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Advancements in Deep Learning for Alzheimer's Disease Diagnosis: A Comprehensive Review

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Abstract

This research aims to advance the diagnosis and management of Alzheimer's disease (AD) by leveraging deep learning methodologies, providing a comprehensive quantitative evaluation of their efficacy compared to traditional machine learning models. A thorough literature review was conducted, focusing on the application of deep learning techniques in AD diagnosis. The study examined various biomarkers and datasets utilized in the field, evaluating their contributions to the accuracy and reliability of diagnostic models. The analysis encompassed both natural language processing and computer vision approaches, highlighting recent trends and innovations. Deep learning models demonstrated superior accuracy in diagnosing AD compared to conventional machine learning techniques. The quantitative analysis revealed significant improvements in early detection and diagnostic precision, showcasing the potential of these advanced methodologies. Despite the advancements, several challenges, such as data variability and model interpretability, were identified, indicating areas for further research. Comparative analysis with existing diagnostic approaches underscored the advancements in accuracy and reliability achieved through deep learning. The novelty of this research lies in its detailed quantitative assessment of deep learning techniques for AD diagnosis, providing a robust foundation for future advancements. Unlike conventional studies, this work offers a comprehensive numerical justification of the efficacy of deep learning models. The integration of diverse biomarkers and datasets, combined with the superior diagnostic performance, sets this study apart, highlighting the potential for significant improvements in AD diagnosis and management through continued innovation in deep learning methodologies.

Keywords: Alzheimer's Disease; Deep Learning (DL); Cognitive Decline; Neural Networks; Biomarkers; Research Trends

Introduction

Alzheimer's Disease is characterized as a enduring neurobiological brain condition that progressively leads to the deterioration of brain cells, resulting in discrepancies in cognitive function and memory. Ultimately, AD speeds up the process of losing the capacity to carry out even the most fundamental duties[1]. In the initial stages of AD, brain imaging and computer-assisted diagnostic techniques are used by medical practitioners to classify the disease. Recent statistics from the World Alzheimer's Association indicates that more than 4.7 million Americans 65 years of age and older are presently suffering from AD. Forecasts indicate that this figure may increase dramatically over the next fifty years, perhaps impacting as many as sixty million people. About 60–80% of dementia cases worldwide are caused by Alzheimer's disease.

A branch of artificial intelligence called deep learning (DL) has become an effective tool across a range of fields, including medical imaging and biomarker analysis. By leveraging neural networks to automatically learn complex patterns from large datasets, deep learning techniques hold promise for enhancing AD diagnosis and understanding disease progression.

Research trends in AD diagnosis and management are increasingly focused on integrating deep learning methodologies with traditional biomarkers and imaging techniques. By harnessing the power of DL, investigators can uncover novel biomarkers, refine existing diagnostic criteria, and develop personalized treatment regimens tailored to individual patients.

This paper aims to provide a comprehensive review of AD detection using deep learning methods. By examining the intersections of cognitive decline, neural networks, machine learning, biomarkers, medical imaging, and research trends, we aim to highlight the potential of deep learning in advancing our understanding and management of AD.

Related Work

Our methodology presents a novel approach to bipedal robot design, featuring 12 degrees of freedom for versatile, human-like motion. We enhance bipedal gait generation by integrating Zero Moment Point (ZMP) with the Linear Inverted Pendulum Model (LIPM). While based on existing concepts, our research pushes the boundaries of this framework for improved stability and walking patterns. This approach reflects our commitment to innovative design and control strategies in the field of bipedal robotics.

Numerous studies have discovered the application of DL techniques in the detection and classification of AD, aiming to enhance accuracy and efficiency in disease prediction and management. An overview of current studies in this emerging topic is given in this part, with emphasis on important approaches, discoveries, and developments.

One notable study by Sarraf and Tofighi demonstrated the effectiveness of convolutional neural networks (CNNs) in automatically detecting AD from structural MRI scans. Their deep learning model achieved high accuracy in discriminating between AD sufferers and unaffected controls, showcasing the potential of CNNs in neuroimaging-based diagnosis[2].

Building upon this work, Zhou et al. suggested a multimodal deep learning framework for AD diagnosis, integrating sMRI and fMRI data. Their model effectively combined spatial and temporal features extracted from both modalities, yielding superior performance compared to single-modality approaches[3].

In addition to neuroimaging modalities, researchers have also explored the utility of other biomarkers in AD detection. For instance, Li et al. investigated the use of cerebrospinal fluid (CSF) biomarkers in conjunction with deep learning algorithms for early AD diagnosis. Their study demonstrated the potential of combining CSF biomarker data with deep learning models to improve diagnostic accuracy and prognostic prediction[4].

Moreover, recent advancements in deep learning have extended beyond traditional imaging and biomarker modalities. Natural Language Processing techniques have been increasingly worked to analyze textual data, such as clinical notes and medical records, for AD diagnosis. For example, Fung et al. established a deep learning-based model to extract and analyze linguistic features from clinical narratives, enabling automated prediction of AD progression and severity[6].

The goal of this investigation is to determine the best artificial neural network design for AD multiclass categorization, using the AD Imaging Initiative (ADNI) dataset, while minimizing the need for extensive image preprocessing and reducing computational complexity[7].

The research paper focuses on the detection and classification of AD using deep learning methods, specifically DenseNet-169 and ResNet-50 CNN architectures. The goal of these models is to correctly categorize AD into four groups: non-dementia, very mild dementia, mild dementia, and moderate dementia[5].

Overall, these studies underscore the growing interest and possibilities of deep learning approaches in Alzheimer's detection. By leveraging advanced neural network architectures and multimodal data integration, researchers are poised to unlock new insights into the pathophysiology of Alzheimer's and improve clinical decision-making in disease management.

Preliminaries

Overall, these studies underscore the growing interest and possibilities of deep learning approaches in Alzheimer's

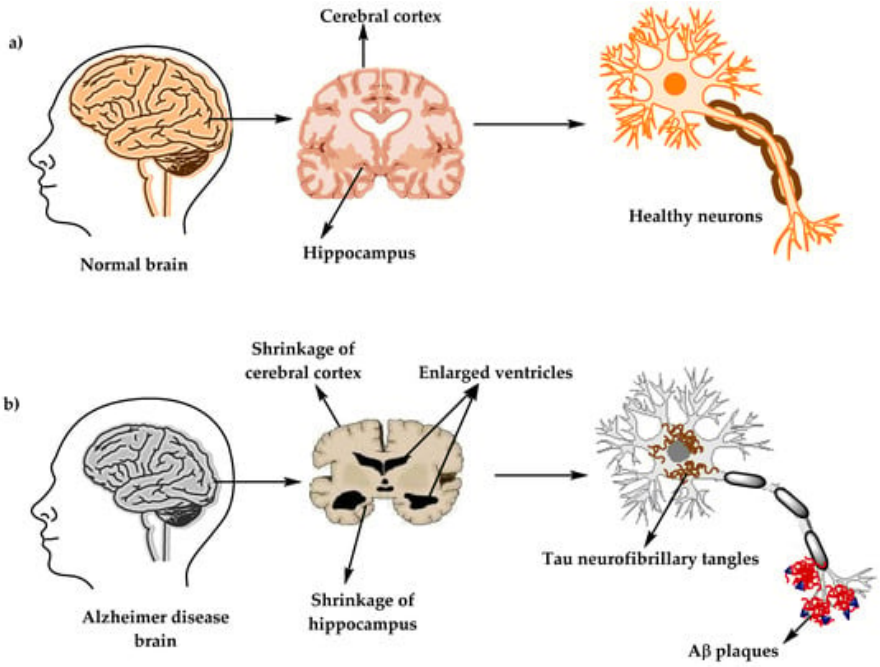

Fig 1. a) Normal brain and b) brain affected by Alzheimer's disease (AD). (Zeinab Breijyeh, et al., (2020)) [5]

detection. By leveraging advanced neural network architectures and multimodal data integration, researchers are poised to unlock new insights into the pathophysiology of Alzheimer's and improve clinical decision-making in disease management.

AD Neuroimaging

The identification and diagnosis of AD depend heavily on neuroimaging markers, which provide information on the anatomical and functional changes in the brain related to the illness.

- **Structural Magnetic Resonance Imaging:** Structural MRI allows for the visualization of macroscopic changes in brain structure, including cortical atrophy, ventricular enlargement, and hippocampal volume loss, which are characteristic features of AD pathology [8]. Hippocampal (HC) volume and cortical thickness, two quantitative metrics obtained from structural MRI, are sensitive indicators for AD-related neurodegeneration.
- **Functional MRI (fMRI):** Applying functional magnetic resonance imaging (fMRI), variations in blood oxygenation levels correlated with neuronal activity can be measured to evaluate brain function. Functional connection patterns have changed during resting-state fMRI studies, especially within the default mode network, which is suggestive of early AD pathology [2]. Task-based fMRI paradigms also provide valuable insights into cognitive impairment and neural dysfunction in AD.
- **Positron Emission Tomography (PET):** The in vivo identification of AD pathology is made possible by PET imaging using radiotracers that target tau and beta-amyloid proteins. In order to visualize and quantify beta-amyloid deposition, beta-amyloid PET tracers, including (18F) florbetapir and (18F) florbetaben, bind to amyloid plaques in the brain [9]. When tau PET tracers, like (18F) flortaucipir, attach to neurofibrillary tangles, they provide further details regarding the tau pathology associated with AD [4].
- **Diffusion Tensor Imaging (DTI):** DTI measures the diffusion of water molecules in brain tissue to provide data concerning white matter integrity and connections. Patients with AD have been found to have changes in the white matter microstructure, which are indicative of axonal degradation and disconnection of brain networks. These changes include decreased fractional anisotropy and increased mean diffusivity [9].

AD Datasets

Studies on Alzheimer's disease uses several publicly available datasets for different objectives, encompassing diagnosis, prediction, and understanding disease progression. Sample of dataset MRI Images as shown in Figure 2.

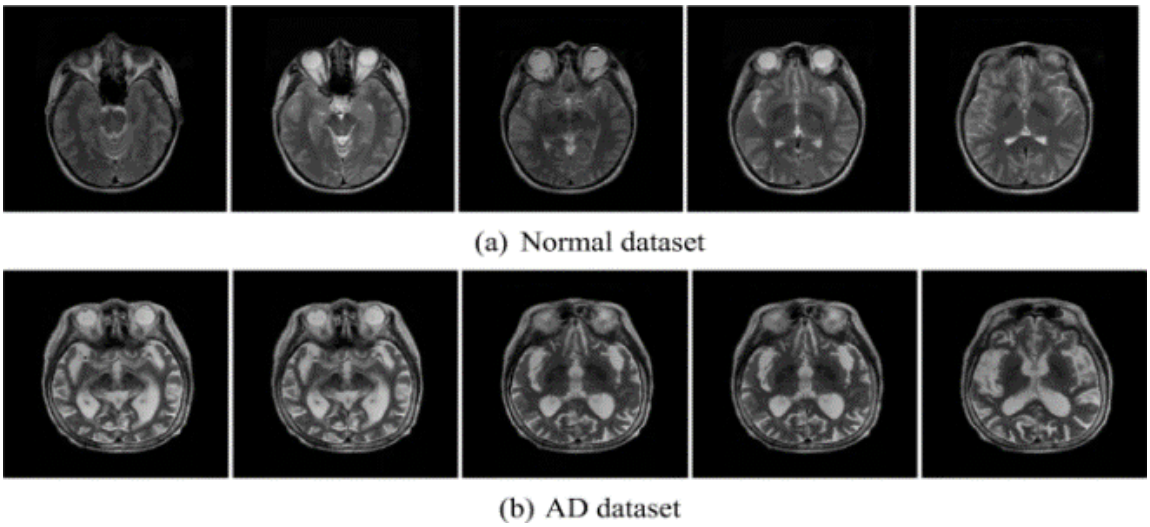

Fig 2. Normal Brain and AD Brain MRI Images of Dataset (Zeinab Breijyeh, et al., (2020)) [5]

a. Alzheimer's Disease Neuroimaging Initiative (ADNI)

When it went public in 2003, several non-profit organizations, including the Food and Drug Administration, the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and commercial pharmaceutical companies, collaborated on its development. This five-year, USD 60 million public-private partnership sought to determine if Mild Cognitive Impairment (MCI) and Early Alzheimer's Disease could be well pursued by serial measures of MRI imaging, CSF test, PET scans, clinical examinations, and factors related to neuropsychology. The ADNI datasets have been divided into four categories: ADNI-1, ADNI GO, ADNI-2, and ADNI-3, based on the participant pool. The URL to access the data is http://adni.loni.usc.edu/.

b. Open Access Series of Imaging Studies (OASIS)

The OASIS dataset from the Washington University Knight Alzheimer Disease Research Center incorporates clinical, MRI scans and PET scans data from several patients with ages ranging from 42 to 90 above. There are 493 people in varying stages of cognitive impairment and 605 adults who are cognitively intact. The 15-year dataset includes over 2000 MRI scans with functional and anatomical sequences. In addition, there are over 1500 after processing images from the PET Unified Pipeline and PET metabolic and amyloid imaging raw imaging samples. Longitudinal cognitive and clinical outcomes have been offered by OASIS, together with information on dementia state and APOE genotype. This open-access dataset, which contains both cross-sectional and longitudinal information, aids in the study of dementia and old age. The dataset is publicly available and can be accessed at http://www.aibl.csiro.au/.

c. Australian Imaging Biomarkers and Lifestyle (AIBL)

It is a longitudinal research project focused on understanding aging and Alzheimer's disease (AD). Participants are recruited from all throughout Australia, and information is gathered on clinical evaluations, cognitive tests, genetics, lifestyle choices, and brain imaging like MRI and PET. AIBL aims to monitor biomarkers, and imaging characteristics to advance research on AD progression, risk factors, and interventions. Accessible to researchers globally, AIBL contributes crucial insights into aging-related neurodegenerative diseases and informs strategies for early detection and treatment. The dataset is accessible at http://www.aibl.csiro.au/ and is open to the public.

d. Medical Image Resource for Alzheimer's Disease (MIRIAD)

MRI samples from people with AD, Healthy Controls (HC), and Mild Cognitive Impairment (MCI) are all encompassed in the collection. Researchers can examine alterations in brain structure linked to several phases of Alzheimer's disease progression thanks to this heterogeneous subject pool. MIRIAD contains a comprehensive collection of structural MRI scans, including T1-weighted images, which provide detailed information about brain anatomy and morphology. In addition to MRI data, MIRIAD may also include clinical information such as cognitive assessments, genetic data, and demographic details for participants. The dataset can be obtained from http://www.ucl.ac.uk/drc/research/miriad.

Preprocesing

Preprocessing brain MRI data is essential to guaranteeing the accuracy and consistency of the analysis that follows for

categorization of AD. Below is a summary of the typical preprocessing actions:

- **Skull Stripping:** The procedure of removing non-brain tissue from MRI scans is known as "skull stripping." This step is important to eliminate artifacts and unwanted signal from the surrounding structures, enabling accurate segmentation and analysis of the hippocampus. Various algorithms and software packages, such as FSL's Brain Extraction Tool (BET) or FreeSurfer's skull stripping module, can be employed for this purpose.
- **Motion Correction:** Motion artifacts can significantly affect the quality of MRI data, particularly in longitudinal or multi-modal studies. Motion correction techniques are applied to align the images and minimize the impact of subject movement. Rigid body transformations or advanced motion correction algorithms, such as those available in tools like FSL or SPM, can be used to address motion-related issues.
- **Intensity Normalization:** MRI images may exhibit variations in intensity due to scanner-related factors or acquisition parameters. Intensity normalization techniques, such as histogram matching or Z-score normalization, are applied to standardize the image intensities across subjects. This step helps to reduce inter-subject variability and improves the comparability of the hippocampal features extracted from different individuals.
- **Bias Correction:** MRI images may suffer from intensity inhomogeneities or bias fields, which can impact the accuracy of subsequent analysis. Bias correction methods, such as N3 or non-parametric non-uniform intensity normalization (N3 or N4ITK), are commonly used to remove these spatially varying intensity distortions. This step ensures that the segmentation and measurement of hippocampal volumes are not affected by intensity biases.
- **Spatial Registration:** Spatial registration is performed to align the hippocampus MRI data to a common anatomical space or template. This step helps to normalize anatomical variations across individuals, enabling group-level analysis. Registration algorithms, like rigid, affine, or non-linear transformations, are applied to achieve accurate alignment of the hippocampal regions[10].

Feature Extraction

- **Hippocampus Volume:** The volume of the segmented hippocampus is a widely studied feature in Alzheimer's disease research. It is typically calculated by counting the number of voxels within the hippocampal region of interest. Patients with AD have been shown to have a smaller hippocampal volume than healthy controls.
- **Shape Features:** Various shape-based features can be extracted from the segmented hippocampus, providing information about its morphological characteristics. These features may include surface area, sphericity, compactness, elongation, and asymmetry measures. Shape features can detect anatomical changes in the brain areas associated with the ethology of AD.
- **Texture Features:** The brain hippocampus's texture features quantify the pixel intensities' spatial distribution. They provide information about the local variations and patterns in the MRI data. To compute texture characteristics, one can employ a variety of methods, such as Local Binary Patterns, Gray-level Co-occurrence Matrix, and Gray-level Run Length Matrix. These characteristics represent irregularities in hippocampal textural patterns associated with Alzheimer's disease.
- **Intensity Features:** Intensity-based features can be derived from the MRI intensities within the segmented brain region. These features include mean intensity, standard deviation, skewness, and kurtosis. They can capture variations in signal intensity within the hippocampus associated with tissue alterations in Alzheimer's disease.
- **Voxel-based Features:** Voxel-based features extract information from individual voxels within the hippocampus. These features may involve statistical measures, such as mean, median, or variance, computed directly from the voxel intensities. Voxel-based features can provide localized information about the hippocampus, enabling the detection of subtle changes associated with Alzheimer's disease[5–7,11,12].

Deep Learning Models

Using several neuroimaging modalities, such as MRI and PET scans, various deep learning models have been developed for the purpose of identifying and categorizing AD.

The steps involved in applying DL models for AD diagnoses is provided by the general block diagram of AD detection and classification in Figure 3, but specific implementations may differ based on the dataset, deep learning strategies, and clinical needs.

A. Convolutional Neural Network (CNN)

CNNs have showed impressive performance in a range of image classification applications, including the classification of AD. They use pooling layers for spatial down-sampling and convolutional layers to extract local and global characteristics from the MRI Imaging data, allowing them to automatically develop hierarchical representations. CNNs have demonstrated a high degree of accuracy in categorizing Alzheimer's disease cases, especially when used in conjunction with transfer learning that makes use of CNN pretrained models on

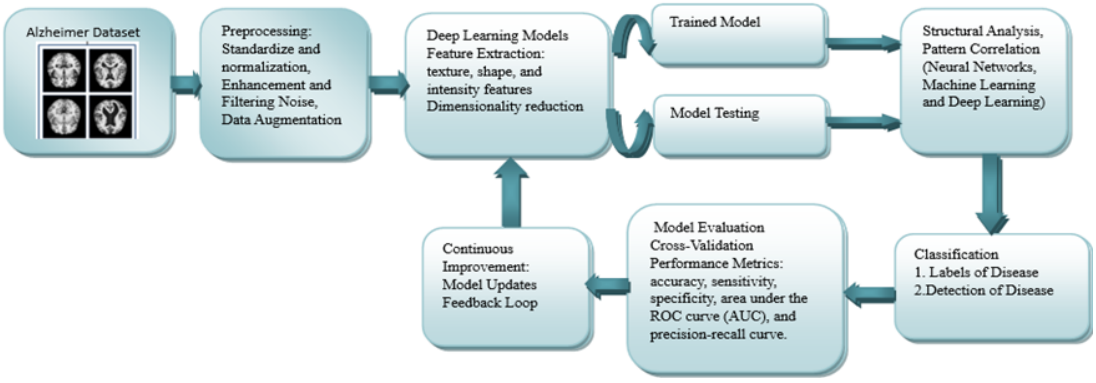

Fig 3. A general block diagram showing how deep learning models are used to detect and classify AD

extensive image datasets[13].

B. Recurrent Neural Networks (RNN)

RNNs, and in particular Long Short Term Memory (LSTM) networks, have been studied for their ability to recognize sequential patterns and temporal dependencies in MRI data pertaining to the classification of Alzheimer's disease. RNNs are able to model the gradual changes in the disease and generate predictions based on the full sequence by taking into account the temporal sequence of hippocampal MRI scans. However, due to the limited temporal information available in cross-sectional MRI data, the performance of RNNs may be less prominent compared to CNNs.

C. 3D Convolutional Neural Networks (3D CNN)

3D CNNs can directly process volumetric data, such as 3D hippocampus MRI scans, preserving the spatial information in all three dimensions. By considering the 3D context, these models can capture fine-grained structural patterns and relationships within the hippocampus. 3D CNNs have shown promise in Alzheimer's disease classification, particularly when dealing with voxel-level data. Still, in comparison to 2D CNNs, they can need more computer power and training data[14].

D. Autoencoders (AE)

Autoencoders are models for unsupervised learning that utilise a compressed latent representation of the input data to reconstruct it. They have been used in Alzheimer's disease classification to learn low-dimensional representations of hippocampus MRI data. Anomalies in the reconstructed pictures of MRI scans from Alzheimer's patients can be used for categorization by training an autoencoder on healthy controls. Autoencoders provide a data-driven approach for feature extraction and have shown potential in identifying subtle changes associated with Alzheimer's disease.

E. Generative Adversarial Network (GAN)

Deep learning models called GANs are made up of a discriminator network and a generator network. GANs have been investigated for the purpose of classifying AD by producing artificial hippocampal MRI images that closely mimic real scans. The generator can learn to produce realistic scans by training the discriminator to discern between genuine and synthetic scans. GANs can be applied to data augmentation, data rectification for imbalances, and the creation of informative representations for the classification of AD[5].

It is imperative to keep in mind that multiple factors, such as the dataset's quality and accessibility, the models' architecture and hyperparameters, and the preprocessing and augmentation methods used, can affect how well deep learning models perform.

To classify Alzheimer's illness, this study examined several DL morels, such as stacked autoencoders, 2D CNN, and 3D CNNs. Results showed that 3D CNNs achieved higher accuracy (91.5%) compared to 2D CNNs (85.2%) and stacked autoencoders (78.1%). The study highlighted the importance of volumetric information captured by 3D CNNs for accurate classification[15]. The results demonstrated that a 3D CNN with two convolutional layers achieved the highest accuracy of 88% in categorizing AD patients and normal controls. The study highlighted the effectiveness of 3D CNNs in capturing spatial relationships within the hippocampus[16].

This study compared various machine learning models, including deep learning architectures (e.g., stacked autoencoders), for AD classification using multi-atlas-based features extracted from brain MRI data. The results showed that stacked autoencoders achieved an accuracy of 90.7% and outperformed Random Forest (RF), support vector machine (SVM), and logistic regression, among other machine learning models. The study emphasized the advantages of deep

learning in capturing complex patterns in multi-atlas-based features[17].

To facilitate an early detection of AD, examined the efficacy of multi-modal deep neural networks that combine data from structural MRI scans and PET scans. The results showed that the multi-modal deep neural network achieved an accuracy of 91.8%, outperforming single-modality models (MRI or PET) and traditional machine learning methods. The study highlighted the benefits of integrating multiple imaging modalities and leveraging deep learning for improved classification accuracy[18].

Unsupervised learning uses unlabeled train dataset. The objective of training is to categories or separate the observed values. The deep model is highly helpful for extracting important features from data in a hierarchical fashion, as opposed to a well-designed feature extractor with shallow architecture that necessitates human design and specialized knowledge[19]. Restricted Boltzmann Machines and Autoencoders are two further subcategories of unsupervised learning. (Tomczak and Gonczarek, Feb 2017). Unsupervised deep neural networks are used to extract features, which are then taken from MRI, PET, and other sources and categorized using classifiers like support vector machine. In 2017, Shi et al. proposed a stacked denoising sparse auto-encoder that uses support vector machine for classification. Results were better than SVM thanks to a deep belief network (DBN) that Faturrahman et al. (2017) assembled from a stacked model of a Restricted Boltzmann Machines and structured AD detection.

Supervised learning is more widely used as compared to unsupervised learning. CNNs, RNNs, and DNNs are common networks used in supervision techniques (Böhle, Ei-tel, Weygandt & Ritter, 2019). (Nguyen et al., 2020). Among all the deep models, CNN is the most efficient. Many sophisticated CNN models, including as VGGNet, AlexNet, ResNet, DenseNet, Inception, and Puttagunta & Ravi's Inception, can carry out efficient AD detection (Yang & Mohammed, 2020; Guttery, 2020; Alotaibi & Alotaibi, 2020).

Researchers with similar interests can set up a CNN-based private architecture. Wang et al. (2018) used leaky ReLU and experience to build an 8-layer CNN with a 97.65% accuracy rate. Huang et al. (2020) employed DenseNet with dense and quick connections to accurately classify medical images using the feature map generated by the PCANet upgrade. Despite being superior to most conventional feature extraction methods, for training CNN needs a lot of image data because to its lengthier training period. A long-standing issue in the medical industry is the scarcity of image samples. Image augmentation and TL are typical remedies. Pre-trained VGG16 was employed by Jain et al. (2019) as a feature extractor to categorize AD, CN, and MCI. Wang et al. (2021) proposed the VGG Inspired Network as the backbone to expand the data collection and integrated the convolution block attention moduleThe ResNet network was utilized by Prakash et al. (2021) to detect AD with a 98.37% detection accuracy. Since neuroimaging offers a spatial link between images, 3D CNN is also widely used in the diagnosis of AD.

CNN was proposed as a diagnostic method for AD by Khvostikov et al. (2018) in a 3D based on Inception. In comparison with the standard AlexNet network, there is a notable improvement in performance.

Every paper included in Table 1 contributes to the expanding amount of research on deep learning-based methods for AD classification and detection. These models leverage various biomarkers and imaging modalities to achieve high accuracy in distinguishing between different stages of cognitive impairment and healthy individuals. It serves as a reference point for understanding the context and timeline of the studies conducted. Speech transcripts, MRI, fMRI, PET, and demographic data may all be used in this investigation. Different biomarkers provide unique insights into AD pathology and progression. MRI was the most often used biomarker in all of the examinations, followed by multi-modal biomarkers. Datasets used in the research, which serve as the basis for training and evaluating the deep learning models. ADNI, OASIS, Kaggle datasets, and other resources are several samples. The choice of dataset influences the generalizability and applicability of the findings. The ADNI dataset was predominantly utilized across most studies for AD diagnosis. Common methods include CNN (Convolutional Neural Network), RNN (Recurrent Neural Network), GAN (Generative Adversarial Network), and DNN (Deep Neural Network). CNN was used in most studies to diagnose AD, and then hybrid DL models. Every technique has advantages and uses for examining various kinds of data. the study's performance indicators for the deep learning models that were assessed. In AD detection and classification tasks, metrics counting Accuracy, Sensitivity, Specificity, Area Under the Curve, Recall and F1-score offer valuable information about the models' predictability and efficacy.

Challenges and Future Scope

- **Data Scarcity and Quality:** Neuroimaging data, essential for AD diagnosis, is often decentralized and housed within hospital systems, making access for research challenging. Furthermore, acquiring labelled data for the diagnosis of AD is expensive and necessitates specialized knowledge. The diverse nature of electronic medical records and the lack of labelled data provide major obstacles for DL algorithms attempting to distinguish signal from noise.

Table 1. A summary of deep learning-based techniques for AD detection and categorization

Ref.	Year	Biological Markers	DL Models	Datasets	Metrics
[11]	2019	MR Images	CNN Model	ADNI-150 samples, class (CN -50, AD -50, MoCI -50)	Acc (CN Vs. AD):99 % Acc (AD Vs. MCI): 99% Acc (CN Vs. MCI): 99%
[12]	2019	T1-weighted MR images	3D CNN	ADNI-811 classes (AD-192, pMCI-165, sMCI-231, NC-223	Acc (AD/NC):92% Acc (pMCI/sMCI):75% Acc (MCI/NC):74.64%
[15]	2019	MRI	CNN+TVP	ADNI-352 classes: (AD-77, NC- 129, MCI- 146) GARD-326 classes (AD- 81, NC- 171, and MCI- 74)	ADNI Accuracy (AD/NC):85.55% GARD Accuracy (AD/NC):90.05%
[16]	2019	MRI T1/T2-weighted	UG-net and GAN	CIND- 32 classes: (AD-7, NC-21, MCI- 4)	UG-net Accuracy 84.9% GAN Accuracy 91.6%
[17]	2019	Transcripts of Speeches	CNN and RNN	Dementia Bank Dataset	AUC (NC vs.AD):83.8%
[18]	2020	fMRI, PET	CNNs	ADNI-54 classes (AD-27, HCp-27) fMRI Dataset ADNI -2675 classes (AD -900, HCp-1775) PET Dataset	Acc (ADNI (fMRI)): 99 % Acc (ADNI(PET): 73 %
[20]	2020	T1w and T2w MR images	Deep Supervised UNET CNN	Kulaga-Yoskovitz dataset -25 subjects-HC Winterburn dataset-5 subjects	Kulaga-Yoskovitz -Accuracy (HC/AD) :91.16%$\pm$0.0014 Winterburn – Accuracy (HC/AD): 67.04$\pm$0.0045
[21]	2020	T2-weighted TSE image	FuseNet	NITRC dataset -25 subjects-HC	Acc Hippocampus: 0.961$\pm$0.005
[22]	2020	MRI	DBN driven LB	OASIS-1 classes:(MCI- 34, NC-29, and AD-37.	Diceμ+δ (NC/MCI/AD): 0.87 $\pm$0.05
[23]	2020	MRI	DCNN	OASIS-382 classes (ND, VMD, MD, MAD)	Acc (ND/VMD/MD/MAD):99.05%
[24]	2021	fMR Imaging	CNNs	ADNI - 675 images	Acc (LAD) : 98. % Acc (MAD) :95 % Acc (MoAD) :89% Acc (SAD) :87 %
[25]	2021	T1w images	DCNN (U-Net)	ADNI- 135 subjects (AD / MCI)	Dice (HC-AD/MCI): 92.30% Computation Time: 323.4 s
[8]	2021	MRI	DNN	GARD- 326 images, subjects (NC-171, ADD- 81, aAD- 35, mAD-39)	LH-DNN Accuracy (AD/NC): 94.82% RH-DNN Accuracy (AD/NC): 94.02%
[26]	2021	MRI	DCNN	ADNI -179 images, Classes (AD: 58, MCI: 48, CN: 73).	Acc (AD/CN): 85% Acc (MCI/CN): 76% Acc (AD/MCI)): 72%
[27]	2021	MRI	DEMNET	Kaggle- 6400 Images, classes (MID:896), (MOD:3200), (ND:2240), and (VMD:64)	Acc (4 class): 95.23%
[28]	2021	T1-weighted MRI	Dense CNN	ADNI -933 images, class (AD: 326, CN: 607)	Acc: 92.52%, Sensitivity: 88.20%, Specificity: 94.95%, AUC: 97.89.
[29]	2021	Cross- sectional MRI	Fused Deep Learning models	ADNI- 503 images, class (AD: 266, MCI: 104, CN: 132).	Acc (CN /AD): 0.86 $\pm$ 0.04 Acc (CN /MCI /AD): 0.85 $\pm$ 0.03 Acc (CN /AD/ MCI)): 0.89 $\pm$0.03
[30]	2021	T1-weighted MRI	CNNs	ADNI- 450 Images, classes (AD -150, MCI -150, NC -150)	Acc (NC Vs. AD): 90% Acc (MCI Vs. AD):87% Acc (NC Vs. MCI):83%
[31]	2022	MRI	U-net	MSD- 263 3D mono modal MRI volumes	Accuracy: 99.7%, Dice: 89.00%, Specificity: 99.00%,
[15]	2022	MRI	NCSA, and GDMM	ADNI- 1,251 images, subjects (AD: 419, CN: 832) AIBL- 530 images, subjects (AD: 79, CN: 451)	ADNI (Acc: 89.2%, Sen: 90.3% Spe: 94%, Auc: 90%) AIBL (Acc: 92.2% Sen: 82.9% Spe: 85. 5%, Auc: 88.9)

Continued on next page

Table 1 continued

[20]	2022	T1w and T2w MR images	UNET CNN	Kulaga‑Yoskovitz- 25 subjects Winterburn dataset- 5 subjects	Kulaga-Yoskovitz (Acc: 0.9001 ± 0.0130 Winterburn (Acc: 0.7202 ± 0.0288)
[32]	2022	T1-weighted MRI	Res SEblock GAN	ADNI- 130 subjects	Dice coefficient: 0.8946 Jaccard coefficient: 0.8518
[33]	2022	MRI+PET	Convolutional auto-encoder and CNN	ADNI-1 and ADNI -2: 959 images, class NC:264 sMCI: 273 pMCI: 204 AD: 218	Acc (NC /AD): 98.24% Acc (MCI /NC): 94.59% Acc (pMCI / sMCI)): 87.25%
[34]	2022	T1-weightedMRI	CNN	ADNI- 450 classes (AD-163, MCI-163, NC-163)	ACC: 96.12, SEN: 94.99, SPE: 97.73, Precision: 95.50, F1-score:95.23
[14]	2022	MRI	ADD-Net	Kaggle- 6400 samples, (NOD: 3200, VMD: 2240, MD: 896, and MOD: 64)	ACC: 97.05, AUC: 99.89, Recall: 97, Precision: 97, F1-score:97.05
[35]	2022	MRI	DCNN	ADNI- 2619 images, subjects (CN: 782 MCI: 1089) AD: 748) NACC- 2025 (CN: 1281 MCI: 322) AD: 422)	AUROC: 89.21%
[36]	2022	MRI	Conditional Triplet-VGG	OASIS- 382 (ND: 167 VMD: 87 MD: 105 MAD: 23)	Acc: 99 %
[37]	2022	3D MRI	Resnet	ADNI and AIBL	ADNI BACC: 0.766 ± 0.015 ADNI AUC: 0.843±0.016 AIBL BACC: 0.728±0.015, AIBL AUC: 0.813±0.015
[38]	2022	MRI	3D CNN	ADNI- (AD: 975, MCI: 582)	AUROC = 0.973
[39]	2023	MRI	DCNN	ADNI- (NC: 801, MCI: 617, EMCI:333, LMCI:178, SMC: 111, AD:416)	ACC: 98.68, SPE: 99.74, Recall: 98.68 Precision: 95.50, F1: score:98.68
[40]	2023	MRI	VGGNet and LFA algorithm	Kaggle- (MID: 896, MOD: 64, ND: 3200, and VMD: 2240)	ACC: 0.98, PR:0.99, PRE: 0.99, and FS: 0.99
[41]	2023	MRI	Curvelet Transform-based CNN	Kaggle- (MID: 896, MOD: 64, ND: 3200, and VMD: 2240)	Acc: 98.62% F1: score: 99.21%
[42]	2023	MRI (axial, coronal, sagittal)	CNN	ADNI- 300, subjects (100 AD, 100 MCI, and 100 NC)	ACC: 0.98, PR:0.99, PRE: 0.96, and FS: 0.97
[43]	2023	MRI	CNN	ADNI- 2294, subjects (133 AD, 311 MCI, and 195 CN)	Acc: 95.18%

- **Over-fitting:** Deep learning algorithms need a lot of data compared to their number of parameters because they are complicated. However, obtaining sufficient data for training DL models for AD diagnosis is challenging due to privacy restrictions, data decentralization, and the high cost of obtaining labeled data. Over-fitting remains a concern when training DL models on limited datasets, potentially leading to poor generalization performance.
- **Interpretability and Transparency:** DL models are not transparent by nature, It makes understanding the features the model learns difficult and the reasoning behind its predictions. The development of clinically interpretable models is hampered by this lack of transparency, which makes it difficult to determine the significance of traits in AD diagnosis.
- **Reproducibility:** DL algorithms' success is based upon hyperparameters such batch size, dropout rate, and learning rate. Reproducing experimental results across different settings and datasets can be challenging due to variations in hyperparameter values, data preprocessing techniques, and random initialization of model weights. Ensuring reproducibility is essential for validating the toughness and generalizability of DL models for AD diagnosis.
- **Integration with Clinical Workflows:** Seamless compatibility with clinical decision support tools, medical imaging systems, and electronic health records is necessary for integrating DL models into current clinical processes. However, the complexity of DL algorithms and the lack of standardized protocols for data integration pose challenges in deploying DL-based solutions in clinical settings. Collaborative data sharing initiatives among healthcare institutions and research organizations, supported by regulatory frameworks, can address data scarcity and quality challenges in AD diagnosis using DL models. Leveraging transfer learning and data augmentation techniques can mitigate over-fitting concerns, enhancing model generalization from limited datasets. Developing Explainable AI (XAI) methods tailored to AD diagnosis can improve model interpretability and transparency, fostering trust among clinicians. Standardizing protocols and benchmarking studies can enhance reproducibility and guide future research and clinical implementation. Integration of DL models into Clinical Decision Support Systems (CDSS) can optimize diagnostic decision-making, while multimodal fusion techniques and biomarker discovery enable personalized treatment strategies and disease monitoring. These efforts collectively advance DL-based AD diagnosis, enhancing patient care and outcomes.

Conclusions

In this work, we approved out a thorough examination of the most advanced techniques now employed to diagnose AD, with an additional focus on Deep Learning approaches. Based on neuroimaging data, we investigated the efficacy of several DL models, such as CNNs, DNNs, RNNs, AEs, DBNs, GANs, and hybrid deep learning models, in modelling the course of AD. We additionally looked at the vast range of biomarkers, such as speech transcripts, genetic testing, MRI, fMRI, PET, EEG, MEG, and CSF tests, that are crucial for the diagnosis of AD. We also found well-known datasets that are used in research on AD diagnosis, including the ADNI, OASIS, Dementia Bank, HABS, and MCSA datasets. We found that CNN was the most popular deep learning technique for diagnosing AD after a comprehensive examination of the literature, with hybrid DL models following closely behind. Moreover, MRI and the ADNI dataset emerged as predominant choices for biomarkers and datasets in DL-based AD diagnosis studies, respectively. Even with the significant progress made possible by DL methods in AD diagnosis, several obstacles still exist. These challenges include issues of overfitting, data quality assurance, interpretability of DL models, transparency in decision-making processes, and reproducibility of results. In order to guarantee the dependability and relevance of DL-based techniques in clinical contexts, these obstacles must be removed.

References

1) Liu S, Liu S, Cai W, Che H, Pujol S, Kikinis R, et al. Multimodal neuroimaging feature learning for multiclass diag nosis of Alzheimers disease. *IEEE Transactions on Biomedical Engineering*. 2015;62(4):1132–1140. Available from: https://doi.org/10.1109/tbme.2014.2372011.
2) Sarraf S, Tofighi G. Deep Learning-based Classification for Alzheimer's Disease Detection, IEEE. In: 2016 Future Technologies Conference (FTC). IEEE. 2017;p. 1–6. Available from: https://doi.org/10.1109/FTC.2016.7821697.
3) Zhou J, Goyal A, Yu S, Ding J, Xiong Z. Multi-Modal Deep Learning Framework for Alzheimer's Disease Diagnosis. In: Proceedings of the 2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM). IEEE. 2019;p. 2418–2425.
4) Li Y, Peng Q, Wang F, Yan J, Zeng G. Deep Learning-based Early Diagnosis of Alzheimer's Disease Using Cerebrospinal Fluid Biomarkers. In: Proceedings of the 2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM). IEEE. 2019;p. 2434–2438.
5) Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*. 2020;25(24):1–28. Available from: https://doi.org/10.3390/molecules25245789.
6) Fung G, Moung L, Lo WC, Ng AWY, Lau AYS. Deep Learning-based Natural Language Processing for Alzheimer's Disease Progression Prediction from Clinical Notes. In: IEEE International Conference on Bioinformatics and Biomedicine (BIBM). IEEE. 2020;p. 1947–1952.
7) Armonaite K, Ventura ML, Laura L. Alzheimer's disease detection from magnetic resonance imaging: a deep learning perspective. *Exploration of Neuroprotective Therapy*. 2023;3:139–150. Available from: https://doi.org/10.37349/ent.2023.00043.
8) Basher A, Kim BC, Lee KH, Jung HY. Volumetric Feature-Based Alzheimer's Disease Diagnosis From sMRI Data Using a Convolutional Neural Network and a Deep Neural Network. *IEEE Access*. 2021;9:29870–29882. Available from: https://dx.doi.org/10.1109/access.2021.3059658.
9) Ebrahimighahnavieh MA, Luo S, Chiong R. Deep learning to detect Alzheimer's disease from neuroimaging: A systematic literature review. *Computer Methods and Programs in Biomedicine*. 2020;187. Available from: https://doi.org/10.1016/j.cmpb.2019.105242.
10) Hazarika RA, Maji AK, Sur SN, Paul BS, Kandar D. A Survey on Classification Algorithms of Brain Images in Alzheimer's Disease Based on Feature Extraction Techniques. *IEEE Access*. 2021;9:58503–58536. Available from: https://dx.doi.org/10.1109/access.2021.3072559.
11) Jain R, Jain N, Aggarwal A, Hemanth DJ. Convolutional neural network based Alzheimer's disease classification from magnetic resonance brain images. *Cognitive Systems Research*. 2019;57:147–159. Available from: https://doi.org/10.1016/j.cogsys.2018.12.015.
12) Alam S, Kwon GR, Kim JI, Park C. Twin SVM-based classification of Alzheimer's disease using complex dual-treewavelet principal coefficients and LDA. *Journal of Healthcare Engineering*. 2017;2017:1–12. Available from: https://doi.org/10.1155/2017/8750506.
13) Liu J, Li M, Luo Y, Yang S, Li W, Bi Y. Alzheimer's disease detection using depthwise separable convolutional neural networks. *Computer Methods and Programs in Biomedicine*. 2021;203. Available from: https://dx.doi.org/10.1016/j.cmpb.2021.106032.
14) Pandey P, Khare A, Srivastava P. Detection of Alzheimer's disease using CNN architectures. *ADBU Journal of Engineering Technology*. 2022;11(1):1–6. Available from: https://journals.dbuniversity.ac.in/ojs/index.php/AJET/article/view/3672.
15) Acharya UR, Fernandes SL, Weikoh JE, Ciaccio EJ, Fabe MKM, Tanik UJ, et al. Automated detection of Alzheimer's disease using brain MRI images a study with various feature extraction techniques, PubMed. *Journal of Medical Systems*. 2019;43(9). Available from: https://doi.org/10.1007/s10916-019-1428-9.
16) Tufail AB, Abidi A, Siddiqui AM, Younis MS. Automatic classification of initial categories of Alzheimer's disease from structural MRI phase images: A comparison of PSVM, KNN and ANN methods. *Int J Biomed Biol Eng*. 2012;6(12):713–717. Available from: https://publications.waset.org/15213/automatic-classification-of-initial-categories-of-alzheimers-disease-from-structural-mri-phase-images-a-comparison-of-psvm-knn-and-ann-methods.
17) Kruthika KR, Maheshappa HD, Rajeswari. CBIR system using Capsule Networks and 3D CNN for Alzheimer's disease diagnosis. *Informatics in Medicine Unlocked*. 2019;14:59–68. Available from: https://doi.org/10.1016/j.imu.2018.12.001.
18) Jo T, Nho K, Risacher SL, Saykin AJ. Deep learning detection of informative features in tau PET for Alzheimer's disease classification. *BMC Bioinformatics*. 2020;21:1–13. Available from: https://doi.org/10.1186/s12859-020-03848-0.
19) Silva IRR, Silva GSL, De Souza RG, Santos WPD, Fagundes RADA. Model Based on Deep Feature Extraction for Diagnosis of Alzheimer's Disease. In: 2019 International Joint Conference on Neural Networks (IJCNN). IEEE. 2019;p. 1–7. Available from: https://doi.org/10.1109/IJCNN.2019.8852138.
20) Manjón JV, Romero JE, Coupe P. A novel deep learning based hippocampus subfield segmentation method. *scientific reports* . 2022;12:1–9. Available from: https://doi.org/10.1038/s41598-022-05287-8.
21) He G, Lu T, Zhu H. 2020.
22) Liu Y, Yan Z. A Combined Deep-Learning and Lattice Boltzmann Model for Segmentation of the Hippocampus in MRI. *Sensors*. 2020;20(13):1–16. Available from: https://doi.org/10.3390/s20133628.
23) Mehmood A, Maqsood M, Bashir M, Shuyuan Y. A deep siamese convolution neural network for multi-class classification of alzheimer disease. *Brain Sciences*. 2020;10(2):1–15. Available from: https://doi.org/10.3390/brainsci10020084.
24) Amini M, Pedram M, Moradi A, Ouchani M. Diagnosis of Alzheimer's Disease Severity with fMRI Images Using Robust Multitask Feature Extraction Method and Convolutional Neural Network (CNN). *Computational and Mathematical Methods in Medicine*. 2021;2021:1–15. Available from: https://doi.org/10.1155/2021/5514839.
25) Carmo D, Silva B, B CY, Rittner L, Lotufo R. Hippocampus segmentation on epilepsy and Alzheimer's disease studies with multiple convolutional neural networks. *Heliyon*. 2021;7(2):1–9. Available from: https://doi.org/10.1016/j.heliyon.2021.e06226.
26) Prajapati R, Khatri U, Kwon GR. An Efficient Deep Neural Network Binary Classifier for Alzheimer's Disease Classification. In: 2021 International Conference on Artificial Intelligence in Information and Communication (ICAIIC). IEEE. 2021;p. 231–234. Available from: https://doi.org/10.1109/ICAIIC51459.2021.9415212.
27) Murugan S, Venkatesan C, Sumithra MG, Gao XZ, Elakkiya B, Akila M, et al. DEMNET: A Deep Learning Model for Early Diagnosis of Alzheimer Diseases and Dementia From MR Images. *IEEE Access*. 2021;9:90319–90329. Available from: https://dx.doi.org/10.1109/access.2021.3090474.
28) Zhang J, Zheng B, Gao A, Feng X, Liang D, Long X. A 3D densely connected convolution neural network with connection-wise attention mechanism for Alzheimer's disease classification. *Magnetic Resonance Imaging*. 2021;78:119–126. Available from: https://dx.doi.org/10.1016/j.mri.2021.02.001.
29) Venugopalan J, Tong L, Hassanzadeh HR, Wang MD. Multimodal deep learning models for early detection of Alzheimer's disease stage. *Scientific Reports*. 2021;11(1). Available from: https://dx.doi.org/10.1038/s41598-020-74399-w.
30) Turkson RE, Qu H, Mawuli CB, Eghan MJ. Classification of Alzheimer's Disease Using Deep Convolutional Spiking Neural Network. *Neural Processing Letters*. 2021;53(4):2649–2663. Available from: https://dx.doi.org/10.1007/s11063-021-10514-w.
31) Sohail N, Anwar SM. A Modified U-Net Based Framework for Automated Segmentation of Hippocampus Region in Brain MRI. *IEEE Access* . 2022;10:31201 –31209. Available from: https://doi.org/10.1109/ACCESS.2022.3159618.

32) Deng H, Zhang Y, Li R, Hu C, Feng Z, Li H. Combining residual attention mechanisms and generative adversarial networks for hippocampus segmentation. *Tsinghua Science and Technology*. 2022;27(1):68–78. Available from: https://dx.doi.org/10.26599/tst.2020.9010056.

33) Böhle M, Eitel F, Weygandt M, Ritter K. Layer-Wise Relevance Propagation for Explaining Deep Neural Network Decisions in MRI-Based Alzheimer's Disease Classification. *Frontiers in Aging Neuroscience*. 2019;11. Available from: https://dx.doi.org/10.3389/fnagi.2019.00194.

34) Faisal FUR, Kwon GR. Automated Detection of Alzheimer's Disease and Mild Cognitive Impairment Using Whole Brain MRI. *IEEE Access*. 2022;10:65055–65066. Available from: https://dx.doi.org/10.1109/access.2022.3180073.

35) Oktavian MW, Yudistira N, Ridok A. Classification of Alzheimer's Disease Using the Convolutional Neural Network (CNN) with Transfer Learning and Weighted Loss. *IAENG International Journal of Computer Science*. 2023;50(3):1–7. Available from: https://www.iaeng.org/IJCS/issues_v50/issue_3/IJCS_50_3_16.pdf.

36) Orouskhani M, Zhu S, Rostamian S, Zadeh FS, Shafiei M, Orouskhani Y. Alzheimer's disease detection from structural MRI using conditional deep triplet network. *Neuroscience Informatics*. 2022;2(4):1–7. Available from: https://doi.org/10.1016/j.neuri.2022.100066.

37) Kim J, Jeong M, Stiles WR, Choi HS. Neuroimaging Modalities in Alzheimer's Disease: Diagnosis and Clinical Features. *International Journal of Molecular Sciences*. 2022;23(11):1–22. Available from: https://doi.org/10.3390/ijms23116079.

38) Feng X, Provenzano FA, Provenzano, Small SA. A deep learning MRI approach outperforms other biomarkers of prodromal Alzheimer's disease, PubMed, NCBI. *Alzheimer's Research & Therapy*. 2022;14(1):1–11. Available from: https://doi.org/10.1186/s13195-022-00985-x.

39) Shamrat FMJM, Akter S, Azam S, Karim A, Ghosh P, Tasnim Z. AlzheimerNet: An Effective Deep Learning Based Proposition for Alzheimer's Disease Stages Classification From Functional Brain Changes in Magnetic Resonance Images. *IEEE Access*. 2023;11:16376–16395. Available from: https://doi.org/10.1109/ACCESS.2023.3244952.

40) Kim CM, Lee W. Classification of Alzheimer's Disease Using Ensemble Convolutional Neural Network With LFA Algorithm. *IEEE Access*. 2023;11:143004–143015. Available from: https://doi.org/10.1109/ACCESS.2023.3342917.

41) Chabib CM, Hadjileontiadis LJ, Shehhi AA. DeepCurvMRI: Deep Convolutional Curvelet Transform-Based MRI Approach for Early Detection of Alzheimer's Disease. *IEEE Access*. 2023;11:44650–44659. Available from: https://doi.org/10.1109/ACCESS.2023.3272482.

42) Pusparani Y, Lin CY, Jan YK, Lin FY, Liau BY, Ardhianto P. Diagnosis of Alzheimer's Disease Using Convolutional Neural Network With Select Slices by Landmark on Hippocampus in MRI Images. *IEEE Access*. 2023;11:61688–61697. Available from: https://doi.org/10.1109/ACCESS.2023.3285115.

43) Mercaldo F, Giammarco MD, Cesarelli M, Ravelli F, Martinelli F, Santone A. TriAD: A Deep Ensemble Network for Alzheimer Classification and Localization. *IEEE Access*. 2023;11:91969–91980. Available from: https://doi.org/10.1109/ACCESS.2023.3307702.