

A novel CNN based Alzheimer's disease classification using hybrid enhanced ICA segmented gray matter of MRI

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ABSTRACT

Predicting Alzheimer's Disease (AD) from Mild Cognitive Impairment (MCI) and Cognitive Normal (CN) has become wide. Recent advancement in neuroimaging in adoption with machine learning techniques are especially useful for pattern recognition of medical imaging to assist the physician in early diagnosis of AD. It is observed that the early abnormal brain atrophy and healthy brain atrophy are same. In our endeavor, we proposed a model that differentiation MCI and CN more accurately to escalate early diagnosis of AD. In this paper, we applied both binary and multi class classification, 4463 Slide are divided in to two groups one for training and another for testing at subject level, achieves 100 % of accuracy, 100 % of sensitivity and 100 % of Specificity in the case of AD-CN. 96.2 % of accuracy, 93 % Sensitivity and 100 % Specificity in the case of AD-MCI. 98.0 % of accuracy, 96 % of sensitivity, 100 specificity in the case of CN-MCI. 86.7 % accuracy, 89.6 % of sensitivity, 86.61 % of specificity in the case of AD-MCI-CN. The model is further tested using 10 fold cross validation and obtained 98.0 % of accuracy, to differentiate CN and MCI. Our proposed framework generated results are significantly improving prediction of AD from MCI and CN than compare to the previous work flows and used to differentiate the AD at early stage.

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1. Introduction

Alzheimer's Disease (AD) is a progressive dementia, effect elders that results in loss of connection between nerve cells. Owing to Alzheimer's disease brain get shrinks, hippocampal size gets decreased and enlarged brain ventricles. As Alzheimer's disease progresses it debases memory, thinking ability, and face problem in day to day activity. Understanding Alzheimer's disease, Mild Cognitive Impairments (MCI) and Cognitive Normal (CN) manifestation is one of the most challenging tasks that neurologist face from past few years. AD is diagnosed using physical test and Mini Mental State Examination (MMSE) (Klekociuk et al., 2014; Weissberger et al., 2017). As medical imaging technique develops, neuroimaging play major role to diagnose structural and functional changes in the brain, encompass Computer Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Functional Magnetic Resonance Imaging (fMRI), Single Photon Emission Computed Tomography (SPECT). Owing to easy

access, MRI is used to analyse structural changes caused due to AD, CN and MCI manifestation. The most common MRI sequences are T1-weighted and T2-weighted scans. We use T2 -Weighted scans in our work. As shown in the Fig. 1, it is observed that AD MRI having cortical atrophy, change in hippocampal size and enlargement of ventricles compare to CN and MCI with annotation. It is evidence that texture of the brain get change from CN to MCI to AD. The T2w image had a skewed distribution for both GM and WM with long tails indicating lower homogeneity and discriminability for these tissues. As a result, T2w had non-overlap of intensity values between White Matter (WM) and Gray Matter (GM) and provided better discriminability between tissues. So T2 weighted MRI used for tissue classification for analysis of neurological disorders.

Prediction of AD at early stage is a challenging task, classification of AD is performed by collecting different parameters and develops bio markers to test the AD. 5 stages of route map were developed by collecting CSF and clinical information from PET (Frisoni et al., 2017). In CSF-based diagnosis preclinical AD uses A β ratios rather than A β 42 (Adamczuk et al., 2015). Morphological changes are observed in brain due to AD brain textures, structural features, are usually used to perform classification of MRI in addition to machine learning algorithms (Weissberger et al., 2017). The early effect of AD is observed based on changes in Hippocampal, its size is used to analyse the AD stage (Adaszewski et al., 2013). AD is classified using volume of interest (Liu et al., 2004) High dimensional and

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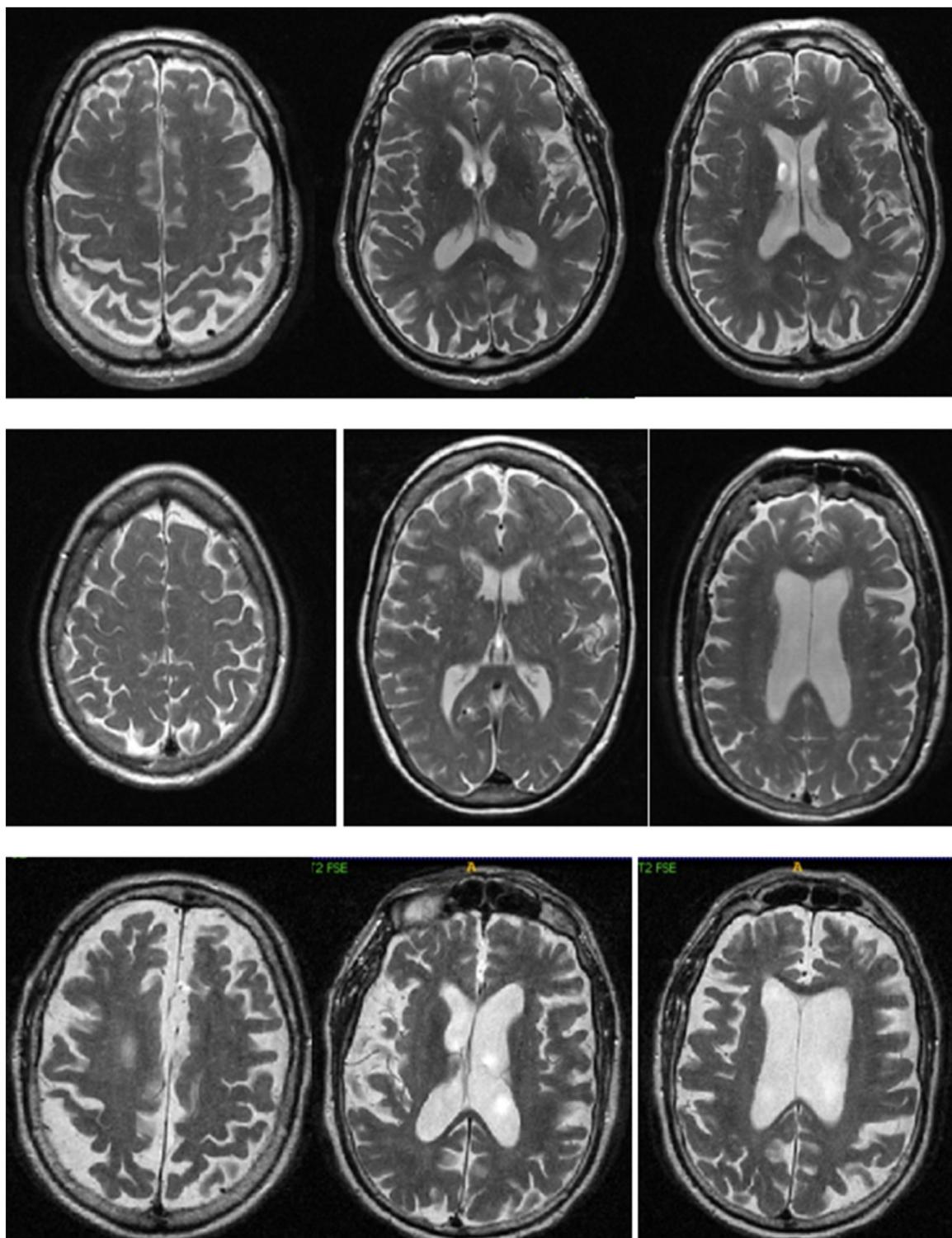
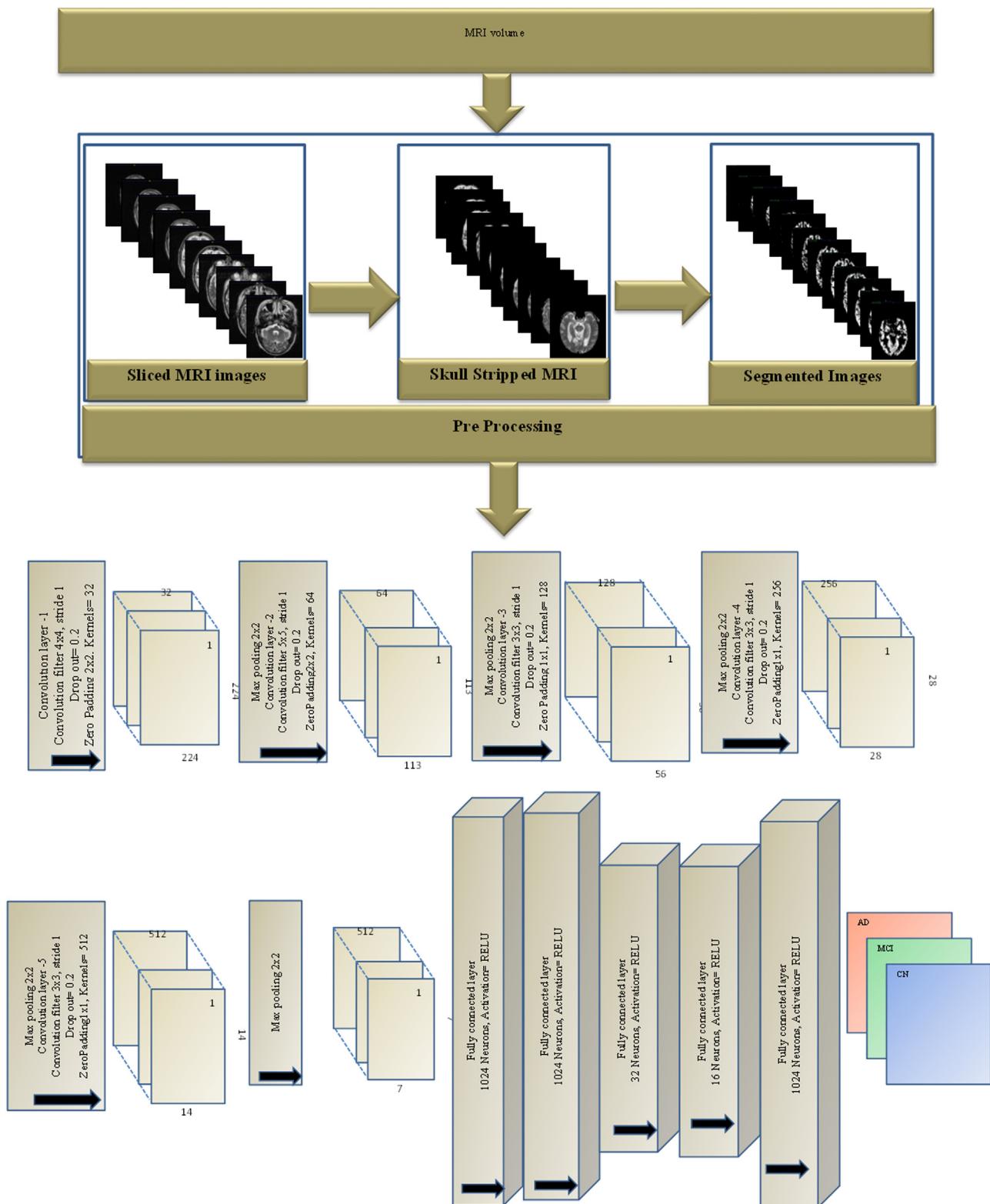


Fig. 1. Cross sections from MRI images of CN (the top row), MCI (the middle row) and AD (the bottom row).

shape transformation is used as morphological signature of the brain structure. The huge morphological information is reduced via wavelet transformation where the classification is carried using voxel by voxel instead of entire data (Lao et al., 2004). Selecting an appropriate voxel and relevant area will give the good specificity and sensitivity (Fung and Stoeckel, 2007). Change in WM is estimated to analyse the affected area of brain due to AD (Maggipinto et al., 2017). Grey matter segmented from the voxel is used to analyse AD (Klöppel et al., 2008).

From last few years Computer Aided Diagnose (CAD) system is used to assist and give second opinion to the physicians. [Machine learning is a computational technique to analyses patterns of medical data](#). Different Machine learning approaches such as regression, classification and clustering are used in CAD system. Among different classification techniques artificial neural networks are used in most of the diagnose systems (Suk et al., 2016). In our proposed system we perform classification of MRI images into CN, MCI and AD.

**Fig. 2.** Proposed Work Flow Block Diagram.

2. Related work

Many of the CAD systems are developed using machine learning techniques to detect the structural, functional changes in brain using machine learning techniques to reduce the time for diagnosis of disease. (Goceri and Songül, 2017). CAD systems provide fast reliable and robust decision of the different disorders with great

accuracy and reduce work load on doctors (Goceri, 2018a, b; Goceri, 2019b). EEG Signals collected from Patient are used to classify AD or Healthy using KNN (Kulkarni and Bairagi, 2018). Single modality and Multi-modality are used to make the differentiation of AD vs MCI (Shen et al., 2014).

Sobolev gradient based optimization in CNN has been applied (Goceri, 2019a) since chosen scalar products on gradient decent

Table 1

Demographic representation of MRI Images collected from ADNI respiratory with 1.5 T.

Research Group	Number of subjects	MMSE Score	GD Scale Total Score	Age (Years)	Number of MRI Volumes	NPI-Q Total Score	Global CDR
AD	65	21 to 27	0–15	55–93	70 No's	0–20	0.5 to 2
CN	28	29–30	0–10	71–96	29 No's	0–10	–1 to 0.5
MCI	32	27–29	0–12	61–96	38 No's	0–9	–1 to 0.5

algorithm can affect results (Gocer, 2015). Hippocampal volume is verified patch wise using hybrid classifier by combining Recurrent Neural Network (RNN) and Convolutional Neural Network (CNN) (Li and Liu, 2019). Small variability of brain network leads to a large variation in brain neuron network structure. These small variations are not significantly analysed using the existing statistical methods to accurately classifies the MCI and CN using inter group brain functional network distinctions play a significant role (Zhang et al., 2020). As the number of features are more it make complication to train the machine accurately greedy score is used to select the important features, kernel based discriminative method is used to perfume feature selection of complex features (Lama et al., 2017). Hybrid features extracted from segmented brain image and clinical data is used for multi class classification (Altaf et al., 2018) Hierarchical classifier is used to make the differentiation of AD and FTP using discriminative features of the brain MRI (Kim et al., 2019). Patch based image textures are extracted from Gabor filter and perform classification using weak classifier (Hett et al., 2018) these methods are working on hand picked features of the image. To perform the feature selection professional and medical experts with expertise knowledge are most important.

In deep convolutional neural networks, hierarchical layers are connected and have the advantage over artificial neural networks. Deep learning is achieving good performance in medical image analysis Deep learning is achieving good performance in medical image analysis (Goceri et al., 2017) due to its efficient formulations (Goceri, 2018a), the parameters and functions chosen appropriately (Goceri, 2018b; Goceri, 2019c, d; Shen et al., 2017). Deep radiomic features are extracted from 3D MRI image using entropy CNN to perform AD classification (Chaddad et al., 2018). Deep learning generates large number of features and to reduce those features local descriptors are used in remote sensing applications (Liu et al., 2020). Multi model 3D CNN used to extract the features and make the classifications (Li et al., 2017). Features from stacked auto encoders and low level features in combine help to build classification model (Suk and Shen, 2013) Extracting texture from the center slides of MRI image and use those as input for making the classification of the AD using boot strap algorithm as the region of interest is used to collect the features from MRI (Vaithinathan and Parthiban, 2019). Transfer learning using VGG 16 pre train model is used to perform the classification of AD-NC-MCI (Jain et al., 2019).

In this paper, we proposed a CNN classifier for automatic classification of AD from MCI and CN using GM. We evaluated the architecture performance by comparing both T1, T2 weighted MRI's collected from a standardized dataset, Alzheimer's disease Neuroimaging Initiative (ADNI). The contribution of the paper is summarized as:

- Performance is compared using raw T1 and T2 weighted MRI images
- To improve the classification accuracy in multi class classification, Raw T2 weighted MRI images are preprocessed using Gaussian filters.
- Threshold and morphological operations are performed to remove the unwanted tissues from the T2 weighted MRI slides.
- In this paper, Hybrid Enhanced Independent Component Analysis is used to perform the segmentation of the GM from T2 weighted MRI images.

e) We Further Compared the performance of the Model trained with raw T2 Weighted MRI image and GM segmented MRI images and observed the performance of the system by testing it with independent images separated at subject level

The aim of this work is to develop a computer-based diagnosis system that provides additional support for the medical staff to support their diagnosis evidence.

3. Material and methods

3.1. Material

In our work, a total of 137 MRI volumes are obtained from Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). We used 1.5T, T2 weighted MRI volumes, which are 420 × 462 × 32 slides. We collected AD, MCI and CN MRI's of different age groups both Male and Female with different MMSE score, NPI-Q total Score, Global CDR and GD Scale. MRI's and their demographic representation is shown in Table 1. Here we collected 70 CE MRI's from, 25 MCI MRI's and 20 CN MRI's from 120 subjects.

3.2. Methodology

In our work, we had analysed the performance of the model on both T1 and T2 weighted MRI images collected from the same set of subjects and evaluate different parameters under both binary and multi class classification. Further the model is analysed on T2 weighted MRI images and proposed GM segmented MRI images.

To perform the segmentation of T2 weighted MRI images, MRI's are initially sliced into slides. These slides are preprocessed to correct geometric distortion and reduce noise using Gaussian filter. Non-brain tissues are removed from the slides using skull stripped algorithm. Structural and texture changes in the brain are used to differentiate healthy and diseased, Enhanced ICA used to perform segmentation of brain pathology into WM, GM and Cerebrospinal Fluid (CSF). Brain tissue atrophy is used to detect AD stage. AD is a progressive disease, brain volume experience change in GM, WM textures and volume as well as expansion of ventricles. In our work, we classify the AD based on GM atrophy. GM is having neuron cell bodies and non-neuron brain cells called glial cells. GM undergoes development and growth throughout childhood and adolescence, it is used to carry glucose to the brain, changes in this effects the memory, speech, and motor controls. In our work we mainly focused on the gray matter's, to classify the AD. We used CNN as a classifier which is used in different computer vision techniques, from the past couple of years. Our classification approach is having 3 major sections (1) Preprocessing (2) train and test the model at with subject level splitting (3) Test the model using 10 fold cross validation. The block diagram of the proposed system is shown in the Fig. 2.

3.3. Preprocessing

3.3.1. Skull stripping algorithm

Skull stripping is the most important pre-processing technique (Goceri, 2017). For accurate classification of images, unwanted and non-brain tissues are initially removed from the slides the brain tissues are left. The proposed skull stripping algorithm is having

a sequence of steps. Before applying skull stripping the image is enhanced using Gaussian filter to reduce detail information and noise. The skull stripping algorithm steps are numbered below.

```

 $I(x,y)$  is the input image
 $k(x,y)$  3X3 Kernel
 $I_5$  is the output image

Step1:  $I = \text{input image}$ 
Step2:  $I_1 = \text{enhanced image}$ 
Step3: Convolution of input image and kernel  $I_2 = I_1 \text{ conv } k$ 
Step4: Threshold the image  $\text{for } i = 1: \text{row length of } I_2$ 
     $\text{for } i = 1: \text{column length of } I_2$ 
         $\text{if } I_2(x,y) \leq 254$ 
             $I_2(x,y) = 0$ 
         $\text{else}$ 
             $I_2(x,y) = 1$ 
         $\text{end if}$ 
     $\text{end if}$ 
Step5: Erode:  $I_3 = \text{erode } I_2 \text{ image}$ 
Step6: Active Contour:  $I_4 = \text{Perform active contour on } I_3$ 
Step7: Skull stripped image  $I_5 = I \times I_4$ 
```

3.3.2. Segmentation algorithm

Blind separation of Brain tissues in MRI is carried by using an unsupervised segmentation approach. In our work, we used Hybrid Enhanced Independent component analysis (HEICA). K- Means and Expected Maximization (E.M) are combined to form a Hybrid strategy to cluster the brain tissues in MRI. This combination achieves the capability of providing clusters for well distributed image pixels and compactness through E.M.

In our proposed Hybrid Enhanced ICA, the concept of Mixture model is introduced and it is characterized into mutually exclusive classes. In the modified GMM approach Spatial Information is added to GMM using Markov Random Field (MRF) and takes spatial dependency into account. In Expected maximization (EM), Expected step is computed using log likelihood with mean and variance are calculated using modified K-mean ([Goceri, 2018c](#)) and latent variable is calculated through Gibbs density function. The above mentioned parameters are used as input parameters to HEICA to perform the segmentation of the Brain MRI slides. The algorithm is further explained using the following steps. The resultant images are shown in [Fig. 3](#).

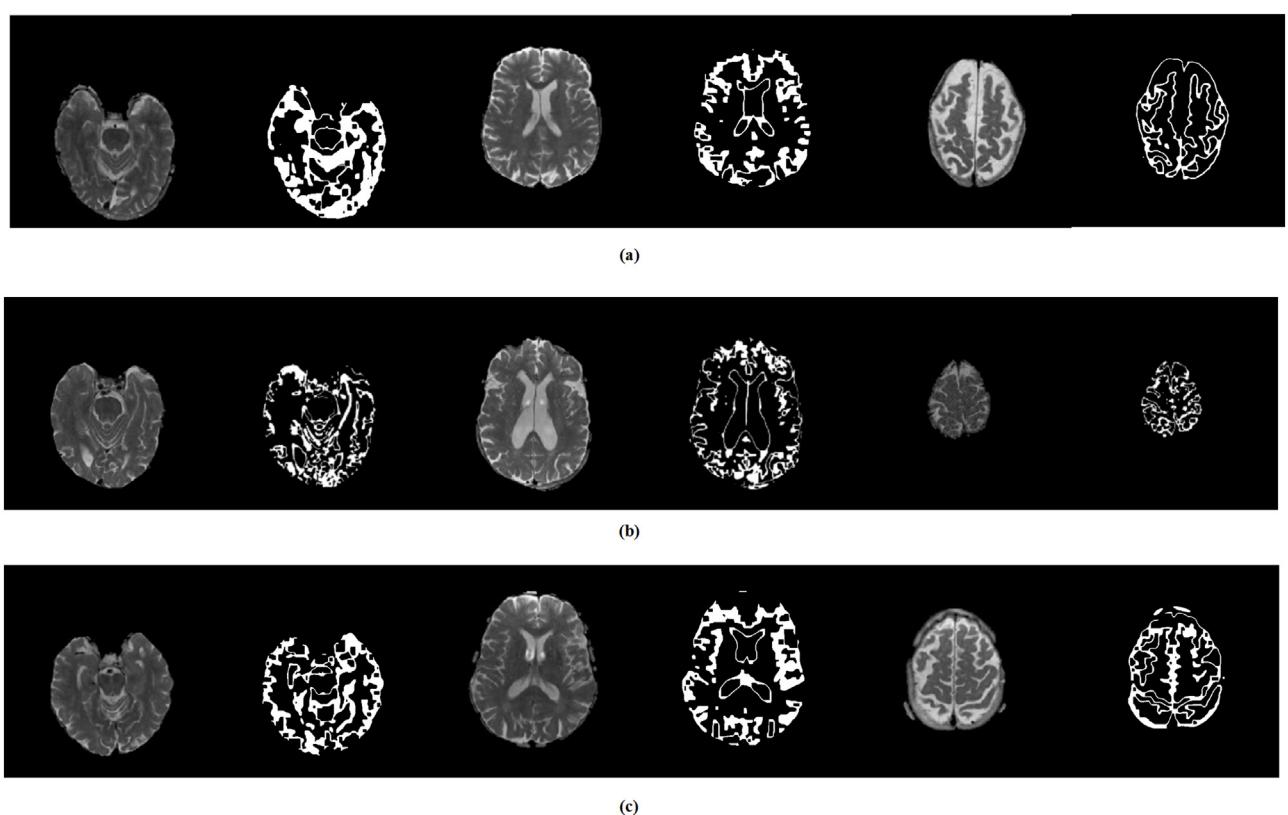


Fig. 3. T2 weighted skull stripped image to GM Segmented image (a) AD Skull stripped T2 Weighted MRI image to GM Segmented image (b) MCI Skull stripped T2 Weighted MRI image to GM Segmented image (c) CN Skull stripped T2 Weighted MRI image to GM Segmented image.

<i>g(x,y)</i> is the input image into k identically independent GMMs with parameters $\theta_k = \{\mu_k, E_k\}$
Step 1: Represent <i>g(x,y)</i> in vector $\{g_i : i = 1, 2, 3, 4, \dots, N\}$
Step 2: Modified K mean to find the Prior information of the Gaussian mixture model such as mean and covariance $\{\text{Mixing Coefficient } \pi_k : i = 1, 2, 3, 4, \dots, N\}$, g_i is the gray level.
<ol style="list-style-type: none"> Partition of N pixels into K equal sets Center of each set as a centroid $c_1, c_2, c_3, \dots, c_k$ Find the distance between Euclidean distance between <i>g(x,y)</i> and the cluster centers Find the centroid that is close to the particular <i>g(x,y)</i> Recalculate the centroids of the each clusters Repeat the steps from c to e If the distance between <i>g(x,y)</i> and new cluster center is less than or equal to the previous distance then <i>g(x,y)</i> will be in the same cluster otherwise it move to another cluster based on the distance. The process get continue till the clusters get convergence Collect mean and covariance of the clusters $\theta_k = \{\mu_k, E_k\}$
Step 2 : $\theta_k = \{\mu_k, E_k\}$ for i=1: pixels for k=1: number of k Probability density of the mixture model is considered as $p(x_i \pi, \theta) = \sum_{k=1}^c \pi_k^k p(x_i \theta_k)$ end end
Step 3: log likely hood of the density function is calculated to find the probability of pixel belong to the particular Gaussian $\ln p = p(X \theta) = \sum_{i=1}^N \ln p(x_i \theta)$, $\theta = \{z, \mu, \sigma\}$, z , latent variable and calculated using Expectation and Maximization
Step 4: E step for i: $Q_{(i)}(z^{(i)}) := P(z^i x^i, \theta)$
Step 5: M Step for all z $\theta := \operatorname{argmax}_{\theta} \sum_i \sum_z Q_i(z^i) \log \frac{p(x^i, z^i; \theta)}{Q_i(z^i)}$, Q_i the posterior distribution of (z^i)
Step 6: Prior distribution of π is given by MRF model through gibbs density function $p(\pi) = \exp \frac{-\beta \sum_{i=1}^N V_{Ni}(\pi)}{a}$, a is a normalizing constant $V_{Ni}(\pi)$ is the clique potential function
Step 7: Process stops when $\ \theta^{\text{new}} - \theta^{\text{old}}\ \leq \text{error}$

3.4. Classifier

To perform the classification, CNN is used. In our paper, we used 224 × 224 size images as input to the CNN. The performance of the CNN depends on the network architecture and weights that are set. The architecture of the CNN depends on the specific task, and it needs to know about the requirements of the data for the network. The size of the MRI slide, filter size, number of kernels, padding and strides determine the particular convolution layer size. Our classifier has 5 convolution layers with 32, 64, 128, 256 and 512 number of filters with different sizes (4,4), (5,5), (3,3), (3,3), (3,3) at different stages of stride 1, padding followed by max pooling layers are used to extract features and 6 fully connected layers to perform classification. The network is trained using back to back propagation with 200 epoch, we used Adam optimizer. Eqs. (2)–(6) show the layer wise parameter calculation and activation functions used at Convolution layer and Fully Connected layers.

Convolution_{width}

$$= \frac{\text{Input MRI Slice Size}_{\text{width}} - \text{Filter}_{\text{width}} + (2 \times \text{Padding})}{\text{Strides}_{\text{width}}} + 1 \quad (2)$$

Convolution_{height}

$$= \frac{\text{Input MRI Slice Size}_{\text{height}} - \text{Filter}_{\text{height}} + (2 \times \text{Padding})}{\text{Strides}_{\text{height}}} + 1 \quad (3)$$

No. Of Neurons in Convolution layer = *Convolution_{width}*

$$\times \text{Convolution}_{\text{height}} \times \text{Number of Filters} \quad (4)$$

$$\text{MaxPooling resultant image size} = \frac{\text{Convolution}_{\text{width}}}{2} \quad (5)$$

$$\begin{aligned} \text{Fully Connected layer parameters} &= \text{No. Of parameters from previous} \\ &\text{stage} \times \text{No. Of nodes in the present layer} \end{aligned} \quad (6)$$

Rectified linear unit used as activation function $f(x)$

$$= \begin{cases} 0 & \text{for } x < 0 \\ x & \text{for } x \geq 0 \end{cases} \quad (7)$$

$$\text{softmax function} = \frac{e^{xi}}{\sum_{j=1}^n e^{xj}} \text{ for } i = 1, 2, 3, \dots, n \quad (8)$$

4. Experiments and result

We compare the performance of the system while train and test with T1 weighted MRI, T2 weighted MRI images and segmented gray matter T2 weighted MRI images.

4.1. Experiment setups

In our work, we used MATLAB R2015b to perform slicing, skull stripping, and segmentation of the image. To train deep neural network data, parallel processing is needed, so we used open source package python 3.0, Google Colab to perform the training and validation of the classifier (GPU: 1xTesla K80, having 2496 CUDA cores, compute 3.7, 24GB(23.439GB Usable) GDDR5 VRAM). We used Keras library over Tensorflow modules to design our proposed model.

Table 2
Summarize the architecture of CNN.

Layer-1	Kernel Size	Feature map
Input image	224 × 224	—
Convolution layer -1	4 × 4	221 × 221 × 32
Drop out layer-1	20%	—
Zero padding layer-1	3 × 3	227 × 227 × 32
Max pooling-1	2 × 2	113 × 113 × 32
Convolution layer -2	5 × 5	109 × 109 × 64
Drop out layer-2	20%	—
Zero padding layer-2	2 × 2	113 × 113 × 64
Max pooling-2	2 × 2	56 × 56 × 64
Convolution layer -3	3 × 3	54 × 54 × 128
Drop out layer-3	20%	—
Zero padding layer-3	1 × 1	56 × 56 × 128
Max pooling-3	2 × 2	28 × 28 × 128
Convolution layer -4	3 × 3	26 × 26 × 256
Drop out layer-4	20%	—
Zero padding layer-4	1 × 1	28 × 28 × 256
Max pooling-4	2 × 2	14 × 14 × 256
Convolution layer -5	3 × 3	12 × 12 × 512
Drop out layer-5	20%	—
Zero padding layer-5	1 × 1	14 × 14 × 512
Max pooling-5	2 × 2	7 × 7 × 512
Fully Connected layer-1	1024	—
Fully Connected layer-2	1024	—
Fully Connected layer-3	32	—
Fully Connected layer-4	16	—
Fully Connected layer-5	1024	—
Fully Connected layer-6	3	—

Table 3
Training set, validation set and test set sizes.

Classification Type	Class Label	Training	Test set	Total Images
Multiclass Classification	AD	1857	464	2321
	MCI	793	198	991
	CN	921	230	1151
Binary Class Classification	AD-MCI	2650	662	3312
	AD-CN	2778	694	3472
	CN-MCI	1714	428	2142

In our work CNN model with 5 Convolution layers each followed by drop out, padding and max pooling layers followed by 6 fully connected layers are used in our model. In the training process of deep learning, the momentums are set to 0.9. The initial learning rate is 0.0001, and the max iteration number is 200. Proposed model is summarized in Table 2.

4.2. Creating training and test set

In our experiment we used 4463 MRI slides. We split the image data in to 80: 20 train and test sets purely based on subjects to overcome the intra relation among the split data to perform the classification without biasing. We used this data set for multiclass and binary classification and the data set is summarized in Table 3. The image data is augmented to resist the model from noise and geometrical changes.

4.3. Results

During training, the model is activated to classify MR brain images for 200 epochs. The loss and accuracy graphs for validation sets are carried on single fold. Our model have 5 convolution layers with 32,64,128,256 and 512 number of filters with different sizes 4,4,5,5,3,3,3,3,3 at various stages of stride 1, padding and follow by max pooling, the feature extractor followed by 6 fully connected layers. The networked is trained by Adam Optimizer using back to back propagation with the 200 epochs.

4.3.1. Studies on subject wise classification

We used independent images collected from 25 Patients those are not included in train and validation to test the model using T1 weighted MRI and T2 weighted MRI images.

We used the model for binary classification and multiclass classification of the T1 Weighted MRI images, T2 Weighted MRI images and Gray level Segmented MRI images. We initially train the Model using T1 weighted MRI images and test the model. Accuracy and loss curves of T1 weighted MRI images are shown in Fig. 4

We observed that the train and validation accuracy curve and loss curve of AD-CN are not mutually following one with another and there is huge variation between validation and train curve as shown in Fig. 4(a) and (b). We conclude that the system is not trained accurately to perform binary classification of T1 weighted Raw MRI images into AD and CN.

The Model is also trained with AD-MCI T1 weighted MRI images. Fig. 4(c) and (d) shows the accuracy and loss curves of the model. We observed that the features generated from T1 weighted MRI are not accurately classifying the images into AD-MCI.

CN-MCI T1 Weighted MRI images are used to train the Model. Fig. 4(e) and (f) show the train, validation accuracy and loss curves. From the curves we conclude that the model is not able to generate the features from T1 weighted MRI and the system not perform the required classification.

To perform Multi class Classification into AD-CN-MCI using our proposed system. We used T1 weighted MRI images of AD-MCI and CN, Train and Validation Accuracy and loss curves are shown in the Fig. 4(g) and (h). We observe that T1 weighted MRI images are not generating the required features to perform the multi class classification

The Model is further trained using T2 Weighted Raw MRI images to perfume the Binary and Multi class Classification the resultant accuracy and loss curves are shown in the Fig. 5

We trained our model using T2 Weighted raw MRI images from Fig. 5 we observe that the training and validation of accuracy and loss curves of binary and multi class classification are mutually follow one another the features extracted from T2 Weighted images are more likely useful for binary and multi class classification of images.

On comparing the T1 Weighted raw MRI accuracy and loss curves with T2 weighted raw MRI accuracy and loss curves we observed that the features extracted from T2 are more accurate to perform the classification of the AD-MCI and CN. We further analyze the parameters of classification using accuracy, sensitivity and specificity of both multi class and binary class classification of the T1 and T2 weighted raw MRI images. Tables 4 and 5 shows the performance parameters of the model trained with T1 and T2 weighted MRI images

On comparing the parameters generated from T1 weighted raw MRI images with T2 weighted raw MRI images, we observe CNN model trained with T2 weighted MRI are making better classification than compared with T1 weighted MRI both in binary classification and multi class classification.

In AD-CN, AD-MCI binary classifications model trained with T1 weighted MRI images generates better accuracy more than 50 %, whereas CN-MCI binary classification it generates only 19 % of accuracy it is the most remarkable variation that we had observed. We are interested to make prediction of AD from CN and MCI but without perfect classification of CN from MCI it will degrade the performance of system. On other hand the CNN model trained with T2 weighted raw MRI are making remarkable prediction of CN-MCI and it increase the overall performance of the system for multi class Classification. The performance is compared in Fig. 6

To further increase the performance of the model in order to classify AD from CN and MCI, T2 raw images are preprocessed

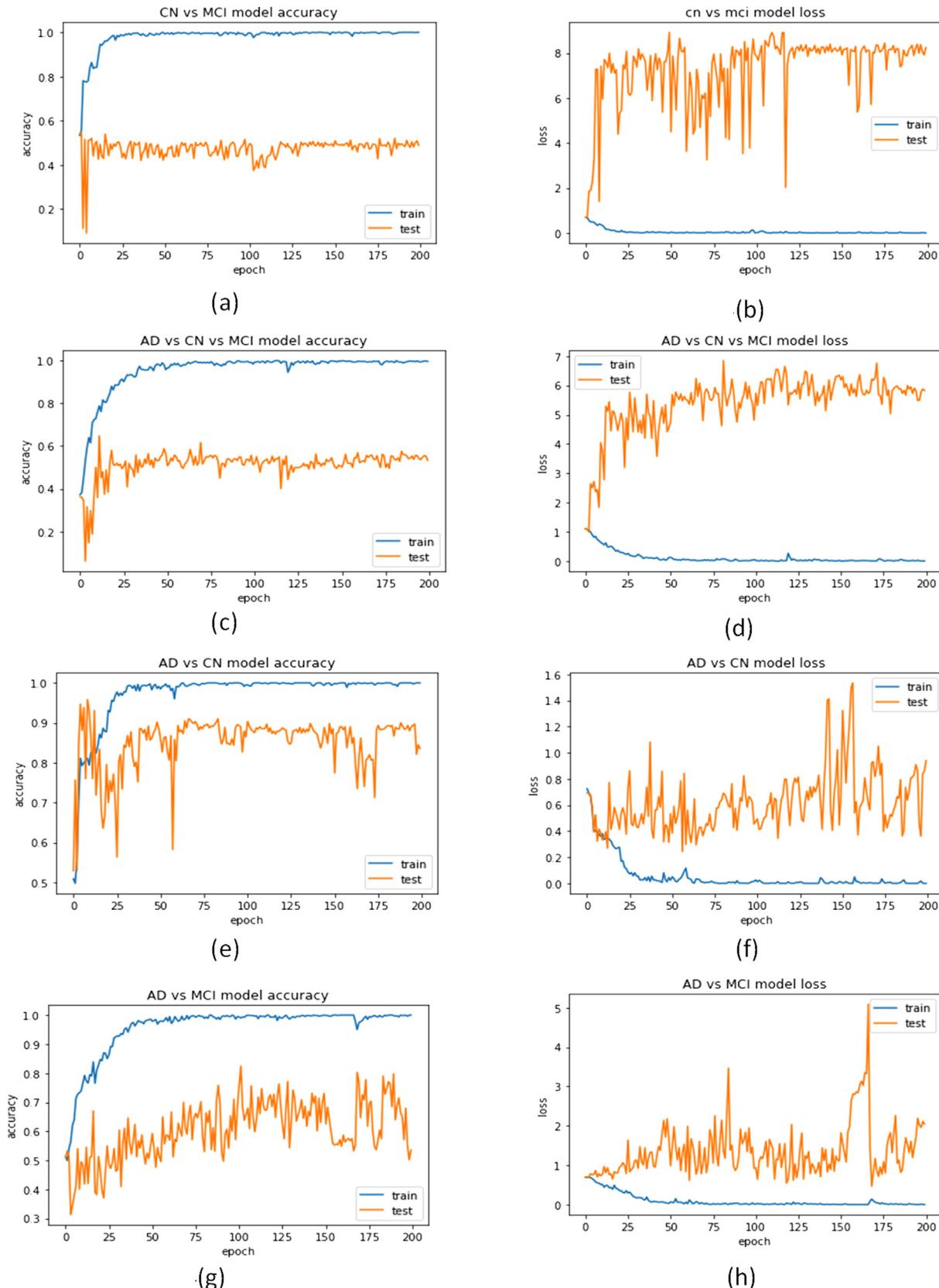


Fig. 4. Accuracy and loss Calculation of AD-CN, during training and testing of T1 weighted MRI (a) AD-CN Accuracy Calculation, (b) AD-CN Loss Calculation (c) AD-MCI Accuracy Calculation, (d) AD-MCI Loss Calculation (e) AD-CN Accuracy Calculation, (f) AD-CN Loss Calculation, (g) AD-CN-MCI Accuracy Calculation, (h) AD-CN-MCI Loss Calculation.

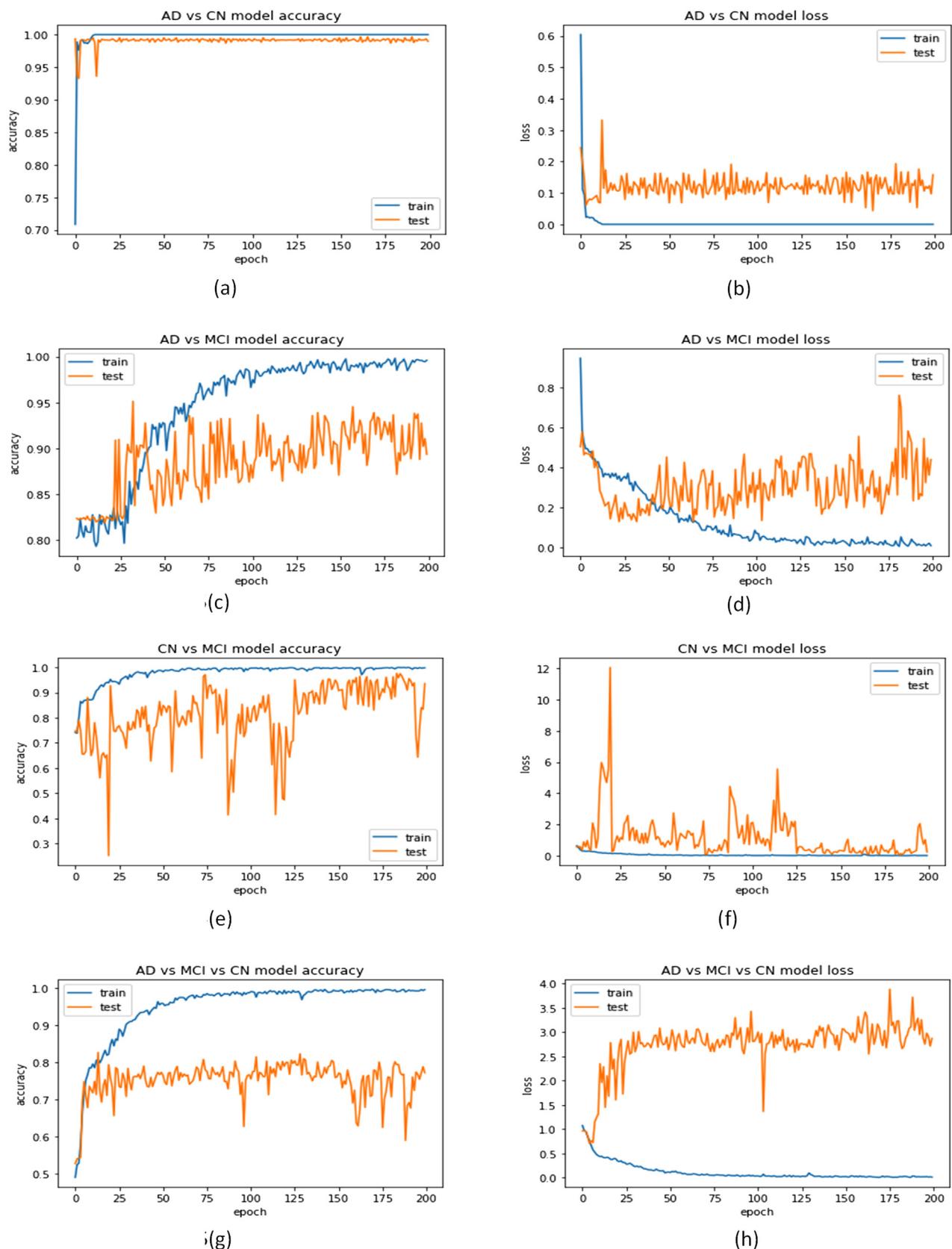


Fig. 5. Accuracy and loss Calculation of AD-CN-MCI, during training and testing T2 weighted MRI (a) AD-CN Accuracy Calculation, (b) AD-CN Loss Calculation (c) AD-MCI Accuracy Calculation, (d) AD-MCI Loss Calculation (e) AD-CN Accuracy Calculation, (f) AD-CN-MCI Accuracy Calculation, (g) AD-CN- MCI Loss Calculation.

Table 4

Performance parameters of the Model trained and tested with T1 weighted MRI images.

Classification	Modeling	Accuracy	Sensitivity	Specificity	AUC	Images used for test	
Binary Classification	AD-CN	55 %	76 %	56 %	87 %	AD	464
	AD-MCI	51 %	51 %	75 %	60 %	CN	230
	CN-MCI	19 %	19 %	14 %	50 %	AD	464
Multi Class Classification	AD-CN-MCI	34 %	34 %	22 %	55 %	MCI	198
						CN	230
						MCI	198
						CN	230
						MCI	198
						AD	464

Table 5

Performance parameters of the Model trained and tested with T2 weighted MRI images.

Classification	Modeling	Accuracy	Sensitivity	Specificity	AUC	Images used for test	
Binary Classification	AD-CN	97 %	97 %	97 %	98 %	AD	464
	AD-MCI	97 %	97 %	97 %	98 %	CN	230
	CN-MCI	68 %	68 %	70 %	85 %	AD	464
Multi Class Classification	AD-CN-MCI	73 %	74 %	74 %	96 %	MCI	198
						CN	230
						MCI	198
						AD	464

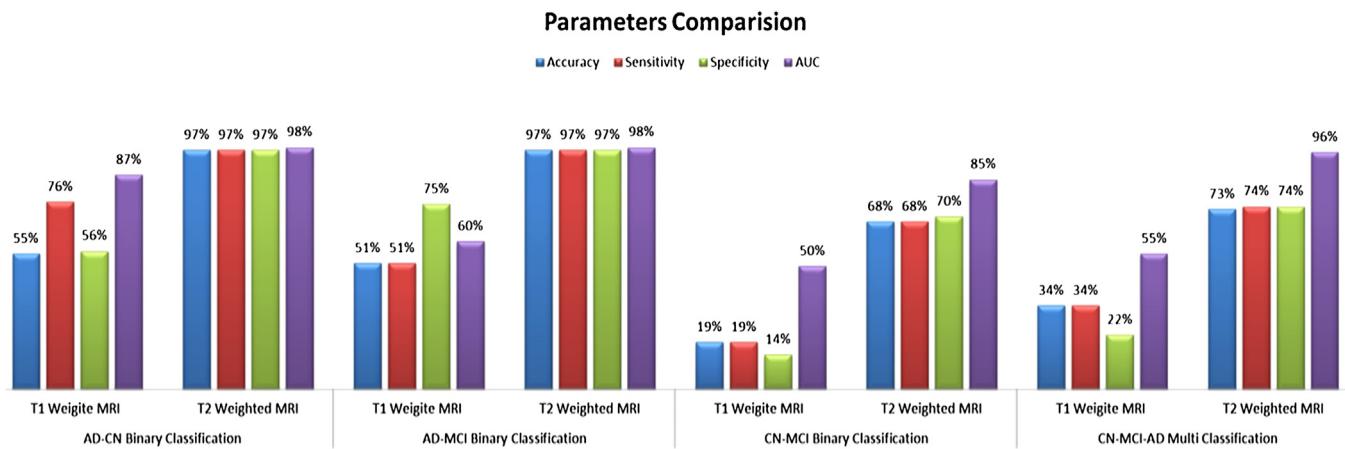


Fig. 6. Performance comparison of the model trained using T1 and T2 weighted MRI images.

by eliminating irrelevant tissues presented in T2 MRI image such as ears, eyes, Dura and skull using skull stripped algorithm and segmented the image into WM, GM and CSF. Gray matter of T2 weighted segmented MRI image is used as input to the CNN.

Our model trained with gray segmented MRI images has generated notable results than compared with T2 raw MRI images Fig. 7 Show the train and validation accuracy and loss curves of the model while train with GM segmented MRI images

We observed that the difference between the train and validation curves are very less and follow one with the other and gives better AUC. One of the significant observations is CN-MCI accuracy loss curves are having less variation than compared with T2 raw MRI images and follow one with another to yield better classification of CN-MCI incorporate to increase the accuracy of multi class classification using segmented MRI images.

We compare the performance of the proposed model trained with raw MRI images and GM segmented MRI images in Fig. 8. We observed that the accuracy, sensitivity, specificity and AUC of the model trained with Gray matter segmented image is better than compared with raw T2 MRI images, especially better parameters

Table 6

Accuracy of the model using 10 fold cross validation applied on gray segmented image.

Modeling	Accuracy	Sensitivity	Specificity
AD-CN	97 ± 0.3 %	96 ± 0.6 %	96 ± 0.8 %
AD_MCI	94 ± 0.2 %	90 ± 0.7 %	94 ± 0.8 %
CN-MCI	96 ± 0.1 %	93.0 ± 0.9 %	97 ± 0.8 %
AD-MCI-CN	86 ± 0.5 %	89 ± 0.5 %	85 ± 0.8 %

are observed that CN and MCI binary classification will further improve the performance of the algorithm under multi class classification.

Layer wise features are useful for clear verification of the model here we represent the features generated layer wise for anatomical verification of MCI and AD images in Fig. 9 and 10. As the initial layer retain the most of the image information and edge information of the image applied, as the network become deep the image abstract is appeared in the resultant image and give more information about their class.

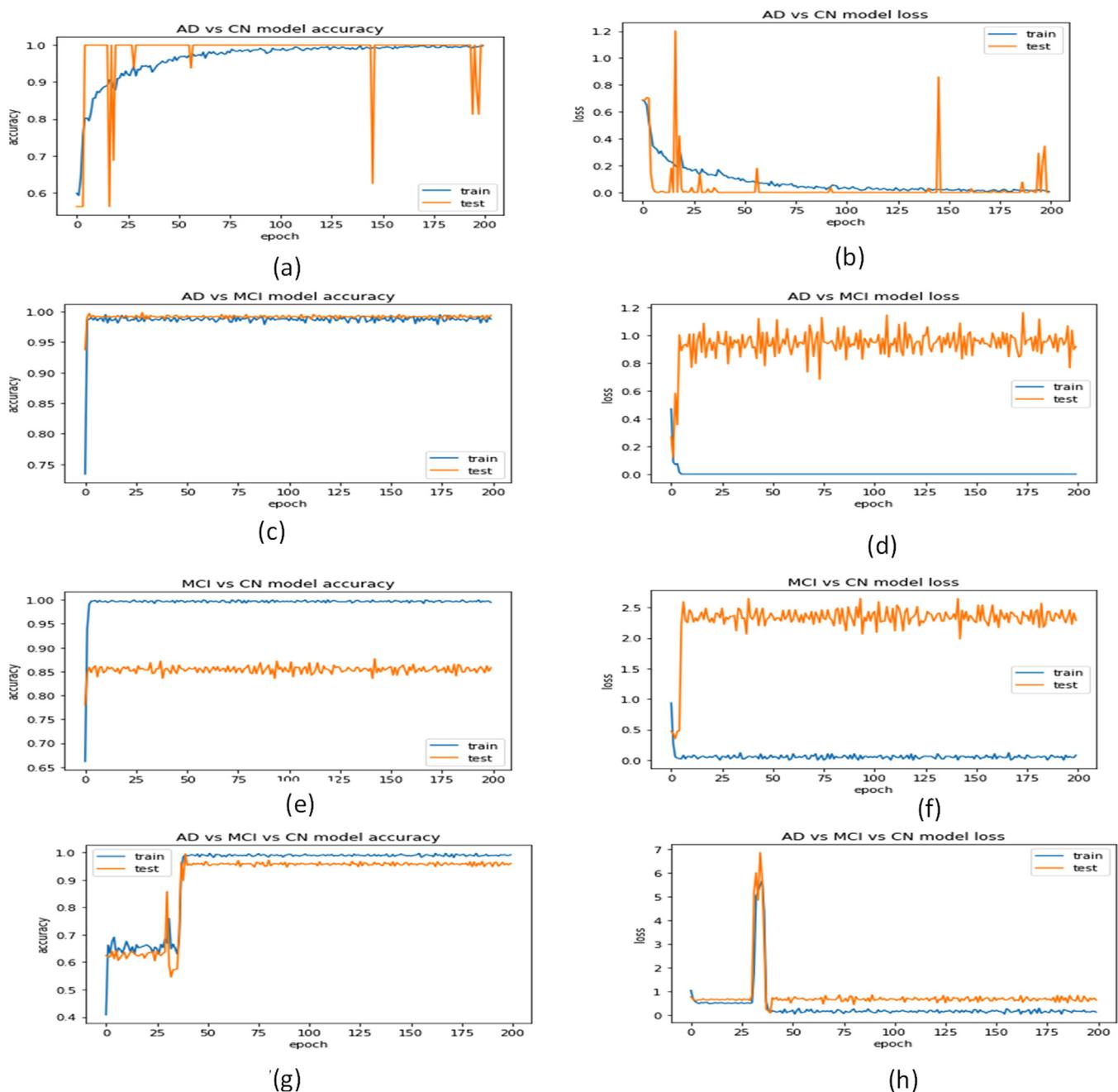


Fig. 7. Accuracy and loss Calculation of AD-CN-MCI, during training and testing of GM extracted from T2 Weighted MRI (a) AD-CN Accuracy Calculation, (b) AD-CN Loss Calculation (c) AD-MCI Accuracy Calculation, (d) AD-MCI Loss Calculation (e) AD-CN Accuracy Calculation, (f) AD-CN Loss Calculation, (g) AD-CN-MCI Accuracy Calculation, (h) AD-CN-MCI Loss Calculation.

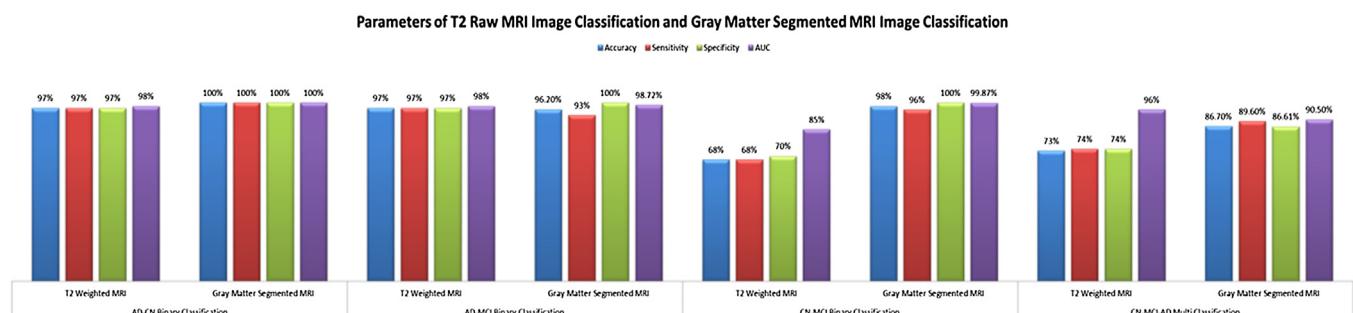


Fig. 8. Comparing the performance parameters of the proposed model trained by T2 raw MRI images and Gray matter segmented MRI images.

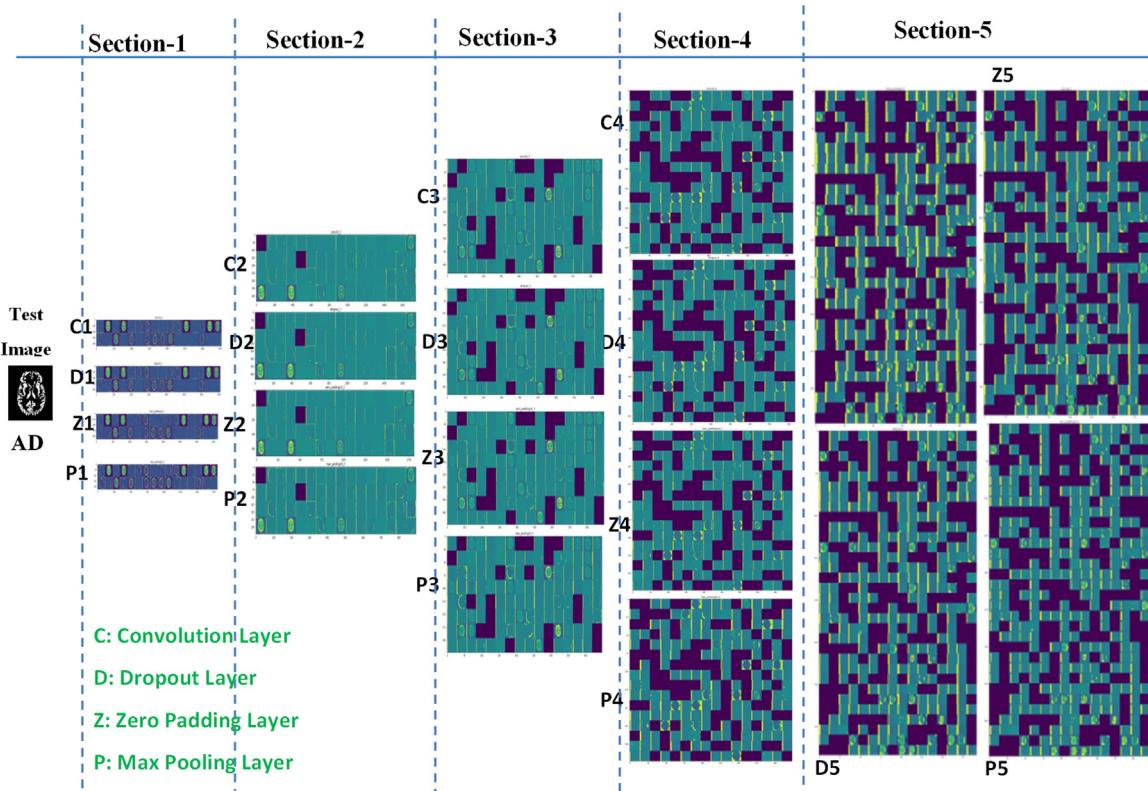


Fig. 9. Layer wise features extracted from MCI images for anatomical analysis.

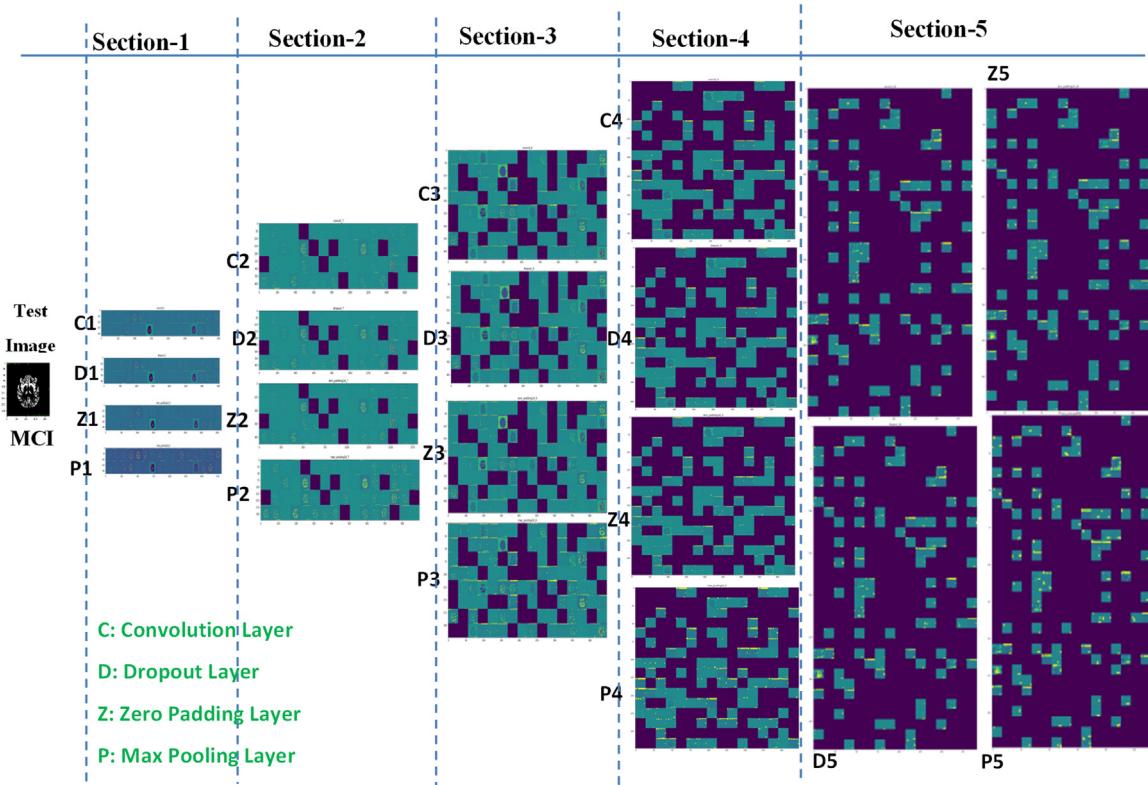


Fig. 10. Layer wise features extracted from AD images for anatomical analysis.

Table 7
Comparing the proposed model with different work flow models.

Author, year	Resources	Processing and Training	Classification	Modalities	Accuracy	Sensitivity	Specificity	AUC
Fung and Stoeckel (2007)	SPECT	Relevant area and selection of Voxel	SVM	AD-HC	-	84.40 %	90.90 %	-
J. Escudero, 2011	MRI	Volumetric and cortical thickness of Hippocampal	SVM	AD-HC AD-MCI AD vs. HC	89.20 % 72.70 % 95.50 %	-	-	-
Suk and Shen (2013)	MRI, PET	SAE	Multi kernel SVM	MCI vs HC MCI _C vs MCI _{NC} HC	85.00 % 75.80 % 80.30 %	-	-	-
Adaszewski et al. (2013)	MRI	Hippocampal temporoparietal atrophy	SVM	AD cMCI ncMCI	73.50 % 63.70 % 69.00 %	-	-	-
K.R. Gray, 2013	PET	MRI volumes, voxel-based FDG-PET signal intensities, CSF biomarker measures, and categorical genetic information	Random Forest	AC-HC AD-MCI	89 % 75 %	-	-	-
Andrés Ortiz, 2013	MRI	Tissue information	SVM	AD-CN	90 %	95 %	-	-
Fan Li, 2017	MRI	Multi Model features	CNN	AD-HC SVM IVM	88.31	91.4	84.42	92.73
Lama et al. (2017)	MRI	Cortical thickness, folding index	10-fold CV LOO CV	RELM SVM IVM RELM	59.5 77.3 78.01 73.36	62.3 62.12 75.81 70.97	62.85 79.85 79.12 75.95	77.22
Altaf et al. (2018)	MRI	GLCM, SIFT,LBP,HoG's,Clinical Data	SVM	AD -CN AD vs MCI CN vs MCI	97.80 % 85.30 % 91.80 %	100 % 75.00 % 90.00 %	95.65 % 94.29 % 93.33 %	-
Hett et al. (2018)	MRI	Gray Matter + Gabor Filter	Weak classifier	Intensity-based grading histo Texture-based grading histo	CNvsAD CN vs. pMCI AD vs. sMCI sMCI vs. pMCI CNvsAD CN vs. pMCI AD vs. sMCI sMCI vs. pMCI	93.5 90 81.1 74.9 94.6 92 82.6 76.1	95.5 81.8 78.5 77.6 94.2 92.5 77.6 74.9	82.7 81.4 68.3 67.2 86.6 81.2 72.6 70.2
Chaddad et al. (2018)	MRI	Selecting MRI Based on Entropy, Intensity.texture,shape	CNN	AD - HC	-	-	-	92.58 %
Kim et al. (2019)	MRI	Cortical Thickness	Hierarchical Approach	CN -Dimentia AD vs FTD bvFTD vs PPA nfvPPA vs svPPA	86.10 % 90.80 % 86.90 % 92.10 %	87.00 % 87.50 % 92.10 % 97.40 %	85.40 % 92.00 % 77.10 % 88.00 %	0.917 0.955 0.865 0.955
Vaithinathan and Parthiban (2019)	MRI	Region of Interest	SVM + Bootstrapped	AD-CN AD-NC	-	89.58	85.82	-
Li and Liu (2019)	MRI	Hippocampal	CNN + RNN	MCI - NC pMCI-sMCI	-	-	-	91.00 % 75.80 % 74.60 %
Silvia Basaia et al. (2019)	MRI	No feature engineering	CNN	AD-NC AD-MCI MCI-NC	99.2 75.4 87.1	98.9 74.5 87.8	99.5 76.4 86.5	-
Proposed Method	MRI	Segmented Gray matter using Enhanced ICA	CNN	AD-CN-MCI AD-CN AD-MCI CN-MCI	86.7 100 96.2 98.0	89.6 100 93.0 96.0	86.61 100 100 100	90.50 100 98.72 99.87

4.3.2. Study using 10 fold cross validation

To evaluate the performance of the proposed system without biasing the model is evaluated using 10 fold cross validation where gray segmented images are divided into train and tested as one part of the images are used for test and remaining images are used for training and this is repeated for 10 times. We used accuracy, sensitivity and specificity as scoring parameter for both binary class and multi class classification the result is given **Table 6**. It is observed that the T2 segmented image data gives better classification accuracy to diagnose the early stage of AD. It observed that $98 \pm 0.1\%$ of accuracy had achieved and it is the remarkable variation that we had observed

5. Discussion

Various studies had conducted on classification of AD from MCI and CN by extracting features and make classification using different techniques. We had used preprocessed image to extract local features and perform classification using our model. We compared the performance of proposed system with different models discussed in literature review as shown in **Table 7**. It is observed that our classifier gives remarkable performance both in binary classification and multiclass classification.

It is observed form the **Table 7** that, different features are extracted to make the classification of the AD such as relevant area and selection of Voxel (Fung and Stoeckel, 2007), Volumetric and cortical thickness of Hippocampal (Escudero, Javier et al., 2011) Hippocampal temporoparietal atrophy (Basheera and Ram, 2018), Tissue information Andrés Ortiz et al. (2013) are used to make the decision using SVM. Hybrid features are also used to make the prediction of AD using Volume and Shape of the tissues (KR Gray et al., 2013) using Random Forest. As the hybrid features are using then the irrelevant data make the system over fitting to reduce the number of features PCA is used and make the decision using SVM. To analyse and improve the accuracy of prediction second order statistical parameters are used to make the required classification features such as GLCM, SIFT, LBP, HoG's, along with Clinical Data (Altaf et al., 2018) are used as features and decision taken by applying SVM over the features. Gabor filtered GM images are used to generate features and predict the class using weak classifier. As state of art of developing deep learning algorithms are used and make the classification using CNN and RNN with end to end operations on raw images. In this work we used CNN model and that model is trained with gray segmented MRI image.

5.1. The main advantage of our experiment

- 1 This is the first study used T2 weighted MRI images to make the differentiation of AD from MCI and CN.
- 2 Generally most of the classification techniques are used to differentiate the images at AD and CN or AD and MCI. In this study we work on both Binary and multi class classification
- 3 In our endeavor, we Segmented T2 MRI image using Hybrid Enhanced ICA
- 4 Gray segmented MRI Images are used to train and test the model.
- 5 We mainly concentrate at early diagnosis of AD, this is accomplished by making the differentiation of MCI and CN more accurate.
- 6 We tested our model with independent set of images other than train data separated at subject level
- 7 We use heterogeneous MRI volumes of different age groups and gender with different MMSE scores, GD Scale Total Score, NPI-Q Total Score, Global CDR.

- 8 In our work we observed that the frame work is not effected with noise and data augmentation.

5.2. Limitations of our work

- 1 Clinical information is not taken adopted in the model.
- 2 It is only limited to differentiate AD from MCI and CN, not tested on various neurological disorders.
- 3 It is not to replace physician, it is used to strength the decision taken by the physician

5.3. Research line

- 1 If multiple numbers of clinical evaluations are added to train the model it will become strong and make the physician decision more strong and reduce the work load.

6. Conclusion

In this study, we employed a 5 layer CNN with 6 fully connected deep learning model to classify MR images into Alzheimer's Disease, Mild Cognitive impairment and Normal Cognitive categories. These models are tested using Alzheimer's disease Neuroimaging Initiative (ADNI) database T2 MR brain images database of 4463 images. Our results show that T2 weighted MRI image with segmented GM image give highest accuracy than compared to existing techniques. Especially early diagnosis of AD in the stage of MCI -CN gives high accuracy of 98.0 %. This helps the patient to get featured treatment.

Author contributions section

Shaik Basheera had contributed in data set collection, pre-processing the images, CNN model designing, train and test the model using T1w, T2w and Gray matter segmented MRI images. He also contributed in Manuscript preparation, comments on reviews.

M Satya Sai Ram, had contributed in Data set Collection and simulation and Manuscript preparation.

Declaration of Competing Interest

None.

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