ABSTRACT

Alzheimer’s disease (AD) is a heterogeneous type of dementia. Mild cognitive impairment (MCI) is the early stage of cognitive decline before AD. Predicting the MCI-to-AD conversion remains challenging due to the heterogeneity of patients. Previous evidence shows that the brain network generated from diffusion MRI promises to classify dementia. However, the limited availability of diffusion MRI obstructs the training of deep learning models. Here, we firstly develop a cross-modal approach to generate brain networks from anatomical MRI under the guidance of diffusion MRI. We then construct the healthy ageing trajectories of controls with a generative model. Finally, we design a recurrent neural networks-based approach to model the longitudinal deviation of patients’ brain networks from the healthy ageing trajectory. Numerical results show that the proposed methods outperform the benchmarks in the prediction task. We also visualize the model interpretation to explain the prediction and identify abnormal changes in white matter tracts.

Index Terms—Brain networks, Graph neural networks, Alzheimer’s disease

1. INTRODUCTION

1.1. Alzheimer’s disease and mild cognitive impairment

Alzheimer’s disease (AD) is the most common cause of dementia, characterized by continuous decline in cognition, memory and brain functions [1]. Mild cognitive impairment (MCI) is regarded as the intermediate stage of cognitive decline between healthy ageing and AD, where a proportion of MCI cases could be reversible. Further, although lacking curative treatment, earlier identification and intervention could modify the disease trajectory of AD progression and impact patient outcomes. Therefore, it is of crucial significance to accurately predict the conversion from MCI to AD, which remains a significant challenge due to the heterogeneous nature of AD[2].

1.2. Neuroimaging and brain networks

Magnetic resonance imaging (MRI) is a commonly-used non-invasive technique for managing neuropsychiatric conditions. The MRI-derived biomarkers are reported significantly associated with cognitive decline, indicating the clinical value of MRI in dementia prediction[3].

The structural brain network, constructed from diffusion MRI (dMRI) or anatomical MRI, is promising to characterize the connectivity between cortical/subcortical regions defined according to prior knowledge of neuroanatomy. Specifically, dMRI-derived brain networks utilize tractography to quantify the connectivity strength of tracts that link brain regions. At the same time, anatomical MRI examines the possible associations among brain regions by calculating the covariance of the anatomical features (e.g., grey matter volume) among brain regions. Both types of structural brain networks are reported to effectively generate useful graph theoretical biomarkers associated with various neuropsychiatric conditions [4, 5] including dementia [6]. Although dMRI provides more direct connectivity estimation than anatomical MRI, it is more difficult to acquire. In parallel to the efforts in developing data augmentation approaches [7], there is a pressing need to generate robust brain networks from more commonly available anatomical MRI.

1.3. Deep learning for neuroimaging

Deep learning models demonstrate reasonable performance in classifying AD and predicting MCI-to-AD conversion based on neuroimaging [8]. However, the majority models are developed for computer vision tasks, which may not capture the connectomic properties of the brain. Therefore, the model performance could be limited for complex tasks involving domain knowledge, e.g., predicting disease trajectory of AD. Moreover, the interpretability of these models could be further improved to facilitate clinical translation. In parallel, the emerging graph neural network (GNN), designed for learning non-Euclidean data, is widely used in characterizing neuropsychiatric diseases [9], which has shown encouraging performance in AD research, e.g., tau spread networks, brain struc-
1.4. Related work

In general, the approaches of predicting the MCI-to-AD conversion are categorized as static models (based on single time point data) or dynamic models (based on longitudinal data). Static models predict whether the conversion will happen in 36 months solely based on the baseline images [8, 12], which, however, ignores the longitudinal changes along the disease trajectory. Therefore, although such approaches require fewer data, they could be sub-optimal due to the static nature of the predicting models. In contrast, dynamic models are emerging approaches to predict MCI-to-AD conversion, particularly with the availability of longitudinal datasets, e.g., the Alzheimer’s Disease Neuroimaging Initiative (ADNI). A recent study applies GNN and recurrent neural networks (RNN) to predict the patient outcomes in 18-month follow up by modeling the longitudinal brain networks from the baseline to 12-month as dynamic graphs [13]. However, this method showed limited performance, which might be due to its attempts to directly model the heterogeneous dementia population using the end-to-end training scheme. Moreover, the input brain networks are constructed solely from grey matter features, which ignores the common white matter abnormalities in AD.

1.5. Proposed framework

Previous studies show that anatomical MRI and dMRI share common features in reflecting brain structure [14]. Hence, it could be feasible to generate brain networks from anatomical MRI with the guidance of dMRI that provides more specific information regarding white matter tracts. In this way, we could fully characterize both grey matter and white matter of the brain. In addition, accumulating research shows that AD patients demonstrate accelerated brain ageing compared to healthy controls (CN) and MCI patients [15, 12]. Therefore, we hypothesize that the MCI-to-AD conversion could be predicted by modelling the deviation of AD patients from the healthy ageing trajectory, which could mitigate the challenge of modelling brain networks in the heterogeneous AD population.

Here we propose a learning framework to model the healthy ageing trajectory of brain networks with a graph encoder and a variational autoencoder (VAE). In addition, we design an RNN based algorithm that predicts the MCI-to-AD conversion based on the past longitudinal deviations/residuals of patients from the predicted ageing trajectory. In order to generate brain networks from commonly available anatomical MRI, we propose a self-supervised approach that uses an autoencoder to extract node features from T1 images and a cross-modal contrastive representative learning approach to extract edge features guided by dMRI. Our contributions include:

- A cross-modal learning approach to generate brain networks by extracting features from anatomical MRI under the guidance of dMRI.
- A generative approach to predict the healthy ageing trajectories of brain network features using graph neural networks and variational autoencoders.
- A recurrent learning algorithm that models longitudinal residuals between patient’s actual features and patient’s predicted features from the healthy ageing trajectory for future disease status prediction.
- An interpretation approach that identifies the abnormality introduced from MCI-to-AD conversion by comparing the actual diseased brain networks and the predicted healthily aged brain networks from a customized graph decoder.

2. METHODS

2.1. Data preparation

A longitudinal MRI dataset of AD, MCI and CN subjects is downloaded from ADNI website. Each subject has one T1 images at baseline, 6 months, 12 months and 18 months respectively. In total, the longitudinal dataset includes 191 stable CN, 126 stable MCI, and 91 converted MCI. Another independent baseline cohort including 113 CN and 96 AD with dMRI and T1 available are also downloaded from the ADNI website.

T1 images of all subjects are transformed to the standard MNI-152 space by coregistrating with MNI-152 standard T1 of the FMRIB Software Library (FSL) using Advanced normalization tools. For the dMRI of the independent baseline cohort, fractional anisotropy (FA) maps are derived using the FMRIB’s Diffusion Toolbox and transformed to the standard space by coregistrating with the standard FA map.

2.2. Brain network construction

Node and edge features of brain networks are both learnt from the independent baseline data. (Fig 1). The Desikan grey matter atlas is used as the node atlas that divides cortical and sub-cortical regions into 68 separate areas with cerebellum excluded (Fig 1A). For each subject, the Desikan node atlas is transformed back to the native space of the subjects using the inverse coregistration file from data preparation. The voxels enclosed by the node atlas are extracted and fed into an autoencoder for dimension reduction (Fig 1B). All node voxels are sampled and zero-padded to 3000 as the input of the autoencoder, which consists of 4 layers, and the output dimension is 32.

The IIT white matter atlas [16] is a tractography atlas that indicates the path of 2227 the white matter tracts/edges connecting 68 regions of the Desikan atlas (Fig 1C). Similar to nodes voxel extraction, the tract pathways of the IIT atlas are transformed back to the native space. Voxels of T1 and corresponding FA enclosed by IIT atlas are extracted and sampled as
The learning framework for predicting MCI-to-AD conversion consists of three models that are trained separately.

A GNN consisting of three GATConv [17] layers and one global pooling layer is pretrained to extract dementia-related features $F_1$ from the brain networks $G_1$ by performing AD/CN classification on the independent baseline cohort with BCELoss (binary cross-entropy loss) (Fig 2A). The dimension of the output graph feature is 256.

A VAE with a 3-layer MLP encoder and a 3-layer MLP decoder is trained to model the healthy ageing trajectories of the longitudinal stable CN cohort (Fig 2B). The task of the VAE is to predict the future features of brain networks $F_{t+n}$ by inputting a starting feature $F_t$ and age gap $n$. Specifically, the encoder projects the $F_t$ to a latent space which the age gap $n$ is fed into as a one-hot vector (dimension: 16). Then the decoder predicts the $F_{t+n}$ after the age-gap $n$ by training with the mean squared error loss (MSELoss) between predicted features $F'_{t+n}$ and the actual features $F_{t+n}$.

An RNN with long short-term memory (LSTM) kernel is trained to predict the MCI-to-AD conversion based on the longitudinal cohort containing both stable and converted MCI cohorts (Fig 2C). Specifically, the RNN predicts whether the conversion will happen in $t + 2$ based on all information aggregated from previous time-points. The prediction of conversion in last time-point will be made based on all information aggregated from previous time-points.

For interpretation purposes, a graph decoder with two MLP is trained with VAE: the first MLP decodes node embedding from the brain network feature $F'_{t+n}$, and the second MLP decodes features of connecting edges between two nodes from the concatenated node embedding. The residual between the predicted and actual graph features of brain networks repre-
sents the patient’s deviation from the healthy ageing trajectories during the MCI-to-AD conversion. By comparing the predicted and actual brain networks that converted to AD, we could identify the abnormal changes that cannot be explained by the healthy ageing effect.

2.4. Benchmarks

To evaluate the performance of brain networks generated using our approach, we constructed traditional diffusion MRI and T1 based structural brain networks, respectively for comparison. For dMRI based brain networks (white matter connectivity), we performed whole-brain tractography on independent baseline CN cohort using the Anatomically-Constrained Tractography of MRtrix. The mean FA value of the tract fiber and the fiber counts is calculated as the edge weight among the nodes on the Desikan node atlas. For T1 based edge matrices (grey matter association), we measured the grey matter volumes constrained by the node atlas. We calculated a covariance matrix to characterize the connectivity between brain regions. All benchmark networks and our proposed networks were utilized in the classification of AD/CN of independent baseline cohort for evaluation using the graph encoder of the learning framework.

For the task of predicting MCI-to-AD conversion, we included two benchmarks representing static modal and dynamic model, respectively. The static prediction benchmark is a residual neural network (ResNet) proposed in [8]. Note that the original study predicted the conversion in 36 months, while we are predicting the conversion in 18 months. The interpretable temporal graph neural network (referred to as ITGNN) proposed in [13] was selected as the dynamic model benchmark, which consists of a GNN and an RNN. Briefly, the GNN encodes graph features of brain networks, and a LSTM learns from the graph feature to predict patients’ outcomes (AD/CN/MCI). For benchmark purposes, we only included the longitudinal stable and converting MCI patients for training/testing and predict the patient status in 18 months. In addition, we input both the grey matter covariance networks and our proposed brain networks to produce two benchmark results.

3. RESULTS

Results in table 1 show that our proposed method of generating brain networks achieved the highest performance for classifying AD/CN. Results in table 2 show that our proposed method achieved highest prediction accuracy for the MCI-to-AD conversion in 18 months.

The interpretation approach produces a residual brain network with high dimensional features. For visualization purposes, we average the residuals of edge features, retain the edges with top 5% highest residuals, and present one case example in Fig 3. The interpretation results suggest that the proposed methodology is capable of capturing the abnormalities in brain networks from MCI-to-AD conversion, particularly the white matter hyperintensities related to cognitive decline. Particularly the white matter hyperintensities related with cognitive decline.

4. DISCUSSION AND CONCLUSION

This study proposes an approach to construct structural brain networks with imaging representation as the node and edge features and an approach to predict MCI-to-AD conversion based on the neuroscience knowledge that AD patients tend to deviate from healthy ageing trajectories. The proposed method outperforms benchmark methods. In addition, interpretation suggests that the proposed method is sensitive to abnormal structural changes in the brain. Future possible improvements include integrating separate training stages and introducing a quantitative model interpretation. Overall, the proposed method shows promise to aid prognosis and risk assessment.
5. COMPLIANCE WITH ETHICAL STANDARDS

This study was performed in line with the principles of the Declaration of Helsinki. Data was obtained from open dataset.

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