Thalamocortical Connectivity in Preclinical Alzheimer's Disease

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Introduction

Pathological changes underlying Alzheimer's Disease (AD) begin several years before clinical symptoms emerge. However, sensitive functional markers for these early stages have proven difficult to identify. In this research project, we investigate resting-state thalamocortical connectivity alterations in individuals at risk of AD using a novel gradient-based approach to uncover subtle disruptions in thalamocortical connectivity.

Objectives:

- ❖ To Identify early functional markers of thalamocortical connectivity through analysis of functional gradients.
- ❖ To further explore identified thalamocortical biomarkers for potential applications towards personalized diagnosis.

To achieve these objectives, we make use of thalamocortical gradient-based methods, first developed for developmental brain research.

Methods

Label	Count	Age	Sex	Education	MOCA	CAIDE
Normal Cognition (NC)	34	64.9	24F	15	27.49	7.8
Cognitive Impairment (CI)	34	66.1	26F	13.9	27.49	7.7

MOCA = MOntreal Cognitive Assessment, CAIDE = Cardiovascular Risk Factors, Ageing and Dementia

Participants:

34 individuals who converted to cognitive impairment and 34 matched control participants from the PREVENT-AD database (cognitively normal at baseline and having two follow-up imaging sessions).

MRI Data Processing & Analysis:

- ❖ Structural T1w MRI processed using Freesurfer for segmenting brain regions
- ❖ rsfMRI preprocessed with fMRIprep, denoising/confound regression with XCP-D
- ❖ Surfaces projected onto a standard cortical surface (32k fs_LR) using Ciftify

Thalamocortical Connectivity Analysis:

First, 10 thalamic connectopic maps (CMAPS), and 10 thalamocortical projection maps (PMAPs) were created for each participant using Congrads tool to measure connectivity between the thalamus and the cortex. Then connectivity maps were aligned to a group template using Procrustes alignment. Network-Based Projection Scores (NPS) were calculated for several brain networks using the Schaefer 400 (7 and 17-network) atlases.

Statistical Analysis & Classification (p=0.01 FDR) :

- ❖ Analysis of NPS between the CI/ NC groups at month 0, 12, and 24
- ❖ Longitudinal analysis of changes in NPS over time between groups using MANOVA
- ❖ Random Forest classifier with Leave-One-Out Cross-Validation used to distinguish between groups based on the identified connectivity features
- ❖ Findings explored with the MANGO toolbox (BrainMap) and NiMARE (Neurosynth)

Discussion

Gradient-based analysis of thalamocortical connectivity detected DMN-specific dysconnectivity emerging approximately **3.7 years before CI conversion** in an at-risk of AD cohort. These thalamic-DMN NPS alterations, particularly involving the left thalamus and DMN-A/B subnetworks, are predictive of CI.

Our findings suggest that thalamus-DMN connectivity is a sensitive early indicator of AD-related pathology, highlighting the potential of these advanced methods for developing preclinical AD biomarkers. Future work will integrate these measures with other AD biomarkers (e.g., amyloid/tau PET, plasma p-tau217) using larger clinical datasets.

Primary Results

First three thalamic gradients, and cortical projection maps revealed distinct principal connectivity axes, and cortical projections.

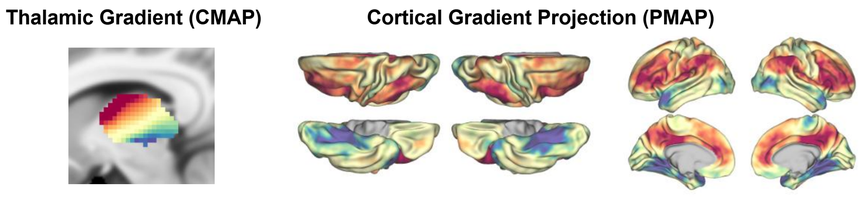

Figure 1: Baseline population based thalamic gradient (CMAP) 1 left, and cortical gradient projection (PMAP) 1 right.

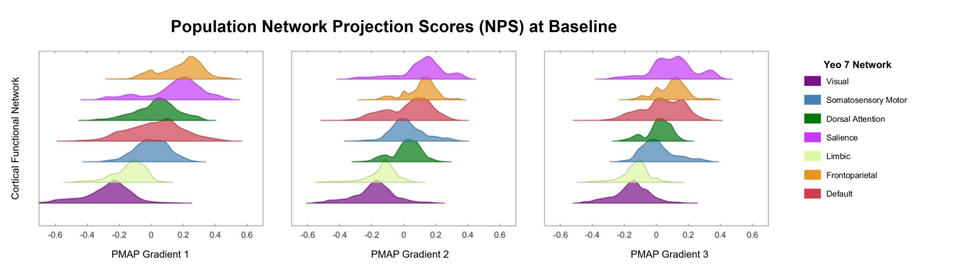

Figure 2: Network base Projection Scores (NBP) from population based cortical gradient projection (PMAP) across first three gradients.

Significant NPS alterations seen in the default mode network (DMN) 24 months after initial imaging session using pairwise t-tests (FDR corrected, p=0.01), 3.7 years before any initial symptoms of cognitive decline.

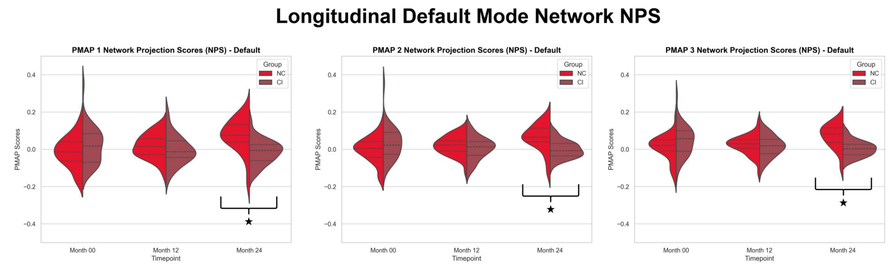

Figure 3: First three gradient derived Network Projection Scores (NPS) across initial baseline (month 00), month 12, and month 24 imaging sessions.

Extended Results

- ❖ Alterations seen in specific default mode subnetworks A and B, which demonstrate specific links to CI and AD behavior and disease profiles. Longitudinal MANOVA highlights DMN effects over three imaging sessions and highlight the left thalamus projections with increased alterations. Furthermore, random forest analysis can use these default mode network scores to classify between participant groups with high accuracy (81.6% AUC).

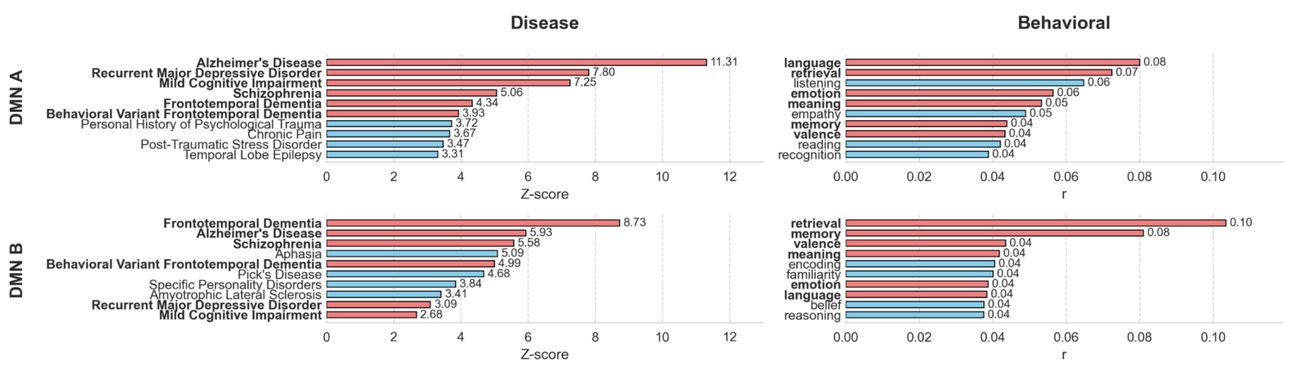

Figure 4: Default Mode Network (DMN) subnetworks A, and B evaluated with MANGO (disease analysis, left), and NiMARE (behavior analysis, right), showing common (significant) features highlighted in red.

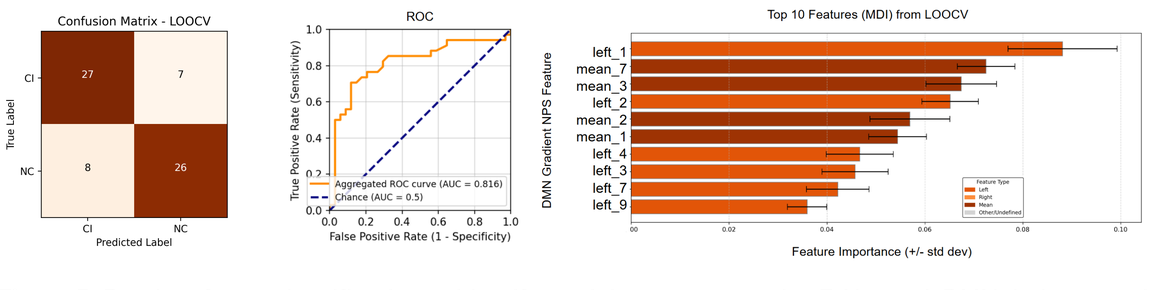

Figure 5: Random forest classification to identify participant groups using 7-Network DMN thalamocortical features derived from left, right, and bilateral/mean PMAP features.

References

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