Classification of Alzheimer's Disease from MRI Data Using an Ensemble of Hybrid Deep Convolutional Neural Networks

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***Abstract*—Although there is no cure for Alzheimer's disease (AD), an accurate early diagnosis is extremely important for both the patient and social care, and it will become even more significant once disease-modifying agents are available to prevent, cure, or even slow down the progression of the disease. In recent years, classification of AD through deep learning techniques has been one of the most active research areas in the medical field. However, most of the existing techniques cannot leverage the entire spatial information; hence, they lose the inter-slice correlation. In this paper, we propose a novel classification algorithm to discriminate patients having AD, mild cognitive impairment (MCI), and cognitively normal (CN) using an ensemble of hybrid deep learning architectures to leverage a more complete spatial information from the MRI data. The experimental results obtained by applying the proposed algorithm on the OASIS dataset show that the performance of the proposed classification framework to be superior to that of the some conventional methods.**

***Index Terms*—Alzheimer's Disease, MRI Data, Deep Convolutional Neural Networks, Classification**

I. Introduction

Alzheimer's disease (AD) is a progressive and degenerative brain disease affecting millions of people worldwide. According to the world health organization 2019 report, in the United States alone, it is estimated that the number of people living with AD is 5.8 million, and it is a huge concern that this number may grow to 13.8 million by mid-century. One of the major changes in the brain associated with AD is atrophy or shrinkage of the brain which occurs due to the gradual deterioration of nerve cells. This change is thought to have begun 13 years before the onset of cognitive symptoms such as memory loss and other behavior changes [1]. Magnetic resonance imaging (MRI) is a non-invasive way to view the brain atrophy changes and it has been widely used in AD research because of its good spatial resolution, increased accessibility, high contrast, and no radiation in the scanning process [2]. Although lots of research have been made, in current clinical practice, there is no definite diagnosis due to similar and overlapping symptoms. The existence of AD can be definitely confirmed only after the death of the patient through a postmortem examination of brain tissue. Hence, an accurate early diagnosis of AD is extremely important for both patient and social care, and it will become even more significant once treatments are available to reverse the progression of the disease.

In recent years, a lot of hand-crafted based machine learning techniques have been developed for the accurate early diagnosis of AD [2]–[6]. These methods extract user defined discriminate features from the brain imaging data for the classification of AD. The study from [7] shows that the machine learning based techniques can predict AD much better than radiologists. However, it is always difficult to define features that completely discriminate each class without domain experience. Of late deep learning based techniques have been popularly used for the classification of AD [8]–[12]. Most of the existing deep learning techniques extract the hidden features from measurements of region of interests (ROIs) of multiple brain imaging data for the classification of AD. For instance, Shi et al. [9] exploit the volumes of grey matter tissue as a feature from 93 ROIs of MRI brain imaging data and the average intensities of the same ROIs from the PET imaging data. They next train a two-stage deep polynomial networks to fuse and learn feature representation from MRI and PET neuroimaging data for AD diagnosis. However, the ROI-based methods cannot leverage the complete spatial information. Although these methods significantly reduce the dimension of the features, they may ignore some minute abnormal changes [13]. The deep convolutional neural networks (CNNs) can alleviate this problem, but due to high computational cost, most of the existing methods rely on single 2D CNN and even do not consider the inter-slice features into account for the classification of AD using 3D MRI data which is often represented as a sequence of 2D slices in general.

In this paper, we propose a computationally efficient classification algorithm to discriminate the patients having AD, mild cognitive impairment (MCI), and cognitively normal (CN) using an ensemble of hybrid deep learning architectures to leverage the complete spatial information from 3D MRI

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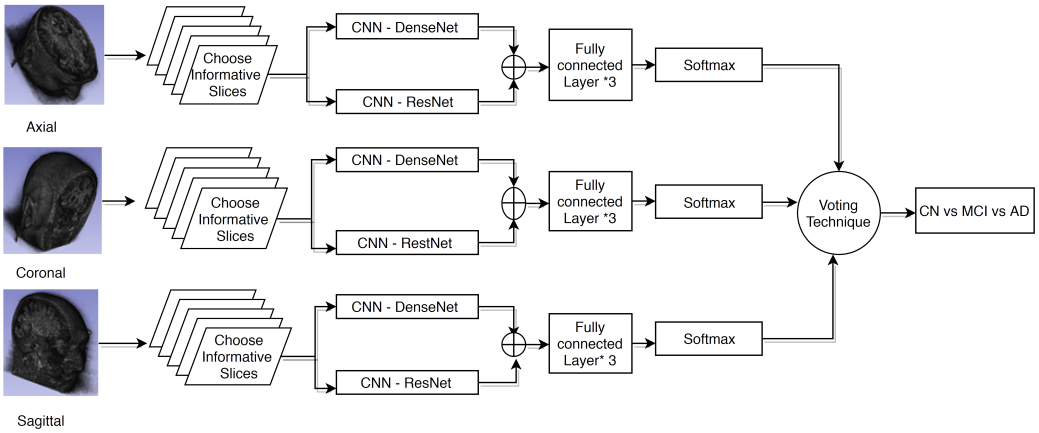

Fig. 1. Block diagram of the proposed classification framework for multiclass diagnosis of AD. The bottleneck features extracted from the two CNN architectures on each pipeline are concatenated and fed to three successive fully connected (dense) layers followed by a softmax classifier. A voting technique is used to determine the final output.

brain imaging data. First, each hybrid deep CNN architecture makes a decision from all the three physical planes, namely axial, coronal, and sagittal planes of MRI data. A voting technique is then used to predict the final output label. The idea behind the proposed method is to initialize a base CNN that is coarsely optimized with pre-trained ImageNet weights. Then, a small fully-connected model is finely tuned using the bottleneck features extracted from the baseline CNN. ResNet [14] and DenseNet [15] are the two state-of-the art CNN architectures which strengthen feature propagation and resolve vanishing gradient problem. In view of this, our classification framework uses ResNet and DenseNet architectures to extract more correlated and diversified features, respectively.

The paper is organized as follows. Section II describes the proposed methodology for the classification of AD diagnosis. Section III presents the experimental results on the Open Access Series of Imaging Studies (OASIS) database, followed by some concluding remarks in Section IV.

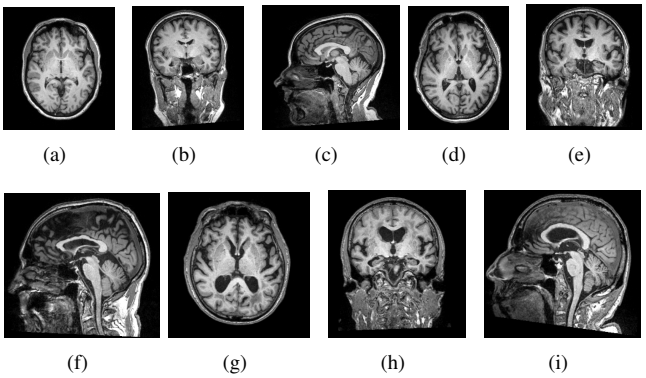

Fig. 2. Sample images from the OASIS dataset (a), (b), (c) are the images of a CN patient in axial, coronal, and sagittal planes, respectively. (d), (e), (f) are the images of a MCI patient in axial, coronal, and sagittal planes, respectively. (g),(h).(i) are the images of a AD patient in axial, coronal, and sagittal planes, respectively.

II. Proposed Methodology

The pipeline of the proposed deep learning based classification framework to distinguish the patients having Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitively normal (CN) clinical status using MRI neuroimaging data is shown in Fig.1.

A. Data

The structural MRI data used in this work is obtained from the Open Access Series of Imaging Studies (OASIS) database (http://www.oasisbrains.org) [16]. It has three different projects, namely OASIS-1, OASIS-2, and OASIS-3 with both cross-sectional and longitudinal types of neuroimaging data. Among these, OASIS-3 is the latest version and it contains 2,168 longitudinal MR sessions which include T1w, T2w, FLAIR, ASL, SWI, time of flight, resting-state BOLD, and DTI sequences. Fig.2 shows the sample MR images of cognitively normal (CN), mild cognitive impairment (MCI), and Alzheimer's disease (AD) patients in three different planes.

B. Choosing the Most Informative Slices

In practice, training a deep convolutional neural network (CNN) model from scratch consumes more time and requires a lot of labeled training data which may be difficult to achieve in the medical domain. Instead, fine tuning provides an option to use a small number of training data. However, to generalize a model for unseen data it is important to choose the most informative training slices from the available data. To leverage the whole spatial information, we consider input data from all the three physical planes of MRI data and train it on different pipeline and predict the output by fusing classifiers. In common, most of the existing techniques select training data in a random manner. As reported in [17], in this work, we select 100 slices from each of these 3D MRI data based on

the value of the entropy which is a measure used to provide average information in an image.

C. Deep CNN Architectures

In general, a deep CNN architecture consists of an input layer, a number of hidden layers followed by an output layer. The most important layers in the hidden layers are convolutional layers that transform an input into higher levels of feature representation. To extract the complementary features, in this work, we employ ResNet (ResNet50) [14] and DenseNet (DenseNet-201) [15] deep CNN architectures. Let $H_L(.)$ be the the mapping function of several stacked layers such as convolution, relu, pooling and batch normalization for a layer L. Then, the output of a residual unit can be defined as:

$$x_L = H_L(x_{(L-1)}) + x_{(L-1)} \tag{1}$$

where $x_{(L-1)}$ and x_L are the input and output of layer L. It is to be noted that the skip connection simply perform identity mapping. i.e., the input is getting added to the output of the stacked layer [14]. DenseNet is the another CNN architecture in which features from each layer is getting concatenated with all the feature maps from preceding layers. It is defined as:

$$x_L = H_L([x_0, x_1, x_2, x_3.....x_{(L-1)}]) \tag{2}$$

where $[x_0, x_1, x_2, x_3.....x_{(L-1)}]$ is the concatenation of feature maps from the previous layers. It has less number of training parameters than the ResNet architecture. The above two architectures avoid data vanishing problem by having good feature propagation along the network.

In our proposed method, we initialize both DenseNet and ResNet with pretrained weights using natural images from ImageNet [18]. Then, we run each model on our training and validation images once to extract the bottleneck features. Then, we concatenate the bottleneck features obtained from these two architectures and feed to three hidden layers with 256, 128, and 64 neurons, respectively. The last layer is the dense layer with three units with softmax activation function to predict the patients having Alzheimer's disease (AD), mild cognitive impairment (MCI), cognitively normal (CN) clinical status.

D. Ensemble Classifiers for Final Decision

To predict the most appropriate label for a subject, we have to combine the results from all the different pipelines specifically the models created using three planes of the 3D MRI data. We ensemble the output classification label of the each model using a voting technique [19]. Each classifier votes for a specific class, and the class with majority votes is assigned as a class label for the input data. However, if there is a tie in the voting, the class label that maximizes the sum of the predicted probabilities are assigned.

III. Experimental Results

The performance of the proposed algorithm is assessed on the longitudinal neuroimaging data available in the Open Access Series of Imaging Studies-3 (OASIS-3) project. We categorize the subjects based on the value of clinical dementia rating (CDR). The CDR value of 0 is considered as cognitively normal (CN), 0.5 is considered as mild cognitive impairment (MCI), and the value greater than 0.5 is considered as Alzheimer's disease (AD) clinical status. We choose 120 MRI data from each clinical status, where each MRI data is of size 176 $\times$ 256$\times$ 256.

First, we convert 3D MRI data into axial, coronal, and sagittal 2D slices and select the most informative 100 slices as described in Section II(B), which resulted in 12,000 images along each direction. Ten-fold cross validation technique is used on each pipeline to assess the stability of the model. The images are divided into ten subsets of nearly equal size in each fold with 80% - 20% split between training and validation. The deep network is implemented using keras library [20] with tensorflow [21] backend. The entire network is trained on NVIDIA GeForce RTX 2070 GPU with dedicated 6GB memory and the whole model takes approximately 20 minutes.

TABLE I
AVERAGE ACCURACY (%) FROM 10-FOLD CROSS VALIDATION FOR VARIOUS BATCH SIZES AND DENSENETS WITH RESNET50.

Batch Size \ Model	DenseNet121	DenseNet169	DenseNet201
32	88.32	92.23	**95.23**
16	76.94	78.45	80.46
8	75.64	77.56	78.77

TABLE II
COMPARISION WITH THE STATE-OF-THE-ART METHODS IN TERMS OF ACCURACY (%) .

Methods	Modalities	Accuracy
Liu et al [10]	MRI+PET	53.79
Altaf et al [2]	MRI+Clinical features	78.8
Islam et al [8]	MRI	93.18
Proposed	MRI	**95.23**

Fig. 3. Performance curve on training and validation Datasets from one of the 10-fold validation techniques.

We experiment DenseNet architectures with different variants, namely DenseNet121, Densenet169, and DenseNet201 in combination with ResNet50. The numbers in each variant correspond to the depth of the model. We also experiment for various batch sizes 8, 16, and 32 for 100 epochs. i.e., the number of training samples used for the training before updating the network parameters. The stochastic gradient descent method with a learning rate of $1e^{-3}$ and momentum value 0.9 is used for optimization. Table I shows the average accuracy results obtained from 10-fold cross validation technique for different batch sizes along with DenseNet variants. It is observed from the Table I that the average accuracy obtained using Densenet201 with batch size 32 provides better accuracy than other variants. Also, it is noticed that deeper the layers better the classification accuracy. We also compare our proposed algorithm in terms of accuracy with some of the recent multiclass diagnosis frameworks based on machine learning approaches and the results are shown in Table II. It is observed that the accuracy obtained by the proposed method is superior to that of the conventional methods. Fig.3 shows the performance curves, model accuracy and loss curves, on both training and validation datasets from one of the ten validation techniques using DenseNet201 in combination with ResNet50 CNN for the batch size of 32. We also run our model for 500 epochs and found that proposed model converges approximately after 100 epochs on each validation. We have also noticed that validation loss is higher than the training loss to only a very small extent. i.e., the gap between the curves, which shows that our proposed model generalizes well on unseen data. We have also observed that the loss of the training data is slightly higher than the validation data for the first few epochs. We believe that this is because of the dropout layers used in the fine tuning model, which apply only on the training phase and not on the validation phase.

IV. Conclusion

In this paper, we have proposed a multiclass diagnosis framework based on an ensemble of hybrid deep convolutional neural networks (CNNs) using the most informative images from the three planes of 3D MRI data to identify patients having Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitively normal (CN) clinical status. We employ three different pipelines that learn features from different views of the MRI data and leverage a more complete spatial information. The experimental results obtained by applying a combination of voting from these hybrid CNN pipelines on the OASIS neuroimaging dataset, using the ten-fold cross validation technique, yield a performance superior to that provided by some of the state-of-the art methods. Deeper the CNN architectures, higher is the accuracy. As the proposed method uses pretrained weights instead of full training with random initialization and selects the most informative training data, it is also computationally more efficient. In future, we plan to test the proposed method on different datasets.

References

[1] "2019 Alzheimer's disease facts and figures," *Alzheimer's & Dementia*, vol. 15, no. 3, pp. 321 – 387, 2019.

[2] T. Altaf, S. M. Anwar, N. Gul, M. N. Majeed, and M. Majid, "Multi-class Alzheimer's disease classification using image and clinical features," *Biomedical Signal Processing and Control*, vol. 43, pp. 64 – 74, 2018.

[3] J. Liu, J. Wang, B. Hu, F. Wu, and Y. Pan, "Alzheimer's disease classification based on individual hierarchical networks constructed with 3-D texture features," *IEEE Transactions on NanoBioscience*, vol. 16, no. 6, pp. 428–437, Sep. 2017.

[4] T. Tong, K. Gray, Q. Gao, L. Chen, and D. Rueckert, "Multi-modal classification of Alzheimer's disease using nonlinear graph fusion," *Pattern Recognition*, vol. 63, pp. 171 – 181, 2017.

[5] J. Zhang, M. Liu, , Y. Gao, and D. Shen, "Alzheimer's disease diagnosis using landmark-based features from longitudinal structural MR images," *IEEE Journal of Biomedical and Health Informatics*, vol. 21, no. 6, pp. 1607–1616, Nov 2017.

[6] J. Zhang, Y. Gao, Y. Gao, B. C. Munsell, and D. Shen, "Detecting anatomical landmarks for fast Alzheimer's disease diagnosis," *IEEE Transactions on Medical Imaging*, vol. 35, no. 12, pp. 2524–2533, Dec 2016.

[7] S. Klöppel, C. M. Stonnington, J. Barnes, F. Chen, C. Chu, C. D. Good, I. Mader, L. A. Mitchell, A. C. Patel, C. C. Roberts *et al.*, "Accuracy of dementia diagnosis—a direct comparison between radiologists and a computerized method," *Brain*, vol. 131, no. 11, pp. 2969–2974, 2008.

[8] J. Islam and Y. Zhang, "An ensemble of deep convolutional neural networks for Alzheimer's disease detection and classification," *arXiv preprint arXiv:1712.01675*, 2017.

[9] J. Shi, X. Zheng, Y. Li, Q. Zhang, and S. Ying, "Multimodal neuroimaging feature learning with multimodal stacked deep polynomial networks for diagnosis of Alzheimer's disease," *IEEE Journal of Biomedical and Health Informatics*, vol. 22, no. 1, pp. 173–183, Jan 2018.

[10] S. Liu, S. Liu, W. Cai, H. Che, S. Pujol, R. Kikinis, D. Feng, and M. J. F. and, "Multimodal neuroimaging feature learning for multiclass diagnosis of Alzheimer's disease," *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 4, pp. 1132–1140, April 2015.

[11] C. Lian, M. Liu, J. Zhang, and D. Shen, "Hierarchical fully convolutional network for joint atrophy localization and Alzheimer's disease diagnosis using structural MRI," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 2018.

[12] K. Bäckström, M. Nazari, I. Y.-H. Gu, and A. S. Jakola, "An efficient 3d deep convolutional network for Alzheimer's disease diagnosis using MR images," in *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*. IEEE, 2018, pp. 149–153.

[13] M. Liu, D. Cheng, and W. Yan, "Classification of alzheimer's disease by combination of convolutional and recurrent neural networks using FDG-PET images," *Frontiers in neuroinformatics*, vol. 12, p. 35, 2018.

[14] K. He, X. Zhang, S. Ren, and J. Sun, "Deep residual learning for image recognition," in *Proceedings of the IEEE conference on computer vision and pattern recognition*, 2016, pp. 770–778.

[15] G. Huang, Z. Liu, L. Van Der Maaten, and K. Q. Weinberger, "Densely connected convolutional networks," in *Proceedings of the IEEE conference on computer vision and pattern recognition*, 2017, pp. 4700–4708.

[16] D. S. Marcus, A. F. Fotenos, J. G. Csernansky, J. C. Morris, and R. L. Buckner, "Open access series of imaging studies: longitudinal MRI data in nondemented and demented older adults," *Journal of cognitive neuroscience*, vol. 22, no. 12, pp. 2677–2684, 2010.

[17] M. Hon and N. M. Khan, "Towards Alzheimer's disease classification through transfer learning," in *2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. IEEE, 2017, pp. 1166–1169.

[18] O. Russakovsky, J. Deng, H. Su, J. Krause, S. Satheesh, S. Ma, Z. Huang, A. Karpathy, A. Khosla, M. Bernstein *et al.*, "Imagenet large scale visual recognition challenge," *International journal of computer vision*, vol. 115, no. 3, pp. 211–252, 2015.

[19] L. Lam and S. Suen, "Application of majority voting to pattern recognition: an analysis of its behavior and performance," *IEEE Transactions on Systems, Man, and Cybernetics-Part A: Systems and Humans*, vol. 27, no. 5, pp. 553–568, 1997.

[20] F. Chollet *et al.*, "Keras," https://keras.io, 2015.

[21] M. Abadi *et al.*, "TensorFlow: Large-scale machine learning on heterogeneous systems," 2015, software available from tensorflow.org. [Online]. Available: http://tensorflow.org/