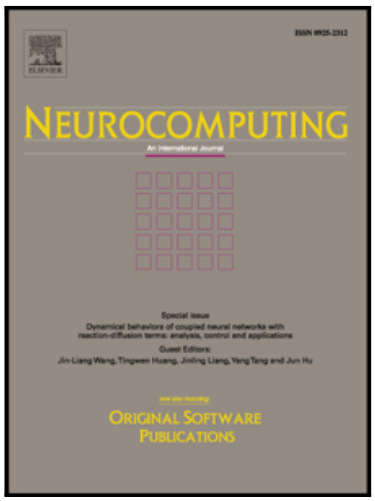

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Classification of Autism Spectrum Disorder by Combining Brain Connectivity and Deep Neural Network Classifier

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Abstract

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that seriously affects communication and sociality of patients. It is crucial to accurately identify patients with ASD from typical controls (TC). Conventional methods for the classification of ASD/TC mainly extract morphological features independently at different regions of interest (ROIs), rarely considering the connectivity between these ROIs. In this study, we construct an individual brain network as feature representation, and use a deep neural network (DNN) classifier to perform ASD/TC classification. Firstly, we construct an individual brain network for each subject, and extract connectivity features between each pair of ROIs. Secondly, the connectivity features are ranked in descending order using F-score, and the top ranked features are selected. Finally, the selected 3000 top features are used to perform ASD/TC classification via a DNN classifier. An evaluation of the proposed method has been conducted with T1-weighted MRI images from the Autism Brain Imaging Data Exchange I (ABIDE I) by using ten-fold cross validation. Experimental results show that our proposed method can achieve the accuracy of 90.39% and the area under receiver operating characteristic curve (AUC) of 0.9738 for ASD/TC classification. Comparison of

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experimental results illustrates that our proposed method outperforms some state-of-the-art methods in ASD/TC classification.

Keywords: ASD, morphological features, individual network, deep neural network, classification

1. Introduction

Autism spectrum disorder (ASD) is a common complex neurodevelopmental disorder. It is associated with several comorbid disorders, including intellectual impairment, seizures and anxiety [1, 2]. The 2013 report showed that 1 in 55 children aged 6-17 years had been identified with ASD [3]. These who have ASD behave mild to severe impairments in social interaction and communication along with restricted, repetitive of behaviors and interests [4]. It is a crucial step to accurately identify patients with ASD from typical controls (TC).

At present, neuroimaging technology has widely been used in the study of various brain diseases, such as ASD [5, 6], alzheimer's disease [7, 8] and schizophrenia classification [9, 10]. Magnetic resonance imaging (MRI) is a powerful and safe technique, which provides high quality three-dimensional (3D) images of brain structures and detailed structural information. Morphological studies based on MRI images have been applied to the related diseases, and have achieved good results. For example, Akshoomoff et al. [11] used six preselected brain volume-based features to perform ASD classification, and the results indicated that variability in cerebellar and cerebral size is correlated with ASD. Jiao et al. [12] used regional cortical thickness extracted from surface-based morphology to perform ASD classification and achieved good classification performance. Wee et al. [13] extracted morphological features of different ROIs (including mean cortical thickness, regional cortical volume etc.) to perform alzheimer's disease classification. Han et al. [14] extracted the morphological features of MRI data to classify schizophrenia and showed that the gray matter density of frontal lobes in the schizophrenic patients is lower than that in the normal control groups [15, 16]. In this study, we use the morphological fea-

tures derived from T1w MRI to investigate the predictive power in ASD/TC classification.

Traditional machine learning methods are widely used in disease classification [17, 18, 19, 20, 21]. For example, Ecker et al. [18] used SVM classifier to investigate the predictive value of whole-brain structural volumetric changes in ASD. Xiao et al. [21] applied three popular machine learning classifiers including RF, NB and SVM to perform ASD classification. Due to the deep feature representation can be extracted from the deep neural network, the DNN framework has been widely used for medical image classification[22, 23]. For example, Hinton et al. [24] proposed the first deep autoencoder network to effectively address some of most challenging problems in computer vision learning. Cruz-Roa et al. [25] proposed convolutional autoencoder neural network architecture for histopathological image representation learning. It can be seen that the combination of deep learning technology and MRI images will become a research trend [26]. In this study, we propose a deep neural network classifier based on stacked autoencoder to perform ASD classification. The DNN classifier consists of two autoencoders and a softmax function. First of all, we construct an individual brain network to extract cortical gray matter volume (CGMV) from the structural MRI image. Then, all features are ranked by F-score in descending order, and the top ranked features are selected. Finally, the selected 3000 top features are used to perform ASD/TC classification via the DNN classifier.

The rest of the article is organized as follows. First, we describe the details of our proposed ASD/TC classification method in Section Materials and Methods. Then, we illustrate the experiments of ASD/TC classification and discuss comparison results in Section Results and Discussion. Finally, we draw conclusions in Section Conclusion.

2. Materials and Methods

2.1. Image Acquisition and Preprocessing

A subset of the T1w MRI images from the Autism Brain Imaging Data Exchange I (ABIDE I) site: NYU Langone Medical Center is used to evaluate our proposed method. This subset includes 182 subjects with T1w MRI images, which are composed of 78 subjects with ASD and 104 TC subjects. The demographic information of 182 subjects is shown in Table 1. It is worth mentioning that the average age of subjects with ASD and TC subjects in this study are about 15 years old, and male subjects are significantly more than female subjects. For more details with the ABIDE I, please see `http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html`.

All T1w MRI images are preprocessed by using FreeSurfer image analysis suite [27]. The preprocessing procedures in this study mainly include motion correction, intensity normalization, skull stripping and cerebellum removal.

Table 1: Demographic information of 182 subjects from NYU Langone Medical Center

Type	Number	Age	Gender(M/F)
ASD	78	14.54 ± 5.29	68/10
TC	104	15.87 ± 5.04	78/26

M: Male; F: Female. The values are denoted as mean ± standard deviation.

2.2. Construction of individual networks

In order to parcellate the whole brain, Destrieux atlas proposed by Destrieux et al. [28] is used in this study. This atlas parcellates the brain into 148 cortical regions (74 in each hemisphere). Details of the Destrieux atlas are shown in Table 2. For more details with Destrieux atlas, please see `http://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation`.

Since brain network can unravel the extraordinary complexity of neuronal connectivity, it plays an important role in the studies of brain disease [29, 30]. In this study, we propose to construct an individual network based on cortical

Table 2: Cortical regions defined in this study

Cortical Regions (74 in each hemisphere)			
Regions	*ID*	*Regions*	*ID*
G_and_S_frontomargin	1	G_temporal_middle	38
G_and_S_occipital_inf	2	Lat_Fis-ant-Horizont	39
G_and_S_paracentral	3	Lat_Fis-ant-Vertical	40
G_and_S_subcentral	4	Lat_Fis-post	41
G_and_S_transv_frontopol	5	Pole_occipital	42
G_and_S_cingul-Ant	6	Pole_temporal	43
G_and_S_cingul-Mid-Ant	7	S_calcarine	44
G_and_S_cingul-Mid-Post	8	S_central	45
G_cingul-Post-dorsal	9	S_cingul-Marginalis	46
G_cingul-Post-ventral	10	S_circular_insula_ant	47
G_cuneus	11	S_circular_insula_inf	48
G_front_inf-Opercular	12	S_circular_insula_sup	49
G_front_inf-Orbital	13	S_collat_transv_ant	50
G_front_inf-Triangul	14	S_collat_transv_post	51
G_front_middle	15	S_front_inf	52
G_front_sup	16	S_front_middle	53
G_Ins_lg_and_S_cent_ins	17	S_front_sup	54
G_insular_short	18	S_interm_prim-Jensen	55
G_occipital_middle	19	S_intrapariet_and_P_trans	56
G_occipital_sup	20	S_oc_middle_and_Lunatus	57
G_oc-temp_lat-fusifor	21	S_oc_sup_and_transversal	58
G_oc-temp_med-Lingual	22	S_occipital_ant	59
G_oc-temp_med-Parahip	23	S_oc-temp_lat	60
G_orbital	24	S_oc-temp_med_and_Lingual	61
G_pariet_inf-Angular	25	S_orbital_lateral	62
G_pariet_inf-Supramar	26	S_orbital_med-olfact	63
G_parietal_sup	27	S_orbital-H_Shaped	64
G_postcentral	28	S_parieto_occipital	65
G_precentral	29	S_pericallosal	66
G_precuneus	30	S_postcentral	67
G_rectus	31	S_precentral-inf-part	68
G_subcallosal	32	S_precentral-sup-part	69
G_temp_sup-G_T_transv	33	S_suborbital	70
G_temp_sup-Lateral	34	S_subparietal	71
G_temp_sup-Plan_polar	35	S_temporal_inf	72
G_temp_sup-Plan_tempo	36	S_temporal_sup	73
G_temporal_inf	37	S_temporal_transverse	74

regions of Destrieux atlas, denoted G_{CGMV}. For G_{CGMV}, the gray matter volume of each ROI is defined as the node of the individual network. The correlation between each pair of ROIs is defined as the edge of the individual network. The correlation is calculated as follows:

$$c(a,b) = \frac{1}{d(a,b)+1}, (a \neq b) \tag{1}$$

$$d(a,b) = |t(a) - t(b)|^2 \tag{2}$$

where $d(a,b)$ is defined as the difference between ROIs a and b, and $t(a)$ and $t(b)$ are the gray matter volume of ROIs a and b, respectively. Finally, each subject can be represented by a $148 \times (148-1)/2 = 10878$ dimensional vector.

2.3. Feature Ranking

Solving classification problems with data of high dimensionality is a challenging task due to the curse of dimensionality. It is particularly obvious for neuroimaging classification problems. With the presence of uninformative, irrelevant or redundant features, learning models tend to overfit and become less generalizable. Feature ranking is a useful and important means to identify relevant features for dimensionality reduction and improving generalization performance [31, 32]. In this study, we use the F-score [33] to rank all features extracted above.

F-score is a simple technique which measures the discrimination of two sets of real numbers. Given training vectors $\boldsymbol{x}_k$, $k = 1, ..., m$, if the number of positive instances and negative instances are n_+ and n_-, respectively, then the F-score of the i-th feature is defined as:

$$F(i) = \frac{\left(\overline{\boldsymbol{x}}_i^{(+)} - \overline{\boldsymbol{x}}_i\right)^2 + \left(\overline{\boldsymbol{x}}_i^{(-)} - \overline{\boldsymbol{x}}_i\right)^2}{\frac{1}{n_+-1}\sum_{k=1}^{n_+}\left(\boldsymbol{x}_{k,i}^{(+)} - \overline{\boldsymbol{x}}_i^{(+)}\right)^2 + \frac{1}{n_--1}\sum_{k=1}^{n_-}\left(\boldsymbol{x}_{k,i}^{(-)} - \overline{\boldsymbol{x}}_i^{(-)}\right)^2} \tag{3}$$

where $\overline{\boldsymbol{x}}_i$, $\overline{\boldsymbol{x}}_i^{(+)}$, $\overline{\boldsymbol{x}}_i^{(-)}$ are the average of the i-th feature of the whole, positive, and negative data sets, respectively; $\boldsymbol{x}_{k,i}^{(+)}$ is the i-th feature of the k-th positive instance, and $\boldsymbol{x}_{k,i}^{(-)}$ is the i-th feature of the k-th negative instance. The

numerator indicates the discrimination between the positive and negative sets, and the denominator indicates the one within each of the two sets. The greater the F-score value, the more the discernment of this feature may be.

2.4. Deep Neural Network classifier

An autoencoder (AE) is a simple neural network which can reconstruct the input as much as possible, that is, tries to learning a function model of $h_{w,b}(\boldsymbol{x}) \approx \boldsymbol{x}$. As is shown in Figure 1, an autoencoder is composed with an encoder and a decoder. Firstly, the raw signal $\boldsymbol{x}$ is input to the encoder, which corresponds to a lower dimensional hidden layer representation $\boldsymbol{c}$. Then, the representation $\boldsymbol{c}$ is input into the decoder, and accordingly there is an output $h_{w,b}(\boldsymbol{x})$. Finally, we continue to adjust the parameters of model by back-propagation to minimize the error between the input $\boldsymbol{x}$ and the output $h_{w,b}(\boldsymbol{x})$. There are many kinds of autoencoder, such as sparse autoencoder [34], denoising autoencoder [35], contractive autoencoder [36], etc. Sparse autoencoder often can better learn the representation of the raw data. The loss function of the sparse autoencoder is defined as follow:

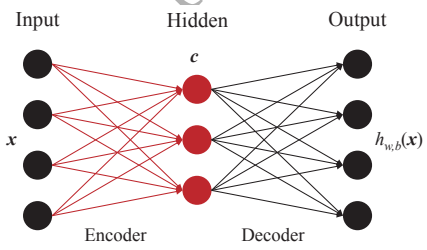

Figure 1: An example of an autoencoder.

$$J_{sparse}(W,b) = J(W,b) + \beta * \sum_{j}^{n} KL(\rho \parallel \widehat{\rho}_j) + \frac{\lambda}{2} \sum_{k}^{2} \sum_{i}^{k} \sum_{j}^{k+1} \left(w_{ij}^{(k)}\right)^2 \tag{4}$$

$$J(W,b) = \frac{1}{m} \sum_{i=1}^{m} \left(\frac{1}{2} \left\| h_{w,b}(x^{(i)}) - y^{(i)} \right\|^2\right) \tag{5}$$

$$KL(\rho \parallel \widehat{\rho}_j) = \rho \log \frac{\rho}{\widehat{\rho}_j} + (1-\rho) \log \frac{1-\rho}{1-\widehat{\rho}_j} \tag{6}$$

$$\widehat{\rho}_j = \frac{1}{m}\sum_{i=1}^{m}[a_j^{(2)}(x^{(i)})] \tag{7}$$

where $J_{sparse}(W,b)$ represents the loss function of the input and reconstructed output, $J(W,b)$ is the mean square error, m is the number of samples, $h_{w,h}(x^{(i)})$ denotes the output of the i-th sample, $x^{(i)}$ denotes the input of the i-th sample, $KL(\rho \parallel \widehat{\rho}_j)$ a sparse penalty term, which can learn relatively sparse features, ρ denotes a sparse penalty parameter, $\widehat{\rho}_j$ denotes the average activation level of hidden layer neuron j, $a_j^{(2)}(x^{(i)})$ denotes the output of the j-th neuron in the hidden layer of the i-th sample, $w_{ij}^{(k)}$ denotes the weight decay term.

Compared to single autoencoder, stacked autoencoder has stronger learning ability [37]. Therefore, stacked autoencoder is widely used in complicated problems. For example, Wei et al. [38] proposed a deep learning based predictor by using stacked autoencoder. As shown in Figure 2, a stacked autoencoder neural network is stacked by n autoencoders. For the raw data $\boldsymbol{x}$, we obtain the hidden layer representation $\boldsymbol{c}_1$ by AE_1, then put the representation $\boldsymbol{c}_1$ as the raw data of AE_2, until to the last layer. The whole network is trained through greedy layer-wise method.

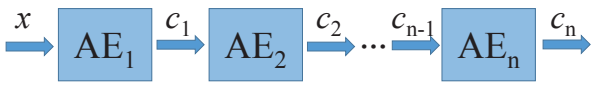

Figure 2: An example of an stacked autoencoder.

Based on the above analysis, we propose to use two sparse autoencoder and a softmax layer to form a deep neural network classifier as shown in the Figure 3. The input represents the top ranked features. The two hidden layer represent two autoencoder, which are trained in an unsupervised manner to obtain the hidden features and to decrease the features dimension. The softmax layer is trained in a supervised manner with the features obtained from the hidden layer and label to perform ASD/TC classification. The output represents the class identified by the DNN classifier.

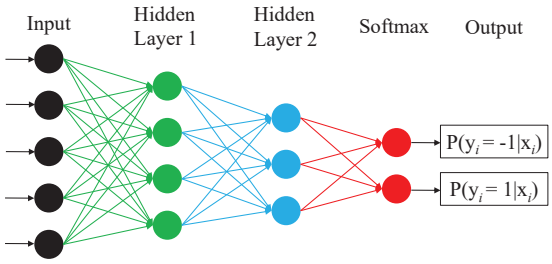

Figure 3: Our proposed deep neural network classifier.

2.5. Evaluation

An overview of the proposed ASD/TC classification framework is depicted in Figure 4. Firstly, we construct an individual network for each subject, and extract connectivity features of each pair of ROIs. Next, we use F-score to rank all features in descending order and select top features to identify subjects with ASD from TC subjects via a DNN classifier.

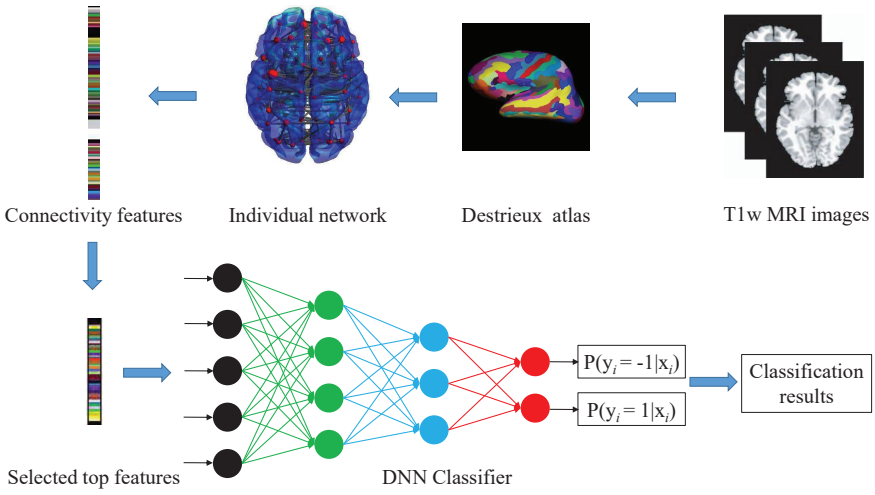

Figure 4: An overall flowchart for ASD/TC classification in this study.

Four indicators including accuracy (ACC), sensitivity (SEN), specificity (SPE), and the area under receiver operating characteristic curve (AUC) are calculated

to evaluate the performance of our proposed ASD/TC classification method. The accuracy, sensitivity and specificity can be formulated as follows:

$$Accuracy = \frac{TN + TP}{TN + FN + TP + FP} \tag{8}$$

$$Sensitivity = \frac{TP}{TP + FN} \tag{9}$$

$$Specificity = \frac{FN}{TN + FP} \tag{10}$$

where TP, FP, TN and FN are the number of true positive subjects, false positive subjects, true negative subjects and false negative subjects, respectively. The larger the AUC, the better the classification performance.

3. Results and Discussion

3.1. Classification performance

We use a ten-fold cross-validation strategy and repeat twenty times to evaluate our proposed method. To avoid overfitting, firstly, all subjects for each classification are randomly equally partitioned into 10 subjects $\{S1, S2, ..., S10\}$ and $S1$ is selected to as testing set. Then, $\{S2, ..., S10\}$ as a whole data set is further randomly equally into 10 subsets, and one subset is randomly selected as validation set and the other 9 subsets are used to train a classifier. We have done a series of experiments based on different numbers of top ranked features as shown in Figure 5. As can be seen from Figure 5, when we select 3000 top features, our proposed method achieves the highest classification accuracy, and its accuracy, sensitivity, specificity and AUC are 90.39%, 84.37%, 95.88% and 0.9738, respectively.

3.2. Comparison with different morphological representation

In this section, we investigate the performance of different morphological features (CGMV, cortical thickness (CT) and standard deviation of cortical thickness (CTstd)) based on our proposed framework for ASD/TC classification.

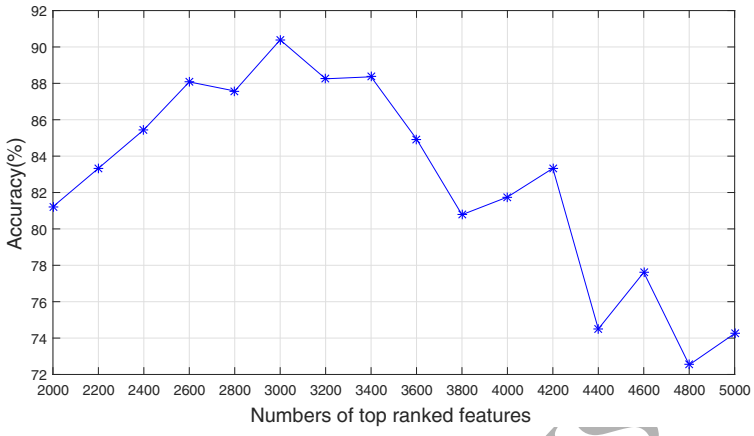

Figure 5: The classification accuracy of different numbers of top ranked features.

The experimental results are shown in Table 3. As can be seen from Table 3, CGMV outperforms other morphogical features (CT and CTstd) in terms of ACC, SEN, SPE, AUC. Therefore, it is more reasonable to use CGMV for ASD/TC classification.

Table 3: Comparison of different morphological representation for ASD/TC classification

Type	ACC(%)	SEN(%)	SPE(%)	AUC
CT	67.58	56.66	75.46	0.7150
CTstd	69.17	57.94	77.33	0.7832
CGMV	90.39	84.37	95.88	0.9738

3.3. Comparison with Existing Classification Methods

Recently, some existing methods have achieved relatively good results for ASD/TC classification. Katuwal et al. [39] investigated the predicitve power in ASD classification with brain morphological features and random forest. Xiao et al. [21] proposed to generate relatively stable predictive model based on anatomical brain features to perform ASD/TC classification. To demonstrate the superiority of our proposed method in ASD/TC classification, we compare

the above two methods with the same dataset. The experimental results are shown in Table 4. As can be seen in Table 4, our proposed method is superior to the other two method.

Table 4: Comparison to existing methods using NYU dataset for ASD/TC classification

Type	ACC(%)	SEN(%)	SPE(%)	AUC
Xiao et al. [21]	59.56	72.68	42.05	0.6226
Katuwal et al. [39]	74.46	63.97	82.62	0.8389
Our proposed	90.39	84.37	95.88	0.9738

To further prove the superiority of our proposed method, we repeat the same experiment with T1w images from ABIDE I: Kennedy Krieger Institute (KKI) site for ASD/TC classification as shown in Table 5. As can be seem from Table 5, our proposed method is also better than the other two existing methods.

Table 5: Comparison to existing methods using KKI dataset for ASD/TC classification

Type	ACC(%)	SEN(%)	SPE(%)	AUC
Xiao et al. [21]	52.35	75.61	17.56	0.4626
Katuwal et al. [39]	71.60	38.88	95.25	0.8309
Our proposed	86.70	67.76	100.00	0.9803

4. Conclusion

In this study, we propose an ASD aided diagnosis method based on deep neural network classifier. We firstly construct an individual network for each subject and extract gray matter volume as features. Then, we use F-score algorithm to rank all features in descend order. Afterwards, the top ranked features are applied to the DNN classifier to obtain the best classification accuracy. The experimental results illustration that our proposed method is an effective assistant diagnostic strategy in ASD/TC classification.

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