Deep Learning Framework for Characterizing Tau-PET Heterogeneity and Exploring Functional Connectivity in Alzheimer's Disease: A Self-supervised Approach

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Background

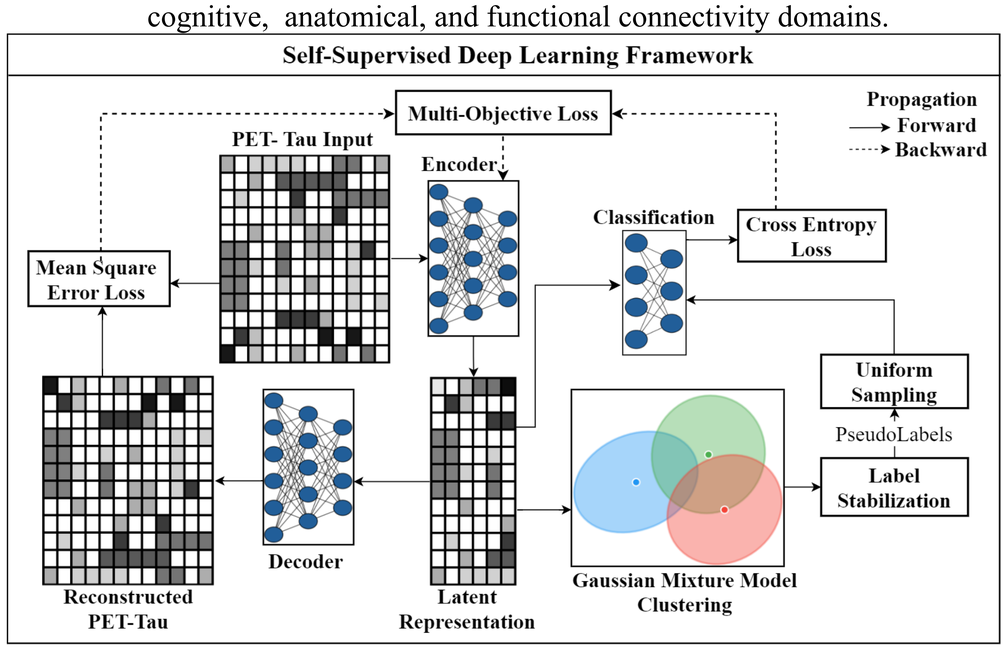
- Extracellular amyloid plaques and intraneuronal neurofibrillary tangles are defining features of Alzheimer disease (AD).
- AD patients exhibit spatially heterogeneous tau-PET composition across brain.
- This cross-sectional study uses self-supervised deep learning to identify tau-PET subtypes and characterize their functional connectivity and clinical profiles

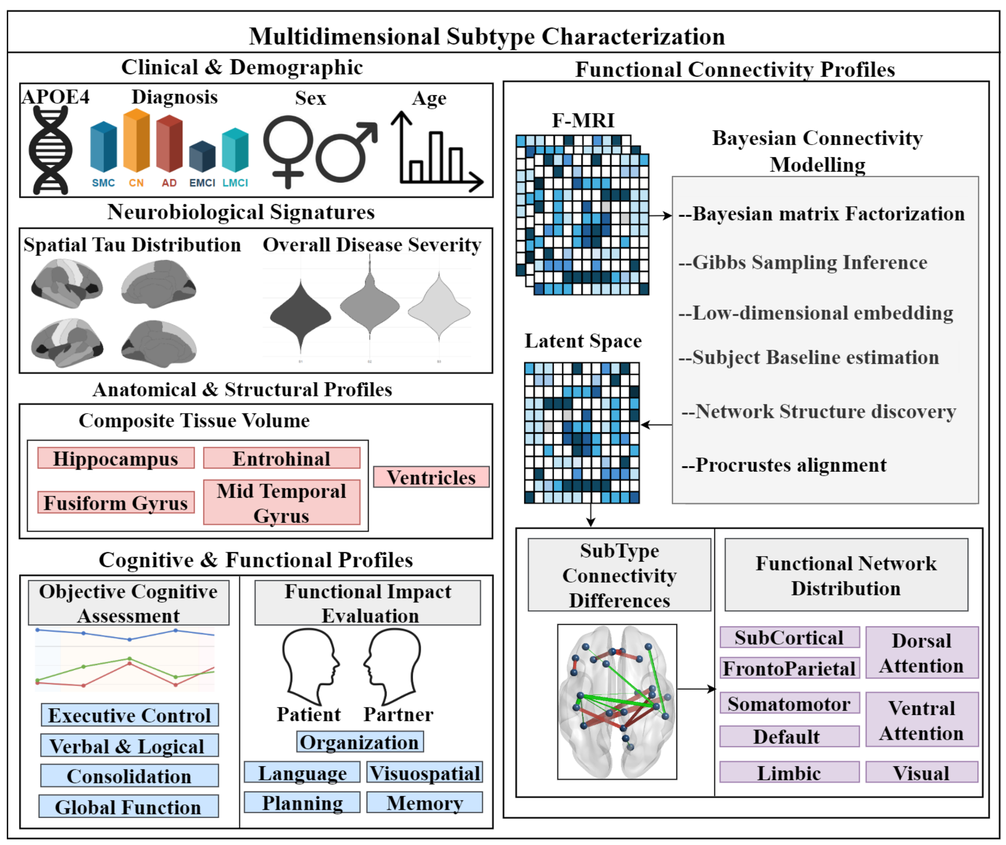
Methods

- ADNI-3 cohort (n=318, ages 55-89): CN, EMCI, LMCI, SMC, AD subjects.
- Tau-PET imaging across 68 cortical regions (Desikan-Killiany atlas).
- Resting-state fMRI for functional connectivity analysis

Stage I Subtype Discovery - Self-supervised deep learning identifies tau subtypes from PET data using Gaussian mixture clustering.

Stage II Subtype Validation - Multidimensional validation across clinical, cognitive, anatomical, and functional connectivity domains.



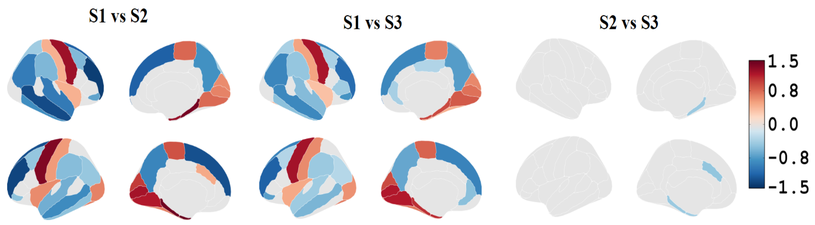


Results

Self-Supervised Framework – Subtype Discovery

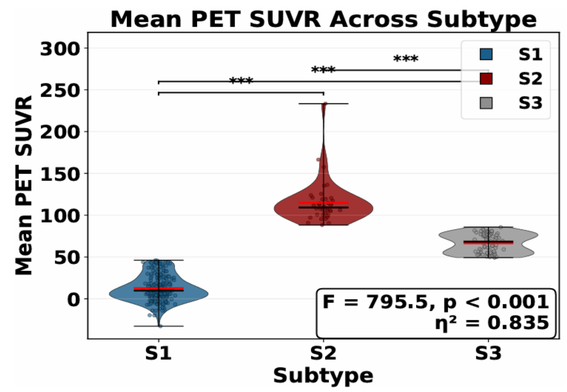
Three Optimal Subtypes
Robust Model Selection & Validation
- 68 cortical regions → 10D latent space for optimal clustering.
- k=3 identified as optimal through multi-criteria evaluation (AIC, BIC, loss, stability) | AMI=0.96 ± 0.09
- Superior stability: 36% lower validation loss variance vs. k=2
- k≥4 showed clear overfitting

Subtype Distribution
S1: 67% (n=213), S2: 13% (n=40), S3: 20% (n=65)



Color: Cohen's d, Warm = 1st higher, Cool = 2nd higher
Significant Pairwise Comparisons ($p_{FDR} < 0.05$) across 68 Regions
S1 vs S2 (48 regions): Large effects (d = 0.907)
S1 vs S3 (51 regions): Large effects (d = 0.745)
S2 vs S3 (4 regions): Small effects (d = 0.472)

Overall Disease Severity



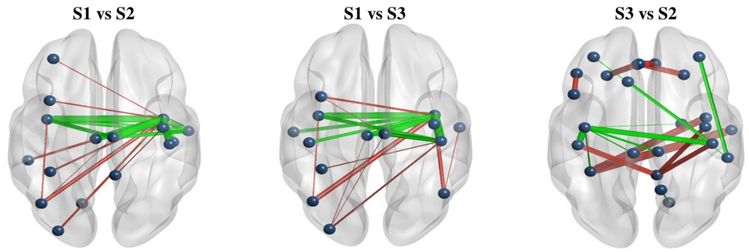
Proportional Tau Distribution Analysis

Three Distinct Spatial Signatures
S1: Visual-sensorimotor-entorhinal pattern (*Contradicts classical Braak staging*)
S2: Widespread neocortical + default mode network
S3: Posterior cortical as S2 subtype + selective limbic-cingulate

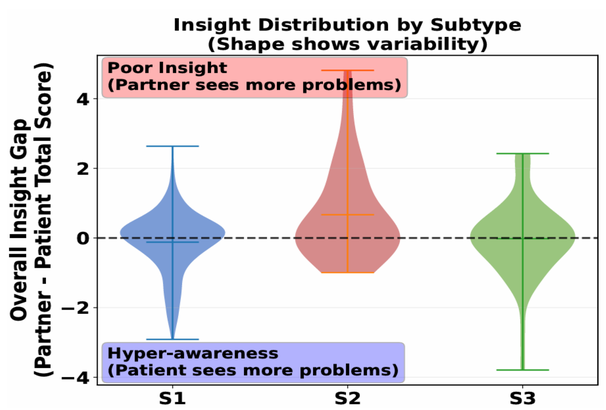
Functional Connectivity Alterations

Bayesian Connectivity Model Performance
- Optimal latent dimensionality: k=5
S1 (r=0.84), S2 (r=0.76), S3 (r= 0.77)

Three Distinct Network Signatures
S1: Consistent Somatomotor-Ventral Attention connectivity (bilateral insula hub)
S2: Insula-mediated cross-network connectivity (Default Mode + Limbic+ Visual)
S3: Default Mode-Ventral Attention coupling + preserved Somatomotor networks



Red=2nd > 1st , Green=1st > 2nd , Thickness=PM magnitude
Top/bottom 10 **strongest** Posterior Mean (PM) differences per comparison quantify connectivity strength
S1 vs S2 (PM: -0.249 to 0.192)
S1 vs S3 (PM: -0.239 to 0.199)
S3 vs S2 (PM: -0.098 to 0.109)



Metacognitive Dysfunction Profiles

Functional Insight Gap
Partner ECog - Patient ECog Scores

Three Distinct Awareness Patterns
S1: Elevated concern about functional decline
S2: Anosognosia-like reduced self-awareness
S3: Highest variability

Conclusion

This study leveraged tau-PET data to uncover spatial heterogeneity in AD. Multimodal analyses revealed anatomical, cognitive, and functional connectivity differences between subtypes, underscoring the potential of deep learning to elucidate AD pathology.

Acknowledgment

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