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SCIENTIFIC PAPER

Multi-class diagnosis of Alzheimer's disease using cascaded three dimensional-convolutional neural network

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Abstract

Dementia is a social problem in the aging society of advanced countries. Presently, 46.8 million people affected with dementia worldwide, and it may increase to 130 million by 2050. Alzheimer's disease (AD) is the most common form of dementia. The cost of care for AD patients in 2015 was 818 billion US dollars and is expected to increase intensely due to the increasing number of patients due to the aging society. It isn't easy to cure AD, but early detection is crucial. This paper proposes a multi-class classification of AD, mild cognitive impairment (MCI), and normal control (NC) subjects using three dimensional-convolutional neural network with Support Vector Machine classifier. A cross-sectional study on structural MRI data of 465 subjects, including 132 AD patients, 181 MCI, and 152 NC, is performed in this paper. The highly complex and spatial atrophy patterns of the brain related to Alzheimer's Disease and MCI are extracted from structural MRI images using cascaded layers of the three dimensional convolutional neural network. The hectic process of segmentation and further extraction of handcrafted features is eliminated. The complete image is considered for the processing, thus incorporating every region of the brain for the classification. The features extracted using four cascaded layers of three dimensional-convolutional neural network are fed into the Support Vector Machine classifier. The proposed method achieved 97.77% accuracy which outperforms state of the art, and this algorithm is a promising indicator for the diagnosis of AD.

Keywords Three dimensional-convolutional neural network · Alzheimer's disease · Mild cognitive impairment · Structural MRI

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Introduction

Alzheimer's is a progressive neurodegenerative disease commonly affecting people at their old ages. It leads to memory impairment and cognitive decline. The condition of the patient will chronically and progressively deteriorate over a long period. Alzheimer's disease (AD) will be a worldwide burden over the coming decades due to people's increased life expectancy. In 2006, around 26.6 million Alzheimer's cases were reported globally, out of which 56 are at the early onset stage. In 2050, the population of the Alzheimer's is anticipated to develop fourfold to 106.8 million [1]. AD progression can be divided into three stages: Preclinical stage, a change in the brain, which begins 20 or more years before AD diagnosis, followed by mild cognitive impairment (MCI) stage, starts reflecting memory impairment and change in cognitive function and last stage a fully established AD patient with total memory loss, reserved cognition and impaired daily activities. The recognition at the MCI stage

is crucial to delay further progression towards AD and take necessary therapeutic measures at the early stage.

To understand the underlying pathology and to find the critical biomarkers for detection and forecast of AD/MCI, various types of neuroimaging modalities have been analyzed, such as magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI), etc. [2, 3]. Structural MRI (SMRI) gives visual data about the brain atrophic regions due to the tissue level changes underlying AD/MCI. PET gives the measure of the cerebral glucose metabolism [4], which reflects the functional brain activity. Cerebro Spinal fluid (CSF) indicates the amount of amyloid beta-protein and amyloid tau tangles deposited in the fluid, an early indicator of AD. SMRI has already proven to be sensitive to pre-symptomatic disease and is a potential biomarker for the disease. In routine clinical practice, MRI seems to be the most sensitive imaging test of the brain [5]. It gives data around the morphology of the gray matter, white matter, and CSF. The atrophic brain regions can be non-invasively captured using structural MRI and help us get the anatomical changes in the brain. Hence, they are identified as a promising indicator of disease progression and are broadly studied with machine learning methods for disease diagnosis [6].

Past investigation frequently centers on a subset of binary classification issues: MCI converter (MCIc) vs. MCI non-converter (MCInc), normal control (CN) vs. AD, or MCI vs. CN [7]. Multi-class classification of Alzheimer's enables one to use the same algorithm to identify the two classes of disease simultaneously, which is not possible with a binary classification algorithm. This contributes to determining the severity of the disease and, hence, helps identify the disease at an earlier stage, i.e., at the MCI stage. Training the architecture with both AD and MCI data improves the performance of discriminating non-diseased from diseased ones. The aforementioned limitations of binary classification in determining the severity conditions and early diagnosis bring forth the significance of multi-class dementia (AD-MCI-CN) classification, which still ought to be examined and made strides to understand the underlying complexity of pathology of AD progression. This work proposes a multi-class AD classification using Support Vector Machine (SVM) classifier with the help of features extracted using three dimensional-convolutional neural network (3D-CNN) layers. The novelty comes in using the SVM layer for the classification rather than using a softmax; we found that features extracted from 3D-CNN if further trained in an SVM classifier would give an outstanding result be a benchmark for Alzheimer's diagnosis and prognosis. Also, the use of 3D-CNN enables the extraction of nonlinear atrophy patterns directly from the MRI image without any segmentation and handcrafted feature extraction process. Our method also assures us to consider the whole image and not leave out any brain regions that may be affected due to dementia.

In recent years, deep learning-based classification and feature extraction from images is increasing due to its high performance. Due to the availability of limited datasets and high dimensional data, it is challenging to get a high result in the case of biomedical images. In this light, we propose an architecture using 3D-CNN to extract the complex and spatial hidden atrophy region of the brain from the whole image without leaving out any regions and classifying to high accuracy with the SVM classifier. We have used a patch-based method that enables the algorithm to concentrate on each part of the brain and extract discriminative subtle local features related to atrophy regions [8]. Whereas the voxel-based method requires more computation overhead due to the whole image analysis and Region of Interest (ROI) based method requires the help of medical experts to select the required features from images [9]. Multi-class AD classification (AD, cMCI, ncMCI, NC) using multilayered stacked autoencoder achieved an accuracy of 47.2% is proposed in [10]. They had used features from 83 regions of interest segmented from MRI and PET images to train and test the architecture. The accuracy for multi-class is very less and also used the conventional method for feature extraction, which requires domain expertise, and it is hectic. In [1], authors used zero maskings with multilayered stacked autoencoders to learn multi-modal features from MRI and PET images and further classify them to AD, cMCI, ncMCI, NC. They achieved an accuracy of 53.7% and a moderate increase in the accuracy but still extracted the features using segmentation, thus leaving the features from other parts of the image.

In [7], a three-way classification of AD-MCI-NC is done using texture features of segmented hippocampus and features from other ROI of the segmented parts of the MRI image. They created two multilayered stacked autoencoders models and achieved an accuracy of 56.6% and 58% for two respective models. The accuracy remains less and needs the domain expertise to segment and extract features from images [11]. The 3D-CNN method is used to extract features and classify MRI images into AD-MCI-NC in [12]. Here the segmentation of the different ROI is eliminated, and the whole image is considered, and features are directly extracted from the image. They achieved an accuracy of 89.4% without any cross-validations for test data. They over resized the image into $68 \times 95 \times 79$, which will take away important regions and features relevant to atrophy, and there is a possibility for lot of misclassification. In [12, 13], authors used 3D-CNN layers trained with 3D autoencoders to classify into AD-MCI-NC and able to attain 89.1% accuracy. It was a good architecture but required heavy computation resources for training the whole image of size

$200 \times 150 \times 50$, which is much costlier and not accessible by everyone.

In [14], many machine learning and artificial neural network (ANN) techniques were used to perform three-class classification and achieve maximum accuracy of 77.1%. They used manually extracted 46 regional cortical volume features, 35 cortical thickness features, three hippocampal volume features, and two demographic measurements total of 81 features. SVM classifier produced only 58.4% accuracy. Nonlinear graph fusion (NGF) method is used in [15] to classify three class and binary classification of Alzheimer's diseases using complementary information from multiple modalities MRI, PET, and CSF. Such methods do not require any parameter tuning. They extracted around 2,39,304 features from MRI, PET, and CSF by defining 83 ROI. The accuracy of the three-way classification is 56.6%, which is very less. In [16], the authors designed a Centred Kernel Alignment (CKA) for initializing the ANN for improved diagnosis of AD. For evaluating the performance of their method, they extracted 324 features from MRI data using freesurfer software and given to an ANN with CKA based initialized parameters to get an accuracy of 70.3%. The complexity of the architecture is very less, but the performance was less, which cannot be used for diagnosis or prognosis. A 3D-CNN based 39-layer architecture inspired by ResNet is proposed in [17] to extract features and classify into AD, MCI, and CN. Similarly, [18] used a 3D VGG based network to classify AD, MCI, and NC. For these deep networks, architecture complexity is more, the number of parameters is very high and requires more resources for computation, and hyperparameter tuning is difficult.

Methods

As discussed earlier, MRI is a powerful imaging modality that helps physicians to diagnose the disease. Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)[1]database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

[1] Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

A total of 465 subjects' details were downloaded, among which 152 NC, 181 MCI, and 132 AD were also chosen for the dataset. The following preprocessing steps are carried out using freesurfer software: Motion correction, Non-Uniform Intensity Normalization, Tailairach Transformation, Intensity Normalization, and Skull Stripping. Figure 1 shows coronal slices of the original image (Top) and preprocessed images (bottom) of AD, NC, and MCI, respectively. All MRI images were resampled to measure $256 \times 256 \times 256$ and downsampled to $128 \times 128 \times 128$ voxels. Further image analysis is done to remove voxels outside the MRI images, and finally, $100 \times 81 \times 80$ voxel size image is used. The full brain picture is partitioned into $3 \times 3 \times 3$ parts to extricate twenty-seven $50 \times 41 \times 40$ voxel size patches. A patch is extracted in such a way that each half overlaps with its neighbor in every direction. The 27 MRI patches extracted from a single image are fed individually into the different stack of four 3D-CNN layers to extract the spatial atrophy and complex features of the brain affected area. Then, all the features are concatenated at the fusion layer. The concatenated features are then given to SVM classifier for classifying into AD, MCI, and NC.

Feature extraction using 3D-CNN

Conventional image processing using handcrafted features such as hippocampus volume, cortical thickness, surface areas, etc. requires segmentation processes and algorithms for feature selection, which requires human expertise. Also, there is a loss of some valuable features that affect the incorrect and early diagnosis of AD. Deep CNN can be used to learn the generic features directly from the images [19]. At present, CNN is widely used in many image processing applications, such as object detection and classification. The main advantage of CNN is that it can learn the various type of features directly from the image with minor preprocessing without any human intervention. Mostly two dimensional-convolutional neural networks (2D-CNN) are used for various applications. In our case, 2D-CNN will not be able to extract rich spatial 3D information from MRI images, so we have employed a 3D convolutional kernel for feature extraction. Deep 3D-CNN [14] is built by cascading multiple 3D Convolutional Layer (CL) and subsampling layers alternatively to extract features hierarchically. A convolutional layer performs convolution between the input image and a learned filter and then adds a bias term and finally applies a nonlinear activation layer to give feature maps from the filters. The 3D convolutional operation is given below

$$u_{pq}^{n}(x,y,z) = \sum_{\delta x}\sum_{\delta y}\sum_{\delta z} G_{p}^{n-1}(x+\delta x, y+\delta y, z + \delta z) \times W_{pq}^{n}(\delta x, \delta y, \delta z) \quad (1)$$

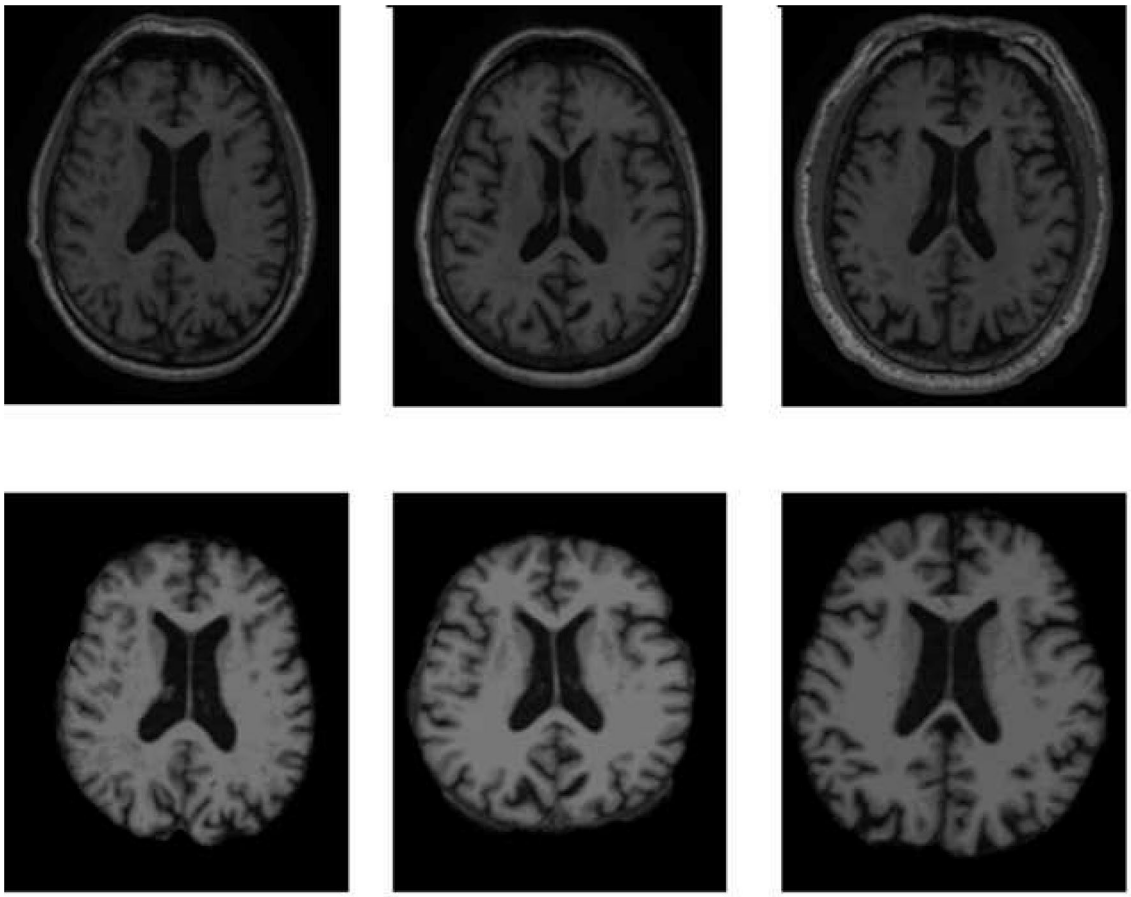

Fig. 1 Coronal slices of original image (Top) and pre-processed images (bottom) of AD, NC and MC

x, y and z represent the position of pixels in a 3D image. $W^n_{pq}(\delta x, \delta y, \delta z)$ indicates kernel weights connecting p^{th} feature and q^{th} feature map of the $n-1$ layer and n^{th} layer respectively, G^{n-1}_p indicates the p^{th} feature map of the preceding $n-1$ layer, and $\delta x, \delta y, \delta z$ are the kernel sizes corresponding to the x, y, z coordinates. $u^n_{pq}(x, y, z)$ is the output of 3D kernel filter. After convolution, *Tanh* is used as the activation function:

$$G^n_q(x, y, z) = tanh(b^n_q + \sum\nolimits_p u^n_{pq}(x, y, z)) \quad (2)$$

where b^n_q is the bias term for the qth feature map of the n layer.

The response maps from different convolution kernels are summed up to obtain the qth 3D feature map of n layer, $G^n_q(x, y, z)$. Spatial correlations captured using 3D-CNN helps to understand the complete volumetric contextual information [20]. The pooling layer is added after each convolutional layer. There are different kinds of pooling layers, such as max pool, average pool, etc. We have used max-pooling to compute the maximum value of the selected cube. This helps to take the most important features and make it more compact while moving from lower layers to higher layers [21]. Also able to achieve robustness in some variations. The third is a fully connected layer where high-level reasoning is done. The output from the stacked convolution layers and max-pooling layers are made into a one-dimensional vector and feed into a fully connected layer. Finally, the softmax layer is attached to the fully connected layer and trained using a cross-entropy loss function.

The complete architecture of the proposed method is shown in Fig. 2 in which the full brain MRI image is divided into numerous neighborhood patches with some overlap and fed to deep 3D-CNN to extract and learn features. The patch-based method enables the algorithm to give more attention to each part of the brain and thereby able to extract subtle local patterns of the atrophy regions [22]. The whole brain is not completely fed into 3D-CNN since it requires a large number of training parameters and will lead to over-fitting due to a lack of large datasets. Thus it increases the overhead of computation and memory. The final classification is done by ensembling all the 3D-CNN trained features of local patches.

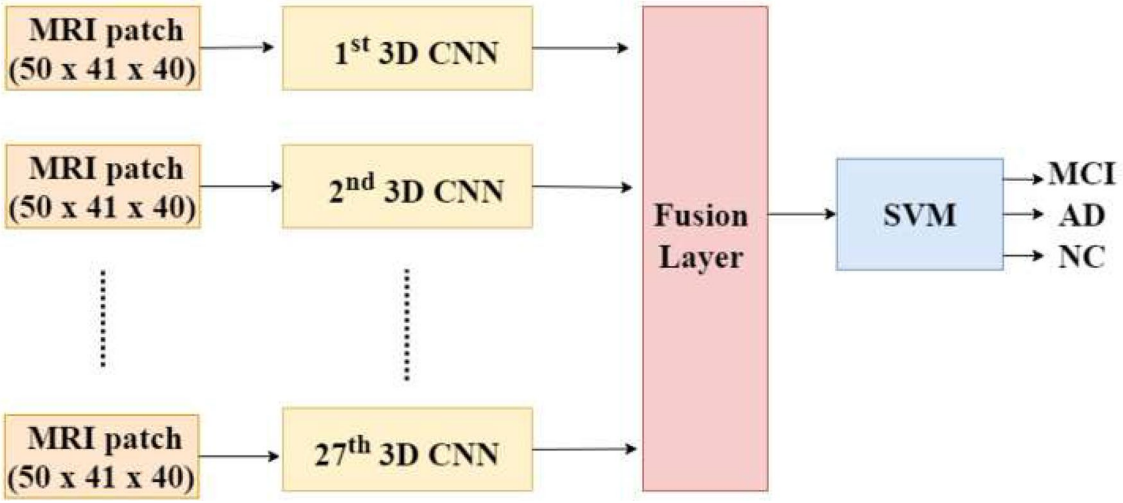

Fig. 2 Proposed architecture for 3 way classification

In this work, we have actualized each deep CNN shown in Fig. 3 by piling up with four convolutional layers, three max-pooling layers, a dense layer, and a softmax layer. The filters used were $3 \times 3 \times 3$ sizes, and the number of filters selected for four convolution layers was 15, 25, 50, 50, respectively. Max pooling is performed on the $2 \times 2 \times 2$ window region. Tanh function is used as the non-linear activation. The weights are randomly initialized with Gaussian distribution using Xavier initialization that helps in proper convergence of algorithm [23]. The parameters are trained using a backpropagation algorithm taking cross-entropy as the loss function. In addition to this, the dropout strategy is included to avoid over-fitting. Hyperparameters were tuned using a vast grid search method. The best parameters were chosen after performing 10-fold cross-validation. After learning the features using 3D-CNN, the feature vectors are extracted from the dense layer, and 27 feature vectors are concatenated to give an overall feature vector. This feature vector is fed to the input of a multi-class SVM classifier to get the required classification of AD, MCI, and NC. Final classification was performed using the SVM classifier instead of a softmax because from an empirical study; we came to know that the softmax gives less efficient output for three or more levels of classification with a limited dataset. So we decided to choose an SVM classifier [24–26] with Radial Basis Function (RBF) kernel and found good classification performance with acquired features of 3D-CNN, and it is due to the kernel trick that converts the existing feature into a linearly separable one for the three classes at higher dimensions.

Results

We have used a total of 900 images, out of which 300 AD, 300 NC, and 300 MCI. Data augmentation methods were used to increase the number of datasets from 465 to 900 images to avoid over-fitting the network. The algorithm is implemented in the Keras framework in python using TensorFlow. The experiment is conducted using a PC with Nvidia GeForce, RTX2080 11 GB GPU. The 27 local 3D-CNN is trained independently to capture local patterns. Adam optimizer is used to train the local 3D-CNN. Dropout, L_1, L_2 regularizers are used to avoid over-fitting. The total learnable parameters of the proposed network are around three million, which is less compared to other standard architectures, so require lesser time and fewer resources for processing. We validate the performance of our developed method using Accuracy.

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

Our result for test data with 30 AD, 30 NC, and 30 MCI came out to be 97.77%. This accuracy is achieved using an RBF kernel with a gamma value of 0.02 and c = 1. Grid search method was used to tune the two hyperparameters i.e., gamma value and c value. One of the reasons why RBF kernel gives high accuracy is because the dimension of features (810) and the number of training samples (810) are the

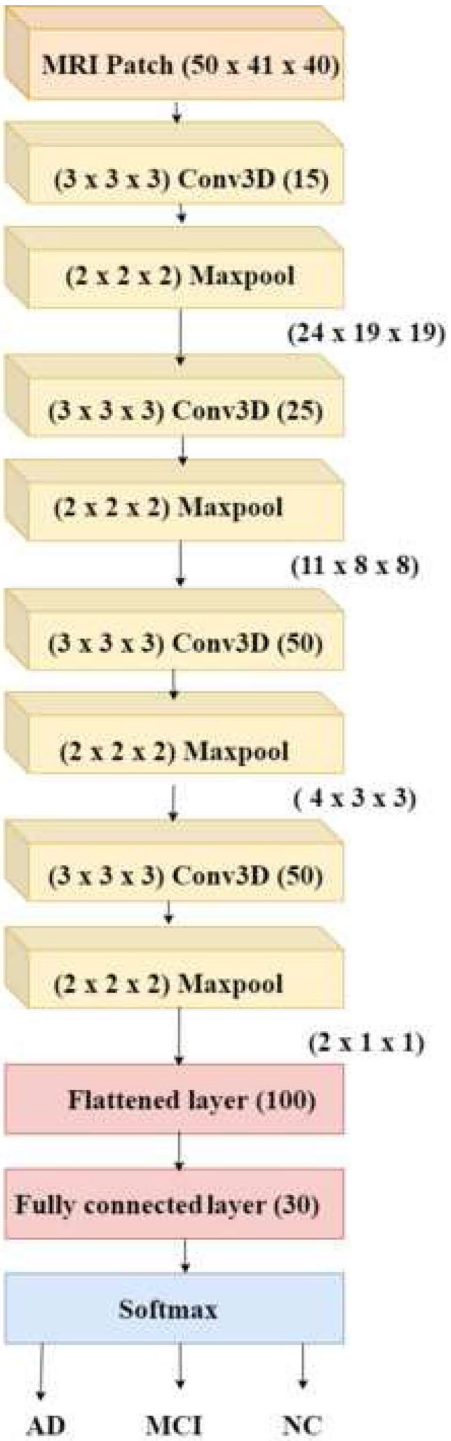

Fig. 3 3D-CNN architecture for feature extraction

same, i.e., the dimension is equal to the number of training samples. The SVM is giving more accuracy compared to a softmax classifier, because of the large margin classifying ability of the SVM from the support vectors. The kernels in SVM help in achieving this result due to the projection of data into higher dimensions and form linear separable

Table 1 Classification performance

Class label	Precision	Recall	F1-Score
AD	0.938	1	0.968
NC	1	1	1
MCI	1	0.933	0.966

Table 2 Confusion matrix of the proposed method

Predicted class	Targeted class		
	AD	NC	MCI
AD	30	0	0
NC	0	30	0
MCI	2	0	28

hyperplanes at this dimension. The confusion metrics are also computed to describe the performance of test data for 3-way classification and given in Table 1. Based on the confusion metrics, we further evaluated our method using Precision, Recall, and F1-Score, as given in Table 2. These metrics can be calculated as

$$Precision/True\ Negative\ Rate/Specificity = \frac{TP}{TP + FP}$$

$$Recall/True\ Positive\ Rate/Sensitivity = \frac{TP}{TP + FN}$$

$$F1 - Score = \frac{2 \times Precision \times Recall}{Precision + Recall}$$

Discussion

This study proposes a novel method for multi-class classification of AD, MCI, and NC subjects using 3D-CNN with SVM classifier. The highly complex and spatial atrophy patterns of the brain, related to AD and MCI are extracted from SMRI images using cascaded layers of the 3D-CNN. The hectic process of segmentation and further extraction of handcrafted features is eliminated. The complete image is considered for the processing, thus incorporating every region of the brain for the classification. The 3D-CNN automatically learns feature representation from input images and is not greatly affected by image processing. Since the performance of the CNN depends on its architecture, we have proposed a 3D-CNN architecture which can classify the three categories with a noticeable accuracy. The features extracted using four cascaded layers of 3D-CNN are fed into the SVM classifier for classification. The proposed method

Table 3 Comparison with existing works

Methods	Accuracy (%)	Image modality	Techniques used
[27]	77.1	MRI	Classification fusion
[28]	47	MRI-PET	SAE with elastic net
[15]	56.6	MRI	Non-linear graph fusion
[16]	68.8	MRI	Neural network pre-trained Using centered kernel alignment
[7] (model 1)	56.6	MRI	SAE+elastic net
[7] (model-2)	58	MRI	SAE+elastic net
[17]	87	MRI	3D-CNN with 39 layers
[12]	89.1	MRI	3D Adaptable CNN
Proposed method	97.77	MRI	3D-CNN with SVM

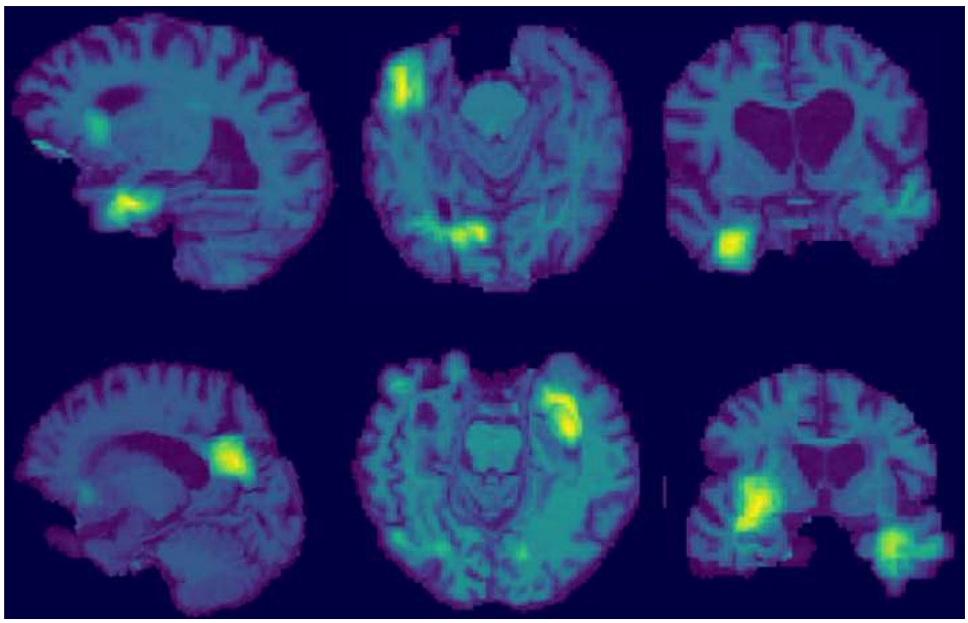

Fig. 4 Saliency map generated by the proposed 3D-CNN for AD

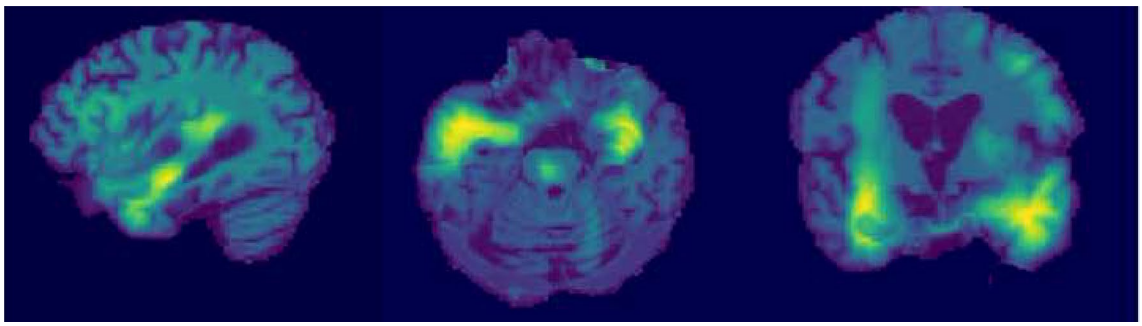

Fig. 5 Saliency map generated by the proposed 3D-CNN for MCI

achieved 97.77% accuracy, which outperforms the state-of-the-art and is shown in the comparison table of previous workflows given in Table 3.

Figures 4, 5 and 6 show the saliency map generated by CNN to differentiate among AD, MCI, and NC individuals obtained using Gradient Weighted Class Activation Mapping (Grad-CAM) [21, 29]. The sagittal, coronal, and axial view with highlighted areas signifies the brain's main affected region for AD and MCI. 3D-CNNs selected the temporal and parietal lobes for accurate classification of AD, NC, and MCI subjects. The saliency maps for AD subjects are shown in Fig. 4. The most discriminative features for the

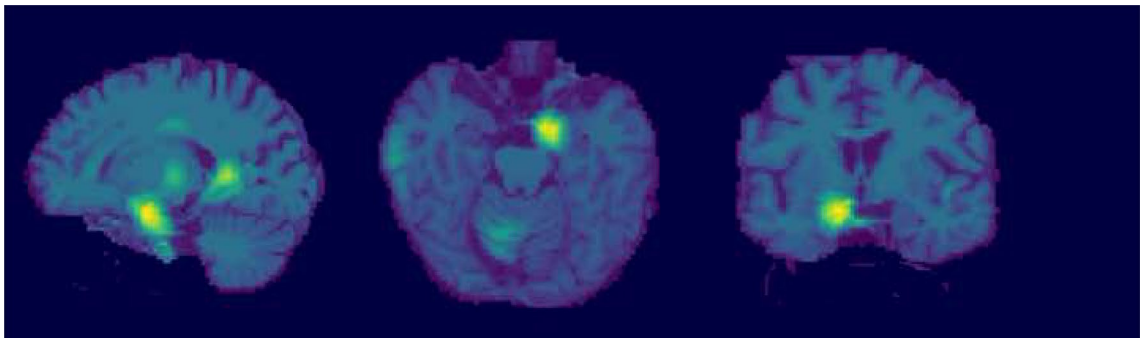

Fig. 6 Saliency map generated by the proposed 3D-CNN for Normal

AD classification task were mainly distributed around the medial temporal lobe and parietal lobe. In the medial temporal lobe, the subcortical structures such as the hippocampus, amygdala, entorhinal cortex, and parahippocampus are the most affected in AD. These brain regions have previously been closely related to dementia in many existing studies [5, 13]. The Hippocampal area is the most discriminative one shown clearly in the coronal section of the image. Hippocampal volume is known to be a biomarker of Alzheimer's disease that precedes cognitive impairment and is very much effective in the auto diagnosis of AD [11]. The coronal section also highlights the atrophy of the entorhinal cortex and parahippocampus, whereas the amygdala is highlighted in the axial section of the image. The atrophy of the parietal region shown in the parasagittal view carries positive predictive value for diagnosing AD. The saliency maps for MCI subjects are shown in Fig. 5. The lateral sagittal, axial, and coronal views of the MCI saliency map specifies the amygdala and hippocampal region as the most differentiating features for detecting MCI patients. The left amygdala is more highlighted, as seen in the axial view when compared to the AD patients, playing a vital role in detecting the early stage of AD [13]. Also, the heat map of coronal view over the lateral ventricles' temporal horn area becomes an important feature for diagnosing MCI as the enlargement of the ventricular region is a measure of Alzheimer's disease progression [5]. Atrophy of the entorhinal cortex and parahippocampus seen in the coronal section also helps in detecting MCI. The saliency maps for Normal subjects are shown in Fig. 6. The most differentiating regions are the amygdala and hippocampus area. This confirms that in the multi-class diagnosis of AD, MCI and NC, the amygdala and hippocampus play a vital role in differentiating them.

This algorithm is a promising indicator for the diagnosis of AD as well as MCI and it is due to the contribution of both the cascaded 3DCNN and SVM classifier. The cascaded structure of 3D-CNN applied to each patch (A patch is extracted in such a way that each half overlaps with its neighbor in every direction in order to prevent any information loss) of brain image will disentangle the complex and structural dependencies of atrophy regions related to disease and learn a higher level of features towards the end of the layers. This will help discriminate between AD and NC and find the important features to classify MCI patients from AD and NC, which is very challenging as only subtle changes exist. The result of the F1-score of MCI i.e., 0.966, verifies the above statement. The features obtained from 27 patches using cascaded 3D-CNN are concatenated to get the global feature of the total image.

Further, the feature is trained and classified using an SVM classifier. After doing much empirical study, it is found that softmax is not efficient in performing three or more classification with the features learned from a limited dataset. So we used the SVM classifier with RBF kernel and found good classification performance. It is due to the kernel trick that converts the existing feature into linearly separable for three classes at higher dimensions. There is more room for improvement either by increasing the number of subjects or using a multi-modal approach. In the latter, we can use PET and CSF datasets to learn complex features and use them for early diagnosis of the disease [30].

Conclusion

A 3D-CNN based architecture using an SVM classifier is built to classify different levels of AD. Multi-class classification enables the detection of the three levels of diseases from the same algorithm. It increases the chance of detecting the disease at the early stage i.e., at the MCI stage. Therefore, we can use this proposed method for the diagnosis and prognosis of the disease, which is not possible with binary level classification algorithms. Cascaded 3D-CNN design helps to learn the most desirable and discriminating generic features of the disease, which results in high performance in the classification. Also, by training the same architecture with both AD and MCI datasets, there is less misclassification into normal controls, which make sure that no diseased

person is left unidentified from the disease, which is most crucial in computer-aided diagnosis. The proposed method achieved 97.77% accuracy, which outperforms the state-of-the-art, and this algorithm is a promising indicator for the diagnosis of AD. Since we are using a CNN, the features are automatically learned from the images and able to avoid the hectic and time-consuming process of segmentation and extraction of handcrafted features. The performance levels can be further increased by including more subjects and using multi-modal data such as PET and CSF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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