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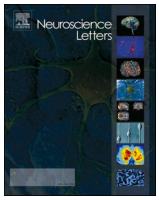

Deep learning based diagnosis of Alzheimer's disease using FDG-PET images

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ABSTRACT

Purpose: The aim of this study is to develop a deep neural network to diagnosis Alzheimer's disease and categorize the stages of the disease using FDG-PET scans. Fluorodeoxyglucose positron emission tomography (FDG-PET) is a highly effective diagnostic tool that accurately detects glucose metabolism in the brain of AD patients.
Material and methods: In this work, we have developed a deep neural network using FDG-PET to discriminate Alzheimer's disease subjects from stable mild cognitive impairment (sMCI), progressive mild cognitive impairment (pMCI), and cognitively normal (CN) cohorts. A total of 83 FDG-PET scans are collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, including 21 subjects with CN, 21 subjects with sMCI, 21 subjects with pMCI, and 20 subjects with AD.
Results: The method has achieved remarkable accuracy rates of 99.31% for CN vs. AD, 99.88% for CN vs. MCI, 99.54% for AD vs. MCI, and 96.81% for pMCI vs. sMCI. Based on the experimental results.
Conclusion: The results show that the proposed method has a significant generalisation ability as well as good performance in predicting the conversion of MCI to AD even in the absence of direct information. FDG-PET is a well-known biomarker for the identification of Alzheimer's disease using transfer learning.

1. Introduction

Alzheimer's disease is a progressive condition that manifests itself slowly, with its symptoms worsening over a period of several years [1]. This gradual decline can be challenging for both the individual and their loved ones, making it important to seek proper medical care and support. Dementia is a growing concern for public health that impacts approximately 50 million people worldwide [2]. It is estimated that every year there are approximately 10 million new cases, and this number is projected to triple by the year 2050. Dementia is a major cause of disability and dependence in the elderly population, and it can have a devastating impact on the lives of those affected by it, including their caregivers and families. In addition, it is important to note that dementia has a significant impact on the economy of countries worldwide. As per projections, the expenses associated with providing care for individuals with dementia are expected to exceed $2 trillion annually by 2030.

Early symptoms of AD often include memory problems, lack of motivation, and difficulty performing everyday tasks [3]. Although there has been extensive research, Alzheimer's disease still has no cure. Therefore, it is crucial to detect and manage the disease early on to treat symptoms and slow down its progression. As the illness advances, the individual may encounter growing difficulties with communication, cognition, behaviour, speech, swallowing, and mobility.

Mild cognitive impairment (MCI) is the term used to describe the phase between normal cognitive function and the development of Alzheimer's disease (AD) [4,5]. Individuals who have received a diagnosis for Mild Cognitive Impairment (MCI) may potentially develop Alzheimer's disease (AD) in the future, which is referred to as progressive MCI (pMCI). Individuals with MCI who do not progress to AD are classified as stable MCI (sMCI). Studying the effects of MCI beforehand is a necessary measure to prevent AD. There are three levels of severity in which Alzheimer's disease symptoms can be classified: mild, moderate, and severe. Individuals with mild Alzheimer's disease often face challenges in remembering their daily routines. At present, these symptoms are not serious and can be easily dealt with without requiring medical assistance. It is essential to address mild Alzheimer's disease in order to impede its progression. As Alzheimer's progresses to its moderate stage, the symptoms of the disease worsen as the brain experiences more damage [6].

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Those affected by Alzheimer's disease may need more assistance from caretakers or loved ones to complete daily tasks due to cognitive decline. In severe cases of Alzheimer's disease, plaques and tangles can spread throughout the brain, resulting in the degeneration of brain cells. This leads to a reduction in brain tissue size. People with this condition often experience limited mobility and difficulties with effective communication. Early recognition of the symptoms of this disease is of utmost importance in halting the progression of severe AD.

In order to identify synaptic activity in the brain, molecular imaging techniques like Single Photon Emission Computed Tomography (SPECT) and FDG-PET can be very useful [5]. These advanced techniques are able to visualise the brain based on certain factors such as blood flow, oxygen utilisation, or glucose consumption. By using these techniques, researchers can gain a better understanding of the workings of the brain. The brain's energy source is glucose, and Fluorodeoxyglucose (FDG) is a substance that closely imitates glucose. Combining FDG with Fluorine-18 and using it in PET scans is an effective way to indicate brain metabolism. It employs powerful radiotracers to identify cell or material changes linked to specific disorders. Amyloid PET imaging is a highly effective technique for detecting Alzheimer's disease. By utilizing radiopharmaceuticals, it can accurately identify the levels of amyloid present in the brain.

Measuring cerebral amyloid levels is a crucial tool in accurately diagnosing and treating individuals with cognitive impairment. PET scans can effectively detect the presence of amyloid deposits by utilizing the highly reliable Pittsburgh (PiB) chemical tracer. There are techniques that can help distinguish Alzheimer's disease from other types of dementia, such as frontotemporal lobar degeneration and dementia with Lewy bodies.

Machine learning and deep learning are powerful tools in medical research, enabling the classification and analysis of patients, accurate prediction of treatment effectiveness, and identification of potential risks [3,7]. By utilizing advanced deep learning and machine learning algorithms, scientists have successfully diagnosed the various stages of neurodegenerative diseases caused by Alzheimer's through the use of imaging-based detection. Feature extraction approaches based on various biomarker methodologies are effectively utilized in automatic pipelines. Through the use of Deep Learning, this technology is capable of independently pre-processing biomarkers and extracting their features. It is also able to construct a model that can accurately identify Alzheimer's disease (AD) and its various stages. Commonly utilized classification techniques for AD include support vector machine (SVM), artificial neural network (ANN), and deep neural network (DNN).

Using 2D T1-weighted MRI scans deep learning techniques have proven to be highly effective in accurately diagnosing and categorizing various stages of Alzheimer's disease. Deep learning (DL) algorithms are becoming increasingly prevalent in the field of medical image analysis, particularly in the treatment of neurological diseases. The reason for its widespread recognition is its ability to identify intricate representations in image data that are challenging for humans to recognize. These approaches eliminate the requirement for manual feature extraction, which is usually necessary in machine learning methods, by effortlessly detecting valuable features.

Research progress has been significantly challenged by the incurable nature of Alzheimer's disease and the difficulty in diagnosing it for decades. The utilization of neuro-imaging techniques has become indispensable for both clinical and research advancements in the field of Alzheimer's disease. These techniques now make it feasible to diagnose Alzheimer's disease in living individuals. However, the diagnosis of Alzheimer's disease remained challenging due to the high degree of similarity in brain patterns. Researchers can improve Alzheimer's disease diagnosis accuracy by using computer-aided diagnosis. Deep learning is undoubtedly the optimal solution for addressing such concerns and has exhibited remarkable outcomes, especially for classification tasks. Deep learning can efficiently classify the stages of brain diseases based on images. In this work, a method is proposed for binary classification of Alzheimer's disease. To classify various stages of AD, the FDG-PET scan is utilized.

The following are the key contributions of this paper:-.

- The analysis of FDG-PET data of AD patients.
- Pre-processing of FDG-PET data using FMRIB Software Library (FSL) software
- The proposed transfer learning model to classify, i.e. AD vs CN, CN vs MCI, AD vs MCI and pMCI vs sMCI

The rest of the paper is structured as follows: the related work is discussed in Section 2. Section 3 describes the materials and methods. Results and discussions are presented in section 4. Conclusion of the present research is given in the last section.

2. AD diagnosis using deep learning

In this section, we briefly introduced the previous work on computer-aided diagnosis of Alzheimer's disease (AD) using FDG-PET scans. Significant progress has been made in early-stage AD detection and prediction through deep learning. The 3D-CNN model can accurately predict the clinical diagnosis of CN, MCI associated with AD [8]. 3D-CNN scans can identify patterns in patients better than humans, leading to improved diagnoses. Model interpretation has demonstrated the brain's ability to differentiate between various neurological diseases, thereby providing strong evidence in support of the conclusions drawn from clinical trials.

A deep learning algorithm was developed to predict clinical diagnoses from FDG PET brain scans with high accuracy [9]. It is possible to make a reliable comparison between the accuracy of the deep learning algorithm and clinical techniques for identifying cases of AD, MCI, or no dementia. Deep learning algorithms can detect subtle features that may be missed in a standard clinical image examination, improving diagnostic accuracy.

A deep learning algorithm has been developed to predict Alzheimer's disease at an early stage using brain scans obtained through fluorine Fluorodeoxyglucose PET. The algorithm has shown 82 % specificity at 100 % sensitivity.

The researchers used the Convolutional Architecture for Fast Feature Embedding (CAFFE) framework for deep learning to create accurate prediction and classification models [9]. With a deep convolution neural network model, they extracted FDG PET image features of each participant, successfully classifying the MCI stage features and predicting their transformation. Convolution3 classification has 91.02 % sensitivity and 77.63 % specificity in predicting MCI transformation. Convolution5 classification accurately distinguishes between LMCI and EMCI with 72.19 % accuracy rate and 73 % sensitivity and specificity values.

The advanced technique, Generalized Matrix Learning Vector Quantization (GMLVQ), confidently analyzed FDG-PET scans of both healthy individuals and patients with AD [10].

The collection of intra-slice information is efficiently facilitated by this framework's use of hierarchical 2D CNN [11]. Meanwhile, the RNN is Gated Recurrent Unit (GRU) was utilized to extract inter-slice features for classification. Rigid image registration and segmentation are for PET images. The ADNI database holds PET images of 339 individuals at baseline, including 93 with Alzheimer's disease, 146 with mild cognitive impairments, and 100 healthy control participants. The method has demonstrated a highly encouraging classification performance, according to experimental results. Specifically, the AUC achieved for distinguishing AD from NC is an impressive 95.28 %, while the AUC for distinguishing MCI from NC is 83.90 %.

The study was effective contrastive-based learning strategy to effectively tackle the inherent issues associated with PET images [12]. To generate more extensive training data, the sections of the 3D PET image are amplified by eliminating the anchors from the initial picture. Contrastive loss was used to improve feature differences between classes

Table 1
Subjects details used in this study.

Diagnosis	CN	sMCI	pMCI	AD
subjects	21	21	21	20
MMSE range	[29–30]	[27–29]	[24–29]	[18–24]

MMSE: Mini mental status examination, CN: control normal, sMCI: stable mild cognitive impairment, pMCI: progressive mild cognitive impairment, AD: Alzheimer's disease, MCI: mild cognitive impairment.

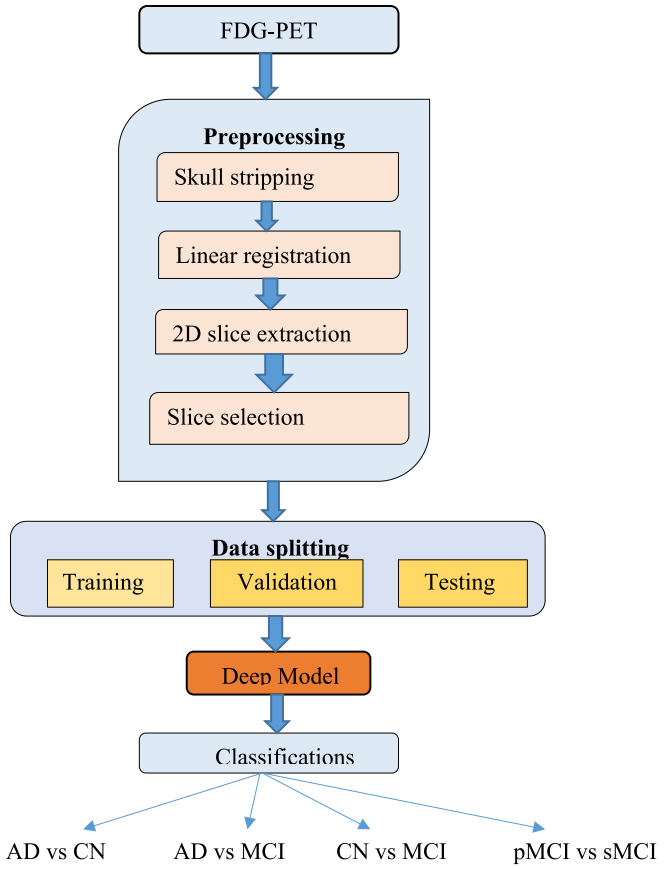

Fig. 1. Proposed classification methodology of AD using FDG-PET with deep learning.

and decrease differences within the same class in fuzzy label supervision. They developed a module with two convolutional layers (7x7 and 5x5 kernels) to better recognize different visual domains.

Using deep neural networks in FDG-PET imaging can help in detecting Alzheimer's disease at early stage [13]. The MiSePyNet is a highly effective network that achieved its goals effortlessly. It can learn from axial, coronal, and sagittal views of PET scans to gain additional information that enables it to make confident decisions. The merging of these learned representations is seamless, which enhances the network's dependability. The method employed separable convolution, starting from slice-wise to spatial-wise, in order to retain spatial information and minimize the number of training parameters. This technique deviates from the customary approach of using 3D convolution operations for 3D images, which can be more intricate and resource-intensive.

3. Materials and methods

In this work, the data from Alzheimer's disease Neuroimaging Initiative (ADNI), specifically FDG-PET, has been downloaded and is being utilized. Usually, individuals receive multiple scans at different time points to monitor their health condition. Only the baseline participants are included in this work as the primary objective is to predict MCI conversion to AD. Therefore, data that meets the specified criteria is selected. The dataset used is presented in Table 1. The Mini Mental State Examination (MMSE) is used to label subjects with different stages of AD. The range of MMSE is given Table 1. The Mini-Mental State Examination, also known as the Folstein test, is an extensively used 30-point questionnaire in clinical and research settings to confidently measure cognitive impairment. It is a widely employed screening tool in the medical and allied health domains to examine for the presence of dementia. This method is an indispensable tool in evaluating the progression and severity of cognitive impairment, tracking cognitive changes over time, and documenting the efficacy of treatment. The MMSE is a useful tool for diagnosing and assessing Alzheimer's disease. It does not require specialized equipment or training, making it simple to administer.

AD: The individuals who were initially diagnosed with AD dementia and did not show any alterations in their condition throughout the follow-up period.

CN: Patients who remain CN (control normal) from the outset and exhibit no alterations over the course of the follow-up duration.

MCI: Progressive MCI (pMCI) is a form of mild cognitive impairment (MCI) that gradually deteriorates and eventually progresses to Alzheimer's disease (AD) within 36 months of being diagnosed. Patients with MCI who stay MCI or return to normal during scans lasting at least 24 months are considered stable MCI (sMCI). Deep learning based methodology classification of AD as shown in Fig. 1.

3.1. Preprocessing

It is highly advisable to perform pre-processing on raw images to ensure accurate findings in data-driven research. Pre-processing is a crucial step in achieving image parity, which in turn facilitates effective segmentation and feature extraction.

3.1.1. Skull stripping

The brain extraction (BET) tool from the FMRIB Software Library

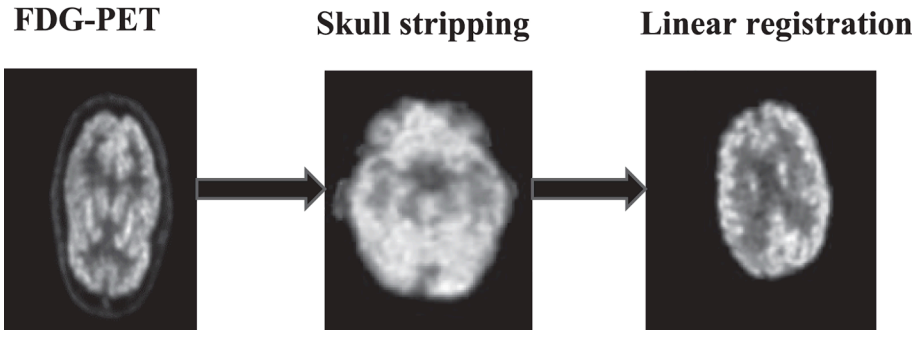

Fig. 2. Skull stripping and linear registration are performed.

Table 2
Testing results of proposed model.

Classification task	Imaging modality	Database	Acc (%)
AD vs CN	FDG-PET	ADNI	99.31
CN vs MCI	FDG-PET	ADNI	**99.88**
AD vs MCI	FDG-PET	ADNI	99.54
pMCI vs sMCI	FDG-PET	ADNI	96.81

CN: control normal, sMCI: stable mild cognitive impairment, pMCI: progressive mild cognitive impairment, AD: Alzheimer's disease, MCI: mild cognitive impairment, FDG-PET: Fluorodeoxyglucose-positron emission tomography.

(FSL) is adeptly utilized to remove non-brain components, such as bones, eyes, head, and neck, from FDG-PET images. The process of extracting non-brain tissue signals from FDG-PET data is called skull-stripping or brain extraction.

3.1.2. Image registration

To ensure precise spatial normalization in medical imaging, it is essential to utilized FMRIB Linear Image Registration Tool (FLIRT). This toolset is highly effective in aligning images with a standard reference template, to make sure that are correctly matched. Image registration is a technique used to align multiple images into a single composite image in image processing. It helps to resolve common issues with overlapping images, such as changes in rotation, scale, and skew. The image pre-processed steps are performed displayed in Fig. 2.

3.1.3. Slice selection

The image saved in the ADNI database was in NIfTI format. To make it suitable for classification, 2D slices need to be selected from the 3D scan. The final dataset comprised 35 consecutive center slices extracted from the 91 slices of each participant, and was utilized for all four categories of subjects. For all classes, a total of 2905 relevant sagittal plane slices have been extracted.

3.2. Transfer learning

VGG-19 is a deep neural network with 19 convolutional layers. It can be loaded with a pre-trained model trained on over a million images from the ImageNet database. The VGG-19 model boasts a sophisticated network architecture featuring compact convolution kernels and pooling sampling domains. As a result, it can efficiently extract abundant image features while keeping the number of parameters in check, thus preventing over-computation and overly complex structures. One potential solution to the challenge of increased difficulty in learning due to the distribution of separate layers in the training process is to find a way to lessen its impact. Accelerating the training and convergence of the network is possible by preventing the gradient from exploding. The decay learning rate has been set up to enhance the overall network's generalization ability. To enhance the overall performance and avoid over-fitting, incorporating dropout layers is a proven technique to break the correlation among neuron nodes. The VGG-19 model has a total of 31,594,562 parameters, which can be classified into two groups: trainable and non-trainable. Of these parameters, 11,554,818 are trainable and 20,039,744 are non-trainable.

4. Results and discussion

The Python 3.7 open-source package and Kaggle online platform are utilized for all the experiments. The model is adeptly trained with 70 % of the data, while 10 % was used for validation and 20 % for testing purposes. Utilized a robust NVIDIA TESLA GPU P100 that boasts an impressive 13 GB RAM capacity. The proposed architecture confidently built using the Keras library with TensorFlow backend. The training process for the network involves 50 epochs, with a batch size of 32. To minimize the cross-entropy loss, an Adam optimizer is utilized. The evaluation of the model performance is based on several metrics, including accuracy, precision, recall, and F1-score. The proposed model classification results are presented in Table 2.

The proposed model showed testing accuracy as shown in Table 2. It is especially good at categorizing different medical conditions, with success rates of 99.31 % for distinguishing between CN and AD, 99.88 % for CN versus MCI, 99.54 % for AD versus MCI, and 96.81 % for pMCI versus sMCI. These results indicate that the proposed model is a trustworthy tool for accurately and efficiently classifying AD stages. This can be beneficial for healthcare professionals and patients alike. The testing results of proposed model are shown in Fig. 3.

The model has been trained successfully for 50 epochs. It is important to note that the accuracy and validation curve showed steady progress after the initial 20 epochs. This indicates that the model has successfully learned and adapted to the data, resulting in improved performance. The discriminative region of AD may be causing over-fitting in the classification between pMCI and sMCI. The proposed model performed very well in the remaining cases. Training and validation accuracy and loss of proposed model are presented in Fig. 4.

The confusion matrix is a useful tool for solving classification problems. By summarizing the number of accurate and inaccurate predictions made by the model, it provides a clear picture of its

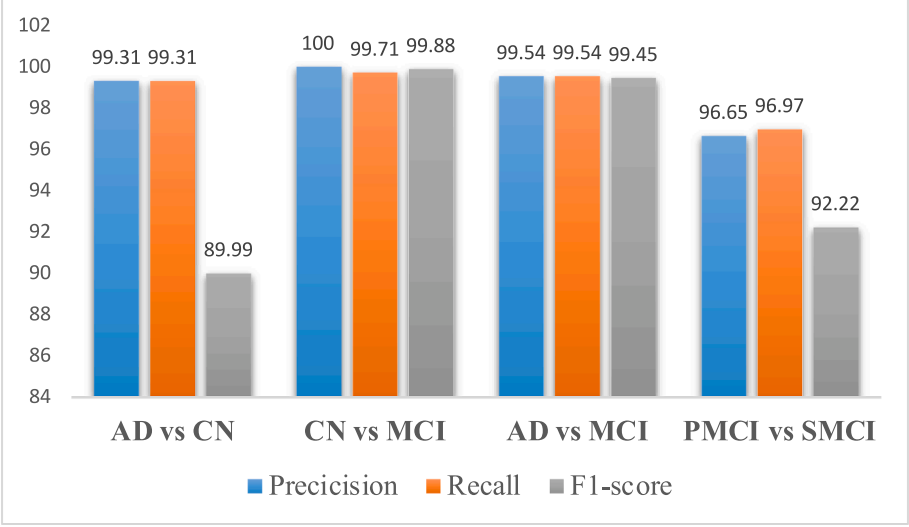

Fig. 3. Proposed model, precision, recall and F1-score.

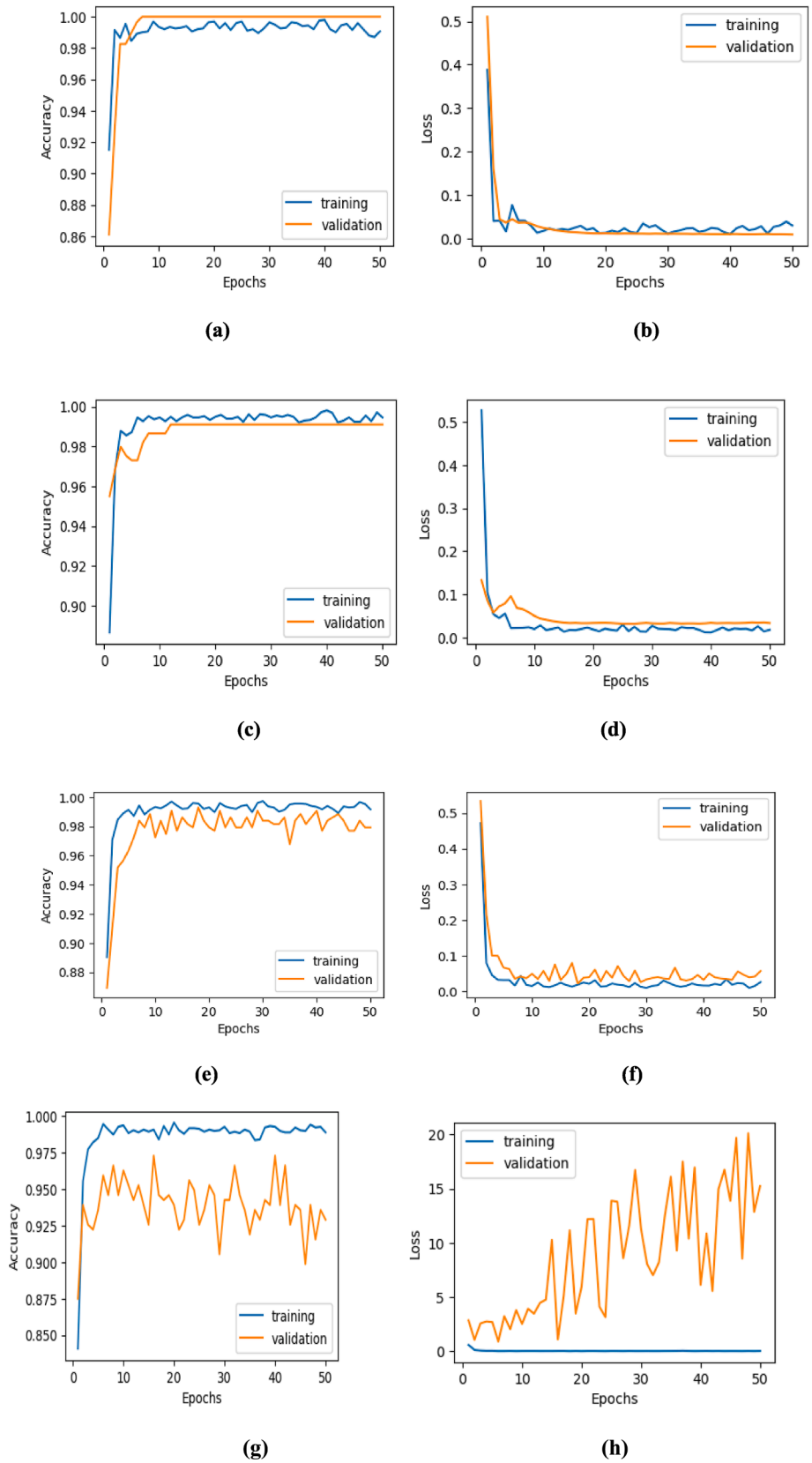

Fig. 4. Training and validation results against number of epochs (a) accuracy of AD vs CN (b) loss of AD vs CN (c) accuracy of CN vs MCI (d) loss of CN vs MCI (e) accuracy of AD vs MCI (f) loss of AD vs MCI (g) accuracy of pMCI vs sMCI (h) loss of pMCI vs sMCI.

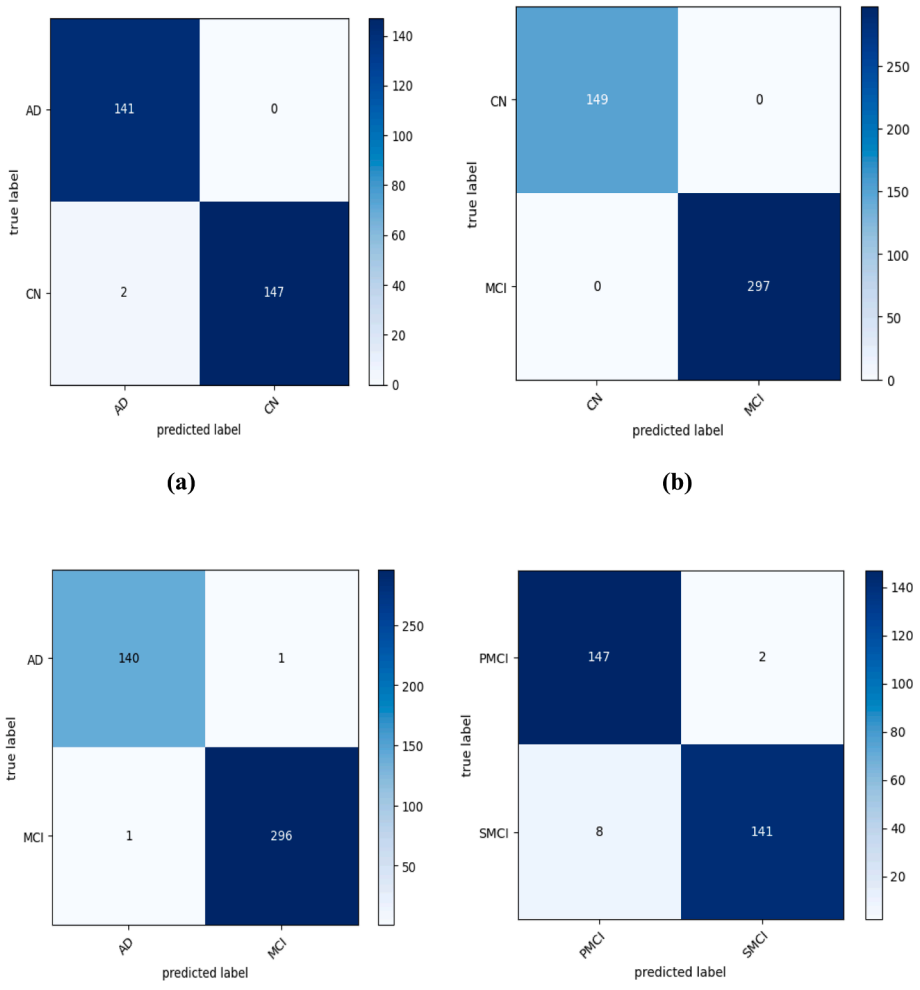

Fig. 5. Confusion matrix of classification task (a) AD vs CN, (b) CN vs MCI, (c) AD vs MCI, and (d) pMCI vs sMCI.

Table 3
Comparison with state of arts method.

Ref.	Methods	Modality	AD vs CN (%)	AD vs MCI (%)	CN vs MCI (%)	pMCI vs sMCI (%)
[9]	CAFFE	FDG- PET		–	–	78.56
[11]	2D CNN and RNN	FDG- PET	91.19	–	78.86	–
[12]	CNN	FDG- PET	98.54	89.31	93.56	–
[13]	MiSePyNet	FDG- PET		–	–	83.05
Proposed		**FDG-PET**	**99.31**	**99.54**	**99.88**	**96.81**

MiSePyNet: Multi-view Separable Pyramid Network, CAFFE: Convolutional Architecture for Fast Feature Embedding, CNN: convolutional neural networks, RNN: Recurrent neural networks, FDG-PET: Fluorodeoxyglucose-positron emission tomography, AD: Alzheimer's disease, CN: control normal, MCI: mild cognitive impairment, pMCI: progressive mild cognitive impairment, sMCI: stable mild cognitive impairment, %: Accuracy.

effectiveness in classification tasks. The confusion matrix of proposed model shown in Fig. 5.

4.1. Comparison with existing methods

In this section, we compared the performance of the proposed model with four state-of-the-art methods. The proposed model show remarkable results in binary classification by making use of FDG-PET as shown in Table 3. The results clearly show that the recommended approach is superior to all other methods.

4.2. Discussion

The primary objective of this study is to present a robust Transfer Learning approach that can effectively classify the different stages of Alzheimer's disease, including AD, sMCI, pMCI, and CN. This approach involves analyzing and interpreting FDG-PET scan results, which can provide valuable insights and information for medical professionals. The proposed method has demonstrated an exceptional accuracy rate of 99.31 % in distinguishing between CN and AD, 99.88 % for CN and MCI, 99.54 % for AD and MCI, and 96.81 % for pMCI and sMCI.

Studies using FDG-PET have revealed the hypometabolism pattern in Alzheimer's disease, providing insights into metabolic changes in patients' brains. A neural network extracted FDG-PET image features, classified MCI stage and predicted transformation [9]. The classification model effectively differentiates between early and late mild cognitive impairment with an impressive accuracy rate of 72.19 %, along with 73 % sensitivity and specificity. The method involves constructing hierarchical 2D convolutional neural networks (CNNs) for the purpose of capturing intra-slice features, followed by the utilization of a gated recurrent unit (GRU) of a recurrent neural network (RNN) to extract inter-slice features [11]. The extracted features are then used for the final classification of FDG-PET images. The results show an accuracy of

91.19 % for AD vs. NC and 78.86 % for MCI vs. NC, demonstrating promising performance.

The method used fuzzy supervised contrastive and cross-entropy losses to reduce brain FDG-PET slice misinformation, obtain higher-level common features, and improve classification performance [12]. The method achieved accuracy rates of 98.54 %, 89.31 %, and 93.56 % for AD vs. CN, AD vs. MCI, and CN vs. MCI, respectively. The developed architecture uses separable convolution to reduce training parameters while retaining spatial information [13]. The proposed method has better performance than traditional and deep learning-based algorithms for predicting the progression of Mild Cognitive Impairment. The accuracy of this method on the ADNI dataset is 83.05 %.

The proposed method has shown exceptional performance, as indicated by the outcomes presented in Table 3**.** The study sample size is small due to certain limitations. Alzheimer's disease (AD) is expected to become more common in the future. Projections suggest that by 2050, over 2 % of the United States population and 1 % of the global population will have this condition. Therefore, it is important to keep researching and developing effective treatments to reduce the impact of AD on people and society. Identifying patients who will be diagnosed with AD at an early stage is a major challenge.

5. Conclusion

The present study aimed to develop deep neural network capable of detecting binary classification of Alzheimer's disease through the analysis of FDG-PET scans. FDG-Positron emission tomography (PET) is a cutting-edge nuclear medicine functional imaging modality used to monitor metabolic processes in vivo and assist doctors in the diagnosis of AD. The results show that the proposed method has a significant generalisation ability as well as good performance in predicting the conversion of MCI to AD even in the absence of direct information. FDG-PET is a well-known biomarker for the identification of Alzheimer's disease. The results of a deep learning approach to Alzheimer's disease detection are promising. However, significant flaws in the research procedure were discovered, such as inadequate database data. It is essential to increase data capacity for extensive research for the AD risk prediction model in the future.

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CRediT authorship contribution statement

Nand Kishore: Conceptualization, Data curation, Methodology, Software, Validation, Writing – original draft. **Neelam Goel:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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