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Original Article

Deep Convolution Neural Network Based System for Early Diagnosis of Alzheimer's Disease

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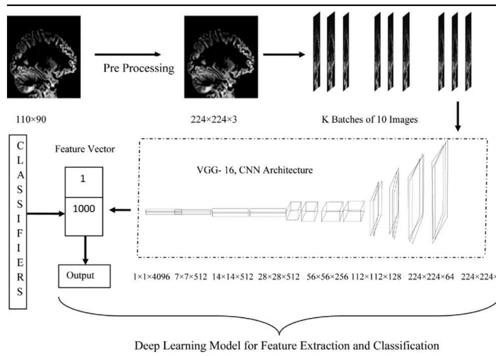
HIGHLIGHTS

- Novel pre processing technique for Alzheimer's images dataset.
- Mutation in layers of deep learning model to increase accuracy of classification.
- Classify the Alzheimer disease from fMRI and PET images.

GRAPHICAL ABSTRACT



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ABSTRACT

Objectives: Alzheimer's Disease (AD) is the most general type of dementia. In all leading countries, it is one of the primary reasons of death in senior citizens. Currently, it is diagnosed by calculating the MSME score and by the manual study of MRI Scan. Also, different machine learning methods are utilized for automatic diagnosis but existing has some limitations in terms of accuracy. So, main objective of this paper to include a preprocessing method before CNN model to increase the accuracy of classification.

Materials and method: In this paper, we present a deep learning-based approach for detection of Alzheimer's Disease from ADNI database of Alzheimer's disease patients, the dataset contains fMRI and PET images of Alzheimer's patients along with normal person's image. We have applied 3D to 2D conversion and resizing of images before applying VGG-16 architecture of Convolution neural network for feature extraction. Finally, for classification SVM, Linear Discriminate, K means clustering, and Decision tree classifiers are used.

Results: The experimental result shows that the average accuracy of 99.95% is achieved for the classification of the fMRI dataset, while the average accuracy of 73.46% is achieved with the PET dataset. On comparing results on the basis of accuracy, specificity, sensitivity and on some other parameters we found that these results are better than existing methods.

Conclusions: this paper, suggested a unique way to increase the performance of CNN models by applying some preprocessing on image dataset before sending to CNN architecture for feature extraction. We applied this method on ADNI database and on comparing the accuracies with other similar approaches it shows better results.

1. Introduction

Alzheimer's Disease is among one of the most famous type of dementia in 65 years and older, in which the mental capability of

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persons progressively decreases and reaches to a point where it becomes difficult for them to lead a normal life. When the disease starts increasing gradually, patients find themselves more dependent on their immediate family member for survival. It is expected that by 2050 one person in a group of 85 people will be affected by this and the quantity of affected persons will be double in upcoming 20 years [1][2]. Alzheimer report two common abnormalities in the brain of this patient, “1. Dense layers of protein deposited outside and between the nerve cells. 2. Areas of damaged nerve fibers, inside the nerve cells, which instead of being directly had become tangled”. Moreover, these plaques and tangles have been used to help diagnose AD [3][20].

To overcome these problems, Diagnosing Alzheimer's needs terribly careful medical assessment, as well as patient's past records, mental state examination (MMSE) [34], and many neurobiological and physical examinations [4]. In addition, s-MRI (structural magnetic resonance imaging) and rs-fMRI (resting state functional magnetic resonance imaging) are most common method of analyzing the regular changes, different activities in the brain [5]. During these tests patients remain in idle condition on a table and not performing any task so this makes the task of data acquisition very easy and to read regular changes in brain [8].

Alzheimer's disease brain tissues and cerebral cortex get smaller and ventricles in the brain are get expand. On the basis of these effects we can predict the progress of disease. This effect can easily be recognized in MR images in the advanced stage of AD. This problem affects those part of brain and network of brain tissues which are associated with thinking, memory, designing and decision making. Since brain tissues in broken regions are diffused so MR image intensities are low in each magnetic resonance imaging and rs-fMRI techniques [5][8][10]. However, some of the signs found within the AD imaging data also are identified in traditional aging imaging data. Distinguishing the visual distinction between AD data and pictures of older subjects with traditional aging effects needs in depth information and knowledge, that should then be combined with additional clinical leads to order to accurately classify the data (i.e., MMSE) [1], there was always a need of a tool or algorithm to categorize MR-based imaging data, such as structural MRI and rs-fMRI data, and, most significantly, to classify brain disorder data from healthy subjects, has field of interest for doctors [10]. Robust computational Intelligence algorithms such as Deep Learning, which is capable in classification of Alzheimer's disease in early stage, can help researchers and doctors in diagnosing this disease [11].

Here, we are proposing a convolution neural network architecture for identification of Alzheimer disease. More specially, proposed method first takes input images in two classes, then it is fed into convolution neural network (CNN) [31][32] for training purpose, finally result is compared using different classifiers. We illustrate the performance of our method using the AD MRI data and AD PET data downloaded from ADNI. We used collection of standard datasets released by ADNI. The dataset definition was downloaded from the ADNI website (http://www.adni.loni.usc.edu/methods/mri-analysis/adni-standardized-data/) [4][12].

Alzheimer's classification has been an area of active interest for researchers around the world. The experiment suggested features extracted by Convolution Neural Network followed by deep learning classification is dominant technique to differentiate medical data from healthy data suing fMRI scans [1], also, S. Sarraf and G. Tofighi utilized deep CNN to identify the classification of Alzheimer's Disease (AD) vs. Normal Human (NH) on Alzheimer's dataset of functional MRI scans and structural MRI scans with an accuracy of 94.79% with LeNet-5 classifier [21] and 96.84% with GoogleNet classifiers [20]. H Suk and D Shen proposed a technique which combines low level features with hidden information using stacked auto encoder to classify Alzheimer's disease [3]. Akhila D B, proposed a technique to use Elman back propagation technique to classify Alzheimer's Disease and extracting features using GLCM (Grey level Co-Occurrence Matrix) [4]. Spiking neural network (SNN) classification is ongoing with test dataset and work is in progress to classify Alzheimer's disease using convolution neural network and neuro-cooperative co evolutionary neural network. An accuracy of 96.251% was achieved through classification with SNN but it needs to be validated.

Jun Jie Ng et al. [5], proposed a method where machine learning algorithms are used to build up knowledge of the patient's behavior over time. It was used mainly to locate the position of patients around the house via the help of Estimote Bluetooth beacons, and could pinpoint which room the patient was in up to an accuracy of 95%. Lauge Sørensen et al. [6], proposed a study, they investigate hippocampal texture [22] as an MRI-based features for identification of Alzheimer's disease at early stage. Through this study accuracy achieved at 83%. Here they found that hippocampal texture feature had a notably superior classification between stable MCIs and MCI-to-AD converters. Siqi Liu et al. used a stacked auto-encoders of deep learning and at output layer they used softmax, to reduce the bottleneck problem [7]. While comparing with other previous techniques, this method can classify data of multiple classes, needs less training data and also needs very less information of input data. They achieved a considerable performance of 87.67% accuracy on classification of all diagnosis groups. They come with a result that, classification techniques needs to combine multiple features to get more accurate classification results. Tong Tong et al. [8], present a paper, they present a categorization structure to accurately utilize the complementarily in the different input dataset. Features from many modalities are then collected using a nonlinear graph mixture process, which produces a fused graph for final classification. Using these fused graphs, they got classification area under curve (AUC) of receiver-operator attribute of 98.1% between normal controls (NC) images and AD images, 82.4% between MCI images and NC images and 77.9% in overall classification. Tong Tong, et al. [9], uses different techniques to take out features from the diffusion Magnetic Resonance Images. First, they use the pixel-wise distribution tensor calculations that have been frame worked using region based spatial statistics. Second, they clustered the pixel-wise distribution calculations using ICA [35], and they calculated the fusion of these features.

Iman Beheshti et al. [11] proposed a CAD based systems which uses the histogram features [23][24][25] for categorization of Alzheimer's disease (AD), they use the support vector machine for classification purpose on cross 10 fold validation. On above CAD system achieved accuracy of 84.07% for classification of MRI measures and achieved accuracy of 97.01% for mix feature of MRI measures and FAQ scores [10]. Bishnupriya Mukherjee published a paper, which eventually presents Artificial Neural Network (ANN) [33], Fuzzy Expert System (FES) [37], Particle Swarm Optimization (PSO) [37] techniques to have an idea about the recent trends in disease diagnosis. According to this paper different diseases have been observed and the average result for Alzheimer's disease (AD) as accuracy is 85%. R. Garg et al. [13] present a study on deep learning based model for detection of Alzheimer disease. In this study, they used a Stack auto encoder architecture for identification of Alzheimer disease and its Mild Cognitive Impairment (MCI) stage [18,19]. When comparing with existing techniques, this technique is able to classify the multiple classes also with less knowledge of input. They achieved accuracy and specificity 47.42% and 83.75% respectively, as compare with SVM classifier.

S. Sarraf et al. [14] presented a paper, in which they used a convolutional neural network for classification of Alzheimer's disease with a normal brain. They used first convolutional neural network architecture LeNet-5 for this task. Results show that they were good enough in identification of fMRI data of Alzheimer's brain

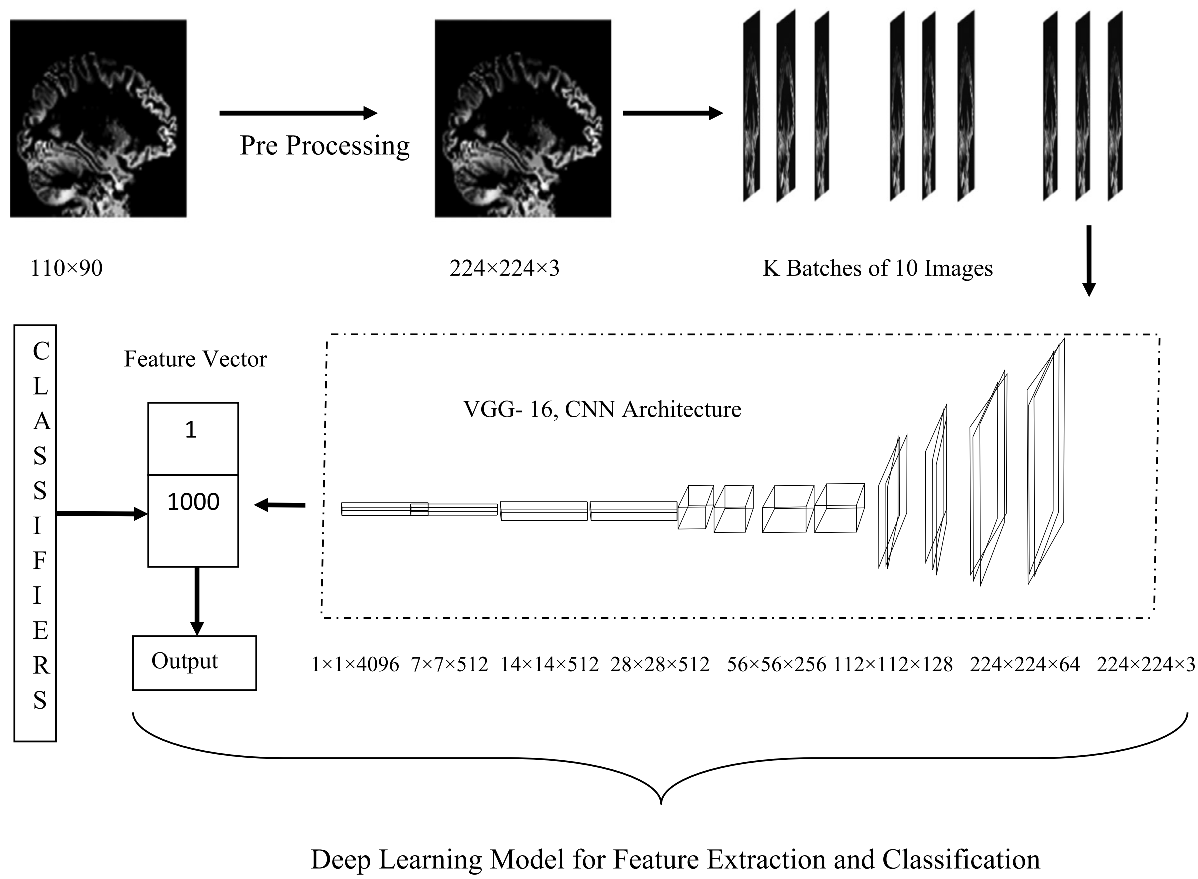


Fig. 1. Flowchart showing stepwise methodology.

from normal controls, and got prediction correctness of 96.85%. A pattern detection method which depends on brain parceling, grouping and tree ensemble algorithms was proposed by M. Wehenkel et al. [15] while comparing this method with other existing method this method generates better results with existing one. Thakre P. et al. [16] proposed an model for detection and following of Alzheimer disease patient, they first apply pre processing of on input EEG information using independent element analysis. Then, they extracted four features using wavelet transform finally; the task of classification is performed by using SVM classifier. For tracking of Alzheimer patient they used GPS and GSM. This monitoring system is useful for Alzheimer's patient to travel without any support. They got accuracy about 95% on using SVM classifier.

Zhang J. et al. [17] proposed a method to get better recognition accuracy. Where, an additional set of leading and consistent features are also acknowledged to direct the identification of Alzheimer disease. Based on the calculated Alzheimer Disease features, other morphological features are extracted which is used to perform training of SVM classifier [36], which is used for prediction of Alzheimer Disease state. While performing experiments, their method is evaluated on identification of disease in sequence. Exclusively, the landmark recognition error (manually prediction vs. automatically detection) of the projected landmark detector is 2.41 mm, and they achieved accuracy 83.7% using this method. In current scenario, many soft computing approaches have been applied for fast detection of Alzheimer Disease from MRI images. MRI images have high number of feature and having small number of subjects, so there are many dimensionality reduction methods applied in many soft computing algorithms [26–28], such as Fishers linear discriminate analysis (LDA) approach [28], Principal component analysis (PCA) algorithm [29], Locally linear embedding (LLE) algorithm [30]. For Alzheimer disease Principal component analysis algorithm has been most commonly applied for the purpose of dimension reduction in Alzheimer's disease diagnosis.

This paper is structured as follows: Section 1 covers the introduction of Alzheimer's disease and also focuses on different methods used by various researchers for Alzheimer disease classification. In section 2, database, pre processing steps, methods and algorithms are described. Section 3 describes the proposed convolution neural network based method for classification of Alzheimer disease; Section 3 presents the performance of various classifiers using 10 fold cross validation, and section 4 contains the conclusion of this paper.

2. Methods

Over all process can be represented by diagram, see Fig. 1.

2.1. Image dataset

In this paper, we acquired data from Alzheimer's Disease Neurological Initiative (ADNI). ADNI is a global research effort that actively supports the study, analysis and improvement in treatments of AD to slow down its growth. The ADNI datasets contain datasets of different modalities which can help researchers in many ways for early detection of Alzheimer disease. With its standard datasets, ADNI facilitates a way for researcher to conduct cohesive research and shares compatible data with other researchers around the world.

The fMRI Dataset consists of 54 Images presented in NIFTI Format and is acquired through the standard protocol presented in the ADNI Site. It consists of 27 males out of which 18 are classified as suffering from Alzheimer's disease with average MMSE score of 32, rest are females out of which 9 are suffering from Alzheimer's

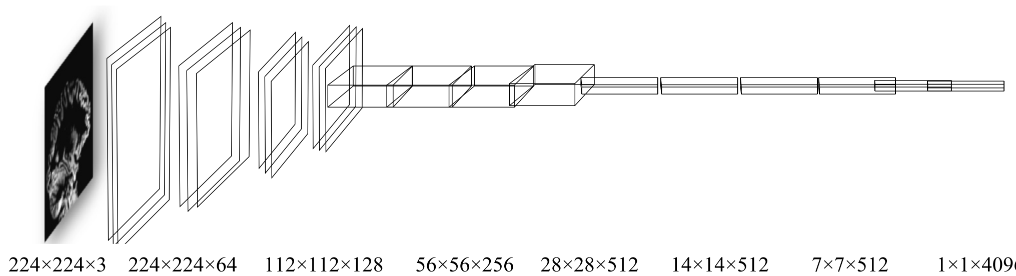


Fig. 2. VGG-16 architecture.

Disease with average MMSE score of 31. The images acquired are structural fMRI scan images. Other dataset considered for research is ADNI PET image dataset, from where 2675 images are randomly selected for testing purpose in which 900 images of Alzheimer's patient and 1775 images of normal person.

2.2. Pre processing

Following algorithm is applied to convert images from NIFTI 3D format to jpg 2D format:

Input: List of 3D Images
Output: List of 2D Images
Begin

1. Read Input image
2. Import dicom // to read nifty images
3. Import Numpy // to modify numpy array
4. FOR EACH Image in 3D Images
5. Read Image ← dicom.load(image)
6. Image_Shape ← Image.shape()
7. Store in x ← Image_Shape[0] // Height
8. Store in y ← Image_Shape[1] // Width
9. Store in z ← Image_Shape[2] // Length
10. FOR n in RANGE 0 to z
11. Save new_image ← Image.Save(x,y)
12. Save .jpg file
13. Save new_image as Image_n // where n is a number for 0 to z
14. End FOR loop
15. End FOR EACH Loop

End

As the dataset contains binary images, so 3D to 2 D conversion may not affect the quality of image. We had also applied some manual segmentation, to remove the corners of image which contains black color boundary and not contain any relevant information. This method will help us to reduce the computation time and increase accuracy and help for better feature extraction.

2.3. Deep learning model for feature extraction and classification

Many soft computing methods are inspired by the human intelligence system. This method is based on some complex algorithms that can extract high level features form data and apply those features using a neural network architecture for classification and for solving other real world complex problems. Since, deep learning a deep neural network with can extract thousands of features from input data and classify the data with very high accuracy. So this property of deep learning motivates us to develop a deep machine learning system which contains similar characteristics to those of the neocortex [1][3].

		Predicted class	
Actual class		Positive	Negative
	Positive	TP	FN
	Negative	FP	TN

Fig. 3. Confusion matrix.

2.3.1. Convolution neural networks (CNNs/ConvNets)

The basic components of CNNs are very similar for example LeNet-5 which composed of three types of layers as the convolution layer, max pooling or average pooling layer and fully connected layers. The objective of the convolution layer is to learn input feature representations. As in the figure shown below convolution layer consist of many convolution kernels for evaluating distinct feature maps.

In CNN network, the kernel initially convolving the inputs and then using an element wise non-linear activation function on convoluted results to obtain new feature map. The complete feature maps are acquired by using many different kernels. Mathematically i-th feature map for l-th layer is calculated as

$$Y^l_{m,n,i} = w^l_i x^l_{m,n} + b^l_i \tag{1}$$

where $x^l_{m,n}$ is input patch centered at location (m, n), w^l_i is weight vector and b^l_i is bias. The activation function produces non-linearity in CNN which desirable for multi layer networks to observe non linear features. Suppose α represent the non linear activation function then convolutional feature $Y^l_{m,n,i}$ is evaluated as

$$Z^l_{m,n,i} = \alpha(Y^l_{m,n,i}) \tag{2}$$

The classic activation functions are Rectified linear units (ReLU) [37], sigmoid and tanh. The objective of pooling layer is that to obtain shift invariance by minimizing the resolution of feature maps. It is generally placed between two convolution layers. Every feature map in pooling layer connected to the previous convolution layer corresponding to its feature map. Let pool(.) represent pooling function then the every feature map represented as

$$X^l_{m,n,i} = pool\left(Z^l_{p,q,i}\right) \forall (p, q) \in R_{m,n} \tag{3}$$

Most commonly used pooling methods are max pooling and average pooling [38]. By various convolution and pooling layers, there can be one or many fully connected layers which objective to perform higher-level reasoning. It's remark that fully connected layer is replaced by single 1×1 convolution layer [39]. The final layer of CNN is an output layer where the softmax operator applies for classification problem. Here, we are using ImageNet architecture of CNN.

2.3.2. Feature extraction using VGG-16 architecture

Vgg stands for Visual Geometry Group, it is a 16 layered convolutional neural network architecture proposed by K. Simonyan and A. Zisserman from the University of Oxford [40], see Fig. 2.

Table 3.1
Predicted using ImageNet pre trained model using vgg-16 CNN architecture applying 10 fold cross validation.

S. no.	Classifier	For fMRI image database					For PET image database				
		Accuracy (in %)	Specificity (in %)	Sensitivity (in %)	PPV	NPV	Accuracy (in %)	Specificity (in %)	Sensitivity (in %)	PPV	NPV
1	SVM	100	100	100	1	1	76.32	64.8	82.1	0.82	0.65
2	K-nearest neighbor	100	100	100	1	1	76.52	64.3	78.2	0.78	0.64
3	Linear discriminant	100	100	100	1	1	71.4	57.8	82.3	0.82	0.56
4	Decision tree	99.89	100	99.77	1	0.997	69.6	54.5	95.0	0.95	0.94

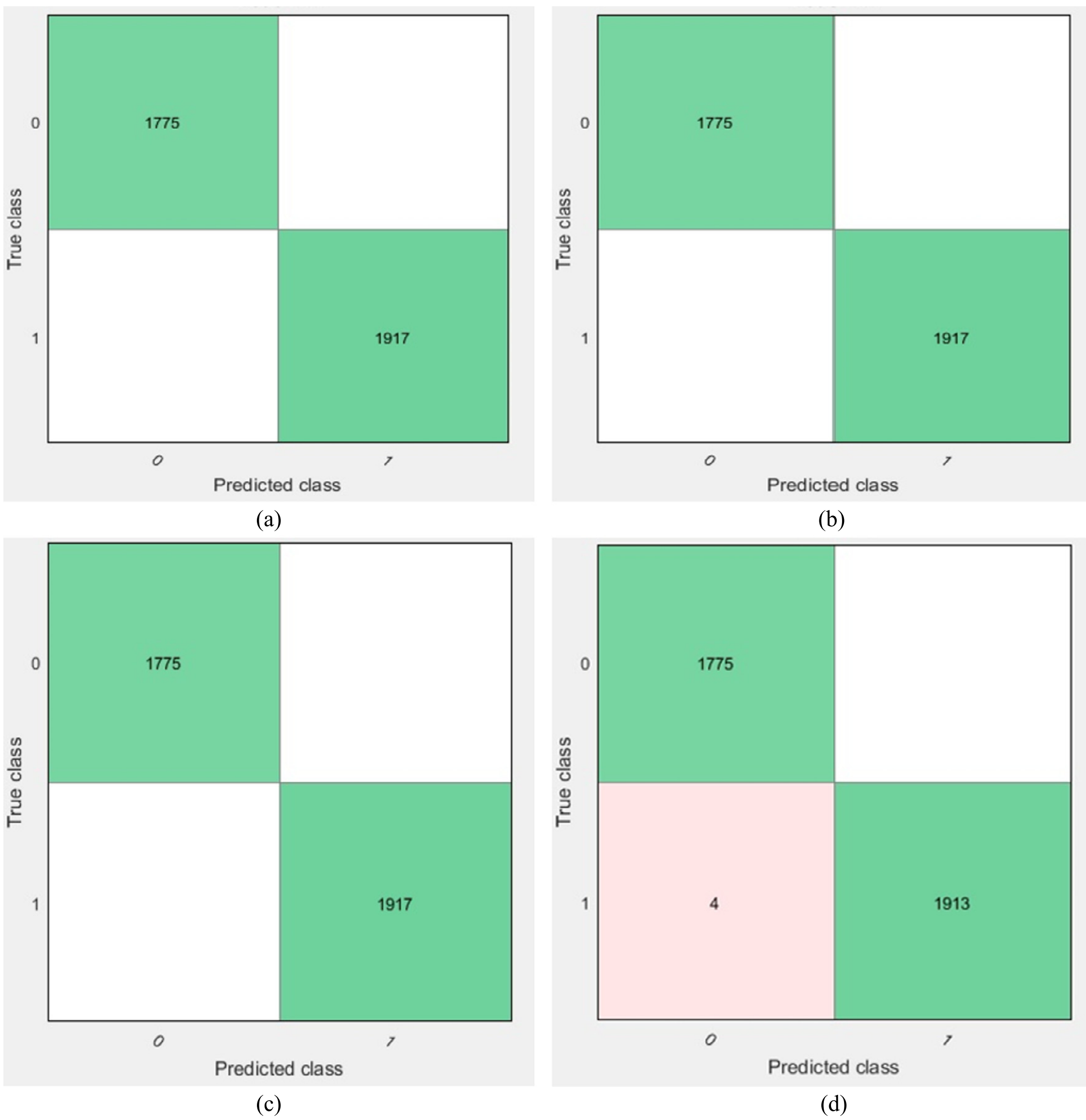
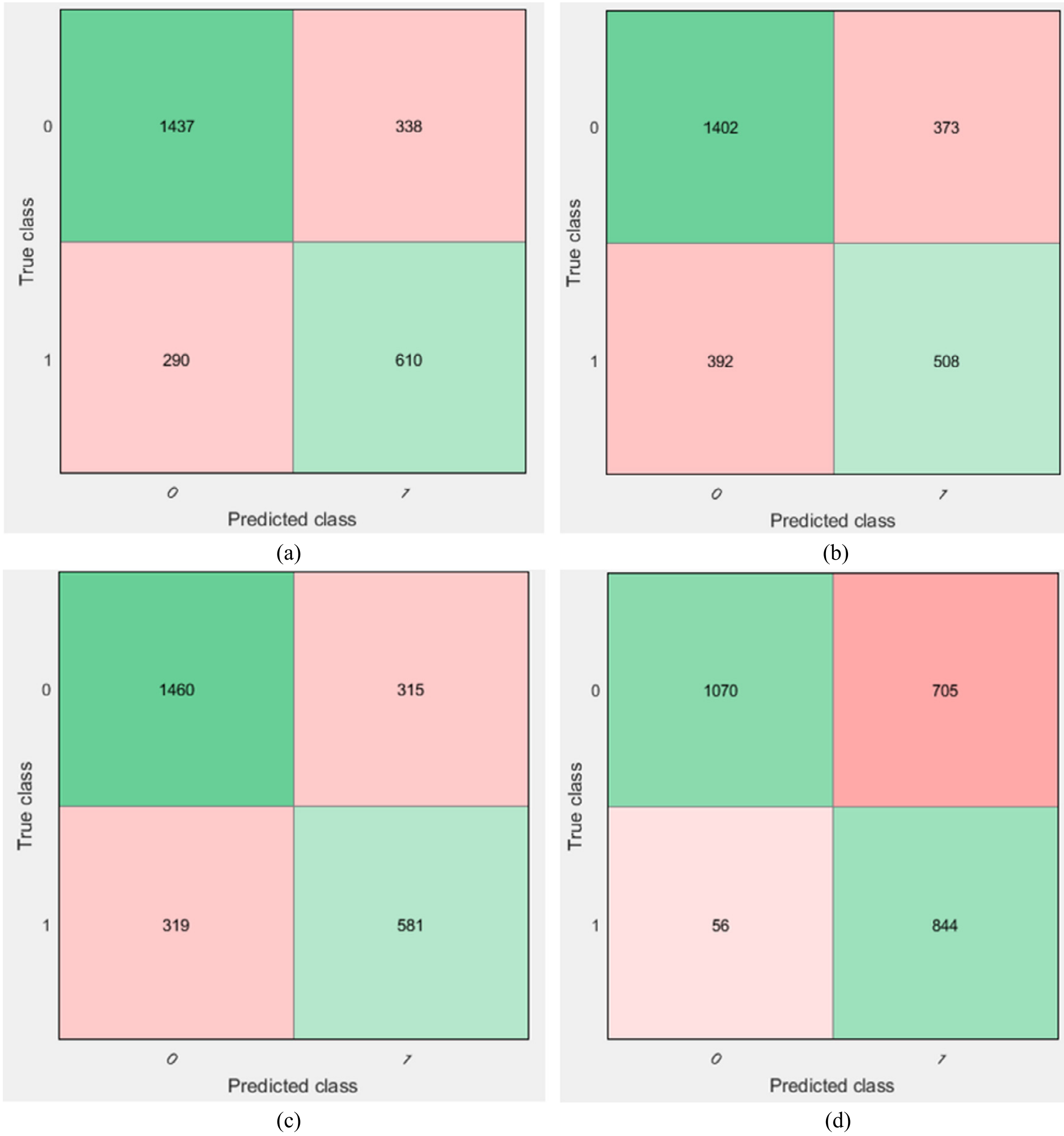


Fig. 4. Confusion matrix on applying different classifiers on fMRI dataset using cross 10 validation (a) after applying k nearest, (b) after linear descriptive classifier, (c) after linear SVM classifier, (d) after applying decision tree.

We are using VGG-16, A 16 layered architecture which strictly uses 3×3 filters with stride and pad of 1, and max pooling layer contains 2×2 filter with stride 2. The reason behind using 3×3 sized filters is that the combination of two 3×3 convolution layers has an effective receptive field of 5×5. To reduce the processing time we used 4 pixel strides in the first convolution layer. The main differences between this architecture and traditional architectures are the reduced number of convolution layers and the dense connectivity between convolution layers. This architecture is suitable for this work because we are dealing with large number of images and VGG16 will help us to get the output quickly.

2.3.3. *Softmax activation function*

Softmax function has been used at dense layer. The output of the softmax function is gives a probability of a particular class. So, it has been used to generate probability of all output classes. Math-



(a) (b) (c) (d)

Fig. 5. Confusion matrix on applying different classifiers on PET dataset using cross 10 validation (a) after applying k nearest, (b) after linear descriptive classifier, (c) after linear SVM classifier, (d) after applying decision tree.

ematically, softmax function can be represented as in equation (4), where z is a vector of the inputs to the output layer and r shows the output units, so $r = 1, 2, ..., L$.

$$\sigma\,(z)\,j = \frac{e^{zr}}{\sum_{L=1}^{L} e^{zL}} \tag{4}$$

2.4. Performance evaluation parameters

Based on confusion matrix following parameters can be calculated to check the performance of a classifier:

$$\text{Accuracy (in \%)} = \frac{TP + TN}{TP + TN + FP + FN} * 100 \tag{5}$$

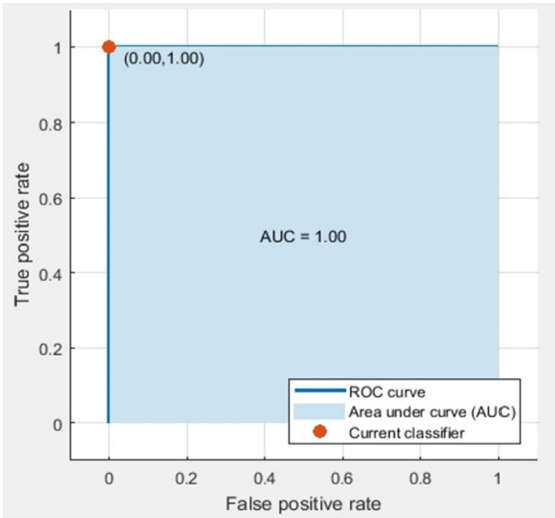
$$\text{Sensitivity (in \%)} = \frac{TP}{TP + FN} * 100 \tag{6}$$

$$\text{Specificity (in \%)} = \frac{TN}{TN + FP} * 100 \tag{7}$$

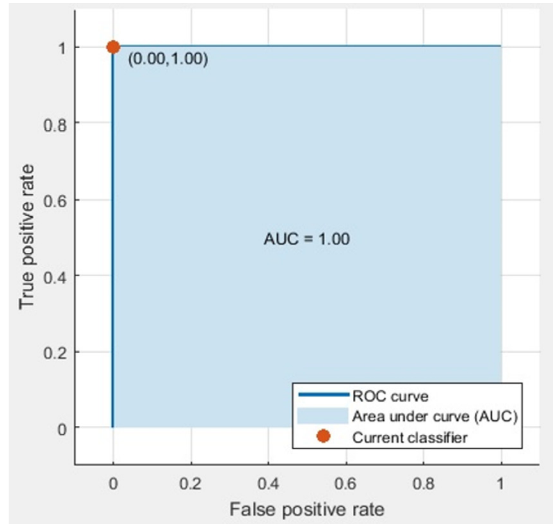
$$\text{Positive Prediction Rate (PPV)} = \frac{TP}{TP + FP} \tag{8}$$

$$\text{Negative Prediction Rate (NPR)} = \frac{TN}{TN + FN} \tag{9}$$

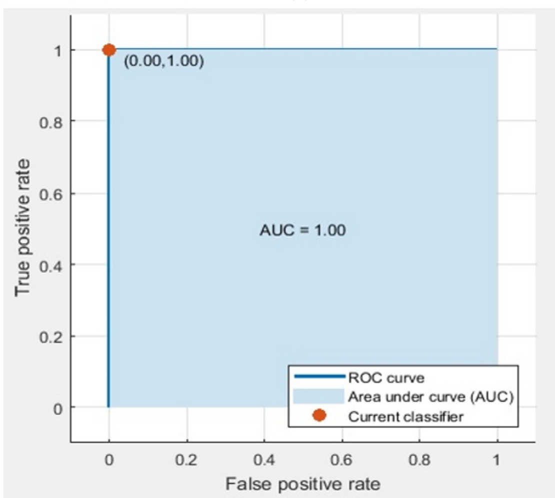
Where,
TP of confusion matrix is all diseased instances that are classified as diseased.
TN of confusion matrix is all non-diseased instances that are not classified as diseased.
FP of confusion matrix is all non-diseased instances that are classified as diseased.
FN of confusion matrix is all diseased instances that are not classified as diseased, see Fig. 3.



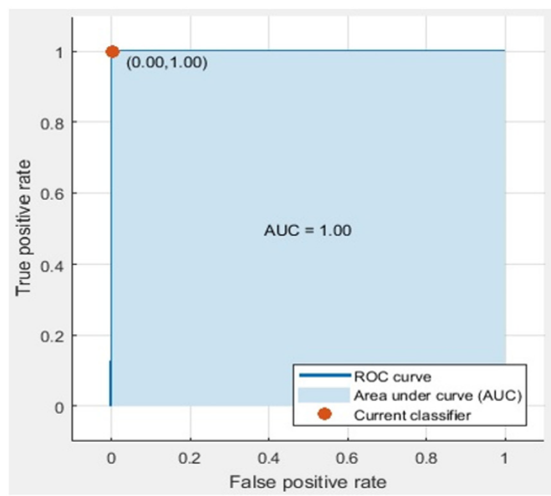
(a)



(b)



(c)



(d)

Fig. 6. ROC curves on applying different classifiers on fMRI dataset using cross 10 validation (a) after applying k nearest, (b) after linear descriptive classifier, (c) after linear SVM classifier, (d) after applying decision tree.

3. Experiment and result

3.1. Comparison of different classifiers

Results are calculated by applying above model on ADNI fMRi and ADNI PET dataset where fMRI dataset contains total 3692 images of two classes, AD (Alzheimer diseased) which contains 1917 images and NL (Normal Images) which contains 1775 images and PET dataset contains 900 diseased images and 1775 normal images. Table 3.1 shows the comparison of different classifiers on applying fMRI and PET dataset.

Fig. 4 and Fig. 5 shows the confusion matrix of k nearest, linear descriptive, support vector machine and decision tree classifiers on ADNI fMRI and PET dataset respectively.

Fig. 6 and Fig. 7 shows the ROC curve of k nearest, linear descriptive, support vector machine and decision tree classifiers on ADNI fMRI and PET dataset respectively.

3.2. Comparison of classifiers on fMRI vs. PET dataset

Fig. 8 shows the comparison of support vector machine, k nearest neighbor, linear discriminant and decision tree classifiers when they are applying on fMRI and PET dataset.

4. Discussion

In this study, we make a model that will increase the accuracy of prediction of Alzheimer's disease. In section 3 we have applied lots of classifiers with different input combinations and finally we got the best average accuracy i.e. 99.95% for identification of Alzheimer's Disease using fMRI images of ADNI dataset. The comparison of results founded during experiment is compared with some existing methods shown in Table 4.1.

Table 4.1 and Fig. 9 shows the comparison of our method with other existing methods, and we can observe that result of classification for fMRI images is better than the existing methods. In [2], author performs many comparisons like Alzheimer Disease vs. Normal, Alzheimer Disease vs. MCI and multi class classification for Alzheimer Disease, MCI and Normal person. Here, in above table we are showing the performance of Alzheimer disease vs. Normal person of fMRI and PET dataset only and comparing the results with similar outputs of above papers.

Contribution: Here, we are proposing a novel algorithm for data pre processing, which is used to convert 3D input image into 2D form. As the ADNI dataset contains binary images, so there will be negligible loss of information during this conversion. We had

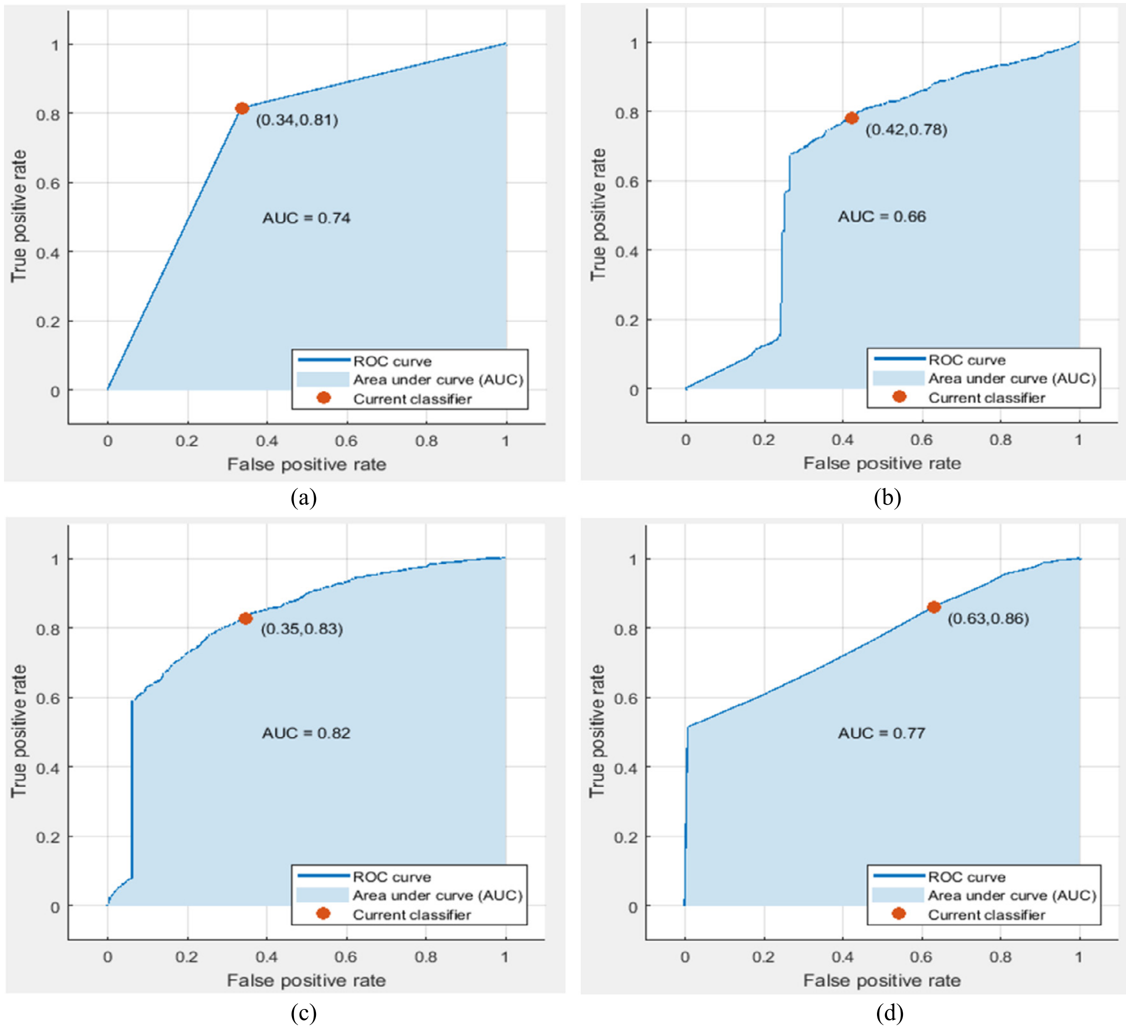


Fig. 7. ROC curves on applying different classifiers on PET dataset using cross 10 validation (a) after applying k nearest, (b) after linear descriptive classifier, (c) after linear SVM classifier, (d) after applying decision tree.

Table 4.1
Accuracy comparison with existing methods.

Reference	Modality	Method used	Average accuracy
Sarraf et al. [1]	MRI+fMRI	LeNet-5 architecture of CNN	98.84%
Suk et al. [3]	MRI	Deep learning stacked auto encoder	94.90%
Zhang et al. [17]	MRI	Support vector machine classifier	93.20%
Sorenson et al. [12]	MRI	Feature extraction of MRI hippocampal texture	87.76%
Sarraf et al. [2]	fMRI	MCADNNet	97.5% (±1.16)
Our method	**fMRI**	**Highest accuracy on using VGG-16 architecture of CNN and SVM, decision tree, linear discriminant and KNN classifiers**	**99.95%**
Our method	**PET**	**Highest accuracy on using VGG-16 architecture of CNN and SVM, decision tree, linear discriminant and KNN classifiers**	**73.46%**

also performed segmentation on the corners of image to remove the unnecessary black color boundary from image. These preprocessed images lead to generate good features and also will save the computation cost, so that we will be able to increase the number of layers in CNN model from 6 layers (3 Convolution layers and 3 max pooling layers) suggested by Sarraf et al. [2] to 16 layers in order to increase the accuracy of model. Here, our experimental result shows that overall accuracy gain with our model is better than the existing similar methods for fMRI image dataset.

5. Conclusion

In this paper, we have effectively categorized Alzheimer Disease data from normal control data with 99.95% average accuracy using Vgg-16 very famous architecture of deep learning (ImageNet), when it is trained and tested on 3692 images of ADNI fMRI dataset. The proposed model is tested in several iteration by varying different input parameters, the best result achieved when data is classified using SVM, K nearest or linear discriminant classifiers,

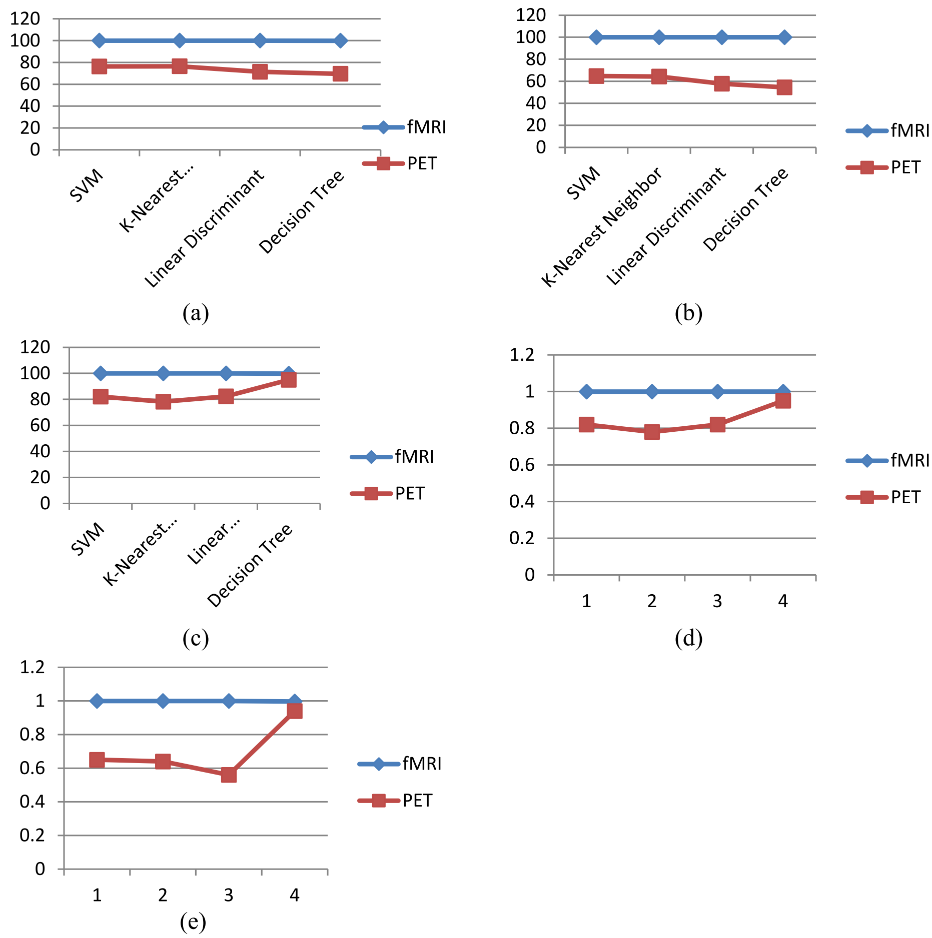


Fig. 8. (a) shows the accuracy of different classifiers on fMRI and PET dataset, (b) shows the specificity of different classifiers on fMRI and PET dataset, (c) shows the sensitivity of different classifiers on fMRI and PET dataset, (d) shows the positive prediction value of different classifiers on fMRI and PET dataset (e) shows the negative prediction value of different classifiers on fMRI and PET dataset.

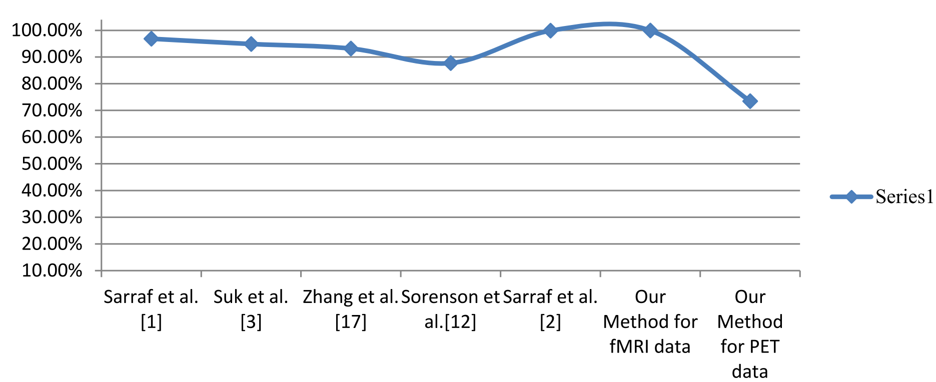


Fig. 9. Shows the comparison of accuracy with other classifiers.

these classifiers produce the accuracy of 100%. Furthermore, if we apply same model on ADNI PET database contains 2675 images accuracy of k nearest classifier was highest i.e. 76.56% and for this dataset average accuracy of 73.46% is achieved after applying other classifiers with multiple iteration. These experiments achieve best average accuracy of 99.95% for classification of ADNI fMRI images. Further work may be done in the direction of reducing the execution time of classification and on other ADNI datasets.

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Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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