

UCSF Weill Institute for Neurosciences

Memory and Aging Center

PSP and CBS update

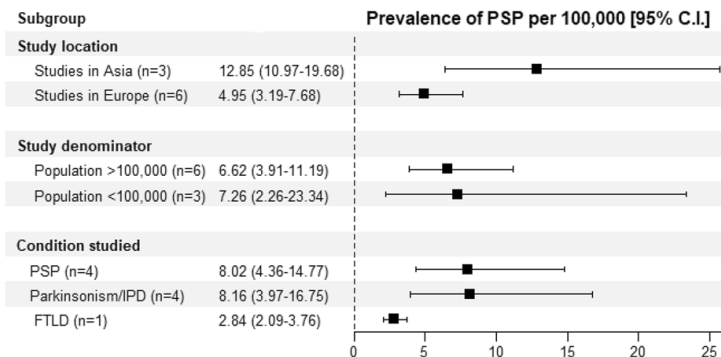
Adam Boxer, MD, PhD
Professor of Neurology

BSN Webinar. July 19, 2024

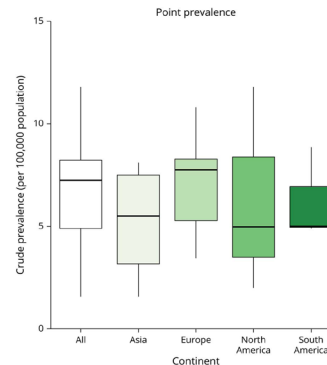


PSP prevalence is similar to ALS, but 10x less research on PSP

Prevalence ~8/100,000



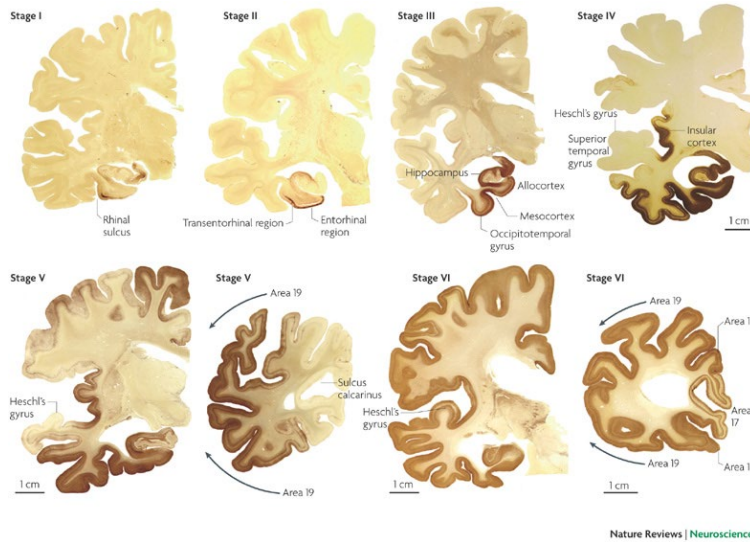
**PSP
(n=9
studies)**



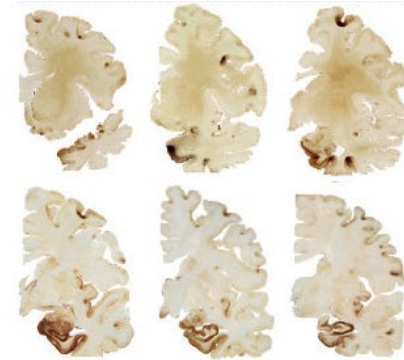
**ALS
(n=89
studies)**

Insoluble tau correlates with clinical features in tauopathies

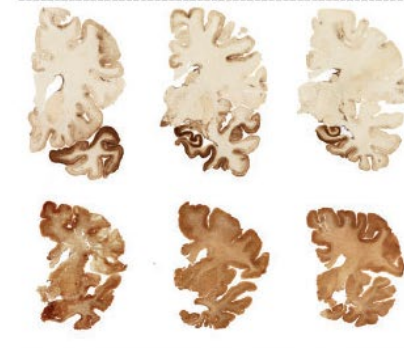
AD



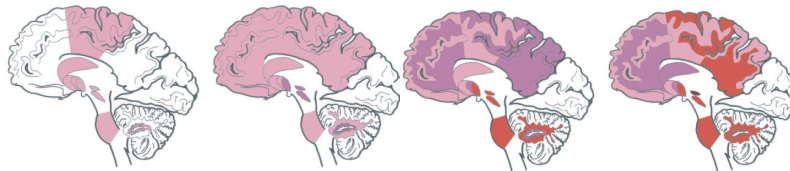
III.



IV.

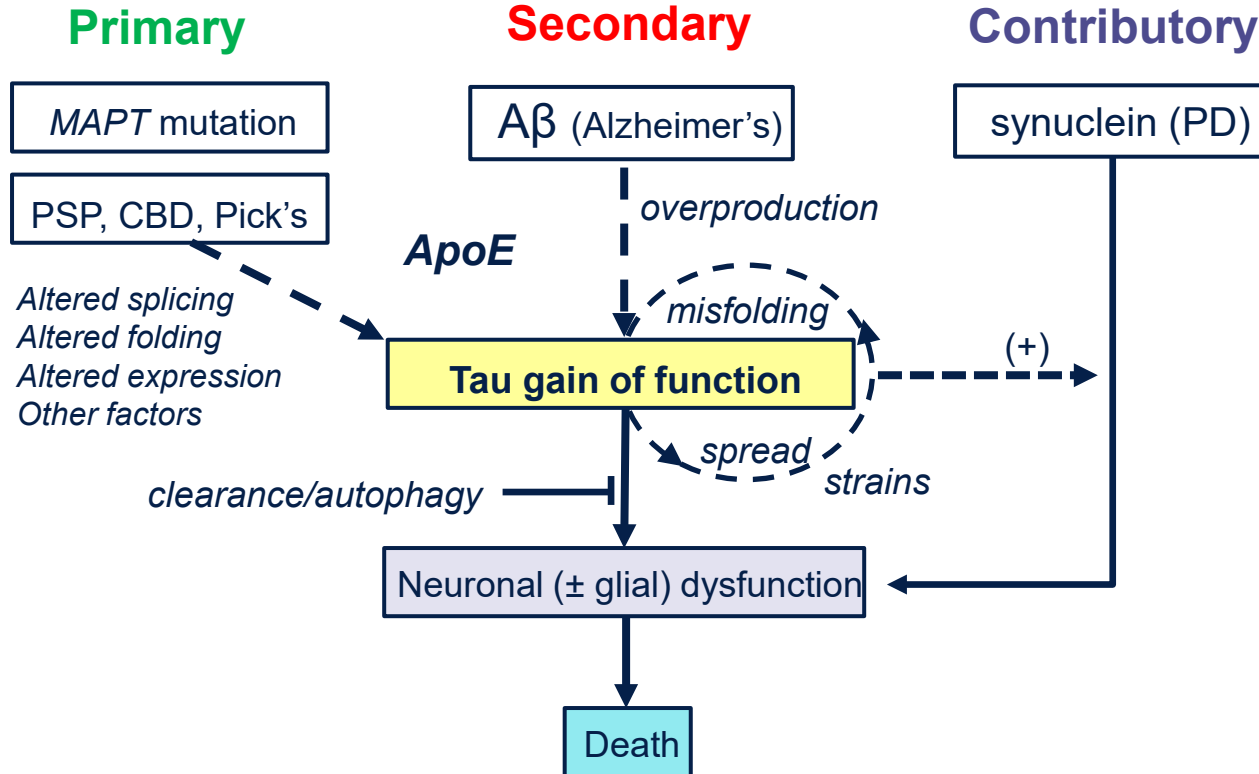


PSP-RS



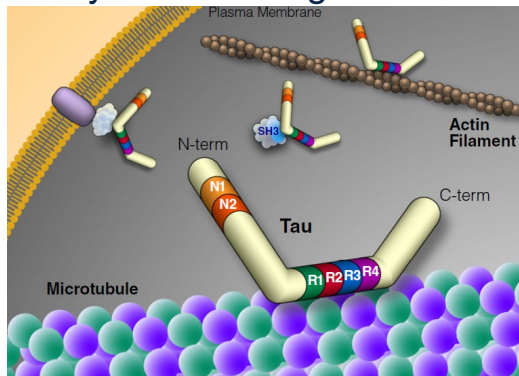
CTE

The tau hypothesis (tauopathies)

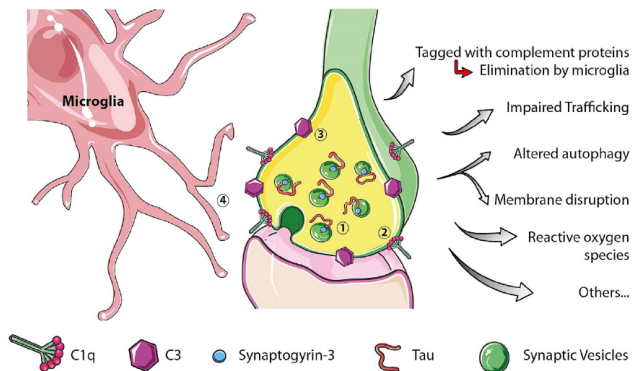


Tau is a multi-functional protein in health and disease

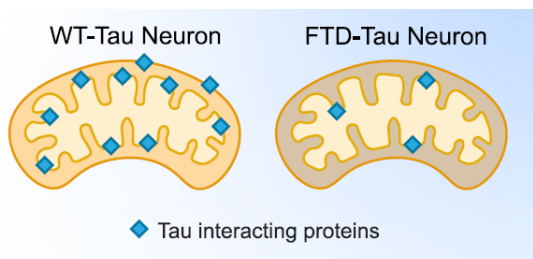
Cytoskeletal regulation



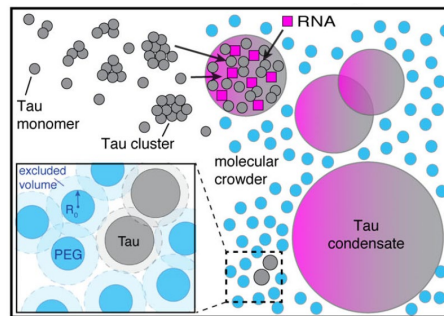
Synaptic vesicle protein binding & dysfunction



Mitochondrial protein binding & dysfunction



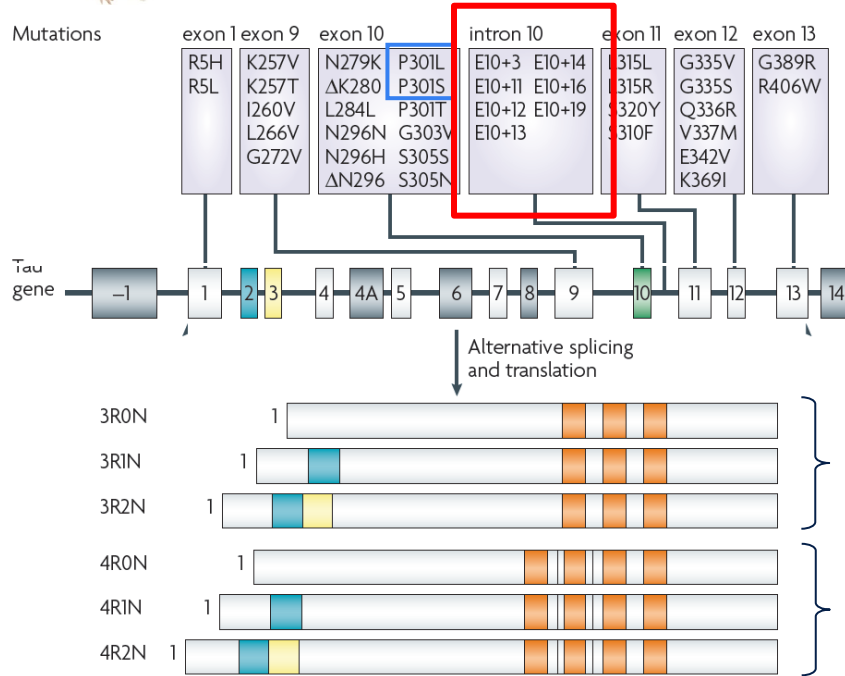
RNA binding & cytosolic condensates



Tau genetics: strong links to primary tauopathies (but not AD)



Mouse models



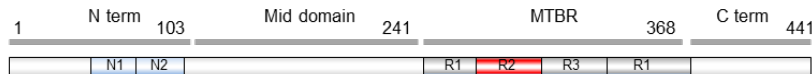
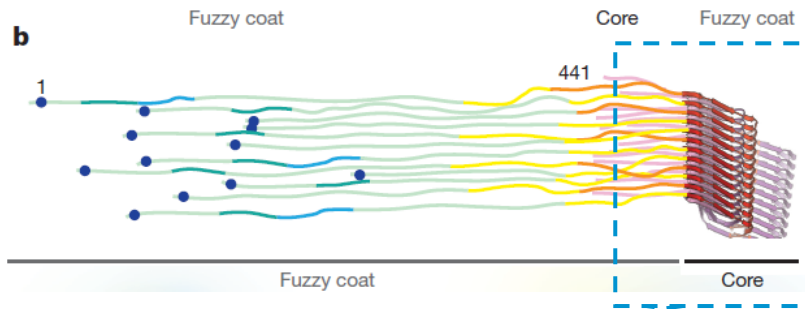
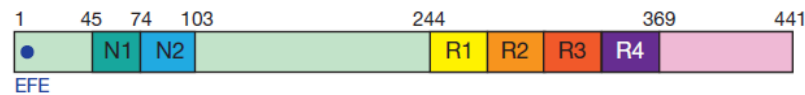
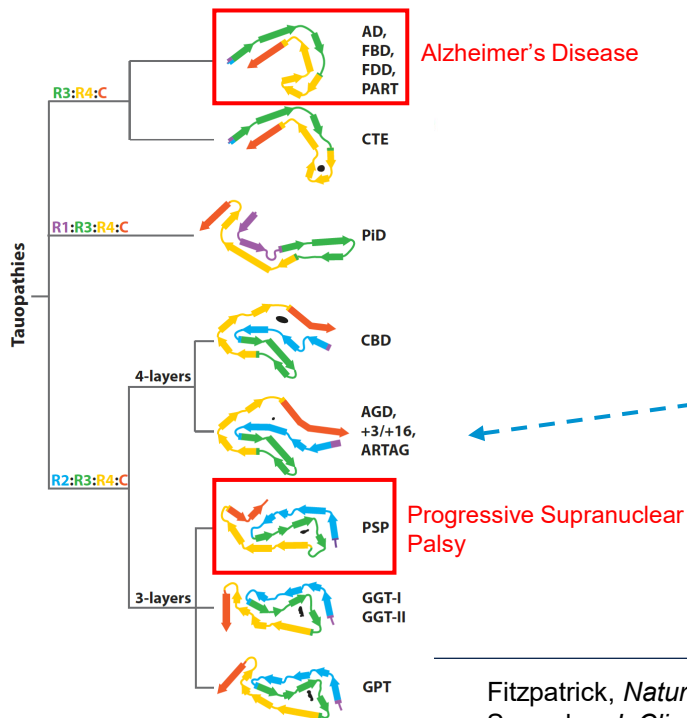
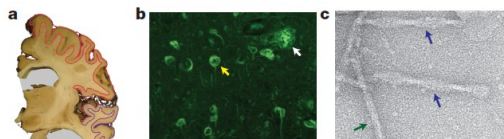
PSP, CBD GWAS

H1/H1 Tau haplotype
OR 5.46 (4.72–6.31)
 $p = 1.5 \times 10^{-116}$

H2 (protective allele) not present in Asia

Greater tau risk
PSP & CBD H1c

Disease specific tau aggregate structures: impact on treatments?

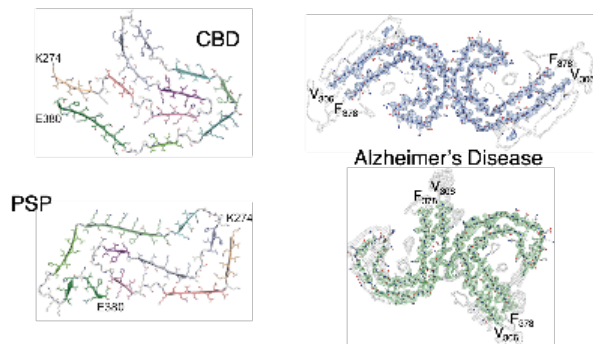


Gosuranemab,
Tilavonemab
Semorinemab

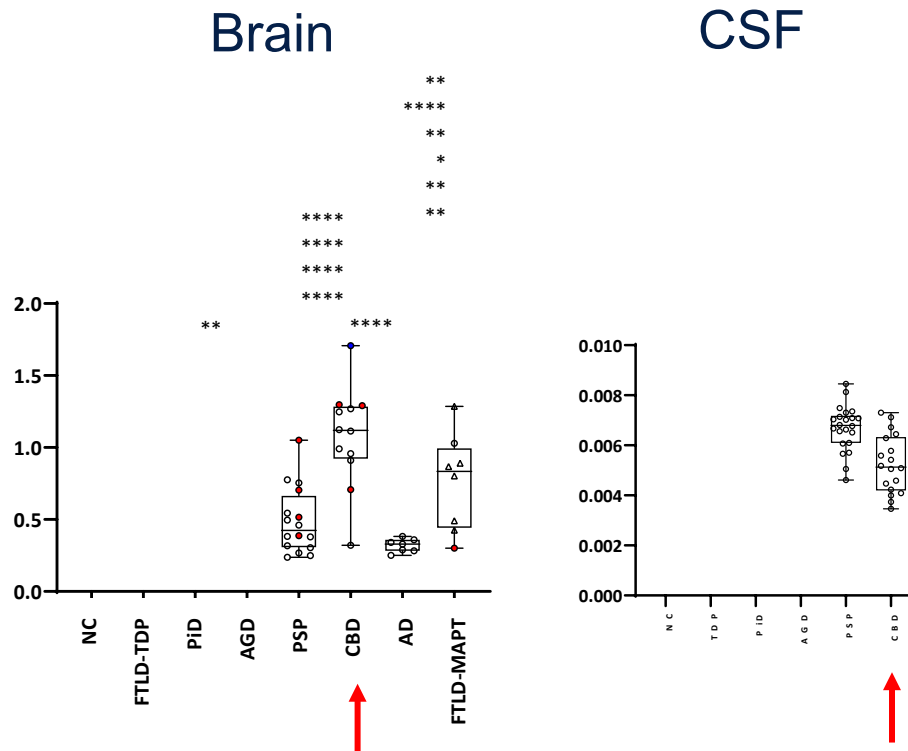
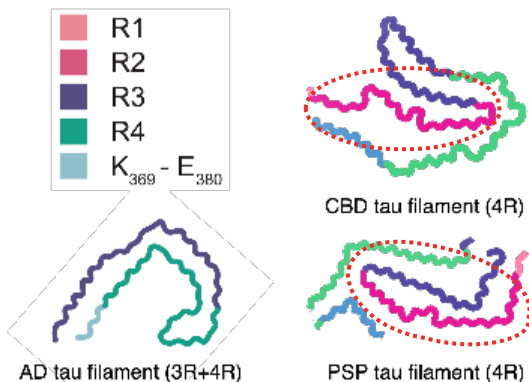
newer mAbs
new CSF biomarkers

Fitzpatrick, *Nature*, 2017; Falcon, *Nature*, 2018; Shi, *Nature*, 2022; Horie, *Brain*, 2021; Samudra, *J. Clin Invest*, 2023; Lane-Donovan and Boxer, *Neurotherapeutics*, 2024

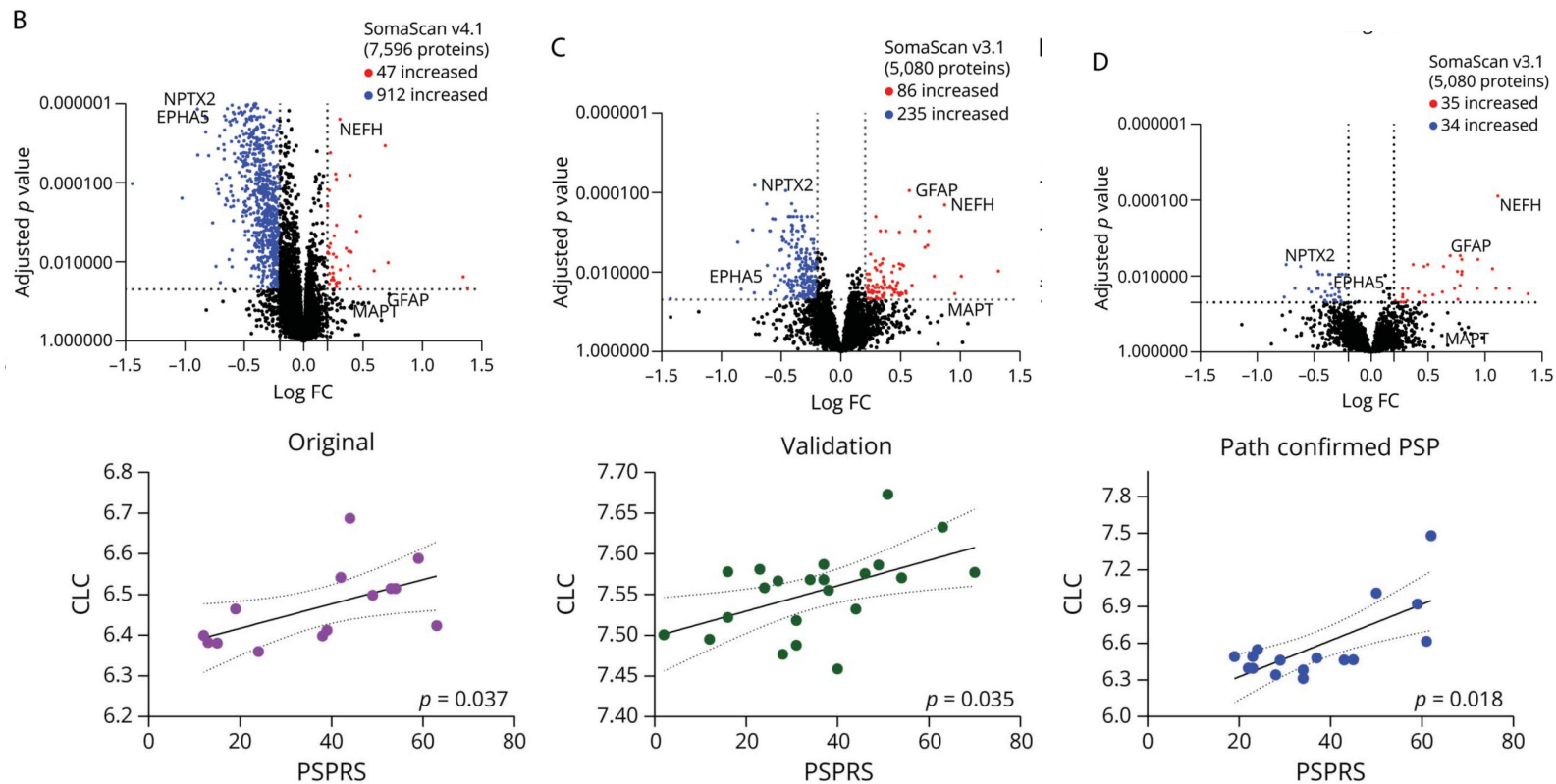
New 3D tau structures informing biomarkers for CBD



Protein DataBank IDs: 5O3L, 5O3O, 5O3T, 6VHA, 6VH7, 6VHL, 6VI3, 7U0Z



CSF Proteomics in Patients With Progressive Supranuclear Palsy

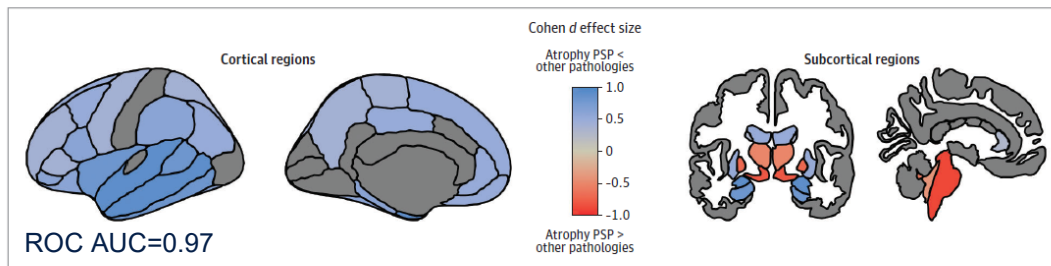


Diagnostic accuracy of vMRI for PSP and CBD pathology

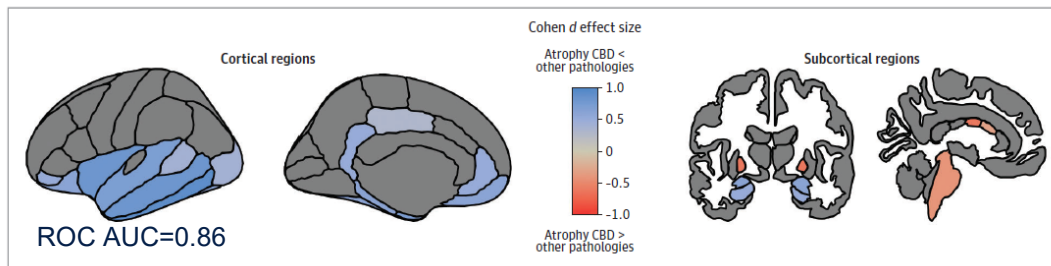
Table 1. Characteristics of the Sample

Characteristics	Participants, No. (%)			
	PSP (n = 68)	CBD (n = 44)	Combined (n = 112)	Other pathologies (n = 214)
4RT				
Age at symptom onset, mean (SD), y	64.1 (6.98) ^a	60.0 (7) ^b	62.5 (7) ^c	57.1 (9) ^{b,d}
Age at MRI, mean (SD), y	69.5 (5) ^a	64.2 (6) ^b	67.4 (6) ^c	62.4 (8) ^{b,d}
Years of education, mean (SD)	16.2 (3)	16.1 (2)	16.2 (3)	16.2 (2)
Biological sex				
Men	32 (47.1)	19 (43.2)	51 (45.5) ^c	125 (58.4) ^d
Women	36 (52.9)	25 (56.8)	61 (54.5) ^c	89 (41.6) ^d
Diagnosis at MRI				
PSP-RS	43 (63.2) ^a	3 (6.8) ^b	46 (41.1) ^c	3 (1.4) ^{b,d}
CBS	11 (16.2)	12 (27.3) ^c	23 (20.5)	22 (10.3) ^e
PSP-RS or CBS	54 (79.4) ^a	15 (34.1) ^f	69 (61.6) ^c	25 (11.7) ^{d,g}
MMSE, mean (SD) ^h	25.5 (4.81) ^c	24.0 (6.24)	24.9 (5.44) ^c	22.6 (7.00) ^{b,d}
Years from MRI to death, mean (SD)	3.69 (2.01) ^a	3.25 (1.62) ^b	3.52 (1.87) ^c	4.82 (3.27) ^{b,d}
Primary neuropathological diagnosis				
PSP	68 (100)	0	68 (60.7)	0
CBD	0	44 (100)	44 (39.3)	0
Pick disease	0	0	0	26 (12.1)
FTLD-TDP				
Type A	0	0	0	26 (12.1)
Type B	0	0	0	34 (15.9)
Type C	0	0	0	26 (12.1)
MND-TDP	0	0	0	11 (5.1)
Other FTLD	0	0	0	32 (15.0)
AD	0	0	0	45 (21.0)
PD, LBD, MSA	0	0	0	11 (5.1)
Other	0	0	0	3 (1.4)

A PSP (n=68) vs other pathologies (n=214)



B CBD (n=44) vs other pathologies (n=214)



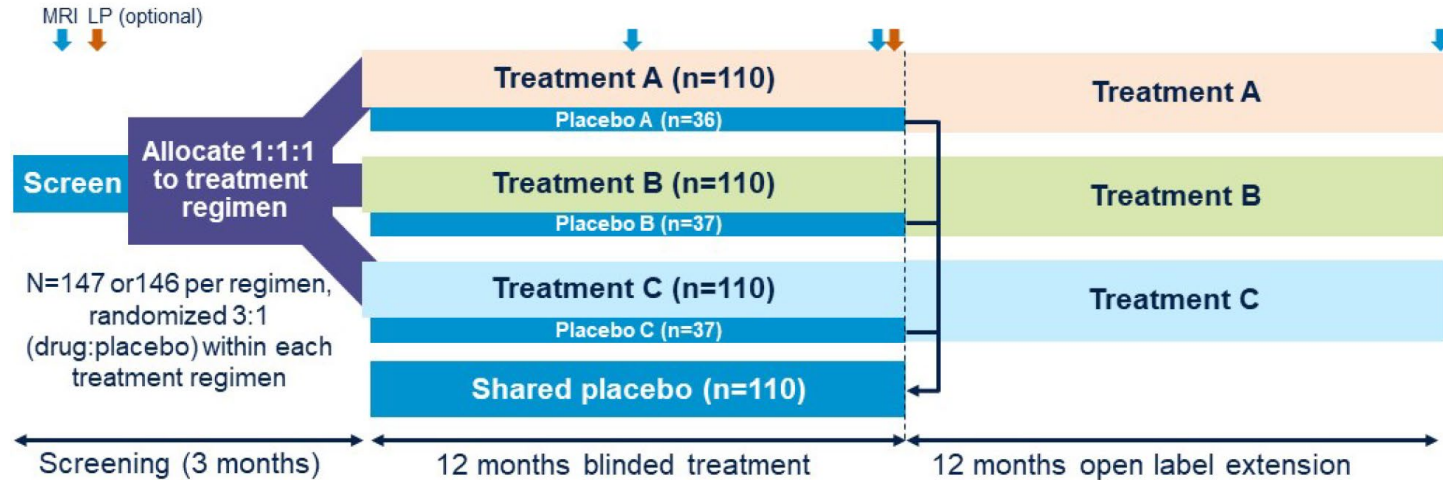
New clinical trials for PSP & CBS

- Amylyx (AMX0035) Phase 3 clinical trial (NCT06122662) - Rojas; enrolling at UCSF
- Ferrer (FNP-223) Phase 2 clinical trial (NCT06355531)

Planned (not definite) for 2025

- Corticobasal syndrome (CBS) phase 1b study
- PSP Trial Platform (PTP)

PSP Trial Platform design



A randomized, placebo-controlled, Phase 2 platform trial in mild-moderate PSP that will simultaneously test at least three different tau related or neuroprotective therapies to determine safety, tolerability, and clinical proof of concept based on a multimodal clinical rating scale, the modified PSP Rating Scale (mPSPRS-15)