



A Systematic Review of Techniques for Early-Stage Alzheimer's Disease Diagnosis Using Machine Learning and Deep Learning

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Abstract: Alzheimer's disease (AD) is a brain-related disease in which the patient's condition worsens over time. Early diagnosis of AD is uniquely challenging due to its primarily neurological and cognitive anomalies, such as beta-amyloid plaque accumulation, tau tangles, and hippocampal atrophy, which are subtle and slowly progressive. Unlike diseases with clear physical or biochemical markers, AD anomalies often overlap with normal aging and require analyzing complex data such as brain imaging and cognitive tests. This study reviews various machine learning and deep learning techniques for early AD detection. The findings reveal that deep learning techniques, especially convolutional neural networks (CNNs), and hybrid architectures such as VGG16 and CNN–long short-term memory models achieve near-perfect performance (accuracy of 99.95% and 99.92%, respectively), while traditional models such as support vector machines excel in smaller datasets (accuracy between 90% and 96%) due to their simplicity and interpretability. The combination of multimodal data (magnetic resonance imaging, positron emission tomography, and cerebrospinal fluid biomarkers) significantly improved diagnostic performance, indicating the potential of innovative artificial intelligence (AI) methods in early AD identification. However, deep learning faces key limitations, including high computational demands, lack of interpretability, and reliance on large, annotated datasets, which can hinder clinical applicability. By pursuing learning techniques, such as transfer learning, to reduce data needs and explainable AI to achieve interpretability, researchers and developers can overcome the bottlenecks and enhance the accuracy and efficiency of real-world AD diagnosis.

Keywords: AD, mild cognitive impairment, MCI, MRI, neurodegenerative disorders, neuroimaging, PET

1. Introduction

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder that causes short-term memory loss, paranoia, and delusional thoughts. It is the most common cause of dementia, particularly in older adults. This disease disrupts the function of a person's brain cells, leading to behavioral changes and difficulty speaking or performing daily tasks. According to the World Health Organization, an estimated 55 million people worldwide suffer from dementia. This number is expected to reach 78 million by 2030 and increase to 139 million by 2050 [1]. In the United States, approximately seven million people suffer from AD, which places a huge psychological and economic burden on patients, their families, and society. Following heart disease, cancer, and brain hemorrhage, it is the fifth leading cause of death among Americans aged 65 and older [2]. While the exact cause of AD is still unclear, factors such as aging, genetics, education, and lifestyle play a role. Additionally, there are various associated neuropathologies that cause clinical dementia [3]. Most of these cases are observed among individuals aged 65 and older. Although only 5% of AD patients are between the ages of 65 and 74, the risk of developing the disease increases by 50% after the age of 85. People with higher education have been found to be less vulnerable. The brain forms more synaptic connections as a result of higher education. In this way, the brain builds up a synaptic reserve that helps patients replace the neurons lost as the disease progresses [4].

There is currently no medication that can cure AD, but early

diagnosis can slow the progression of the disease and improve patient outcomes. The diagnosis and management of AD are challenging due to the complex nature of the disease and the lack of effective treatment options. Early detection and accurate diagnosis of AD are crucial for efficient management and treatment to maintain patient's mental health and delay its effects, allowing patients to live a better life [4]. Machine learning (ML) and deep learning (DL) have emerged as powerful tools for predicting and classifying AD, offering the potential for more accurate and efficient diagnosis. Advancements in ML have shown tremendous potential in healthcare, highlighting the effectiveness of interpretable ML models for early-stage disease prediction using explainable AI (XAI) technique SHAP (SHapley Additive exPlanations) to interpret the model prediction decision and help to understand the factors that have the most influence [5].

In this review article, we provide a comprehensive overview of the current state-of-the-art in ML- and DL-based AD prediction and classification. It aims to summarize current methodologies, assess their performance, highlight common challenges, and evaluate their practicality. By combining insights from recent studies, this study provides guidance for researchers and practitioners in developing interpretable and practical diagnostic tools for early AD detection. The rest of this review article is organized as follows: Section 2 defines the stages of AD. Section 3 provides a review of the available literature, the research challenges and gaps, and describes a comparative study of the experimental results acquired with various performance indicators from those studies as its focus. Section 4 presents the most important neuroimaging modalities utilized for AD diagnosis. Section 5 discusses the dataset used in those research studies. In Section 6 we outline the process of AD diagnosis. Section 7 is dedicated to describing

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and analyzing different ML and DL models developed for the early prediction and classification of AD. Finally, Section 8 discusses the study's pertinent findings, results, challenges, and potential future directions.

2. Stages of Alzheimer's Disease

AD typically progresses slowly over several years, eventually affecting most areas of the brain. The condition highlights its profound psychological impact, emphasizing the urgent need to prioritize mental health as an essential component of care and recovery strategies [6]. Patients initially experience mild cognitive impairment (MCI), which may lead to AD, although not all MCI patients eventually develop AD. Five stages associated with AD are shown in Figure 1 [7]:

Stage 1: Preclinical Alzheimer's disease

Stage 2: Mild cognitive impairment (MCI)

Two distinct types of MCI: progressive MCI (pMCI), which indicates that a person will develop AD, and stable MCI (sMCI), which indicates that a subject will not develop AD

Stage 3: Mild dementia (MD)

Stage 4: Moderate dementia (MoD)

Stage 5: Severe dementia due to Alzheimer's disease

3. Literature Review

In this section, we present a comprehensive summary of noteworthy research articles from 2017 to 2024 that focus on advancements in the early diagnosis of AD through the application of ML and DL techniques using various neuroimaging modalities. Table 1 highlights the research articles included in the study and the datasets used. It also provides the modality and total number of participants used in their study. Table 2 explains the different methods used by the researchers and their results from the dataset.

Zhao et al. [8] proposed a novel method using longitudinal fluorodeoxyglucose positron emission tomography (FDG-PET) scans to predict the progression of MCI to AD. They constructed metabolic networks for each patient using sophisticated techniques such as support vector machine (SVM) with leave-one-out cross-validation, enhanced by feature selection using Lasso regression. Notably, their findings highlighted the predictive superiority of integrating multi-time-point data over single-time-point analysis. While their results are promising, the small sample size and potential generalizability issues suggest that more research is needed to confirm these findings. To address this, k-fold cross-validation can be used to prevent overfitting.

Figure 1
Five stages of Alzheimer's disease

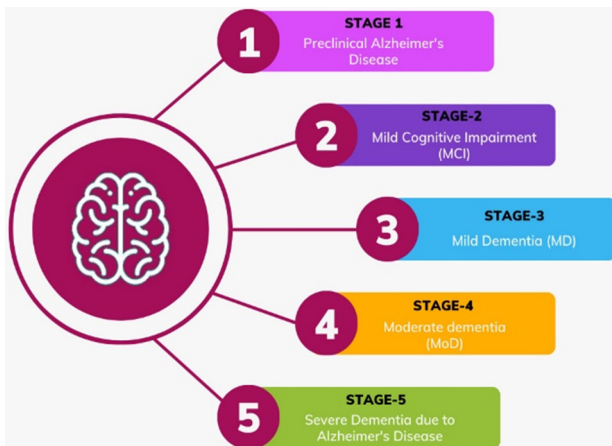


Table 1
Description of dataset and their modalities used in literature included in this study

References	Dataset	Sample Size	Modality
[8]	ADNI	79 participants	PET
[9]	ADNI	115 participants	MRI, CSF
[10]	ADNI	819 participants	MRI
[11]	ADNI	790 participants	MRI
[12]	ADNI	1242 participants	MRI, FDG-PET
[13]	ADNI-1, ADNI-2, and MIRIAD	1526 participants	MRI
[14]	ADNI	80 participants	sMRI; rs-fMRI
[15]	ADNI	818 participants	MRI
[16]	ADNI	1618 participants	MRI, PET, CSF
[17]	ADNI	1409 participants	MRI
[18]	ADNI	267 participants	MRI 1.5T
[19]	OASIS	373 participants	MRI 1.5T
[20]	ADNI	1144 participants	MRI
[21]	ADNI+OASIS	4769 participants	MRI 1.5T
[22]	ADNI+PND	2272 participants	MRI
[23]	ADNI	134 participants	MRI
[24]	ADNI	560 participants	MRI 1.5T
[25]	OASIS	235 participants	MRI 1.5T
[26]	NINCDSA-DRDA	-	PET, EEG
[27]	ADNI	1371 participants	MRI
[28]	ADNI	3692 scans	MRI
[29]	Hospital Clínic de Barcelona (HCB)	339 participants	MRI
[30]	OASIS	150 participants	MRI
[31]	Kaggle	6400 scans	MRI
[32]	ADNI	1060 participants	
[33]	ADNI	294 scans	MRI
[34]	Kaggle	6400 scans	MRI
[35]	ADNI, OASIS	6400 scans	MRI
[36]	ADNI	6400 scans	MRI
[37]	Kaggle	6400 scans	MRI

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; rs-fMRI, resting-state functional MRI; sMRI, structural MRI.

Frölich et al. [9] emphasized the use of a comprehensive mix of biomarkers of MCI to predict AD. The classifiers were improved using SVM and bootstrapping techniques, and the performance of classifiers with an imbalanced class distribution was evaluated and compared using the receiver operating characteristic (ROC) curve. However, a discussion about the difficulties and possible consequences of a small

Table 2
AUC, precision, and recall metrics when evaluating on X-Wines_
Slim dataset

References	Dataset	Method	Results
[8]	ADNI	SVM	Accuracy 83% Sensitivity 87% Specificity 78%
[9]	ADNI	SVM with linear kernel	Accuracy 82% Sensitivity 85% Specificity 70%
[10]	ADNI	SVM	Accuracy 76% Sensitivity 70% Specificity 81%
[11]	ADNI	Binary LR	Accuracy 93% Sensitivity 86% Specificity 83%
[12]	ADNI	Multimodal and multiscale deep neural network (MMDNN)	Accuracy 75% Sensitivity 73% Specificity 76%
[13]	ADNI-1, ADNI-2, and MIRIAD	DMIL	Accuracy 76% Sensitivity 42% Specificity 82%
[14]	ADNI	SVM	Accuracy 96% Sensitivity 94% Specificity 100%
[15]	ADNI	CNNs	Accuracy 79% Sensitivity 84% Specificity 74%
[16]	ADNI	Multimodal DL + RNN	Accuracy 81% Sensitivity 84% Specificity 80%
[17]	ADNI	CNN+RNN	Accuracy 74% Sensitivity 75% Specificity 75%
[18]	ADNI	RF	Accuracy 85.77 Sensitivity 54.7% Specificity 97.44%
[19]	OASIS	KNN + Linear regression	KNN: CNN Sensitivity 98.30% AUC 99.60% LR: Accuracy 98.30% Sensitivity 97.40% AUC 99.70%

Table 2
Continued

References	Dataset	Method	Results
[20]	ADNI	CNN	Accuracy 76% Sensitivity 79% Specificity 76%
[21]	ADNI+OASIS	RF + LR	RF: Accuracy 98.89% Sensitivity 99.19% LR: Accuracy 84.33% Sensitivity 84.14%
[22]	ADNI+PND	SVM+CNN	Accuracy 67% Sensitivity 68% Specificity 66%
[23]	ADNI	SVM	Accuracy 80% Precision 84% Sensitivity 85% Specificity 82%
[24]	ADNI	SVM	Accuracy 90.00% Sensitivity 93.90% Specificity 85.10%
[25]	OASIS	SVM	Accuracy 85.80% Precision 87.83%
[26]	NINCDSA-DRDA	SVM	Accuracy 89% Sensitivity 90% Specificity 88%
[27]	ADNI	LSTM	Accuracy 93.87% Sensitivity 94.07% Precision 94.07%
[28]	ADNI	CNN	Accuracy 97.57% Sensitivity 97.60%
[29]	Hospital Clínic de Barcelona (HCB)	SVM	Accuracy 90%
[30]	OASIS	GaussianNB, decision tree, RF, XGBoost, Voting Classifier, and Gradient-Boost	Voting Classifier Accuracy 96% Precision 100% Recall 43% F-1 Score 60%
[31]	Kaggle	CNN	Accuracy 99.30% Precision 100.00%

Table 2
Continued

References	Dataset	Method	Results
[32]	ADNI	k-means, KNN	Adjusted F Score: KNN 72.70% GMM 71.79% ELM 72.76% SVM 73.59% RF 47.71% AUC: KNN 85.51% GMM 84.53% ELM 84.73% IF 81.51% SVM 86.51% RF 78.23%
[33]	ADNI	LR	AUC 88%
[34]	Kaggle	CNN and fine-tuned VGG16 model	CNN: Accuracy 99.95% Fine-tuned VGG16: Accuracy 97.44%
[35]	ADNI, OASIS	BiLSTM and ANN	ADNI: Accuracy 99.22% Specificity 99.51% Precision 98.26% OASIS: Accuracy 98.96% Sensitivity 98.32% Specificity 99.21%
[36]	ADNI	CNN-LSTM	Accuracy 99.92% Specificity 100.00
[37]	Kaggle	Pipelined LeNet (PLN)	Accuracy 99.5% Sensitivity 99.9% Specificity 99.8%

dataset size was necessary. Additionally, it was determined that k-fold cross-validation was required for smaller datasets to avoid overfitting. There is no doubt that using measurements other than the ROC curve can simplify their work significantly.

Gavidia-Bovadilla et al. [10] presented a framework using longitudinal magnetic resonance imaging (MRI) data, neuropsychological tests, and cerebrospinal fluid (CSF) profiles. They used a linear mixed effects model to analyze changes in MRI biomarkers over five years and trained SVM classifiers on using the residuals to predict subject classifications and early progression of MCI to AD.

Based on the annual rate of change, biomarkers were categorized as variant or quasi-variant. It would be helpful if they included a more diverse dataset showing CSF observations at later stages and features that aid in prediction. Reliance on a specific dataset—the Alzheimer's

Disease Neuroimaging Initiative (ADNI)—the lack of longitudinal data, and limited generalizability posed challenges for this study.

Luk et al. [11] employed a novel three-dimensional (3D) voxel-based texture analysis on T1-weighted MRI scans to predict the progression of MCI to AD. This work suggested a multifactorial predictive model that combined texture features with clinical factors such as APOE-ε4 genotype, cognitive test scores, and hippocampal volume. Although this method demonstrated superior predictive capability over hippocampal volume alone, its limitations include its reliance on a single dataset (ADNI) and a lack of validation in independent datasets. It would be beneficial to consider validating the predictive model in diverse and independent populations, integrating additional clinical markers, and longitudinal data to make the models more applicable to real-world settings.

Liu et al. [13] proposed a comprehensive approach for diagnosing brain disease using MRI, namely, the Landmark-based Deep Multi-Instance Learning framework. It is a combination of landmark-based feature extraction and deep multi-instance learning (DMIL). The method uses anatomical landmarks to extract image patches, enabling the model to capture both local and global structural information. The framework demonstrated strong performance, particularly in distinguishing AD patients from healthy controls, but it does face challenges. It can efficiently process large datasets and provide a level of interpretability in its decision-making process, a key feature for medical applications. However, the study would benefit from further justification of the selected landmarks and exploration of alternative or automated selection methods. Additionally, although the framework performs well, the risk of overfitting remains a concern, particularly with limited data. To ensure robustness and applicability to new, unseen datasets, it is essential to implement strong validation techniques.

Hojjati et al. [14] investigated the integration of structural MRI (sMRI) and resting-state functional MRI (rs-fMRI) to enhance the prediction of MCI progression to AD. Although they used advanced feature selection techniques to identify key markers from both modalities and applied SVM for classification, the small sample size of the study limits generalizability and its reliance on predefined brain atlases may overlook other important biomarkers. Better prediction outcomes require more diverse datasets and detailed classification models.

Lin et al. [15] developed a hybrid convolutional neural network (CNN)-based framework for predicting the progression of MCI to AD using MRI data. Their approach focused on extracting small, informative regions from the hippocampus and enhancing these images with structural adjustments to account for age-related changes. By combining these refined MRI features with additional structural data through an extreme learning machine, they achieved significant improvements in prediction accuracy and reliability. Despite its successes, the reliance of the study on specific brain regions can overlook broader neural changes. The model needs thorough clinical validation in real-world settings before it can be applied to clinical studies.

Lee et al. [16] employed multimodal DL approach using a recurrent neural network (RNN), specifically a gated recurrent unit, to predict AD progression from MCI. They combined neuroimaging, CSF analysis, and cognitive performance data, boosting prediction accuracy from 75% with single data types to 81% when using multiple modalities. To identify key biomarkers and support patient monitoring and treatment planning, they improved their models with attention mechanisms on MRI, PET, and CSF data. They did, however, recognize the difficulties in ensuring consistent model performance by standardizing data from various sources.

Basaia et al. [17] utilized a DL model to analyze 3D MRI scans for detecting MCI and the stages of AD. The model works effectively across different MRI protocols without requiring complex preprocessing. However, it struggled to differentiate between MCI

subtypes. The authors suggested combining MRI data with biomarkers such as PET scans or genetic information for a more comprehensive diagnosis and the need for clinical validation in real-world settings.

Alickovic et al. [18] developed a straightforward approach for detecting AD using ML. They extracted features from MRI scans using histograms and classified them with random forest (RF) algorithm. This method relies on preprocessed data from the ADNI database and achieved an accuracy of 85.77%, with k-nearest neighbors (KNN) value showing a higher sensitivity of 65.28%. While the model is simple and computationally efficient, its sensitivity falls short compared to more complex methods, highlighting the trade-off between ease of use and diagnostic precision.

Battineni et al. [19] proposed an approach to classify dementia patients using principal component analysis (PCA) for feature extraction and three classifiers: SVM, Logistic Regression (LR), and KNN. The use of PCA improved model performance by simplifying the data. Attention to feature interpretability is required to use this approach in broader applications and real-world clinical relevance.

Gao et al. [20] introduced AD-NET, a novel DL model designed to predict the progression of MCI to AD using MRI scans. The model uses age-adjusted dynamic features to capture the difference between a person's biological age and chronological age, which helps refine predictions. AD-NET outperformed other models in terms of area under the curve (AUC, 0.81) and showed the best results on younger patients. However, the interpretation of the decision-making process of DL models remains hindered by their black-box nature. Reliable outcomes depend on consistent preparation and data collection.

Alroobaea et al. [21] developed a method for early AD detection using two different datasets. They applied LR, SVM, and RF, and the preprocessing steps included feature selection, handling missing data, and encoding categorical variables. LR performed best on the ADNI dataset with an impressive accuracy of 99.43%, but the result on the Open Access Series of Imaging Studies (OASIS) dataset was slightly lower at 84.33%. The system performed well on structured datasets but faced challenges in generalizing across different datasets and relied heavily on preselected features, suggesting that more adaptive or robust model training approaches may be needed.

The objective of Bron et al. [22] was clearly specified and they utilized both SVM classifiers and CNN approaches in their study. The research emphasized the comparison between the multi-center Parelnoer Neurodegenerative Diseases (PND) dataset and the ADNI dataset. While the study included external validation results, it lacked detailed metrics and in-depth analysis to fully quantify and explain the observed decline in performance.

In both unimodal and multimodal classification, Arco et al. [23] used searchlight analysis to integrate two data modalities, MRI and neuropsychological testing, and outperformed PCA. The searchlight approach provided valuable insights into specific brain regions associated with AD progression, while the use of nested cross-validation ensured robust and optimized results. However, due to a small sample size, the generalizability of the findings to larger populations is low. Additionally, the exclusive focus on converters overlooks the potential insights from non-converters that could provide a deeper understanding of the various stages of MCI and AD.

Li and Yang [24] compared the effectiveness of SVM, 3D VGGNet, and 3D ResNet for AD classification using MRI data. They used voxel-wise features for SVM and transfer learning to optimize the DL models, achieving 90% accuracy with SVM and 95% with both DL models. Grad-CAM (Gradient-weighted Class Activation Mapping) visualizations identified the cerebral cortex and cerebellum as key regions associated with the disease. However, the small sample size of the study, high computational demands for ResNet, and lack of external validation limited its generalizability.

Savita et al. [25] developed an ML method to detect AD using MRI data from the OASIS dataset, focusing on the hippocampal region. Their approach extracted key features such as entropy and contrast using the gray level co-occurrence matrix (GLCM) and combined artificial neural network (ANN) and SVM to classify the disease stages from normal to severe. Although the method achieved an 85.8% accuracy, its reliance on a single dataset and lack of volumetric analysis limited its broader applicability and potential for higher accuracy.

Rossini et al. [26] used SVMs combined with PCA, to analyze electroencephalography (EEG) data to detect AD in its early stages. The approach demonstrates the potential of EEG as a noninvasive and cost-effective tool, but it requires detailed information about the baseline and follow-up data from the limited dataset.

To improve accuracy and efficiency, El-Sappagh et al. [27] proposed a two-stage model that combines transfer learning and contrastive learning to perform targeted feature extraction on hippocampal image patches. Using 3D Grad-CAM, the study provided insights into brain regions that influence predictions and estimated MCI-to-AD conversion time. However, further research is needed to refine the personalized models, improve prediction accuracy, and validate findings using larger datasets of MCI conversion time.

Shukla et al. [28] proposed an approach to improve AD detection using ML and DL models, focusing on improved data quality through preprocessing. They simplified the four-dimensional MRI scans into two-dimensional (2D) images by applying techniques such as grayscale conversion, histogram equalization, and selective clipping to improve clarity and reduce complexity. The reliance of the approach on intensive preprocessing and high-performance computing resources may limit scalability and real-time applicability in clinical settings.

Pérez-Millan et al. [29] developed a ML method that combined PCA and Multiple Factor Analysis to simplify MRI data and then used SVM to classify AD, frontotemporal dementia, and healthy controls. Using both cross-sectional and longitudinal MRI data, they demonstrated improved accuracy in longitudinal data, achieving up to 90.0% for AD versus controls. However, the study faced challenges, including a small sample size for longitudinal data, reliance on a single center for data collection, and the use of only structural MRI, which limited the inclusion of richer imaging techniques.

Uddin et al. [30] developed an ML model that combined multiple algorithms, including Random Forest, XGBoost, and a Voting Classifier, to predict AD using the OASIS longitudinal dataset. They focused on improving accuracy through data preprocessing, handling missing values, and selecting the most relevant features, ultimately achieving 96% accuracy with the Voting Classifier. The use of multimodal imaging data can further improve the results. The reliance of the study on a single dataset and imputed missing values, as well as the lack of multimodal imaging data, may limit its usefulness in diverse clinical applications.

Altwijri et al. [31] proposed a DL model using EfficientNetB0 to classify AD into four stages—normal, very mild, mild, and moderate—based on MRI images. Their approach included preprocessing techniques such as skull removal, histogram equalization, and image resizing to improve the quality of the input data. The model performed impressively, outperforming other models such as VGG16 and ResNet50. However, its reliance on a single dataset and the difficulty in distinguishing early stages of AD due to limited data highlight challenges of wider application of this method.

Liu et al. [32] predicted MCI conversion using a novel approach to novelty detection (ND) methods. The outcomes are improved through comprehensive analysis that includes hyperparameter tuning and ANN CV-based methods. Additionally, it provides a benchmark for this work by contrasting supervised binary classification algorithms (SVM and RF) with ND techniques. Due to the limited data source, a generalized

dataset was necessary for this investigation. The decision to consider only the overall results of each assessment may ignore potentially important nuances. A sensitivity analysis or feature importance assessment can show the relative value of several modalities because all of them contribute equally to the prediction, but this may not be the case.

Park et al. [33] proposed a new approach called prospective classification to predict whether patients with MCI will progress to AD. By analyzing changes in brain features over time using MRI scans, the method projects current brain data into future states and uses these projections for classification. The approach outperformed traditional methods, achieving a high AUC of 0.881, and identified key brain regions, particularly the frontal and temporal lobes, as being crucial for predicting AD progression. However, the method relies on longitudinal MRI data, which is challenging to obtain in clinical settings, limiting its broader applicability.

Arafa et al. [34] used a custom CNN and fine-tuned VGG16 model and achieved high performance for both models. Apart from the extensive preprocessing and computational requirements of deep models, their approach shows valuable promise for utilizing MRI images for early AD diagnosis.

Matlani [35] proposed a hybrid DL model combining BiLSTM and ANN for early AD diagnosis. This method involves preprocessing images to reduce noise, extracting key features with PCA-NGIST, and optimizing the selection of features using the Improved Wild Horse Optimization algorithm before classification using a BiLSTM-ANN. It requires detailed feature engineering, which poses challenges for its practical application.

In a significant advance in medical imaging, Sorour et al. [36] investigated various DL methods to classify AD using MRI scans. They focused on five distinct approaches, among which CNN-LSTM model stood out, achieving a remarkable accuracy of 99.92% and leveraging the spatial feature extraction of CNNs and the sequence-handling capabilities of LSTMs. The risk of overfitting is a concern with this approach.

Prasath and Sumathi [37] adopted the Pipelined LeNet (PLN) architecture. The approach involved resizing and enhancing low-resolution MRI images through image fusion and extracting ternary features, which were then classified using the PLN model. The system achieved exceptional performance and outperformed conventional methods, however the lack of testing and cross-validation on real-world clinical datasets can affect its applicability in broader settings.

Recent developments in multimodal ML have shown the benefits of combining diverse data types for more reliable and interpretable predictions. Su et al. [38] introduced a framework combining CNN-based image features, text representations from transformers, and tabular data processed through multilayer perceptrons to improve vehicle rating predictions. They used Grad-CAM for visual attention mapping and feature importance scoring for tabular data to further enhance model transparency.

Su et al. [39] reviewed ML approaches for diagnostics and prognostics in industrial systems using open-source Prognostics Health Management Data Challenge datasets. Their study emphasized the use of interpretable models such as decision trees, RFs, and SHAP technique to explain complex model outputs.

All of these studies provide practical insights for developing interpretable and generalizable AI systems that are highly relevant to AD diagnosis, where diverse data modalities and clinical trust are critical for real-world use.

4. Neuroimaging Modalities

Neuroimaging plays a crucial role in the early diagnosis and monitoring of AD. Different modalities can provide detailed description

of brain regions, showing how well different parts of the brain are working, and can reveal changes in how brain networks communicate. Degenerative histological alterations, such as hypometabolism, amyloid plaques, and atrophy, can be seen using biomedical imaging techniques such as MRI and PET. Imaging can provide quantitative biomarkers that point to AD and dementia prognosis [40]. These modalities, combined with advances in AI, make it possible to detect AD earlier and predict how it might progress. Figure 2 shows the diagnosis of AD using different neuroimaging modalities.

In this section, we discuss the most important modalities used to diagnose the early development of AD.

4.1. Magnetic resonance imaging (MRI)

MRI is one of the most widely used noninvasive neuroimaging techniques for studying AD. It provides high-resolution, detailed images of the brain structure and is valuable for detecting physical changes associated with AD, such as spot signs of shrinkage in the hippocampus and entorhinal cortex [42], regions that are often affected early in the disease. This neuroimaging methodology makes it possible to distinguish between the different stages of AD and helps make the right decisions for early AD diagnosis. Figure 3 shows sample MRI scans of healthy and AD patients used to diagnose AD.

4.2. Functional MRI (fMRI)

fMRI is a noninvasive imaging tool for studying functional connectivity between different brain regions. It measures brain activity

Figure 2
Neuroimaging modalities for diagnosing AD patients

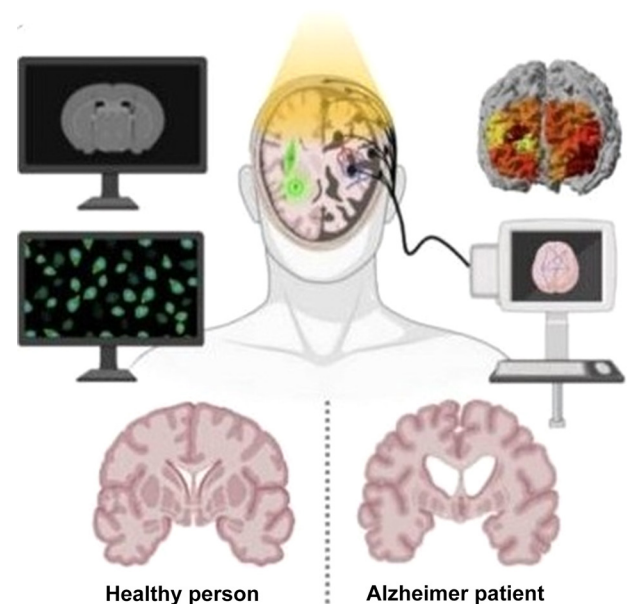
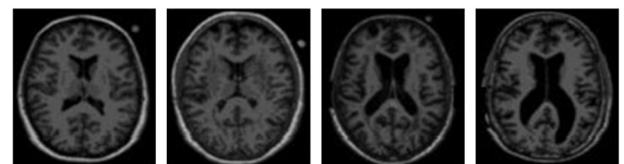


Figure 3
MRI brain image of healthy and AD patients



by detecting changes in blood flow. This helps researchers and clinicians observe how different parts of the brain work together during tasks or at rest. In AD, fMRI often shows disrupted communication between brain regions, particularly within networks such as the default mode network (DMN), which is active when the mind is at rest and involved in memory and self-referential thinking. Changes in activity patterns observed with fMRI can occur even before structural damage becomes visible, making it a promising tool for early detection of the disease [41]. Figure 4 represents fMRI imaging of healthy and AD patients. fMRI is also used to analyze how the brain responds during specific tasks treatments and study how AD affects memory, decision-making, and other cognitive functions.

4.3. PET and FDG-PET modality

PET uses radiotracers injected into the bloodstream to generate 2D or 3D images, showing the chemical distribution within the brain. A major advantage of PET imaging is its ability to clearly show blood flow, oxygen usage, and glucose metabolism in active brain tissues, providing valuable insights into brain function. For the diagnosis of progressive neurodegenerative diseases, PET scans can provide objective measurements of pathophysiological changes through metabolic imaging [40]. FDG-PET determines glucose metabolism in the brain and highlights areas with reduced metabolic activity, which can be used to differentiate between different types of primary dementia. Figure 5 shows examples of PET and FDG-PET images of AD patients.

4.4. Electroencephalography (EEG)

EEG is another noninvasive method that records electrical activity in the brain through electrodes placed on the scalp. It is especially useful for spotting changes in brain wave patterns associated with AD, such as slower waves becoming more dominant and faster waves decreasing [43]. Figure 6 gives a bird's-eye view of EEG data. EEG is valued for its high temporal resolution, which allows for effective real-time monitoring of functional brain activity. It is also cost-effective and widely accessible, making it a useful tool in both research and clinical settings for studying cognitive decline and neurological conditions.

5. Dataset

There are several publicly available datasets that are used in many literature sources. In this section, we discuss the datasets used in AD diagnosis.

ADNI: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is the most widely used dataset. Under the direction of the principal investigator, Dr. Michael W. Weiner, the initiative began in

Figure 4
fMRI brain image of healthy (top) and AD patients (bottom)

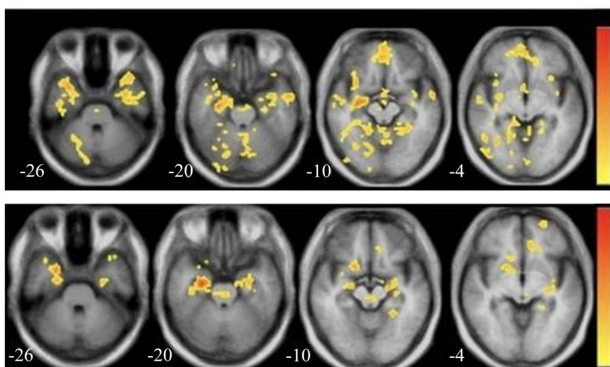


Figure 5
PET image (a) and FDG-PET image (b) of AD patients

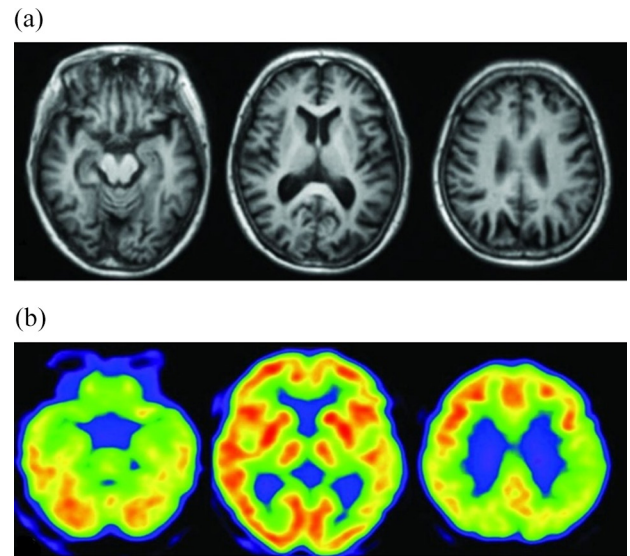
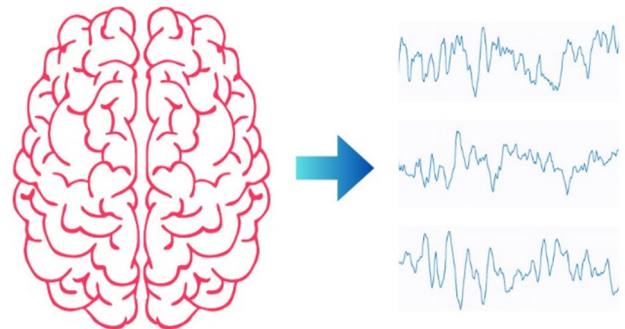


Figure 6
EEG data



2004 with the goal of providing researchers with neuroimages for the accurate diagnosis and prediction of AD [13, 16]. The first ADNI-1 study was conducted in 2009 and was subsequently expanded to ADNI-2 and later ADNI-3. The participants in the project were adults aged 55-90 years from different regions of the United States and Canada [10]. Each version of the ADNI dataset contains images from various neuroimaging modalities: sMRI, fMRI, PET, and FDG-PET.

MIRIAD: The Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) dataset consists of 708 volumetric T1 MRI scans performed by the same radiographer using the same scanner (GE Medical systems, Milwaukee, WI, USA) on 46 patients with mild-to-moderate AD and 23 healthy senior individuals for a total of 69 MRI scans [13]. The subjects were categorized as either normal controls (NC) or AD patients based on their prior analysis of Mini-Mental State Examination scores.

OASIS: Open Access Series of Imaging Studies is another frequently used free neuroimaging dataset. It has three versions: The initial released dataset OASIS-1 contains a collection of 434 cross-sectional MRI datasets from 416 subjects. OASIS-2 includes 150 participants and 373 longitudinal MRI datasets of older adults with and without dementia. OASIS-3 is the most recent version and includes MRI and PET images from 1098 participants aged 18 to 96 years [25].

Kaggle: Kaggle is a website that provides online datasets for analysis and research across a range of disciplines. There are 1279 MRI

scans for testing and 5121 MRI scans for training in the dataset. The dataset was categorized into 2560 Non-Demented, 1792 Very Mild Demented, 717 Mild Demented, and 52 Moderate Demented [34].

6. AD Diagnosis Process

The process of AD diagnosis using ML and DL involves several important steps, each of which is designed to ensure accurate and reliable outcomes.

6.1. Data acquisition

The process starts with collecting high-quality datasets from various sources. There are some datasets publicly available for AD diagnosis. Data can be acquired from those sources. High-quality, comprehensive datasets are crucial for accurate analysis and diagnosis.

6.2. Data preprocessing

Data collected from datasets often require extensive preprocessing, which is essential to ensure its quality, usability, and consistency for analytical use. Preprocessing includes noise reduction, normalization, standardization, and handling of missing data to prepare the datasets for further processing and analysis. Various data preprocessing techniques can be applied to AD datasets to enhance the quality and accuracy of analysis results. This review highlights some of the most commonly used preprocessing methods discussed in the reviewed research articles

Data Cleaning: This step focuses on cleaning up the dataset by finding and fixing any errors, missing information, or inconsistencies. It involves identifying problems, such as gaps, unusual values, or inconsistencies in the data, and then correcting, removing, or filling these problems to improve the quality of the dataset [30].

Imputation: When data are missing, imputation can fill the gaps by estimating the missing values. Techniques such as using the average value (mean), predicting values through regression, or more advanced methods such as multiple imputation are used to complete the dataset and prepare it for analysis [30].

Noise Reduction: Reducing noise in image data preprocessing is essential to make the images clearer and more reliable for analysis. Methods such as smoothing filters, wavelet transforms, or DL models clean up distortions while keeping important details intact and maintaining image quality [35].

Image Normalization: This process involves adjusting the intensity values of images to a standardized scale. Techniques such as normalization, histogram equalization, and contrast stretching are often used to improve image visualization [18].

Cropping and Resizing Image: Cropping helps focus on important parts of an image, such as a specific brain region, by cutting out unnecessary areas. Resizing ensures that all images are the same size. These steps make the data easier to work with while still preserving the important details [20].

Augmentation: This process involves adding images or changing variations of the original image to increase the data size. Augmentation can be achieved by flipping, scaling, and changing the contrast of the image [34].

Segmentation: This is the process of dividing an image into meaningful regions or sections to isolate specific structures or regions of interest (ROIs). Segmentation makes it easier to study and analyze key features. In some articles, GM, WM, and CSF tissues were first obtained using tissue segmentation and then one or more tissues were structurally segmented to obtain relevant parameters including regional cortical thickness [25]. A number of studies divided the whole brain into

anatomical ROIs and directly extracted global characteristics such as volume, surface, and form from the ROIs [33].

6.3. Feature extraction and selection

This is then applied to select the most important and relevant features from the dataset. It reduces the complexity of the dataset by eliminating redundant or irrelevant features, thus improving model efficiency and accuracy. Various techniques such as correlation analysis and PCA can be used for this process [30]. Feature extraction transforms raw data into meaningful and useful representations to create new features using techniques such as PCA, wavelet transform, and DL-based methods [19, 34]. This step ensures that the raw data is converted into a format suitable for analysis.

6.4. Classification

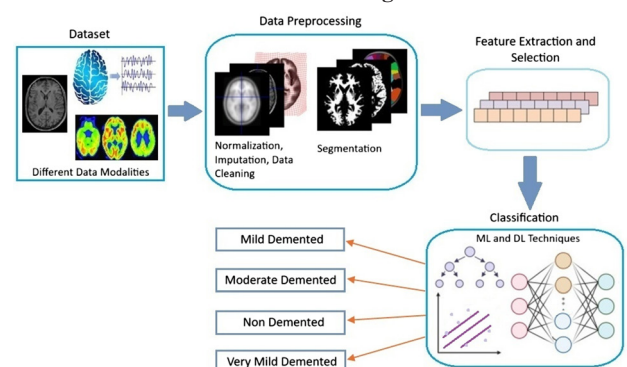
Classification is the process of categorizing data into predefined groups based on its characteristics. This allows for the diagnosis and classification of patients with AD. Most studies use binary classification to classify AD. Common algorithms include SVM, decision trees, LR, and DL models. Figure 7 shows the steps involved in the process of AD diagnosis using different ML and deeper learning techniques.

7. Methodology

For this article, we conducted a systematic review using relevant research articles published between 2017 and 2024. Key sources and databases include IEEE Xplore, PubMed, ScienceDirect (Elsevier), Springer, MDPI, Nature, and Google Scholar. The review includes studies that investigate and analyze different ML and DL techniques using neuroimaging (e.g., MRI, PET) and clinical dataset as modalities for the early prediction of AD.

Although the review followed a structured search process with clear selection criteria to reduce bias, limitations remain due to inconsistent demographic reporting and limited external validation in many studies. Many studies lacked detailed demographic information, limiting insights into data diversity and potential biases. Most studies used standard validation techniques such as k-fold or hold-out methods, few included statistical significance testing such as confidence intervals or p-values, and only a few studies validated their models on external dataset. Overfitting was a common challenge, particularly in DL models trained on limited data, though some studies tried to resolve it using techniques such as dropout, regularization, or data augmentation.

Figure 7
Process of AD diagnosis



Researchers have applied ML and DL methods across various fields [44] and combined them with other techniques, such as SVMs with autoregressive integrated moving average [45], linear regression [46], and ANN with genetic algorithms [47]. Recent advancements in DL-based disease detection frameworks [48] and medical imaging [49] demonstrate their growing impact on healthcare application.

Figure 8 shows the methods used in the different articles reviewed in this study, along with their highest accuracy achieved by each specific classifier.

In this section, the most commonly used ML and DL models in the reviewed studies, emphasizing their application, performance, and advantages. Table 3 summarizes the ML and DL methods applied in this review article.

7.1. ML models

Support Vector Machine (SVM)

SVM is a supervised ML algorithm widely used in AD detection for their ability to handle multiclass, high-dimensional data. SVM finds the optimal hyperplane that separates classes by maximizing the margin between the data points.

$$W^T X + b = 0 \quad (1)$$

Equation 1 defines the linear hyperplane, where W^T is the transpose weight vector, which is the vector that determines the orientation of the hyperplane; X is the feature vector corresponding to the input data point; and b is the bias term that determines the offset or distance of the hyperplane from the origin [50]. SVMs demonstrated robust performance in studies using imaging and clinical data, achieving convincing accuracy. For instance, Hojjati et al. [14] achieved 96.0% and Pérez-Millan et al. [29] reported 90.0% accuracies.

Random Forest (RF)

RF is an ensemble learning method that combines multiple decision trees to improve prediction accuracy and reduce overfitting. It is particularly effective in processing high-dimensional datasets, making it a popular choice for AD detection. This method utilized multiple trees to build a forest, where each tree is trained on a random subset of the data (bootstrapping) and a random subset of features is selected on each branch, ensuring diversity and robustness [30]. To classify data, RF obtained the Gini Index using the following formula:

$$\text{Gini} = 1 - \sum_{i=1}^k (p_i)^2 \quad (2)$$

Figure 8

Methods and their highest accuracy achieved by each specific classifier in the different articles used in the study

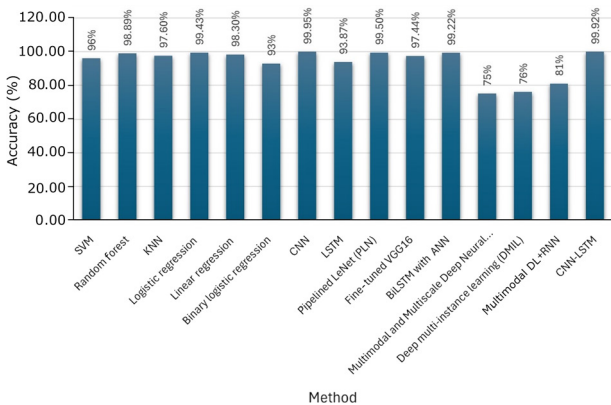


Table 3

Evaluation of the adaptive recommendation by users from the Web platform

References	Method	Technique
[8]	SVM	ML
[9]	SVM with linear kernel	ML
[10]	SVM	ML
[11]	Binary LR	ML
[12]	MMDNN	DL
[13]	DMIL	DL
[14]	SVM	ML
[15]	CNN	DL
[16]	Multimodal DL + RNN	DL
[17]	CNN+RNN	DL
[18]	RF	ML
[19]	KNN and Linear regression	ML
[20]	CNN	DL
[21]	RF + LR	ML
[22]	SVM+CNN	ML
[23]	SVM	ML
[24]	SVM	ML
[25]	SVM	ML
[26]	SVM	ML
[27]	LSTM	DL
[28]	CNN	DL
[29]	SVM	ML
[30]	GaussianNB, decision tree, RF, XG-Boost, Voting Classifier, and Gradient-Boost	ML
[31]	CNN	DL
[32]	k-means, KNN	ML
[33]	LR	ML
[34]	CNN and fine-tuned VGG16 model	DL
[35]	BiLSTM and ANN	DL
[36]	CNN-LSTM	DL
[37]	Pipelined LeNet (PLN)	DL

In Equation 2, p_i is the probability that an object will fall into a particular class or feature and k is the total number of classes. The Gini index ranges from 0 to 1. In AD detection, RF has demonstrated its ability to handle high-dimensional data and its superior specificity. For example, Alickovic and Subasi [18] achieved a specificity of 97.44% and Alroobaea et al. [21] achieved an accuracy of 98.89%, making it effective in processing multimodal datasets and identifying key predictors. Its simplicity, interpretability, and ability to handle complex data make it a valuable tool for early AD diagnosis.

Logistic Regression

LR is a supervised learning algorithm for binary classification. This method is used to predict the binary result (true or false) in classification problems. It analyzes the relationship between input

features and the probability of an outcome that belongs to a specific class.

$$p = \frac{1}{1 + e^{-(b_0 + b_1x + b_2x^2)}} \quad (3)$$

Equation 3 is the LR model, where p is the predicted probability of the positive class, e is Euler's number which is 2.71828, b_0 is the bias term, b_1x is the linear term, and b_2x^2 is the quadratic term that captures the nonlinear relationship between x and p . LR is simple and effective in AD research, with Luk et al. [11] achieving 93% accuracy using ADNI data whereas Alroobaea et al. [21] achieved 84.33% accuracy with the combined ADNI and OASIS datasets.

7.2. DL models

Convolutional Neural Networks (CNN)

CNN is a DL model specifically designed for processing and analyzing structured data, particularly images. In CNN, two images (represented as matrices) are multiplied to generate a new matrix to extract features. It performs two main tasks: feature extraction and classification. CNNs are powerful because they can learn and generalize patterns from large datasets. They use filters to scan images and create feature maps, then apply pooling to simplify the data while keeping the most important details. A type of pooling operation can be expressed as

$$fx, y(S) = \max_{a,b=0} \{S(2x + a, 2y + b)\} \quad (4)$$

Equation 4 describes a maximization operation applied to function S , where the variables x and y are scaled and optionally shifted by the parameters a and b . The value of a and b can either be 0 or 1. Here a and b represent the horizontal and vertical offsets of the subregion from the top-left corner at position $(2x, 2y)$.

The research articles included in this review paper used various CNN models such as LeNet-5, VGG, ResNet-101.

LeNet-5: It was designed for tasks such as handwritten digit recognition and laid the foundation for subsequent developments of CNN. It processes 32×32 grayscale images using convolutional layers for feature extraction, followed by pooling layers to reduce spatial dimensions, and fully connected layers for classification. LeNet uses Tanh activation and outputs probabilities through a softmax layer. While it is simple and efficient for small datasets, it lacks the capacity to handle high-resolution images or complex data, but it still has key influence on modern CNN architectures [37].

VGGNet: VGG is a 2D CNN designed for image classification. It takes 224×224 RGB images as input and uses small 3×3 filters in its convolutional layers, with the number of filters increasing deeper in the network. Rectified linear unit (ReLU) activations add nonlinearity, while max pooling layers (2×2) reduce the size of feature maps and improve translation invariance. The network ends with a layer that outputs classification probabilities, making it ideal for image tasks. Its straightforward design contributes to its popularity, and VGG models come in various depths (e.g., VGG16, VGG19) [50–52].

ResNet-101: Residual networks, or ResNets, address the challenges of training very deep networks. ResNet-101, part of the ResNet family, is a DL model with 101 layers designed for tasks such as image classification. It processes 224×224 RGB images, starting with a 7×7 convolutional layer, followed by batch normalization and ReLU activation. Its core consists of residual blocks with convolutional layers that enable efficient learning. The network ends with a global average pooling layer, a fully connected layer, and a softmax activation layer to output classification probabilities [50–52].

Artificial Neural Network (ANN)

An ANN is a computational model inspired by the structure and function of the human brain and is used to find patterns and relationships in data, such as MRI scans. It works a bit much like the human brain, consisting of layers of interconnected units called neurons, or perceptions. These perceptions process information and help classify data from MRI images based on how the network is set up. Traditional neural networks typically have only two layers, which is insufficient for handling complex tasks such as analyzing large MRI datasets. For this purpose, DL introduces additional layers, ranging from 10 to over 100, depending on the computational requirements. Each neuron passes information through the network, allowing it to uncover hidden details in the MRI images. The neurons in the lower layers start by processing raw data, while those in the deeper layers focus on finding more meaningful patterns and insights. Each neuron in an ANN performs the following operation:

$$z = \sum_{i=1}^n w_i x_i + b$$

$$\alpha = \sigma(z) \quad (5)$$

In Equation 5 x_i are inputs to the neuron, w_i is weights of the connections, b is the bias term, and $\sigma(z)$ is the activation function (e.g., sigmoid, ReLU) [51, 52]. ANNs are widely used in AD detection due to their ability to learn nonlinear relationships in data. Matlani [35] applied ANN to ADNI and OASIS datasets and achieved accuracies of 99.22% and 98.96%, respectively, demonstrating the robustness of the network.

Recurrent Neural Network (RNN)

RNN is a special type of ANN adapted to work for processing time series data and word sequences. RNNs can remember information from previous inputs, making them ideal for tasks where the order of data is important. At each step in a sequence, the network updates its “hidden state,” which acts as its memory. This is done using the current input and the hidden state from the previous step. The output sequence is computed as

$$h_t = \tanh(W_h h_{t-1} + W_x x_t^n) \quad (6)$$

Here h_t is the current hidden state, h_{t-1} is the previous state, W_x are weight matrices, x_t^n is the current input, and \tanh is the hyperbolic tangent activation function [16]. In Lee et al. [16], RNN is applied in AD detection to analyze temporal patterns in longitudinal datasets by combining RNN with multimodal DL, achieving an accuracy of 81%.

Long Short-Term Memory (LSTM)

LSTM is a type of RNN designed to handle long-term dependencies in sequential data, overcoming the limitations of traditional RNNs. They use memory cells and gates (forget, input, and output) to decide what information to forget, keep, or pass on. They use memory cells (C_t) and gates to manage the flow of information at a given time [27]:

Forget gate decides what information to discard:

$$f_t = \sigma(W_f \cdot [h_{t-1}, x_t] + b_f) \quad (7)$$

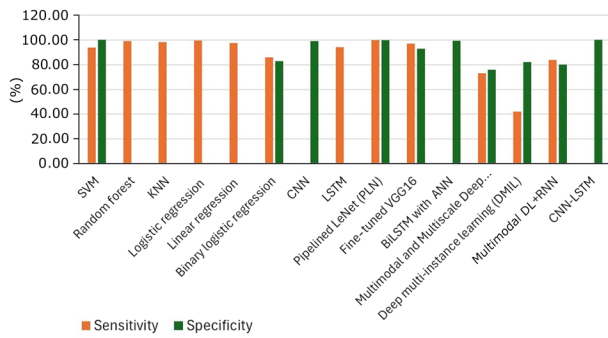
Input gate decides what information to keep:

$$i_t = \sigma(W_i \cdot [h_{t-1}, x_t] + b_i) \quad (8)$$

Cell state update:

$$C_t = f_t \cdot C_{t-1} + i_t \cdot C_t \quad (9)$$

Figure 9
Comparison of performance metrics (sensitivity and specificity) between different methods



Output gate controls the final output:

$$h_t = o_t \cdot \tanh(C_t) \quad (10)$$

In AD detection, LSTMs can effectively analyze time-series data, such as tracking disease progression. El-Sappagh et al. [27] achieved an accuracy of 93.87%, and Sorour et al. [36] combined LSTM with CNNs and achieved an accuracy of 99.92%.

Figure 9 shows the performance of different methods used in the reviewed articles, focusing on sensitivity (true positive rate) and specificity (false positive rate). Of note, some studies did not include sensitivity or specificity in their papers.

8. Discussion and Conclusion

AD remains the most challenging neurodegenerative disease to diagnose in its early stages. Accurate diagnosis of early-stage AD is very crucial in the treatment of patients. Early diagnosis can minimize the effect of AD on neuronal degeneration. This review highlights the significance of ML and DL techniques to improve the accuracy of early diagnosis, providing valuable insights for healthcare professionals and treatment management.

The review shows that DL models, particularly CNNs and hybrid architectures, outperform traditional ML models in terms of accuracy and scalability. However, ML models such as SVMs and RFs remain essential due to their simplicity, interpretability, and effectiveness in small datasets. Among the ML methods, SVMs stood out with 96% accuracy and 94% sensitivity in multimodalities and 90% accuracy with 93% sensitivity in single modality. In contrast, DL models showed even greater potential. The fine-tuned VGG16 achieved a remarkable accuracy of 99.95% and CNN-LSTM hybrids model achieved an accuracy of 99.92%. However, high accuracy alone cannot guarantee the usefulness of a model in real-world clinical settings. A model with high accuracy but low sensitivity could miss early cases, which is crucial for AD detection. To evaluate the effectiveness of the model, in addition to accuracy, metrics such as sensitivity and specificity must be considered carefully. Although accuracy and AUC are widely reported, they do not always capture how a model performs in real-world clinical situations. In AD diagnosis, false-negative results can delay treatment and false positives can cause unnecessary stress. In medical diagnosis it is important to examine how well a model handles these trade-offs by assessing its sensitivity and specificity to ensure its reliability in patient care. The integration of multimodal data, such as MRI, PET, and CSF biomarkers, further improves diagnostic performance. For instance, BiLSTM and ANN models incorporating such diverse data, achieved accuracy of over 99% while maintaining high sensitivity

values, highlighting the value of comprehensive approaches for early diagnosis. These results underscore the potential of DL models for processing complex neuroimaging and longitudinal datasets. However, these models function as “black boxes” and offer little transparency into how decisions are made, which limits their clinical application. In contrast, ML models may not achieve the same level of accuracy but are easier to interpret and implement. This trade-off highlights the need to find a balance between high accuracy and practical use in real-world clinical settings. Our study suggests the integration of multimodal data and the application of fine-tuned architectures are likely to yield more reliable and precise diagnostic tools.

This review also reveals important limitations and challenges that are often overlooked in earlier work. Many studies rely heavily on benchmark datasets with limited demographic diversity, raising concerns about data bias and limited generalizability. In most cases, external validation and testing across different institutions or equipment are lacking, thus limiting clinical applicability. Despite the high accuracy of DL models, their high computational costs, reliance on large annotated datasets, and lack of interpretability hinder their application in real-world clinical settings. Moreover, existing methods often have limited generalizability across diverse populations and datasets, limiting their applicability in real-world scenarios.

To address these limitations, future research must focus on techniques such as transfer learning to reduce data dependency and explainable AI (XAI) such as SHAP and LIME (Local Interpretable Model-agnostic Explanations) to enhance the transparency and trustworthiness of model decisions to clinicians. Federated learning enables secure collaborative training across institutions without compromising patient privacy. Further ensemble learning strategies could help prevent overfitting and enhance model accuracy. New metrics, such as longitudinal change metrics to track gradual cognitive or imaging alterations, and brain network connectivity scores derived from functional MRI, can improve diagnostic accuracy. In addition, newer techniques such as Vision Transformers, Swin Transformers, and graph neural networks (GNNs) also show potential in improving the reliability of predictions. Vision and Swin Transformers help capture complex patterns across whole brain scans while GNNs are suitable for modeling the brain as a network, which helps to understand how different regions interact with each other.

In conclusion, although significant progress has been made in the early diagnosis of AD, challenges such as interpretability, data requirements, and scalability still need to be addressed to fully realize the potential of these models. By focusing on innovative metrics, transparency, better handling of multimodal data, collaborative learning, and real-world validation, these models can become more effective tools for early AD detection, thereby improving patient care and clinical outcomes.

Ethical Statement

The medical images and data presented and used in this article are sourced from public datasets. The authors of this article did not directly collect the images and the data.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

Data are available on request from the corresponding author upon reasonable request.

Author Contribution Statement

Md Minul Alam: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review and editing, Visualization. **Shahram Latifi:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

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