Introducing an ensemble method for the early detection of Alzheimer's disease through the analysis of PET scan images

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder that primarily affects cognitive functions such as memory, thinking, and behavior. In this disease, there is a critical phase, mild cognitive impairment, that is really important to be diagnosed early since some patients with progressive MCI will develop the disease. This study delves into the challenging task of classifying Alzheimer's disease into four distinct groups: control normal (CN), progressive mild cognitive impairment (pMCI), stable mild cognitive impairment (sMCI), and Alzheimer's disease (AD). This classification is based on a thorough examination of PET scan images obtained from the ADNI dataset, which provides a thorough understanding of the disease's progression. Several deep-learning and traditional machine-learning models have been used to detect Alzheimer's disease. In this paper, three deep-learning models, namely VGG16 and AlexNet, and a custom Convolutional neural network (CNN) with 8-fold cross-validation have been used for classification. Finally, an ensemble technique is used to improve the overall result of these models. The results show that using deep-learning models to tell the difference between MCI patients gives an overall average accuracy of 93.13% and an AUC of 94.4%.

Keywords: Alzheimer's disease; convolutional neural networks; PET scan images; voxel-based morphometry; ensemble methods.

1. Introduction

One of the global challenges in the health care industry is Alzheimer's disease [1], making it one of the major global health care challenges [2]. A pivotal phase of this disease is mild cognitive impairment (MCI), and early detection of this is essential for people afflicted [3] because this phase is divided into two modes: stable MCI and progressive MCI [4]. If we detect stable MCI, we can treat it, and if we early detect that we are in progressive MCI, the rate of its progression can be decreased. Today, different neuroimaging techniques have been created to help with the difficult task of predicting the change between stable MCI (sMCI) and progressive MCI (pMCI). In this study, we introduce a promising method based on voxel-based morphometry (VBM) analysis on PET-Scan image data for early prediction of Alzheimer. We survey how

to extract features from sMCI and pMCI subjects based on patterns of gray matter. We use VGG16, AlexNet, and a custom convolutional neural network (CNN) for classifying AD vs. CN and pMCI vs. sMCI. Finally, a method called "ensemble method utilizing majority voting " is used to combine the outputs of several 3D dense networks. It should be noted that to ensure fairness in results, an equal number of samples are allocated to each dataset class. The remainder of this paper is organized as follows; first, section 2 addresses related work in the scope of classification of Alzheimer's disease. In section 3, we present our methodology for the classification and image processing steps used for the dataset. Our computational results and their comparison to the related works are presented in section 4. Finally, the conclusion and future research are presented in section 5.

2. Literature review

In this part, we survey numerous research that have addressed the challenges of the classification of Alzheimer's disease. Naami et al. [5] confronted the high-dimensional problem of brain images by utilizing an artificial neural network (ANN) for classification. This approach adeptly navigated the intricate nature of the data, effectively distinguishing between cognitively normal (CN) and AD individuals. Mahmood et al. [6] proposed a hybrid methodology incorporating principal component analysis (PCA) for dimension reduction and ANN for classification. Accordingly, their method could discriminate between CN and AD individuals with a good accuracy. Turning attention to diffusion tensor imaging (DTI) images, Kar et al. [7] utilized a fuzzy technique to discern between CN and AD subjects. Their approach was successful in handling the complexities of DTI data and achieving precise classification of samples. Veen et al. [8] looked into how well generalized matrix learning vector quantization (GMLVQ) could classify people with AD. This study shows how important it is to look at both global and local correlations for correct disease classification. Biomarkers that are not invasive, like conventional methods in medical image processing, typically use prior knowledge to segment brain images into Regions of Interest (ROI) [9] or Voxel-Based Morphometry (VBM) [10]. Deep-learning algorithms can discover hidden representations among multiple regions of neuroimages, these algorithms outperform conventional methods in identifying AD patterns. Addressing the challenge of selecting significant ROIs in whole-brain analysis, Ortiz et al. [11] introduced a novel strategy using self-organizing maps (SOM). However, this method necessitated prior knowledge for extracting features from specific brain ROIs. Gorji et al. [12] focused on feature extraction from MR images using image moments, while Jha et al. [13] proposed the Dual-Tree Complex Wavelet Transform (DTCWT) as an alternative and said it was better at choosing directions than the Discrete Wavelet Transform (DWT). Principal Component Analysis (PCA) emerged as a widely adopted technique for significantly reducing the dimensionality of the feature space. Lopez et al. [14] employed Bayesian classifiers for AD classification, while Horn et al. [15] utilized Partial Least Squares (PLS) regression to

2

minimize ROI-based features. K-Nearest Neighbors (K-NN) emerged as the most accurate method for CN versus AD classification, indicating its potential for handling AD detection tasks. In the context of survival analysis on patients with head and neck squamous cell carcinoma, Leger et al. [16] explored various machine-learning techniques for feature selection. Hu et al. [17] employed an image dataset to construct a correlation matrix, classifying it using a targeted autoencoder network for AD detection, showcasing the potential of deep learning in neuroimaging analysis. She et al. introduced a multimodal stacked deep probabilistic network (MM-SDPN) for Alzheimer's diagnosis, demonstrating the efficacy of combining multiple data modalities to enhance AD classification accuracy. Suk et al. [18] solved the problem of getting relevant features out of large amounts of data and made AD detection better. In addition, it has been demonstrated that sparse regression models are helpful in managing high-dimensional data with a limited number of training samples [19], holding promise in addressing the challenges posed by limited data availability in AD detection and classification. In summary, the literature review underscores the diversity of methodologies and techniques employed in AD detection, encompassing a range of machine-learning algorithms and deep-learning architectures.

3. Methodology

In this paper, we utilize the original PET images that comprise 323 samples: 96 cognitively normal (CN) subjects and 136 individuals with mild cognitive impairment (MCI), among whom 71 patients have progressive MCI that is expected to progress to Alzheimer's disease and 65 patients have stable MCI that is expected to remain in this phase. Additionally, there are 91 records of Alzheimer's disease (AD) patients. For performing our first stage method, which reduces the number of features, PET scan images that have been processed using co-registration, normalization, and VBM serve as input for the custom CNN, VGG16, and AlexNet models that have been applied to processed images. The comprehensive methodology process is shown in Figure 2.

3.1. Image processing

In this research paper, we employ original PET scan images sourced from the ADNI dataset. These images are three-dimensional and measure $160 \times 160 \times 160$ mm in size. Furthermore, the voxel sizes, which indicate the image's resolution, are configured at $1.5 \times 1.5 \times 1.5$ mm. To provide a visual representation of the images contained within the dataset, Figure 1 showcases a selection of images from each category, all belonging to different subjects. This dataset serves as an invaluable resource for conducting research on Alzheimer's disease. Its detailed three-dimensional imaging and its capacity to categorize data into distinct

groups establish a robust foundation for studies aimed at investigating, diagnosing, or gaining a deeper understanding of the progression of neurodegenerative diseases over time.

A   b   c   d

Fig. 1: Four records from each group of the dataset based on their severity [20].

Alzheimer's disease causes damage to brain cells in the gray matter primarily due to an accumulation of amyloid, resulting in the gradual loss of these cells [21]. Scientists employ voxel analysis, a comprehensive examination of brain regions, to gain insights into this process. Identifying the specific brain regions most impacted is essential for advancing our understanding of the disease. It's important to emphasize that for applying deep learning models, a well-balanced dataset is crucial to achieving accurate classification results [22]. Data augmentation methods, such as padding, rotation, and mirroring, are employed to generate multiple images from a single source, and equal numbers of samples are selected from every class within the dataset. Table 1 shows the information about the samples obtained for each class.

Table1. Information of subjects in each group before and after augmentation.

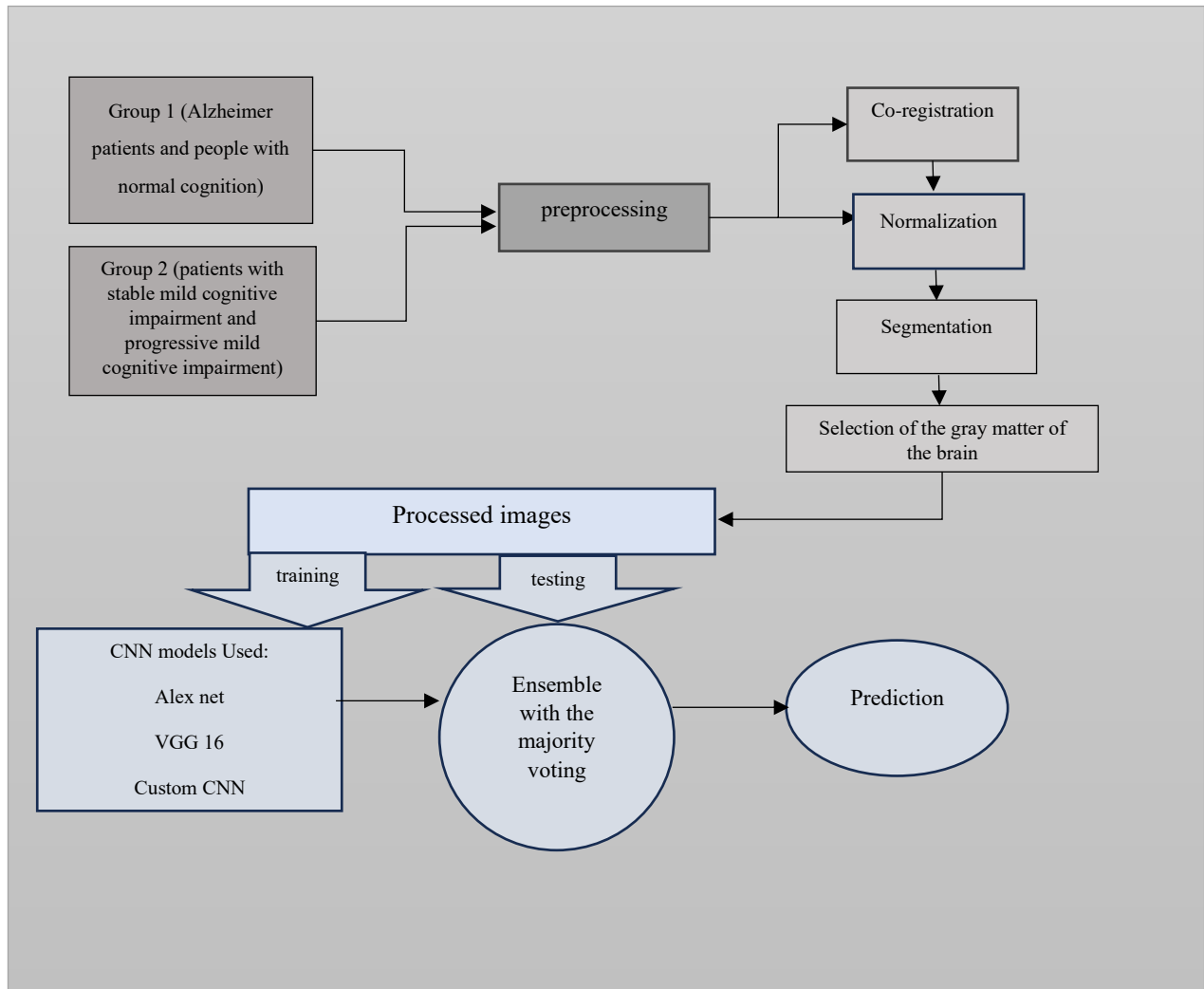| Disease state	Number of subjects before augmentation	Number of subjects after augmentation	Age
CN	96	8352	76.01±4.81
pMCI	89	8352	75.11±6.87
sMCI	87	8352	76.41±7.14
AD	91	8352	75.72±7.36

Fig. 2. The overall procedure of the proposed method.

3.1.1. Co-registration

Co-registration function is pivotal in ascertaining the compatibility of two or more scans [32]. It is essential to perform a thorough verification of co-registration before moving forward.

3.1.2. Normalization function

This function serves the crucial purpose of transferring scans into the standardized MNI space, as utilized in the SPM software. The standard coordinate system in the field of neuroimaging is the MNI space, which the Montreal Neurological Institute created from 152 scans. Given that brain images of the same individual, acquired during different sessions, may exhibit variations in the positioning of the head and brain, a common spatial reference is imperative for effectively comparing datasets from diverse individuals [23].

The process of transferring scans to the MNI space involves two essential steps: Bias correction: This initial step addresses the variations in soft intensity present within the acquired images. Bias correction corrects any consistent differences in image intensity while also enhancing the precision and dependability of the following steps.

Normalization of space: In this step, deformation fields are used to line up the acquired scans with the MNI space. These deformation fields consist of images that represent the displacement amount for each position within the scan. To illustrate, the deformation field encodes the spatial shifts along the X, Y, and Z coordinates, with lighter colors indicating rightward movement and darker colors indicating leftward movement. By executing both bias correction and spatial normalization, the scans are not only standardized but also aligned with one another in the MNI space. This arrangement makes it easier to compare brain images from different people in a meaningful way. This helps researchers learn more about different neurological studies and the human brain in general.
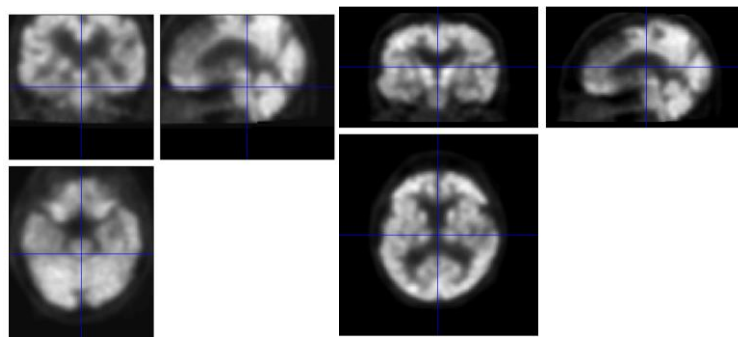

Fig. 3: An example of applying the normalization function to the brain image of an Alzheimer's patient.

In the left image of Figure 3, the example of applying the normalization function to the brain image of a patient from the Alzheimer's group can be seen, and the right image is the image before applying this function.

3.1.3. Segmentation

Image segmentation is defined as an image processing technique that is used to divide an image into two or more meaningful regions [14]. In this research, the segmentation is used to separate the classes of brain tissue: gray matter, white matter, cerebrospinal fluid, skull, and soft tissue.
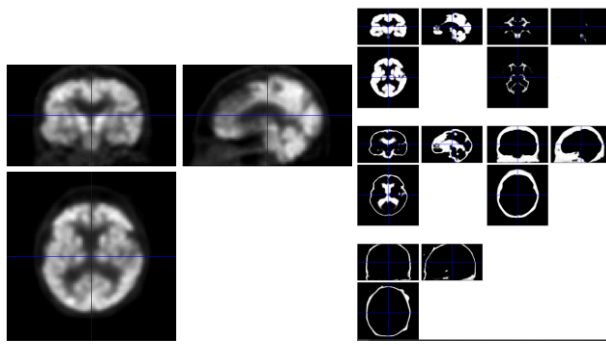
Fig. 4: Segmentation of normalized images.

The figure on the left shows the normalized brain image of a patient from the Alzheimer's group, and the image on the right of Figure 4 is the result of segmentation on this image.

The entire dataset has been divided into three parts: 60% for training, 20% for validation, and 20% for testing.

3.2.VGG16

The Visual Geometry Group (VGG) created the VGG16, which is a significant model in deep learning [24]. It has different layers, including convolutional, pooling, and fully connected layers. Convolutional layers play a crucial role in capturing intricate features within input images. Meanwhile, pooling layers down sample feature maps to refine and retain the essential information. In this paper, we use the VGG with 16 layers with 13 convolutional layers, and each one uses 3×3 filters with a stride of 1 and the Rectified Linear Unit (ReLU) activation function. We also have max-pooling layers with a 2×2 pool size and a stride of 2, to further reduce feature maps. It takes two fully connected layers with 4096 channels to flatten the feature maps that are made after the convolutional and pooling layers. Subsequently, a sigmoid activation layer with two output neurons is employed for binary classification. In Figure 5, the VGG-16 model's architecture used in this paper is shown.
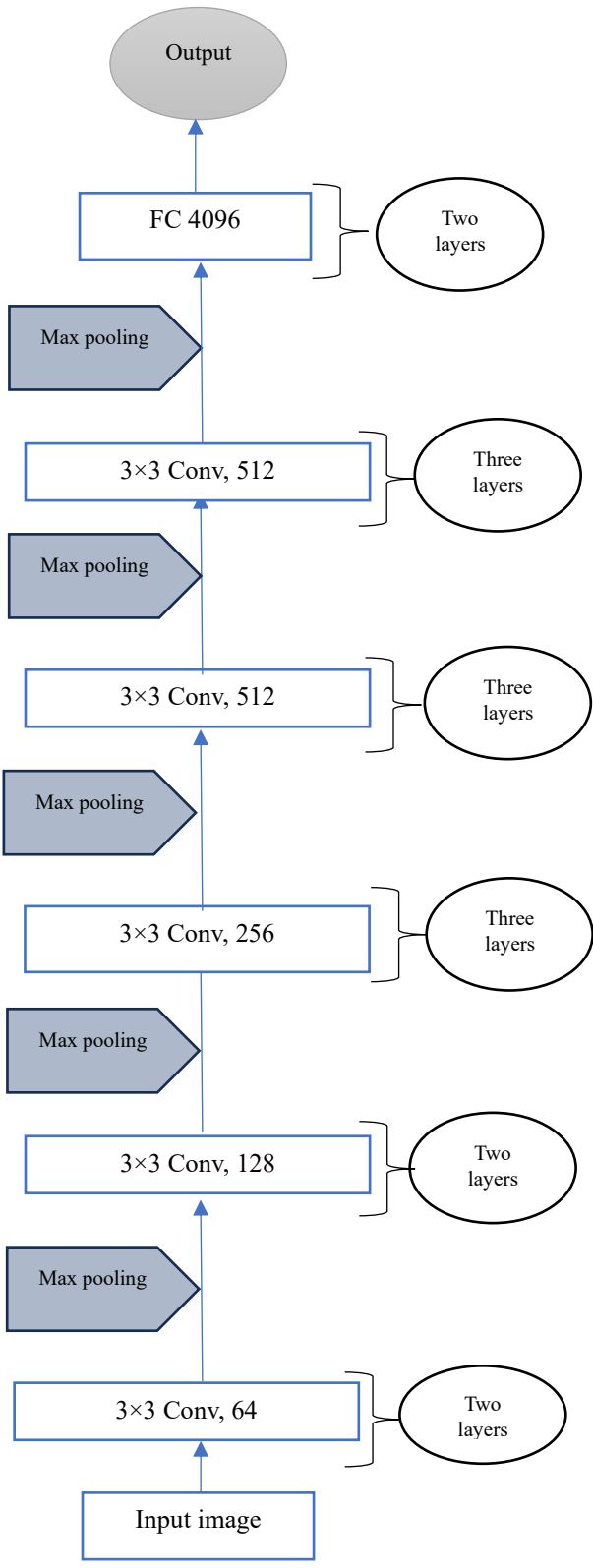
Fig. 5: VGG-16 architecture applied for AD classification.

3.3.Custom CNN

In this paper, we have used a custom CNN architecture for Alzheimer's disease classification, which consists of convolutional, max pooling, sequential and dense layers, which were all repeated in various instances as seen in Figure 6. Also, for reduce overfitting, Dropout regularization technique has used. The initial layers consisted of 4 parameters which included the dimensions meaning height and width, a variable batch size, and the number of filters.

Input Layer	Input: (None, 176, 208, 3)	Output: (None, 176, 208, 3)
Conv Layer	Input: (None, 176, 208, 3)	Output: (None, 176, 208, 16)
Conv Layer	Input: (None, 176, 208, 16)	Output: (None, 176, 208, 16)
Max pooling Layer	Input: (None, 176, 208, 16)	Output: (None, 88, 104, 16)
Sequential Layer	Input: (None, 88, 104, 16)	Output: (None, 44, 52, 32)
Sequential Layer	Input: (None, 44, 52, 32)	Output: (None, 22, 26, 64)
Sequential Layer	Input: (None, 22,26,64)	Output: (None, 11, 13, 128)
Dropout Layer	Input: (None, 11, 13, 128)	Output: (None, 11, 13, 128)
Conv Layer	Input: (None, 11, 13, 128)	Input: (None, 11, 13, 256)
Conv Layer	Output: (None, 11, 13, 256)	Output: (None, 11, 13, 256)
Max pooling Layer	Input: (None, 11, 13, 256)	Output: (None, 5, 6, 256)
Input Layer	Input: (None, 176, 208, 3)	Output: (None, 176, 208, 3)
Dropout Layer	Input: (None, 5, 6, 256)	Output: (None, 5, 6, 256)
Flatten Layer	Input: (None, 5, 6, 256)	Output: (None, 7680)
Sequential Layer	Input: (None, 7680)	Output: (None, 512)
Sequential Layer	Input: (None, 512)	Output: (None, 128)
Sequential Layer	Input: (None, 128)	Output: (None, 64)
Sequential Layer	Input: (None, 64)	Output: (None, 32)
Dense Layer	Input: (None,32)	Output: (None, 4)

Fig. 6: Architecture of the custom CNN used for AD classification.

3.4.AlexNet

This neural network is composed of eight layers [25], which consist of three dense layers and five convolutional layers. The architecture used for classifying Alzheimer's disease is shown in Figure 7. Initially, the input image undergoes a convolution operation with 96 filters of size 11×11, followed by a 2×2 max pooling layer. In the next convolutional layer, 32 input images are convolved with 256 filters of

size 5×5. Each convolutional layer is followed by a max pooling layer, except for the last two layers, which are stacked together. As shown in Figure 7, there is connectivity between the layers facilitated by three dense layers, where all neurons in one layer are connected to those in the next layer. Finally, the output is classified using the sigmoid function, which combines the probabilities of all possible outcomes to produce a single value of one.
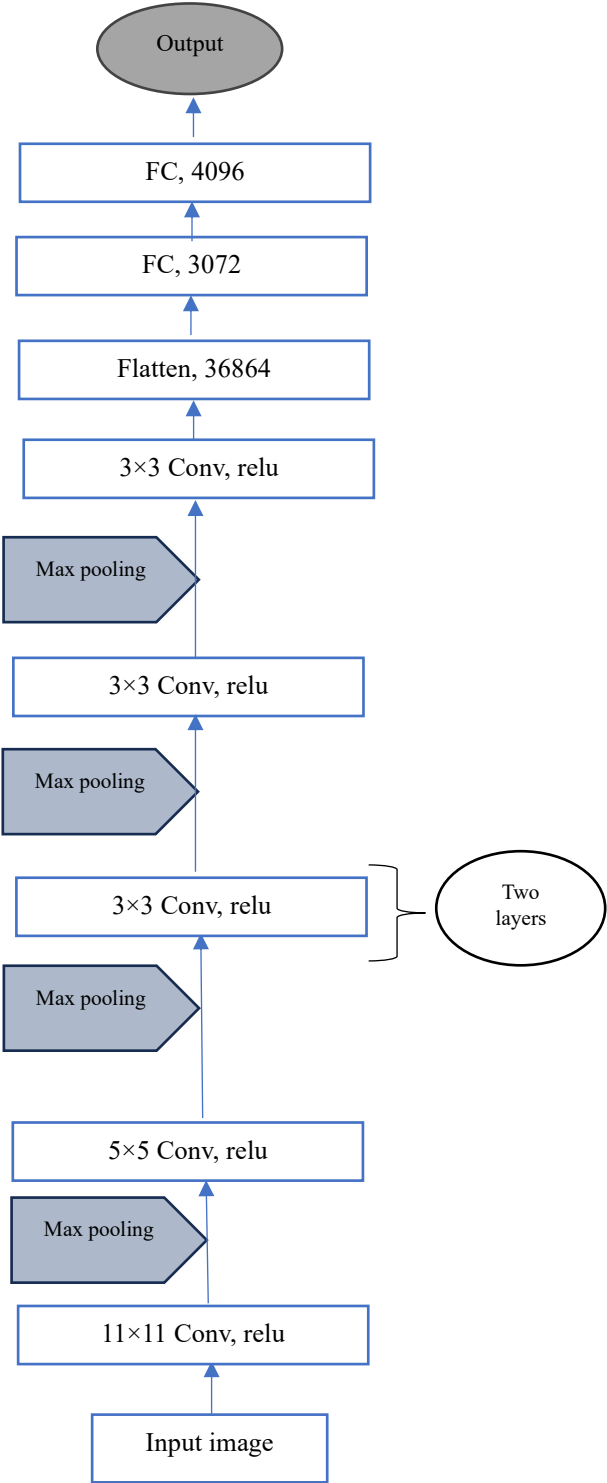
Fig. 7: AlexNet architecture used for AD classification.

3.5. Ensemble

Ensemble techniques are an invaluable tool in the area of deep learning for improving the robustness [26] and reliability of Alzheimer's stage classification models. These models often involve complex neural networks with numerous parameters [27], and as a result, they can be prone to high variance during the training phase. This variance means that the same model, when trained multiple times with different initializations or training data shuffling, might produce slightly different predictions for the same input. To mitigate this issue and enhance the stability of predictions, ensembles are employed. During the training phase of an ensemble for Alzheimer's stage classification, multiple instances of the same model architecture are created. Each of these instances learns a distinct set of weights through gradient descent optimization, which leads to subtle variations in their learned representations. Consequently, when these individual models are used to make predictions on the same input data, their outputs may diverge slightly due to these learned differences. In this paper, instead of relying on just one model's decision, we combine our model's outputs using a majority voting approach.

3.6. Metrics for evaluation of performance

When evaluating the performance of classification models, such as machine learning algorithms, we commonly use metrics like accuracy, precision, and recall. These metrics allow us to assess how well the model makes predictions and performs classification. Here's an explanation of each metric:

Accuracy: These metric measures how accurate the classifier's predictions are by finding the ratio of the number of correctly predicted samples (both true positives and true negatives) to the total number of samples. A higher accuracy score signifies superior overall performance.

Precision: Precision focuses on how well the classifier can find positive samples among all samples that have been marked as positive. You can calculate it by adding the total number of true positives to the total number of true positives plus the number of false positives. A high precision score means that the classifier is probably right when it says that a label is positive.

Recall: Also known as sensitivity or true positive rate, recall gauges the classifier's ability to correctly identify positive samples among all truly positive samples in the dataset. It is calculated as the ratio of true positives to the sum of true positives and false negatives. A high recall score indicates the classifier can effectively locate most positive samples.

Area Under the Curve: In statistics and machine learning, AUC refers to the area under the receiver operating characteristic (ROC) curve. It's a performance measurement for classification problems at various thresholds settings. AUC represents the degree or measure of separability; it tells how much the model is capable of distinguishing between classes.

4. Computational results

In the second stage of methodology used, Table 2 displays the comparison findings of three CNN models for classifying Alzheimer's patients and cognitive normal. The VGG-16 model exhibits a 92.10% accuracy rate, an 88% precision rate, a 100% recall rate, and an AUC of 98%. AlexNet has a 91.4% accuracy rate, 88.5% precision, 86.49% recall, and AUC of 91%, and a custom CNN has a 94.73% accuracy rate, 95.45% precision rate, 95.45% recall rate, and AUC of 100%. According to the results, Custom CNN outperforms all other models for the underlying issue because its weights were better trained for this specific dataset. The majority voting method is used to combine the models' results. This gives an overall accuracy of 96.74%, a precision rate of 92.65%, a recall rate of 95.9%, and an AUC of 98.21% for separating AD patients from CN patients.

Table 2. AD/CN classification using various CNN models.

| CNN Models	Accuracy	Precision	Recall	AUC
VGG16	92.10	88	100	98
Alex Net	91.4	88.5	86.49	91
Custom CNN	94.73	95.45	95.45	100

We also plot the ROC curves in Figure 8 for classifying both AD vs. CN using these CNN models. In classifying AD and CN cases, Figure 8 shows the AUC of VGG16, AlexNet, and the custom CNN models that are 98%, 91%, and 100%, respectively.
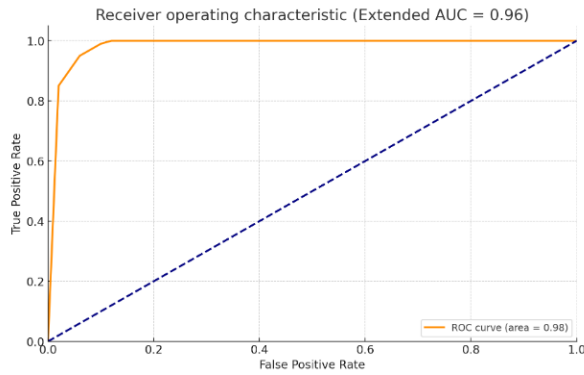
ROC for VGG model
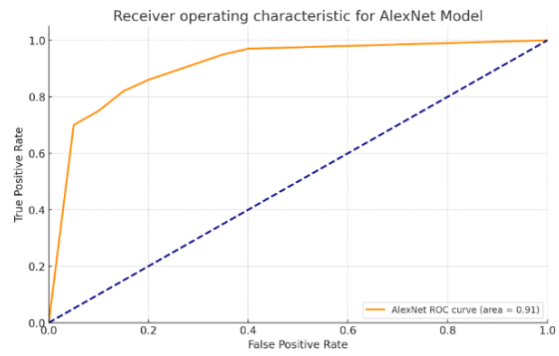
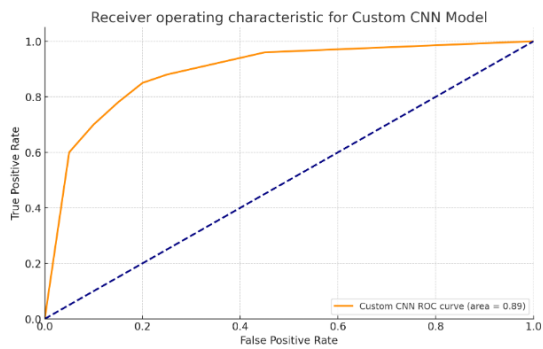ROC for AlexNet model
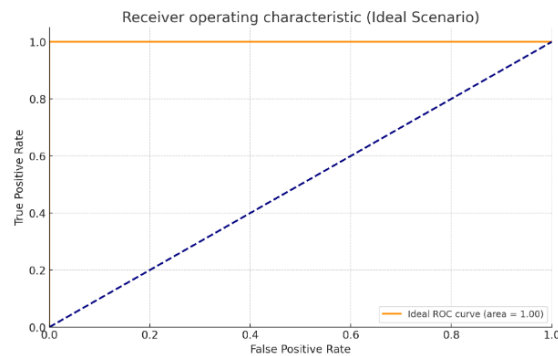
ROC for custom CNN model

Fig 8. ROC curves of the CNN models for AD/CN classification.

Table 3 displays the comparison findings of three CNN models for classifying progressive MCI and stable MCI patients. The VGG-16 model exhibits a 90.90% accuracy rate, an 85% precision rate, an 85.71% recall rate, and an AUC of 89%. AlexNet has an 89.47% accuracy rate, 86.36% precision, 95% recall, and AUC of 89%, and a custom CNN has a 93.01% accuracy rate, 89.13% precision rate, 4.80% recall rate, and AUC of 95%. According to the results, Custom CNN outperforms all other models for the underlying issue because its weights were better trained for this specific dataset. The majority voting method is used to combine the models' results. Table 4 shows that the overall classification of sMCI vs. pMCI patients was accurate 93.13% of the time, with a precision rate of 89.83%, a recall rate of 94.84%, and an AUC of 94.4%.
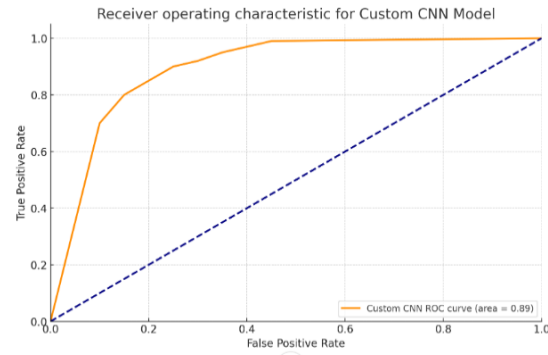
Table 3. pMCI/sMCI classification using various CNN models.

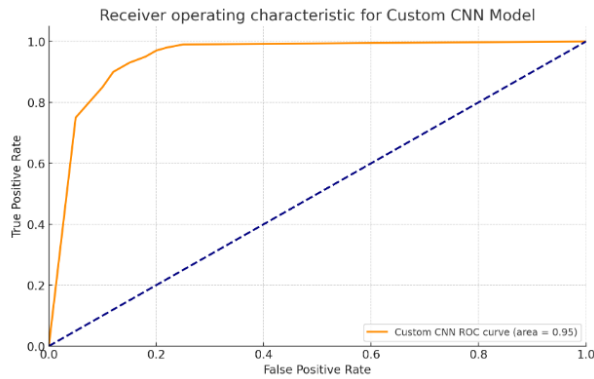| CNN Models	Accuracy	Precision	Recall	AUC
VGG16	90.90	85	85.71	89
Alex Net	89.47	86.36	95	89
Custom CNN	93.01	89.13	94.80	95

In classifying pMCI and sMCI cases, Figure 9 shows the AUC of VGG16, AlexNet, and the custom CNN models that are 89%, 89%, and 95 %, respectively.

ROC 2 for VGG16 model   ROC 2 for AlexNet model

ROC 2 for the Custom CNN model

Fig 9. ROC curves of the CNN models for sMCI/pMCI classification.

Table 4. Results obtained by using ensemble with majority voting technique

CNN Models	Accuracy	Precision	Recall	AUC
AD vs. CN	96.74	92.65	95.98	98.21
pMCI vs. sMCI	93.13	89.83	94.84	94.4

As mentioned before, by using majority voting, each model in the ensemble makes a prediction, and the class that receives the most votes (predictions) is chosen as the final prediction. Majority voting could potentially improve the final performance of classification in distinguishing both AD/CN and sMCI/pMCI.

Related works

In this section, the best results published in other related articles are reviewed and compared with those of the proposed method. Table 5 shows the results of associated articles for the classification of pMCI and sMCI groups. Our proposed method achieves the highest performance among the state-of-the-art articles for the classification of patients.

Table 5. Related works on the classification of progressive and stable MCI

Papers	Model	Performance measures
[28]	CNN model	Accuracy of 73.04%
[29]	CNN-based method	Accuracy of 75%
[30]	-Curvature Analysis+ multi-layer perceptron classifier (MLP)	Accuracy of 79.95%
[31]	The local surface roughness (LSR)	Accuracy of 74.3%
[32]	3D-DenseNet +SHARPM-PDM	Accuracy of 75%
[33]	An ensemble-learning- based MRDATS classifier multi-channels cascaded CNNs (3D-CNN+2D-CNN)	AUC of 81% for TTC of 6 months Accuracy of 71% - AUC of 71.9%

5. Conclusion and Future research

Alzheimer's disease is the most common form of dementia, which leads to memory problems and declining thinking abilities. Mild cognitive impairment (MCI) is a prodromal stage of Alzheimer's. People with MCI can either progress to Alzheimer's or stay the same. Therefore, it's important to detect if MCI is getting worse or staying stable early on to slow down the disease.

In this paper, we have applied a comprehensive methodology for the classification of neurological diseases, with a primary focus on Alzheimer's disease (AD). Our approach begins with precise gray matter segmentation, a fundamental step in neuroimaging, which enables us to identify specific brain regions and detect changes in density and volume indicative of neurological conditions. The application of noise-reduction techniques through mask application follows this segmentation, which is crucial for improving data clarity and quality in medical imaging. We compared three deep learning models: VGG, AlexNet, and a custom convolutional neural network (CNN). For even better results, we used an ensemble technique where the majority of models were voted on. This gave us an overall accuracy of 96.74%, a precision rate of 92.65%, a recall rate of 95.9%, and an AUC of 98.21% for separating AD patients from CN patients, and an overall accuracy of 93.13%, a precision rate of 89.83%, a recall rate of 94.84%, and an AUC of 94.4% for separating sMCI patients from pMCI patients. These findings are better in comparison to using conventional machine-learning techniques. It highlights the potential clinical relevance of our research, suggesting that our methodology could serve as a valuable tool in the early diagnosis and intervention of neurological diseases, ultimately advancing patient care and contributing to the broader field of neuroscience research. Further investigations on larger and more diverse datasets could solidify the utility and generalizability of our approach for the medical community.

Declarations

The authors declare no conflicts of interest.

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