Adaptive Thresholding of Functional Connectivity Networks for fMRI-Based Brain Disease Analysis

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Abstract. Functional connectivity (FC) networks based on functional magnetic resonance imaging (fMRI) data have been widely applied to automated identification of brain diseases, such as attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease (AD). To generate compact representations of FC networks for disease analysis, various thresholding strategies have been developed for analyzing brain FC networks. However, existing studies typically employ predefined values or percentages of connections to threshold the whole FC networks, thus ignoring the *diversity of temporal correlations (particularly strong correlations)* among different brain regions. In addition, in practice, it is usually very challenging to decide the optimal threshold or connection percentage in FC network analysis. To address these problems, in this paper, we propose a weight distribution based thresholding (WDT) method for FC network analysis with resting-state function MRI data. Specifically, for FC between a pair of brain regions, we calculate its optimal threshold value by using the weight (*i.e.*, temporal correlation) distributions of the FC across two subject groups (*i.e.*, patient and normal groups). The proposed WDT method can adaptively yields FC-specific thresholds, thus preserving the diversity information of FCs among different brain regions. Experiment results on both ADNI and ADHD-200 datasets with rs-fMRI data demonstrate the effectiveness of our proposed WDT method.

1 Introduction

The human brain is a complex system that depends on functional interaction among distributed brain regions. This system can be characterized as a connectivity network, where each node represents a brain region and each edge quantifies the connectivity between a pair of brain regions. Network analysis provides

D. Zhang et al. (Eds.): GLMI 2019, LNCS 11849, pp. 18–26, 2019.
https://doi.org/10.1007/978-3-030-35817-4_3

an important tool to explore the core organization of the human brain, as well as the association between brain functional deficits and structural disruption caused by brain diseases [1]. Previous studies have investigated network properties associated with various brain diseases, such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD) and its prodromal stage (*i.e.*, mild cognitive impairment, MCI). In the past decades, advanced imaging techniques, such as functional magnetic resonance imaging (fMRI), provide efficient ways to map functional connectivity (FC) of the brain [2], to help better understand the pathology of brain disorders. Using fMRI data, many studies focus on employing FC networks to quantify the temporal correlation between intrinsic blood oxygen level-dependent (BOLD) signal fluctuations of brain regions for brain disease analysis [3].

Among various studies, graph learning has shown its superiority in the analysis of brain FC networks, which not only provides a quantitative measurement of network properties (characterizing the segregated and integrated nature of brain activity), but also offers a general framework for comparison of heterogeneous graphs/networks [4]. In existing graph learning methods, FC networks are generally fully-connected weighted graphs, where each node (e.g., brain region) is connected to all the other nodes in the graph and weight values (*e.g.*temporal correlations) of edges are continuous within the range $[-1, 1]$. Given P nodes, there will be $(P-1)P/2$ edges in a fully-connected graph. To characterize the topological properties of FC networks and facilitate computer-aided analysis, the thresholding methods are usually used to threshold a FC network for constructing a binary network, where the connection (*i.e.*, edge) between brain regions is either present or not.

Network thresholding methods offer at least three advantages. First, since the connectivity in an FC network represents the temporal correlation between brain regions, some weak and unimportant connections could be obscure the network topology, when using together with strong and important connections. Previous studies have found that brain regions have sparse anatomical connections (*i.e.*, a brain region may be only connected with specific brain regions) [5]. Therefore, it is important to remove those weak or unimportant connections by using thresholding methods [6]. Second, it is simpler to extract meaningful measures from thresholded networks for network analysis [1], because most of the existing network measures are defined on thresholded networks and a large number of connections makes it difficult to extract meaningful network representation [7]. Also, thresholding FC networks can reduce the computational burden of computer-aided network analysis methods [8].

Currently, most of the existing threshold methods can be divided into two categories: (1) single-threshold based methods, and (2) sparsity-based methods. Methods in the first category usually threshold the whole brain network using a predefined value. That is, for any pair of brain regions, there exists an edge between them if and only if the corresponding edge weight (*e.g.*, temporal correlation) is larger than the predefined threshold. In contrast, methods belonging to the second category typically preserve a predefined percentage (*e.g.*, top 30%) of

connections with the strongest temporal correlation. However, these two types of methods ignore the *diversity of temporal correlations (particularly strong correlations)* among different brain regions, thus could not reflect the real difference of FC networks of different subject groups. Figure 1 illustrates two brain FC networks for a normal control (NC) and a patient, respectively. Each network contains three brain regions, denoted as A, B, and C, respectively. For each subject, the weights (*i.e.*, temporal correlations) of FCs between different pairs of brain regions are different, *e.g.*, for the normal, weight of connection is 0.9 for FC between region A and B, and is 0.7 for FC between region B and C. And weights of three FCs in the patient's network have been changed by a brain disease. As shown in Fig. 1, both thresholded networks achieved by the single-threshold based method (see Fig. 1 (a)) and the sparsity-based method (see Fig. 1 (b)) can not characterize the real difference of functional connectivity between brain networks of the NC and the patient.

Intuitively, we could employ FC-specific thresholds to preserve the diversity information of FC among different brain regions. As shown in Fig. 1 (c), we employ a specific threshold for each FC, yielding two thresholded networks that can characterize the real difference between FC networks of two subjects. However, it is challenging to determine the optimal threshold for each FC in brain networks. In practice, we often explore the network properties over a broad range of available thresholds to determine the optimal one [9], which significantly increases the computation burden.

To address these problems, in this paper, we propose a weight distribution based thresholding (WDT) method for brain disease analysis by using fMRI data. Specifically, for FC between each pair of brain regions, we adaptively construct a threshold by using weight distributions of the FC across two subject groups (*i.e.*, patient and normal control), where each distribution is estimated by using weights of the FC from subjects in same group. Our WDT method can adaptively yield FC-specific thresholds to preserve the diversity information of FCs between different brain regions, thus better reflect the difference of FC networks between different subject groups. The proposed method is evaluated on two fMRI datasets for brain disease diagnosis, with experimental results demonstrating promising results compared with existing threshold methods.

2 Method

2.1 Subjects and Image Preprocessing

In this study, we use two datasets with resting state fMRI (rs-fMRI) data. The first dataset is download from the ADNI database, containing 43 later MCI (lMCI, 26 male (M) and 17 female (F), aged 72.1 $\pm$ 8.2 years), 56 early MCI (eMCI) (21M/35F, aged 71.2 $\pm$ 6.8 years), and 50 NCs (21M/29F, aged 75.0 $\pm$ 6.9 years). Data acquisition is performed as follows: the image resolution is 2.29 – 3.31 mm for inplane, and slice thickness is 3.31 mm, TE = 30 ms and TR = 2.2–3.1 s. Another dataset is ADHD-200 from New York University site, including 118 ADHD (25M/93F, aged 11.2 $\pm$ 2.7 years) and 98 NCs (51M/47F,

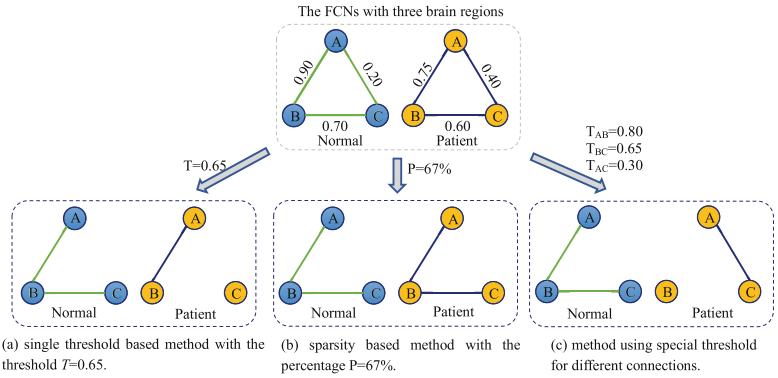

Fig. 1. Examples of functional connectivity (FC) networks (top) for a normal control (NC) and a patient, and the corresponding thresholded networks (bottom). (a) Thresholded networks using a single-threshold based method with threshold $T = 0.65$. (b) Thresholded networks using a sparsity-based method with the percentage of $P = 67\%$. (c) Thresholded networks using with specific thresholds for different connections. Note that there are different temporal correlations (*i.e.*, weights) for different connections in the FC network of the NC (or patient) subject, and the connection weights in the patient's network have been changed. From (a) and (b), we can see that the thresholded networks using a single-threshold or a percentage of connections can not characterize the diversity of functional connectivity in networks of the NC and the patient. We may need threshold FCNs with specific values for different connections, as shown in (c).

aged 12.2 $\pm$ 2.1 years). The acquisition of data in ADHD-200 is performed as follows: the matrix size is 49 $\times$ 58, axial slices is 47, slice thickness is 4 mm, FOV = 240 mm, TR = 2 s, TE = 15 ms, flip angle = 90, and the voxel size is $3 \times 3 \times 4\,\text{mm}^3$.

Following [10], we preprocess images from the ADNI dataset using the standard pipeline, including (1) removing the first 10 rs-fMRI volumes, (2) slice timing and head motion correction, (3) dividing the brain space of fMRI scans into 90 regions-of-interest (ROIs) using the Automated Anatomical Labeling (AAL) template [11], (4) band-pass filtering within a frequency interval of [0.025Hz, 0.100Hz], (5) extracting BOLD signals from the gray matter tissue, and (6) computing the mean time series of ROIs to construct FC networks using the Pearson correlation coefficients (PCCs) as the measures of FC between ROIs. For ADHD-200, we directly used the time series from the Athena preprocessed data, with details shown on the Athena website[1]. Briefly, the data pre-processing steps include: (1) removing the first 4 image volumes, (2) slice timing and head motion correction, (3) extracting the fMRI time series from gray matter regions, (4) temporal band-pass filtering [0.009Hz, 0.08Hz], (5) partitioning the brain space into 90 ROIs using AAL template, and (6) extracting mean time series of ROIs, and (7) constructing FC networks based on PCC.

[1] http://www.nitrc.org/plugins/mwiki/index.php/neurobureau:AthenaPipeline.

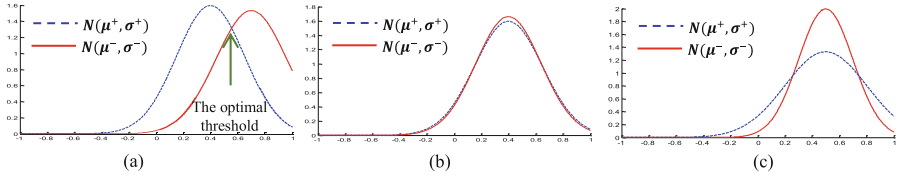

Fig. 2. Illustration of normal distributions of FC for the patient and NC groups, including three cases, *i.e.*, (a) two distributions with different means, (b) the same or similar distributions, and (c) two distributions with the same or similar mean.

2.2 Weight Distribution Based Thresholding Method

To better characterize the diversity of temporal correlations between different pairs of brain regions, we develop a weight distribution based thresholding (WDT) method to adaptively determine the optimal threshold for each FC in brain networks. Given N training subjects along with their response vectors $Y = [y_1, y_2, \cdots, y_N]$, we denote $\mathcal{F} = [F_1, F_2, \cdots, F_N]$ as their FC networks, where F_i is the FC network (*i.e.*, adjacency matrix) of the i^{th} subject and y_i is the corresponding class label (*i.e.*, patient or NC). We partition all training subjects into two groups (*i.e.*, patient and NC groups) according to their class label, denoted as $\mathcal{F}^+ = [F_1^+, F_2^+, \cdots, F_{N_1}^+]$ and $\mathcal{F}^- = [F_1^-, F_2^-, \cdots, F_{N_2}^-]$, respectively.

For FC of a pair of brain regions i and j, we compute its optimal threshold T_{ij} according to weight distributions of the FC across two subject groups. Here, we suppose that the weights of the FC in subjects from the same group follows the normal distribution, denoted as $\mathcal{N}^{+1}(\mu^{+1}, \sigma^{+1})$ and $\mathcal{N}^{-1}(\mu^{-1}, \sigma^{-1})$ for patient and NC groups, respectively. The parameters of two normal distributions can be estimated using the subjects in the corresponding group (*i.e.*, $\mathcal{F}^+$ or $\mathcal{F}^-$). As shown in Fig. 2, there are three cases for these two normal distributions. (1) Two distributions are significantly different with different means, as shown in Fig. 2 (a), implying that FC has been significantly changed in the patient group compared with that in the NC group. Therefore, the optimal threshold is the intersection point of two distributions, located in the range of $[\mu_1, \mu_2]$. (2) These two distributions are the same or very similar, as shown in Fig. 2 (b), suggesting that there is no significant difference for FC between patient and NC groups. For simplicity, we remove their connection (*i.e.*, setting the corresponding threshold $T_{ij} = 1$). (3) These two distributions are different, but their means (*i.e.*, μ^{+1} and μ^{-1}) are the same (or similar), as shown in Fig. 2 (c), indicating that the corresponding FC is unstable for subjects in the same group. This implies that it is difficult to find the stable patterns of FC between the patient and NC groups. After removing the corresponding connection, we can compute the threshold T_{ij} as follows:

$$T_{ij} = \begin{cases} p, & if \quad KL(\mathcal{N}^{+1}, \mathcal{N}^{-1}) > \delta \quad and \quad |\mu^{+1} - \mu^{-1}| > \theta, \\ 1, & \text{otherwise.} \end{cases} \tag{1}$$

Algorithm 1: Proposed Weight distribution based thresholding (WDT) method

Input: A set of FC Networks $\mathcal{F}$, a response vector Y, and two parameters δ and θ

Output: A threshold matrix T

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Divide all training subjects into patient group (denoted as F^+) and NC group
  (denoted as F^-) according to their class labels.
foreach FC between pair of brain regions i and j do
    Estimate the distributions of N^{+1}(μ^{+1}, σ^{+1}) and N^{-1}(μ^{-1}, σ^{-1}) using
      subjects in F^+ and F^-, respectively;
    Compute KL(N^{+1}, N^{-1}) using Eq. 2;
    if KL(N^{+1}, N^{-1}) > δ and |μ^{+1} − μ^{-1}| > θ then
        Calculate the intersection points of two normal distributions;
        Select the intersection point located in the range of [μ_1, μ_2] as p
        Set T_ij = p
    else
        Set T_ij = 1
return T
```

where δ and θ are two predefined positive values. Also, p is the intersection point of two distributions, locating in the range of $[\mu_1, \mu_2]$. The term $KL(\mathcal{N}^{+1}, \mathcal{N}^{-1})$ denotes the Kullback-Leibler divergence that computes the similarity between two distributions, and can be defined as:

$$KL(\mathcal{N}^{+1}, \mathcal{N}^{-1}) = log(\frac{\sigma^{+1}}{\sigma^{-1}}) + \frac{(\sigma^{-1})^2 + (\mu_1 - \mu_2)^2}{2(\sigma^{+1})^2} - \frac{1}{2}. \tag{2}$$

Therefore, the proposed WDT method can adaptively determine an optimal threshold for each FC in FC network. Thus, we can obtain a threshold matrix T for the whole FC network, which reflects the diversity of FCs between different pairs of brain regions. Algorithm 1 summaries the detailed process of the proposed WDT method for adaptive thresholding of brain FC networks.

3 Experiments

Experimental Setup: To evaluate the effectiveness of our WDT method, we test the classification performance of thresholded FC networks in brain disease diagnosis. Specifically, we first extract two kinds of network measures [7] (*i.e.*, local clustering coefficients and community structure) from thresholded FCNs as features of each subject. The clustering coefficient features reflect the prevalence of clustered connectivity around individual brain region. And the community structure features characterize the appearance of densely connected groups of brain regions, with sparser connections between groups.

We first compare our WDT method with two existing methods, *i.e.*, single-threshold based method (called **ST**) and percentage-based threshold method

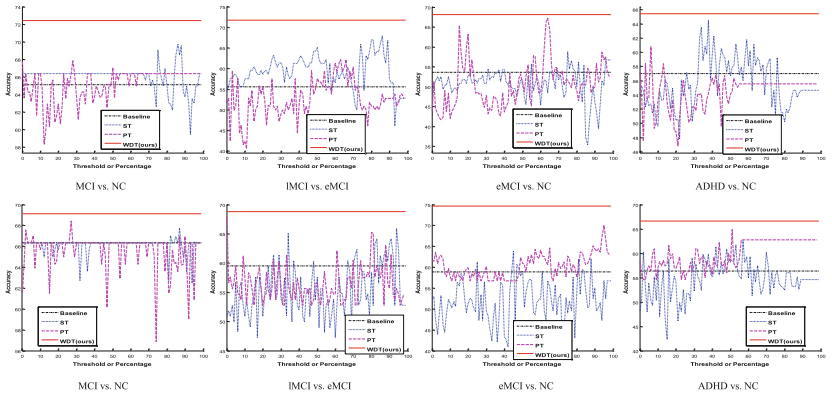

Fig. 3. The accuracy of all four methods in four classification tasks *w.r.t.* different thresholds or percentages of connections when using (top row) clustering coefficient features and (bottom row) community structure features.

(called **PT**). In the ST and PT methods, we extract the local clustering coefficient features and community structure features for classification, respectively. For the fair comparison, we compute the best performance of ST with the threshold ranging from 0.01 to 0.99 (step size: 0.01), and compute the best performance of PT with the percentage from 1% to 99% (step size: 1%). We also compare WDT with the **baseline** method without network thresholding. That is, we directly extract the weighted network measures [7] (*i.e.*, weighted clustering coefficients and weighted modularity) from the FC networks constructed using PCCs as features for classification. In four methods (*i.e.*, WDT, ST, PT and baseline), we perform feature selection using the standard t-test algorithm (with p-value less than 0.05) to select informative features, followed by a linear support vector machine (SVM) with a default parameter (*i.e.*, $C = 1$) for classification.

To evaluate the performance of different methods, we conduct four classification tasks, *i.e.*, (1) MCI vs. NC, (2) eMCI vs. lMCI, (3) eMCI vs. NC, and (4) ADHD vs. NC classification, by using a 10-fold cross-validation. We evaluate the performance via four metrics, including accuracy (*i.e.*, the percentage of subjects that are correctly classified), sensitivity (*i.e.*, the percentage of patients that are correctly classified), specificity (*i.e.*, the percentage of NC that are correctly classified), and the area under the receiver operating characteristic (ROC) curve (AUC).

Results and Analysis: Tables 1 and 2 present the results achieved by four methods in four classification tasks using two types of network measures, respectively. As can be seen from Tables 1 and 2, the proposed WDT method usually outperforms the competing methods in four tasks. For instance, the proposed WDT method, respectively, achieves the accuracy of 72.4%, 71.7%, 68.1% and 65.4% for four classification tasks (*i.e.*, MCI vs. NC, eMCI vs. lMCI, eMCI vs. NC and ADHD vs. NC classifications) when using clustering coefficient features,

while the best accuracies obtained by the competing methods are 69.7%, 67.9%, 67.3% and 64.5%, respectively. Besides, the proposed WDT method, respectively, achieves the accuracy of 69.1%, 68.8%, 74.6% and 66.6% for four classification tasks when using community structure features, while the best accuracies obtained by the competing methods are of 68.4%, 68.0%, 70.1% and 64.9%, respectively. These results suggest the efficacy of our WDT method.

Table 1. Performance of all four methods in four classification tasks when using clustering coefficient features. ACC: ACCuracy; SEN: SENsitivity; SPE: SPEcificity.

Method	MCI vs. NC				lMCI vs. eMCI				eMCI vs. NC				ADHD vs. NC			
	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC
Baseline	65.1	**100.0**	0.0	51.0	55.6	46.5	53.6	55.0	53.6	23.3	76.8	52.0	57.0	**56.1**	57.6	53.2
ST	69.7	85.9	38.0	60.9	67.9	80.4	54.0	71.3	58.9	46.5	67.9	58.1	64.5	55.1	**72.0**	**66.6**
PT	67.8	82.8	38.0	61.1	62.2	60.7	**64.0**	63.0	67.3	**69.8**	64.3	**63.3**	60.8	51.0	68.6	63.1
WDT (Ours)	**72.4**	83.8	**50.0**	**62.0**	**71.7**	**78.6**	**64.0**	**66.9**	**68.1**	51.2	**80.4**	61.4	**65.4**	**59.2**	70.3	60.6

Table 2. Performance of all four methods in four classification tasks when using community structure features. ACC: ACCuracy; SEN: SENsitivity; SPE: SPEcificity.

Method	MCI vs. NC				lMCI vs. eMCI				eMCI vs. NC				ADHD vs. NC			
	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC	ACC	SEN	SPE	AUC
Baseline	66.4	**100.0**	0.0	50.0	59.5	57.1	62.0	60.0	58.9	20.9	87.5	46.8	56.4	50.0	61.9	55.2
ST	67.7	98.0	8.0	**61.2**	66.0	71.4	60.0	62.8	63.9	**60.5**	66.1	64.7	62.7	**61.2**	63.6	60.7
PT	68.4	99.0	8.0	54.1	68.0	66.1	**70.0**	**67.8**	70.1	55.8	80.4	66.9	64.9	39.8	**85.6**	**63.2**
WDT (Ours)	**69.1**	99.0	**10.0**	52.6	**68.8**	**73.2**	64.0	64.7	**74.6**	48.8	**92.9**	**70.4**	**66.6**	52.0	78.8	60.5

Furthermore, Figure 3 plots classification accuracies of two competing methods (*i.e.*, ST and PT) with different thresholds or percentages of connections. For comparison, in Fig. 3, we also present the results achieved by our WDT method and the baseline method. As can be seen from Fig. 3, the proposed WDT method outperforms the competing methods with most of thresholds or percentages, suggesting the effectiveness of the proposed method. In addition, from Fig. 3, we can see that the accuracy of two competing methods (*i.e.*, ST and PT) are largely affected by different thresholds or percentages of connections in four classification tasks, which indicates the selection of threshold or percentage is very important for characterizing network properties and subsequent classification. These results also demonstrate the advantage of WDT in adaptively determining the optimal threshold for FC network analysis.

4 Conclusion

In this paper, we proposed a weight distribution based thresholding (WDT) method for the analysis of brain functional connectivity networks. Different from existing methods that threshold the whole networks by using a predefined value or percentage of connections, our WDT method can adaptively determine an optimal threshold for FC between each pair of brain regions, thus preserving the

diversity of temporal correlations between different brain regions. Experiment results on both ADNI and ADHD-200 datasets demonstrate that the proposed method can significantly improve the performance of disease classification compared with existing thresholding methods.

Acknowledgment. This study was supported by NSFC (Nos. 61573023, 61976006, 61703301, and 61902003), Anhui-NSFC (Nos. 1708085MF145 and 1808085MF171), and AHNU-FOYHE (No. gxyqZD2017010).

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