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

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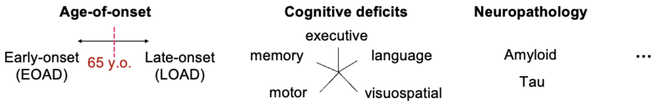
AIMS

(a) Identify sporadic early-onset Alzheimer's disease (EOAD) subtypes with distinct tau patterns by using robust data-driven method (Subtype and Stage Inference [SuStaIn]) on baseline [^{18}F]Flortaucipir-PET Images from the Longitudinal Early-onset Alzheimer's Disease Study (LEADS)

(b) Assess clinical heterogeneity and disease trajectories of the SuStaIn subtypes, focusing on clinical phenotypes, cognitive decline, tau propagation, and atrophy

Background

Alzheimer's disease (AD) is a clinically and biologically heterogeneous condition



Tau-PET allows in-vivo mapping of tau burden, closely tied to symptoms and cognitive decline

Data-driven methods are developed to identify biologically meaningful subtypes with less presumptions

Subtyping the **EOAD** population made possible by **LEADS**[1]

Methodology

Cohort

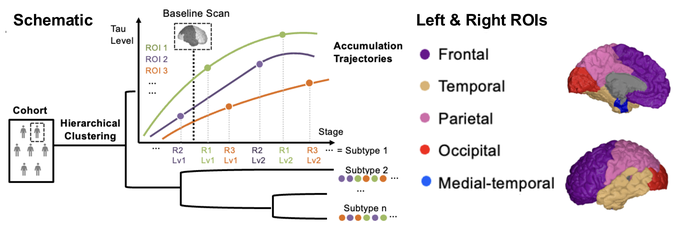
365 [^{18}F]Florbetaben-PET positive patients with EOAD (age of onset < 65) and 85 [^{18}F]Florbetaben-PET negative cognitively normal control from LEADS

Dataset

Baseline and longitudinal T1-weighted MRI, [^{18}F]Florbetaben-PET, [^{18}F]Flortaucipir-PET images, demographic, clinical, APOE4, and cognitive data

Subtype and Stage Inference Model (SuStaIn)[2]

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



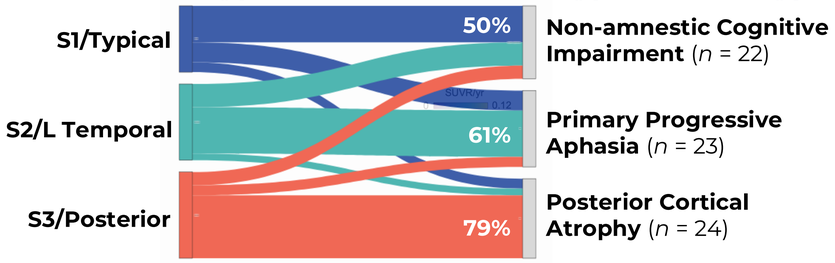
Model Fitting and Statistical Analysis

- Input: Average [^{18}F]Flortaucipir SUVR extracted from patients' baseline images and z-scored + ROI-specific severity thresholds decided with 2-GMM
- # of clusters determined with 5-fold Cross Validation
- Subtype characterized with baseline & longitudinal clinical, cognitive, T1-weighted MRI, [^{18}F]Flortaucipir-PET, and [^{18}F]Florbetaben-PET features

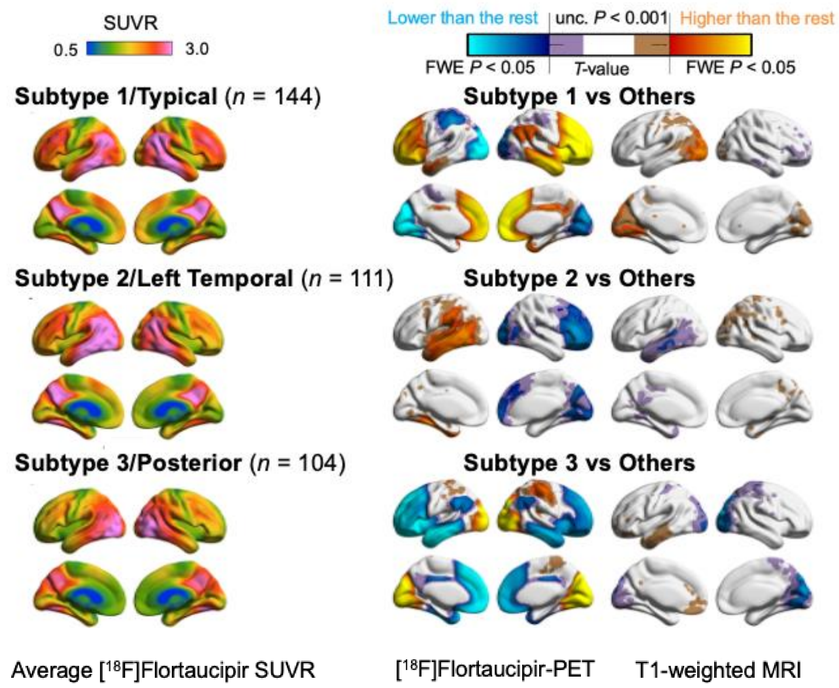
Results

Table 1	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
Years of Education	15.6 (2.5)	15.6 (2.4)	15.8 (2.4)	0.66
Centiloids	103.8 (29.6)	103.5 (24.5)	101.4 (28.9)	0.79
[^{18}F]Flortaucipir SUVR (all cortical ROIs)	2.0 (0.5)	2.0 (0.3)	1.8 (0.4)	**0.04**
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
APOE4 - Carrier	71 (49.3)	59 (53.2)	65 (62.5)	0.36
Phenotype - Amnestic	124 (86.1%)	88 (79.3%)	78 (75.0%)	**<0.001**

SuStaIn Subtypes Correlation with Atypical Phenotypes

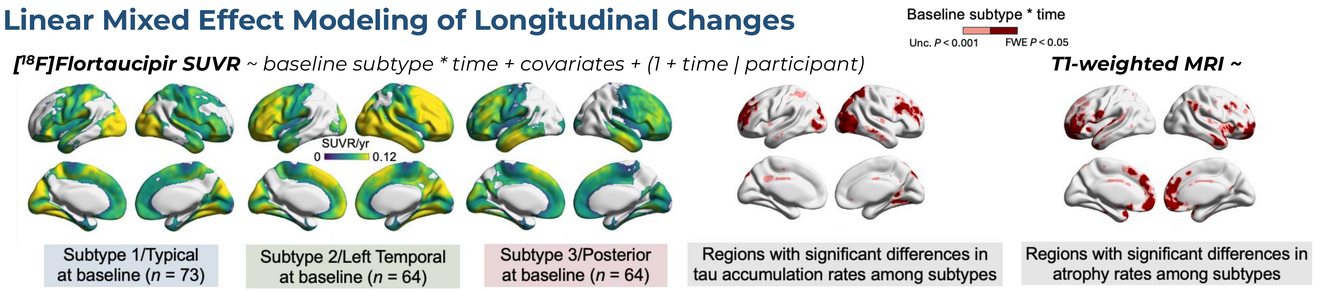


Baseline Pattern and Subtype Comparison



Linear Mixed Effect Modeling of Longitudinal Changes

*[^{18}F]Flortaucipir SUVR ~ baseline subtype * time + covariates + (1 + time | participant)*



Highlight

Identified distinct patterns of [^{18}F]Flortaucipir-PET in EOAD

- Associations with known AD clinical phenotypes
- Recapitulated LOAD SuStaIn subtypes,[3] except without MTL-sparing
- Longitudinal stability and reasonable progression
- Varying trajectories of tau accumulations and atrophy
- Differences in prospective clinical and cognitive decline

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(2) Young AL, Marinescu RV, Oxtoby NP, et al. Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference. *Nat Commun.* 2018;9(1):4273. (3) Vogel JW, Young AL, Oxtoby NP, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med.* 2021;27(5):871-881.

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