Predicting Alzheimer's Disease Progression Using rs-fMRI and a History-Aware Graph Neural Network

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder that affects more than 7 million people in the United States alone. AD currently has no cure, but there are ways to slow its progression if caught early enough. In this study, we propose a graph neural network (GNN)-based model for predicting whether a subject will transition to a more severe stage of cognitive impairment at their next clinical visit. We consider three stages of cognitive impairment in order of severity: cognitively normal (CN), mild cognitive impairment (MCI), and Alzheimer's disease (AD). We use functional connectivity (FC) graphs obtained from resting-state functional magnetic resonance imaging (rs-fMRI) scans from 303 subject visit histories. Our GNN-based model incorporates a recurrent neural network (RNN) block, enabling it to process data from the subject's entire visit history. It can also work with irregular time gaps between visits by incorporating visit distance information in our input features. Our model demonstrates robust predictive performance, even with missing visits in the subjects' visit histories. It achieves an accuracy of 82.9%, with an especially impressive accuracy of 68.8% on CN to MCI conversions – a task that poses a substantial challenge in the field. Our results emphasize the effectiveness of using rs-fMRI scans in predicting the onset of MCI or AD and offer a viable method enabling timely interventions to slow the progression of cognitive impairment.

Keywords: Alzheimer's disease, Longitudinal, Conversion Prediction, fMRI, Graph Neural Network

1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide, posing a substantial clinical, social, and economic burden. Characterized by a gradual decline in cognitive function, AD typically develops over many years, often transitioning from a cognitively normal (CN) state through mild cognitive impairment (MCI) before reaching advanced dementia. While no curative treatment currently exists, early detection of disease progression can enable timely interventions that may slow cognitive decline and improve quality of life. As a result, accurately predicting transitions between stages of cognitive impairment has become a critical objective in Alzheimer's disease research.

Neuroimaging has played a central role in advancing our understanding of AD-related brain changes. In particular, resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a powerful noninvasive modality for studying functional connectivity (FC) patterns in the brain. Alterations in functional brain networks have been shown to correlate with cognitive decline and disease progression, making rs-fMRI a promising data source for predictive modeling. However, effectively leveraging rs-fMRI data remains challenging due to its high dimensionality, complex network structure, and variability across subjects and time.

Recent advances in machine learning, especially deep learning, have enabled more sophisticated analysis of neuroimaging data. Graph neural networks (GNNs) are particularly well suited for modeling functional connectivity, as FC matrices naturally form graph-structured data where brain regions are represented as nodes and functional relationships as edges. Several studies have demonstrated the effectiveness of GNN-based approaches for AD diagnosis and classification. Nevertheless, many existing methods focus on cross-sectional data and fail to fully exploit the longitudinal nature of disease progression.

Longitudinal prediction introduces additional challenges, including irregular time intervals between clinical visits, missing imaging data, and varying visit history lengths across subjects. These issues complicate the modeling of temporal dynamics and limit the applicability of standard sequential or graph-based models. Incorporating patient history in a principled manner is therefore essential for realistic and clinically relevant prediction of cognitive decline.

In this work, we address these challenges by proposing a history-aware graph neural network framework that integrates rs-fMRI-derived functional connectivity graphs with longitudinal visit information. By combining a GNN for spatial brain network representation with a recurrent neural network (RNN) for temporal modeling, our approach captures both the structural properties of functional brain networks and their evolution over time. Furthermore, by explicitly incorporating visit distance information, the model is capable of handling irregular visit intervals and incomplete visit histories. This study demonstrates that leveraging longitudinal rs-fMRI data within a history-aware graph learning framework can significantly improve the prediction of cognitive impairment progression, particularly in the challenging task of identifying early CN-to-MCI conversion.

2. METHOD

2.1 Data

We use rs-fMRI and structural MRI (sMRI) scans provided by the Alzheimer's Disease Neuroimaging Initiative[1] (ADNI) database.[2] This data is available publicly at https://ida.loni.usc.edu/. Resting-state fMRI (rs-fMRI) is a type of brain scan that shows both the structure of the brain and, more importantly, which areas are active in the absence of tasks or external stimuli.[3]

We focus on subjects who have at least two rs-fMRI scan and at least one sMRI scan in the ADNI database. At least two visits are required since we want to make a prediction about a future date and having only one visit would not provide a ground truth value for our prediction.

We remove "reverters", i.e., subjects that convert to a less severe stage in their last visit (AD to MCI, MCI to CN, or AD to CN). This leaves us with 303 participants from the ADNI database meeting this criterion, each one having a different number of available rs-fMRI scans taken at different times.

DEFINITION 2.1 (CONVERTER SUBJECT). *A subject that transitions to a more severe stage of cognitive impairment (CN to MCI, CN to AD, or MCI to AD) in their last visit.*

DEFINITION 2.2 (STABLE SUBJECT). *A subject with the same diagnosis in their last visit as their penultimate visit.*

As seen in Fig. 1, the 303 participants have 1089 rs-fMRI scans in total, with 894 scans from stable subjects and 195 scans from converter subjects. The distances between consecutive scans for subjects are irregular, with a mean of 14.78 months.

Expectedly, the number of scans from stable subjects is much higher than that of converter subjects. Also, subjects with histories longer than 7 visits are rare. We have 250 stable subjects and 53 converter subjects, as shown in Fig. 2. There are no subjects converting from CN to AD in their last visit.

2.2 Preprocessing

FMRI scans need to be preprocessed before we can use them for our task to account for external sources of nuisance imaging artifacts.[4] fMRIPrep is a pre-processing pipeline that has a multitude of features designed to clean and standardize the fMRI data in order to be used for analysis.[4]

As fMRIPrep requires its input images to be in NIfTI format and stored in the Brain Imaging Data Structure (BIDS)[5] directory structure, we convert the downloaded DICOM files to NIfTI and then organize them in the BIDS format. We then run fMRIPrep on the BIDS directory containing structural and functional scans for all subjects to get the preprocessed rs-fMRI scans.
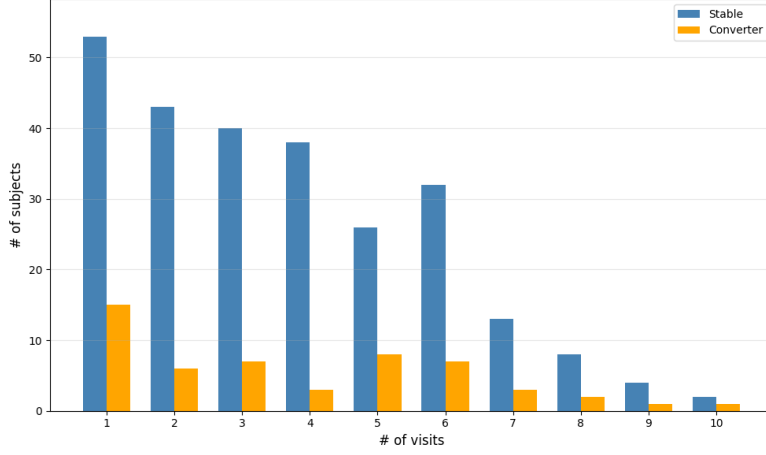
Figure 1. Distribution of subjects based on their number of available rs-fMRI scans. The blue bars represent stable subjects, while the orange bars represent converter subjects.
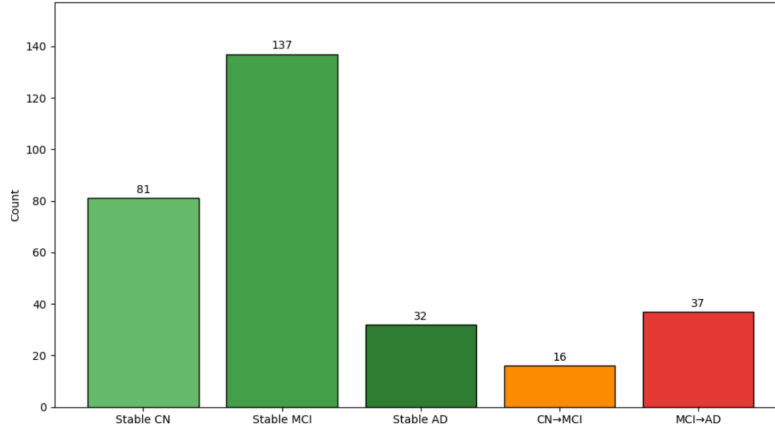

Figure 2. Distribution of subjects based on their diagnosis in their last visit

2.3 Functional Connectivity Matrix Computation

Blood Oxygenation Level Dependencies (BOLD signal) are valuable information derived from fMRI volumes. Due to oxygen in the brain being slightly magnetic, we are able to get the amount of oxygen in each part of the brain at different times.[6] This can be used to find connections between regions of the brain and detect abnormalities in these connections and overall function.

One way to extract information from fMRI scans is to obtain the functional connectivity matrix. To do this, we need to first parcellate the brain into regions of interest (ROIs) to be used as nodes to relate to each other. We utilize the Nilearn library[7] and the Schaefer atlas[8] to parcellate the brain into 100 ROIs. We then extract the time series from each ROI by averaging the signals from all pixels in each ROI and compute the functional connectivity (FC) matrix using Pearson correlation. The FC matrix is a square matrix where each element represents the correlation between the time series of two ROIs.

2.4 Model

We consider a binary classification task where we want to predict whether a subject will convert to a more severe stage of cognitive impairment in their last visit. Similarly to Ref. 9, the input to our model is the first n visits from the visit history $v = (v_1, v_2, \ldots, v_{n+1})$ of a subject, where v_i is the FC matrix of the i-th visit and $n+1$ is the total number of visits. The output is 'stable' if $d_n = d_{n+1}$, where $d_i \in \{$CN, MCI, AD$\}$ is the diagnosis of the

subject in the i-th visit, and 'converter' otherwise. Fig. 3 shows all the steps taken to get to the final prediction from rs-fMRI scans.
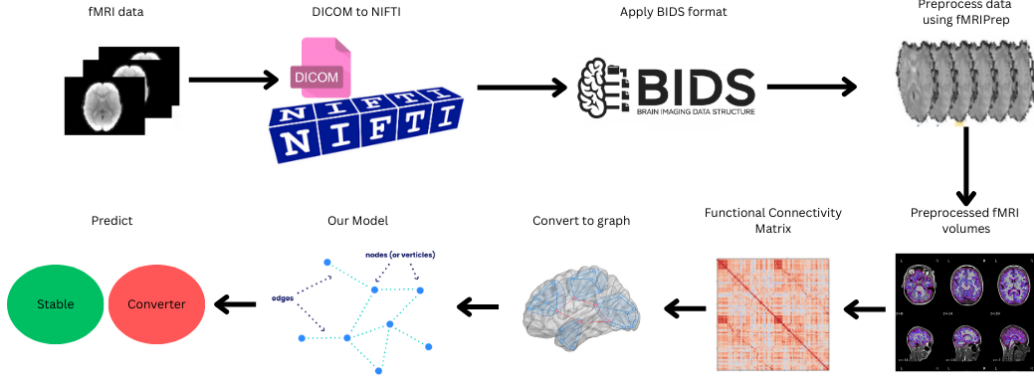

Figure 3. Overview of our workflow, from raw rs-fMRI scans to the binary prediction

In this work, we propose a history-aware graph neural network (GNN) model combining two main components: a graph convolutional network (GCN) and a recurrent neural network (RNN). The GCN is loosely based on the BrainGNN[10] model, having two convolutional blocks. Each block consists of a GraphSAGE layer,[11] a graph normalization layer,[12] a dropout layer, and A topK pooling layer.[10] The RNN component can be any choice of RNN, such as a long short-term memory (LSTM)[13] or a gated recurrent unit (GRU).[14] Fig. 4 shows the architecture of our proposed model in detail.

Between the GCN and RNN components, we concatenate the distances between consecutive visits for the input subject to the rest of our feature vector. This is done to provide the model with information about the time intervals between visits and how far ahead it needs to predict.
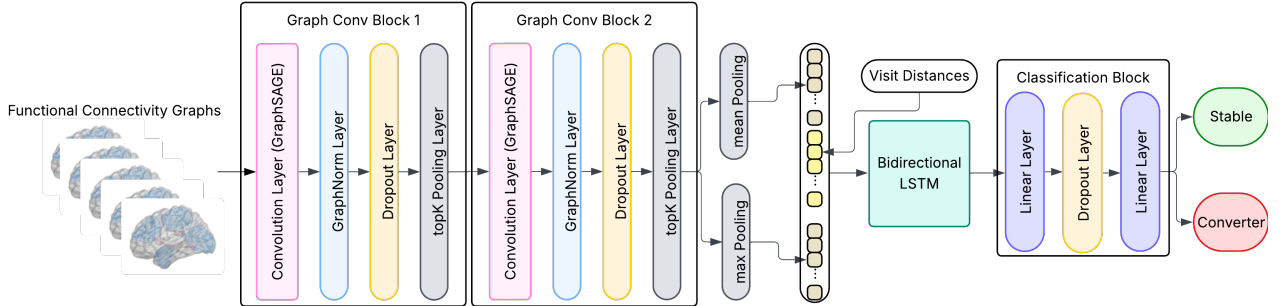

Figure 4. Architecture of our proposed model

2.5 Training and Evaluation

We use a random 20% split of our data to pretrain our GCN component. The pretraining is a 3-class classification task where the model predicts the diagnosis of a subject in a given visit. Unlike our main task, during pretraining, the input consists of a single visit instead of the entire visit history of a subject.

Once pretraining is done, we use 5-fold cross-validation to train and evaluate the model on the main prediction task. We use Bayesian optimization for hyperparameter tuning and utilize focal loss[15] to address the class imbalance present in our data.

To evaluate our model, we use balanced accuracy (BA), which is defined as the average of sensitivity and specificity. We also report the area under the receiver operating characteristic curve (AUC-ROC)[16] and raw accuracy scores.

3. RESULTS

All results are reported as mean ± standard deviation (SD) across the 5-fold cross-validation. The results of the classification task are shown in Table 1.

Table 1. Classification results of the proposed model.

Model	Data	Acc.	AUC	BA	MCI to AD
GraphSAGE + LSTM	rs-fMRI	**0.829 ± 0.058**	0.852 ± 0.065	**0.771 ± 0.114**	**0.676**
GraphSAGE + RNN	rs-fMRI	0.743 ± 0.038	0.771 ± 0.067	0.651 ± 0.114	0.514
GraphSAGE + GRU	rs-fMRI	0.733 ± 0.049	0.786 ± 0.062	0.704 ± 0.071	0.676
Ref. 9	structured	0.824 ± 0.04	**0.890 ± 0.033**	-	-

In addition to the results above, our model also achieves an impressive 68.8% accuracy for CN to MCI conversion, which is often a more difficult task than even the MCI to AD conversion detection. Another paper that worked on the classification of stable and converter patients Moghaddami et al.,[9] provided a total converter detection of 69.4%.

Due to our novel methodology, comparisons with the existing literature are difficult. However, here's a list of papers that come close to our methods. Kim et al.[?] provide an in-depth dive into certain ROIs and their effectiveness in detecting the different stages of cognitive decline. Grammenos et al.[?] look into stable MCI patients versus converter MCI patients and detect the difference between stable and progressive MCI patients. Their best-performing method of XGBoost resulted in an 86% total accuracy across both sMCI and pMCI subjects. Wang et al.[?] test a variety of different modalities, but their best-performing model for ADNI fMRI data achieved an accuracy of 67.65%.

4. CONCLUSIONS

In this study, we establish the effectiveness of using resting-state functional MRI and our proposed history-aware graph neural network model for predicting the progression of cognitive impairment. Using focal loss and pretraining, our model demonstrates a robust ability in predicting converter subjects despite data imbalance, missing visits, and irregular visit distances. The results indicate that our model can effectively capture the temporal dynamics of cognitive impairment progression. Our approach offers a promising method for early detection and monitoring of Alzheimer's disease which is crucial for timely intervention and treatment. Future work will focus on further improving the model's performance and generalizability by incorporating additional data modalities and focusing on the effects of history length on prediction accuracy.

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