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Deep feature extraction method based on ensemble of convolutional auto encoders: Application to Alzheimer's disease diagnosis

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ABSTRACT

Alzheimer's disease is one of the famous causes of death among elderly. Diagnosis of this disease in the early stage is so difficult by conventional methods. Machine learning methods are one of the best choice for improving the accuracy and performance of diagnosis procedure. The heterogeneous dimensions and structure among the data of this disease have complicated the diagnosis process. Therefore proper features are needed to solve this complexity. In this research, proposed method is introduced in two main steps. In the first step, ensemble of pre-trained auto encoder based feature extraction modules are used to generate image feature from 3D input image and in the second step convolutional neural network is used to diagnosis Alzheimer's disease. Three different classification cases, namely; Alzheimer's Disease (AD) versus Normal Condition (NC), AD versus Mild Cognitive Impairment (MCI) and MCI versus NC are studied. Obtained results show that accuracy rate for AD/NC, AD/MCI and MCI/NC are 95%, 90% and 92.5%, respectively. Also, for all cases sensitivity and specially sensitivity rates for proposed method confirm that it could be reliable for diagnosis AD in early stage and has less error to detect normal condition.

1. Introduction

Alzheimer's disease (AD) is one of the most common forms of dementia and is also one of the top six causes of death in the past decades. It can cause serious and irreversible damage to the brain by destroying neurons and destroying memory. It usually occurs more seriously in the elderly over the age of 60 and overwhelms cognitive abilities, memory and speech abilities and etcetera and eventually disrupts their normal lives. Progress in medical sciences and increase in life expectancy result in increase of the aging population of the human community. In other hand, this disease imposes a lot of costs on patients' family, Governments and Healthcare system of the country. Therefore, early diagnosis of Alzheimer plays an important role in human healthcare and prevent increasing life expectancy. Machine learning based techniques help scientists to increase the accuracy of treatment by developing Computer Aided Diagnosis (CAD) systems which are working by medical images. Some biomarkers are usually used to develop Computer Aided Alzheimer's disease Diagnosis (CAADD) system, identification and classification of Alzheimer's disease such as cognitive tests, clinical information, Electroencephalography (EEG) signal and imaging test of brain. One of the most important and useful biomarkers is imaging test that according to the source and provider information could be divided into two major groups which are structural and functional images.

1.1. Functional images

These kinds of images show brain's function such as the amount of oxygen in the blood, the amount of chemical activity of the various parts of the brain and the accumulation of amyloid platelets. Functional magnetic resonance imaging (FMRI) and brain positron emission tomography (PET) scans are famous functional imaging tests.

1.2. Structural images

These kinds of images provide some structural information of brain such as shape, volume and size of different parts of brain which are widely affected by Alzheimer's disease. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are so well-known methods for such imaging test.

Since MRI is non-invasive and less likely to produce an allergic reaction, it is the best choice for brain imaging evaluation. However, there are some challenges that make working with MR images hard for

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developing CAD and specially CAAAD systems. Some challenges are as follow:

1. The first and most serious issue is the volume of data and dimensions of brain images. Usually, images taken from patients are 3D in very high volumes of data that make processing difficult. To solve this problem, it is possible to use 2D images, which will reduce the efficiency of the methods.
2. The next problem is usually the extra information that is captured during imaging. For example, in raw MR images, skull, neck, nose and facial components are also recorded alongside the brain, which separating these parts with great accuracy is one of the challenges of working with this kind of images.
3. Since data images are usually collected over time and with different patients in different locations, some settings are different in capturing images. It could be third challenge. For example, the position of the head or the Center of Gravity (COG) of the images varies with each other, which results in the inefficiency of the processing methods.

In order to overcome over mentioned challenges, machine learning techniques are widely used in the CAD systems and especially CAADD systems [1]. They are used in many applications related to AD, such as: classification of people with AD and healthy ones, classification of AD and other dementia diseases, hippocampus segmentation, different brain texture segmentation, segmentation of the region affected by the tumor and etcetera. According to these applications, machine learning techniques are divided into unsupervised and supervised learning methods.

1.3. Unsupervised learning methods in CAADD

Segmentation is one of the famous approaches in unsupervised learning which is successfully utilized in medical imaging issues as well as the detection and detection of AD including hippocampal segmentation, the classification of all types of brain tissue, and clustering the entire brain. Clustering methods are the best option when labels of data are not available. Data labeling requires too much time and money. For example, K-means applied to separate patients into pathological and non-pathological groups [2]. Or it is used to classify people into healthy and AD by using EEG [3]. In other application, novel strategy introduced for selecting initial clusters' center of K-means based on movements of filter average to segment MRI of brain [4]. Another unsupervised method is Fuzzy C-means (FCM) which is working based on Fuzzy logic to assign membership values for clusters. It is used to segment texture of brain in MRI [5] and also used to cluster texture of brain into grey matter, white matter and Cerebrospinal fluid (CSF) of brain [6].

1.4. Supervised learning methods in CAADD

Supervised learning techniques known as classification techniques learn the system based on labeled data, and also in some cases give the unlabeled data a proper label [7,8]. The accuracy of these methods is highly dependent on the labeled data and the selected and extracted features from raw information. A lot of techniques are developed in AD researches that some of the most used of them are discussed in this section. Support Vector Machine (SVM) is one of the supervised methods which is defined by a hyper plane that has a maximum distance with training data [9,10]. Because of the abilities of SVM in classification application, there has been a growing interest in using SVM in AD studies over the past decade [11,12]. For example, SVM is used to diagnose AD PET images with 92.31% accuracy [13]. Or it is used to classify AD from other dementia diseases [14]. In most applications in using SVM, features are extracted from non-image based biomarkers such as micro RNA, Cortisol, von Willebrand factor, an oxidized LDL antibody [15,16]. It is usually used in AD researches with several variables [17–22].

Logical Regression Classification (LRC) is another supervised method that is used for AD diagnosing in many researches [23–25]. Although, it had a promising performance for classifying small size of structural MR images for AD but in comparison with SVM it didn't has acceptable results for large size of images [26].

In the recent decade, Computational Intelligence (CI) and especially Artificial Neural Network (ANN) based techniques are widely used in CAD systems. They are capable of correctly interpolating information and can provide accurate models of natural phenomena. For example, Multi-Layer Perceptron (MLP) is used to predict the presence of brain injury by using demographic, cognitive and clinical variables as ANN features [27]. Deep learning neural networks in contrast with famous ANNs use raw image as input data. They could be successfully used in diagnosis of AD or Mild Cognitive Impairment (MCI) identification [28–31].

According to all mentioned methods, CAADD systems are made by four main parts: image acquisition, pre-processing and image enhancement, feature extraction and classification (final diagnosis). Although all parts of the CAADD system are very important and should be carefully designed, using efficient feature extraction method play an important role in performance of CAD systems. Discriminative features help diagnosis systems to suffer less computational costs with better performance. Different feature extraction methods are reported for CAADD that could be divided into automatic and knowledge-based methods. In automatic techniques, important area of the image are determined by machine and then features are extracted from them. But in knowledge-based methods, affected area by AD of the image is determined based on medical knowledge and features extraction method are used to make feature vector [32,33], Principle Component Analysis (PCA) and Linear Discriminant Analysis (LDA) are most well-known feature extraction methods which are used in AD diagnosis [34]. The most challenges in PCA and LDA techniques are high computational costs for converting image matrix to vector and over fitting when the amount of attributes are more than the samples. Discrete wavelet transform is another feature extraction tool that is utilized in CAADD [35]. High computational costs because of high dimension of extracted features is the main problem of this method.

Given the relation between extracted features and used classifier (diagnosis technique), using proper feature extraction method helps to reduce all mentioned concerns. In this research, features are extracted in 3D image form. In the first step, in order to cover all possible conditions for diagnosis AD in early stage, 11 templates are selected from whole database (includes normal, Mild Cognitive Impairment (MCI) and AD conditions) by using AP clustering method. Then all training 3D images are registered by the templates and corresponding to each template one Convolutional Auto Encoder-Decoder (CAED) is trained. Finally, in order to extract image feature, 11 extracted feature vectors from the encoder parts are reshaped into 2D images and then by merging them the image feature is extracted. In the second step, Convolutional Neural Network (CNN) is used to diagnose AD. Obtained results show very promising recognition rate.

In the rest of this paper, proposed method is described in section two. Obtained results are discussed in section three and conclusion is presented in section four.

2. Proposed method

In diagnosing process, a physician usually determine AD by considering the variations of the brain MR images of a patient and some clinical information of him/her. Low resolution of the images and human mistakes are two main reason for decreasing the accuracy of physician's diagnosis. CAD systems which are developed by machine learning methods can help physicians to increase accurate diagnosis of the AD. Proposed method includes three main parts: pre-processing, image feature extracting and AD diagnosing.

2.1. Pre-Processing

According to the literatures Grey Matter (GM) area contains most of the brain's neuronal cell bodies. The GM includes regions of the brain involved in muscle control, and sensory perception such as seeing and hearing, memory, emotions, speech, decision making, and self-control that valuable information of the AD disease could be found in this area. Therefore, in order to extract best information and reduce computational cost first step is to extract GM from MRI. One of the main difference between MR images are inhomogeneity in intensity, therefore N4 method [36] which improved version of non-parametric N3 [37] is used to correct intensity. Another problem of database is variation of MRI devices and the time of image acquisition. In order to solve this problem all images are registered on MNI template. By using these two initial steps, all images are becoming in the same form and are ready to be described.

2.1.1. Skull Stripping & Segmentation

After uniformization, the crucial step is to extract GM area. It has been done by skull striping method which is based on morphological techniques [38]. In order to show the procedure of proposed method more clearly, three slices of the image are used for presentation, Viz. coronal, sagittal and axial slices. As shown in Fig. 1 in addition to the skull, the cerebellum, neck and all additional area have been removed in this striping process. The output of this step includes grey matter, white matter and cerebrospinal fluid, therefore by using segmentation method [39] GM area are extracted for using in next steps.

2.2. Image feature extracting

Extracting discriminative features from GM area can play an important role in developing CAADD. In many applications especially in diagnosing AD, Auto Encoder (AE) is used to extract features [40–42]. Although obtained results show promising achievements, but they couldn't extract features from all aspects of GM area. Ensemble of eleven AEs are used to extract features. The number of eleven returns to the number of the templates which are selected by Affinity Propagation (AP) clustering method, automatically.

2.2.1. Auto template selection

As mentioned before, GM includes useful information about AD and can help physicians to diagnose Alzheimer as well. But some variations between the patterns of patients' grey matter area make diagnosis process difficult. Therefore, it is need to categorize them in clusters. It makes some advantages for CAADD system, such as: increasing inter-class similarity and decreasing intra-class similarity, considering all possible styles of AD and providing some templates which are representing the clusters. In fact, generating the features and eventually making the final image feature is done initially by using these templates for image registration.

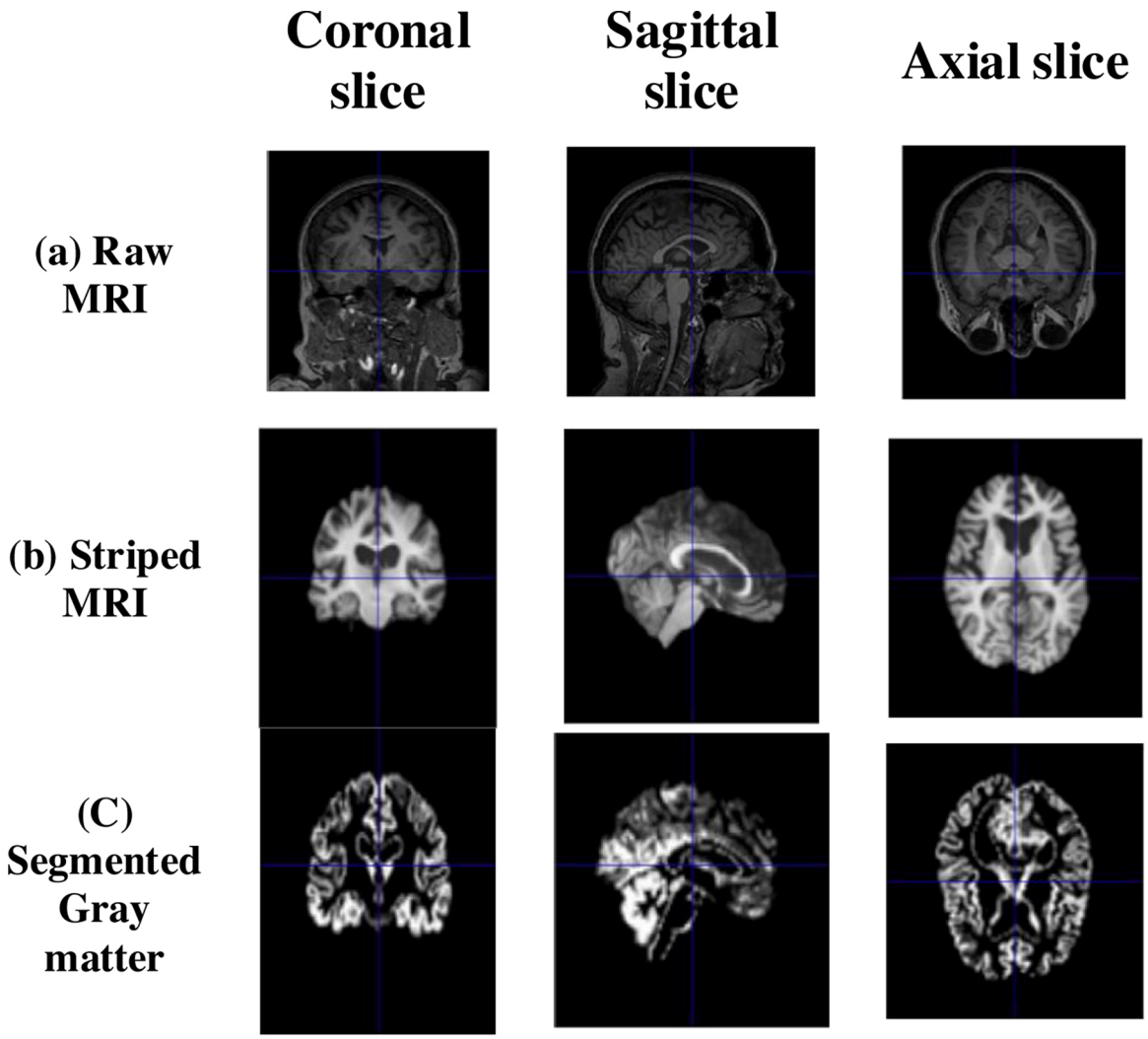

Fig. 1. Figures (a) are raw MR images, figures (b) are striped MR images and figures (c) are segmented grey matter.

Clustering process could be done based on the knowledge of the physician that could be difficult task. Also, clusters could be found by using well-known methods such as k-means and K-medoids. Unfortunately, these methods require the number of clusters to be determined before running the algorithm, whereas it is difficult to estimate the number of clusters for such application. Unlike them, Affinity Propagation (AP) algorithm doesn't need pre-estimated number of clusters and can found them automatically.

AP clustering works based on two important concepts: the availability (A(*i, k*)) and responsibility (R(*i, k*)) that these two concepts describe the capability of the images in data base to be exemplar (templates). Availability shows how much selected k^{th} template is suitable for i^{th} image in data base. In opposite to availability, Responsibility shows how much an image is suited to be a template. In each iteration Responsibility and availability are updated by (1) to (5) [43].

$$R(i,j) = S(i,k) - \max\{A(i,j) + S(i,j)\}, \quad (j \in \{1,2,\cdots,N; j \neq K\}) \tag{1}$$

$$A(i,k) = \min\left\{0, \left(R(k,k) + \sum_{j}\{\max(0, R(j,k))\}\right)\right\}, \quad (j \in \{1,2,\cdots,N; j \neq i, j \neq k\}) \tag{2}$$

$$A(k,k) = P(k) - \max\{A(k,j) + S(k,j)\}, \quad (j \in \{1,2,\cdots,N; j \neq k\}) \tag{3}$$

$$R_{i+1}(i,k) = \rho \times R_i(i,k) + (1-\rho) \times R_{i+1}^{old}(i,k) \tag{4}$$

$$A_{i+1}(i,k) = \rho \times A_i(i,k) + (1-\rho) \times A_{i+1}^{old}(i,k) \tag{5}$$

Where, similarity between two images *i* and *j* is calculated by $S(i,k) = -\|image_i - image_k\|^2$ and ρ is damping coefficient to speed up convergence rate. And finally, templates are estimated by using (6) and this action is repeated until stop criteria is meet.

$$Template_i = \arg_k \max\{R(i,k) + A(i,j)\} \tag{6}$$

Since, the main goal of proposed method is to diagnose AD in early stage, therefore there is need to extract information different conditions of grey matter area, viz. Normal, MCI and AD. Therefore, eleven templates are selected by AP clustering from whole database.

2.2.2. Proposed auto encoder

Convolutional Auto Encoder-Decoder (CAED) is usually introduced for de-noising and reconstructing the input image. Input image is decoded into feature space and then de-noised image is reconstructed by decoding the features. In this paper, decoded features are used to make image feature. In order to increase quality of the features, more than one layer is usually used for encoder space. Eq. (7) depicts the performance of a convolution layer.

$$O_m(i,j) = \phi\left(\sum_{d=1}^{D}\sum_{u=-2k-1}^{2k+1}\sum_{v=2k-1}^{2k+1} F_m^{(1)}(u,v) I_d(i-u, j-v)\right), \quad (m = 1,2,\cdots,n) \tag{7}$$

Where, $I = \{I_1, I_2, \cdots, I_D\}$ and $F_m^{(1)} = \left\{F_1^{(1)}, F_2^{(1)}, \cdots, F_n^{(1)}\right\}$ are input image and a set of n convolutional filters, respectively. D and n return to depth of input image and the number of neuron in each layer, respectively. *O* is convolved output image and φ is activation function. Another action in each layer is down sampling which is done by maximum pooling. Proposed encoder part of CAED with three layers in pipeline framework is shown in Fig. 2. The notation C@H × W × D defines the dimension of the output at the respective layer. C indicates the number of neurons in each layer and H, W and D indicate Height, Width and Depth of convoluted output in each layer, respectively. Rectified Linear Unit (ReLU) is used as activation function, which map negative inputs into zero value and has linear mapping for the positive values as shown in Eq. (8). Variables such as weights are initialized randomly and then optimized with back propagation method with respect to a loss function during training process which is presented in (9).

$$y = \max(0, x) \tag{8}$$

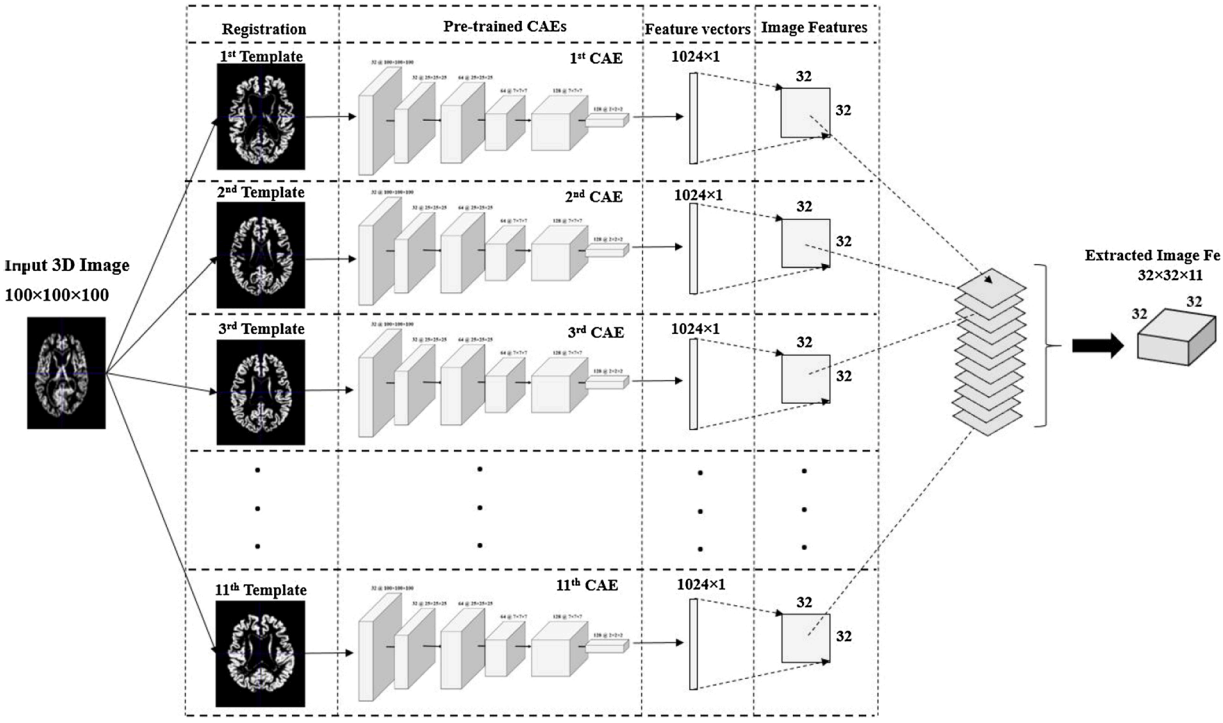

Fig. 2. Proposed framework for extracting image feature.

$$LostFunction_{CAED} = \min\left\{\frac{1}{n-1}\sum_{i-1}^{n}\|I_{in} - I_{out}\|^2\right\} \quad (9)$$

Where, y is the output of ReLU and x is its input. n is the number of training images, I_{in} is the input image which is used as target and I_{out} is output image of decoding part.

2.2.3. Ensemble of CAEs

As mentioned before, the main goal of this research is to generate image features for using them in the next step of CAADD. CAED has three main parts: Encoding part, middle coded features and decoding part. In the unsupervised learning of a CAED, input image is coded into a feature vector and then features are decoded to reconstruct input image. Since, middle codded features contains useful information of the training data, they could be good choice for generating image feature from input image. On the contrary to the raw images, Feature images do not contain redundant information and can provide constructive information from the input images for decision-making system.

Therefore, in this step image feature extraction structure is introduced by using ensemble of pre-trained CAEs. In order to extract powerful features, 2000 epochs are used for unsupervised learning of CAEDs with same padding convolution and maximum pooling. As shown in Fig. 3 in training step, all training 3D images are registered by the selected 3D template and then corresponding feature vector is extracted by unsupervised CAED. In order to extract image feature, input 3D image is registered by the templates and then CAEs generate feature vectors by 1×1024 dimension, then these feature vectors are reshaped into 32×32 image feature and finally by merging them image feature by $32 \times 32 \times 11$ dimension is extracted. Fig. 4 shows the typical extracted feature image of input 3D image shown in Fig. 1. Fig. 4 includes three slices of the image features for Normal templates, AD templates, and MCI templates, respectively. And Fig. 4(d) is final 3D extracted image features which is made by merging the eleven image features.

2.3. AD diagnosing

Second step of proposed method is classification or diagnosis part. So far, many classifiers are introduced for diagnosis AD, among them deep learning based methods such as Convolutional Neural Networks (CNN) show their ability for this case. Therefore, in this part of proposed CAADD, CNN is used as classifier. CNN has high computational cost especially in training step, so choosing best and optimum structure with high performance is an important challenge that should be considered.

The output of the previous part was image feature. It contains many information of different conditions of AD. Therefore, it is need and necessary to fuse information for increasing the quality of the features.

Unlike CAED, CNN is working based on supervised learning. It contains two main parts: feature extraction and Fully Connected (FC). Same as CAED, feature extraction part includes convolution and pooling layers. Input 3D image (I) is fed into the first layer and convolved with filters, usually the dimension of convolved images (CI) are same as input and then by using down sampling techniques such as pooling which could be average or maximum pooling the dimension of CIs are reduced to decrease computational cost and prevent over fitting during training CNN. Usually, filters include some parameters that are adjusted during training, but in order to speed up the training pre-trained filters are used to design CNN. But, it is worth noting that it is better to adapt and optimize filters with data base, as done in CAED of proposed method. Output of the first part is a fused feature which is presented by a vector for FC part. Second part of CNN is fully connected neural network which is working same as Feed Forward Neural Network and is trained by descending gradients. Training procedure in CNN is supervised learning that works based on minimizing the distance between output of CNN and targets which are AD or normal condition.

2.3.1. Proposed architecture

Fig. 5 depict the total framework of proposed structure of CNN. In Feature extraction part, three convolutional layer are used. The number of neurons for each layer are {16, 32, 64} with {5, 5, 5} kernels as filters and after each convolution maximum pooling with {2, 2, 2} windows are used for down sampling. Same padding is considered for convolution and ReLU activation function is used to remove negative values. The proposed FC includes one layer with 1024 neurons. Same as proposed Auto Encoder, Activation function for hidden layers is ReLU and "*Softmax*" activation function is used for output layer to classify input image. As it can be seen in (10), this function maps a k-dimensional input vector $a = \{a_1, a_2, \cdots, a_k\}$ of real numbers into a vector of real number in range (0, 1).

$$\phi(a)_i = \frac{e^{a_i}}{\sum_{j=1}^{k} e^{a_j}}, (j = 1, 2, \cdots, k) \quad (10)$$

In addition, drop out method with 0.5 learning rate is used to prevent over fitting. Also, in order to measure and minimize the distance between the output of CNN (φ_i) and the real targets (T) Cross entropy function is used as (11). Since, the output of the Softmax function could be understood as the probability, thus it can be used as loss function.

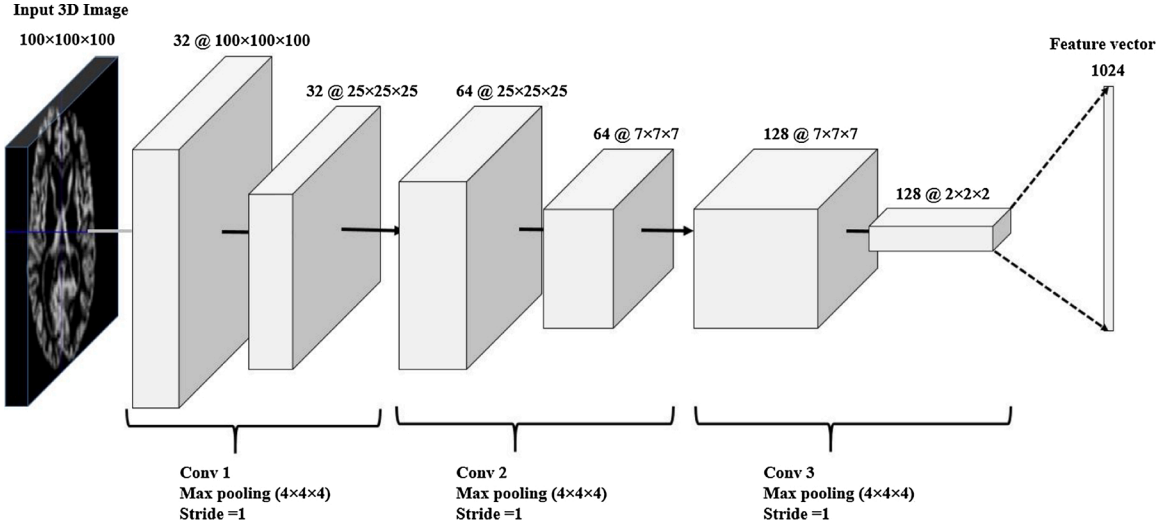

Fig. 3. Structure of proposed CAE.

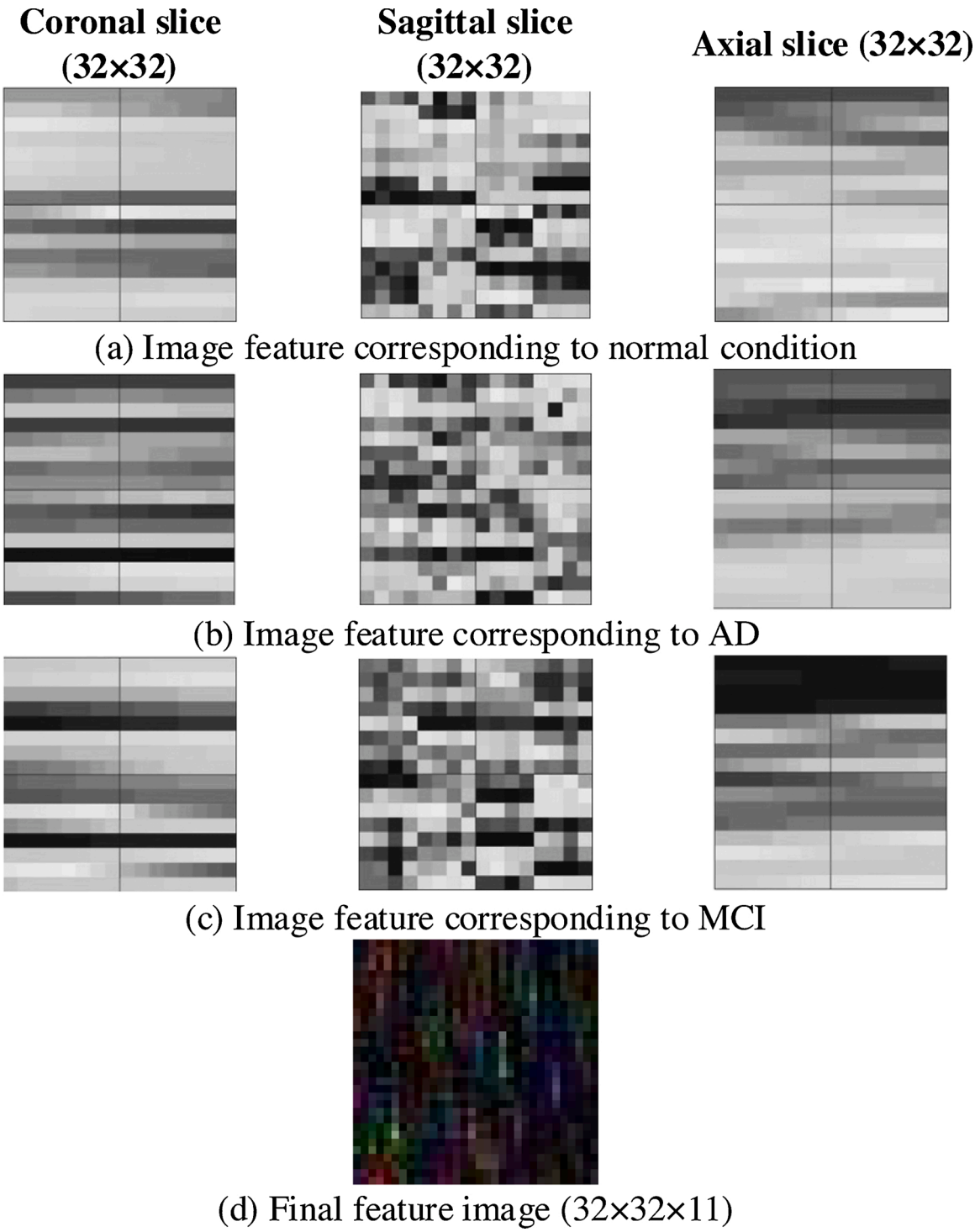

Fig. 4. A typical extracted image feature. Figures (a) to (C) are samples of image features which are extracted based on normal, AD and MCI templates with 32 × 32 dimension and figure (d) is final image feature with 32 × 32 × 11 dimension.

$$H(T,\phi) = -\sum_i T_i \log(\phi_i) \tag{11}$$

And finally, in order to train CNN especially FC part, the Adaptive Moment Estimation or Adam optimization algorithm is used [44]. It is a combination of gradient descent with momentum and RMSprop algorithms. Some advantages of Adam are as follow:

- Relatively low memory requirements.
- Usually works well even with a little tuning of hyper parameters.

According to the structure of the proposed CNN and the extracted image feature from Ensemble of CAEs, input image with 32 × 32 × 11 dimension is mapped into 1024 × 1 vector by convolutional layers and then it is coded into 1024 × 1 vector by FC. Finally, Softmax estimates the output class.

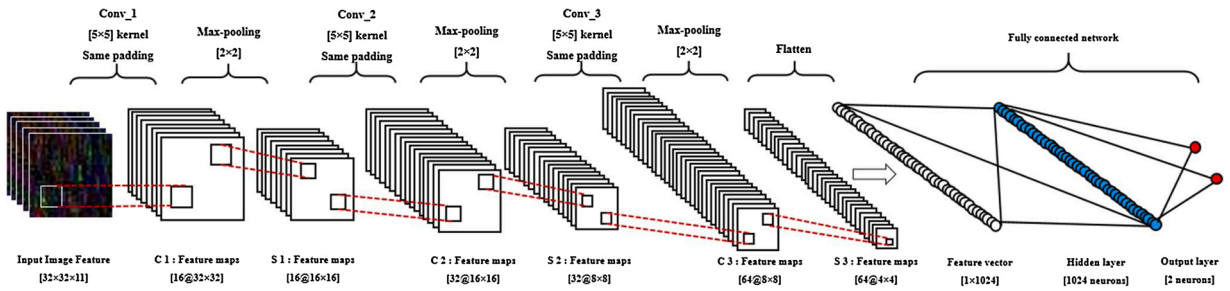

Fig. 5. Proposed architecture of CNN. Cs are convolutional layers and Ss are down sampling steps.

3. Results and discussion

3.1. Database

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database is used in this research. ANDI contains various MRI and PET data from various patients at different stages of their illness. MR images of this database are collected at the 55 sites in North America at multiple time points in 200 elderly cognitively normal, 400 MCI, and 200 AD subjects. Also, all subjects are scanned with 1.5 T MRI at each time point (http://adni.loni.usc.edu/). In this paper, in order to have same situation for all conditions, 100 subjects are randomly selected. (Table 1) presents the information of selected subjects.

3.2. Obtained results with sensitivity analysis

The main goal of the proposed method is to classify AD from NC (AD/NC), however in order to evaluate the ability of the proposed method in classifying other binomial classification such as AD versus MCI (AD/MCI) and MCI versus NC (MCI/NC). Therefore, for each classification 200 subjects was available that from them 20%, 10% and 70% are used as testing, validating and training data, respectively.

The main concerns of the proposed method were the structure of CAE for feature extraction and CNN for diagnosis process. Therefore, in the training step, a sensitive analysis on the number of convolutional layers has been done to achieve best structure for binomial classification of AD and NC. Also, in order to have reliable results 10-fold cross validation in 10 separated simulation were done for each state. It is worth noting that maximum pooling shows better results than average and sum pooling for all simulations. Some parameters such as number of convolutional layers, number of fully connected layers and also number of clusters for image registration could impact on the final results. Therefore, sensitive analysis has been done to find best and optimum parameters. Fig. 6 presents effect of increasing the convolutional layers in CAE and CNN. In order to evaluate the effect of the number of layers in CAE, one convolutional layer is considered for CNN to decrease the effect of CNN in final accuracy. As it can be seen, accuracy is increased by increasing the layers of CAE. Since, variation of the accuracies are not so significant after three layers and increasing the layers will increase computational cost, so the best and optimum number of the layer for CAE is three. In other hand, such variations of accuracy can be found for CNN that by increasing the layers increase of accuracy is visible. A significant increase in the accuracy between two and three layers is evident. However, increasing further layers doesn't help to increase accuracy and leads to a sharp increase in computational cost. Therefore, Best performance for proposed CAEs and CNN is achieved by three layers.

Table 1
Demographic Information of the Studied Subjects from ADNI Database.

Condition	Number	Age	Gender(M/F)
NC	100	76.11 ± 5.10	50/50
MCI	100	75.18 ± 6.97	45/55
AD	100	75.90 ± 6.84	48/52

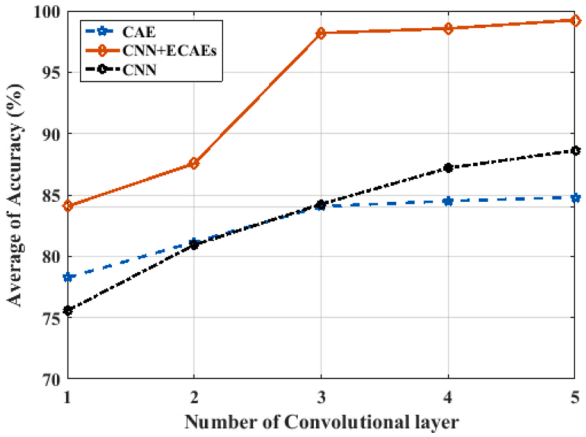

Fig. 6. Effect of the number of convolutional layer based on average of accuracy for ten separated runs (10-fold cross validation) in AD/NC classification.

In addition, effect of the Ensemble of CAEs (ECAEs) can be found in comparison between red and black line in Fig. 6. As it can be seen, maximum accuracy without ECAEs is about 89% with 5 convolutional layers. However, the accuracy can be increased by using ECAE up to 100% for training images.

As mentioned before, output of convolutional layers is 1024 × 1 vector. In order to have optimum number of hidden layers in the FC part of the CNN, four conditions are evaluated; one, two, three and four hidden layers with [1024], [1024, 512], [1024, 512, 256], [1024, 512, 256, 128] neurons, respectively. Obtained results show that increase of hidden layers has no significant change in accuracy while increases time consumption. Therefore, one hidden layer with 1024 neurons is optimum for proposed model.

Finding optimum number of clusters can help to have proper distribution for training data and eventually can lead to develop more reliable model. In the proposed method, AP clustering algorithm shows that 11 is the best number for clusters. In order to show that 11 clusters are optimum, other number of clusters are evaluated. As shown in Fig. 7 low and high number of clusters can lead to less accuracy than 11 clusters.

According to the sensitivity analysis, 11 clusters for image registration, three convolutional layer and one hidden layer with 1024 neurons are optimum parameters for proposed model. Fig. 8 shows one of the best training performance of AD/NC classification accuracy and cross entropy during 200 epochs.

In the test step, proposed ensemble CAEs and CNN are used for three classification cases; AD/NC, AD/MCI and MCI/NC. Fig. 9 depicts confusion matrices for testing images. Also, (Table 2) presents obtained results based on the accuracy, precision, sensitivity (Recall) and specificity rates. As a point of accuracy, proposed method presents so accurate prediction for AD/NC classification by 95% accuracy. However, proposed method is basically developed for AD diagnosis, but it can

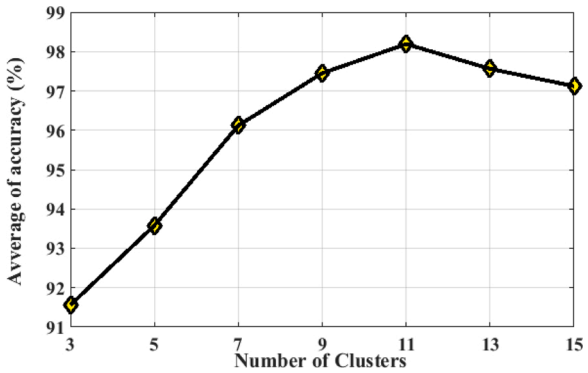

Fig. 7. Effect of the number of clusters for image registration based on average of accuracy for ten separated runs (10-fold cross validation) in AD/NC classification.

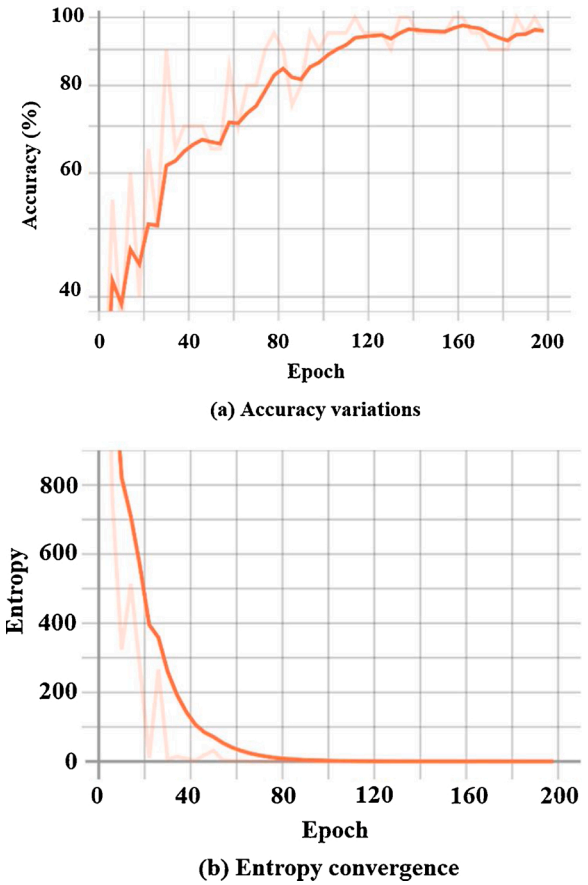

Fig. 8. One of the best training performance of AD/NC classification.

work very well for AD/MCI and MCI/NC classifications. It means that it can help physicians to diagnose AD disease in early stage by more than 90% accuracy. As a point of precision, proposed method has no error in classification of normal subjects. Unfortunately, because of similarities between AD and MCI about 15% error could be found for classifying MCI from AD. As a point of sensitivity, about 92% of AD are correctly classified that is so promising rate in comparison with other methods in literatures. As a point of specificity, proposed method is so reliable for diagnosis normal condition that in most of the cases it has no error to diagnosis NC.

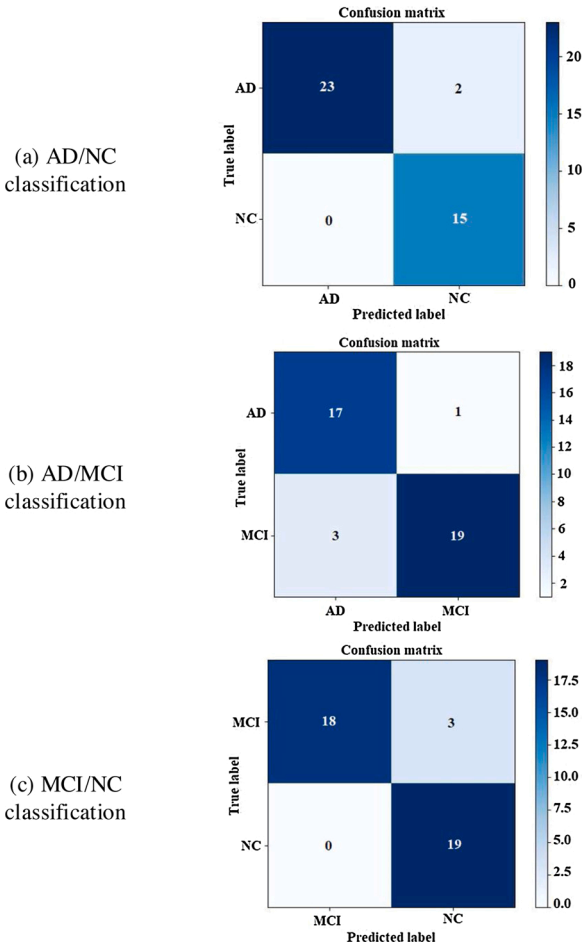

Fig. 9. Confusion matrices of three different classification cases for testing data, (a) AD/NC, (b) AD/MCI and (c) MCI/NC.

Table 2
Results of AD versus NC, AD versus MCI and MCI versus NC Classification for testing data.

Classification	Accuracy (%)	Precision (%)	Sensitivity (%)	Specificity (%)
AD/NC	95	100	92	100
AD/MCI	90	85	94.44	90.48
MCI/NC	92.5	100	85.71	100

3.3. Comparison with other methods

Many researches have been done in the field of AD diagnosis. Some of them focused on feature extraction and others worked on classifier. Some of them just worked with MR images and some others use other AD images such as PET in addition to MRI. Number of subjects and used databases are different in literatures and in order to have fair comparison some literatures with same database or with close number of subjects with this paper are considered for comparison. Comparison has been done in three classification cases as presented in (Table 3). According to the AD/NC results, proposed method shows promising performance based on accuracy and also has no error to detect NC rather than other methods. Although sensitivity rate is less than some other methods but it is in top performances. According to the AD/MCI results, the prominent advantage of proposed method could be found in sensitivity that is more than other methods and it can help physicians to correctly diagnosis the condition of patient. According to the MCI/NC results, all rates are more than other methods and it means that proposed

Table 3
Comparison between proposed method and other methods which are introduced in literatures in different classification cases for testing data.

classification	Method	modality	# total subjects	ACC (%)	SEN (%)	SPE (%)
AD vs. NC (AD/NC)	Islam et al. [46]	MRI	416	93.18	93	n.a.
	M. Liu et al [47]	MRI	225	92.51	92.89	88.33
	Lu et al. [48]	MRI	626	81.9	75.5	92.3
	Feng et al. [49]	MRI + PET	397	94.29	96.59	92.38
	Kwak et al. [50]	MRI	319	94.17	94.49	93.05
	Cuingnet et al. [51]	MRI	299	88.58	81.00	95.00
	Zhang et al. [52]	MRI	103	86.20	86.00	86.30
	M. Liu et al. [53]	MRI	427	90.80	86.32	94.76
	M. Liu et al. [54]	MRI	427	92.00	91.00	93.00
	Koikkalainen et al. [55]	MRI	203	86.00	81.00	91.00
	Min et al. [56]	MRI	225	91.64	88.56	93.85
	Min et al. [57]	MRI	225	90.69	87.56	93.01
	Zhu et al [60]	MRI + PET	99	95.7	96.6	98.2
	Proposed method	**MRI**	**200**	**95**	**92**	**100**
AD vs. MCI (AD/MCI)	M. Liu et al [47]	MRI	225	73.69	76.44	70.76
	Lu et al. [48]	MRI	626	75.74	73.27	76.19
	Lu et al. [48]	MRI + PET	626	82.93	79.69	83.84
	Kwak et al. [50]	MRI	319	81.62	88.30	78.71
	Cuingnet et al. [51]	MRI	299	70.40	57.00	78.00
	Min et al. [56]	MRI	225	72.10	77.00	71.00
	Min et al. [57]	MRI	225	72.41	72.12	72.58
	K. Liu et al [58]	MRI	234	68.8	64.29	74.07
	Cheng et al [59]	MRI	99	73.4	74.3	72.1
	Proposed method	**MRI**	**200**	**90**	**94.44**	**90.48**
MCI vs. NC (MCI/NC)	Feng et al. [49]	MRI + PET	397	64.47	70.43	48.41
	Kwak et al. [50]	MRI	319	85.89	85.46	86.71
	Zhu et al [60]	MRI + PET	99	79.9	97.0	59.2
	Proposed method	**MRI**	**200**	**92.5**	**85.71**	**100**

method can be reliable to detect early stage diagnosis.

4. Conclusion

In this paper, deep learning based methods are used to introduce reliable and accurate CAD for diagnosis AD in early stage. Proposed method includes two main part that are carefully designed, such as feature extraction and classification parts. Main novelty is introduced in the feature extraction part which uses ensemble of eleven convolutional auto encoders. According to the obtained results performance of proposed method with and without ECAEs is so difference and it shows that ECAEs play an important role in the proposed method. In addition, convergence of CNN's entropy lost function become close to zero value just around 200 epochs while without using ECAEs around 12,000 epochs needs to reach less entropy. It helps us to reduce computational cost and save time during training step. Eleven templates are selected by AP clustering technique that they are representative of all conditions in training data. Evaluation of the number of clusters show that for this database eleven is optimum, therefore they are used for registration and then registered image is fed into CAEs to generate image feature. Finally, image feature is classified by CNN. In order to evaluate the performance of proposed method, three classification cases are considered, AD/NC, AD/MCI and MCI/NC. Obtained results in comparison with other methods show that proposed method has very impressive performance with high accuracy rate with reliable sensitivity and specificity. Less error in diagnosing normal condition and high sensitivity to diagnosis AD in early stage are some advantages of proposed method.

Future work

Finding optimum and adaptive filters in convolutional structure for both auto encoders and CNN can help proposed model to adapt with all different type of data. And it needs more training data with different sources. Also, our other future work is to develop deep learning based models to predict the percentage of Alzheimer's Disease progress, it can help physicians to give better advices to patients.

CRediT authorship contribution statement

Rohollah Hedayati: Software, Methodology, Investigation, Writing - review & editing. **Mohammad Khedmati:** Investigation, Software. **Mehran Taghipour-Gorjikolaie:** Supervision, Writing - original draft, Project administration, Conceptualization, Software, Methodology.

Declaration of Competing Interest

The authors report no declarations of interest.

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