Published in final edited form as:

Med Image Comput Assist Interv. 2020 ; 12267: 44–52. doi:10.1007/978-3-030-59728-3_5.

Persistent Feature Analysis of Multimodal Brain Networks Using Generalized Fused Lasso for EMCI Identification

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Abstract

Early Mild Cognitive Impairment (EMCI) involves very subtle changes in brain pathological process, and thus identification of EMCI can be challenging. By jointly analyzing cross-information among different neuroimaging data, an increased interest recently emerges in multimodal fusion to better understand clinical measurements with respect to both structural and functional connectivity. In this paper, we propose a novel multimodal brain network modeling method for EMCI identification. Specifically, we employ the structural connectivity based on diffusion tensor imaging (DTI), as a constraint, to guide the regression of BOLD time series from resting state functional magnetic resonance imaging (rs-fMRI). In addition, we introduce multiscale persistent homology features to avoid the uncertainty of regularization parameter selection. An empirical study on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database demonstrates that the proposed method effectively improves classification performance compared with several competing approaches, and reasonably yields connectivity patterns specific to different diagnostic groups.

Keywords

Brain connectivity; Multimodal; Persistent homology; EMCI

1 Introduction

Mild cognitive impairment (MCI) is a preclinical and presymptomatic stage of dementia and may increase the risk of developing Alzheimer's disease (AD) in the future. In particular, an accurate detection of early MCI (EMCI), commonly characterized by early clinical symptom of cognitive deficits, can be beneficial to early intervention for delaying the transition from EMCI to MCI through medications as well as non-medication approaches. In past years, neuroimaging-based techniques have revealed that brain characteristics can be measured

from the perspective of connectivity, which is associated with the interactions between neuronal activation patterns of anatomically segregated brain regions within a complex network. Currently, most of functional brain network modeling approaches for EMCI classification are based on pairwise correlation such as Pearson's correlation (PC). This approach allows for analyzing the brain as a functionally related network of dynamically interacting pairwise brain regions. However, recent studies have demonstrated that the neurological processes involve the interactions of many co-activated brain regions (i.e., more than two regions) rather than just pairwise interactions.

The least absolute shrinkage and selection operator (Lasso) method and sparse representation (SR) have been applied to construct a sparse brain network [1] by considering more complex interactions among multiple co-activated brain regions. Nevertheless, the Lasso approaches have their own deficiencies. For example, most of them use a fixed regularization parameter λ that may not be optimal to control the model sparsity. It will lead to an uncertainty to quantify the sparse brain network using some measurements, such as local efficiency, betweenness centrality, and so on. Moreover, another problem with Lasso is that, feature extraction of sparse networks needs a constructed network with precise connection strengths. However, traditional lasso method has been shown biased [2], and may not provide reliable estimation for building brain networks. Therefore, a subsequent connectivity strength estimation process should be performed to eliminate the shrinking effect, which naturally adds the complexity of modeling. In order to address above limitations, a novel persistent homology framework [4, 5] is proposed in this study. The proposed method constructs the brain network over multiscale regularization parameter space and only focuses on the network structure (binary network) rather than connection strength (weight network) between regions.

Currently, a lot of brain network modeling methods only consider the neurological processes from a single modality [7], while compelling evidences have demonstrated the advantage of acquiring and fusing complementary information via different neuroimaging modalities for accurate classification. Especially, diffusion tensor imaging (DTI) has been applied to map white matter tractography that outputs structural connectivity (SC). On the other hand, resting state functional MRI (rs-fMRI) measures intrinsic functional connectivity (FC) through spontaneous fluctuations of brain activity. Joint investigation of SC and FC can offer a complete characterization of the brain network incorporating both structural and functional connectivity.

In this paper, we propose a novel multimodal modeling method for EMCI identification, which integrates brain connectivity information from both rs-fMRI and DTI data. Specifically, a novel generalized fused lasso framework is applied to linearly regress BOLD time series, and is guided by SC prior information. In addition, the pairwise correlation is further introduced as an additional guidance to regularize regression coefficients between ROIs. Furthermore, we develop a multiscale network quantification method using persistent homology for the proposed model. We show that after integrating the brain network information with different sparsity for each subject, persistent homology can effectively characterize the multiscale networks via graph filtration, which overcomes the uncertainty of optimal parameter selection.

To the best of our knowledge, no previous brain network modeling methods ever fuse both generalized fused lasso and persistent homology features into a sparse representation, upon which our novel framework is built. Based on the proposed method, we perform our empirical study using rs-fMRI and DTI data from the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Participants in this study include 29 EMCI subjects, and 29 healthy controls (CN). We demonstrate the promise of our method over the competing methods on both classification performance and connectivity pattern identification.

2 Materials and Methods

2.1 Dataset and Preprocessing

Data were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. In this study, the rs-fMRI, DTI, and T1 imaging data were collected from 58 subjects, and divided into two diagnostic groups: EMCI group (N=29, 19 males and 10 females, age 63~89), cognitive normal (CN) group (N=29, 13 males and 16 females, age 61~87). The rs-fMRI data were preprocessed by SPM8 and DPABI, and then used to extract the mean value of BOLD time series corresponding to each ROI in the AAL template. The rs-fMRI scans are co-registered to the individual T1 image after realignment. For the preprocessing of DTI data, we used a package called pipeline toolbox for analyzing brain diffusion images (PANDA) based on the FMRIB Software Library (FSL). The DTI data with significant distortion in co-registration with FA and T1 image or with T1 image and MNI template were excluded from the study. Of note, since T1 scans were used for jointly guiding both DTI and rs-fMRI registrations, the multimodal images were registered onto a same reference template.

2.2 Methods

Multimodal brain networks modeling.—Let us assume that we have N subjects and M ROIs. For each ROI, a regional mean fMRI time series (BOLD signal) is available. We suppose that the BOLD time series with respect to the i -th ROI can be denoted as $x_i = \{x_{1i}, x_{2i}, \dots, x_{Ti}\} \in R^M$, where T is the number of time points. $\beta_i = \{\beta_{1i}, \beta_{2i}, \dots, \beta_{Mi}\} \in R^M$ is the coefficient vector that represents the indices of other co-activated ROIs associated with the i -th ROI. We can estimate the whole-brain network $B = \{\beta_1, \beta_2, \dots, \beta_M\} \in R^{M \times M}$ by solving the following l_1 -norm problem:

$$\min_{\beta} \underbrace{\frac{1}{2} \left\| x_i - \sum_{j \neq i}^M x_j \beta_{ji} \right\|_2^2}_{\text{Loss Function}} + \underbrace{\lambda_1 \sum_{j \neq i}^M D_{ji} |\beta_{ji}|}_{\text{Regularization}} + \underbrace{\frac{\lambda_2}{2} \sum_u^M \sum_{u \neq v}^M P(x_u, x_v) |\beta_{(u,i)} - \beta_{(v,i)}|}_{\text{Generalized Fused Lasso}} \quad (1)$$

Where, λ_1 is a non-negative regularization parameter. D_{ji} represents the structural information from DTI to guide the functional network modeling. A stronger structural

connectivity will lead to a larger functional connectivity, and in turn a lower penalty to $\{\beta_i\}_{i=1}^M$. Hence, we set $D_{ji} = \exp(-\rho_{ji}^2/\sigma)$ to penalize the estimated connection between j -th and i -th ROIs, where ρ_{ji} denotes the structural connectivity coefficient, and σ is the average of standard variances of all subjects' structural network elements. In the generalized fused lasso term, $P(x_u, x_v)$ is a non-negative Pearson correlation coefficient between u -th and v -th ROIs, which controls the similarity by shrinking the differences between all pair of ROIs toward zero see (Fig. 1a).

Feature quantification using persistent homology.—Because there is no definite rule to determinate the proper λ_1 and λ_2 for the proposed model in (1), it will lead to inconsistency of network structure and uncertainty of results that follow. The problem can be remedied by using persistent homology to perform statistical inference over every possible λ . More specifically, suppose that a group of brain networks $N_G = (N_{\lambda_1}, N_{\lambda_2}, \dots, N_{\lambda_n})$ corresponding to different regularization parameters ($\lambda_1 < \lambda_2 < \dots < \lambda_n$) rather than a fixed parameter (see Fig. 1b), we can integrate the network group into an integrated network N_{int} . The elements in N_{int} can be defined as probability-of-appearance of an edge in the network group N_G .

Assuming $\gamma = 1$ or 0 represents an edge exists or not, n is the number of networks in the group, we use distance network N_d to convert the elements of N_{int} by

$d_{ij} = \sqrt{1 - (\sum_l^n \gamma_{ij}^l / n)^2} \in N_d$ (see Fig. 1c). Furthermore, a nested brain network group — also called graph filtration in persistent homology can be constructed over the distance network N_d as follow [6]:

1. Initial step is corresponding to the set of all brain regions;
2. Linearly increase the filtration distance ε (i.e., threshold) within the interval $[0, 1]$, where the maximum number of generated networks is set as 1000.
3. For each ε , threshold the weighted distance network N_d using $\rho_{ij} < \varepsilon$ to construct a binary network.
4. In the final step, all brain nodes should be connected to one large unit.

Persistent homology can be used to encode the graph filtration by tracking the change of connected component number using barcode curves. A theme in functional data analysis is the possibility of also using information on the rates of change or derivatives of the curves [3], since these curves are intrinsically smooth. The derivative of barcode curve can magnify the curve's features, the ensuing derivative curve (see Fig. 1d) can be used to quantify the features of graph filtration with respect to the network.

Feature selection and classification.—A linear regression method based on common fused Lasso (see Fig. 1d) is adopted to choose the discriminative features as follow:

$$\min_{\theta} \frac{1}{2} \|l - F\Theta\|_2^2 + \omega \|\Theta\|_1 + \varphi \sum_{i=2}^T |\theta_i - \theta_{i-1}| \quad (2)$$

Where, I represents the label for patients with EMCI ($I = -1$) and CN ($I = 1$); $F \in R^{1 \times T}$ is the sample with T features; the selected feature index is $\Theta = \{\theta_1, \theta_2, \dots, \theta_T\} \in R^{T \times 1}$. It should be noted that the feature extraction and selection just involve the training samples. The testing sample will execute a dimensionality reduction corresponding to the selected indices. A support vector machine (SVM) is trained using the selected features for EMCI classification. We apply a two-layer leave-one-out cross validation (LOOCV) framework to evaluate classification performance. The outer layer is used to evaluate the classification performance, while the inner layer is applied for parameter optimization. A grid search is applied to search the optimal parameter combination. For obtaining the sequence of networks with different sparsity, a group of regularization parameter λ_1 are selected in the range of $[0, 0.9]$ with a uniform step size. We set the sampling number of λ_1 values as a free parameter $N_{sam}(\lambda_1)$, and the candidate values for grid search are $[100, 200, \dots, 500]$. The candidate values for generalized fused lasso parameter λ_2 are $[0.1, 0.2, \dots, 0.9]$. For the feature selection parameters ω and ϕ , the candidate values both are $[0.1, 0.2, \dots, 0.8]$. In a word, the proposed method involves four parameters $\{N_{sam}(\lambda_1), \lambda_2, \omega, \phi\}$ that should be optimized for receiving the best classification performance using inner LOOCV.

3 Results

3.1 Classification and Performance Evaluation

We compared our proposed method with several competing methods, such as Pearson's correlation (PC), Lasso, and group Lasso (GLasso). Moreover, we evaluated the performances of using different features for quantifying the brain network, including local efficiency (LE), upper triangular of connectivity matrix (UTCM), and persistent homology (PH). Specifically, we directly extracted the features of LE and UTCM from the PC-based dense network. For PH quantification of the network, we set a series of linearly increasing thresholds to construct a graph filtration. For networks from SR-based models (Lasso, GLasso, and proposed), we employed a grid search to determine the optimal regularization (without feature selection in Eq. 2) and extracted the features of LE and UTCM from the sparse network. Moreover, each of these SR-based methods was analyzed with our PH method following the entire framework shown in Fig. 1. From Table 1, persistent homology features show a relatively better classification performance than other quantification methods, and the proposed model with persistent homology quantification achieves the best classification performance with an accuracy of 79.31% (see Fig. 2b). GLasso method gains 5% accuracy improvement over Lasso, and the proposed method gains 3.45% further improvement over GLasso. The UTCM and PH show the significant improvement tendency for different models, whereas LE doesn't show that. ROC curves (see Fig. 2a) indicate that the proposed method yields the largest area under curves (AUC) of 0.87.

3.2 The Influence of Regularizations

We examine a specific set of optimal parameters $\{N_{sam}(\lambda_1), \lambda_2, \omega, \phi\} = \{300, 0.3, 0.3, 0.6\}$ using inner LOOCV in the first case, i.e., holding out the first subject. For exploring the advantage of regularization, we fix the feature selection parameters ω and ϕ , and then a grid search is used to evaluate the classification performance by a sequence of regularization

parameters using LOOCV with all subjects. The same process to fix $N_{sam}(\lambda_1)$ and λ_2 is also executed. The results in Fig. 3a and 3b show the classification accuracies with different settings of regularization parameters. The best classification performance is achieved with the accuracy of 82.76% when $\{\hat{N}_{sam}(\lambda_1), \hat{\lambda}_2\} = \{400, 0.4\}$ (see Fig. 3a), which is very close to the accuracy in our results with the optimization of four parameters. The same effect for $\{\hat{\omega}, \hat{\varphi}\} = \{0.3, 0.6\}$ is also produced (see Fig. 3b) receiving the accuracy of 84.48%. It should also be seen that a smaller $N_{sam}(\lambda_1)$ leads to less accuracy. That is because an inadequate sampling number in $[0, 0.9]$ may ignore some edges with the change of sparsity level, persistent homology could not capture the information with respect to these edges. Moreover, a large $N_{sam}(\lambda_1)$ will bring biases which are defined as that some edges that drop at a certain sparsity level λ_1 may come back as λ_1 goes larger, and then quickly disappear again.

3.3 Connectivity Pattern Identification

During the procedure of graph filtration for each subject, some edges continue to appear with the growth of filtration distance. Moreover, because of appearance of the new connections, the number of connected components tends to decrease, i.e., accelerate the downtrend of the barcode curve. Particularly, these edges can be defined as hub connections controlling the globality and locality of a brain network, which indicates an interesting neurobiological communication pattern.

We record all the hub connections during the graph filtration for individual subjects. Furthermore, a group analysis is performed to evaluate the frequency connections for different diagnostic groups, and then a network difference analysis between EMCI and CN groups is carried out, which outputs the specific connections for different groups. Furthermore, EMCI—CN (see Fig. 4a) indicates that compared with CN group, EMCI subjects exhibit the hub connections that could be decreased functional connectivity within left frontal gyrus mainly involving middle frontal gyrus, precentral gyrus, inferior frontal gyrus. The connectivity from left paracentral lobule and left gyrus rectus to right medial prefrontal cortex is revealed. Moreover, EMCI group show the specific connectivity from the right Thalamus to the whole brain. Some EMCI specific brain regions such as Lingual gyrus, precuneus, and olfactory also can be observed. CN—EMCI (see Fig. 4b) shows the CN specific connectivity mainly concentrates on left hippocampus and parahippocampus, and the brain integration involving left inferior parietal lobule to right postcentral gyrus, superior occipital gyrus, caudate nucleus and calcarine cortex. In other words, CN—EMCI can be regarded as the sub-network for the EMCI patients with disrupted connectivity compared to health subject, while EMCI—CN is used for compensating the loss of network centrality and efficiency.

4 Conclusion

We have proposed a novel multimodal brain network modeling framework coupled with a subsequent persistent homology feature analysis approach. The proposed method is different from most existing methods focusing on single modality analysis, and also different from current network evaluation methods with fixed regularization parameters.

The main methodological contributions are: 1) proposing a multimodal framework for EMCI identification, which fuses the information from rs-fMRI and DTI data using sparse representation; 2) developing a multiscale network quantification method using persistent homology for characterizing the multimodal brain network. Experimental results using the ADNI data show that our method outperforms the existing methods on classification performance and can discover the specific disease-related brain connectivity for biomarkers.

Acknowledgment.

The work was supported by the National Natural Science Foundation of China (61773134 and 61803117), the Natural Science Foundation of Heilongjiang Province of China (YQ2019F003), the Fundamental Research Funds for the Central Universities (3072020CF0402) at Harbin Engineering University. This work was also supported in part by the National Institutes of Health (R01 EB022574) at University of Pennsylvania. Data used in preparation of this article were obtained from the Alzheimer's disease neuroimaging initiative (ADNI) database (adni.loni.usc.edu). A complete listing of ADNI investigators and the complete ADNI Acknowledgement can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Fig. 1.

a) Proposed multimodal brain network modeling framework; b) Production for a group of networks with different sparsity levels, which correspond to a sequence of regularization parameters; c) After integrating the network group using a distance matrix, a graph filtration for the distance matrix can be constructed with a visualization via barcode curves; d) The derivative curves corresponding to each barcode curve can be used to feature selection and SVM classifier.

Fig. 2.

The comparison of classification performance among different methods. a) The ROC curves for different methods; b) A histogram for visualizing the difference among approaches.

Fig. 3.

The classification performance corresponding to: a) the influence of model parameters; and b) the influence of feature selection parameters.

Fig. 4.

The hub connections for EMCI and CN groups, where a) EMCI—CN represents the specific connectivity for EMCI; b) CN—EMCI represents the specific connectivity for CN.

Table 1.

Performance comparison on classification

Method	Features	ACC(%)	SEN(%)	SPE(%)	BAC(%)	AUC
PC	LE	60.34	60.00	60.17	60.36	0.61
	UTCM	60.34	60.00	60.17	60.36	0.61
	PH	63.79	63.33	64.29	63.81	0.67
Lasso	LE	65.52	63.64	68.00	65.82	0.68
	UTCM	68.97	68.97	68.97	68.97	0.70
	PH	70.69	71.43	70.00	70.71	0.77
GLasso	LE	67.24	67.86	66.67	67.26	0.68
	UTCM	72.41	69.70	76.00	72.85	0.74
	PH	75.86	72.73	80.00	76.36	0.83
Proposed method	LE	63.79	65.38	62.50	63.94	0.67
	UTCM	72.41	70.97	74.07	72.52	0.79
	PH	79.31	77.42	81.48	79.45	0.87