A Novel Multimodal MRI Analysis for Alzheimer's Disease Based on Convolutional Neural Network

Yan Wang, Yanwu Yang, Xin Guo, Chenfei Ye, Na Gao, Yuan Fang, Heather T. Ma*, *Member IEEE*

Abstract— **Recent years, Alzheimer's disease (AD) has become a significant threat to human health while the accurate screening and diagnosis of AD remain a tough problem. Multimodal Magnetic resonance imaging (MRI) can help to identify the variation of brain function and structure in a non-invasive way. Deep learning, especially the convolutional neural networks (CNN), can be utilized to automatically detect appropriate features for classification, which is well adapted for computer-aided AD screening and identification. This paper proposed a multimodal MRI analytical method based on CNN, which is also suitable for single type MRI data analysis. First, the human brain network connectivity matrix were extracted from multimodal MRI data, used as the input data for CNN. Then a novel CNN framework was proposed to process the network matrix and classify AD, amnestic mild cognitive impairment (aMCI) patients and normal controls (NC). The advantage of this method lies in that we combined multimodal MRI information through CNN convolution kernel, and achieved a higher classification accuracy. In our experiments, the comprehensive classification accuracy of AD, aMCI patients and NC was as high as 92.06% when using multimodal MRI data as input, which is effective enough to provide a reference for multimodal MRI data analysis.**

I. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease that slowly destroys brain cells, resulting in the loss of memory and thinking skill losses, and ultimate loss of the ability to carry out even the simplest tasks. As the population ages, the risk for AD is gradually increasing [1]. Therefore, accurate screening and diagnosis of AD have profound influence on the subsequent therapy for AD patients. Magnetic resonance imaging (MRI) analysis is an effective solution. MRI can provide a non-intrusive method to detect AD, which includes many imaging modalities. Diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) are two important imaging modalities of MRI, which are used for structural and functional imaging data analysis respectively. DTI reflects the micro structure of white matter by water molecules diffusion in neuron fibers, and fMRI reflects the brain activation through blood oxygen content of the brain. Recently, more and more attentions have been attracted to MRI analysis.

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Yan Wang, Yanwu Yang, Xin Guo, Chenfei Ye, Na Gao, Yuan Fang, Heather T. Ma are with the Department of Electronic & Information Engineering, Harbin Institute of Technology Shenzhen Graduate School, Shenzhen, China. (Corresponding author: Heather T. Ma. Phone: +86-755-26033608; fax:+86-755-26033608; e-mail:tmahit@outlook.com).

Brain network research has always been the focus for MRI analysis. The fiber connection of brain network can be observed through the DTI. Since the obtained fiber connection can reflect the structural connection of the brain, the network is called DTI structural connectivity network (DTISCN). Similarly, the functional connectivity network (FCN) can be extracted through fMRI, which exhibits the functional connection between brain regions [2]. With the introduction of graph theory analysis, brain network research are well developed. In many studies, brain network analysis has been successfully applied to investigate the brain functional and structural change of AD patients [3][4][5]. AD is considered as a disconnection disease, so brain network research is necessary.

In order to make computer aided detection (CAD) possible in AD diagnosis, deep learning and machine learning method have been applied. In previous studies, the conventional methods of machine learning contain support vector machine (SVM), independent component analysis (ICA) and so on, which have yielded some results in differentiating AD from NC [6][7]. After machine learning, deep learning, especially the convolutional neural networks (CNN) has become another promising solution in MRI analysis. Gupta et al. [8] employed 2D Convolutional Neural Network (CNN) for slice-wise feature extraction of MRI scans. Unlike classical machine learning techniques which require plenty of works to find appropriate features for classification, CNN deep learning do not need to create a set of hand-crafted features. At present, CNN has already been used in AD classification with positron emission tomography (PET) data and MRI data [9][10] and in brain image segmentation [11].

In our research, a new multimodal MRI analytical method based on CNN was proposed. Different types of MRI data were used as inputs for some classification by using this method, and the classification accuracy can be obtained. CNN was utilized to analyze the network connectivity matrix of multimodal MRI, and CNN convolution kernel was implemented for multimodal MRI information fusion. Finally, the multimodal MRI analysis methods proposed in this paper was discussed.

II. Methodology

A. Subjects

Three-class subjects with balanced sample size were separately considered in this study, including 35 AD, 30 aMCI patients and 40 normal controls from Beijing Xuanwu Hospital. Each subject consists of DTI and fMRI data. Subjects with left-handedness and other brain diseases are excluded to ensure the neuron fiber connection alterations are not resulted from the influence other than AD. The demographic information was shown in Table I.

All subjects went through whole-brain MRI scanning on 3 Tesla GE Medical Systems, anatomical T1-weighted spoiled gradient echo (SPGR) sequences (matrix size = 256x256, voxel size = 1.2x1.0x1.0 mm3, TI = 400 ms, TR = 6.98 ms, TE = 2.85 ms, flip angle = 11°), the functional imaging (matrix size = 64x64, TR = 2000ms, TE = 40ms, flip angle = 90°, slice thickness = 4mm, slices = 33) and diffusion-weighted images (single-shot spin EPI sequence, TR = 10000ms, TE = 83ms, matrix size = 256x256, slice thickness = 2mm, diffusion gradients = 60, b0 = 1000).

B. DTI and fMRI pre-processing

fMRI data processing was performed by using the Resting State Functional Magnetic Resonance Imaging Data Processing Assistant (DPARSF) toolbox [12]. To start with, the first 5 functional images were discarded, because the initial signal of fMRI scanning is instable. Then, the standardization fMRI prep-processing procedures was carried out, including slice-timing correction, Motion correction and so on. Finally, the data was normalized into the Montreal Neurological Institute (MNI) space.

Pre-processing of the DTI date was implemented using a pipeline toolbox, PANDA [13]. During the process, potential head moving affect was removed by rigid body transformation and tri-linear interpolation with the help of PANDA toolbox, and the DTI data was also normalized into the MNI space. At the same time, fractional anisotropy (FA) data was generated.

C. FCN images and DTISCN images extraction

Both FCN and DTISCN required precise brain segmentation results as a template. Anatomical Atlas Labeling (AAL) brain atlas is a good choice, and it was proposed by the MNI and includes 90 brain regions. Define each region in the AAL brain atlas as a node, and the network had a total of 90 nodes.

With Graph Theoretical Network Analysis (GRETNA) toolbox [14], the functional connectivity matrices were constructed and analyzed. We calculated the Pearson correlation coefficients between the time sequences of all pairs of nodes in AAL brain atlas to build the FCN image.

The strength of the fiber connectivity could be reflected by the FA data and whole brain white matter tracking could be easily conducted by the assistance of PANDA toolbox. FA threshold would be set to 0.2 based on the assumption that voxels with a FA value under 0.2 are not whiter matter or neuron fiber disconnect at this voxel. Angle threshold was set to 35 under which there are two crossed different neuron fibers when a tracking path with a corner higher than 35.After neuron fiber tracking, utilization of AAL brain atlas, the strength of the fiber connectivity between 2 regions can be derived. After above processing, whole brain fiber connectivity matrices can be obtained and whole brain DTISCN image can be built. Figure 1 shows images of FCN and DTISCN with the help of GRETNA toolbox.

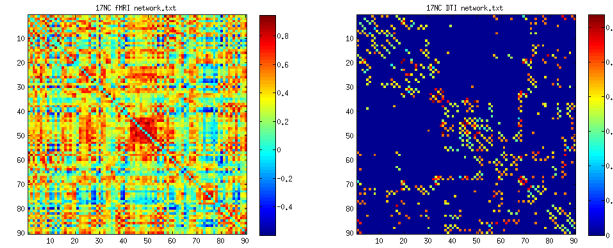

Figure 1. A FCN image and a DTISCN image.

D. Analysis based on CNN

In deep learning, CNN is mainly applied to image spatial correlation and has shown to be very effective. Considering that the FCN and DTISCN images we got in the previous step are ideal for CNN, a new CNN framework was proposed

TABLE I. DEMOGRAPGHICS AND CLINICAL CHARACTERISTICS

	AD	**aMCI**	**NC**
No. of participants	35	30	40
Age	66.7 ± 12.3	60.5 ± 7.7	62.4 ± 11.9
Males/females	24/11	17/13	22/18
MMSE score	$18 - 23$	$22 - 29$	$14 - 30$
CDR score	1	0.5	0

TABLE II. THE ADJUSTED ARCHITECTURE OF CONVOLUTIONAL NEURAL NETWORK

Name	**Layer**	**k-s-p**	**Dr/Dense**
Convolution Group1	Conv1_1	3-1-1	/
	ReLU1	/	/
	Conv1_2	3-1-1	/
	ReLU2	/	/
	max Pooling1	2-2-0	/
	Dropout1	/	0.25
Convolution Group2	Conv2_1	3-1-1	/
	ReLU1	/	/
	Conv2_2	3-1-1	/
	ReLU2	/	/
	max Pooling2	2-2-0	/
	Dropout2	/	0.25
Full connection layer	Fc1	/	33856
	Fc2	/	3

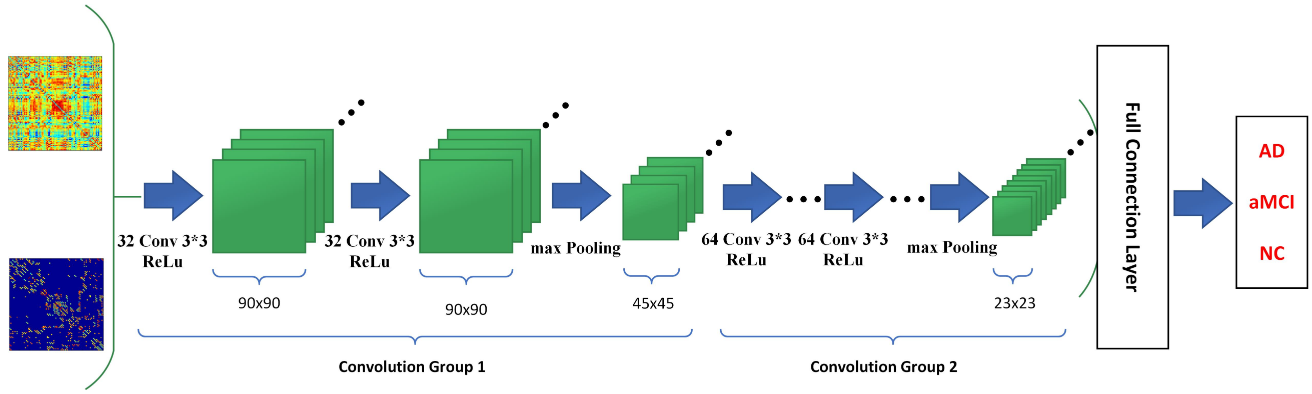

Figure 2. The structure of new convolutional neural network framework

in this paper. Figure 2 and Table II show the composition and architecture of CNN deep learning model, it includes two convolutional groups and two full connection layer. Each convolutional group consists of two convolutional layers with ReLU activation function in the end of each convolution layer, one pooling layer and one dropout layer in the end of each convolutional group. Each convolution layer has a fixed structure, with stride = 1, kernel size = 3x3, padding = 1, to keep the images input and output in the same size. Followed convolutional layers, we use max Pooling layers with pool size = 2x2, which resize the output one quarter of the input.

The outstanding feature of CNN architecture is that it can learn data spatial correlation through CNN convolution kernel. According to this feature, structural parameters and functional parameters were associated with CNN in this work. When FCN and DTISCN images were input, DTI and fMRI multi-dimensional information of one node could be learned by CNN. Then, multimodal MRI features found by CNN were used to determine AD, aMCI patients and NC. Remarkably, adequate data training is vital for CNN to increase the classification accuracy, which would avoid over-fitting. After training, the probability of different categories corresponding to each sample can be obtained. Although the proposed CNN architecture is simple, it reduces the waste of computer resources, shortens the training time while satisfying the requirement.

In this paper, the FCN and the DTISCN images of size 2x90x90 were used as input, which would turn into 64x23x23 after two convolutional groups. Then, a fully connected layer with 33856 dimensions was used to unfold each block into a line with each voxel as a feature. In the last step, the probabilities of three groups are calculated with a softmax activation, i.e. AD, aMCI, and NC.

III. Experiments and Results

Adequate sample data is necessary for the data training. The 105 samples have been used for the experiment, each of which composed of DTI and fMRI data. In order to avoid the inaccuracy caused by data deficiency, data enhancement is implemented before the experiment. Given the fact that the network matrix obtained in the process of connectivity extraction is diagonal symmetry, we could extract the upper and lower triangular matrix without dropping information by the network non-directionality, thus getting 315 samples, which is three times of the original samples. With data enhancement, the generalization ability of CNN model and the classification accuracy can be both improved.

TABLE III. Recognition rate of different input types

MRI type	Accuracy
DTI	87.30%
fMRI	82.54%
Multimodal MRI (DTI&fMRI)	92.06%

Three experiments were conducted after data enhancement. The first experiment involves classification based on the SCN image extracted from DTI data. The second one is similar with the first one, but based on the FCN image from fMRI data. The last experiment utilizes both FCN and SCN images in classification process. In each experiment, 80% of the overall samples were used for training, the rest 20% for testing, both of which contain samples of three groups, i.e. AD, aMCI and NC. The classification accuracy was then calculated. The classification accuracy is the ratio of the sample size of the correct classification to the total sample size.

The results are shown in Table III. With the proposed method above, the classification accuracies were all above 82% when using fMRI, DTI and multimodal MRI (DTI and fMRI) data as input. The highest accuracy, 92.06%, came from multimodal MRI, which was much better than using fMRI or DTI data alone.

IV. Discussion

In this paper, a multimodal MRI based analytical method was proposed, which is also suitable for single DTI or fMRI data. First, DTI and fMRI data were processed to extract connectivity network images. Deep learning was then performed on the fused connectivity network images. Finally, the classification results were obtained. In previous studies, many conclusions have suggested the obvious differences of FCN and DTISCN between AD and NC [3][15][16], for example, the overall network efficiency of FCN is decreasing step by step among NC, aMCI and AD, which goes for DTISCN too. Combining that the three experiments all achieved classification accuracy above 82%, therefore, it's feasible to classify AD, aMCI and NC with network diversity of DTI and fMRI.

The proposed method has two advantages, which is well adapted for computer-aided AD screening and identification. On the one hand, multimodal data were integrated in the research, which is more effective. As shown by the experimental results, higher classification accuracy, 92.06%, were achieved when DTI and fMRI were used as input simultaneously. Furthermore, the method resolved the problems of analytical methods disunity, high data dimension and large data quantity in the joint analysis process of multimodal data. On the other hand, accuracy and efficiency were improved with the CNN model in deep learning. Unlike classical machine learning, researchers was not required plenty of works to find appropriate features for classification, and this can improve the efficiency of scientific research. In previous studies, the differences were firstly obtained as feature, and then machine-learning approach like SVM and ICA were employed in the classification process, the accuracy of which is not enough [17].

Certainly, the proposed method has some limitations. First of all, features used for classification were not provided to researchers, although the accuracy and efficiency of classification were improved. In addition, we should attempt 3D neural convolution instead of 2D method, which may lead to better performance. Ultimately, for this method, it's meaningful to further enhance the accuracy and efficiency of AD identification.

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