

AT[N]-Net: multimodal spatiotemporal network for subtype identification in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous, multifactorial neurodegenerative disorder, where beta-amyloid (A), pathologic tau (T), neurodegeneration ([N]), and structural brain network (Net) are four major indicators of AD progression. Most current studies on AD rely on single-source modality and ignore complex biological interactions at molecular level. In this study, we propose a novel multimodal spatiotemporal stratification network (MSSN) that is built upon the fusion of multiple data modalities and the combined power of systems biology and deep learning. Altogether, our stratification approach could (1) ameliorate limitations caused by insufficient longitudinal imaging data, (2) extract important spatiotemporal features vectors from imaging data, (3) exploit the subject-specific longitudinal prediction of a holistic biomarker set, and (4) generate symptoms related fine-grained subtype classification.

KEYWORDS

Alzheimer's disease, deep learning, subtype identification,

amyloid and tau diffuse on structural brain network (tilde) [1], [2].

Based on predicted spatiotemporal AT[N] trajectories across brain networks, we propose a clinical assessments guided AT[N]-Net stratification network where (1) Encoder Network extract distinct progression pattern and map neuroimage data to low dimension feature vector, (2) *Subtype Network* stratifies subjects into fine-grained subtypes with distinct symptoms, and (3) *Prediction Network* predicts subjects clinical assessments scores based on subtype assignment probabilities [3].

Multimodal Spatiotemporal Stratification Network

Computational Systems Biology & Deep predictive Neural Network

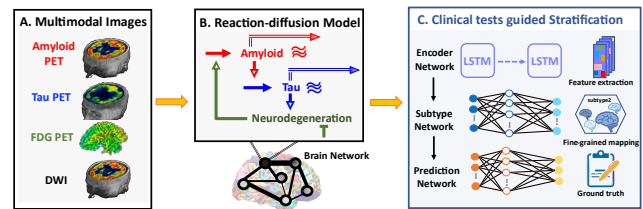


Figure 1. Framework. (A) Amyloid-, Tau-, FDG-PET, and DWI scans are processed to indicate regional amyloid, tau, neurodegeneration, and network connectivity level (AT[N]-Net), respectively. (B) The bistable systems biology model takes multimodal imaging as input and predicts subject-specific long-term AT[N] trajectory. (C) The stratification network maps subjects to fine-grained subtypes based on clinical assessments.

1 Introduction

Alzheimer's disease (AD), a common neurodegenerative disorder, leads to progressive cognitive decline, altered behavior, and ultimately death. No effective treatments for AD have been found, urging the need for early diagnosis and intervention. To best facilitate prompt prognosis, it is critical to stratify the aging population into fine-grained subtypes defined by both reliable biomarkers and close associations with clinical outcomes.

2 Methods

Here, we propose a multimodal spatiotemporal stratification network (MSSN) that combines the power of systems biology and deep learning (Fig. 1). A diffusive AT[N] cascade model was proposed based on several canonical AD pathways (Fig. 1B), where (1) amyloid and tau have constant production (solid arrows), density-based degradation (double arrows) rates, (2) amyloid activates hyperphosphorylation of tau, tau triggers subsequent neurodegeneration, and damaged neurons release more amyloid to the brain (hollow arrows), (3) regional resilience serves as a moderator against cognitive decline (inhibition 'T'), (4)

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3 Result

Training our MSSN on spatiotemporal dataset, our long-term biomarker predictions closely align with the end-state of each subject, and our stratification results beat K-means and SuStaIn in both inter-cluster heterogeneity and intra-cluster homogeneity of various clinical scores. We identify six subtypes across the spectrum of AD where each subtype is associated with distinct AT[N] profiles and clinical symptoms suggested by Everyday Cognition Questionnaire (ECog) score. We further quantify the probability of subtype transition and summarize AD evolution pathways for various end-state in cognitive continuum spectrum to serve as complementary information in AD diagnoses.

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