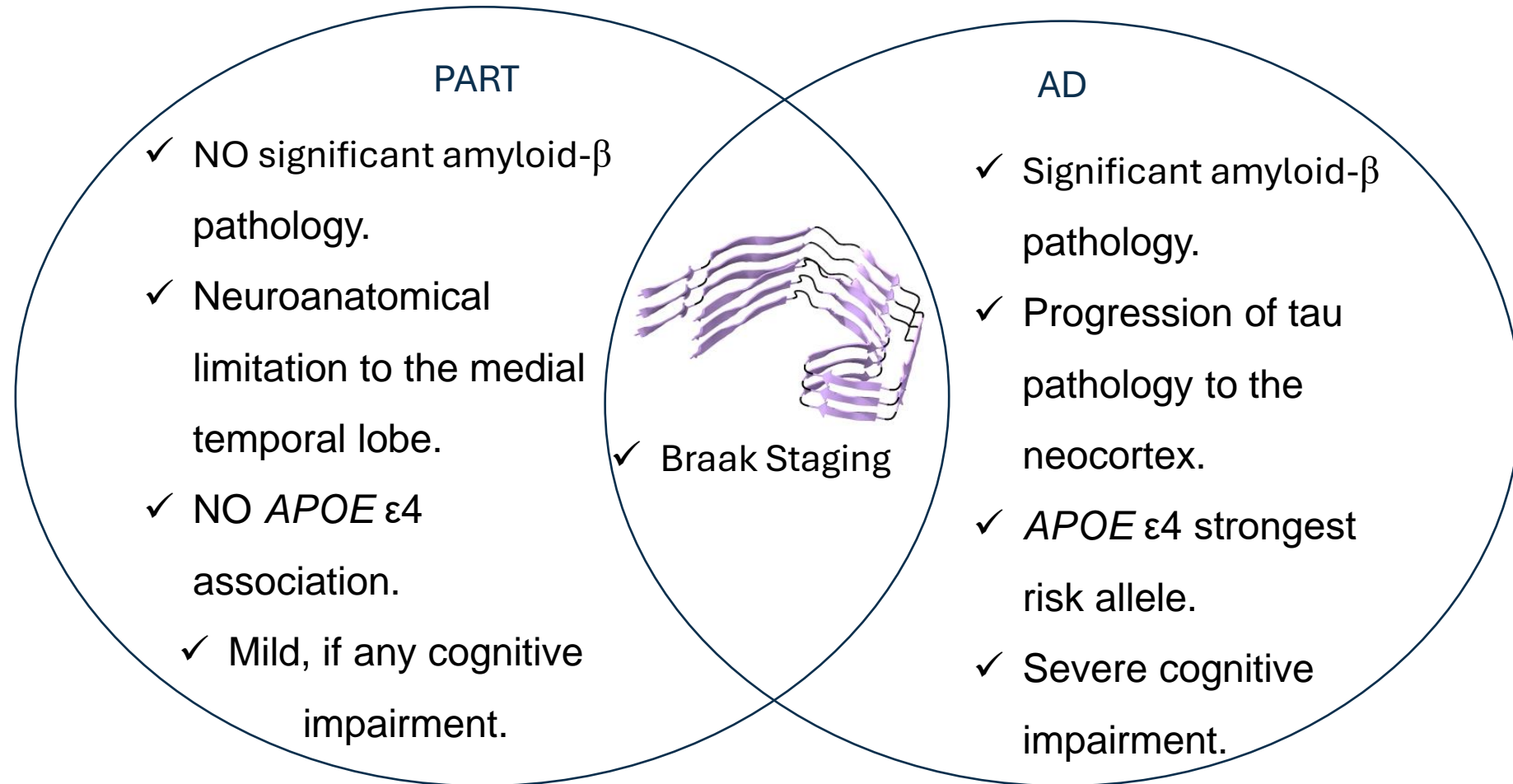
Tau and α -synuclein seeding activities precede overt neuropathology, and prevalently co-occur across neurodegenerative diseases



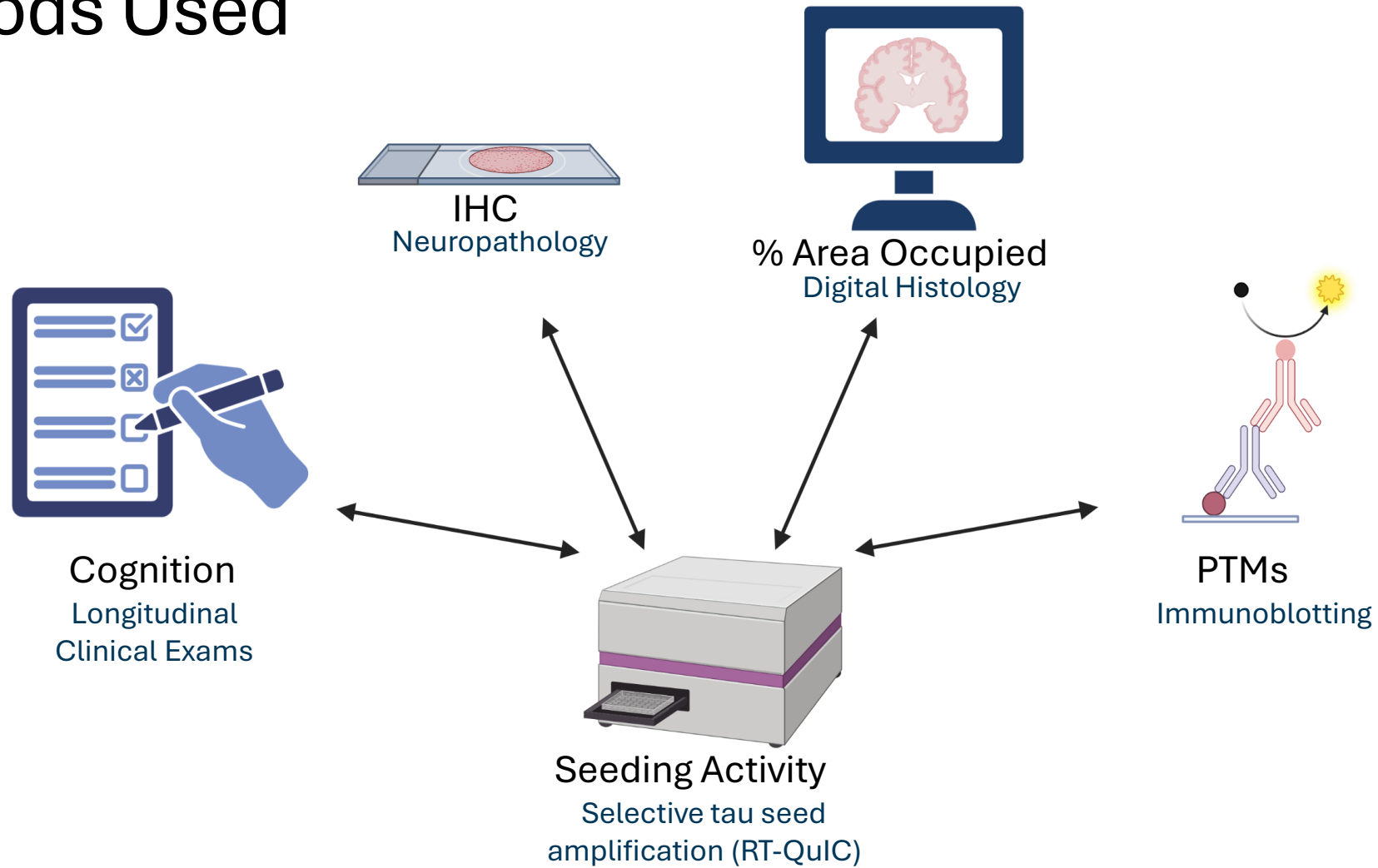
Tau: A structural basis for disease



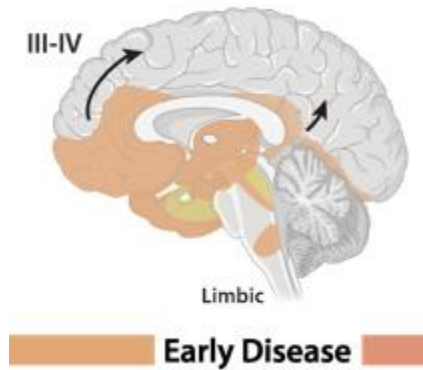
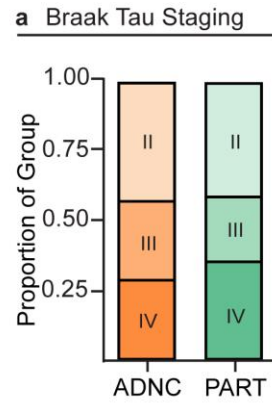
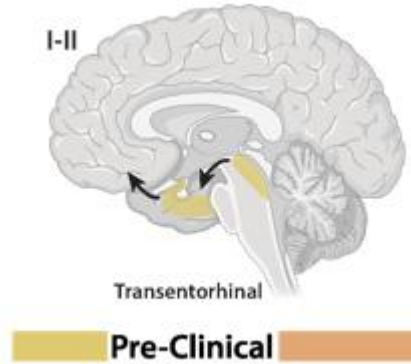
Understanding heterogeneity in core-sharing tauopathies: PART and AD



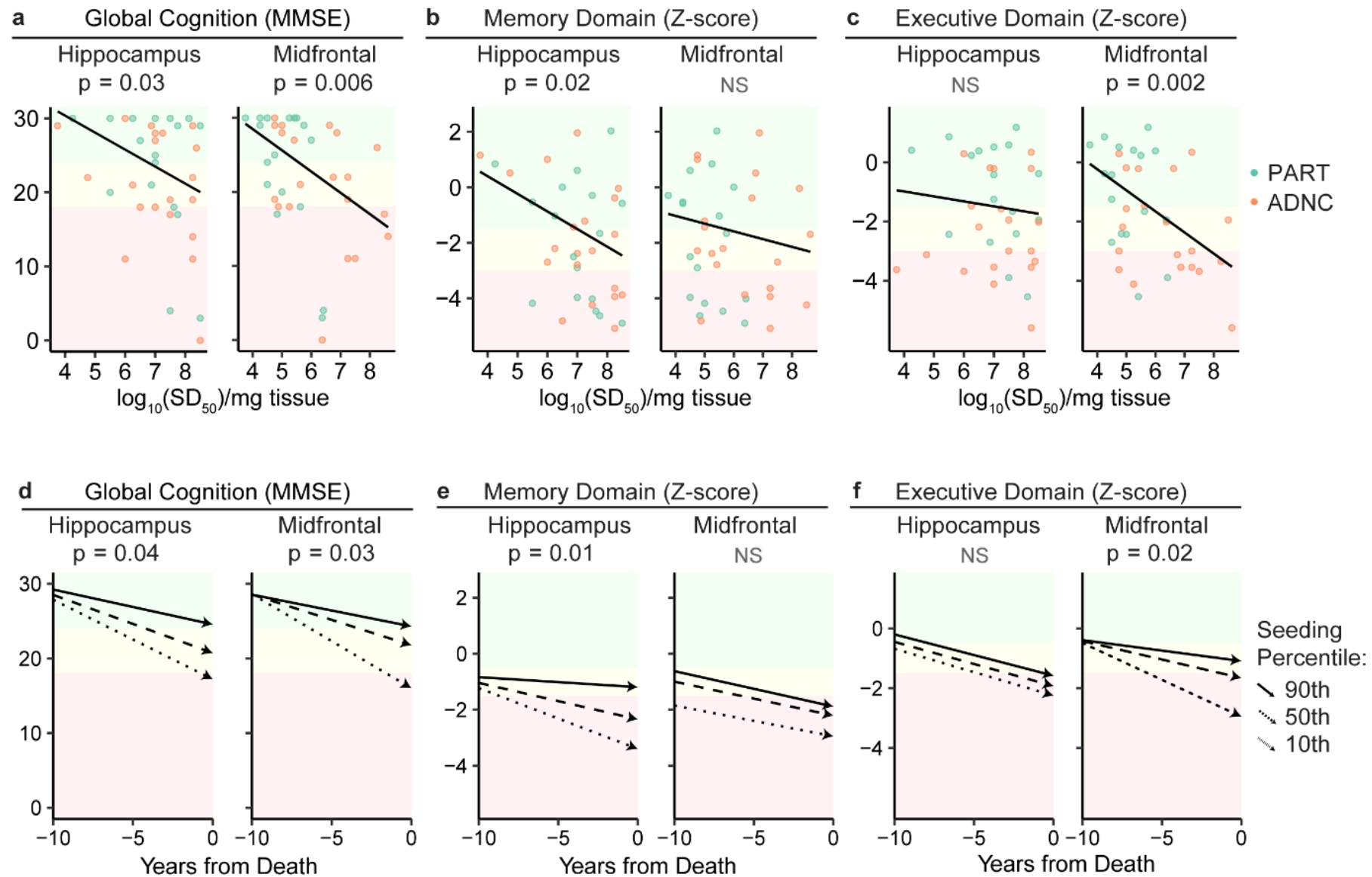
Methods Used



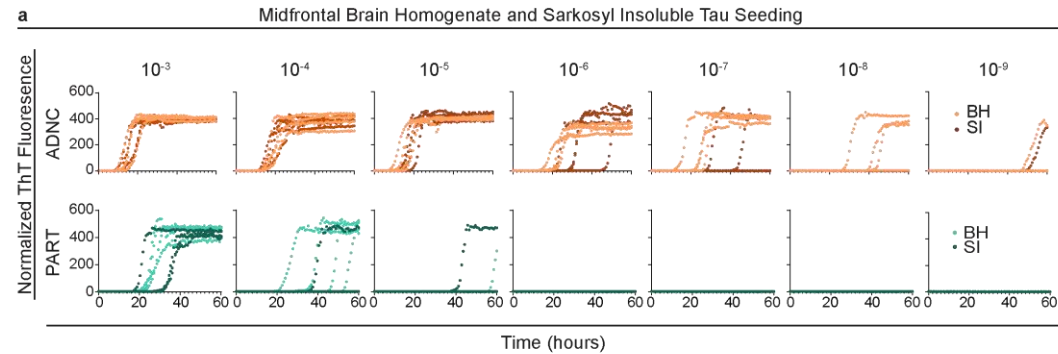
Brain region specific 3R/4R tau seeding activities differentiate ADNC and PART



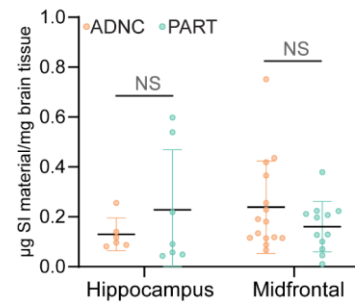
Tau seeding activity correlates with global and region-specific cognition and longitudinal decline



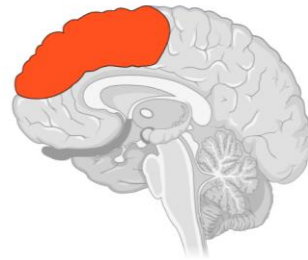
Biochemically distinct cortical tau species differentiate ADNC and PART



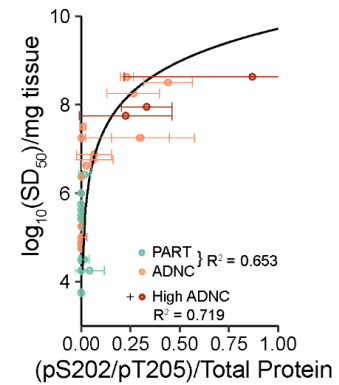
a μg SI Material per mg Brain Tissue



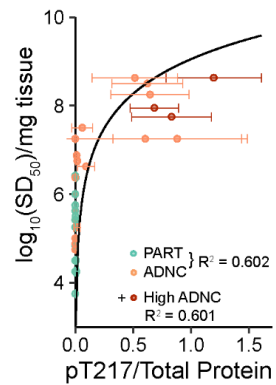
Distinct midfrontal tau PTMs mark highest-seeding ADNC cases



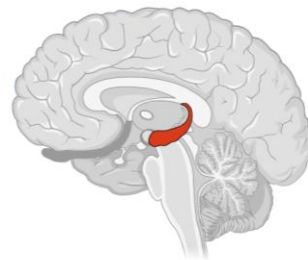
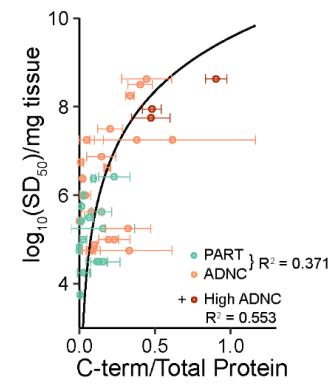
a MF SD₅₀ vs pS202/T205



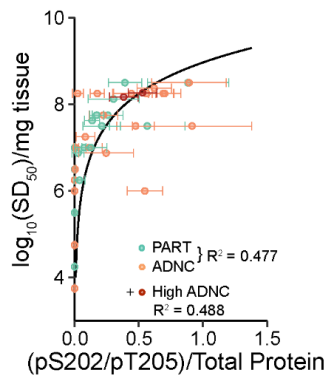
b MF SD₅₀ vs pT217



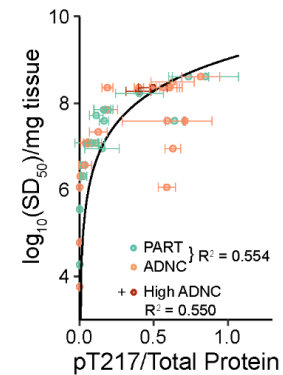
c MF SD₅₀ vs C-term



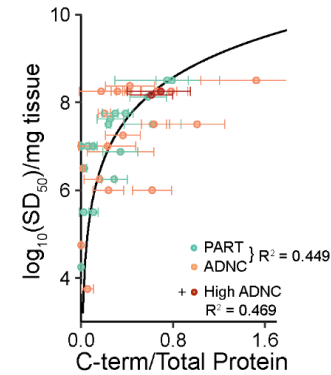
d HP SD₅₀ vs pS202/T205



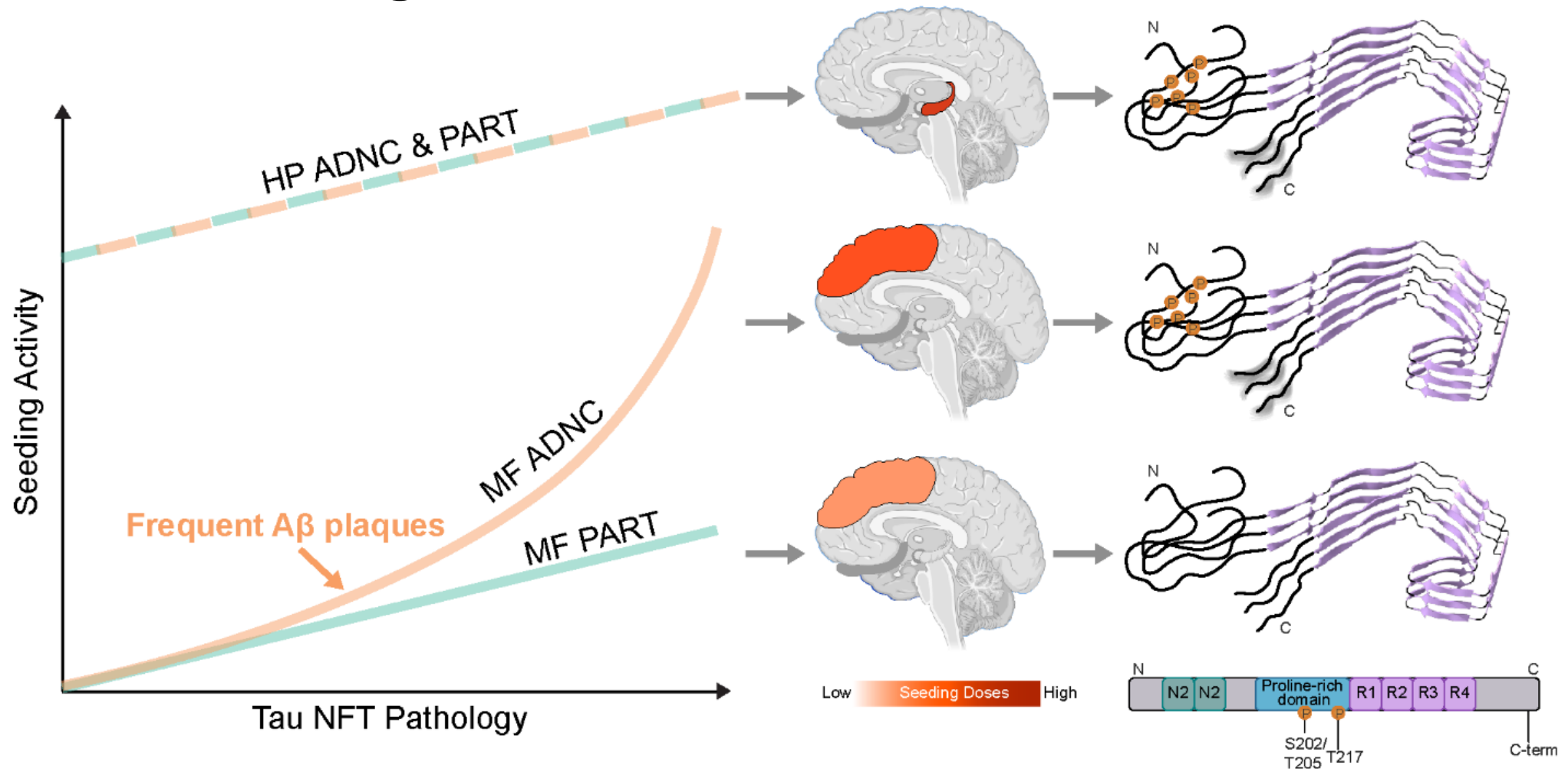
e HP SD₅₀ vs pT217

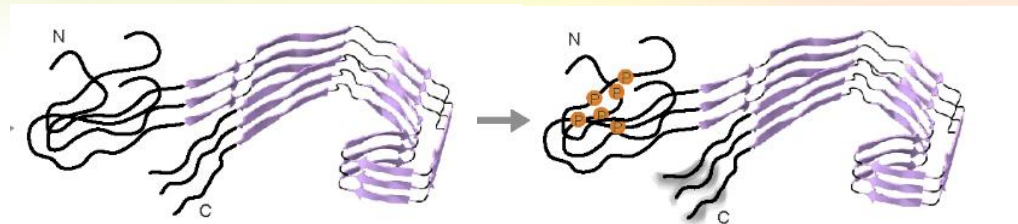
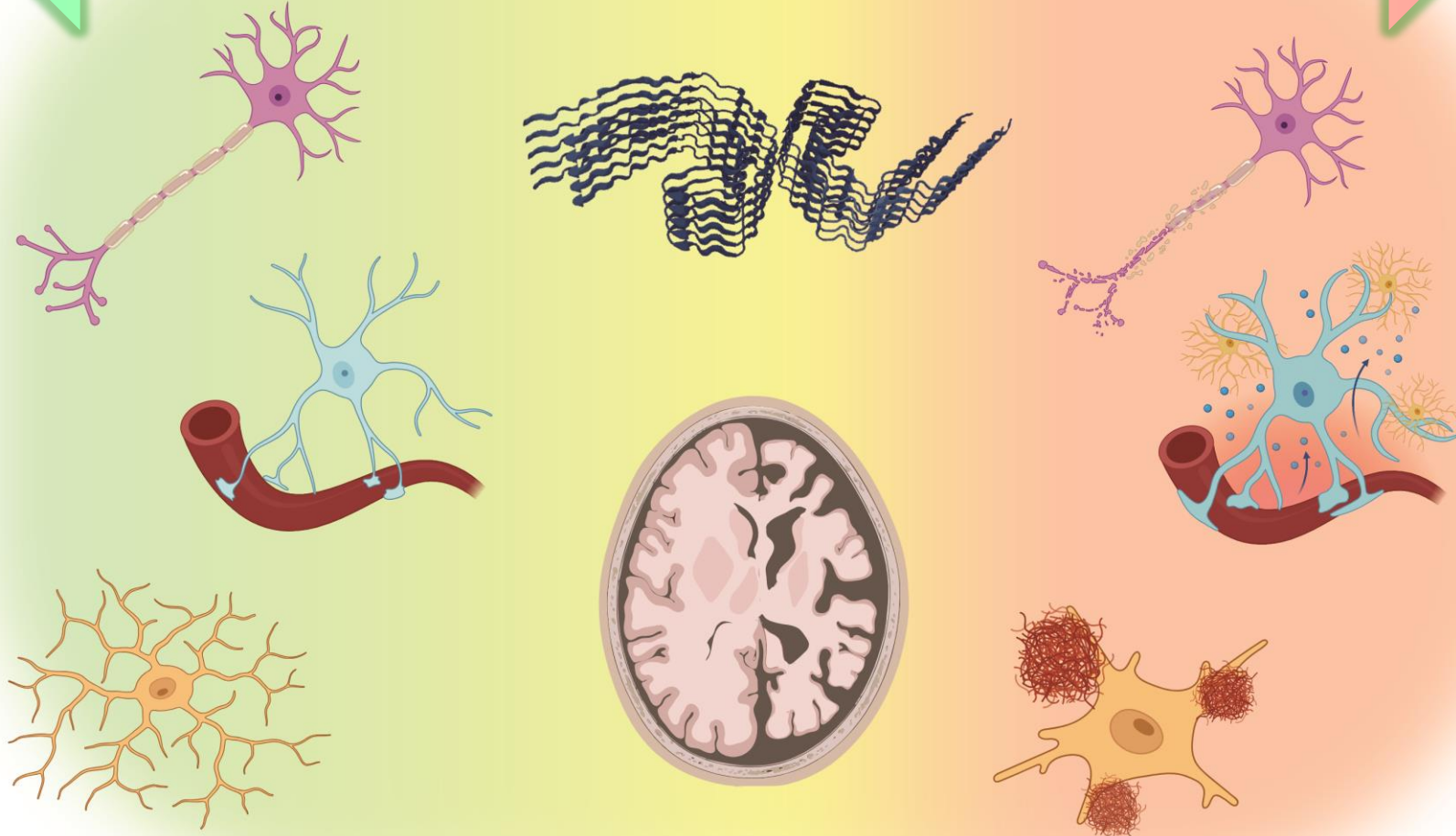
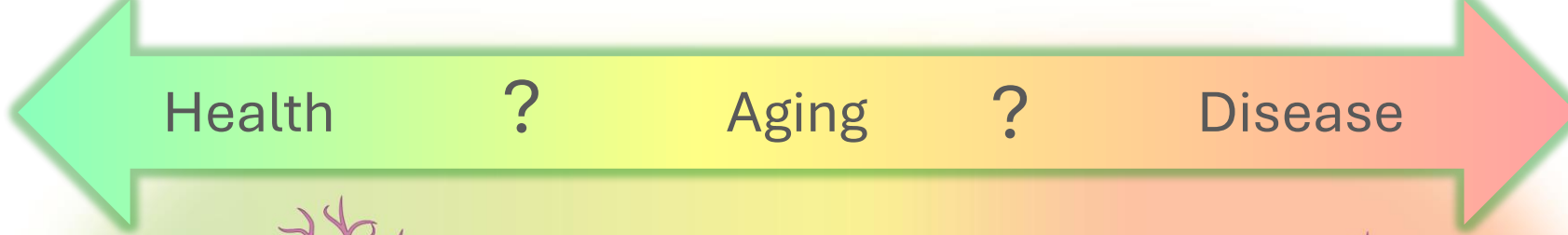


f HP SD₅₀ vs C-term



Distinct midfrontal tau PTMs mark highest-seeding ADNC cases





The amyloid spectrum in health and disease



- 3R/4R tau seeds occur broadly across neurodegenerative diseases, including in LBD
- Prevalent protein seed co-occurrence (3R/4R, 4R tau and α -synuclein) is observed in both primary synucleinopathy and tau-based diseases
- α -synuclein and tau seeding activities are observed at 100% prevalence in Lewy body disease cases examined, and differ from the prevalence of seed co-occurrence and levels thereof in ADNC, PART or 4R tauopathies
- Tau PTMs and seeding activities differ between PART and ADNC; evidence that the biochemical complexity of seeding proteoforms differs in distinct clinicopathologically relevant microenvironments

Implications for mechanisms of disease, biomarker development?

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We thank the families and donors who have made this research possible.

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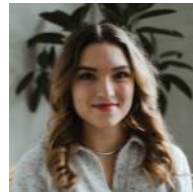
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UF

David Vaillancourt

University of Verona

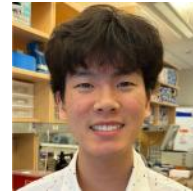
Gianluigi Zanusso



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Heidi
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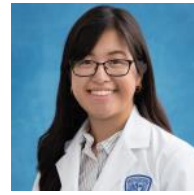
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Shin



Hannah
Zamore



Caitlin
Swanberg MS



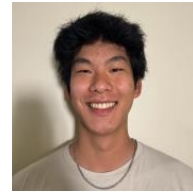
Iris
Peng



Antonio
Cornacchia MS



Matteo
Manca PhD



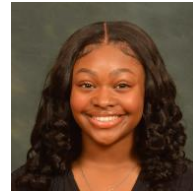
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Dementia with Lewy Bodies Consortium



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