Journal of
Computer & Electrical and Electronics Engineering Sciences

Review

DOI: 10.51271/JCEEES-0035

Detection of Alzheimer's disease from magnetic resonance images with deep learning

Aslıhan Güngör[1]*, Necaattin Barışçı[2]

[1]Department of Computer Science, Institute of Informatics, Gazi University, Ankara, Turkiye

[2]Department of Computer Engineering, Faculty of Technology, Gazi University, Ankara, Turkiye

Cite this article as: Güngör, A. & Barışçı, N. (2026). Detection of Alzheimer's disease from magnetic resonance images with deep learning. *J Comp Electr Electron Eng Sci, 4*(1), 34-45.

Received: 27.01.2026 ◆ **Accepted**: 27.03.2026 ◆ **Published**: 25.04.2026

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative process that leads to irreversible cognitive impairment in the elderly population and constitutes a significant socio-economic burden on a global scale. The lack of a definitive cure for the disease has made early diagnosis strategies based on magnetic resonance imaging (MRI) data critical. This study offers an innovative perspective to the literature by systematically examining current deep learning approaches used in AD diagnosis. The review includes a comprehensive technical evaluation of innovative preprocessing techniques, specialized convolutional neural network (CNN) architectures, and different input representation strategies (2D, 3D, and stacked sections) used in the process from raw data to clinical prediction. Focusing on methodological gaps in the existing literature, this study discusses key obstacles threatening diagnostic validity, such as class imbalance and data leakage, and highlights application suggestions for overcoming these problems. Ultimately, the research gaps identified in light of the findings and the practical solutions offered aim to contribute to the design of next-generation diagnostic systems by providing researchers with a strategic roadmap in terms of model generalizability and clinical integration.

Keywords: Alzheimer's disease, deep learning, MRI, classification

INTRODUCTION

Alzheimer's disease (AD) is a slow neurological disease that directly affects the development of mental abilities and neurocognitive functionality, destroying the thought process and consciousness of a person (Srivastava et al, 2021). The exact cause of the disease is unknown, but it is more common in older people, and can be fatal, although it is more frequently seen in people with chronic diseases such as diabetes, cardio problems, and hypertension (Srivastava et al, 2021) in later life (Alzheimer Derneği, 2015; Alzheimer Derneği, 2016). It is the leading cause of dementia in the elderly due to damage to neurons related to human memory (Breijyeh & Karaman, 2020) and questioning and learning functions (Jack et al, 2008). The neurological disorder begins with a gradual deterioration, and symptoms increase day by day (Han & Kaushik, 2020). Memory problems are one of the first signs of Alzheimer's disease (Alzheimer Derneği, 2015), but these symptoms can vary from person to person (Alzheimer Derneği, 2016). Factors such as difficulty finding appropriate and correct words during speech, spatial problems, and loss of reasoning ability are also among the symptoms (Han & Kaushik, 2021). The appearance of the first symptoms of mild cognitive impairment is considered an early signal that a person may have AD (Üngar et al., 2014). Although there is no complete cure for AD, early detection can help in taking preventive measures and improve AD symptoms (Breijyeh & Karaman, 2020).

Alzheimer's disease can be diagnosed and its progression monitored using clinical measurements, but identifying these symptoms requires expertise and is a very time-consuming process (Kundaram & Pathak, 2021; Nasır et al., 2021). Early diagnosis is very difficult unless symptoms become very pronounced. Early detection of AD can help reduce the risk of neuronal damage (Dadar et al., 2022; Aderghal et al., 2018). Early diagnosis raises awareness of the need for patients to take precautionary measures to reduce the risk of the disease progressing from mild cognitive impairment to Alzheimer's disease (Srivastava et al, 2021). Studies suggest different machine learning and deep learning methods for predicting the stages of AD through self-regulating analysis of magnetic resonance imaging (MRI) images, providing efficient and improved diagnostic results for AD (Aderghal et al., 2018; İbrahimi & Luo, 2021; Faruk et al., 2017). The main factors or parameters used by researchers are the cortical thickness of the human brain, gray matter (GM) density in the brain, ventricular enlargements, and brain crumples. Many research studies claim a relationship between gray matter reduction and some brain diseases such as Alzheimer's disease (Dadar et al., 2022). The hippocampus is the part of the brain affected

Corresponding Author: Aslıhan Güngör, aslihankaralok@gmail.com

in the first stage of Alzheimer's disease. White matter (WM), GM, and cerebrospinal fluid are the main and most primitive tissues in images of the human brain. Researchers have discovered that of these three basic tissues of the brain, GM shrinkage corresponds more to physical decline in mild cognitive impairment (Hızır et al., 2015).

METHODS

Ethics

Ethical approval was not required for this study as it does not involve human participants, animal subjects, or identifiable personal data. All procedures were carried out in accordance with the ethical rules and principles.

Datasets

In recent years, many research centers around the world have been collecting and releasing a large amount of medical and visual data to the public. Publicly available data plays a significant role for researchers conducting research and development on AD. Online datasets generate biomarker information such as neuroimaging methods, genetic and blood information, clinical and cognitive assessments. Among the most widely used datasets are the Alzheimer's disease neuroimaging initiative (ADNI) (Jack et al., 2008), the Australian Imaging, Biomarker and Lifestyle Flagship Study of Aging (AIBL) (Ellis et al., 2009), the Open Access Imaging Studies Series (OASIS) (Marcus et al., 2010; Marcus et al., 2007; LaMontagne et al., 2019), and Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) (Malone et al., 2013).

ADNI stands out as the most widely used, longitudinal, and multicenter study. The aim of ADNI is to investigate whether a combination of MRI, PET, other biomarkers, and clinical and neuropsychological assessments can measure the progression of mild cognitive impairment and early AD. ADNI-1, ADNI-GO, ADNI-2, and ADNI-3. The following collections are complementary and improved upon the previous ones. ADNI researchers collect various data types from patients, including clinical, genetic, MRI, PET images, and biological samples. ADNI-1 includes 200 NC, 400 MCI, and 200 AD. ADNI-GO adds 200 MCI to ADNI-1. ADNI-2 expands on ADNI-1 and ADNI-GO with 150 NC, 100 early MCI, 150 late MCI, and 150 AD. ADNI-3 expands on the existing ADNI-1, ADNI-GO, and ADNI-2 by adding 133 NC, 151 MCI, and 87 AD. It collects imaging and medical data from 211 individuals with AD, 133 individuals with MCI, and 768 healthy individuals without cognitive impairment. OASIS aims to share neuroimaging brain datasets with researchers in related fields. There are three versions of OASIS: OASIS-1 contains 434 MRI scans from 416 subjects. OASIS-2 contains 373 MRI scans from 150 subjects. OASIS-3 contains 2,168 MRI and 1,608 AIBL PET scans from 1,098 subjects.

The MIRIAD dataset contains 708 MRI scans from 46 AD patients and 23 NC volunteers.

Some research uses the above datasets in conjunction with their own datasets. For example, the 2016 study by Suk et al. (2016b) used images from ADNI-2 and its in-house dataset with 37 participants, consisting of 12 MCI subjects and 25 NC subjects. In the study conducted by Basaia et al. in 2019, 3D T1-weighted images were collected from 124 patients with AD probability, 50 patients with HBB and 55 healthy controls, and the dataset was named "Milan" dataset.

Preprocessing

The size of the training and test datasets affects the classification performance. In the studies conducted, the data are used after passing through preprocessing steps. Some MRI software such as FreeSurfer (Fischl, 2012), computational anatomy toolbox (CAT12), FMRIB Software Library (FSL) (Jenkinson 2012), statistical parametric mapping (SPM), ANTS (Avants et al., 2009) are preprocessing libraries used. Recording, normalization, smoothing, segmentation, skull scraping, noise reduction, temporal filtering, and covariate extraction are among the most commonly used preprocessing techniques.

Registration: It is the spatial alignment of image scans to ensure anatomical consistency between individuals and studies. It is also used in multimodal tasks for common registration. MIN 305, Collin27 and MNI152 are among the most commonly used templates. Liu et al. (2016) reported higher performance in their 2016 study adopting multiple templates over a single template. By using multiple templates for feature extraction, it selects the most representative features of each template. By training multiple DVM classifiers, it combines the results of all classifiers. However, multiple templates lead to high computational costs, especially in image registration.

Normalization

Density normalization, also known as area correction or density inhomogeneity correction (Zhao et al., 2023), means rescaling the density of each pixel to a normalized density. During MR imaging, devices with different capabilities scan different subjects or the same subject at different time intervals, which can lead to significant density changes. Large density changes significantly affect the performance of preprocessing such as registration and segmentation.

Skull stripping: Brain scan involves removing extra-brain tissues such as skull, fat, eye, etc., and separating the remaining GM, WM, and cerebrospinal fluid (CSF) (Zhao et al., 2023).

Tissue segmentation: Tissue segmentation means dividing an image scan into segments corresponding to various tissues. Tissue volume is a frequently used measurement after tissue segmentation. GM probability maps are a popular input form in classification tasks. Preprocessing techniques such as density normalization and registration are usually required (Zhao et al., 2023).

Data enhancement: Data enhancement is one of the methods of enhancing a dataset by generating new data samples from existing data without engaging in new data collection, in order to overcome the limitation of the number of subjects in a dataset. Data enhancement techniques include clipping, mirroring, random translation, gamma correction, scaling, random rotation, elastic transformation, vertical flipping, horizontal flipping, and different types of blurring. In addition, new synthesis techniques such as autoencoders and generative adversarial networks are also used in data enhancement. However, synthesis techniques need further proof of the effectiveness of the images generated in AD-related classification and prediction tasks (Zhao et al., 2023).

Figure shows a flowchart illustrating the preprocessing process for MRI images used for Alzheimer's disease.

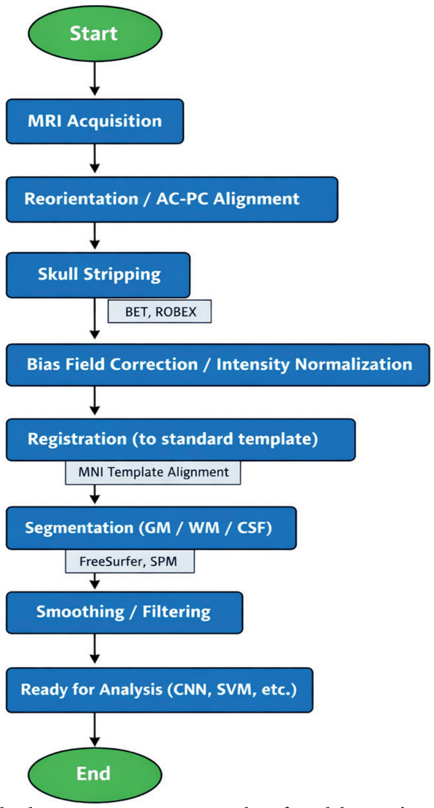

Figure. Standard MRI preprocessing pipeline for Alzheimer's studies
MRI: Magnetic resonance imaging

LITERATURE REVIEW

Traditional Machine Learning

Support vector machines (SVMs) are one of the supervised learning methods used to solve classification and regression problems. SVMs map the input to points in a multidimensional space to maximize the margin between hyperplanes of different data types. A kernel function, such as a Gaussian or polynomial function, maps the existing multidimensional space to a higher-dimensional space. SVMs can be used alone or in conjunction with other methods for traditional machine learning and deep learning methods. Since SVMs can achieve relatively good performance and their operating principles are clear and understandable, SVMs are widely applied in industrial and scientific fields. In a study by Suk et al. in 2014, a linear SVM is used to work with feature representations found by a Deep Boltzmann Machine (DBM) for hierarchical classifiers. In the study by Suk et al. in 2015, multi-core SVMs are used to classify integrated features from multi-mode inputs, while in the study by Suk et al. in 2016, a linear SVM classifier is used. In the study by Shi et al. in 2018, a model is proposed that takes stacked deep polynomial networks (DPN) as feature extractors and a linear kernel SVM as a classifier.

When comparing multi-core and single-core SVMs, multi-core algorithms are seen to offer greater flexibility. Although multi-core SVMs have performed well in most tasks, efficiency is one of the most important problems in developing multi-core SVMs. The computational complexity and difficulty of multi-core SVMs are much more significant than those of single-core SVMs. In terms of space, multi-core SVM algorithms need to calculate the core combination coefficients corresponding to each core matrix, therefore multi-core matrices need to be included in the processing. The need to store multi-core matrices in memory simultaneously is among the challenges encountered. If the number of samples is very large, the size of the core matrix will be very large. If the number of cores is also very large, it will undoubtedly occupy an enormous amount of memory space. In terms of time, training multi-core SVMs is time-consuming. High time and space complexity are among the main reasons why multi-core SVM algorithms are not widely used (Suk et al., 2025, Shi et al., 2018).

Random forest (RF) is an ensemble algorithm consisting of decision trees. Multiple decision tree classifiers form the random forest. While the decision trees are trained in parallel, the Random Forest combines all classification voting results and ultimately selects the class with the most votes. Random Forest is a flexible and practical method, capable of processing inputs without dimensionality reduction and working well on large datasets. When working with multiple inputs, it can estimate the importance of different variables depending on the type of problem. Computing multiple decision trees and integrating their outputs can consume many computational resources. In 2015, Moradi et al. (2018) proposed a novel biomarker-based diagnostic for classifying different stages of MCI using a low-density separation classifier and a random forest classifier. Lebedev et al. in 2014 tested the random forest on the ADNI and AddNeuroMed datasets using a combination of MRI images and morphometric measurements with ApoE-genotype and demographic (age, sex, and education) MRI images. Bi et al. in 2020 proposed a clustering evolutionary random forest architecture to handle multimodal data from ADNI to detect abnormalities in the brain and pathogenic genes, aiming to overcome the small sample size problem.

Convolutional Neural Networks (CNN)

Deep learning is a machine learning technique where the learning process is carried out with a hierarchical structure. Interest in deep learning techniques has increased significantly in recent years and is widely used in various brain research. Convolutional neural networks are also among the successful deep learning methods. Convolutional Neural Networks (CNNs) are artificial neural networks that use convolutional operations to filter input data and extract useful features. Research on CNNs is rapidly advancing. They play a role in various stages of detection, classification, and segmentation problems in different fields, including medical imaging and natural language processing, achieving high-accuracy results. The success of CNNs in classification studies and the segmentation of realistic images is increasing the application of CNNs in the medical field. Recent studies show that CNNs perform well in segmentation and disease detection problems. The classic CNN structure consists of a series of convolutional layers, a pooling layer, an activation layer, and fully coupled layers. A SoftMax function is applied to classify the input image with probability values between zero and one. The convolution layer includes local receiver areas, shared weights, filters, step, and padding concepts. A filter contains unknown parameters to be learned during training. Convolution involves the process where a filter shifts from top left to bottom right across the entire image and convolutions with the input image to calculate the weighted sum. Step refers to the step size a filter moves per slice. However, the pixels at the edges are never at the center of a filter, and a filter cannot extend beyond the edge region. After each convolution between the input and the filter, only a portion of the pixels at the edge are detected, and information at the image boundary is lost. Padding is designed to overcome this problem.

Padding means filling some values along the input boundaries to increase the input dimension, usually the filled values are zero. Padding is necessary in applications where dimensions must remain constant before and after convolution to prevent information loss. The size of the filters determines the receiver area in the convolutional layers. Convolutional layers are the most suitable feature extraction tool for image datasets with high spatial redundancy due to their ability to resolve features of images with shared weights. By reducing spatial redundancy, the feature vector generated from the outputs of the convolutional layers represents the content of the image. The pooling layer is a dimensionality reduction process in feature maps that aims to reduce training time by reducing the number of parameters to be trained. Maximum pooling, average pooling, and global pooling are the most commonly used pooling layers. Maximum pooling gives the maximum value within the region of the feature map covered by the filter. Average pooling calculates and presents the average value of the elements presented in the feature map region covered by the filter. Global pooling reduces each channel in the input to a single value.

The activation layer provides a nonlinear mapping to the output of the convolution layer to improve the network's reasoning ability. The most commonly used activation functions include ReLU, Sigmoid, Tanh, etc.

The fully connected layer takes the inputs of the feature extractor and predicts the correct label along with probabilities.

CNN can be used as a feature extractor and classifier or as a feature extractor only. CNN is used to obtain target-level representations generated from sparse regression for clinical decision-making (Suk et al., 2017). In the study conducted by Feng et al. in 2020, 3D-CNN with MRI is applied to perform AD classification using MRI images. By using SoftMax as a classifier together with an SVM, this 3D-CNN-SVM model achieves better classification performance than 2D-CNN and 3D-CNN. When comparing traditional machine learning and deep learning methods in AD-related fields; in general, deep learning methods provide better performance than traditional machine learning methods. The appropriate size of training samples should not be <1,000. A dataset containing more than five thousand samples can be considered sufficient to train a deep learning model that provides high accuracy (Zhao et al., 2021).

CNN algorithms: Commonly used CNN algorithms in Alzheimer's disease include LeNet, AlexNet, VGG, GoogleNet, ResNet, and DenseNet.

LeNet: In 1998, LeCun et al. proposed LeNet, the first study to use CNN as a solution to a character recognition problem. By introducing the fundamental concepts of convolutional, pooled, and fully connected layers in a single architecture, they laid the groundwork for the idea of local receptive fields within the CNN, which is the basis of other deep learning modules. In a study by Yang and Liu in 2020, they proposed their models with LeNet-5 for classification and prediction. In the model, which was constructed using PET images of 350 subjects with MCI from ADNI, they achieved 91.02% and 77.63% accuracy and specificity in predicting MCI transformations (Yang & Liu, 2020).

AlexNet: In 2017, Krizhevsky et al. proposed AlexNet, an important architecture following LeNet. The rectified linear unit (RELU) is used as the activation function, and a method for training networks using multiple GPUs is presented.

In a study conducted by Padmavathi et al. in 2023, a classifier is created to distinguish Alzheimer's disease using the AlexNet and ResNet50 methods. The model is fed with a dataset. Then, the classification and processing of the image is performed by comparing it with the key features obtained during preprocessing and feature extraction. The entire extraction process is performed before training the mode in the convolution and pooling phases. The model achieves an accuracy of 54% with AlexNet and 56% with ResNet50 (Padmavathi et al., 2023).

VGG: In a study by Simonyan and Zisserman in 2015, VGG is proposed. A stack of 3×3 convolution filters is used to replace large convolution filters such as 5×5, 7×7, 9×9, or 11×11 convolution filters. A small stack of convolution filters yields better results than a single large convolution filter. By using small filters, deeper networks are obtained with fewer parameters, allowing for the training of a more complex model in a shorter time (Jain et al., 2019).

In a study by Jain et al. in 2019, a transfer learning approach is applied to create an AD classification model using VGG16, pre-trained on ImageNet, as a feature extractor. By converting 3D MRI images into 2D slices, they select 32 slices with the most informative features as a result of preprocessing steps and feed these selected slices as input to VGG16, then reach the result with fully linked layers. Although the datasets contain MRI images of 150 subjects from ADNI, the model achieves an accuracy of 99.14%, 99.30%, and 99.22% for the classifications of CN for AD, MCI for AD, and CN for MCI, respectively. Despite the high classification accuracy for the aforementioned tasks, the generality of the proposed model is quite doubtful due to the very small size of the dataset.

In a study conducted by Lim et al. in 2022, they tested a CNN, VGG-16, and ResNet-50 as feature extractors to distinguish NC, AD, and MCI using MRI images. While training the CNN from scratch, they pre-trained VGG-16 and ResNet-50 using the ImageNet database. VGG showed the best performance with 83.90% accuracy, 82.49% precision, 83.90% recall, and 83.19% F1 score.

GoogleNet: Instead of manually determining whether to use 3×3, 5×5, or 7×7 filters in the initial studies, a new model is proposed that allows the network to automatically learn how to reach the optimal structure. The batch normalization introduced in Inception v2 reduces the internal covariate shift created after convolution operations. Inception v3, while maintaining the consistency of the statistical properties of the data during the training phase, replaces the large convolution kernel with a small convolution kernel. By dividing an N×n convolution kernel into a batch or parallel form of 1×n and 1×n convolution kernels, the proposed general network design principles gradually reduce the information dimension to the desired extent (Szegedy et al., 2015; Szegedy et al., 2016; Szegedy et al., 2017).

In the study conducted by Ding et al. in 2019, using 2,109 PET images of 1,002 patients from ADNI as the dataset, they used Inception v3, which was pre-trained on ImageNet (Ding et al., 2019).

In 2016, He et al. proposed deep residual neural networks (ResNet) to handle vanishing and exploding gradients. Before the introduction of ResNet, designing such a deep network presented challenges because the gradient vanished rapidly as the network deepened. As the number of network layers increased, more complex feature models could be extracted. Theoretically, better results should be obtained as the model deepens. As network depth increases, network accuracy becomes saturated or even decreases. ResNet overcomes this problem by adding shortcut connections that skip one or more layers. The accumulation layer will only perform identity mapping when the residual is zero, preventing network performance degradation, ensuring the residual is not zero, and allowing the accumulation layer to learn new features based on input features. Since the residual will generally be small, training the model will be easy.

In a study conducted in 2017 by Korolev et al., a CNN network similar to 3D ResNet and VGG was proposed to extract features necessary for 3D image classification of brain MRIs. Although both networks perform well in classifying AD and NC, they fail to separate AD and NC from MCI.

Islam and Zhang (2018) tested an architecture combining Inception v4 and ResNet to identify different stages of AD and achieved an accuracy of 93.18% in OASIS.

In the study by Abrol et al. in 2020, a 3D ResNet network is proposed for classification and prediction. First, the model is trained for MCI detection using 3D gray matter images as input, then the trained model is transferred to the NC and AD classification domain, utilizing the transfer learning method.

DenseNet: In 2017, Huang et al. proposed the DenseNet approach to fully utilize features across all layers. There are two main approaches to improving neural effects; going deeper and going broader. DenseNet directly connects all layers. In other words, the input of each layer is derived from the output of all previous layers. By doing this, DenseNet reduces the vanishing gradient and ensures optimal use of features to improve the effect. At the same time, the number of parameters is reduced to some extent.

In a study by Wang et al. in 2018, a combined 3D-DenseNets method is proposed for the diagnosis of AD and MCI. Due to the limited data problem, the DenseNet method is adopted, and several 3D-DenseNets are trained with varying hyperparameters. The final result is generated by the weighted sum of each basic 3D DenseNet, and the model achieves an accuracy value of 97.19%.

In the study by Wang et al. in 2019, a model is proposed in which 3D DenseNet is adopted as the backbone classifier, followed by fully connected layers and a SoftMax function. Each 3D DenseNet is initialized separately and trained on images of 833 subjects in the ADNI dataset. Probability scores generated by each independent classifier are voted on and integrated into the proposed model.

In the study by Liu et al. in 2020, multitasking deep CNN and DenseNet models are integrated together for hippocampal segmentation and AD classification. In detail, multitasking deep CNN is used to extract features during the segmentation and classification phase, and 3D DenseNet is trained using features for disease classification. Finally, the model combines features learned from multitasking CNN and DenseNet models to perform the classification (Wang et al., 2019).

Zhang et al. (2021) proposed a method using 3D DenseNet in 2021. Training a deep learning model like DenseNet with such a small dataset often results in a high risk of overfitting. Voting strategy is used to try to compensate for this error. However, training multiple deep learning models from scratch is a time-consuming and inefficient practice. Transfer learning can be a good choice.

Input types: CNN is a powerful tool capable of processing features of varying sizes, and it is categorized into four main methodology categories based on four different input types: 2D slice-based, 3D patch-based, 3D region of interest (ROI-based), and 3D topic-level.

2D dimensional slice: 2D slice-based approaches extract 2D slices from 3D images to reduce the number of hyperparameters, based on the hypothesis that useful features for classification or prediction tasks can be extracted from 2D slices. A common method for extracting 2D slices from a 3D image involves projecting the entire brain scan onto sagittal, coronal, and axial planes. These planes are also referred to as the median, anterior, and horizontal planes. Images from the central part of the brain are more informative because their information entropy is greater than others. Therefore, not all slices will be used during training. Slices from sagittal, coronal, and axial images contain complementary information, and features extracted from these images are integrated and used. While it is easy to obtain a large number of samples when working with 2D slices, a deep learning model incorporating a 2D CNN generally requires fewer parameters and a shorter training time compared to a 3D model. The disadvantage of slice-based approaches is that 2D slices of a brain image lose spatial information between each other because each 2D slice is processed independently. Sarraf et al. (2017), Wang et al. (2018) and Jain et al. (2019) use 2D MRI slices as input type in their studies. In 2017, Sarraf et al. achieved an accuracy of 96.86% for AD and NC classification using LeNet-5 as the CNN method. Wang et al. (2018) established and trained their own 2D CNN model from scratch. In 2019, Jain et al. used 2D MRI slices as input type in their model, while using VGG-16, pre-trained on ImageNet, as a feature extractor. In their 2018 study, Lin et al. (2018) attempted to integrate PCA and Lasso methods with CNN to predict the conversion from MCI to AD. They used CNN as a feature extractor in the training phase to input 2.5D patches, while using PCA and Lasso to reduce dimensions and aiming to select the most informative features. The selected features fed overlearning in the classification phase. Furthermore, by testing features generated from FreeSurfer together with CNN-based features, it was revealed that using both features could provide better performance than using only CNN-based or FreeSurfer-based features.

3D patch: 3D patch-based approaches work similarly to 2D slice-based methods, but instead of sampling projections that cut across specific planes, the 3D brain is studied by scanning it as a series of stepped 3D patches as a hyperparameter. The sample size is larger after the cutting operations. 3D patch-based methods compensate for spatial information loss compared to 2D slice-based methods, but patches are generally used independently during the training phase. When a model is run on the same network for each patch, 3D patch-based methods require low memory. If you train an independent network separately for each patch and combine the results from previous independent networks to use a structure, the overall complexity of the network becomes high. One of the challenges in 3D patch-based methods is selecting informative patches from the brain scan, while another challenge is selecting the most distinctive features. Qiu et al. (2020) and Zhang et al. (2021) use 3D patches as the input type.

Region of interest based (ROI based): 3D ROI-based methods represent a 3D image of a segmented brain region, paying attention to specific regions that have been clinically proven to be associated with AD. The selected regions are usually informative, such as gray matter volume, hippocampal volume, and cortical thickness. The use of an ROI-based method does not easily lead to overfitting, and the interpretability of the model is near perfect, as the contribution of each region in the model can be seen. The shortcoming of ROI-based methods is the prerequisite of selecting regions in AD. In their 2014 study, Liu et al. extracted features in clustered sparse ADs by taking 3D ROI-based input. In their 2015 study, Liu et al. adopted 3D ROI-based input and used an SVM classifier.

3-dimensional subject level: 3D subject-based methods capture the 3D brain scan as a whole, thus preserving full integration of spatial information. Since a patient provides only one sample at a time, the sample size is very small compared to the number of subjects in popular datasets. Consequently, the risk of overfitting is high when using 3D subject-based methods. MRI scans are globally similar; small changes are not easily detected in MRIs.

Autoencoder (AE)

An AE is an artificial neural network model where the input and learning objectives are the same, aiming to learn latent representations of the input in an unsupervised manner. An autoencoder consists of an encoder and a decoder. Given an input domain and a feature domain, an autoencoder decodes the mapping between the input and output to minimize the error in reconstructing the input feature. In other words, the latent layer feature, the encoded feature generated by the encoder, can be considered as a representation of the input data. The representational capacity of an AE is limited. Stacked AEs consist of a combination of several AEs stacked together. In stacked AEs, the output of the hidden features of one AE is used as input to another AE at a deeper layer. As stacked AEs go deeper, their representational power increases, and they can also be used in transfer learning. As self-supervised learning, stacked AEs can be used as feature extractors by effectively extracting hidden representational features from input data. By training the AE with the training dataset, it can replace a decoder classifier for classification studies. The hidden representation extracted in the AE can be used in pre-training. Stacked AEs are widely used in tasks lacking datasets, such as AD classification and prediction. The networks proposed in the 2013 study by Suk and Shen (2013), the 2015 study by Suk et al. (2015), and the 2016 study by Suk et al. (2016a) use stacked AEs as feature extractors. SVM is used as a classifier to process features for the purpose of performing classification. Two separate studies by Hosseini-Asl et al. (2016a, b) use a 3D CNN pre-trained with stacked 3D convolutional AEs. In their 2015 study, Payan and Montana compare the classification accuracy of 2D and 3D approaches using sparse AEs and CNN. The 3D approach provides an increase in performance compared to the 2D method.

Transformer

The use of cutting-edge models proposed in computer vision studies significantly improves the performance of AD classification and prediction. The attention mechanism method is being proposed as an idea to improve AD performance. The attention mechanism, proposed by Vaswani et al. in 2017, is initially designed to solve natural language processing (NLP) problems. Although the transformer's nature focuses on solving weighted sum problems, it demonstrates incredible and spectacular performance in a wide variety of fields. The image transformer (Vit), proposed by Dosovitskiy et al. in 2020, abandons the CNN structure and uses a pure transformer. As a new type of feature extractor, Vit focuses on attention at the patch level rather than the pixel level. Vit outperforms CNN in various tasks in computer vision. If Vit can be successfully used in AD diagnosis, it is thought that the interpretability of the model will increase as it shows the importance of each area. The disadvantage of Vit is that the size of the input feature is very large due to the use of 3D images in most AD-related studies. While using Vit to process a feature vector with such a large size is unrealistic, it's a hypothetical scenario. Because 3D images contain far more spatial redundancy than 2D images and text, duplication reduction is necessary before processing. With masked language models such as bidirectional encoder representations (BERT) (Devlin et al., 2019) from Transformers proving highly successful for pre-training in NLP, a new transfer learning method can also help improve performance. Masked Autoencoder (MAE), proposed by He et al. in 2021, explains the natural difference between language and vision. Language is expressed as having a high density of concrete and semantic information, while vision is expressed as a continuous signal involving repetition in space. Masked parts are more likely to be recovered in an image application. An original image can be reconstructed based on the given partial observational information.

Transfer Learning

Today, problems in one field can be solved faster by utilizing existing knowledge in another field. In many studies, researchers train deep learning models from scratch, which makes the training process time-consuming and often inefficient as it requires datasets containing millions of images. Due to the high cost of training a network or system from scratch, researchers aim to overcome this high cost by developing systems that use existing knowledge to help learn new information faster and better. Transfer learning means transferring learned information from one study to another. The source is defined as the field containing existing knowledge, and the target is the field to which the existing knowledge is transferred. Since all of the most commonly used backbone networks such as LeNet, AlexNet, VGGNet, ResNet, DenseNet, and GoogleNet are trained on ImageNet, ImageNet has become the most common source dataset for transfer learning (Ardalan & Subbian, 2022). Researchers utilize transfer learning methods to pre-train deep learning algorithms in order to overcome the problem of the scarcity of data samples.

Fine-tuning means applying a pre-trained model and using the weight data of the pre-trained model to initialize a new model to be trained. Since a model does not need to be trained from scratch, fine-tuning helps save a lot of time for training. Researchers can choose to freeze parts of the model, fine-tune, and initialize randomly. According to the study by Ardalan and Subbian in 2022, most researchers prefer to fine-tune in convolution and fully connected layers. Since the prediction of MCI transformation is more difficult than the classification between AD and HC, the structural changes in the brain of HBB are very subtle. However, the study between AD and HC due to classification is highly correlated with the MCI prediction task. Researchers generally initialize network parameters in MCI classification operations by transferring weights learned from AD classification. In the study by Khan et al. in 2019, an attempt is made to solve the big dataset problem with transfer learning. Fine-tuning is done by deploying transfer learning strategies and adjusting at the layer level; while a predefined group of layers is trained, other layers are frozen. In the study conducted by Liu et al. in 2021, AlexNet and GooLeNet were implemented as basis for transfer learning with 91.4% and 93.02% accuracy respectively, with GooLeNet achieving slightly higher performance since it contains deeper layers and more convolutions than AlexNet.

In a study by Li et al. in 2015, the CNN is pre-trained with an unsupervised RBM. Similarly, in a study by Payan et al. in 2015, convolutional layers were pre-trained with a sparse autoencoder and used to initialize the CNN. In a study by Hosseini-Asl et al. in 2016, a 3D convolutional autoencoder is pre-trained in the source domain (CAD dementia) and fine-tuned in the target domain (ADNI). In a study by Basaia et al. in 2019, transfer learning is implemented where CNN weights are transferred to other CNNs and used as pre-trained initial weights to classify HC against AD in ADNI. In a study by Lian et al. in 2020, weight values learned from the AD and HC classification study are transferred to the MCI classification study. In the study conducted by Odusami et al. in 2021, a pre-trained ResNet18 network is used as a transfer learning method for the detection of Alzheimer's, and all layers are resolved to update the network parameters.

In the study conducted by Arafa et al. in 2024, the Kaggle dataset, presented in JPEG format with dimensions of 176*208, was resized to 64*64 and divided into two classes, mild dementia and non-dementia, using CNN and VGG16 methods. While the proposed CNN model achieved accuracy values of 99.95% and 99.99%, the VGG16 model, pre-trained with the ImageNET dataset, was finely tuned and achieved an accuracy of 97.44% for AD stage classifications.

A 2024 study by Chen et al. proposes an ensemble deep learning model for AD classification that incorporates a Soft NMS into a Faster R-CNN architecture, utilizing a ResNet50 network in the feature extraction phase to improve candidate information integration and detection accuracy. In the array data processing phase, a Bi-Gated Recurrent Unit (Bi-GRU) is used in the feature extraction network. The accuracy rate is 98.91% for binary AD and CN classification, while it drops to 84.37% for ternary AD, MCI, and CN classification.

In a study conducted by Sait et al. (2024), the ResNet152V2 architecture, which successfully captures local features, is combined with the Inception-Transformer block, which can establish global contextual relationships. In this study, conducted on ADNI and OASIS datasets, the generalizability of the model is increased by performing histogram equalization and Gaussian noise reduction operations on the images. This hybrid structure achieves an accuracy of 98.35%, exhibiting superior performance compared to traditional CNN models in classifying complex cases.

In a study conducted by Ahmad et al. in 2024, the focus is on lightweight models based on MobileNetV2 and EfficientNetV2, prioritizing clinical accessibility. Using Kaggle and ADNI datasets, this research employs the ADASYN (Adaptive Synthetic) sampling method to address dataset imbalances. The study demonstrates that AD diagnosis can be performed with high accuracy even on low-computation devices, creating a significant reference for mobile health applications and achieving an accuracy rate of 99.22%.

A study by Rao and Kumar (2025) adopts a multimodal approach combining MRI data with DTI (diffusion tensor imaging) images to improve diagnostic accuracy. In this study, the YOLOv11 architecture, normally used for object detection, is adapted to segment and stage atrophic regions in the brain. This method, applied after advanced preprocessing steps such as skull-stripping and bias-field correction, stands out particularly for its high sensitivity in early-stage (EMCI) diagnosis, achieving an accuracy rate of 97.33%.

Table shows the datasets, methods, and preprocessing techniques used in the studies. The reported accuracy values correspond to different classification tasks, including binary (AD vs. NC), ternary (AD vs. MCI vs. NC), and multi-class classification. Therefore, direct comparison of accuracy values should be interpreted with caution.

DISCUSSION

Artificial Intelligence, particularly traditional machine learning and deep learning methods, continues to evolve and be applied in AD-related studies. Datasets in the AD field remain small compared to those used in other computer vision studies due to the privacy concerns of medical data. Given the complexity of AD-related applications, a large-scale dataset is needed for a researcher to develop more effective and powerful models. Studies show that researchers focus more on AD, MCI, and NC classification than on prediction. Early detection of AD remains a challenging issue. Comparing the performance of each proposed model is also a difficulty, due to the use of varying numbers of samples, modalities, preprocessing techniques, feature extractors, classifiers, etc. Multimodal models, which can combine information from different modalities, perform better than models with a single modality because they contain complementary information (Khedher et al., 2015; Liu et al., 2020).

The most common problem encountered in datasets is class imbalance. Data belonging to one class is either more or less abundant compared to other classes. This problem can be solved by increasing the number of images of the class with fewer members or by decreasing the number of images of the class with more members. The Synthetic Minority Oversampling Technique (SMOTE) (Chawla et al., 2002), proposed to solve the class imbalance problem in datasets, randomly replicates the minority image class in the dataset to minimize validation. In their 2021 study, Murugan et al. also used the SMOTE method to overcome the class imbalance problem and achieved training and validation accuracy values of 99% and 94%, compared to 96% and 78% when SMOTE was not applied. The data augmentation method increases the number of samples in the class with a small number of members, while the data reduction method reduces the number of images in the oversampled class. In their 2019 study, Afzal et al. achieved high performance for Alzheimer's disease diagnosis by using data augmentation to solve the class imbalance problem in AD detection using 3D MRI images from OASIS. Using a balanced dataset improves

Table. Datasets, methods, and preprocessing techniques used in the reviewed studies

Study	Type of scan	Dataset	Subjects	Accuracy (classification task)	Method	Preprocessing
Suk and Shen (2013)	MRI + PET	ADNI	202 (HC: 52, AD: 51, MCI: 99)	98.8% (Binary: AD vs NC)	Stacked AEs + SVM	AC-PC correction, skull stripping, segmentation
Liu et al. (2014)	MRI + PET	ADNI	311 (HC: 77, AD: 65, pMCI: 67, sMCI: 102)	91.4% (Ternary: AD vs MCI vs NC)	Stacked sparse AE + softmax	Registration, segmentation
Lebedev et al. (2014)	MRI	ADNI + AddNeuroMed	896	86.6% (Binary: AD vs NC), 86.25% (Binary: AD vs NC)	RF	FreeSurfer segmentation
Suk et al. (2014)	MRI + PET	ADNI	398 (HC: 101, AD: 93, MCI: 204)	95.35% (Binary: AD vs NC)	DBM + SVM	AC-PC, skull stripping
Payan & Montana (2015)	MRI	ADNI	2,264 (HC: 755, AD: 755, MCI: 755)	95.39% (Binary: AD vs NC)	3D CNN + AE	Normalization
Moradi et al. (2015)	MRI	ADNI	825 (HC: 231, MCI: 394, AD: 200)	75% (Ternary: AD vs MCI vs NC)	LDS + RF	Normalization, segmentation
Hosseini-Asl (2016a)	MRI	ADNI + CADDementia	240	99.3% (Binary: AD vs NC), 100% (Binary: AD vs MCI), 94.6% (Ternary: AD vs MCI vs NC)	3D CNN	Normalization
Liu et al. (2016)	MRI	ADNI	459 (HC: 128, AD: 97, sMCI: 117, pMCI: 117)	93.06% (Ternary: AD vs MCI vs NC)	Ensemble SVM	Bias correction, segmentation
Suk et al. (2017)	MRI	ADNI	805 (HC: 226, AD: 186, pMCI: 167, sMCI: 226)	90.28% (Binary: AD vs NC), 74.20% (Binary: MCI vs NC), 73.28% (Binary: pMCI vs sMCI)	Sparse regression + CNN	AC-PC alignment, skull stripping
Korolev et al. (2017)	MRI	ADNI	231 (HC: 61, AD: 50, sMCI: 77, pMCI: 43)	88% (Binary: AD vs NC)	ResNet + VGG	Skull stripping
Sarraf et al. (2017)	MRI	ADNI	446 (HC: 183, AD: 263)	100% (Binary: AD vs NC, overfitting)	GoogLeNet + LeNet-5	Registration, skull stripping
Lin et al. (2018)	MRI	ADNI	818 (HC: 229, AD: 188, MCI: 401)	79.90% (Ternary: AD vs MCI vs NC)	PCA + Lasso + CNN	Registration, normalization
Basaia et al. (2019)	MRI	ADNI + Milan dataset	1,385	99% (Binary: AD vs NC), 75% (Binary: cMCI vs sMCI)	CNN	Normalization
Wang et al. (2019)	MRI	ADNI	833 (HC: 315, AD: 221, MCI: 297)	97.52% (Binary: AD vs NC)	3D CNN	Skull stripping, alignment
Liu et al. (2020)	MRI	ADNI	449 (HC: 119, AD: 97, MCI: 233)	88.9% (Binary: AD vs NC), 76.2% (Binary: MCI vs NC)	3D DenseNet	Hippocampus segmentation, registration
Stoleru (2023)	MRI-T1	ADNI	AD: 122, CN: 169	99.96% (Binary: AD vs NC)	ResNet-152	Grad-warping, skull stripping
Arafa (2024)	MRI	Kaggle	5,125	99.99% (Multi-class: DeMente vs NonDeMente vs Mild vs Moderate)	CNN	Augmentation
Chen (2024)	MRI	ADNI1	406 (CN: 185, MCI: 106, AD: 115)	98.91% (Binary: AD vs NC), 84.37% (Ternary: AD vs MCI vs NC)	Faster R-CNN	Cropping, normalization
Sait et al. (2024)	MRI	ADNI & OASIS	7854 (ADNI: 5154, OASIS: 2700)	98.35% (Multiclass: NC, AD, EarlyMCI, Late MCI)	ResNet152 + Transformer	Histogram Equalization, Gaussian Noise Reduction
Ahmad et al. (2024)		Kaggle/ADNI	1240	99.22% (Binary: AD, NC)	MobileNetV2 (Lightweight)	ADASYN Sampling, Density Clipping
Rao et al. (2025)		ADNI (MRI+DTI)	12000	97.33% (Multiclass: NC, AD, EarlyMCI, Late MCI)	YOLOv11 + data fusion	Skull-stripping, MRI-DTI Registration

MRI: Magnetic resonance imaging, PET: Positron emission tomography, ADNI: Alzheimer's disease neuroimaging initiative, AD: Alzheimer's disease, CNN: Convolutional neural networks, DTI: Diffusion tensor imaging

performance even when the dataset is small (Farooq et al., 2017). Another way to solve unbalanced class problems is to reconstruct medical images. In a 2020 study by Hu et al., a Generative Adversary Network (GAN) is proposed to reconstruct neuroimages. Using newly reconstructed images to augment the unbalanced dataset, they train two 3D dense convolutional linked networks, one with the raw dataset and the other freshly balanced, and test the performance of these two networks. Neuroimages generated from the GAN help to increase the classification accuracy from 67% to 74%.

Data leakage refers to the use of test data during training (Wen et al., 2020). Incorrect data splitting, late splitting, incorrect transfer learning, and lack of independent test sets constitute four main causes of data leakage. Late splitting is performed through data augmentation techniques before separating the dataset into training, testing, and validation. As a result, images generated from the same data source are split into different data subsets, leading to an unbiased and inaccurate evaluation. Incorrect data splitting means splitting images of a subject at different times into various training, testing, and validation sets. Incorrect data splitting can occur when using 2D slices and 3D patches as input to deep learning. Proper splitting should occur at the subject level. Data leakage is a critical issue that can significantly distort model performance evaluation. In particular, studies reporting near-perfect accuracy (e.g., 99.9% or 100%) should be interpreted with caution, as such results may stem from improper experimental design rather than true model generalization. Practices such as late data splitting and incorrect subject-level separation can lead to the presence of highly similar or even identical samples across training and testing sets. This artificially inflates performance metrics and results in biased evaluations. Therefore, it is essential to ensure strict subject-level data separation and the use of independent test sets to obtain reliable and generalizable results.

Biased transfer learning occurs when the source and target domains of transfer learning overlap. Using different source and target datasets is the most appropriate way to prevent biased transfer learning. In research where the dataset is separated into training and test sets, there is no independent validation set. The test set should only be used in the evaluation phase and should not be used for the hyperparameter. A separate validation set and test set that do not overlap with the optimization can be used to optimize the hyperparameter of the model.

In the articles reviewed, it is mostly seen that reprocessing techniques are used. Although deep learning studies require data to go through preprocessing steps, it is also possible to not use any preprocessing techniques in CNN networks [53,75]; Especially in studies where the traditional machine learning method is used as the main backbone, it is recommended that raw data be processed through preprocessing steps such as density correction, skull stripping, registration, normalization and tissue segmentation according to the standard sequence before use. SVM is seen as the most widely used and increasingly popular method. Deep learning approaches perform better than traditional methods in detection studies. Significant disadvantages of deep learning include its lack of interpretability and transparency, its black-box nature, the difficulty in understanding its internal working mechanism, and the need for more time to train it. Advantages include higher-performance graphics processing units and enormous amounts of storage space. While most research is conducted using a single dataset, it has also been observed that multiple datasets are used for specific purposes (Liu et al., 2017; Poloni & Ferrari, 2022). Multiple datasets are also used at different stages to increase the number of subjects; studies using ADNI as the training dataset and AIBL, FHS, and NACC as the test dataset (Qiu et al., 2020), and ADNI as the training dataset and ADNI + Milan as the test dataset (Basaia et al., 2019) are examples of these.

Since 2D images are easier to process and help scale the dataset, 3D images can be sliced from various angles to create 2D slices. Generally, 2D slices with greater entropy in the center are selected, further reducing the input size. However, correlational information can be lost due to 3D image slicing. Like 2D slice-based methods, 3D patch-based methods also provide a large dataset and require training on many classifiers. Extracting features and selecting the most comprehensive patches from all 3D patches can be challenging. While ROIs are often informative, only one or a few regions are considered in a model. Since AD often encompasses multiple brain regions, a 3D ROI-based method with sufficient interpretability can be a suitable solution. Subject-level methods, containing only one sample per patient, generally have very few samples for a complex task like AD detection. While there is no exact recipe for determining a suitable method or input format, generally, larger and more complex models are expected to perform better. In the study by Elharrouss et al. in 2022, DenseNet-121 and ResNet 101 were found to have a complexity of 0.525a and 7.6 Giga Floating Point Operations per Second (GFLOPs). AlexNet's complexity is ten times greater than ResNet-101, with first 1 error rates of 25.02% and 19.87%, respectively; a 5.15% reduction in first 1 error rate means a fourteenfold increase in complexity.

CONCLUSION

Compared to CNNs, one of the most significant advantages of autoencoders is that they are an unsupervised learning method, unlike CNNs which require labeled data to function. However, autoencoders learn to capture as much information as possible, but the captured information may not be relevant to solving the problem. If the most relevant information to a problem consists of only a small portion of the input, autoencoders can lose much of this information. Image transformers, after a costly preprocessing step, perform better than CNNs in some image classification tasks. Performance and complexity should be balanced, and the most suitable model should be selected according to hardware conditions and application requirements. The flat CNN architecture has learned sufficient distinguishing features to differentiate classes in the dataset. Transformer-based components added to hybrid structures have introduced additional complexity to the model, but this complexity has not resulted in a performance increase; on the contrary, it has led to a decrease in accuracy. This shows that transformer-based structures are not suitable for every problem, and CNN-based approaches can produce more stable results, especially in limited datasets. Furthermore, although Transformer-based architectures have recently attracted significant attention in medical imaging, their advantages over CNN-based models remain limited in the context of Alzheimer's disease datasets, which are typically small in size. While Transformers have shown strong performance in large-scale natural image tasks, their effectiveness in medical imaging is constrained by data scarcity and increased computational requirements. In particular, the high spatial redundancy present in 3D MRI data enables CNN-based models to effectively capture local structural patterns with fewer parameters and greater stability. In contrast, incorporating Transformer-based components, especially within hybrid architectures, often introduces additional model complexity without yielding consistent performance improvements. In some cases, this added complexity may even lead to a decline in accuracy. These observations indicate that Transformer-based approaches are not universally suitable for all problems. Instead, model selection should consider the trade-off between performance and computational cost. For current Alzheimer's disease classification tasks, CNN-based methods remain more robust, efficient, and practical, particularly under limited data and hardware constraints.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was not required for this study as it does not involve human participants, animal subjects, or identifiable personal data.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: AG, NB; Design: AG, NB; Control: AG, NB; Resources: AG, NB; Materials: AG, NB; Data Collection and/or Processing: AG, NB; Analysis and/or Interpretation: AG, NB; Literature Review: AG, NB; Writing the Article: AG, NB; Critical Review: AG, NB.

REFERENCES

Abrol, A., Bhattarai, M., Fedorov, A., Du, Y., Plis, S., & Calhoun, V. (2020). Deep residual learning for neuroimaging: An application to predict progression to Alzheimer's disease. *Journal of Neuroscience Methods*, *339*, 108701. https://doi.org/10.1016/j.jneumeth.2020.108701

Aderghal, K., Khvostikov, A., Krylov, A., Benois-Pineau, J., Afdel, K., & Catheline, G. (2018). Classification of Alzheimer disease on imaging modalities with deep CNNs using cross-modal transfer learning. *2018 IEEE 31st International Symposium on Computer-Based Medical Systems (CBMS)*, 345-350. https://doi.org/10.1109/CBMS.2018.00067

Afzal, S., Maqsood, M., Nazir, F., Khan, U., Aadil, F., Awan, K. M., ... & Song, O. Y. (2019). A data augmentation-based framework to handle class imbalance problem for Alzheimer's stage detection. *IEEE Access, 7*, 115528-115539. https://doi.org/10.1109/ACCESS.2019.2932786

Ahmad, M. (2024). EfficientNetV2 and MobileNetV2-based lightweight deep learning framework for Alzheimer's disease classification. *Scientific Reports*, *14*, 11234. https://doi.org/10.1038/s41598-024-61234-x

Alzheimer's Association. (2015). 2015 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *11*(3), 332-384. https://doi.org/10.1016/j.jalz.2015.02.003

Alzheimer's Association. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *12*(4), 459-509. https://doi.org/10.1016/j.jalz.2016.03.001

Arafa, D. A., Moustafa, H. E. D., Ali, H. A., Ali-Eldin, A. M., & Saraya, S. F. (2024). A deep learning framework for early diagnosis of Alzheimer's disease on MRI images. *Multimedia Tools and Applications, 83*(2), 3767-3799. https://doi.org/10.1007/s11042-023-15738-7

Ardalan, Z., & Subbian, V. (2022). Transfer learning approaches for neuroimaging analysis: a scoping review. *Frontiers in Artificial Intelligence, 5*, 780405. https://doi.org/10.3389/frai.2022.780405

Avants, B. B., Tustison, N., & Song, G. (2009). Advanced normalization tools (ANTs). *Insight Journal*, *2*, 1-35.

Basaia, S., Agosta, F., Wagner, L., Canu, E., Magnani, G., Santangelo, R., ... & ADNI. (2019). Automated classification of Alzheimer's disease and mild cognitive impairment using a single MRI and deep neural networks. *NeuroImage: Clinical*, *21*, 101645. https://doi.org/10.1016/j.nicl.2018.101645

Bi, X. A., Hu, X., Wu, H., & Wang, Y. (2020). Multimodal data analysis of Alzheimer's disease based on clustering evolutionary random forest. *IEEE Journal of Biomedical and Health Informatics*, *24*(10), 2973-2983. https://doi.org/10.1109/JBHI.2020.2975767

Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules*, *25*(24), 5789. https://doi.org/10.3390/molecules25245789

Chawla, N. V., Bowyer, K. W., Hall, L. O., & Kegelmeyer, W. P. (2002). Smote: synthetic minority over-sampling technique. *Journal of artificial intelligence research*, *16*, 321-357. https://doi.org/10.1613/jair.953

Chen, Y., Wang, L., Ding, B., Shi, J., Wen, T., Huang, J., & Ye, Y. (2024). Automated Alzheimer's disease classification using deep learning models with Soft-NMS and improved ResNet50 integration. *Journal of Radiation Research and Applied Sciences, 17*(1), 100782. https://doi.org/10.1016/j.jrras.2023.100782

Dadar, M., Manera, A. L., Ducharme, S., & Collins, D. L. (2022). White matter hyperintensities are associated with grey matter atrophy and cognitive decline in Alzheimer's disease and frontotemporal dementia. *Neurobiology of Aging*, *111*, 54-63. https://doi.org/10.1016/j.neurobiolaging.2021.11.002

Devlin, J., Chang, M. W., Lee, K., & Toutanova, K. (2019). "BERT: pretraining of deep bidirectional transformers for language understanding," in NAACL HLT 2019-2019 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies-Proceedings of the Conference, Vol. 1 (Minneapolis, MN), 4171-4186.

Ding, Y., Sohn, J. H., Kawczynski, M. G., Trivedi, H., Harnish, R., Jenkins, N. W., ... & ADNI. (2019). A deep learning model to predict a diagnosis of Alzheimer disease by using 18F-FDG PET of the brain. *Radiology*, *290*(2), 456-464. https://doi.org/10.1148/radiol.2018180926

Dosovitskiy, A., Beyer, L., Kolesnikov, A., Weissenborn, D., Zhai, X., Unterthiner, T., ... & Houlsby, N. (2020). An image is worth 16x16 words: transformers for image recognition at scale. *arXiv preprint arXiv:2010.11929.*

Ebrahimi, A., Luo, S., & ADNI. (2021). Convolutional neural networks for Alzheimer's disease detection on MRI images. *Journal of Medical Imaging*, *8*(2), 024503. https://doi.org/10.1117/1.JMI.8.2.024503

Elharrouss, O., Akbari, Y., Almaadeed, N., & Al-Maadeed, S. (2022). Backbones-review: feature extraction networks for deep learning and deep reinforcement learning approaches. arXiv Preprint arXiv:2206.08016.

Ellis, K. A., Bush, A. I., Darby, D., De Fazio, D., Foster, J., Hudson, P., ... & AIBL. (2009). The Australian imaging, biomarkers and lifestyle (AIBL) study of aging. *International Psychogeriatrics*, *21*(4), 672-687. https://doi.org/10.1017/S104161020900911X

Farooq, A., Anwar, S., Awais, M., & Rehman, S. (2017). A deep CNN based multi-class classification of Alzheimer's disease using MRI. *2017 IEEE International Conference on Imaging Systems and Techniques (IST)*, 1-6. https://doi.org/10.1109/IST.2017.8261460

Farooq, A., Anwar, S., Awais, M., and Alnowami, M. (2017). "Artificial intelligence based smart diagnosis of Alzheimer's disease and mild cognitive impairment." *In 2017 International Smart Cities Conference, ISC2 2017 (Institute of Electrical and Electronics Engineers Inc.).* https://doi.org/10.1109/ISC2.2017.8090871

Feng, W., Halm-Lutterodt, N. V., Tang, H., Mecum, A., Mesregah, M. K., Ma, Y., ... & ADNI. (2020). Automated MRI-based deep learning model for detection of Alzheimer's disease process. *International Journal of Neural Systems*, *30*(6), 2050032. https://doi.org/10.1142/S012906572050032X

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774-781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Han, Y. F., & Kaushik, B. (2020). Computer vision technique for neuro-image analysis in neurodegenerative diseases: A survey. *2020 International Conference on Emerging Smart Computing and Informatics (ESCI)*, 346-350. https://doi.org/10.1109/ESCI48226.2020.9167645

Han, Y. F., & Kaushik, B. (2021). Neuro-image classification for prediction of Alzheimer's disease using machine learning techniques. *Machine Intelligence and Data Science Applications*, 483-493. https://doi.org/10.1007/978-981-33-4046-6_40

He, K., Chen, X., Xie, S., Li, Y., Doll, P., & Girshick, R. (2021). Masked Autoencoders are Scalable Vision Learners New Orleans, LA: IEEE. https://doi.org/10.1109/CVPR52688.2022.01553

He, K., Zhang, X., Ren, S., & Sun, J. (2016). Deep residual learning for image recognition. *Proceedings of the IEEE CVPR*, 770-778. https://doi.org/10.1109/CVPR.2016.90

Hızır, L., Ramírez, J., Gorriz, J. M., Brahim, A., Segovia, F., & ADNI. (2015). Early diagnosis of Alzheimer's disease based on PLS, PCA and segmented MRI images. *Neurocomputing*, *151*, 139-150. https://doi.org/10.1016/j.neucom.2014.09.070

Hosseini-Asl, E., Gimel'farb, G., & El-Baz, A. (2016a). Alzheimer's Disease Diagnostics by a Deeply Supervised Adaptable 3D Convolutional Network Frontiers in BioscienceLandmark.

Hosseini-Asl, E., Keynton, R., & El-Baz, A. (2016b). "Alzheimer's disease diagnostics by adaptation of 3D convolutional network." *Proceedings-International Conference on Image Processing, ICIP (Phoenix, AZ),* 126-130. https://doi.org/10.1109/ICIP.2016.7532332

Hu, S., Yu, W., Chen, Z., & Wang, S. (2020). "Medical image reconstruction using generative adversarial network for Alzheimer disease assessment with class-imbalance problem." *In 2020 IEEE 6th International Conference on Computer and Communications (ICCC) (Chengdu: IEEE),* 1323-1327. https://doi.org/10.1109/ICCC51575.2020.9344912

Huang, G., Liu, Z., Van Der Maaten, L., & Weinberger, K. Q. (2017). Densely connected convolutional networks. *Proceedings of the IEEE CVPR*, 4700-4708. https://doi.org/10.1109/CVPR.2017.243

Hür, G. (2021). PRISMA kontrol listesi 2020 güncellemesi. *Online Türk Sağlık Bilimleri Dergisi*, *6*(4), 603-605. https://doi.org/10.26453/otshbd.941914

Islam, J., & Zhang, Y. (2018). Brain MRI analysis for Alzheimer's disease diagnosis using an ensemble system of deep convolutional neural networks. *Brain Informatics*, *5*(2), 2. https://doi.org/10.1186/s40708-018-0080-3

Jack, C. R., Jr., Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., ... & ADNI. (2008). The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging*, *27*(4), 685-691. https://doi.org/10.1002/jmri.21049

Jain, R., Jain, N., Aggarwal, A., & Hemanth, D. J. (2019). Convolutional neural network based Alzheimer's disease classification from magnetic resonance brain images. *Cognitive Systems Research*, *57*, 147-159. https://doi.org/10.1016/j.cogsys.2018.12.017

Jain, R., Jain, N., Aggarwal, A., & Hemanth, D. J. (2019). Convolutional neural network based Alzheimer's disease classification from magnetic resonance brain images. *Cognitive Systems Research*, *57*, 147-159. https://doi.org/10.1016/j.cogsys.2018.12.015

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782-790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Khan, N. M., Abraham, N., & Hon, M. (2019). Transfer learning with intelligent training data selection for prediction of Alzheimer's disease. *IEEE Access 7*, 72726-72735. https://doi.org/10.1109/ACCESS.2019.2920448

Khedher, L., Ramírez, J., Górriz, J. M., Brahim, A., & Segovia, F. (2015). Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented mri images. *Neurocomputing, 151*, 139-150. https://doi.org/10.1016/j.neucom.2014.09.072

Korolev, S., Safiullin, A., Belyaev, M., & Dodonova, Y. (2017). Residual and plain convolutional neural networks for 3D brain MRI classification. *2017 IEEE ISBI*, 835-838. https://doi.org/10.1109/ISBI.2017.7950647

Krizhevsky, A., Sutskever, I., & Hinton, G. E. (2017). ImageNet classification with deep convolutional neural networks. *Communications of the ACM*, *60*(6), 84-90. https://doi.org/10.1145/3065386

Kundaram, S. S., & Pathak, K. C. (2021). Deep learning based Alzheimer's disease detection. *4th International Conference on Microelectronics, Computing and Communication Systems*, 587–597. https://doi.org/10.1007/978-981-15-5546-6_52

LaMontagne, P. J., Benzinger, T. L. S., Morris, J. C., Keefe, S., Hornbeck, R., Xiong, C., ... & ADNI. (2019). OASIS-3: Longitudinal neuroimaging, clinical, and cognitive dataset for normal aging and Alzheimer disease. *medRxiv*. https://doi.org/10.1101/2019.12.13.19014902

Lebedev, A. V., Westman, E., Van Westen, G. J., Kramberger, M. G., Lundervold, A., Aarsland, D., ... & ADNI. (2014). Random forest ensembles for detection and prediction of Alzheimer's disease. *NeuroImage: Clinical*, *6*, 115-125. https://doi.org/10.1016/j.nicl.2014.08.016

LeCun, Y., Bottou, L., Bengio, Y., & Haffner, P. (1998). Gradient-based learning applied to document recognition. *Proceedings of the IEEE*, *86*(11), 2278-2323. https://doi.org/10.1109/5.726791

Li, F., Tran, L., Thung, K. H., Ji, S., Shen, D., & Li, J. (2015). A robust deep model for improved classification of AD/MCI patients. *IEEE Journal of Biomedical and Health Informatics*, *19*(5), 1610-1616. https://doi.org/10.1109/JBHI.2015.2429556

Lian, C., Liu, M., Zhang, J., & Shen, D. (2020). Hierarchical fully convolutional network for joint atrophy localization and alzheimer's disease diagnosis using structural MRI. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *42(4)*, 880-893. https://doi.org/10.1109/TPAMI.2018.2889096

Lim, B. Y., Lai, K. W., Haiskin, K., Kulathilake, K. A. S. H., Ong, Z. C., Hum, Y. C., ... & ADNI. (2022). Deep learning model for prediction of progressive MCI to Alzheimer's disease using structural MRI. *Frontiers in Aging Neuroscience*, *14*, 876202. https://doi.org/10.3389/fnagi.2022.876202

Lin, W., Tong, T., Gao, Q., Guo, D., Du, X., Yang, Y., ... & Alzheimer's Disease Neuroimaging Initiative. (2018). Convolutional neural networks-based MRI image analysis for the Alzheimer's disease prediction from mild cognitive impairment. *Frontiers in Neuroscience*, *12*, 777. https://doi.org/10.3389/fnins.2018.00777

Liu, J., Li, M., Luo, Y., Yang, S., Li, W., & Bi, Y. (2021). Alzheimer's disease detection using depthwise separable convolutional neural networks. *Computer Methods and Programs in Biomedicine*, *203*, 106417. https://doi.org/10.1016/j.cmpb.2021.106417

Liu, M., Li, F., Yan, H., Wang, K., Ma, Y., Shen, L., ... & Alzheimer's Disease Neuroimaging Initiative. (2020). A multi-model deep convolutional neural network for automatic hippocampus segmentation and classification in Alzheimer's disease. *NeuroImage 208*, 116459. https://doi.org/10.1016/j.neuroimage.2019.116459

Liu, M., Zhang, D., & Shen, D. (2016). Relationship induced multi-template learning for diagnosis of Alzheimer's disease and mild cognitive impairment. *IEEE Transactions on Medical Imaging*, *35*(6), 1463-1474. https://doi.org/10.1109/TMI.2016.2515025

Liu, M., Zhang, J., Adeli, E., & Shen, D. (2018). Landmark-based deep multi-instance learning for brain disease diagnosis. *Medical Image Analysis*, *43*, 157-168. https://doi.org/10.1016/j.media.2017.10.005

Liu, S., Cai, W., Pujol, S., Kikinis, R., and Feng, D. (2014). "Early diagnosis of Alzheimer's disease with deep learning," *In 2014 IEEE 11th International Symposium on Biomedical Imaging (Beijing: IEEE),* 1015-1018. https://doi.org/10.1109/ISBI.2014.6868045

Malone, I. B., Cash, D., Ridgway, G. R., MacManus, D. G., Ourselin, S., Fox, N. C., ... & ADNI. (2013). MIRIAD–public release of a multiple time point Alzheimer's MR imaging dataset. *NeuroImage*, *70*, 33–36. https://doi.org/10.1016/j.neuroimage.2012.12.044

Marcus, D. S., Fotenos, A. F., Csernansky, J. G., Morris, J. C., & Buckner, R. L. (2010). Open Access series of imaging studies: Longitudinal MRI data. *Journal of Cognitive Neuroscience*, *22*(12), 2677–2684. https://doi.org/10.1162/jocn.2009.21407

Marcus, D. S., Wang, T. H., Parker, J., Csernansky, J. G., Morris, J. C., & Buckner, R. L. (2007). Open access series of imaging studies (OASIS): Cross-sectional MRI data. *Journal of Cognitive Neuroscience*, *19*(9), 1498-1507. https://doi.org/10.1162/jocn.2007.19.9.1498

Moradi, E., Pepe, A., Gaser, C., Huttunen, H., & Tohka, J. (2015). Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. *NeuroImage*, *104*, 398–412. https://doi.org/10.1016/j.neuroimage.2014.10.002

Murugan, S., Venkatesan, C., Sumithra, M. G., Gao, X. Z., Elakkiya, B., Akila, M., & Manoharan, S. (2021). Demnet: a deep learning model for early diagnosis of alzheimer diseases and dementia from mr images. *IEEE Access 9*, 90319-90329. https://doi.org/10.1109/ACCESS.2021.3090474

Nasir, A., Tamur, M., & Azhar, A. (2021). Computer-aided COVID-19 diagnosis and comparison of deep learners using augmented CXR. *Journal of X-Ray Science and Technology*, *30*(1), 1-21. https://doi.org/10.3233/XST-210967

Odusami, M., Maskeliunas, R., Damaševicius, R., and Krilavicius, T. (2021). Analysis of features of Alzheimer's disease: detection of early stage from functional brain changes in magnetic resonance images using a finetuned resnet18 network. *Diagnostics, 11*, 1071. doi: 10.3390/diagnostics11061071

Padmavathi, B., Deeksha, R., Darshitha, H., & Ashwath, B. (2023). Alzheimer classification using Deep Learning technique. *Journal of Survey in Fisheries Sciences, 10*(3S), 2854-2864.

Payan, A., and Montana, G. (2015). "Predicting Alzheimer's disease: a neuroimaging study with 3D convolutional neural networks." *In ICPRAM 2015-4th International Conference on Pattern Recognition Applications and Methods,* Vol. 2 (Lisbon), 355-362.

Poloni, K. M., & Ferrari, R. J. (2022). Automated detection, selection and classification of hippocampal landmark points for the diagnosis of Alzheimer's disease. *Computer Methods and Programs in Biomedicine*, *214*, 106581. https://doi.org/10.1016/j.cmpb.2021.106581

Qiu, S., Joshi, P. S., Miller, M. I., Xue, C., Zhou, X., Karjadi, C., ... & Kolachalama, V. B. (2020). Development and validation of an interpretable deep learning framework for Alzheimer's disease classification. *Brain, 143*, 1920-1933. https://doi.org/10.1093/brain/awaa137

Rao, P., & Kumar, S. (2025). Real-time Alzheimer's stage detection using YOLOv11 and 3D-MobiBrainNet with MRI-DTI data fusion. *IEEE Transactions on Medical Robotics and Bionics*, *7*(1), 42-56.

Sait, S. (2024). Multi-class classification of Alzheimer's disease using a hybrid ResNet152V2 and Inception-Transformer model. *Journal of Real-Time Image Processing*, *21*(3), 88-105. https://doi.org/10.1007/s11554-024-01442-y

Sarraf, S., DeSouza, D. D., Anderson, J., Tofighi, G., & ADNI. (2017). DeepAD: Alzheimer's disease classification via deep convolutional neural networks using MRI and fMRI. *bioRxiv*, 070441. https://doi.org/10.1101/070441

Shi, J., Zheng, X., Li, Y., Zhang, Q., & Ying, S. (2018). Multimodal neuroimaging feature learning with multimodal stacked deep polynomial networks. *IEEE Journal of Biomedical and Health Informatics*, *22*(1), 173–183. https://doi.org/10.1109/JBHI.2017.2655720

Simonyan, K., & Zisserman, A. (2015). Very deep convolutional networks for large-scale image recognition. *3rd ICLR*, 1–14.

Srivastava, S., Ahmed, R., & Khare, S. K. (2021). Alzheimer hastalığı ve farklı yaklaşımlarla tedavisi: Bir gözden geçirme. *European Journal of Medicinal Chemistry*, *216*, 113320. https://doi.org/10.1016/j.ejmech.2021.113320

Stoleru, G. I., & Iftene, A. (2023). Transfer learning for Alzheimer's disease diagnosis from MRI slices: a comparative study of deep learning models. *Procedia Computer Science, 225*, 2614-2623. https://doi.org/10.1016/j.procs.2023.10.253

Suk, H. I., & Shen, D. (2013). Deep learning-based feature representation for AD/MCI classification. *MICCAI 2013*, 583–590. https://doi.org/10.1007/978-3-642-40763-5_72

Suk, H. I., Lee, S. W., & Shen, D. (2014). Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis. *NeuroImage*, *101*, 569-582. https://doi.org/10.1016/j.neuroimage.2014.06.077

Suk, H. I., Lee, S. W., & Shen, D. (2015). Latent feature representation with stacked auto-encoder for AD/MCI diagnosis. *Brain Structure and Function*, *220*(2), 841-859. https://doi.org/10.1007/s00429-013-0687-3

Suk, H. I., Lee, S. W., & Shen, D. (2017). Deep ensemble learning of sparse regression models for brain disease diagnosis. *Medical Image Analysis*, *37*, 101-113. https://doi.org/10.1016/j.media.2017.01.008

Suk, H. I., Lee, S. W., Shen, D., & ADNI. (2016a). Deep sparse multi-task learning for feature selection in Alzheimer's disease diagnosis. *Brain Structure and Function*, *221*(5), 2569-2587. https://doi.org/10.1007/s00429-015-1059-z

Suk, H. I., Wee, C. Y., Lee, S. W., & Shen, D. (2016b). State-space model with deep learning for functional dynamics estimation in resting-state fMRI. *NeuroImage*, *129*, 292-307. https://doi.org/10.1016/j.neuroimage.2016.01.005

Szegedy, C., Ioffe, S., Vanhoucke, V., & Alemi, A. A. (2017). Inception-v4, Inception-ResNet and the impact of residual connections on learning. *Thirty-First AAAI Conference*, 4278-4284. https://doi.org/10.1609/aaai.v31i1.11231

Szegedy, C., Liu, W., Jia, Y., Sermanet, P., Reed, S., Anguelov, D., ... & Rabinovich, A. (2015). Going deeper with convolutions. *Proceedings of the IEEE CVPR*, 1-9. https://doi.org/10.1109/CVPR.2015.7298594

Szegedy, C., Vanhoucke, V., Ioffe, S., Shlens, J., & Wojna, Z. (2016). Rethinking the inception architecture for computer vision. *Proceedings of the IEEE CVPR*, 2818-2826. https://doi.org/10.1109/CVPR.2016.308

Ungar, L., Altmann, A., & Greicius, M. D. (2014). Apolipoprotein E, gender, and Alzheimer's disease: An overlooked, but potent and promising interaction. *Brain Imaging and Behavior*, *8*(2), 262–273. https://doi.org/10.1007/s11682-013-9272-x

Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A. N., ... & Polosukhin, I. (2017). Attention is all you need. *Advances in Neural Information Processing Systems*, *30*.

Wang, H., Shen, Y., Wang, S., Xiao, T., Deng, L., Wang, X., ... & ADNI. (2019). Ensemble of 3D densely connected convolutional network for diagnosis of MCI and Alzheimer's disease. *Neurocomputing*, *333*, 145-156. https://doi.org/10.1016/j.neucom.2018.12.018

Wang, S. H., Phillips, P., Sui, Y., Liu, B., Yang, M., & Cheng, H. (2018). Classification of Alzheimer's disease based on eight-layer CNN with LReLU and max pooling. *Journal of Medical Systems*, *42*(5), 85. https://doi.org/10.1007/s10916-018-0932-7

Wang, S., Wang, H., Shen, Y., & Wang, X. (2018). Automatic recognition of MCI and Alzheimer's disease using ensemble based 3D DenseNet. *2018 17th IEEE ICMLA*, 517-523. https://doi.org/10.1109/ICMLA.2018.00084

Wen, J., Thibeau-Sutre, E., & Diaz-Melo, M. (2020). Convolutional neural networks for classification of Alzheimer's disease: overview and reproducible evaluation. *Medical Image Analysis*, *63*, 101694. https://doi.org/10.1016/j.media.2020.101694

Yang, Z., & Liu, Z. (2020). The risk prediction of Alzheimer's disease based on the deep learning model of brain 18F-FDG PET. *Saudi Journal of Biological Sciences*, *27*(2), 659-665. https://doi.org/10.1016/j.sjbs.2019.12.004

Zhang, J., Zheng, B., Gao, A., Feng, X., Liang, D., & Long, X. (2021). A 3D densely connected convolution neural network with connection-wise attention mechanism. *Magnetic Resonance Imaging*, *78*, 119-126. https://doi.org/10.1016/j.mri.2021.02.001

Zhang, J., Zheng, B., Gao, A., Feng, X., Liang, D., & Long, X. (2021). A 3D densely connected convolution neural network with connection-wise attention mechanism for Alzheimer's disease classification. *Magnetic Resonance Imaging*, *78*, 119-126. https://doi.org/10.1016/j.mri.2021.02.001

Zhao, X., Ang, C. K. E., Acharya, U. R., & Cheong, K. H. (2021). Application of AI techniques for the detection of Alzheimer's disease using structural MRI images. *Biocybernetics and Biomedical Engineering*, *41*(2), 456-473. https://doi.org/10.1016/j.bbe.2021.03.004

Zhao, Z., Chuah, J. H., Lai, K. W., Chow, C. O., Gochoo, M., Dhanalakshmi, S., ... & Wu, X. (2023). Conventional machine learning and deep learning in Alzheimer's disease diagnosis using neuroimaging: a review. *Frontiers in Computational Neuroscience*, *17*, 1038153. https://doi.org/10.3389/fncom.2023.1038153

Zhou, L., Wang, S. H., & Zhang, Y. D. (2022). Alzheimer's disease identification via deep learning: a review. *International Journal of Imaging Systems and Technology*, *32*(4), 1145-1165. https://doi.org/10.1002/ima.22723