Artificial neural network inspired by neuroimaging connectivity: application in autism spectrum disorder

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***Abstract*—Distinguishing the autism spectrum disorder (ASD) from typical control (TC) using resting-state functional magnetic resonance imaging (rs-fMRI) is very difficult because ASD has heterogenetic properties and induce small changes in the brain structure. Moreover, distinguishing ASD from TC using the data obtained from many sites is even more difficult because many factors might negatively affect the classification model leading to unstable results. This difficulty is especially true for existing rs-fMRI analysis methods such as functional connectivity analysis. Recent studies have shown better ASD classification performance using models constructed using recurrent neural network (RNN). However, a blinded application of RNN not considering the multi-site factors is sub-optimal. In this paper, we present an artificial neural network model inspired by the existing functional connectivity analysis modeling. Our model includes layers that play the role of spatial reduction, temporal feature extraction, and combining phenotypic data (inclusive of multi-site data) for classifying ASD. We applied the cross-validation framework to the multi-site rs-fMRI dataset to test the proposed model. Our best model showed an accuracy of 74.54%, which is superior to the existing functional connectivity analysis with an accuracy of 54.05%.**

Keywords—Autism Spectrum Disorders, Classification, Neural Networks, Resting-state fMRI

I. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is a noninvasive medical image acquisition technique to measure the hemodynamic response of the brain. This imaging method is actively used to evaluate developmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [1,2]. Resting-state fMRI (rs-fMRI) is a method to measure brain activity that occurs in a resting state when no stimulus has been given. Many studies have found an association between brain activity and developmental disorders through neuroimaging analysis using rs-fMRI [1,2]. Most existing studies adopted the functional connectivity (FC) analysis as the feature extraction technique [1,2]. FC is defined as correlated functional activations between brain regions that share functional properties.

Rs-fMRI is a high dimension data with 3D spatial and 1D temporal information and has a very low signal-to-noise ratio. Therefore, selecting a meaningful brain region is necessary to calculate significant features to evaluate ASD. Existing rs-fMRI studies mostly define the brain region by using a structurally pre-defined brain atlas or data-driven approach using independent component analysis [3]. However, since the regions defined by these methods still contain a majority of regions not related to ASD, disease-specific region definition is necessary to better evaluation of ASD.

There is no designed stimulus given when we acquire images using the rs-fMRI method. Even if subjects are told rest and not to think, their brain states change over time. Therefore, there is a need to reflect the temporal fluctuation of brain activity. Existing rs-fMRI-based studies mostly use FC calculated as a temporal correlation between distinct regions, which results in discarding the temporal information and does not take into account the dynamic state changes of brain activity. To compensate for this, several studies have used functional connectivity via a sliding window approach [4] or hidden Markov modeling to estimate the hidden parameters of changing brain states [5]. More recently, the adoption of the recurrent neural network (RNN) has shown higher performance [6-9]. However, simply applying the RNN might increase the accuracy of the ASD classification, but might not result in interpretable results.

In this paper, we propose a deep learning model to solve the three problems of the existing methods. First, we can infer the regions of the brain associated with ASD by adding a convolution layer that identifies the combinations of regions associated with ASD classification. Second, by combining the temporal convolution layer and RNN, we can obtain the hidden state of the hemodynamic feature that changes over time. Finally, by adding the information of the multi-site, the differentiation between the sites can also be modeled. We apply the proposed model and compare them to other models in terms of ASD classification performance. We also evaluated what combination of the regions would lead to a good association between brain activity and ASD.

II. MATERIALS

A. Participants

The present study used rs-fMRI of the Autism Imaging Data Exchange (ABIDE). This consortium aggregated rs-fMRI

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data collected from 24 laboratories throughout the world and we used the first collection of their dataset ABIDE I. Of the 1102 subjects of ABIDE I, subjects without phenotypic information of IQ (FIQ, VIQ, and PIQ) was excluded. The image quality was assessed by the Preprocessed Connectomes Project (http://preprocessed-connectomes-project.org/abide/) and subjects with severe distortion were also excluded. Different sampling rate causes different temporal characteristics [10]. Thus, we included the imaging data only acquired by 2 seconds of repetition time (TR). As the result, we included rs-fMRI data and phenotypic information including age, sex, site index, and IQs from 270 ASD subjects and 305 typical controls (TC) from 10 different imaging sites with different acquisition parameters as summarized in Table 1. Table 1 reports the distribution of age and sex in two types of subjects and the autism diagnostic observation schedule (ADOS) score for ASD subjects.

B. Preprocessing

Fig. 1 (a) presents an overview framework of the data preprocessing. We used noise reduced and registered rs-fMRI data from the Preprocessed Connectomes Project. The rs-fMRI data were processed using open-source rs-fMRI preprocessing pipeline software C-PAC. The rs-fMRI data were processed as follows. Slice timing effects and head motion were corrected and intensity was normalized with the mean value of 10,000 across all individual data. Nuisance signal regression was performed with 24 motion parameters and a component-based noise correction method was applied with 5 components including linear and quadratic trends of low-frequency drifts [11]. The data were then band-pass filtered with 0.01-0.1 Hz and registered onto the MNI152 brain template with voxel size as 3 mm isotropic. The BrainNetome atlas (BNA) was used to calculate the mean time series for regions of interest and the fMRI signal was normalized along time by subtracting mean and dividing by the standard deviation of the time series. As a result, the mean time series were stacked across ROIs which was used for ASD classification.

TABLE I. PHENOTYPE SUMMARY

	ASD			TC	
Site	Age Avg (SD)	ADOS (SD)	Count	Age Avg (SD)	Count
CALTECH	24.8 (7.5)	13.8 (4.0)	M 3, F 1	28.2 (11.5)	M 6, F 4
CMU	25.4 (4.3)	12.0 (2.4)	M 5, F 0	26.4 (4.0)	M 7, F 1
NYU	14.8 (7.1)	11.3 (4.0)	M 64, F 10	15.7 (6.1)	M 73, F 26
SDSU	14.8 (1.7)	11.6 (3.8)	M 11, F 1	14.1 (1.8)	M 15, F 6
STANFORD	9.8 (1.6)	+	M 13, F 3	10.0 (1.6)	M 16, F 4
TRINITY	17.0 (3.0)	11.0 (2.8)	M 21, F 0	17.1 (3.7)	M 25, F 0
UM_1	12.7 (2.4)	+	M 43, F 8	13.8 (3.1)	M 34, F 16
UM_2	14.9 (1.5)	+	M 12, F 1	16.7 (3.9)	M 20, F 1
USM	23.5 (8.2)	13.0 (3.1)	M 46, F 0	20.9 (8.1)	M 24, F 0
YALE	12.7 (3.0)	11.0 (0.0)	M 20, F 8	12.8 (2.6)	M 19, F 8

M: Male, F: Female. ADOS score: + means the site did not have this information.

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III. METHODS

A. Functional connectivity model

From rs-fMRI data, we obtained the mean time course from 246 ROIs of BNA and used the first 146 time points to match the length of the timeseries. 146 was from the data with the shortest duration. Fig. 1 (b) presents the process of the FC analysis of this study. FC matrix was constructed in a graph form with atlas labels of BNA as graph node. To calculate the graph edge (brain connectivity), the Pearson correlation coefficient between the two regions were calculated. Then to satisfy small-world ness and correct for negative edges, soft thresholding was conducted with power-law adjacency function with scale factor 6. Then, Fisher's r-to-z transformation was used to normalized the edge values. Degree centrality (DC) is a widely used centrality score to measure the connection property of each brain region. In this study, DC was defined as the sum of the normalized edge weights connected to a node, which quantifies the sum of information associated with the particular node. So, a node with higher DC is regarded as an important region in brain networks. Random forest classifier consists of 10 trees with criterion as the Gini index was used to classify ASD and TC using the degree centrality metrics.

B. Proposed model

Fig. 1 (c) presents an overview framework of the proposed classification method. The mean time course data with the same regions and time points used for the FC model were used as input to the proposed model. While FC models eliminate time information by computing the correlation, our model was directly applied to mean time series data stacked across ROIs to classify between ASD and TC using four types of layers that corresponding to existing fMRI analysis modeling: 1) spatial dimension reduction layer 2) temporal convolution layer 3) densely connected gated recurrent unit (GRU) layer and 4) combining phenotypic data layer. Each layer is configured as follows:

1) Spatial dimension reduction layer: This layer may be helpful in extracting semantic features because it can account for distributing weights of each brain region. Inspired by 1×1 convolutional layer in the inception module [12], we designed an architecture using a simple 1D-convolution layer by setting the input channel as the regions and output channel as 20 resulting in feature maps whose size is 20 (reduced ROI)×146 (time points). This simple layer plays a role in reducing the spatial dimension and selecting regional combinations among significant brain regions associated with the ASD classification.

2) Temporal convolution layer: This layer serves to calculate the hemodynamic temporal features corresponding to

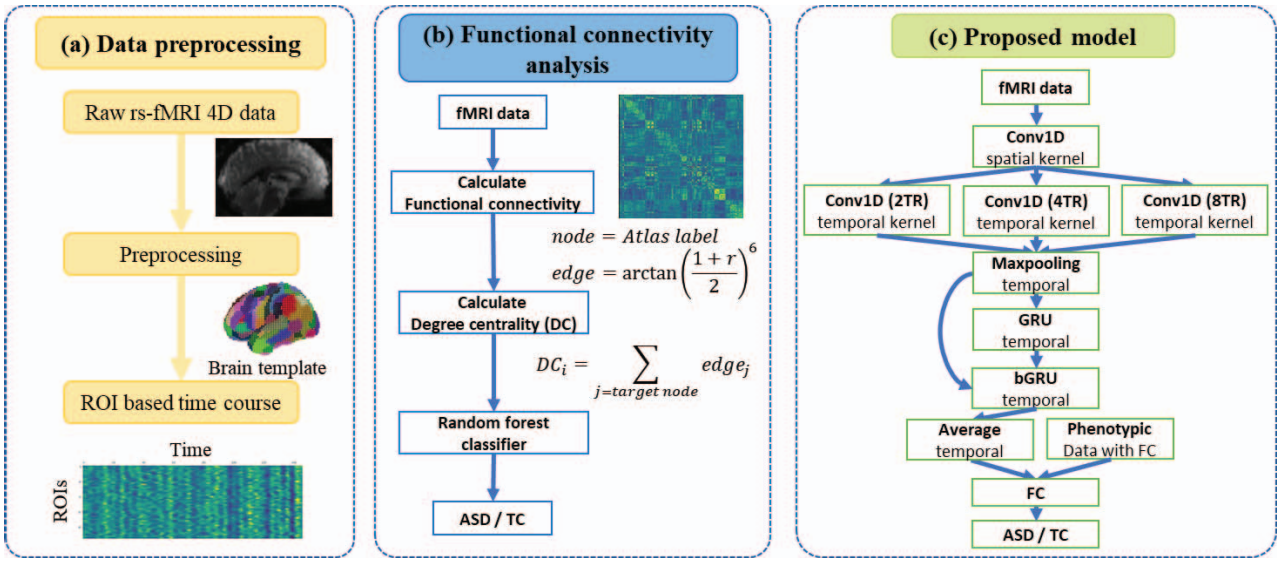

Fig. 1: The overview of the distinguishing autism spectrum disorder patients from typical controls. (a) Data preprocessing to make mean timecourse data across ROIs. The output of this process was used to classification. (b) Functional connectivity analysis pipeline using random forest classifier. (c) Proposed model based on deep learning framework.

4 s, 8 s and 16 s in length for the combined ROIs using a 1D-convolution layer with different kernel sizes (2 TR, 4 TR and 8 TR). In this layer, 20 reduced ROIs are used as the input channel and the output channel represents 32 different features. Thereafter, the outputs from three different kernel sizes were concatenated onto the feature dimension. A max-pooling layer performs down-sampling operation along the time dimensions with a filter size of 3 and a stride of 3, resulting in features of 96 (temporal feature) x 44 (time points).

3) Densely connected RNN layer: A two-layer stacked GRU RNN was used to calculate hidden states of the sequential data. The dimension of the hidden state was set to 16. We densely connected the output of the first RNN layer and output of the temporal convolution layer to feed to the second RNN layer to prevent the gradient vanishing problem [13]. To reflect the change in a brain state that occurs during the rs-fMRI session, combining all hidden features by averaging all of the output of the second RNN was conducted.

4) Phenotypic combination layer: In previous studies of classifying ASD using RNN, it is known that using phenotypic data better distinguishes ASD from TC. In this study, we used age, sex, three types of IQ and site index as phenotypic data. Age was normalized by dividing it into 100 and IQ was divided into 200. The site index was one hot encoded so resulting phenotypic data had a dimension of 15. We constructed two fully connected layers for phenotypic data as shown in the previous study [8] and the resulting output had a dimension of 15. Then, we concatenated the 15 phenotypic features from the fully connected layers with temporally averaged 32 RNN output features. Using the concatenated features, classification was conducted with another two fully connected layers with the configuration: 47-16-1, followed by sigmoid.

C. *Model implementation*

The proposed model was trained by minimizing the binary cross-entropy using the Adam optimizer with L2 norm regularization with a weight 0.1 and learning rate 0.001. The training lasted until the validation loss stopped decreasing for 200 epochs. Leaky rectified linear unit (ReLU) with a negative slope of 0.01 was used as the activation function of all convolutional layers and ReLU was used for fully connected layers. Both the FC model and the proposed model were validated using fivefold cross-validation framework. Each fold was designed to have the same distribution of ASD/TC ratio and site information. The performance of identifying ASD from TC was evaluated by accuracy (ACC), sensitivity (SEN) and specificity (SPE).

IV. Results and Discussion

A. *ASD classification*

We compared our model with a random forest classifier using FC. The performance of each classifier is listed in Table 2. The average (standard deviation, SD) accuracy of the FC model across all folds was 0.5405 (0.0319) but the baseline average (SD) accuracy of all folds was 0.5307 (0.0087). so ASD cannot be classed well using the FC values. The classification accuracy of the proposed model was 0.7454 (0.0140) which shows relatively improved performance across folds.

B. *Identified regions from the model*

The spatial dimension reduction layer performs combining fMRI signal across ROIs by weighting each ROI. We inspected the weight of the layer from the five folds of the trained model. The weight ranged from -0.0289 to 0.0283. We applied a z-

normalization to the weights of a spatial kernel for each fold and 20 channels. Then we selected dominant weights by defining the cut-off of z-score exceeding 2.576 or -2.576 (99% confidence interval) that occurred at least three times out of five folds. The significant positive weights were associated with 6 regions including two subregions of superior frontal gyrus, middle frontal gyrus, orbital gyrus, superior temporal gyrus and precuneus. There was only one significant negative weight associated with superior frontal gyrus.

TABLE II. CLASSIFICATION PERFORMANCE

	FC model			Our model		
Fold	ACC	SEN	SPE	ACC	SEN	SPE
1	0.5159	0.2373	0.7612	0.7540	0.4102	0.8806
2	0.4959	0.3729	0.6094	0.7642	0.7627	0.7656
3	0.5776	0.4182	0.7213	0.7414	0.5636	0.9016
4	0.5741	0.4694	0.6610	0.7222	0.6531	0.7797
5	0.5392	0.3958	0.6667	0.7451	0.5833	0.8889
Avg (SD)	0.5405 (0.0319)	0.3787 (0.0776)	0.6839 (0.0524)	0.7454 (0.0140)	0.6346 (0.0707)	0.8433 (0.0582)

ACC: accuracy, SEN: sensitivity, SPE: specificity, SD: standard deviation

V. CONCLUSIONS

In the current study, we aimed to develop a new artificial neural network model for discriminate ASD and TC using rs-fMRI inspired by neuroimaging connectivity analysis. The significant combination of ROIs was calculated and then the functional features were computed by the temporal 1D convolutional kernel and RNN layers. We used our model to classify between ASD and TC and it led to fair results (mean ACC = 0.7454).

Our proposed model inspired by the existing neuroimaging connectivity technique performed better than the existing methods in classification performance. In addition, we can infer which brain regions better describes the ASD by analyzing the weights of our model. As a future study, we will need to explore techniques to find out the meaning of the weights obtained from the RNN layer. This analysis might lead to understanding how significant hemodynamic response pattern is different between ASD and TC.

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