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Diagnosis and Prognosis of Alzheimer's Disease Via 3D CNN

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Abstract: ***Mild Cognitive Impairment (MCI) is an early symptom of Alzheimer's disease (AD). The feature extraction and deep learning architecture of the convolutional neural network in 3D brain images is applied to the problem of Alzheimer's disease. The Structural Magnetic Resonance (sMRI) and Positron Emission Tomography (PET) image of the patient's brain are classified according to the vigorousness of the disease and is labelled to be either in MCI or in AD or Normal Control (NC) condition. In this paper, we proposed a model and presented the baseline convolutional CNN with four layers viz., Convolutional layer, Leaky Rectified Linear Unit(LReLU), S3Pool layer and Global average pooling. Further, the 3D image data is used to perform the binary and ternary classifications and its performance are examined. The strength of the network has improved interior resource utilization evaluated with medical images, sMRI and PET on hippocampal ROI. The results of our proposed CNN architecture have achieved an accuracy level of 0.945, 0.859 and 0.748 respectively, when compared to the conventional AlexNet based network. The obtained data from the ADNI database shows better performance with our proposed model.***

Keywords: Brain imaging, Alzheimer's Diseases, Deep learning, Convolutional neural network, sMRI and PET.

I. INTRODUCTION

Alzheimer's disease prevails commonly for people in their older age. The disease affects the brain which may lead to the loss of memory and other cognitive capabilities too. Alzheimer's Disease is prone to the majority of people below 65 years of age. The symptoms like diminishing cognitive activity and memory loss may be assumed as the consequence of ageing, but the real reason behind it may be Alzheimer's disease[1]. There is no perfect cure for this deadly disease but when identified in early stages with the assistance of treatments the harm of the disease can be postponed. Still, the researchers are mining the possible drug for a permanent cure to the disease[2]. This disease impacts mainly on the neuron, as time passes the affected neuron's count starts to replicate. The disease thus jams the functioning of millions of neurons as it replicates[3].

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Symptoms of the Alzheimer's disease are memory loss, confusion, disability in learning, leading to abnormalities in the day to day habits, disorientation in behavior, difficulty in speaking and walking, etc. it's very vital to find the disease in early stages and provide them with very good care and affection. The last few years all researchers are focused on neuroimaging studies as well as analysis of imaging data, and it has been increasing day by day, some imaging data such as functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging(sMRI), photon emission tomography(PET) and single photon emission computed tomography(SPECT), in addition to that diffusion tensor imaging(DTI)[4]. This neuroimaging data are given so many improvements to detect the AD diseases.

The advancement in the convolutional neural network algorithm has made it possible to diagnose the neurological disease in the early stages[5]. This advancement has thus given the way to find the AD and MCI in early stages[6]. Mostly MRI and PET images are used in such diagnosis of neurological diseases[7]-[8]. These methodologies are very much preferred as they are noninvasive and the nearly no pain is being incurred by the patients. In addition, MRI provides a high resolution when compared to the other image modalities of the brain[9]-[10]. The image set of MRI data describes brain atrophy and brain size[11].

The majority of the research work concentrated on a voxel-based morphometric approach (VBM) using sMR images[12], which is very useful to differentiate the brain changes in diseases. The VBM approach especially concentrating on grey matter (GM) volume from the frontal lobe. GM atrophy is to begin, and important atrophy in the hippocampal region[13]. Atrophy will spread to the remaining regions of the brain for AD diseases[14].Tensor-based morphometry (TBM)[15] method brain image technique that identifies the brain regions and local structural changes from the gradients of the deformation fields[16].

Almost, various brain image modalities and classification techniques are applied to detect Alzheimer's diseases. Especially we focused domain knowledge on the most important ROI. In these diseases, hippocampal subregions like some specific regions are highly dominated[17]. In most of the research like a content-based image or computer, vision studies are going through a feature-based method[18]. In AD detection also performed a feature-based approach. For example, the features are corners, edges and other 2D or 3D[19][20][21][22].

In recent times, implantation of a feature-based approach in machine learning is continuously replaced with various deep learning architecture[23]-[24]. In our present work, we build a new network to classify the diseases using the different images modalities. This proposed method is based on the supervised machine learning (CNN) with different architecture is called Inception block.

Our improvement in Brain sMRI and PET data fusion analysis for Alzheimer's Diseases prediction using 3D CNN is based on the following literature. The main strength of this network is reducing the using number of parameters without affecting the classification accuracy. We designed new architecture and compared with a conventional AlexNet based network. It reaches a good accuracy level when compared to the existing network. In this network, we used 3 dimensional hippocampal ROI as an input. Two image modalities are sMRI and PET are used and obtained from ADNI datasets(http://adni.loni.usc.edu) for AD patients.

The organization of this paper is as follows. Section II focuses on the background and existing classification method of the related works. Section III, we propose the new AlexNet based CNN architecture. Section IV presents details of the experimental setup, results and Discussions. Sections V accommodate Conclusion of the paper.

II. RELATED WORKS

The adni dataset is of 3D sMR image and PET images which comprises of the complete brain's structure. This AD and MCI detection using ROI biomarkers, voxel-based morphometry, patch-based and domain knowledge are applied for feature extraction. Sometimes these biomarkers have blurry images and cannot meet the expected criteria. In the ROI features is complete brain is considered for feature extraction[25]. Various machine learning techniques have been used along with these features extraction, feature selection, classification and performance evaluation (Accuracy, Sensitivity and Specificity) for diagnosing the AD and Mild Cognitive Impairment patients. In this part, we are going to discuss the existing works on feature-based classifications and neural network classification. Feature type with classification has performed with different types of image modalities. For example, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) single-photon emission computed tomography(SPECT) and so on. But here we discuss and about sMRI and PET images for AD detection.

H. Tabatabaei-Jafari et al.[26] they focused on combining hippocampal index and hippocampal volume by cerebral volume with mini-mental state for predicting the MCI to AD conversion for getting practically accurate results with the several assessments. S. Lahmiri and A. Shmuel et al.[27] deserves a multi-parametric MRI research for identifying the alteration, specific to bvFTD and EOAD. The features like cortical thickness and WM microstructure are applied on Random forest and receiver operator characteristics(ROC) assure analysis to find the capability of MRI in clinical syndromes (cortical thickness and WM) classification. In[28] Jane Maryam Rondina et al. compared the fMRI, sMRI datasets to generate atlas using machine learning algorithm (SVM classification) which helps in obtaining the exact and most relevant region of the brain for AD and MCI patients. From this, they got an accuracy level of 92.5%, 84% for F-FDG-PET and ROI-MKL for the entire brain. They introduced new CAD based on machine learning classifiers to classify Alzheimer's Diseases and normal control subjects. For this, the features such as fractals obtained from MRI-based cerebral cortex surfaces, cortical thickness, ADAS cognitive test score, and gyrification index have been considered. SVM shows better accuracy in distinguishing the AD from a normal subject. T. Altaf et al[29].the author presented an algorithm to detect the Alzheimer disease into three types(AD, MCI and Normal Control) by using visual word approach that improves the GLCM (Gray level co-occurrence matrix), a local binary pattern, feature transformation of scale invariant, and the gradient histogram. A. L. Aziz et al[30].focused on changes in neuroimaging biomarkers based on age and the presence of amyloid biomarkers in cerebrospinal fluid. In [31] proposed the diagnosis for AD using MR image preparation, feature extraction using SVM and PCA. The SVM parameters are optimized using SDPSO (switching delayed particle swarm optimization) algorithm to classify MCI and AD patients.

C. Ieracitano et al[32]proposed a Dl model which evaluates PSD of non-invasive scalp EEG recordings for the classification of AD, MCI and Healthy control patients and obtained an accuracy level of 89.8% in binary classification and 83.3% in multiclass classification. In [33], a deep learning predicting algorithm is used with single cross-section brain MRI images to diagnose AD and predict convertible MCI. CNN used to get better accuracy and reduced the network parameters for regularization. T. Yeet al[34].proposed a selective multitask model for selecting the most important features from 93 Region of Interest (ROI) for distinguishing MCI and AD. Further, he used a linear regression model for all image modality. In [35], they introduced an ordinal ranking and data-driven model with one ROI for distinguishing the AD and MCI. Further, the author analyzed several brain regions tolearn the feature automatically. H. Il Suk et al[36].developed a framework which combines the methods of deep learning with sparse regression for AD and MCI prognosis and diagnosis. To achieve this, they used sparse regression models for feature selection with CNN for multiple sparse regression models. S. Spasov et al[37].proposed a deep neural network that combines MRI, demographic, neuropsychological and Apoe4 genotype and extracts features according to classification. Structural and warp field characteristics are taken along with network parameters to avoid overfitting. They got an accuracy of 86% for CMRI and 100% for classifying NC v AD. In [38], introduced a multiple cluster dense CNN model using MR images.

In this model, the brain is initially partitioned into various local regions and 3D patches are extracted and clustered by using a k-means clustering method with an accuracy of 89.5% for AD and 73.8% for MCI. K. R. Kruthikaet al[39].proposed a CBIR system using 3D-autoencoder, 3D CNN, and 3D Capsule Network for early detection of Alzheimer's diseases. This method is capable of fast learning and handling the transitions and rotations of images using CapsNets. It acquires an accuracy of 98.42 % in AD classification. In [40], a deep-learning framework is developed for identifying subjects at the stage of MCI using the images of FDG-PET with non-AD / non-progressive. This model acquired an accuracy of 82.51% in classification using single modality measures. D. Zafeiriset al[41].studied and evaluates an ANN model to discover biomarkers and validated the AD. The proposed model analyzes data with an algorithm that predicts gene interaction. In [42], they proposed a CNN based ResNet34 model that classifies healthy and AD.MR images and which is trained with data augmentation techniques, optimal learning rate finder and fine-tune methods. It mainly eliminates the manual selection of features. M. Talo et al[43].introduced the new CNN to multi-modal and multi-level features of PET and MR image the problem of AD. First, 3D CNN isbuilt on local images and 2D CNN constructed for upper high-level images by softmax layer for MCI and AD classification. Finally,these trained features are combined with a fully connected layer for the detection of AD. H. Liet al[35].proposed an ordinal ranking and data-driven model with one ROI for distinguishing the AD and MCI. Further, they analyzed several brain regions tolearn the feature automatically. Finally, they compared with the multi-category classification model. The author attained a good accuracy level with an sMRI dataset from the ADNI database.

III. PROPOSED METHOD

In this section, we will present the Inception based CNN architecture in detail Fig.3.1**.** Our proposed Inception block does not give any premise for specific structural neuroimaging. Mostly T1 weighted MR images available, frequently used and its non-invasive method for AD detection.

The proposed Inception block architecture analyses the brain image recognition task and it gave the better performance with low-level computational cost. The main purpose of this network have chooses some specific layer at every level. This network performs on input along with one filter size (1 X 1). Additionally, we added a max pooling operation. The main Inception block has four pipelines and it works simultaneously. The first block has 1 X 1 X 1 filters are used to reduce the parameter in the network by reducing the dimension. specifically, the first part of the network has three convolutions. 1 X 1 X 1,3 X 3 X 3 its equivalent to 5 X 5 X 5 convolutional, 1 x N and N X 1. The Convolutional filter size 3 X 3 splits into two parts that are 1 X N and N X 1 convolutions. For example, 3 X 3 or 5 X 5 convolutions are equivalent to 1 X 3 or 1 X 5 convolutions. This layer is cheaper than 3 X 3 convolutions. The second part of the network has only two convolutions. 1 X 1 X 1, 1 X N and 1 X N. third band of the network has only max pooling layer and fourth having one 1 X 1 X 1 convolution filters. Likewise, all bands started with 1 X 1 X 1 convolution filters except max pooling operations.

In this network,we have used batch normalization in all convolutional layers for speed up the training process and to reduce the overfitting. The network gets 10 times more improvement after applying the batch normalization and plays a very important role is regularize data in every hidden layer of the network. Finally, we add the Leaky rectified linear unit(LReLU) function for activatingevery layer instance of ReLU. The function has a small negative slope (0.01, or so on).

Function is

$$f(x)=1\ (x<0)\ (x\ \alpha) +1(x>=0)\ (x) \quad (1)$$

where α is a small constant value.

The proposed Inception block has n features based on the input and shown in Fig.3.2**.** The main advantage of this network has reduced the parameter inside the network. This main idea of this network has transformed the spatial data from source to destination feature space.

The proposed Inception block compared with conventional AlexNet network architecture

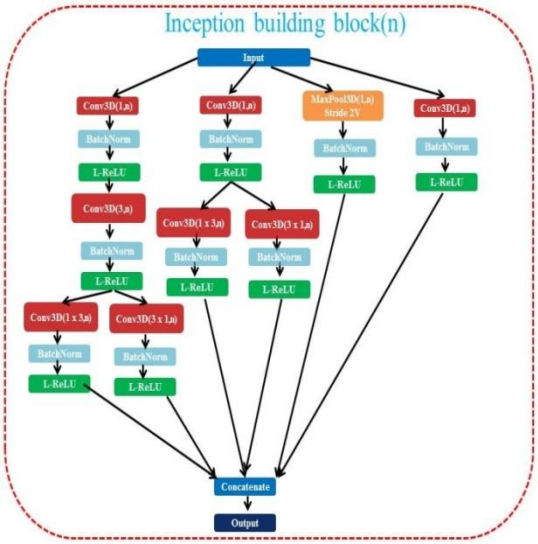

Fig.3.1: Proposed Inception block network architecture.

Here n stands for the number of input ROI as a feature. Conv3D(s,m) stands for the 3 Dimension convolutional with size and filters.MaxPool3D(p,q) stands for 3D max pooling layer for down-sampling operation with stride q and pool size p.

The Convolutional filter size nxn split into two parts that are 1xn and nx1 convolutions. For example, 3x3 or 5x5 convolutions are equivalent to 1x3 or 1x5 convolutions, which is performed first and second performing 3x1 or 5x1 convolutions which is an output of the final layer. This concatenation of two convolutions is very cheaper than 3x3 convolutions.

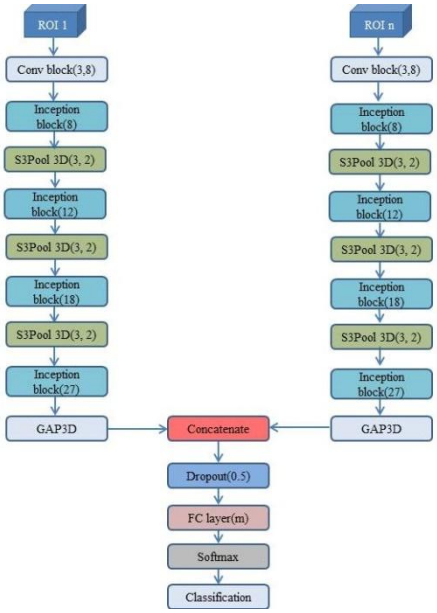

Fig.3.2. Proposed architecture.

Here S3Pool 3D layer stands for down-sampling operation with stride q and pool size p. GAP3D stands for Global Average Pooling.

Table 3.1. Number of total subjects for every class.

Diagnosis	AD	MCI	NC
Total Subjects	51	252	228
Train set	34	212	190
validation set	3	22	22
Test set	14	18	16

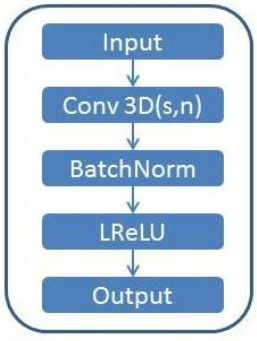

Fig. 3.3: The Convolutional block of our network. Conv3D *s,n - three dimensional with a number of filters of size.

Our proposed network has n number of ROI from the brain scan and variety of image modality use a separate pipeline. Finally, the entire above pipelines are concatenated along with dropout, fully connected and softmax layer for classification to produce the result as shown in Fig. 3.2. Additionally,we added S3Pooling layers instant of Max pooling in our proposed network architecture.

IV EXPERIMENTAL SETUP

In this proposed work, we analyzed conventional AlexNet-based network for the problem of Alzheimer's diseases compare with proposed network. Here we used two types of neuroimaging modalities (sMRI, PET) on the classification of AD or MCI. The implementation results are displayed in a Table 4.3 and are discussed.

A. ADNI Neuroimaging Data

In this paper, neuroimaging data for our proposed method from the Alzheimer's Disease Neuroimaging Initiative (ADNI) organizations(http://adni.loni.usc.edu/). The ADNI dataset organization was started in the year 2003. ADNI comprises of neuro images of the patients who have been affected by the alziemer's disease, it has been developed by the National Institute of Aging. It is a non-profit Organization, led by the Principal Investigator Michael W. Weiner, MD. The Primary goal of this ADNI has been to visit to test whether sMR imaging, single-photon emission computed tomography (SPECT), Positron Emission Tomography (PET) and other biological markers along with the clinical scores and assessment ratings combined with to detect the early Alzheimer's Disease(AD) or mild cognitive impairment(MCI).www.adni-info.org From this database the data can be downloaded where this database also monitors the regular research works done. First ADNI was recruited 800 subjects from these three protocols are ADNI-2 and ADNI-GO. Consist of totally 1,500 subjects which have been divided into early Ad, early MCI or late MCI and normal control based on the age which must be within the range55 to 90.

B. Analysis Datasets and selection

The detailed data obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) dataset is used for the training set, validation set and testing set. We acquired 531 subjects: AD category - 51, the MCI category - 252 and Normal control - 228. The entire subjects are selected from ADNI 2-GO and ADNI 3 datasets. For each and every patients having T1 weighted structural MRI as well as PET images.

Both ADNI 2-Go and ADNI 3 of the same ADNI group (Table 4.1), all the values are denoted as std and mean. The Baseline characteristics of the participants are displayed (Table 4.1). We have selected age, education, gender, MMSE score and CDR for every patient subjects. In this paper, we focused on the hippocampal ROI and neighbouring brain regions for our research.

In the present paper, we performed a preprocessing method as a stage 1 to select the most discriminative ROI in the brain image of MRI and PET to classify the patients with AD and MCI. In stage 2 we proposed neural network architecture and selected ROI as an input.

C. T1 MRI and 18F-AV-45 PET image acquisition.

We obtained high resolution of 3D T1 weighted mr images with the sagittal plane format by using an MP-RAGE pulse sequence with some following parameters. TE = 4.19, TR = 12.2, pixel bandwidth = 88.73, flip angle 15^{o}, matrix size is 256 X 256 Voxel size is 0.85 X 0.85 X 1.6mm, the slice thickness is 1.6 and 204 slices, these MRIdata we obtained from ADNI using LX 8.3 1.5 Telsa Scanner.

Similar to T1 weighted MR images, PET data obtained from ADNI dataset from January 2005 to December 2007. All PET subjects have blood glucose levels beginning of the scanning.This includes a learning of cerebral glucose metabolism. PET data have some special parameter with some specific scanners. The subjects were injected with a high dose of 370 MBq of 18F-AV-45. According to the ADNI database status, after the eye opens PET scans recorded along with the subject. The image scans were started 50 to 60 minutes after FDG administration. All sites were performed by 3D scanning protocol with 15 Minutes time of acquisition. The image was performed by LSO-PET 16 slice PET/CT scanner. Matrix size is 256 X 256 with a smoothing factor of 5.

D. Preprocessing of T1– MRI and PET images

T1 weighted MR images and PET images were obtained from the ADNI datasets with different scanners and specific parameters. In this work, we focused on only tissue probability maps. Every individual subject estimated by the tissue probability method. Then this probability method aligned with atlas space for ROI selection. This image preprocessing method gives the importance of each ROI which means particular power. Unwanted brain tissue was removed from T1- MRI anatomical by using Freesurfer tool v6.0.0 (Segonne et al., 2004)(http://surfer.nmr.mgh.harvard.edu). Then N3 algorithm used for intensity normalization (Sled et al., 1998) and Brain Extraction Tool (BET) used for final unwanted brain tissue removal (Smith, 2002) by FSL tool (www.fmrib.ox.ac.uk/fsl). The MR image was segmented into white matter(WM), gray matter(GM) and cerebrospinal fluid(CSF)by usingStatistical Parametric Mapping (SPM8)(http://www.fil.ion.ucl.ac.uk/spm;) and its MarsBar plugin, are mostly used by the researcher and physicians for the ROI selection in image processing. Second, the 18F-AV-45 PET image was co-registered to the skull by using SPM. Then, to avoid the regional brain atrophy we applied PVE correlation to the co-registered images. It is important to register the segmented images normalized to the standard MNI152 space by using the DARTEL algorithm for further network construction and qualitative data analysis. The MNI152 stands for Montreal Neurological Institute (MNI) and it refers to space. Between acquisition space and MNI space resolved by with two-step registration. First, to achieve the spatial normalization, the spatial transformation parameter was registered to the functional image (FDG-PET) to T1 weighted MR images (structural images) and taken from the same image of mr images. Second, the registration spatial transformation parameter obtained from structural MR images into MNI space. More-over, after completing the preprocessing method, the obtained sMRI and PET images were aligned to 121 X 145 X 121 voxels.

In order to examine for the nextanalysis, we selected nine ROI from MR image and three ROI from PET data. We perform individual analysis for ROI selection by using Automated Anatomical Labeling (AAL) atlas. Most of the researchers were not taken the cerebellum region. Because the affected percentage is very minimal in this area. Each image in the Automated Anatomical Labeling is combined12 Region of Interests (In the left and right hippocampal formation, left and right para hippocampal gyrus, left and right entorhinal cortex, left middle temporal gyrus, right amygdala, right Precuneus Precentral Gyrus (PcG), Superior Temporal Gyrus (STG) and Middle Frontal Gyrus (MFG), which is most important part and affected first in the brain for AD detection.

E. Dataset arrangement and augmentation

In dataset augmentation, the data has divided into majorly three parts, training set, testing test and validation set. 14 subjects are selected randomly for testing, 34 subjects for the training set and 3 subjects for validation at the Table 3.1. Both categories of training and validation divided the average scale is a 9:1 ratio. Mostly, some common issue will be accrued in the network like overfitting whenever the limited dataset we used for the training set. That's the reason we used data augmentation forpreventing the network. This process happened in only the training set. As we discussed early, most of the medical images are imbalanced. In our performance, AD datasets are very small when compare to the remaining dataset of MCI and NC. We performed a balancing procedure while the training period to avoid the various class capacities. The data balancing procedure was showed[44] to reach high classification accuracy. In our work, we performed data augmentation and class balancing for various features on the proposed model. Parameter τ is used for data augmentation. The new images are taken from source place and randomly shifted into 2 pixels in each and every XYZ dimensions.

In this paper, we analyze about batch of size of the training data is assembled. Each and every image are selected from the dataset randomly and performed the augmentation process within the boundary size of the parameter. It will perform n number of times and forming the training data. While experimenting with the process in a network the number of training subjects is multiplied by augmentation and the factor is τ at one single training epoch. In this work we fixed the augmentation factor size is τ =5. With 436 subjects are taken from training dataset and it is trained.

To avoid the overfitting and prevent the network we divided into three parts. As I said earlier, this process will continue and repeated automatically after every training epoch.

Table 4.1: Baseline characteristics of participants:

Dataset	Group	Subjects	Male/Female	Age(SD) in y	MMSE (SD)	Education	CDR score
ADNI 2-GO	NC	110	42/68	73.43±7.42 (56.30 – 91.77)	27.38.±1.99(25 -30)	14.7(3.1)	0.025(0.11)
	AD	46	20/26	75.30 ±7.4 (55.72 - 91.83)	23.80±2.42(18 – 27)	16.0(2.8)	4.304(1.60)
	MCI	115	52/63	73.38±7.48 (55.21-91.75)	27.18±1.99(24 – 30)	15.7(3.8)	1.255(0.77)
ADNI 3	NC	118	54/64	75.30±8.20 (55.80 - 95.40)	-	14.8(3.1)	0.025(0.11)
	AD	5	02-Mar	71.30±7.40 (71.72 - 83.65)	-	15.4(3.8)	4.304(1.60)
	MCI	137	60/77	75.73±7.81 (57.58 – 88.42)	-	14.0(3.0)	1.255(0.77)

Abbreviations:NC= Normal Control; AD=Alzheimer's disease; MCI=Mild Cognitive Impairment; SD= standard deviation; CDR= Clinical Dementia rating; MMSE = Mini-Mental State Examination It has five scales CDR-0 has no cognitive impairment and remaining four scales are different types of stages. CDR-0.5 is very mild dementia. CDR-1 is mild dementia, CDR-2 is moderate dementia and the final stage of CDR-3 is a serious stage. [MCI patients who changed over to AD (MCI.C) MCI Patients not converted into AD with 18 months (MCI.NC)];

F. Implementation details

Our proposed architecture is evaluated with less weight and same batch size as compared to the conventional AlexNet based architecture. Both the networks have the same structure viz., convolutional blocks (inception block of our proposed method), 3D S3 pooling (S3Pool 3D) along with Global Average Pooling(GAP) are shown in Fig.3.2. As earlier stated, nine ROI from sMRI images and three ROI from PET images is tested. Initially, base pipeline is created followed by data fusion. To detect an early sign of AD, mild cognitive impairment, we compared both sMRI and PET images. The selected ROI is fed as an input to our proposed CNN model.

Table 4.2: 9 ROI from sMRI images and 3 ROI from PET images

Images	Left	Right
sMRI	Hippocampal formation	Hippocampal formation
	Parahippocampal gyrus	Parahippocampal gyrus
	Entorhinal cortex	Entorhinal cortex
	Middle temporal gyrus	Middle temporal gyrus
	Amygdala and precuneus	
PET	Precentral gyrus	
	Superior temporal gyrus	
	Middle frontal gyrus	

Twelve ROI from both datasets (sMRI_L + sMRI_R + PET) configured and displayed as shown in Table. 4.2. The number of parameter used in the proposed network is reduced when compared to the conventional AlexNet architecture. Moreover, weight is used for our model.We performed loss function[45] and RMSprop optimizer[46]for train the network. Gradient value will be divided by current magnitudes at running time and the training rate gradually decreases when the test loss drop. The starting value will be turned in to depending upon the network and batch size. In similarly the starting learning rate will decrease in n times whenever the batch size is increased at n times. Finally, in every network architecture, the starting learning rate took automatically.

For implementing our proposed network architecture, we used open source library like Keras along with high-level API for tensorflow open source library for backend which is used for high-performance numerical computation. Here we used two high-end systems for our proposed network. 1. The personal computer has a Linux operating system with 8thgen i7-7500U CPU along with GPU NVidia GeForce GTX 1070 Ti with 8 GB GDDR5. Moreover, Google cloud service with NVIDIA® Tesla® K80.

Table 4.3: Binary classification results on test datasets using the ROI method. Two image modalities were used sMRI, PET, here α ± β represents the metrics.

Patient class	Network Model	Accuracy	Specificity	Sensitivity
AD vs NC	Baseline AlexNet	0.9 ± 0.107	0.933 ± 0.089	0.867 ± 0.121
	Proposed Method	0.945 ± 0.085	0.955 ± 0.085	0.945 ± 0.085
AD vs MCI	Baseline AlexNet	0.833 ± 0.133	0.867 ± 0.122	0.8 ± 0.143
	Proposed Method	0.859 ± 0.143	0.944 ± 0.09	0.8 ± 0.143

	Baseline AlexNet	0.667 0.168	±	0.53 0.178	±	0.8 0.143	±
MCI vs NC	Proposed Method	0.748 0.149	±	0.89 0.123	±	0.812 0.143	±
	Baseline AlexNet	0.62 0.142	±	-		-	
AD vs MCI vs NC	Proposed Method	0.706 0.145	±				

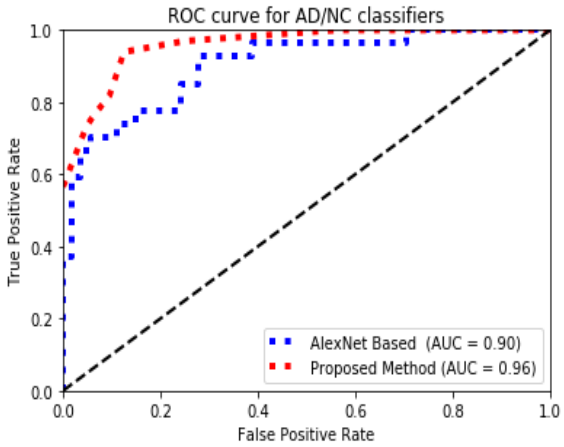

Fig .4.1: ROC curve of the proposed model and baseline model for binary AD vs NC classification

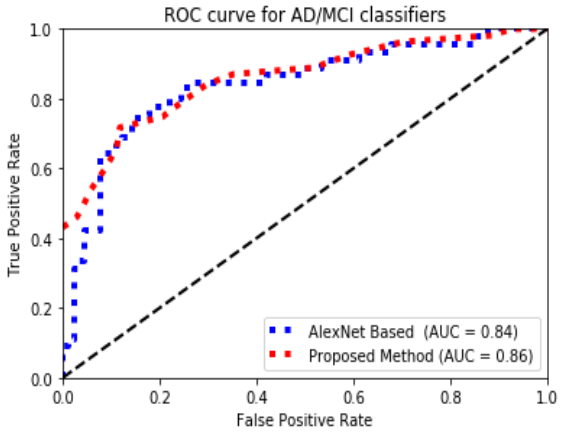

Fig. 4.2: ROC curve of the proposed model and baseline model for binary AD vs MCI classification

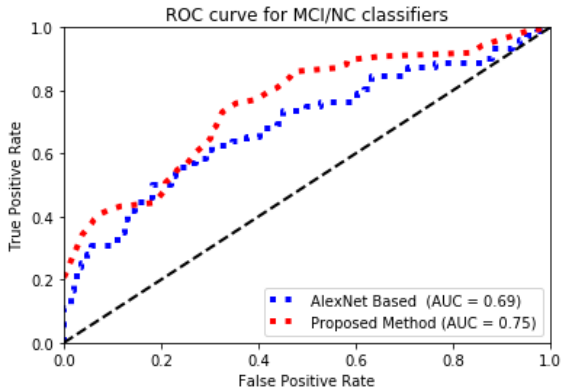

Fig.4.3.ROC curve for binary MCI vs NC classification with proposed model and baseline model.

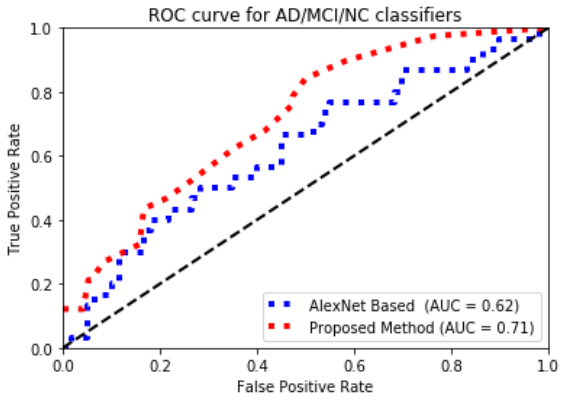

Fig.4.4: ROC curve for ternary AD vs MCI vs NC classification with proposed model and baseline model.

G. Result and Discussions

Since our proposed method shows better performance in all comparisons. In our work we performed three binary classifiers AD vs NC, AD vs MCI, MCI vs NC and one ternary classifier is AD vs MCI vs NC to detect the AD diseases in an early stage. The results are displayed (Table 4.3). In our experimental highest accuracy(ACC), specificity(SPC) and sensitivity(SEN) were obtained in the patient class of AD vs NC (higher than 94%) using ADNI dataset.

Here, to generate the confidence interval we fixed the confidence level is 95% for classification.

The confidence interval formula for estimation:

$$\hat{W} + Z\frac{s}{\sqrt{(n)}} \qquad (2)$$

Where $\hat{W}$ is a mean value, Z is a value for calculating the confidence interval, the value N is a number of observations in the set and s is a standard deviation. The confidence range is 95%. Here we noticed that the confidence interval value depends upon the number of observations in the set. Moreover, the number of observation n=30 for binary classifiers AD/NC, AD/ MCI, MCI/ NC and n=45 for ternary classifiers (AD/MCI/ NC)

As we discussed early, Fig. 4.1, 4.2, and 4.3 show the obtained result of accuracy for the case of binary and Fig. 4.4 shows ternary classification AD vs NC, AD vs MCI, MCI vs NC and AD vs MCI vs NC with AlexNet based network architecture. We found that all four classifications slightly increased and given better performance when compared to a conventional network in Table 4.3 while implementing the work. This proposed network has less weight with the same batch for the training data and given faster and robust.

We experiment with the number of epoch for convergence to AlexNet based network model and our proposed network model Table 4.3.

Almost testing time is slightly getting differ in both cases of binary and ternary classification. 5 and 10 minutes time taken for the classification of conventional AlexNet and 5 and 8.5 minutes time taken for our proposed network architecture. Finally, we achieved a good accuracy level compare to the conventional AlexNet based network. The classification result was 0.945, 0.859 and 0.748 respectively.

Table 4.4: The results are obtained with an estimated training time in minutes with a number of epoch for convergence.

Patient class	Network Model	Convergence on epoch	Training
AD vs NC	Baseline AlexNet	34	54
	Proposed Method	40	45
AD vs MCI	Baseline AlexNet	26	40
	Proposed Method	20	21
MCI vs NC	Baseline AlexNet	29	48
	Proposed Method	25	30
AD vs MCI vs NC	Baseline AlexNet	30	73
	Proposed Method	25	44

We used two image modalities are sMRI and PET, batch size is 15 by using GPU NVidia GeForce GTX 1070 Ti with 8 GB GDDR5.Efficient and specific Alzheimer's Diseases diagnoses are very critical in the early detection stages. The strength of our research paper mostly relative to many neural network architectures in the problem of AD. Therefore, we compared our proposed neural network method with many classification state-of-the-arts method. Most of the researchers are using the same data obtained from the ADNI database. Moreover, many of the studies focused normal pre-processing based method, feature extraction based method, feature selection method and neural network method gives good performance level and compared to the normal conventional volumetric methods that also performed by a normal medical expert at manual level. Furthermore, many of the researchers have dedicated much more efforts to diagnosis the AD with the Computer-aided Diagnosis method, which can diagnosis the diseases in early stages and on a separate basis.

As it was mentioned previously, many of the revised algorithms were compared for our method to diagnosis the AD, which is unimaginable for the results and taken learning images from various organizations with different sizes. Besides, different classification problem were performed with different categories. Most of the researcher focused in their research two-class classification, three-class classification and 4- class classification, likewise AD/NC, AD/MCI/NC and AD/EMCI/NC/IMCI classification. In this research paper, we build AlexNet based new network architecture having fewer weights to predict the individual diagnosis of MCI and AD at the early stages. The result was demonstrated for our proposed method and given good performance with the accuracies of 0.945, 0.859 and 0.748 respectively, the sensitivity of 0.945, 0.8 and 0.812 respectively, and specificity of 0.955, 0.944 and 0.89 respectively for the binary classification problem of AD vs NC, AD vs MCI and MCI vs NC. Finally, three class classifications of AD vs MCI vs NC were obtained the accuracy level is 0.702. But only one image modalities having huge dataset is used for the training process. Our proposed method is able to differentiate MCI and AD patients from normal healthy controls in predicting AD conversion within 36 months. Generally, our proposed method performed well with the various size of imaging datasets with protocols and scanners and it is not trained by the well-known operator to patient data.

Furthermore, we compared with the method of feature-based on sMRI and DTI modalities in[47] the Conventional Neural Network has performed with better performance. Continuously full brain structure approaches are collected, Such as[48][49]Payan proposed the best performance with huge datasets on single sMR imaging modalities. From the learning here we noticed that for analyzing of full brain structure need a good high-performance computational system for the resolution of 3D image modalities.

In our proposed method the network was trained, validated and tested using two imaging modalities (sMRI and PET) with different scanners and protocols. Then the architecture uses the interior network with less weight with the same depth compared to the conventional AlexNet architecture. Infact, our proposed approach overcomes conventional ALexNet architecture. Especially, the proposed neural network method contains a number of parameters, such as two image modalities (sMRi and PET) and 4 layers with 10 times less compared to the conventional method. Accuracy level was slightly increased after using optimization techniques and by almost 4 to 7% for binary classification and 8 % was increased for AD/MCI/NC and AD/EMCI/NC/IMCI classification in Table 4.3. With regard to the above mentioned that our method hasfewer weights than AlexNet network, and it has trained, validated and tested with larger datasets with the same batch size on GPU. Moreover, the proposed method will be trained with less time of ~1.5, it showed Table 4.4, which is also more practical for this work if we increase the training data as well as fine-tuning the network.

V. CONCLUSION

In summary, we demonstrated a new model for the brain image classification of patients concerned by MCI, AD and NC by using the new convolutional neural network based approach on sMRI and PET. The proposed CNN is tested with 531 subjects of two image modalities sMRI and PET from the ADNI database.

The obtained results exhibit high accuracy level of 0.945, 0.859 and 0.748 respectively, in binary classification AD vs NC, AD vs MCI and MCI vs NC and 0.702 in ternary classification AD vs MCI vs NC problem. In this work, we used only one hippocampal ROI. Future work can be extended by adding more number of ROI biomarkers for the detection of AD diseases using a different network.Aslo, our proposed model shows better performance with previously reported systems.

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