DEEP MULTI-MODAL SCHIZOPHRENIA DISORDER DIAGNOSIS VIA A GRU-CNN ARCHITECTURE

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Abstract: Schizophrenia is a complex mental disorder associated with a change in the functional and structural of the brain. Accurate automatic diagnosis of schizophrenia is crucial and still a challenge. In this paper, we propose an automatic diagnosis of schizophrenia disorder method based on the fusion of different neuroimaging features and a deep learning architecture. We propose a deep-multi-modal fusion (DMMF) architecture based on gated recurrent unit (GRU) network and 2D-3D convolutional neural networks (CNN). The DMMF model combines functional connectivity (FC) measures extracted from functional magnetic resonance imaging (fMRI) data and low-level features obtained from fMRI, magnetic resonance imaging (MRI), or diffusion tensor imaging (DTI) data and creates latent and discriminative feature maps for classification. The fusion of ROI-based FC with fractional anisotropy (FA) derived from DTI images achieved state-of-the-art diagnosis-accuracy of 99.50 % and an area under the curve (AUC) of 99.7 % on COBRE dataset. The results are promising for the combination of features. The high accuracy and AUC in our experiments show that the proposed deep learning architecture can extract latent patterns from neuroimaging data and can help to achieve accurate classification of schizophrenia and healthy groups.

Key words: *CNN, data fusion, deep learning, functional connectivity, GRU, multi-modality analysis, schizophrenia*

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1. Introduction

Schizophrenia (SZ) is a highly debilitating mental illness that is marked by obstacles in thinking, behavior, perception, emotions, etc. [1]. The World Health Organization (WHO) estimates that about 20 million people worldwide are living with schizophrenia disorder. This mental illness imposes a heavy burden on patients, their family members, and society. Therefore, it is crucial to investigate

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the exact method of diagnosing schizophrenia disorder [2]. Although psychiatrists generally diagnose schizophrenia based on the history of the disease and mental status examination [3], many researchers have recently attempted to provide the basis for automated diagnosis of schizophrenia. Most of these studies have utilized extracted features of neuroimaging data along with machine learning techniques [4]. For instance, Ardekani et al. [5] derived fractional anisotropy (FA) and mean diffusivity (MD) maps from diffusion tensor imaging (DTI) data. They applied Fisher's linear discriminant analysis (LDA) as a classifier method. Chyzhyk et al. [6] used resting-state functional magnetic resonance imaging (rs-fMRI) data and extracted functional connectivity (FC) measures, regional homogeneity (ReHo), and fractional amplitude of low-frequency fluctuations (fALFF) as derived features from them. Their proposed approach is consists of dimensional reduction, feature selection, and classification with SVM steps. In contrast to the methods that have used single neuroimaging modality, some studies have suggested using multi-modal neuroimaging data [7]. Although these methods may require additional time, cost, and information, they achieved higher accuracy because of the use of complementary data. Cetin et al. [8] used fMRI and magnetoencephalography (MEG) data and derived static and dynamic functional network connectivity (FNC) from them to diagnose schizophrenia patients from healthy controls. Their experiments showed that combined fMRI and MEG features improved the classification accuracy (achieved accuracy is 85.71 %) compared to using each modality data alone (achieved accuracy is 75.82 %). Qureshi et al. [9] combined some structural measures extracted from sMRI and four functional connectivity based features gathered from fMRI. They achieved an accuracy of 99.3 % for classifying SZ/HC with the extreme learning machine (ELM) classifier. Zhuang et al. [10] used sMRI, DTI, and rs-fMRI features for diagnosis of drug-naïve first-episode schizophrenia (FES). They reported a classification accuracy of 84.29 % with the SVM method. Liang et al. [11] combined MRI and DTI features for classifying FES/HC with an accuracy of 75.05 %, which was better than achieved accuracy from single modality measures. Deep learning is a new branch of machine learning that nowadays increasingly employs in medical studies. In many recent works on the automated diagnosis of brain disorders such as schizophrenia, Different methods of deep learning were used [13–15]. Convolutional neural network (CNN) is a supervised deep learning framework and has hierarchical architecture. CNN models have a 2D structure that suitable for applying on 2D data such as images. Ji et al. [16] used 3D-CNN for video classification that is 3-dimensional data. Similar to video data, some neuroimaging data such as MRI or extracted features from them have a 3-dimensional essence; thus, some studies employed 3D-CNNs [12, 13, 17, 18] to learn discriminative hidden features from this type of data. Recurrent neural networks (RNNs) [19] are other deep learning methods that are capable of modeling temporal data. RNNs consist of recurrent units. These units create an internal memory. Internal memory makes RNNs suitable for processing arbitrary sequences of inputs. Recently, in many medical applications, RNNs and their derived models such as long short-term memory (LSTM) [20] and gated recurrent unit (GRU) [21] employed. Yan et al. [22] proposed a multi-scale CNN-GRU model for discriminating schizophrenia using time courses of fMRI data. They obtained an accuracy of 83.2 %. Dakka et al. [23] used an LSTM framework with segments of 4D fMRI recordings for diagnosis schizophrenia and reported 74 % accuracy. Cui et al. [24] proposed an architecture by combination CNN and bidirectional gated recurrent units (BGRU) layers to longitudinal analysis of MRI images for AD diagnosis. Wang et al. [25] proposed an RNN model for recognizing brain states from fMRI data. Dvornek et al. [26] used the LSTM network with resting-state fMRI time-series for diagnosis autism disorder. Functional connectivity (FC) is a temporal correlation between region of interest (ROI) or voxel time series of different brain portions from fMRI data [27]. Although any pair-wise criterion can beneficial to measure of similarity between different ROI or voxel time series, the majority of studies employ Pearson's correlation coefficient for this end [28]. FC is useful in detecting brain abnormalities in a state of illness [29]. More studies showed structural and functional connectivity changes in schizophrenia [30], and thus, FC can be considered as a biomarker to diagnose it [31]. In this paper, we present a deep-multi-modal classification framework based on combination CNNs and GRUs for diagnosis schizophrenia. As far as we know, the proposed model is the first attempt to the fusion of functional connectivity data and other extracted neuroimaging features with a deep architecture. We firstly use an GRU-CNN model to create a feature map from ROI-based fMRI-FC measures, on the other hand, a sequence 3D-CNNs designed to learn latent features from DTI data and creating a new feature map. Then, we combine obtained feature maps to use for the classification. In this study, we examine various features extracted from MRI, fMRI, and DTI to find the best combination for diagnosis schizophrenia.

2. Material and method

2.1 Convolutional neural network (CNN)

The convolutional neural network is a special implementation of the neural network which exclusively handles array data such as images; thus, frequently is used in computer vision and medical image processing. The architecture of a CNN typically consists of convolution layers, pooling layers, and non-linear activation units. The input of a convolution layer convolved with some kernel and create distinct feature maps. The dimension of each feature map is reduced to a smaller matrix by pooling the adjacent values. Activation units allow multiple layers stacked to create a deep neural network. In this paper, we use both 2D and 3D CNN to find the latent feature maps from input data. The basis of 2D and 3D CNNs is similar, except that in 3D-CNN, kernels have three dimensions. The 3D-CNNs are successful in learning local patterns and spatial information modeling for 3D input data [16]. It is noteworthy that to maximize the performance of the network and to prevent overfitting. Thus a compromise must be made between the number of convolutional layers and the number of features maps in each layer [17].

2.2 Gated recurrent unit (GRU)

GRU models are a specific type of recurrent neural networks. GRU uses gates that regulate the flow of data and learn long-term dependency on them, the same as in the long short-term memory (LSTM) model. However, there are some structural differences between GRU and LSTM models. An LSTM cell block has three gates: input gate, forget gate, and output gate. On the other hand, the GRU structure has two types of gates: the reset gate (r_t), which controls the effectiveness of a candidate's state from a previous state, and the update gate (u_t), which determines the amount of retaining the stored data as well as the amount of new data added [32]. Thus, GRU is simpler than LSTM and has fewer parameters than it. However, the performance of both is about the same [33]. Fig. 1 shows the structure diagram of the GRU model. If we consider: x_t as the network input, h_t as the new hidden state, h_{t-1} as the previous hidden state and $\tilde{h}_t$ as the current new state, the GRU transition equations define as follows [21]:

$$u_t = sigmoid\left(W_u x_t + U_u h_{t-1} + b_u\right), \tag{1}$$

$$r_t = sigmoid\left(W_r x_t + U_r h_{t-1} + b_r\right), \tag{2}$$

$$\tilde{h}_t = \tanh\left(W_h x_t + r_t \odot \left(U_h h_{t-1}\right) + b_h\right) \tag{3}$$

$$h_t = (1 - u_t) \odot h_{t-1\text{-}} u_t \odot \tilde{h}_t \tag{4}$$

In these equations, $W_u, U_u, b_u, W_r, U_r, b_r, W_h$, and U_h are learnable GRU parameters.

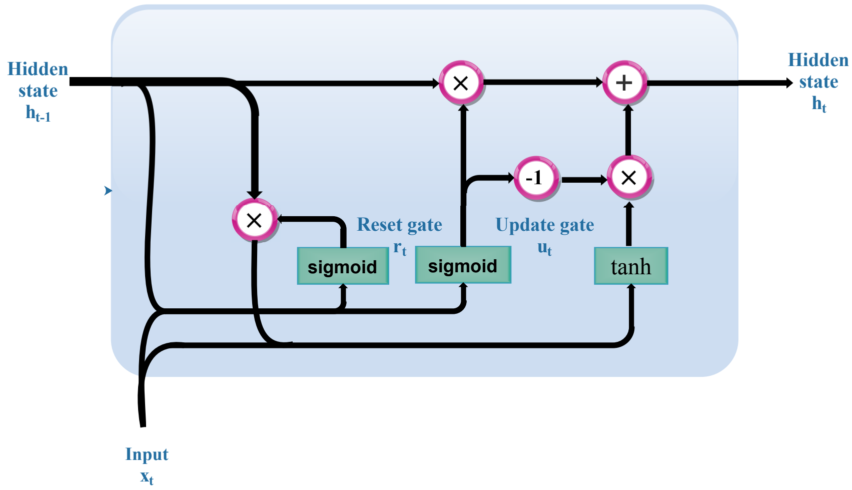

Fig. 1 *The architecture of GRU cell applied in DMMF model.*

2.3 Dataset and pre-processing

In this study, we use the 'Center for Biomedical Research Excellence' (COBRE) dataset [34], which is publicly accessible on the website (www.schizconnect.org). We select only subjects from the dataset that all modalities (sMRI, fMRI, and DTI) available for them. Thus, the applied dataset in our experiments contains 81 samples in healthy control (HC) class and 64 samples in the schizophrenia-strict (SZ) class. There are 21 females and 60 males with an average age of 37.98 in HC class and 13 females and 51 males with an average age of 38.92 in SZ class.

2.4 sMRI data acquisition and pre-processing

The T1-weighted images in the COBRE dataset are scanned using a single 3T SIEMENS MAGNETOM TrioTim Syngo B17 MR scanner. Parameters of the used multi-echo MPRAGE (MEMPR) sequence with are as follow: TR = 2530 ms, flip angle = 7°, FOV read = 256 mm, FOV Phase=100 %, Slices per slab = 192, Voxel size = $1 \times 1 \times 1$ mm, TE = [1.64, 3.5, 5.36, 7.22, 9.08] ms, TI=1200 ms. We first register MRI images to the MNI152 template then apply the BET tool from Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) software to registered images for eliminating none brain regions. We use an MRI 3D patch with no further pre-process in our experiments.

2.5 fMRI data acquisition and pre-processing

The fMRI scanning parameters are: echo time TE = 29 ms, voxel size = $3.8 \times 3.8 \times 3.5$ mm, slice thickness = 3.5 mm, number of slices = 33, FoV read = 240 mm, FoV phase = 100 %, flip angle = 75° and repetition time TR = 2000 ms. All the fMRI images pre-process using the Data Processing and Analysis of Brain Imaging (DPABI) toolbox [35]. Pre-processing steps are as the following: (1) discard the initial ten volumes to ensure that the fMRI signal reached steady state (2) slice timing by adjusting the measured signal in each slice according to the midpoint slice at the of each TR. (3) Realignment using a least-squares approach and a six parameter (rigid body) spatial transformation (4) apply a 4-mm FWHM Gaussian kernel for spatial smoothing. After pre-processing, we extract some of the most referenced features from fMRI: amplitude of low-frequency fluctuations (ALFF) [36], fALFF [37], ReHo [38], Voxel-Mirrored Homotopic Connectivity (VMHC) [39] and ROI-based functional connectivity (FC) according to the Automated Anatomical Labeling (AAL) atlas [36].

2.6 DTI data acquisition and pre-processing

In COBRE dataset the diffusion tensor imaging (DTI) acquisition parameters are set as: no. of slices = 72, FoV read = 256 mm, FoV phase = 100 %, slice thickness = 2 mm, TR = 9000 mm, TE = 84 ms, b-value = 800 s/mm, and voxel size = $2 \times 2 \times 2$ mm. We pre-process DTI images using FSL. The pre-processing steps include (1) Eddy current correction, which not only corrects distortions in diffusion MR images generated by different gradient directions but also removes the effects of head movement and realigns all 3D scans to a standard reference for each subject; (2) brain extraction, the non-brain tissue and background noise removed by applying BET tool from images. After pre-processing, we calculate DTI metrics, including FA [40], MD, and mode of anisotropy (MO) [41].

2.7 Proposed method

Fig. 2 shows the architecture of the proposed DMMF model for diagnosing schizophrenia, which consists of two main channels.The fMRI and DTI belonging to the same person, are the input of the proposed model. In the first channel, after pre-processing fMRI data as stated in the previous section, the FC measures are calculated based on a standard atlas. In this study, we calculate FC feature maps according to AAL standard atlas [36]. The number of brain ROIs in this atlas is 116; thus, for 140 time-course in each fMRI data, we obtain a 140×116 matrix as input. These feature maps are the input of a recurrent neural network with GRU units. We set the number of GRU units equal to fMRI time courses. In this way, the outputs of GRU units are hidden feature maps that are used as the input of a 2D-CNN with a convolution layer, ReLu activation function, and a max-pooling layer. CNN obtains a comprehensive representation from the input signal by recognizing the local features. We apply 16 different 2D kernels with a size of 3×3 and a 2×2 max-polling for 2D-CNN. On the other hand, in the second channel after pre-processing MRI, fMRI, and DTI modalities and extracting related features, as discussed in the previous section, the extracted feature maps are fed into a 3D-CNN with three layers. Each of the 3D-CNN layers consists of a convolution layer, ReLu activation function, and a max-pooling layer. We use 16 different 3D kernels with the size of $3 \times 3 \times 3$, 32 different 3D kernels with the size of $5 \times 5 \times 5$ and 64 different 3D kernel with the size of $3 \times 3 \times 3$, respectively. We set the size of all 3D max-poolings as $2 \times 2 \times 2$. The initial weights of the 2D and 3D convolutional kernels are randomly set with a Gaussian distribution. We apply cross-entropy [42] as a loss function to update the weights and biases parameters and the network architecture train via Adam algorithm [43] with an initial learning rate of 0.001. The outputs of 2D-CNN and 3D-CNN were flattened and were concatenated. Finally, two fully connected, dropout, and softmax layers were used for classification. The softmax layer generates a probabilistic score over each class. We set 1000 hidden units in the first and 100 hidden units in the second fully connected.

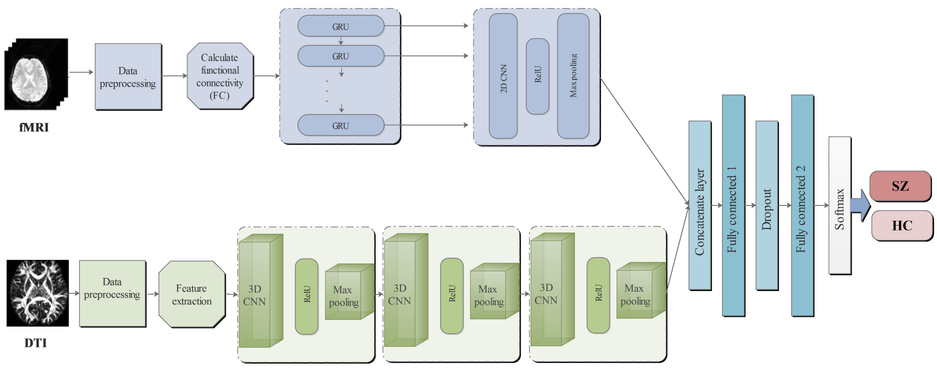

Fig. 2 *The flowchart of the proposed deep-multi-modal fusion algorithm.*

3. Experiments and results

3.1 Experiments setup

We implemented our proposed deep-multi-modal method in Python with Keras library [44] and used the Google Colaboratory (https://colab.research.google.com/) system for running our model. To determine the effectiveness of our proposed model and comparison with other studies, we calculate the accuracy of classification (ACC), sensitivity (SEN), specificity (SPE), area under ROC (AUC), and demonstrate the receiver performance curves (ROC) [9]. We use a ten-fold cross-validation manner, eight folds for the training step, one for the validation, and one for testing step. The validation part is used to end the training process when obtaining the optimized weight for the model. We repeat all experiments for ten times and report the average performance measures. In this study for brevity, we have named ROI-based FC, according to AAL atlas as AAL-FC. The network input size for AAL-FC is 140×116, and we set 116 hidden states for the GRU network. In all experiments, the batch size is set to 16.

3.2 The fusion of functional connectivity measures and fMRI features

In this section, we combine AAL-FC with fMRI extracted features (ALFF, fALFF, VMHC, and ReHo) in separate experiments. We set the size of all these features as $61 \times 61 \times 61$. This size is the closest to all features that include all values. Thus, the input of the first 3D-CNN is $61 \times 61 \times 61$. Tab. I shows the performance of our deep-multi-modal method to classification SZ/HC by fusion of FC features and the most referenced fMRI features. Fig. 3 shows the ROC curves in this experiment based on FC measures.

	Sensitivity [%]	Specificity [%]	Accuracy [%]	AUC [%]
AAl-FC, ALFF	99.14	97.25	98.35	99.2
AAl-FC, fALFF	98.41	96.88	97.78	98.9
AAl-FC, VMHC	95.98	93.26	94.85	97.9
AAl-FC, ReHo	99.63	99.13	99.42	99.7

Tab. I *Comparison of classification performance on the fusion of FC measures and fMRI features.*

3.3 The fusion of functional connectivity measures and DTI features

To determine the best combination of features with the DMMF model, in this section, we test the fusion of FC measures, and DTI extracted features in separate experiments. The DTI features that we use in our experiments are FA, MD, and MO. We set the dimensions of each of them as $128 \times 128 \times 128$ value. This size is the closest to all features that include all values. Tab. II shows the obtained results

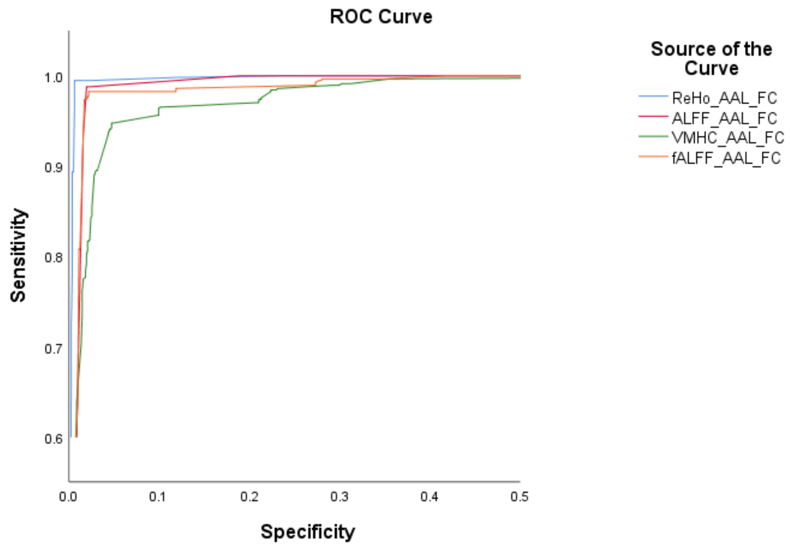

Fig. 3 *The ROC curve of the fusion of fMRI features with AAL_FC.*

of the SZ/HC classification with the fusion of FC measures and all DTI features. Fig. 4 shows the ROC curves related to these experiments.

	Sensitivity [%]	Specificity [%]	Accuracy [%]	AUC [%]
AAl-FC, FA	99.75	97.13	99.50	99.7
AAl-FC, MD	98.78	97.40	98.21	99.1
AAl-FC, MO	99.51	98.44	99.07	99.4

Tab. II *Comparison of classification performance on the fusion of FC measures and DTI features.*

3.4 The fusion of functional connectivity measures and MRI data

To reduce complexity, we use MRI patches with a size of $70 \times 70 \times 70$ to fusion with FC measures. In these experiments, MRI data is used with no further processing. 3D-CNNs can extract and learn latent features from MRI patches and provide for fusion with FC features. Tab. III shows classification results in these experiments and Fig. 5 illustrates the corresponding ROC curves.

3.5 Comparison with existing methods

To compare the performance of the presented approach in this study, we have listed some previous studies on the classification of schizophrenia and healthy control in Tab. IV We report the result of the fusion of AAL-FC and FA data in this

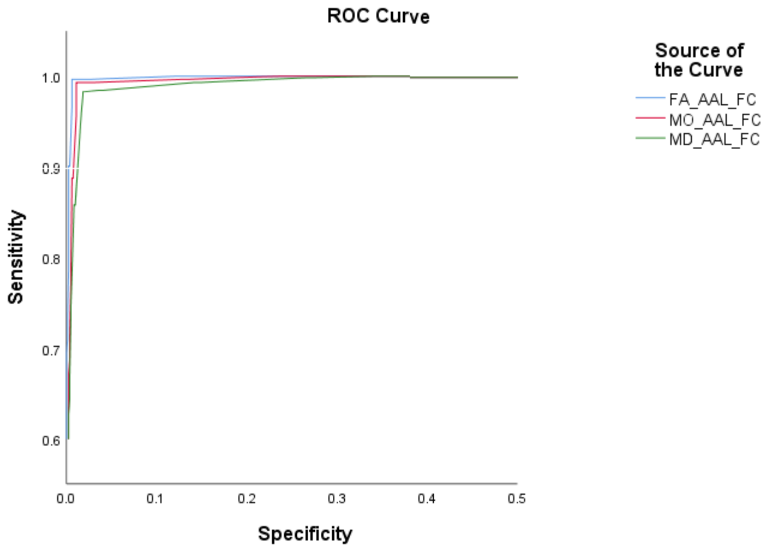

Fig. 4 *The ROC curve of the fusion of fMRI features with AAL_FC.*

	Sensitivity [%]	Specificity [%]	Accuracy [%]	AUC [%]
AAl-FC, MRI	96.46	89.78	93	96.70

Tab. III *Classification performance on the fusion of the FC measures and MRI patches.*

table. Note that, due to differences in the size and data acquisition parameters of the datasets, and different approaches to extracting features, comparison of characteristics of different methods is not entirely fair. However, our approach uses only two feature from fMRI and DTI modalities and have no hand-crafted features. Our approach with this promising performance can be used in practical applications for the automatic diagnosis of schizophrenia.

4. Discussion

Some studies have shown that schizophrenia occurs because of the disconnection between different brain regions [45]. Functional connectivity analysis is a powerful technique for investigating functional brain connections [46]. Many researchers have focused on diagnosing schizophrenia based on different types of fMRI functional connectivity. For example, in [47–49] researchers used ICA based connectivity maps that are a type of Data-Driven Analysis. Data-driven methods for estimating functional connections do not require specifying predefined brain regions or voxels [29]. Some approaches used model-driven approaches, such as ROI-based functional connectivity [50]. These methods are based on prior knowledge, such as predefined atlases. Functional network connectivity (FNC) analysis combines

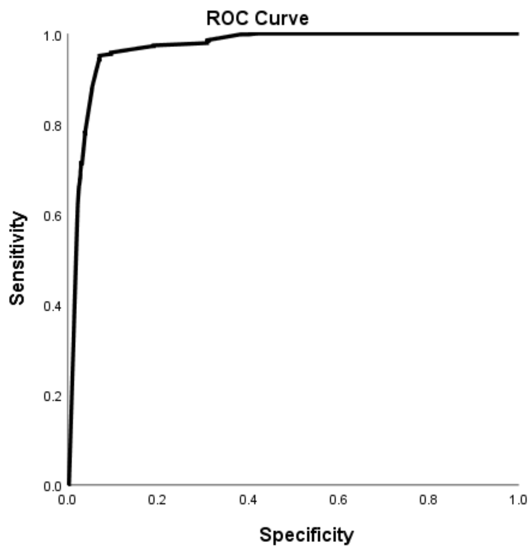

Fig. 5 *The ROC curve of the fusion of fMRI features with AAL_FC.*

model-driven and data-driven methods and is another method used for classifying SZ an HC sub-groups [51, 52]. In the present study, we presented a new approach that uses ROI-based functional connectivity measures and combines them with a neuroimaging feature to find robust and latent features for diagnosing schizophrenia. The proposed DMMF architecture uses the benefits of recurrent neural networks (RNNs) and convolutional neural networks (CNNs) to extract and learn hidden features. In the experiments, we examined ROI functional connectivity based on the AAL atlas. AAL atlas is a spatially normalized and single-subject atlas that consists of 116 ROIs. The best-achieved result in our experiment was from the fusion of fractional anisotropy and AAL-FC as 99.65 %. The finding of some studies shows a significant difference between FA measures in SZ and HC subjects [53, 54]. This difference is the result of white matter deficits in schizophrenic patients. Thus, we can use FA as a discriminative feature. We extracted latent patterns from fractional anisotropy maps with 3D-CNNs and combined them with extracted features from AAL-FC measures. The promising result of the "FA-AAL-FC" experiment shows that FA can complement ROI-based FC for the diagnosis of schizophrenia. Results of the combination of MO and MD are almost similar to that of FA, possibly due to their interdependence; however, this issue needs further research. The next promising result was obtained from "ReHo-AAL-FC". Xu et al. [55] and Xiao et al. [56] showed that the ReHo measure could be used as a biomarker for diagnosing schizophrenia. In our experiments, we find that ReHo complements AAL-FC to this end. This finding is important because instead of using multi-modal data, only fMRI data is enough to achieve good diagnostic accuracy. This method saves time and cost and provides a less diagnostic system. Finally, the relatively good result of "MRI-AAL-FC" is considerable because no need to combine hand-crafted features, and only the 3D-CCNs extract MRI fea-

Study	Modality	Samples	Method	Accuracy [%]
Ref. [57]	fMRI DTI sMRI	SZ : 35 HC : 28	mCCA+ jICA model	79
Ref. [14]	rs-fMRI	SZ : 474 HC : 607	Deep discriminant auto-encoder Neural network with sparsity constraint (DANS)	85
Ref. [58]	fMRI, Single nucleotide polymorphism (SNP) data	SZ : 20 HC : 20	Support vector machine	87
Ref. [8]	fMRI, MEG	SZ : 46 HC : 45	Linear discriminant classifier (LDC) Naïve Bayes classifier (NBC) non-linear SVM (nSVM)	90
Ref [47]	rs-fMRI, fMRI	SZ : 28 HC : 28	Kernel principal component analysis Fisher's linear discriminant analysis	98
Ref. [18]	MRI, fMRI	SZ : 72 HC : 72	3D-CNN	98.09
Ref. [9]	sMRI, fMRI	SZ : 72 HC : 72	ELM	99.29
Ref. [59]	fMRI	SZ : 98 HC : 102	Transfer Learning, VGG16	84.3
Proposed method	sMRI, DTI	SZ : 64 HC : 81	Deep-multi-modal architecture	99.50

Tab. IV *Performance comparison with existing methods.*

tures automatically from MRI patches. Deep learning methods are powerful tools in processing high-dimensional data and are successful in many medical image processing. However, most deep techniques, such as CNN, need training data and are prone to overfitting. The significant limitation of our study is the small sample size of the dataset applied for training the model. Due to the sensitive nature of medical images, it was not reasonable to use any data augmentation as [18] to avoid overfitting during training our model; Therefore, further dropout layers after GRU, 2D-CNN, and 3D-CNN layers were considered.

5. Conclusion

In this paper, we presented a deep-multi-modal method based on deep learning for diagnosing schizophrenia disorder. We, for the first time, combined functional connectivity measures with hand-crafted features extracted from fMRI, DTI data, or MRI patches. Our deep multi-modal method applies the GRU network and 2D-CNN respectively to construct a feature map from FC measures and use 3D-CNNs for the extraction of latent patterns from neuroimaging features. Then these features combine to classify SZ/HC subgroups. We achieved state-of-the-art performance to diagnosis schizophrenia. Additionally, we found that not only the fusion of the AAL-FC and FA features (fMRI and DTI modalities) yields the best performance, but the fusion of AAL-FC and ReHo (both are fMRI features) is also very promising, this meaning that only fMRI data can be used with this model to detect schizophrenia. In the future, we will compare the fusion of other types of functional connectivity with neuroimaging features and use a multi-site dataset to train deep architecture.

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