Tau topography subtypes account for clinical heterogeneity and longitudinal trajectories in early-onset Alzheimer's disease

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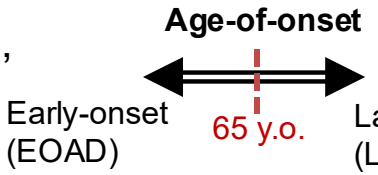
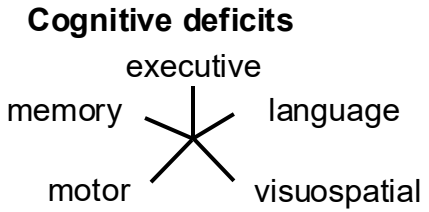
RAB LAB

Background: Alzheimer's disease (AD) heterogeneity

Characterizing AD heterogeneity improves diagnostic accuracy and disease monitoring

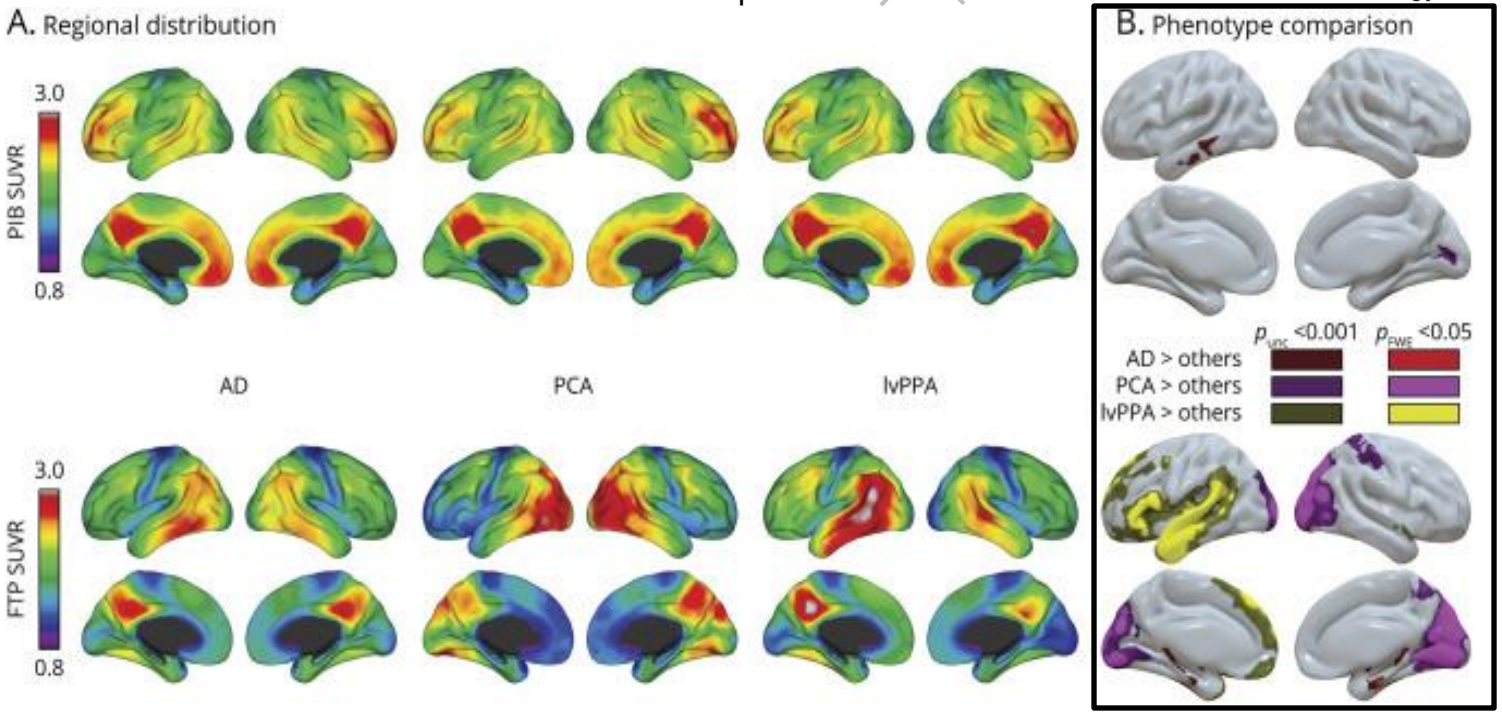
AD heterogeneity is multi-faceted: e.g.,





Neuropathology

La Joie et al, *Neurology 2021*



Amyloid

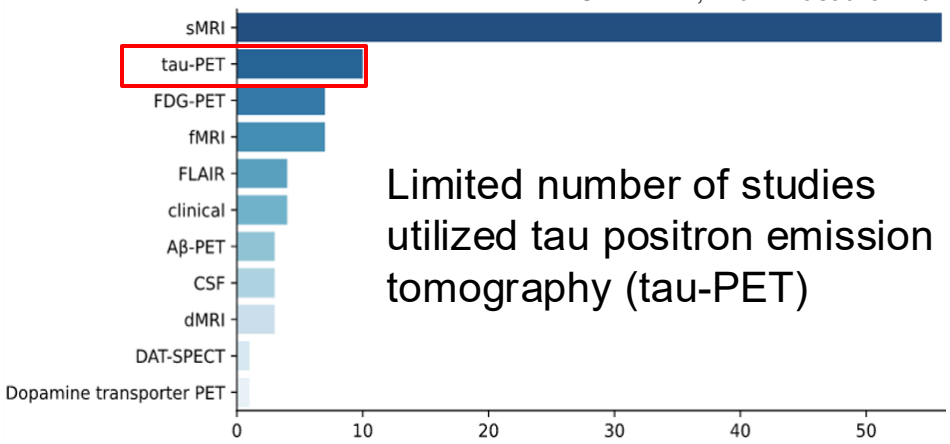
Tau

AD heterogeneity in clinical syndromes best reflected by tau topography

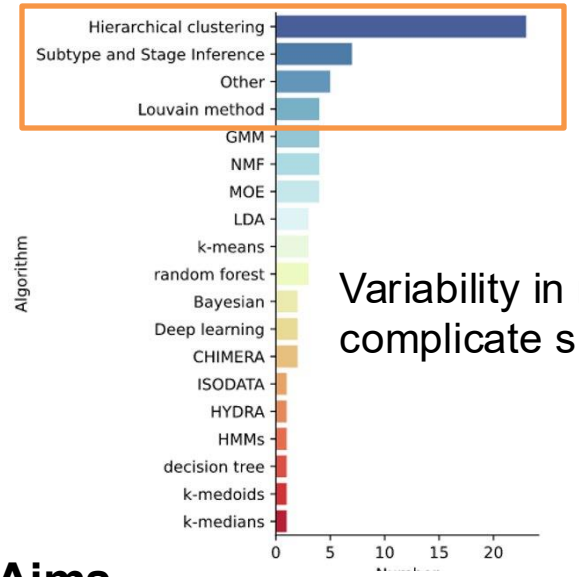
Hypothesis-based → **Data-driven subtyping**

Background (cont.)

Chen et al, *Brain Research 2024*

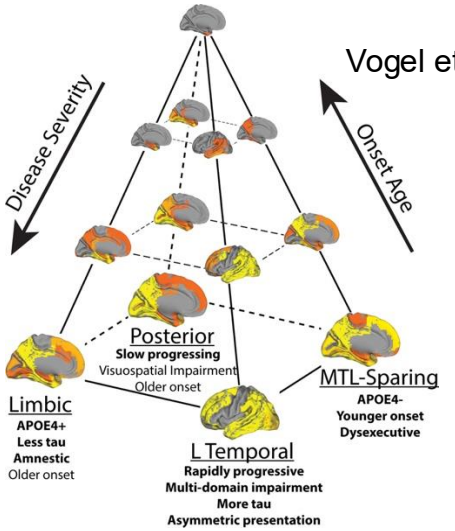


Limited number of studies utilized tau positron emission tomography (tau-PET)

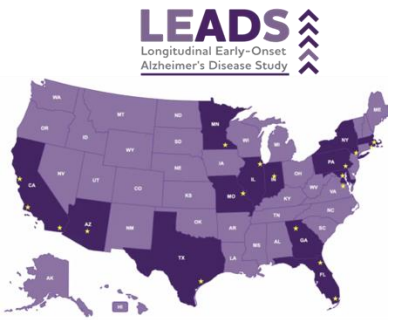


Variability in methods complicate subtype validation

Vogel et al., *Nat Med 2021*



Previous study limited to participants w/ late-onset, amnestic clinical profiles



Better representation of heterogeneity in an early-onset cohort (less co-pathology, more ”atypical” cases)

Aims

Identify Sporadic EOAD Subtypes with distinct tau patterns by using robust data-driven method (SuStaIn) on baseline tau-PET from Longitudinal Early-onset Alzheimer’s Disease Study (LEADS)

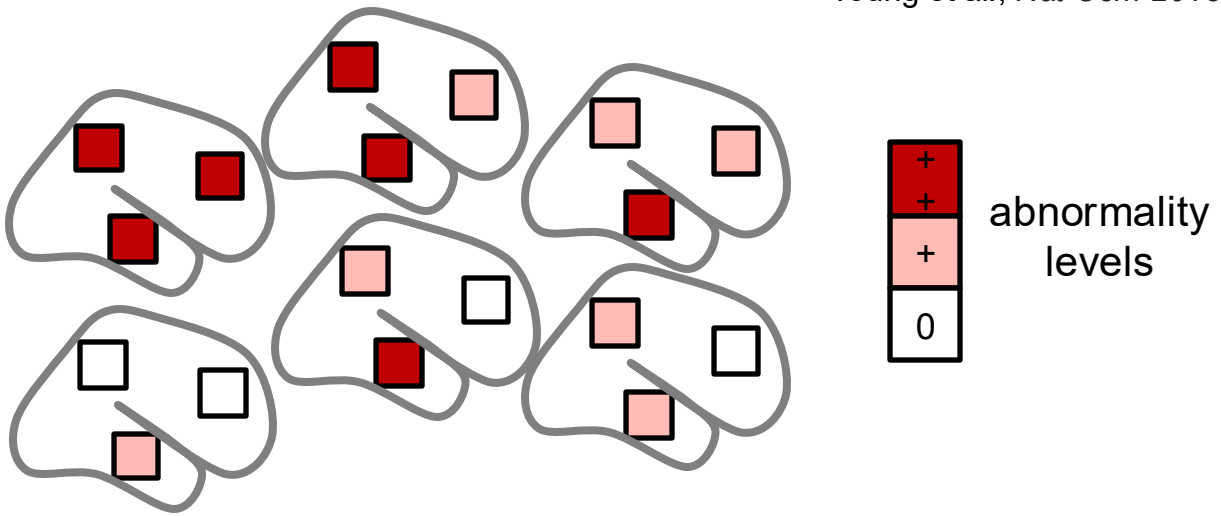
Assess Clinical Heterogeneity and Disease Trajectories of the SuStaIn subtypes, focusing on AD clinical phenotypes, cognitive decline, tau propagation, and atrophy

Subtype and Stage Inference Model (SuStaIn)

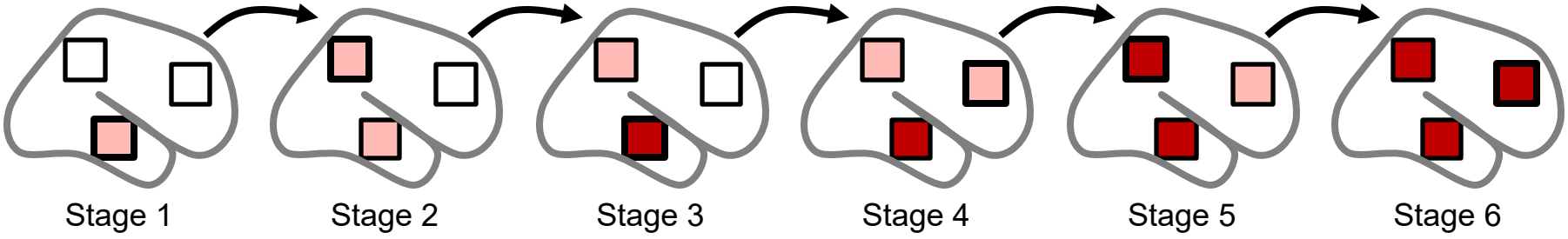
Unsupervised machine learning algorithm using
cross-sectional data to identify
subgroups of individuals with
distinct pseudo-temporal progression patterns

Young et al., *Nat Com 2018*

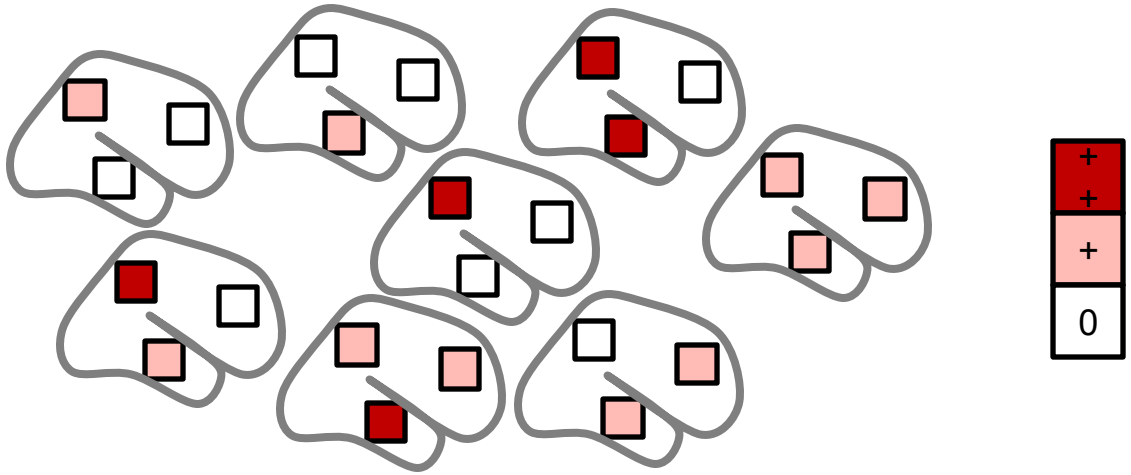
N = 6 patients w/
3 measures each



Reconstructed disease progression (assuming monotonicity of abnormality)



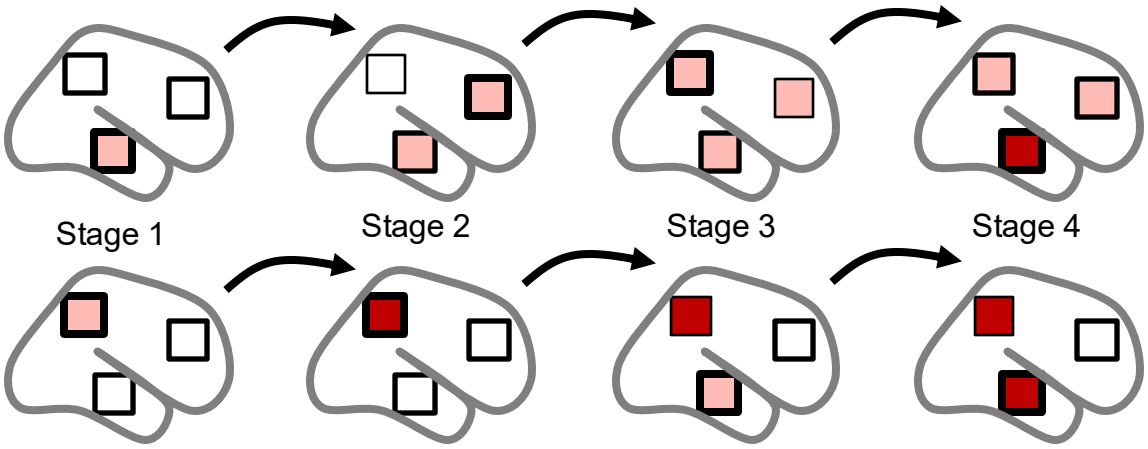
N = 8 patients
w/ 3 measures each



NOT possible to put everyone on a single trajectory

Subtype A

Subtype B



Dataset

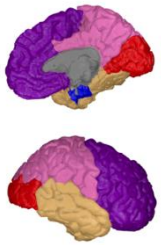
SuStaIn Input

dx	L_MTL	L_frontal	L_occipital	L_parietal	L_temporal	R_MTL	R_frontal	R_occipital	R_parietal	R_temporal
CN	1.212698	1.029354	1.103603	1.074372	1.127232	1.210549	1.025647	1.109314	1.074605	1.142007
EOAD	1.856240	2.413739	2.957153	3.012157	2.856721	1.695600	2.197533	2.754564	2.772873	2.635381
EOAD	1.329493	1.744891	2.092321	2.439468	2.290511	1.271227	1.697044	1.870114	2.304942	2.221782

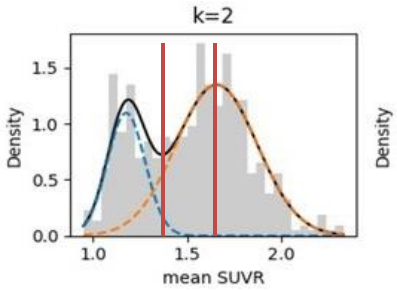
Lobar ROI

5 Left + 5 Right = 10 ROI

- Frontal
- Temporal
- Parietal
- Occipital
- Medial-temporal



Standardization
(e.g. Left Medial-temporal)



- PET and MRI
- Clinical phenotype
- Cognitive data
- Demographics
- APOE4 status
- …

Subtype characterization

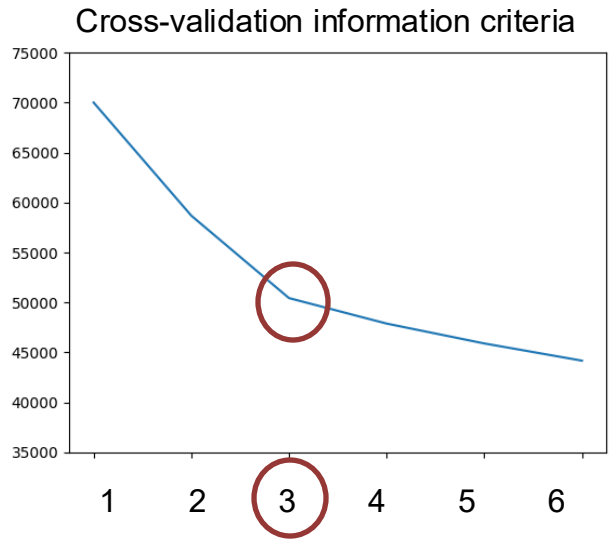
- LEADS (aβ- CN: 85; EOAD: 365) baseline 6mm tau-PET images
- Co-registered to MRI, normalized w.r.t. inferior cerebellar gray region for SUVR images
- Parcellations using the Desikan–Killiany atlas
- Combined into ten lobar ROIs
- For each ROI, calculate the volume-weighted mean SUVR
- Derive z-scores using 2-component Gaussian Mixture Model fitted on CN+EOAD
- Thresholds (2/ROI): intersection of lower- and higher-mean components, higher mean

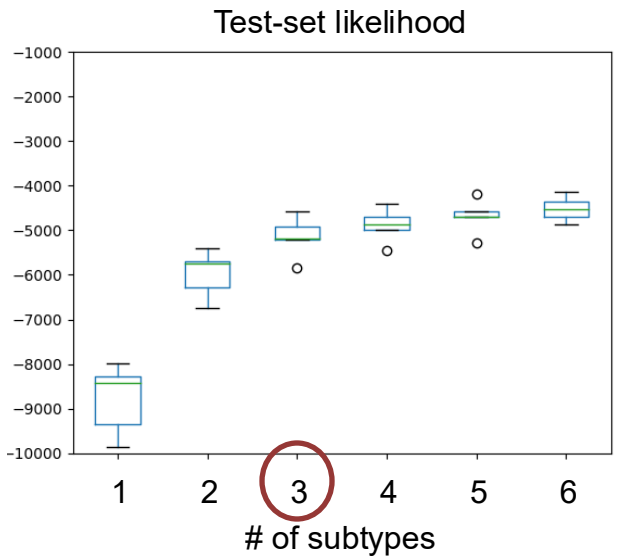
For post-clustering analysis: demographic, cognitive, clinical, PET and MRI data…

CN: cognitively normal; MRI: magnetic resonance imaging; APOE: apolipoprotein E; SUVR: standardized uptake volume ratio = quantification of radiotracer (18F-Flortaucipir) uptake ≈ tau level

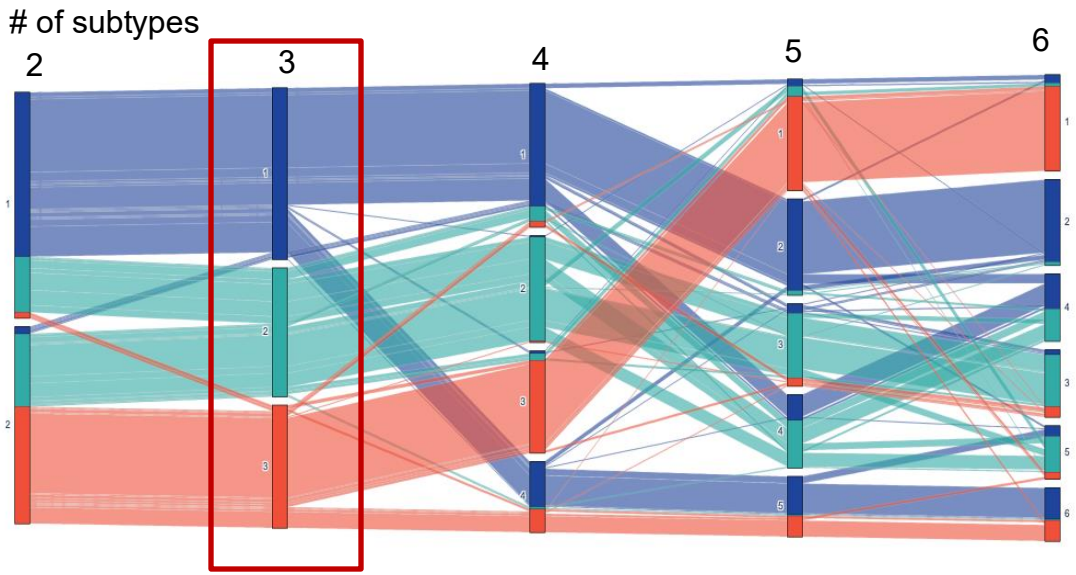
SuStaIn model fit

Subtype number determination



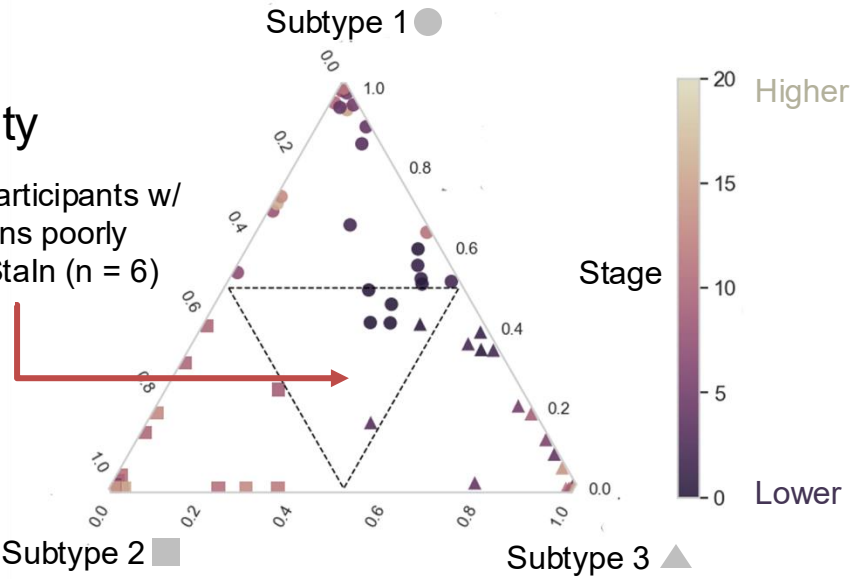


Subject assignment as # of subtypes increases



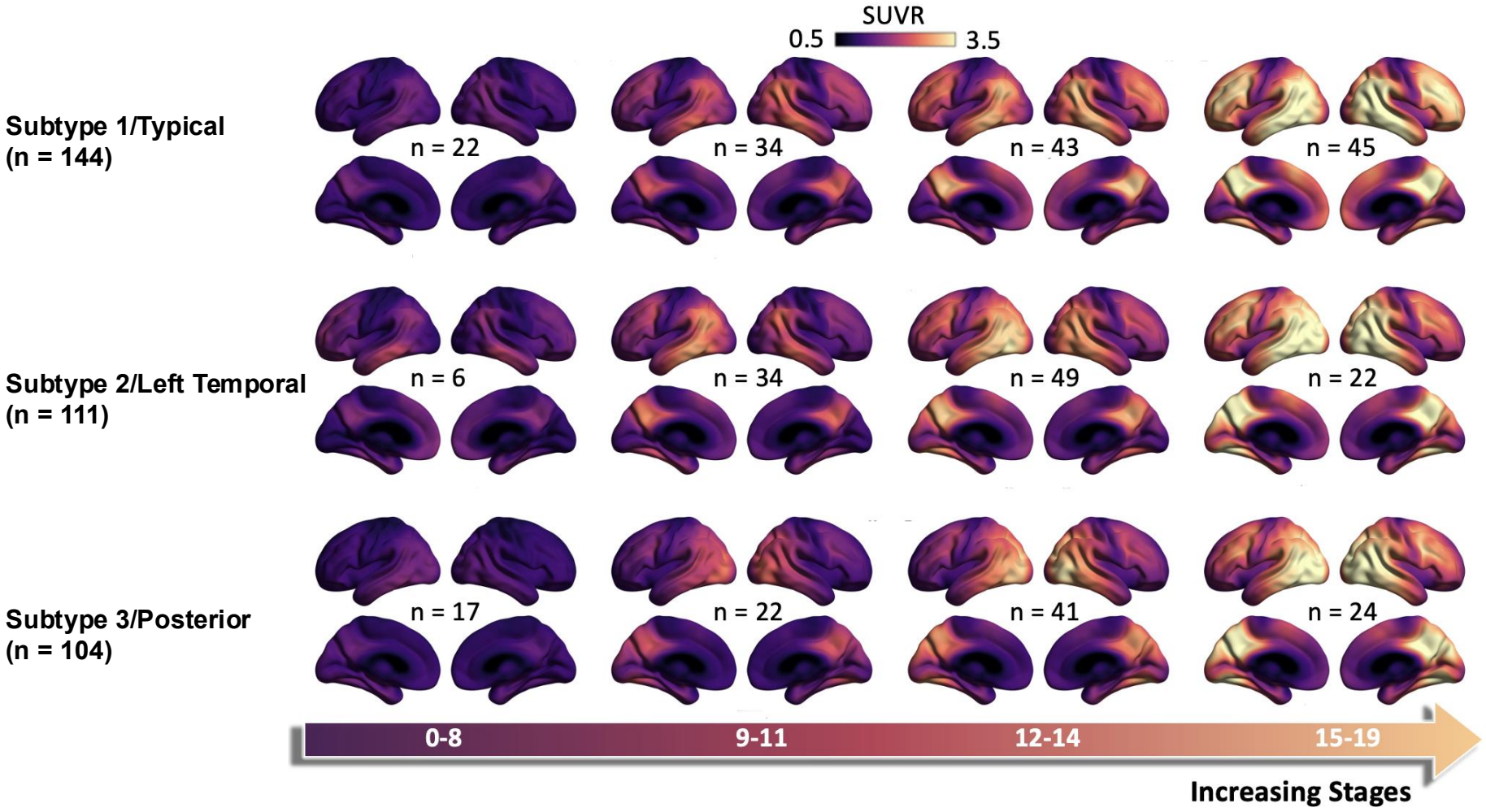
Subtype probability

Exclusion: participants w/ baseline scans poorly fitted by SuStaIn (n = 6)

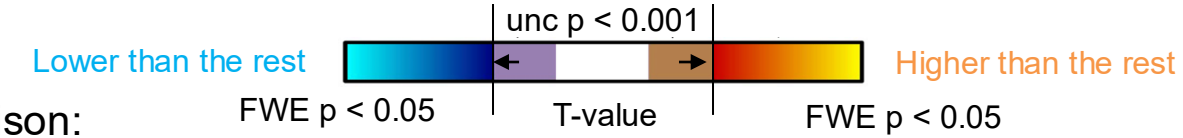


Spatial-temporal trajectories

Average tau-PET images across SuStaIn subtypes and stages



Baseline imaging characteristic



Average tau-PET images

Comparison:

Subtype 1/Typical (n = 144)

Subtype 2/Left Temporal (n = 111)

Subtype 3/Posterior (n = 104)

SUVR 0.5 3.0

Tau

MRI

Amyloid-PET

S1 vs. others

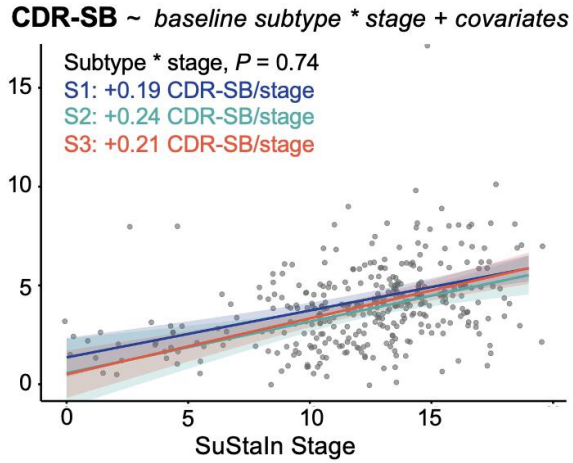
S2 vs. others

S3 vs. others

Baseline demographic, clinical, and cognitive characteristics

+: higher score on this test indicates worse performance

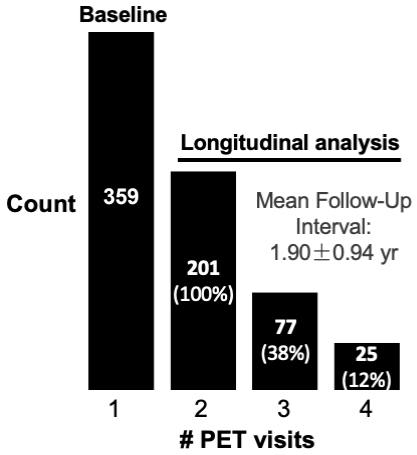
	S1/Typical	S2/L Temporal	S3/Posterior	P-value
Baseline	**(n = 144)**	**(n = 111)**	**(n = 104)**	
Age	58.9 (4.1)	58.9 (3.9)	59.6 (3.9)	0.31
Sex - Female	78 (54.2%)	63 (56.8%)	57 (54.8%)	0.92
Yrs. of Education	15.6 (2.5)	15.6 (2.4)	15.8 (2.4)	0.66
Tau SUVR	2.0 (0.5)	2.0 (0.3)	1.8 (0.4)	**0.04**
Centiloids	103.8 (29.6)	103.5 (24.5)	101.4 (28.9)	0.79
MMSE	21.1 (5.7)	20.6 (5.5)	22.2 (4.6)	0.07
CDR-SB+	4.1 (2.3)	3.7 (1.8)	3.8 (1.8)	0.22
Clinical Stage - Dementia	108 (75.0%)	84 (75.7%)	75 (72.8%)	0.61
Phenotype - Amnestic	124 (86.1%)	88 (79.3%)	78 (75.0%)	**<0.001**
ApoE4 - Carrier	71 (50.7%)	59 (54.6%)	65 (63.7%)	0.36
SuStaIn Stage	12.1 (4.2)	12.6 (2.6)	11.8 (3.9)	0.29
Cognitive assessment (domains)				



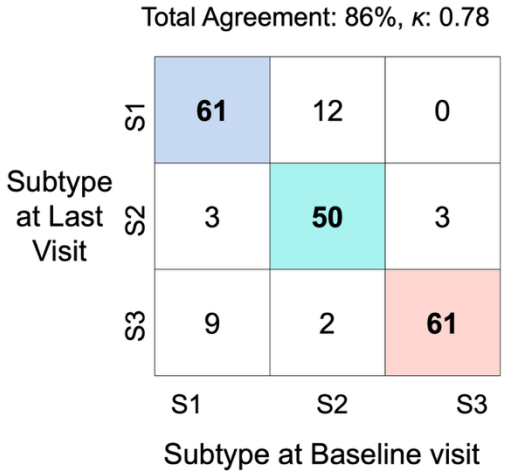
Mean (SD); n (%).
Centiloid: standardized measure of global amyloid burden
MMSE: Mini-Mental State Examination
CDR-SB: Clinical Dementia Rating – Sum of Boxes
P-values correspond to omnibus tests (analysis of variance/chi-squared) comparing the three subtypes.

Longitudinal analysis

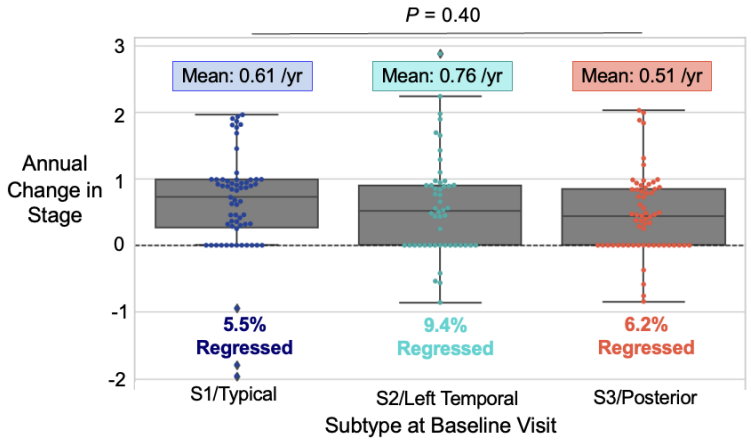
Follow-up Visits Overview



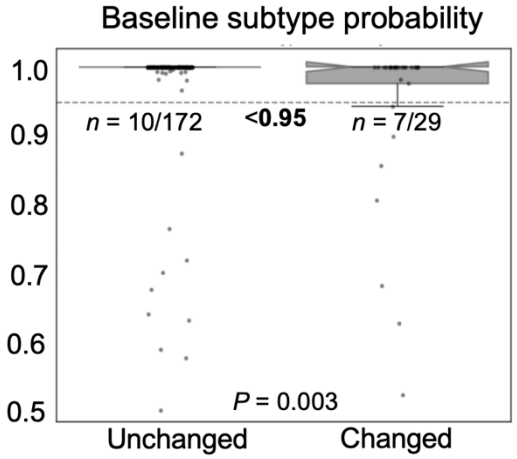
Subtype stability over time

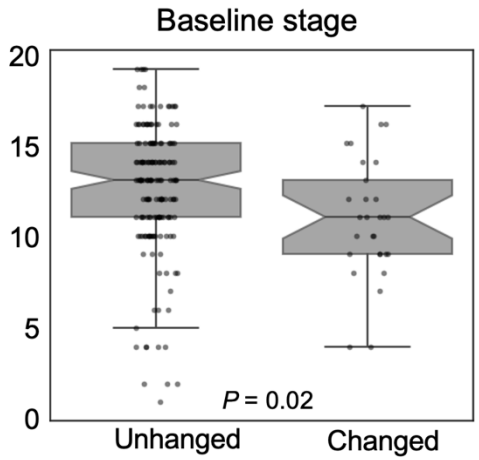


Stage progression over time



Changed vs. Unchanged

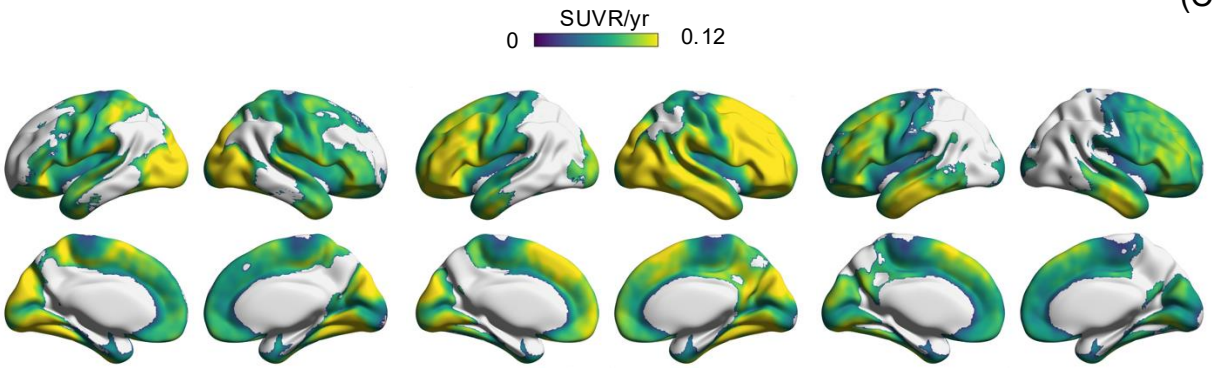


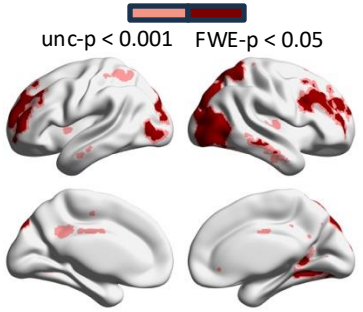


Voxelwise analysis of longitudinal change in tau based on baseline subtype

Tau SUVR *~ baseline subtype * time + sex + yrs. of education + age + Centiloid + CDR-SB + SuStaIn stage + (1 + time | participant)*

(Covariates are all baseline measurements)





Subtype 1/Typical at baseline (n = 73)

Subtype 2/Left Temporal at baseline (n = 64)

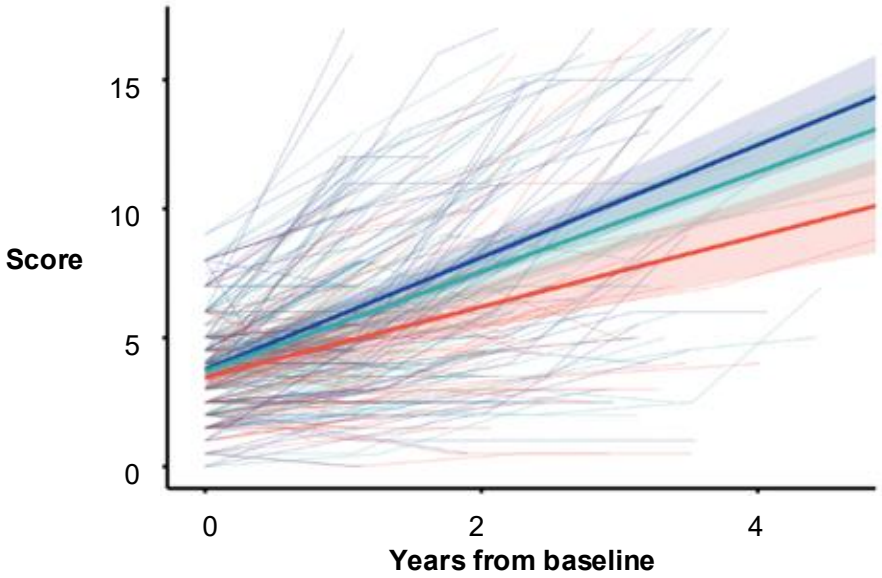
Subtype 3/Posterior at baseline (n = 64)

Regions with significant differences in tau rates among subtypes

Baseline subtype * time, FWE p < 0.05

Longitudinal modeling of cognitive scores, e.g.

CDR-SB *~ baseline subtype * time + sex + yrs. of education + age + Centiloid + (1 + time | participant)*



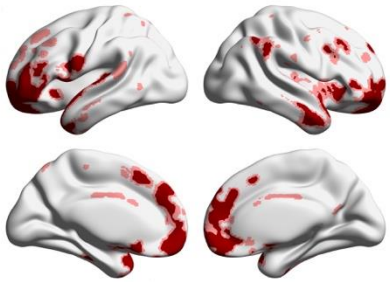
Subtype * stage, p = 0.005

S1: +2.18 CDR-SB/yr

S2: +1.97 CDR-SB/yr

S3: +1.43 CDR-SB/yr

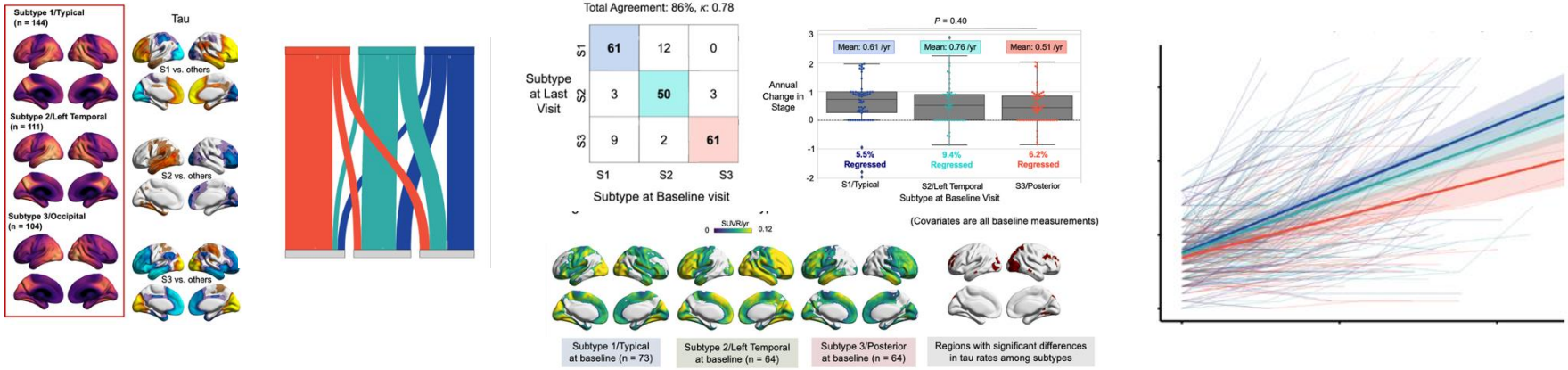
MRI



Summary

Identify **distinct patterns of tau-PET in EOAD** (through SuStaIn), characterized by

- Associations with known AD clinical phenotypes
- Longitudinal stability and reasonable progression
- Varying trajectories of tau accumulations and atrophy
- Differences in prospective clinical decline



Implication: potential to refine prognosis and improve disease progression monitoring in clinical practice and trials

Thank you for listening!

Questions?