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Master’s Degree Thesis

Diagnosis of Alzheimer’s Disease using Effective Deep Learning Approach

Graduate School of Chosun University

Department of Information and Communication Engineering

Vyshnavi Ramineni

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효과적인 딥러닝 접근법을 이용한
알츠하이머병 진단

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Advisor: Prof. Goo-Rak Kwon

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비슈나비 라미네니

지도 교수: 권구락

정보통신공학과

조선대학교

알츠하이머병(AD)은 경도 인지 장애를 동반한 신경 퇴행성 질환으로 기억력 저하, 행동 장애, 자기 관리 능력 저하 등을 유발한다. 이러한 문제를 해결하기 위해서 조기진단은 중요하며, 조기 발견을 위해 뇌영상 촬영법을 가장 많이 사용한다. 최근 가중치 영상을 기반으로 하는 다양한 차원 분류 기법이 등장하고 있으며, 그 중에서 T1-가중치 영상은 알츠하이머병, 초기 경도 인지 장애(EMCI), 후기 경도 인지 장애(LMCI) 및 정상 대조군 환자를 구별하기 위해 개발되었다.

본 논문에서는 자기공명영상에서 알츠하이머병을 검출하기 위해 유용한 바이오마커를 추출하며, 모델의 복잡성을 줄이기 위해 기계학습 모델을 사용하고, 알츠하이머병을 4단계로 분류하기 위하여 딥러닝 모델을 제안한다.

초기 방법으로 모델의 복잡성을 완화하고 오버피팅 문제를 해결하기 위한 기계 학습 기법을 활용하고자 한다. 이를 위해 주성분 분석(PCA)과 제한된 볼츠만 머신(RBM)을 결합한 향상된 특징 선택 방법과 래퍼 특징 방법을 적용한다. 이 결합된 접근법은 차원을 축소하고 적절한 특징을 선택하는데 있어서 중요한 역할을 한다.

본 연구는 알츠하이머병 진단을 위하여 구조적 자기 공명 영상(sMRI) 이미지의 활용에 중점을 두었다. 다중 클래스 분류 실험을 통해 모델의 성능을 평가하는 것이 주요 목적이다.

계산의 복잡성을 줄이기 위하여 합성곱 신경망(CNN)을 사용하며, 기존 방법과 비교하여 이 방법은 우수한 결과를 얻을 수 있다. 제안하는 모델은 Residual Network에서 Skip Connection과 Visual Geometry Group을 적용한 CNN 모델이다. 기존의 다른 모델에 비해 낮은 복잡도와 적은 매개변수를 사용하여 향상된 정확도를 달성하였다. 결과는 매개변수, 정확도, 특이성, 회수율 및 F1 점수를 고려하여 비교하였다. 제안된 모델은 정확도와 특이성이 각각 95.67% 및 97.34%의 결과값을 가진다.

Abstract

Diagnosis of Alzheimer’s Disease using effective Deep Learning Approach

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Alzheimer’s disease (AD) is a neurodegenerative disease with mild cognitive impairment, causing memory loss, behavioral issues, and poor self-care. Early diagnosis is crucial for interventions, and neuroimaging is a promising area for early detection. Recently, Various dimensional classification techniques based on weighted T1-Weighted images have been developed to distinguish between AD, early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and normal control patients.

Machine learning techniques to reduce the model complexity by traditional models. In this thesis, I have used the deep learning method that has been proposed to extract useful Alzheimer’s disease biomarkers from magnetic resonance images and classify brain imaging into the 4 stages of Alzheimer’s disease.

In this thesis, the initial approach involved the utilization of machine learning techniques aimed at mitigating model complexity, addressing a prevalent overfitting concern. To accomplish this, an enhanced feature selection method, combining Principal Component Analysis (PCA) and Restricted Boltzmann Machine (RBM), alongside a wrapper feature method, was applied. This combined approach was instrumental in reducing dimensionality and selecting the most pertinent features.

This study focused on the utilization of structural Magnetic Resonance Imaging (sMRI) images for the diagnosis of Alzheimer's disease. The primary objective was to assess the model's performance in classification through multi-class classification experiments.

The method uses the convolutional network to reduce the computational complexity and produces superior results compared to the existing methods. The proposed model is the Convolutional neural network that used the visual Geometry Group with the skip connection from the residual network with this proposed model we have achieved better accuracy with a less complex model and fewer parameters compared with other models that existed. The results are compared by noting the parameters, accuracy, specificity, recall, and F1 score. The proposed model shows the accuracy and specificity as 95.67% and 97.34% respectively1

1. Introduction

1.1 Motivation

The most prevalent type of dementia, Alzheimer's disease impairs memory and impairs our ability to recognize our surroundings. The number impacted is currently over 50 million and is projected to rise to 10 million by 2050[1], [2]. Memory loss occurs within a few weeks to months and is the primary indication of dementia, a collection of symptoms brought on by brain damage[3]. Alzheimer's disease diagnosis is still insufficient because of illnesses or changes in the body and mind.

Using clinical observations and cognitive tests, significant attempts have been undertaken to identify and diagnose this illness early on. Numerous studies have used positron emission tomography (PET) and magnetic resonance imaging (MRI) to emphasize the prevalence of dementia. [4] as indicators of dementia in particular cases of Alzheimer's disease (AD). The brain's shrinking in comparison to a healthy brain can be used to measure it. Large-scale multimodal neuroimaging data integration for disease fining has become difficult because to rapid advances in neuroimaging techniques. Consequently, there is growing interest in deep learning and computational machine learning approaches for integrative analysis [5]. By combining large-scale speed, deep learning is a promising technique for Alzheimer's disease diagnosis and healthcare quality improvement. It greatly enhances medical applications by helping with training and illness prediction, recognizing diagnostic subjects and settings, and exposing patterns in data. Because of this, a lot of research is investigating the potential of deep learning and machine learning methods for Alzheimer's disease characterization and detection[6].

1.2 Research Objectives

In the study of health care using digital tools, deep learning has the unique ability to solve a massive scale. Machine learning and deep learning models to create an architecture is time-consuming and computationally seeks help from predefined feature engineering. Moreover, Researchers are investigating simplified deep learning (DL) algorithms as an alternative to restrained Machine learning (ML). Deep learning[7] a technique involving multiple processing layers, has significantly improved by using a backpropagation algorithm to discover intricate structures in large data sets, and deep convolutional neural networks have revolutionized the processing of images.

Deep learning has gained a lot of attention in medical image processing for analysis and classification. All the achievements have gained my research interest, to improve the CNN [8] based system for AD diagnosis. Considering this my study started with machine learning and deep learning in medical image processing. The study of the research is identified as follows:

- In the study, the dataset is collected and analyzed from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database taken image type is Pre-processed Structural Magnetic Resonance Imaging, for machine learning, the aim resolves the problem with overfitting and make the model complex free by using feature selection strategies which helps to categorize individual subjects.
- For deep learning, the aim is to understand and classify the single convolutional network and later on with provide the less computationally less expensive and effective model foe diagnosis of Alzheimer's disease in 4 classes, AD, health brain, EMCI and late mild cognitive impairment .

1.3 Contributions

The effectiveness of machine learning algorithms in Alzheimer's disease classification has been a subject of extensive debate. However, researchers continually seek ways to identify features that can enhance the accuracy of AD diagnosis through machine learning models. In this study, we present the following key components:

- Feature Extraction: We focused on extracting subcortical and cortical features from brain images using Free Surfer, a widely-used tool in neuroimaging research.

- Feature Reduction and Selection: We introduced a combination of feature reduction and selection algorithms, integrating Principal Component Analysis (PCA) with Restricted Boltzmann Machine (RBM) and wrapper methods. This approach was designed to address challenges related to overfitting and model accuracy.
- Evaluation of Classifier Performance: To diagnose Alzheimer's disease, we carried out a thorough analysis of several machine learning classifiers, such as Support Vector Machine, k-Nearest Neighbors, and Random Forest.
- Deep Learning: In several medical image processing applications, deep learning has shown to be remarkably successful. To better the practical identification of Alzheimer's disease, we presented an upgraded CNN in this context.
- Enhancement of Efficiency: We investigated the convolutional layer's computational efficiency, focusing on conventional convolutional layers that have a depth-wise convolutional structure. This method attempted to increase model accuracy while lowering the total number of parameters and related expenses.
- Feature Extraction Model: Our proposed model excels in extracting valuable features from input data without the need for extensive pre-processing, delivering strong performance.

- Comparison with Baseline Models: We compared our proposed method with established models like ResNet-50 and VGG. Notably, our proposed model achieved superior accuracy with fewer parameters and excelled in other parameter indices.

1.4 Organization of Thesis

1. **Chapter 2** provides background information on Alzheimer's disease, the arrangement of datasets, diagnosis techniques, and past research.
2. **Chapter 3** provides the proposed machine learning and deep learning models.
3. **Chapter 4** provides results and evaluation of the proposed models.
4. **Chapter** 5 provides summary and conclusion of thesis.

1. Background

2.1 Alzheimer's Disease

Alzheimer's disease stands as the preeminent etiological factor contributing to dementia, characterized by a neurodegenerative pathology within the brain that precipitates a constellation of debilitating symptoms, foremost among them memory impairment and cognitive dysfunction of a magnitude sufficient to impede daily functioning. Notably, AD represents a pervasive affliction, accounting for an overwhelming 60-80%[9] of all documented dementia cases, thereby underscoring its prominence in the landscape of cognitive disorders.

Within the context of developed nations, Alzheimer's disease assumes an imposing economic burden, standing out as one of the costliest neurodegenerative ailments. An estimated 26.6 million people worldwide were suffering from Alzheimer's disease as of 2006[10], and predictions show a concerning trend. whereby, by the year 2050, a disconcerting 1 in 85 individuals will succumb to its grasp.

The troubling reality is that more than two-thirds of dementia sufferers live in low- and middle-income countries, which are expected to have a significant increase in dementia cases soon as these areas continue their rapid development trajectory. This upcoming increase poses many complex challenges, the most significant of which is the fact that Alzheimer's disease patients in these nations heavily rely on unofficial networks of caregivers. As a result, effectively providing treatment and care becomes increasingly difficult as the disease's prevalence rises. From a fiscal standpoint, Alzheimer's disease exacts a substantial toll, amounting to approximately 1.01[11] percent of the global Gross National Product. Worrisomely, things are predicted to get worse in the years to come, with an estimated 85% [12]increase in global societal costs predicted by 2030, assuming no changes to relevant background variables occur in between.

I must emphasize that, despite the fact that some Alzheimer's disease symptoms may appear to be similar to normal aging-related cognitive changes, it is vital to understand that dementia in general and Alzheimer's disease specifically do not represent normal or innate aspects of aging. As dementia progresses, its clinical manifestations follow a gradual trajectory. As of right now, Alzheimer's disease cannot be completely cured; instead, the main goals are to slow down the illness's progression, improve symptom presentation, treat behavioral issues, and optimize overall quality of life.

However, currently available pharmacological therapies may temporarily halt the unstoppable advance of dementia when the condition's indicators are recognized earlier on. It is worth noting that the pursuit of more efficacious treatments, preventive strategies, and, ultimately, a cure constitutes a paramount, long-term aspiration[13]. Early diagnosis, in this context, emerges as a pivotal determinant, offering prospects of more favorable therapeutic outcomes. Despite the substantial body of research dedicated to Alzheimer's disease, the pressing imperative to develop a reliable diagnostic tool endures, reflecting the ongoing complexities and challenges inherent to the condition's diagnosis and treatment.

2.2 Magnetic Resonance Imaging

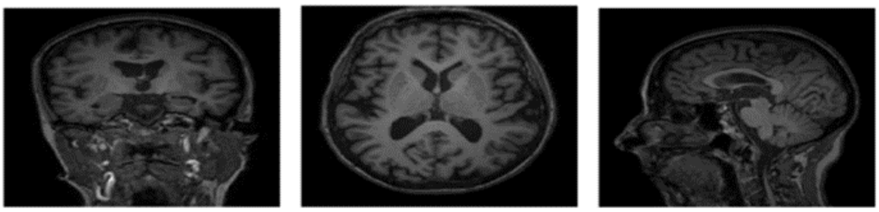
Magnetic Resonance Imaging (MRI) stands as a pivotal clinical imaging modality in radiology, facilitating comprehensive assessments of physiological states in both health and pathology, along with the visualization of anatomic structures. Through precise manipulation of radio waves, magnetic field gradients, and strong magnetic fields, MRI generates intricate images of body structures. Structurally, MRI employs these elements to construct detailed representations of internal organs, offering invaluable insights into their composition and spatial relationships. The strength and configuration of magnetic fields, coupled with precisely orchestrated magnetic field gradients and radiofrequency waves, collaborate seamlessly to create high-fidelity portrayals of anatomical structures.

Most important significance, structural Magnetic Resonance Imaging exemplifies a non-invasive imaging modality, characterized by its ability to produce three-dimensional anatomical scans with exceptional clarity and resolution. This capability is achieved without subjecting patients to the risks of ionizing radiation. This attribute renders sMRI an indispensable tool for medical practitioners, serving as a cornerstone for the identification, diagnosis, and longitudinal monitoring of a diverse spectrum of medical conditions and diseases. Magnetic Resonance Imaging is a crucial clinical imaging modality in radiology, enabling comprehensive assessments of physiological states in health and pathology, as well as the visualization of anatomic structures. Precise manipulation of radio waves, magnetic field gradients, and strong magnetic fields allows MRI to generate intricate images of body structures.

Structurally, MRI utilizes these components to construct detailed representations of internal organs, providing invaluable insights into their composition and spatial relationships. The strength and configuration of magnetic fields, in conjunction with precisely orchestrated magnetic field gradients and radiofrequency waves, collaborate seamlessly to create high-fidelity portrayals of anatomical structures.

Significantly, structural Magnetic Resonance Imaging represents a non-invasive imaging modality known for producing three-dimensional anatomical scans with exceptional clarity and resolution. This capability is achieved without exposing patients to the risks of ionizing radiation, rendering sMRI an indispensable tool for medical practitioners. It serves as a cornerstone for the identification, diagnosis, and longitudinal monitoring of a diverse spectrum of medical conditions and diseases.

The resulting pictures display various grayscale tones that are distinguished by variations in tissue thickness and water content. T1-weighted imaging, a fundamental MRI technique, yields images that exhibit distinct patterns based on the density of tissues. Notably, tissues with minimal hydrogen protons, such as dense bone and air, are rendered in dark hues, thereby manifesting as comparatively black regions. Conversely, tissues abundant in hydrogen protons, such as fat, the brain MRI images of various stages are shown as follows figure 2.1:



(1) axial (2) sagittal (3) coronal

Figure 2.1 Brain MRI images from the ADNI database of three planes.

The pixel values within the images, each representing a specific voxel, are assigned varying shades of gray contingent upon their respective signal strengths. In this quantification, a grayscale spectrum spanning 255 discrete levels is employed, with pixel values ranging from 0, indicative of complete blackness, to 255, signifying complete whiteness. This gradation facilitates the detailed depiction and discrimination of diverse anatomical structures and tissues within the MRI images.

2.3 Database Organization

This section acknowledges the pivotal role played by an organization dedicated to enhancing the comprehension of Alzheimer's disease and facilitating the global research community by curating and disseminating clinical datasets. Without their invaluable support and contributions, the undertaking of this thesis would have been rendered exceedingly challenging. The Alzheimer's Disease Neuroimaging Initiative is the organization to which this article refers. It is a long-standing and groundbreaking research project that is carefully planned to support the development of clinical, imaging, genetic, and biochemical markers intended for the early detection and long-term observation of Alzheimer's disease. Commencing its six-year-long exploration in 2004, ADNI commenced with a cohort comprising 400 individuals diagnosed with Mild Cognitive Impairment (MCI), 200 with early-stage Alzheimer's disease, and an equivalent number of cognitively intact control subjects.

Subsequently, during the period spanning 2009 to 2011, ADNI underwent a pivotal expansion known as AGNI-GO, a phase that incorporated an additional 200 participants afflicted with early MCI, each subjected to meticulous biomarker assessments at the nascent stages of the disease. This pivotal evolution of ADNI signifies a momentous stride towards the development of refined diagnostic methodologies that bear the potential to not only defer the progression of Alzheimer's disease but also, ultimately, proffer avenues for its prevention. For those seeking further in-depth information regarding ADNI's mission, datasets, and research activities, comprehensive details can be accessed on the ADNI official website: https://ida.loni.usc.edu/

2.4 Machine Learning

The Alzheimer's Disease Neuroimaging Initiative is a pioneering and longstanding research project designed to facilitate the development of markers—clinical, imaging, genetic, and biochemical—for early detection and long-term monitoring of Alzheimer's disease. At its essence, ADNI is a scientific endeavor focused on instructing computers to mimic human cognition, autonomously refining their learning processes through exposure to real-world data and empirical observations. Central to the architecture of a machine learning algorithm is its learning system, a constituent responsible for comprehending and adapting to patterns within the provided data[14]. The follow of Machine learning will be as follows according to figure 2.2.

Within the domain of machine learning, three overarching paradigms emerge: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning concerns itself with labeled training data, wherein input instances are associated with corresponding target outputs.

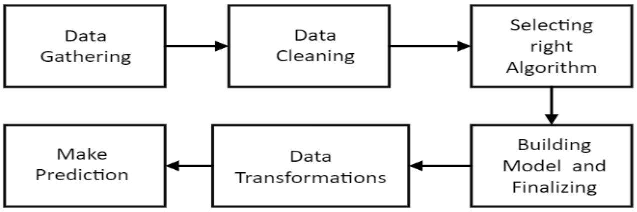


Figure 2. 2 Working process of Machine Learning.

Contrastingly, unsupervised learning grapples with unlabeled data, striving to elucidate underlying structure or patterns without the guidance of predefined output labels. Reinforcement learning, resembling a dynamic agent navigating an environment, centers on the pursuit of predefined objectives through a series of actions, adapting behavior based on received rewards, all while lacking explicit instructions regarding proximity to goal attainment.

Supervised and unsupervised learning encompass a variety of machine learning models and algorithms, each grounded in distinct a priori assumptions addressing the inherently ill-posed nature of the problems they tackle. The limitations of training data availability contribute to challenges such as imprecise mapping, data insufficiency, and intrinsic noise[14]. These issues necessitate diverse assumptions critical for tailoring learning processes effectively. The concept of inductive bias plays a pivotal role, representing a set of priors or expectations that guide learning algorithms in generalizing beyond observed training instances. This bias, also known as learning bias, significantly influences how the model extrapolates from provided training data to unseen inputs, shaping the model's predictive capabilities. At the core of machine learning is error minimization, exemplified by approaches like mean squared error and least mean squares. These processes iteratively refine the model's parameters, or weights, aiming to reduce discordance between predicted values and actual observations in the training dataset. This iterative refinement enhances the model's ability to generalize to novel data points.

The present study is centered upon a thorough exploration of supervised learning methodologies, specifically focusing on Random Forest, k-Nearest Neighbor, and Support Vector Machine techniques. Additionally, it encompasses the application of unsupervised learning methods for data preprocessing, including Principal Component Analysis and Restricted Boltzmann Machines. This comprehensive investigation seeks to elucidate the utility and performance of these machine learning approaches within the context of the research domain.

2.4.1 Deep Learning

Deep learning, a subset of representation learning, employs computational models characterized by multiple layers of processing units that acquire and represent input data at varying levels of abstraction, mirroring the complex processes of human information analysis. These models, known as deep neural networks or artificial neural networks, autonomously discern optimal data representations directly from raw input, eliminating the need for prior feature selection. Utilizing a hierarchical architecture with layers of varying complexity, deep learning enables sequential nonlinear transformations to raw data, resulting in higher-level features that are less susceptible to input noise.

Deep neural networks comprise interconnected layers that cooperatively recognize, classify, and characterize elements within input data. Forward propagation, involving computations passing through the network layers, incorporates visible layers for input and output. Backpropagation, complementing forward propagation, uses algorithms like gradient descent to compute prediction errors and adjust the network's weights and biases, facilitating model training. This iterative application enhances prediction precision over time.

While this outlines the fundamental structure of deep neural networks, it's crucial to note the intricate landscape of deep learning, encompassing diverse neural network architectures tailored to specific domains. Examples include Convolutional Neural Networks for computer vision tasks and image classification, surpassing human performance in object identification in 2015, and Recurrent Neural Networks (RNNs) adept at handling sequential or time-series data in natural language processing and speech recognition domains.

Convolutional Neural Network

Convolutional Neural Networks stand as widely utilized deep learning architectures with applications spanning image recognition, mobile vision, object identification, and surveillance. Inspired by biological organisms' optic nerves, CNNs employ interconnected neurons for precise data analysis. However, their computational demands and data storage requirements pose challenges to computational performance and energy efficiency. These challenges, not adequately addressed by conventional processors, have led to the proposal of various CNN accelerators across different hardware platforms. A typical CNN comprises two main components: feature extraction and classification. The feature extractor processes input data, extracting invariant features like edges and corners, mapping them to a low-dimensional vector output feature map. These aggregated characteristics then feed into the classifier, a fully connected neural network determining the input's class or category through computational and sub-sampling layers. The operational flow of a CNN for processing an input image and performing object classification based on feature values is illustrated in the accompanying figure 2.3 [15].

CNN layers are categorized into three fundamental types:

- Convolutional Layer
- Pooling Layer
- Fully Connected Layer

Convolutional layer: The initial layer within a convolutional network is the convolutional layer, serving as the locus for most computational operations.

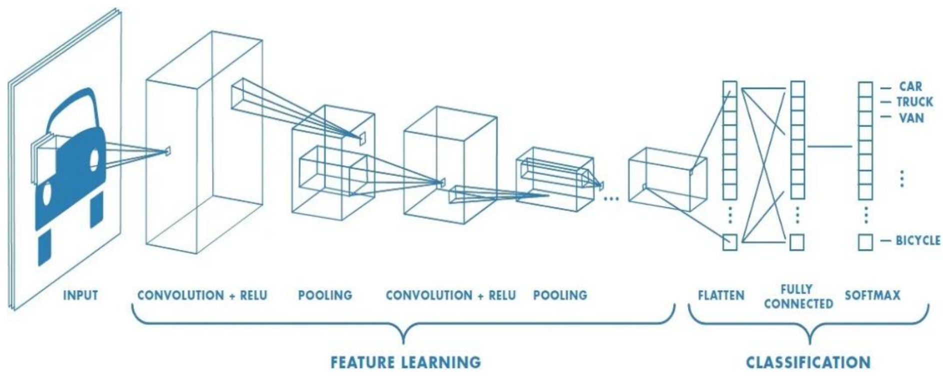


Figure 2.3 Convolutional neural Network structure[15].

This layer necessitates input data, a filter (commonly referred to as a kernel), and a feature map, among other components. Consider an input resembling a color image, constituting a 3D matrix of pixels, embodying height, width, and depth dimensions, corresponding to the RGB color space.

The feature detector, a weighted 2D array, serves as a window onto an image segment with a typical 3x3 matrix configuration determining the receptive field size. Applied to the image through dot product computations between the input pixels and the filter, the filter shifts iteratively with a predefined stride until traversing the entire image. This sequence produces a feature map, activation map, or convolved features, encapsulating extracted salient information.

Pooling layer: Pooling layers, alternatively termed down sampling layers, serve as dimensionality reduction mechanisms, curtailing the number of elements within the input. Analogous to the convolutional layer, pooling entails the traversal of a filter across the input; however, this filter operates without any weights. Instead, the kernel employs an aggregation function to populate the output array using values from the receptive field. Pooling falls into two primary categories.

Max Pooling: This method selects the pixel with the highest value within the receptive field as the filter progresses across the input. Max pooling is the preferred strategy compared to average pooling.

Average Pooling: It computes the mean value within the receptive field as the filter traverses the input, transmitting this value to the output array.

Although pooling layers entail some information loss, they confer several advantages to CNNs, including complexity reduction, computational efficiency enhancement, and the mitigation of overfitting risks.

Fully Connected layer: The fully connected layer, constituting the final segment of a CNN architecture, differs from earlier layers by establishing direct connections between every node in the output layer and every pixel value in the input image. In contrast to prior layers, which connected nodes to specific input areas, fully connected layers create direct connections between every node. Crucial for classification tasks utilizing features from earlier layers, this layer employs Rectified Linear Unit (ReLU) functions in convolutional and pooling layers for input categorization, while SoftMax activation functions are common in fully connected layers. This yields probability scores ranging from 0 to 1 for each class.

2.5 Related Work

Many techniques have surfaced in the last few years to improve the classification performance in the field of neuroimaging, considering the benefits provided by ML and DL models. This paper investigates various machine learning classification frameworks employed in neuroimaging, alongside approaches based on Convolutional Neural Networks.

2.5.1 Classification of Alzehimer’s Disease using ML

Recently, binary and multi-class classification techniques have been used to identify Alzheimer's disease early using a range of machine learning algorithms. For instance, A fully automated classification system based on cortical thickness characteristics was created by Kim et al [16]. and Long et al. [17] investigated regional morphological changes in the brain and discovered that deformations in the amygdala and hippocampus were suggestive of mild cognitive impairment. Additionally, their research showed how crucial diffusive structural changes in the gray matter of the whole brain are in determining the presence of mild to moderate Alzheimer's disease. A linear support vector machine was used to categorize the individuals SVM.

In contrast, Guo et al. [18] proposed a data-saving method for feature extraction that used a multi-kernel support vector machine to classify brain regions and functional magnetic resonance imaging-derived subgraph features. This approach effectively preserved both global topological information and sensitivity to regional brain changes. In contrast, Guo et al. [18] used using independent component analysis to mine the gray matter (GM) for features, white matter (WM) and CSF. Following that, AD was classified using an SVM classification tool. Tong et al. [19] also developed a multiple-instance learning technique based on features produced by graph-mapping isolated MRI voxel patches for the classification of dementia. To distinguish AD patients from normal control volunteers, an SVM classifier was employed.

Subsequently, Zhang et al [20] devised a multimodal classification strategy that leveraged biomarkers, such as Cerebrospinal fluid (CSF) and positron emission tomography (PET) are used to differentiate between AD (or MCI) and normal control. sMRI, positron emission tomography, and cerebrospinal fluid, to distinguish between AD (or MCI) and normal control participants via a multiple-kernel SVM. Their proposed model demonstrated high accuracy for AD classification and promising accuracy for MCI classification in binary classification scenarios. Using principal component analysis for feature extraction and support vector machines for classification, In a different study, Salvatore et al. [7]employed MR images as a biomarker for early Alzheimer's disease classification. Their study effectively identified the entorhinal cortex, basal ganglia, gyrus rectus, precuneus, cerebellum, and hippocampal regions as crucial areas involved in the pathophysiological mechanisms of Alzheimer's disease using a nested 20-fold cross-validation technique.

Moreover, Baron et al. [21] introduced a voxel-based feature extraction method for diagnostics that makes use of statistical voxel features. Furthermore, Gupta et al. [22] classified atrophic states, such as AD, normal control, and asymptomatic Alzheimer's disease, by incorporating combined voxel-based morphometry (VBM) features, cortical and subcortical volumetric features (CSC), and hippocampal volumetric features using machine learning algorithms like SVM, K-nearest neighbor, and Random Forest.

2.5.2 CNN appraches for Alzheimer's Disease classification

Understand of pervious study, with supporting paper. 461 MRI scans were taken from the ADNI dataset by Jyoti Islam et al.[23]who then cropped the images to improve them. Using patches from the horizontal, frontal, and median planes, the author created a patch-wise feature extraction method that produced a 93.18 percent accuracy when put into a 2D ConvNet deep learning framework ensemble.

818 MRI images from the ADNI collection were subjected to both a machine learning technique and a deep learning technique by Weiming Lin et al. [24]. The pre-processing workflow applied to these images included age correction, registration, and skull stripping. In addition, 151 patches were extracted from each MRI for additional improvement. The data obtained by passing Free Surfer on the original scans were coupled with additional features acquired by feeding 2.5 dimensional patches to ConvNet and submitting it to extreme machine learning. Despite the fact that this method relied on a manual feature extraction process, the simulation results were accurate to 79.9%.

Pre-processed MRI scans (using Free surfer) are converted to 2D slices in the Rachna Jain et al [25]. study. The 32 most knowledgeable slices are then selected and cropped to create 3 Channel slices, which are then fed into the VGG-16 model and combined with dense layers to produce a binary and three-class Alzheimer's categorization. After 4800 slices were taken from the 150 participants in the experiment, the three-class accuracy AD/MCI/NC was 95.73 percent.

Their three-dimensional models (3D-ResNet and 3D-VGG) are widely used in studies to categorize 3D medical pictures. Additionally, the application of 3D CNN was concentrated in the classification of Alzheimer's Disease Neuroimaging Initiative data by Ahsan Hosseini-Asl et al. [26] The biomarkers for several AD classes were found and features extracted from MRIs using a 3D convolutional neural network.

Suggested the diagnostic model AD, which combines major characteristics and spatial data taken from MRIs. It is based on an attention-driven mechanism with a densely linked 3D CNN. The depthwise separable convolution was proposed by J Liu et al. [27] as an alternative to the standard convolution. Their concept was trained using the transfer learning models of GoogLeNet and AlexNet, which drastically lowered the computing cost and parameters.

On the other hand, Liu.J et al. [28] built a CNN-based architecture utilizing the OASIS dataset employing the ADNI data, they obtained 78.02% accuracy for multiclass classification, and 84.65% accuracy for MCI versus CN, which is 72.96% accuracy for AD vs MCI, with 75.2% efficiency for MCI vs CN classifications. Later, they refined their work to use a deep separable convolution model to lower the number of parameters, and they reached 77.79% accuracy by reducing the model's parameters by 87.94% in the same study. Furthermore, to extract characteristics from gray matter MRI images, Xu et al.[29] proposed a modified model of Tresnet architecture in their article. They were able to categorize AD vs. CN with an accuracy of 86.9% and multiple classes with an accuracy of 63.2%.

2. Proposed Method

3.1 Overview

The results of the experiments described in Chapter 1 are presented in this chapter. In the context of this thesis, I have utilized deep learning and machine learning techniques to develop a successful classification strategy that separates Alzheimer's from other diagnostic categories. The chapter is structured into two distinct segments. The initial segment is dedicated to the exposition of the proposed machine learning-based model, while the subsequent portion delves into the discussion of the deep learning-based model.

3.2 ML approach for Alzheimer's disease Classification

The ADNI dataset comprises nearly 6,000 individuals, spanning an age range of 18 to 96 years. From this extensive pool, a selection process was undertaken to preprocess images pertaining to 278 patients in accordance with the ADNI protocol, and these images were employed in the present study. Detailed demographic information regarding the subjects utilized in this investigation is provided in Table 1.

In order to ensure an impartial and rigorous analysis, the dataset was partitioned using a 75/25 ratio. Specifically, 75% of the dataset was designated for training purposes, while the remaining 25% was reserved for testing.

Furthermore, this dataset offers accompanying metadata, which encompasses demographic details such as gender, initial subject weight, age, and diagnostic group for each image. The data employed in the formulation of this research paper was obtained from the ADNI consortium.

Table 1. Demographic representation of all subjects.

Group	Noof Subjects	Age Range
AD	58	76.65 ± 8.6
LMCI	73	72.80 ± 6.9
EMCI	75	74.83 ± 6.1
HC	72	79.83 ± 5.7

AD: Alzheimer's disease; LMCI: Late Mild Cognitive Impairment; EMCI: Early Mild Cognitive Impairment; CN: Normal Control.

3.2.1 Selected Features

In the context of this thesis, Free Surfer Software was employed to extract a pair of volumetric features.

- Cortical Features
- Subcortical Features

3.2.2 Volumetric volumes

The phrase "volumetric feature" pertains to the quantification of volume within designated cerebral regions by summing the voxels encompassed by the delineated region of interest (ROI). In the scope of this research, 930 features were extracted from the cortex and subcortical volumes of each subject's brain utilizing the Free Surfer toolbox.

3.2.3 Cortical and Subcortical dementia

The cerebral cortex, colloquially known as the "cortex," is a prominent brain region crucial for cognitive processes such as language and memory. Cortical dementia conditions, including Alzheimer's disease, frontotemporal dementia, Binswanger's disease, and Creutzfeldt-Jakob disease, manifest as gray matter involvement, leading to symptoms like aphasia, memory loss, and comprehension difficulties. In contrast, subcortical dementias, affecting brain areas below the cortex, primarily impact white matter and include conditions like AIDS dementia complex, Parkinson's dementia, and Huntington's disease

These diseases exhibit cognitive function slowing and personality changes, with intact language and memory functions in the early stages. While most dementia types involve widespread cerebral cortex degeneration, some, termed "subcortical dementia," specifically damage areas beneath the cortex.

3.2.4 Extraction of Features

In all, 930 features from subcortical and cortical segmentation were used in this investigation. Free surfer software has been used to automate workflow which performs the stage of pre-processing step to get the designed result of brain parcellation images of the data of each subject's space. T1-weighted images are taken from the extracting the features in the method where cortical and subcortical preprocessing images are used in this thesis.

3.2.5 Selection of Features

The extracted data have been normalized from the preprocessing – zero mean and variance using scalar $f(x)$. Normalizing the data help clear out the abnormality in the data, by doing so the analysis can be complicated. The normalized matrix of element $x(i, j)$ is given by:

$$x_{norm} = \frac{x(i-j)-mean(x_j)}{std(x_j)} \tag{1}$$

3.2.5.1 Principal Component Analysis

One popular method for reducing the dimensional sample from higher to lower sample/features is Principal Component Analysis. The dimensional feature can be reduced from 2D to 1D plane using this method. Therefore, we have utilized this technique in this case to minimize the feature of both subcortical and cortical features extracted from the free surfer toolbox. Using a starting feature and a linear combination of dataset features in d-dimension space, PCA builds a k-dimensional subspace using k less than d. PC obtains Variables k, all of which are addressed to the maximum, except for the variation, which is already accounted for in all subsequent components.

Below is the formula that can be used for computing PCs(2):

$$Pc_1 = a_1x_1 + a_2x_2 + \cdots \quad (2)$$

PCA can be used extensively for feature selection and just for dimension reduction.

3.2.5.2 Restricted Boltzmann Machine

Restricted Boltzmann Machines are a class of unsupervised learning algorithms within machine learning, excelling in modeling intricate data patterns, particularly in complex modalities like images, speech, and textual information. Architecturally, RBMs consist of a visible layer and a hidden layer with undirected interconnections allowing bi-directional information flow. The "restricted" nature of connections within the same layer streamlines both learning and inference procedures.

Fundamentally, RBMs iteratively adjust connection weights to acquire a probabilistic representation of input data, minimizing the disparity between input and learned distributions. This training process enables RBMs to perform tasks such as dimensionality reduction, feature extraction, collaborative filtering, and data generation. Recognized for capturing intricate data patterns, RBMs find versatile applications in recommendation systems, image recognition, and natural language processing. Additionally, RBMs are foundational in deep learning, contributing to the development of advanced architectures like deep belief networks and deep neural networks.

3.2.5.3 Forward and Backward Feature selection

Forward Feature Selection and Backward Feature Selection represent fundamental techniques applied within the realm of feature selection, a pivotal process in the fields of machine learning and data analysis. These methodologies assume a critical role in augmenting the efficacy and proficiency of diverse modeling and classification endeavors.

a. Forward Feature Selection:

Forward Feature Selection manifests as a systematic procedure, commencing with an empty feature set and iteratively augmenting it with additional features. At each step, it assesses the model's performance following the inclusion of a feature and selects the most pertinent feature based on specific criteria, which may encompass classification accuracy, information gain, or error reduction. This process persists until a predefined termination criterion is satisfied, which could involve reaching a designated feature count or attaining a desired level of model performance.

Within academic discourse, Forward Feature Selection occupies a prominent position as a method of paramount significance for the refinement of feature subsets in machine learning models. Its application is often centered on the identification of the most informative variables that contribute to a model's predictive capabilities, all while mitigating concerns related to overfitting and computational complexity.

b. Backward Feature Selection:

In contrast, Backward Feature Selection initiates with a complete feature set and progressively prunes features based on specific criteria. It adheres to a stepwise methodology, systematically eliminating the least informative features in each iteration. Analogous to Forward Feature Selection, the process concludes upon meeting a termination criterion.

Within academic deliberations, Backward Feature Selection enjoys widespread recognition for its role in simplifying intricate models by preserving exclusively the most relevant features. This method is lauded for its ability to enhance model interpretability, reduce susceptibility to overfitting, and augment computational efficiency.

In the domain of academic research and scholarly publications, both Forward and Backward Feature Selection techniques find comprehensive exploration and are juxtaposed within diverse contexts of machine learning and data analysis tasks. Researchers frequently expound upon these methodologies, their application domains, and their implications for model performance, concurrently engaging in discourse concerning the relative advantages and drawbacks of each approach across varying scenarios.

3.2.6 Classification

To assess the classification accuracy predicated on subcortical and cortical attributes, three distinct and widely recognized classifier algorithms were employed.

3.2.6.1 Random Forest

Random Forest, a prominent ensemble machine learning technique utilized in classification and regression tasks, enhances predictive accuracy and mitigates overfitting by amalgamating predictions from multiple decision trees. Its strength lies in introducing randomness through bootstrapping and feature sampling. Bootstrapping involves random selection of training data subsets, fostering diversity in individual decision trees and reducing the risk of overfitting. Feature randomness is introduced by considering random subsets of features during tree construction, further improving model performance. Renowned for its robustness and effectiveness with complex datasets, Random Forest provides feature importance scores, aiding interpretability. Its versatility spans domains like finance, healthcare, image analysis, and natural language processing. Adaptable to various dataset sizes and scalable on multicore processors or distributed clusters, Random Forest is a reliable and accurate modeling technique, making it a go-to choose for predictive tasks.

3.2.6.2 Support Vector Machine

The Support Vector Machine is a versatile machine learning algorithm, highly applicable to classification and regression tasks. It revolves around the optimization of a hyperplane to segregate data points or make numerical predictions while maximizing the margin, signifying the spatial separation between the data points and the hyperplane. Key facts of SVM by figure 3.1.

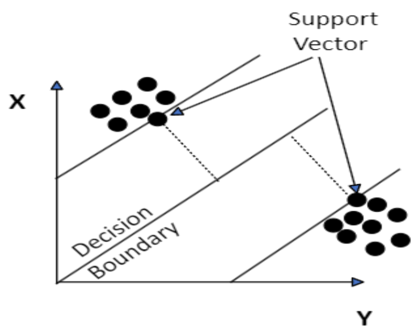


Figure 3. 1 Support Vector Machine.

Epsilon-Support Vector Regression: Predicting numerical values with 'epsilon' controlling prediction error. SVM excels with high-dimensional data, especially in modest to moderate dataset sizes, applied broadly in fields such as image classification, text categorization, and bioinformatics.

3.2.6.3 K-Nearest Neighbors

K-Nearest Neighbors stands as a foundational and intuitively comprehensible machine learning algorithm, adeptly employed in the realms of both classification and regression tasks. Its core operational tenet revolves around the concept of proximity, whereby it ascertains the classification of data points or prognosticates numerical values. This determination is predicated on the consensus of the majority class for classification tasks or the mean values for regression tasks within the local neighborhood of the data points in the feature space. KNN's appeal lies in its inherent simplicity, rendering it an esteemed choice for diverse applications. It particularly shines when the data exhibits inherent spatial locality or clustering characteristics.

3.2.7 Proposed Method

The process is as following:

1. Obtain an already preprocessed dataset that includes subjects with Alzheimer's disease, Early Mild Cognitive Impairment, Late Mild

Cognitive Impairment, and a control group of subjects who are Normal.

2. Utilize the Free Surfer toolbox for the extraction of subcortical and cortical features.
3. Feature normalization
4. Dimension reduction
5. Feature selection
6. Classification of Alzheimer's disease into four distinct groups employing machine learning techniques.

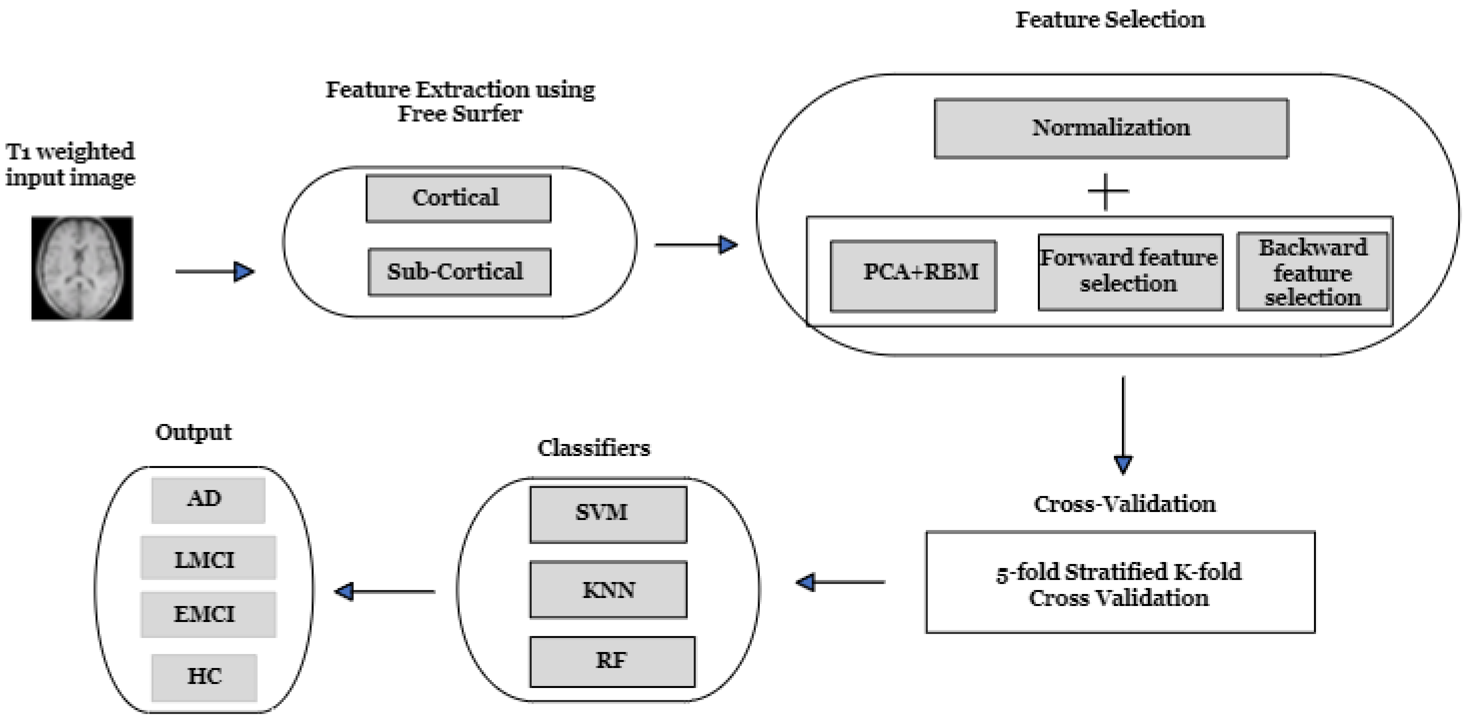
3.3 Architecture

3.3.1 Implementation Details of Machine learning

In the realm of Alzheimer's disease, the integration of computational analysis tools offers promising prospects for early-stage diagnosis. Machine learning plays a pivotal role in healthcare, leveraging computational and statistical techniques to efficiently process vast datasets and identify patterns for diagnostic purposes. Four stages, ranging from MCI to severe AD, are used to identify the disease based on observed morphological changes in both gray and white matter, indicating the disease's stage. This study focuses on using structural MRI and emphasizes cortical and subcortical thickness as biomarkers for AD classification. Feature extraction, utilizing both subcortical and cortical features, incorporates Principal Component Analysis for dimensionality reduction and wrapping methods for effective feature selection. In the context of multi-class classification, traditional machine learning techniques like Support Vector Machine, k-Nearest Neighbor, and Random Forest are evaluated for their efficacy in enhancing accuracy and simplifying model application to medical images. SVM is adept at handling regression, classification, and overfitting issues, while k-NN utilizes labeled data within a straightforward algorithmic framework. This experimental project integrates PCA and RBM to facilitate feature selection in Alzheimer's disease classification. In the integration of PCA and RBM, seeing in the figure 3.2, PCA serves as a conventional technique for reducing the dimensionality of samples, transitioning from higher to lower sample/features dimensions.

Utilizing Principal Component Analysis to reduce dimensional features from 2D to 1D, this method minimizes dimensions for both subcortical and cortical features extracted from the Free Surfer toolbox[30]. PCA maps features from the original dataset in d-dimensional space to a K-dimensional subspace, maximizing variance with each principal component. PCA serves for feature selection and dimension reduction, with its output used as input for Restricted Boltzmann Machine to facilitate feature classification without intricate manual engineering. Forward and Backward feature selection methods are implemented as wrapper-type algorithms, progressively adding, or eliminating features based on performance. In the classification phase, after feature extraction, normalization, and specific feature selection, SVM, K-NN, and RF models discern the presence or absence of Alzheimer's disease. The experiment's workflow encompasses these machine-learning models, implemented using the Scikit-Learn package in Python.

Figure 3. 2 Machine Learning based Proposed Method Architecture.



3.3.2 Implementation Details of Deep learning

The present investigation involved the construction of a two-dimensional (2D) model utilizing three-dimensional (3D) structural magnetic resonance imaging scans acquired from a sample of 600 participants. This sample comprised 150 individuals diagnosed with Alzheimer's disease, 150 with Early Mild Cognitive Impairment, 150 with Late Mild Cognitive Impairment, and 150 cognitively normal individuals. The initial magnetic resonance (MR) pictures were subjected to resampling to attain a resolution of 96 × 96 × 1. The brain fields were demarcated based on certain anatomical orientations (axial, coronal, and sagittal) to facilitate training and testing procedures. Consequently, a dataset consisting of 72,000 feature fields was obtained. Out of the total, 18,000 instances were associated with the AD group, 18,000 with EMCI, 18,000 with LMCI, and 18,000 with the CN group.

During the experimental phase, random partitioning was conducted for each group, resulting in three subsets: Training (70%), validation (10%), and testing (20%). The categorization methods outlined in the proposal was executed using Python 3.9.13, utilizing the Keras library built on the TensorFlow framework. The network parameters were initially randomized, and an optimizer called Adaptive Moment Estimation (Adam) was utilized. In order to address the issue of overfitting, a dropout layer was used. The method under consideration was utilized to perform a multiclass classification task. More specifically, its objective was to differentiate between individuals diagnosed with Alzheimer's disease, those who are cognitively normal, as well as individuals in the early MRI and late MCI stages of mild cognitive impairment.

3.3.2.1 Deep learning Architectures

The VGG-Net model:

This network is a well-known Convolutional Neural Network model that was created at Oxford University in the beginning of 2014 by Simonyan and Zisserman. The 1,000 distinct class images in the ImageNet ILSVRC dataset were used to pretrain the Visual Geometry Group, or VGG. The training dataset consisted of 1.3 million images, with an additional 50,000 images for validation purposes. A specific architectural version of VGG, VGG-19, with 19 deeply interconnected layers, has consistently demonstrated superior performance when compared to other state-of-the-art models.

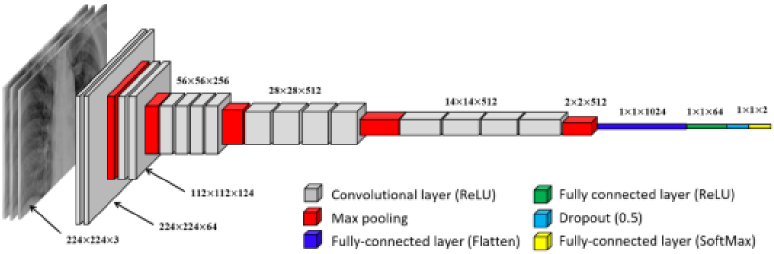


Figure 3. 3 Basic architecture of VGG-Net [31].

Effective feature extraction is made possible by the model architecture of VGG-19, which consists of a few convolutional layers that are strongly and densely linked. Additionally, it uses max pooling instead of down sampling and prior to last classification via the SoftMax function as activation function, as opposed to average pooling. In this work, the VGG-19 baseline model is applied to the ADNI dataset to classify Alzheimer's disease into different stages. The basic architecture of the VGG model is shown visually in the accompanying figure 3.3.

ResNet Model:

During ILSVRC-2015, the Residual Network emerged as the top performer in classification, localization, and detection tasks. Researchers began to explore whether enhancing learning involved merely adding more layers atop an existing network. However, they encountered a challenge known as the degradation problem, where the performance of earlier models, such as VGG, did not improve beyond a certain layer depth but rather worsened. To address this issue, they introduced the concept of the residual function, which serves as the foundational component of a [32]Residual Network (ResNet).

ResNet was directly used in this study based on the 50-layer non-bottleneck architecture. This architecture included links with progressively larger dimensions, such as identity links with padding and projection links utilizing 1x1 filter size convolutions. Using the ADNI dataset, the base model for ResNet is used and residual network skip connection is shown in figure 3.4.

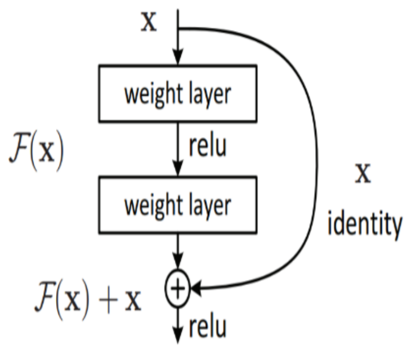


Figure 3. 4 Basic residual network represents the skip connection.

3.3.3 Proposed Model

Convolutional layers are the cornerstones of any deep Convolutional Neural Network, utilizing sophisticated activation functions to produce the best results. The proposed methodology employs a deep CNN to autonomously extract insights from complete brain MRI data and identify Alzheimer's disease.

The suggested workflow is illustrated graphically in figure 3.6, which consists of three main steps: CNN processing, 3D volume partitioning, and brain volume segmentation. Table 2, displays the ADNI subjects utilized in the deep learning technique. Our method presents a simple yet incredibly effective convolutional technique, which concurrently employs standard convolutional layers, depth-wise convolution, and a subsequent skip convolutional layer. This strategy enables the model to learn multifaceted features from brain MRI scans, taking inspiration from the architectural pattern of ResNet.

Table 2. Demographic Representation of ADNI Subjects.

Group	No of Subjects	Age Range	Gender (M/F)
AD	150	73.62 ± 7.6	77/73
LMCI	150	76.34 ± 6.9	91/59
EMCI	150	78.09 ± 8.1	70/80
HC	150	79.56 ± 3.7	84/66

Standard Convolution:

Figure 3.5 shows the typical folding procedure. Here, a standard convolutional layer receives an input feature map I with dimensions $D_f \times D_f \times M$ [40] and outputs an O feature map with dimensions $D_g \times D_g \times N$. Here, D_f denotes the M indicates the number of the input feature map channels, N indicates the number of output value map channels, and the width and height of the input map channels Visual representation was shown in figure 3.5. To extract the features, a convolution kernel with $D_k \times D_k$ dimensions is employed. The convolution kernel's width and height are indicated by the symbol D_k. When going using a feature map I to highlight feature map O, the standard convolution is calculated using the following formula, which is as follows:

$$G_{k,h,n} = \Sigma_{i,j,m} k_{i,j,m,n}.I_{K+i-1,l+j-1,m,} \tag{3}$$

In this case, the convolution kernels are represented by k, the initial feature maps by I, and the outcome feature maps by G. i , j determine where the elements are located within the convolutional kernel. In addition, the elements' positions in the input and output feature maps are indicated by the variables k The parameters for standard convolution are parameter and computed in the following manner:

$$F = M \times N \times D_k^2 \tag{4}$$

$$G = M \times N \times D_k^2 \times D_k^2 \tag{5}$$

The following notations are used in this context: D_f stands for the width and height squared of the input feature map; D_k for the width and height of the convolution kernel; M for the number of channels in the input feature map; N for the number of channels in the output feature map; and F for the total number of model parameters.

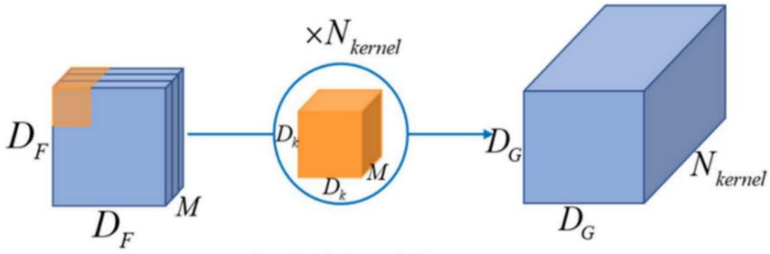


Figure 3. 5 Standard Convolutional Architecture[33].

Proposed model Implementation Details:

Convolutional layers are fundamental components of complex deep Convolutional Neural Networks, utilizing advanced activation functions to enhance performance. The proposed approach utilizes a convolutional neural network will automatically extract features from MRI scans in context of Alzheimer's disease diagnosis. The graphic presented illustrates the suggested pipeline, which consists of 3 main stages: brain measure like volume scaling, 3D volume slicing, and Convolutional neural network processing. Our proposed convolutional method is influenced by the architecture patterns of ResNet and ConvMixer. It follows a simple yet better approach as shown in Figure 3.6 and layer sizing in table 3. The proposed methodology involves the concurrent implementation of a conventional convolutional layer, followed by a skip convolutional layer, which allows the model to capture multi-level characteristics from brain MRI scans.

These MRI scans were initially resampled to a resolution of 96 × 96 × 1. Subsequently, 40 brain regions were generated for each subject, including axial, coronal, and sagittal views, resulting in a total of 72,000 feature fields. These features were distributed as 18,000 for AD, 18,000 for EMCI, 18,000 for LMCI, and 18,000 for NC groups.

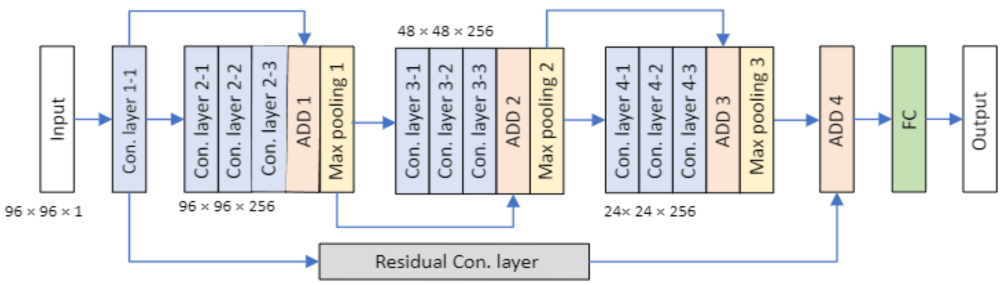


Figure 3. 6 The structure of the suggested model.

3. Results

3.1 Performance Metrics

The evaluation of multi-class classification is conducted through the utilization of the confusion matrix, as presented in Table 3. Model performance is assessed using SVM, KNN, and RF classifiers, with each classifier responsible for predicting the correct number of outputs in the form of a matrix.

Table 3. Proposed Architecture layers.

Layer Type	Size	Input	Output
Con. Layer 1-1	7 × 7 × 256	96 × 96 × 1	96 × 96 × 256
Con. Layer 2-1	7 × 7 × 256	96 × 96 × 256	96 × 96 × 256
Con. Layer 2-2	7 × 7 × 256	96 × 96 × 256	96 × 96 × 256
Con. Layer 2-3	7 × 7 × 256	96 × 96 × 256	96 × 96 × 256
ADD 1		96 × 96 × 256	96 × 96 × 256
Max pooling 1	1 × 1 × 256	96 × 96 × 256	96 × 96 × 256
Batch Normalization	0.4		
Con. Layer 3-1	7 × 7 × 256	96 × 96 × 256	48 × 48 × 256
Con. Layer 3-2	7 × 7 × 256	48 × 48 × 256	48 × 48 × 256
Con. Layer 3-3	7 × 7 × 256	48 × 48 × 256	48 × 48 × 256
ADD 2		48 × 48 × 256	48 × 48 × 256
Max pooling 2	1 × 1 × 256	48 × 48 × 256	48 × 48 × 256
Batch Normalization	0.4		
Con. Layer 4-1	7 × 7 × 256	48 × 48 × 256	24 × 24 × 256
Con. Layer 4-2	7 × 7 × 256	24 × 24 × 256	24 × 24 × 256
Con. Layer 4-3	7 × 7 × 256	24 × 24 × 256	24 × 24 × 256
ADD 3		24 × 24 × 256	24 × 24 × 256
Max pooling 3	1 × 1 × 256	24 × 24 × 256	24 × 24 × 256
Batch Normalization	0.4		
Residual Con. Layer	7 × 7 × 256	96 × 96 × 1	24 × 24 × 256
ADD 4		24 × 24 × 256	24 × 24 × 256
FC	3	256	3

Con. Layer: Convolutional Layer; Residual Con. Layer: Residual Convolutional Layer.

This matrix can be further dissected into distinct components, namely, truly positive (TP), true negative (TN), false positive (FP), and false negative (FN). Below offers a mathematical representation elucidating the comprehension of these calculations. True negative and true positive correspond to the accurate identification of control cases, while false positive and false negative denote instances of incorrect identification. Nonetheless, accuracy may not provide a reliable measure due to the variable class distribution. Therefore, additional metrics, namely precision, recall, and F1-score, are incorporated. Sensitivity, denoted as the capacity to predict group accuracy, and recall, which assesses accuracy in the absence of the group, are included. The F1-score, in turn, represents the harmonic mean of both precision and recall.

In the context of multi-class classifiers, evaluation and accuracy represent pivotal parameters for computing the confusion matrix with table 4.

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \tag{6}$$

$$Specificity = \frac{TN}{TN+FP} \tag{7}$$

$$Sensitivity(Recall) = \frac{TP}{TP+FN} \tag{8}$$

$$Precision = \frac{TP}{TP+FP} \tag{9}$$

Table 4. Multiclass confusion matrix Prediction classification.

Prediction classification					
Actual classification	classes	AD	LMCI	EMCI	HC
	AD	**TP**	F_{AL}	F_{AE}	F_{AH}
	LMCI	F_{LA}	**TP**	F_{LE}	F_{LH}
	EMCI	F_{EA}	F_{EL}	**TP**	F_{EH}
	HC	F_{HA}	F_{HL}	F_{HE}	**TP**

3.2 Results of Machine learning

The outcomes were derived through the implementation of classification methodologies, specifically SVM, K-NN, and RF. These methods relied on the utilization of both cortical and sub-cortical features to yield the results. The classification results obtained using PCA, PCA & RBM, Forward feature selection, and Backward feature selection are presented in tables 5. Upon examining the accuracy, it becomes evident that, in comparison to forward feature selection, backward feature selection demonstrates superior accuracy.

Conducted within a Python environment, the feature selection process in both subcortical and cortical regions, coupled with the experimental classification, demonstrated commendable performance. The proposed model, integrating PCA and RBM with the Random Forest classifier, outperformed, achieving an impressive 88.65% accuracy in multi-class classification. In RF classification, all models, including PCA, PCA and RBM, and forward and backward feature selection, demonstrated strong performance with accuracy rates of 81.49%, 88.65%, 84.45%, and 85.16%. Notably, while wrapping methods promising results, the PCA with RBM approach achieved slightly superior accuracy across all three classifiers. Classifiers.

Table 5 . Results of Machine Learning model.

Classifier's	**PCA**			**PCA and RBM**			**Forward Feature selection**			**Backward Feature selection**		
	ACC %	PRE %	RECA %	ACC %	PRE %	RECA %	ACC %	PRE %	RECA %	ACC %	PRE %	RECA %
SVM	79.48	76.66	84.69	**85.69**	83.39	90.78	80.51	74.68	83.3	83.3	82.31	87.9
K-NN	80.73	78.25	83.67	**83.67**	80.45	89.32	75.9	73.91	79.89	79.89	76.04	84.78
RF	**81.49**	77.62	89.87	**88.65**	85.82	93.23	**84.45**	81.87	88.56	**88.56**	83.33	89.36

ACC: Accuracy; PRE: Precision; RECA: Recall

Table 6. Comparison of methods performance for multi-class classification.

Method	**ACC%**	**SEN%**	**SPE%**	**Precision%**	**F1-score%**
ResNet 50	95.17	**95.15**	96.49	94.77	94.75
VGG 13	91.27	92.31	95.63	91.39	91.32
Proposed Model	**95.67**	94.16	**97.34**	**95.43**	**95.51**

ACC: Accuracy; SEN: sensitivity; SPE: Specificity

4.3 Deep Learning Results

ResNet and VGG Net, both standard models utilized in the study, were compared. Applying standard classification performance metrics, including sensitivity, specificity, precision, F1 score, and accuracy, to ResNet revealed an accuracy of approximately 95.34% (see Table 6). The improved feature propagation and the addition of skip connections are responsible for this higher accuracy. Nevertheless, the suggested model outperformed VGG Network and ResNet, displaying the greatest accuracy of 95.67%. When accounting for other performance metrics, our proposed model outperformed the baseline models. For instance, it exceeded the baseline models with 95.43% precision and 97.34% specificity. ResNet produced a slightly higher sensitivity score of 95.31%, overall, our model performed much better than. The ADNI dataset and the accompanying confusion matrix as shown in figure3.7 displaying the accuracy for the training and validation datasets show how effective our CNN model is in multi-class classification.

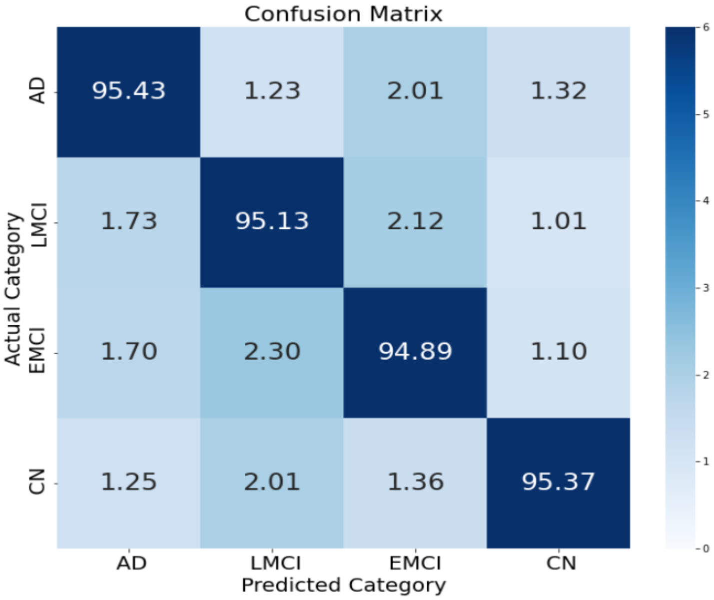


Figure 3. 7 Confusion matrix of the deep learning method.

4. Discussion

Numerous investigations have been conducted to address Alzheimer's disease symptoms and improve early detection. A few classification methods based on T1-weighted images have been presented to differentiate patients into AD, MCI, and HC groups. The most notable use of structural and functional measurements has been in the classification of patients with Alzheimer's disease.

For instance, Liu et al. [41] used ROI methods to extract all the features from the brain, and the multiple kernels boosting (MKBoost) algorithm was used to classify the results. Using a one sMRI modality for dataset, Lie achieved 94.65% accuracy for AD vs. CN, 89.63% accuracy for AD vs. MCI, and 85.79% accuracy for MCI vs. CN classification. However, Sun et al. [42] proposed spatial-anatomical using a SVM method for extraction. To further induce structural sparsity, they added a group lasso penalty. Their method produced classification results of 95.1% accuracy for AD versus CN, 70.8% accuracy for MCI versus CN: 65.7% accuracy for AD versus MCI. Moreover, S. Kadiioury et al [34] presented a semantically labeled PET image feature group classification method, achieving an accuracy of 91.2% for AD vs HC classification. Khajehnejad et al [35] employed a manifold-based semi-supervised learning approach for AD diagnosis, achieving an accuracy rate of 93.86%.

This study aims to improve the accuracy of the model by combining a feature selection technique with previous research. The research explores the application of a combined feature set that includes subcortical volume and cortical thickness for classification in AD, EMCI, LMCI, and HC. Using an effective combined feature selection method, it evaluates the performance of several learning classifiers (Random Forest, K-NN, and SVM). The multi-class classification yielded the following results table 7. Key findings and publishing techniques.

For the implementation of machine learning algorithms in disease classification, preprocessing techniques are typically necessary, making it a time-consuming and computationally intensive task. Thus, researchers have directed their efforts toward developing computer-based systems capable of early-stage Alzheimer's disease detection. CNN-based image classification is increasingly applied in medical disease diagnosis. However, developing an efficient CNN model that yields favorable results is a challenging endeavor. Consequently, this study introduces an approach that prioritizes accuracy and minimizes parameters.

Traditionally, contemporary models concentrated on increasing network depth and complexity to enhance classification performance, often obtained with the vanishing gradient issue. In response, this study proposes a modified convolutional network to address and mitigate the vanishing gradient problem[36], promote feature reuse, and drastically reduce the number of parameters. The CNN network structure incorporates standard convolutional layers along with skip convolutional layers to capture global data features while simplifying model complexity. Moreover, a comparative study is carried out between the suggested model and the current deep learning techniques. Hosseini et al.'s study [37] developed a 3D convolutional based on auto-encoder that produced multi-class classification accuracy of 89.1%. With 99.2% accuracy, Basaia et al. [38] developed a deep learning algorithm based on structural cross-sectional MRI scans for the diagnosis of individual cases of Alzheimer's disease. Aderghal et al [35]relied on a transfer learning scheme with CNN obtaining an accuracy of 91.86%. The table below provides a parameter-wise comparison of various deep learning.

Table 7. Result of deep learning model with comparison.

References	Subjects	No of Samples	Method	ACC %	SEN%	SPEC %
Hosseini et al.,*[26]*	MRI	AD-70, MCI-70, CN-70	3D Con-Auto Encoder	89.10		
Jyoti Islam et al., *[23]*	MRI(OASIS)	416	2D CNN	93.18	94	93
Liu. J et at., *[27]*	MRI(OASIS)	AD-90, MCI-136, CN-266	Multi-Layer Neural Network	78.02	83.21	75.32
Nitika Goenka et al., *[39]*	MRI	AD-70, MCI-224, CN-475	3D CNN	95.37	**97.2**	82.7
Liu. M et al.,*[28]*	MRI	AD-97, MCI-233, CN-119	3D Dense Net	88.90	86.60	90.80
Rachna Jain et al., *[25]*	MRI	AD-50, MCI-50, CN-50	Conventional +DL	**95.73**		
Xu et al., *[29]*	MRI	AD-85, MCI-244, CN-133	Tresnet_L+Sk_module	63.20	84.0	85.40
Min Lin et al., *[24]*	MRI	AD-188, MCI-361, CN-229	3D CNN	79		
This study	MRI	AD-150, LMCI-150, EMCI-150, CN-150	Proposed Method	**95.67**	94.16	**97.34**

AD = Alzheimer’s disease; MCI = mild Cognitive Impairment; CN = Cognitive Normal; LMCI =Late mild Cognitive impairment, EMCI = Early mild cognitive impairment.

5. Conclusion

This thesis leveraged machine learning and deep learning techniques for the classification of Alzheimer's disease and other diagnostic groups using the ADNI dataset. In the context of machine learning, the thesis introduced a novel approach that combines dimension reduction and feature selection methods to effectively predict Alzheimer's disease and healthy groups within the ADNI dataset. An automated toolbox was used to combine subcortical and subcortical features in this method. Three classifiers SVM, KNN, and RF were used to complete the classification task. In all three cases, the experimental results showed promising performance.

In the domain of deep learning, this thesis optimized CNN for 3D whole-brain images, achieving the highest accuracy through a repeated convolutional block network architecture. This proposed method surpassed existing state-of-the-art systems. Notably, the method operates autonomously and at remarkable speed. It provides a means to uncover significant data patterns, validate previous expert findings, aid in diagnostic scenarios, and potentially detect patterns related to diseases beyond Alzheimer's.

Future research endeavors may explore achieving comparable or superior results for pre-processed images that have undergone skull alignment and subtraction. Additionally, there is potential in integrating patient history data to complement the MRI information, informing decision-making, and establishing connections with a patient's background.

References

[1] A. Association, "2015 Alzheimer's disease facts and figures," Alzheimers Dement., vol. 11, no. 3, pp. 332–384, 2015, doi: 10.1016/j.jalz.2015.02.003.

[2] J. A. M. Sidey-Gibbons and C. J. Sidey-Gibbons, "Machine learning in medicine: a practical introduction," BMC Med. Res. Methodol., vol. 19, no. 1, p. 64, Mar. 2019, doi: 10.1186/s12874-019-0681-4.

[3] R. A. Sperling et al., "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," Alzheimers Dement., vol. 7, no. 3, pp. 280–292, May 2011, doi: 10.1016/j.jalz.2011.03.003.

[4] M. A. DeTure and D. W. Dickson, "The neuropathological diagnosis of Alzheimer's disease," Mol. Neurodegener., vol. 14, no. 1, p. 32, Aug. 2019, doi: 10.1186/s13024-019-0333-5.

[5] A. H. Syaifullah, A. Shiino, H. Kitahara, R. Ito, M. Ishida, and K. Tanigaki, "Machine Learning for Diagnosis of AD and Prediction of MCI Progression From Brain MRI Using Brain Anatomical Analysis Using Diffeomorphic Deformation," Front. Neurol., vol. 11, 2021, Accessed: Feb. 02, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fneur.2020.576029

[6] "A Novel Deep Learning Based Multi-class Classification Method for Alzheimer's Disease Detection Using Brain MRI Data | SpringerLink." Accessed: Sep. 20, 2023. [Online]. Available: https://link.springer.com/chapter/10.1007/978-3-319-70772-3_20

[7] T. M. Schouten et al., "Individual classification of Alzheimer's disease with diffusion magnetic resonance imaging," NeuroImage, vol. 152, pp. 476–481, May 2017, doi: 10.1016/j.neuroimage.2017.03.025.

[8] C. Lian, M. Liu, J. Zhang, and D. Shen, "Hierarchical Fully Convolutional Network for Joint Atrophy Localization and Alzheimer's Disease Diagnosis Using Structural MRI," IEEE Trans. Pattern Anal. Mach. Intell., vol. 42, no. 4, pp. 880–893, Apr. 2020, doi: 10.1109/TPAMI.2018.2889096.

[9] C. Wattmo, E. Londos, and L. Minthon, "Risk factors that affect life expectancy in Alzheimer's disease: a 15-year follow-up," Dement. Geriatr. Cogn. Disord., vol. 38, no. 5–6, pp. 286–299, 2014, doi: 10.1159/000362926.

[10] A. Wimo and M. Prince, "Alzheimer's Disease International World Alzheimer Report 2010 The Global Economic Impact of Dementia," 2010.

[11] L. J. Bain et al., "Healthy Brain Aging: A Meeting Report From The Sylvan M. Cohen Annual Retreat Of The University of Pennsylvania

Institute On Aging," Alzheimers Dement. J. Alzheimers Assoc., vol. 4, no. 6, pp. 443–446, Nov. 2008, doi: 10.1016/j.jalz.2008.08.006.

[12] C. R. Jack et al., "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease," Alzheimers Dement. J. Alzheimers Assoc., vol. 14, no. 4, pp. 535–562, Apr. 2018, doi: 10.1016/j.jalz.2018.02.018.

[13] P. Tiraboschi, L. A. Hansen, L. J. Thal, and J. Corey-Bloom, "The importance of neuritic plaques and tangles to the development and evolution of AD," Neurology, vol. 62, no. 11, pp. 1984–1989, Jun. 2004, doi: 10.1212/01.wnl.0000129697.01779.0a.

[14] M. I. Jordan and T. M. Mitchell, "Machine learning: Trends, perspectives, and prospects," Science, vol. 349, no. 6245, pp. 255–260, Jul. 2015, doi: 10.1126/science.aaa8415.

[15] S. Albawi, T. A. Mohammed, and S. Al-Zawi, "Understanding of a convolutional neural network," in 2017 International Conference on Engineering and Technology (ICET), Aug. 2017, pp. 1–6. doi: 10.1109/ICEngTechnol.2017.8308186.

[16] J. P. Kim et al., "Machine learning based hierarchical classification of frontotemporal dementia and Alzheimer's disease," NeuroImage Clin., vol. 23, p. 101811, 2019, doi: 10.1016/j.nicl.2019.101811.

[17] X. Long, L. Chen, C. Jiang, L. Zhang, and Alzheimer's Disease Neuroimaging Initiative, "Prediction and classification of Alzheimer disease based on quantification of MRI deformation," PloS One, vol. 12, no. 3, p. e0173372, 2017, doi: 10.1371/journal.pone.0173372.

[18] H. Guo, F. Zhang, J. Chen, Y. Xu, and J. Xiang, "Machine Learning Classification Combining Multiple Features of A Hyper-Network of fMRI Data in Alzheimer's Disease," Front. Neurosci., vol. 11, 2017, Accessed: Oct. 16, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnins.2017.00615

[19] T. Tong, R. Wolz, Q. Gao, R. Guerrero, J. V. Hajnal, and D. Rueckert, "Multiple instance learning for classification of dementia in brain MRI," Med. Image Anal., vol. 18, no. 5, pp. 808–818, Jul. 2014, doi: 10.1016/j.media.2014.04.006.

[20] D. Zhang, Y. Wang, L. Zhou, H. Yuan, D. Shen, and Alzheimer's Disease Neuroimaging Initiative, "Multimodal classification of Alzheimer's disease and mild cognitive impairment," NeuroImage, vol. 55, no. 3, pp. 856–867, Apr. 2011, doi: 10.1016/j.neuroimage.2011.01.008.

[21] J. C. Baron et al., "In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease," NeuroImage, vol. 14, no. 2, pp. 298–309, Aug. 2001, doi: 10.1006/nimg.2001.0848.

[22] Y. Gupta et al., “Early diagnosis of Alzheimer’s disease using combined features from voxel-based morphometry and cortical, subcortical, and hippocampus regions of MRI T1 brain images,” PloS One, vol. 14, no. 10, p. e0222446, 2019, doi: 10.1371/journal.pone.0222446.

[23] J. Islam and Y. Zhang, “Brain MRI analysis for Alzheimer’s disease diagnosis using an ensemble system of deep convolutional neural networks,” Brain Inform., vol. 5, no. 2, p. 2, May 2018, doi: 10.1186/s40708-018-0080-3.

[24] M. Lin, Q. Chen, and S. Yan, “Network In Network.” arXiv, Mar. 04, 2014. doi: 10.48550/arXiv.1312.4400.

[25] R. Jain, N. Jain, A. Aggarwal, and D. J. Hemanth, “Convolutional neural network based Alzheimer’s disease classification from magnetic resonance brain images,” Cogn. Syst. Res., vol. 57, pp. 147–159, Oct. 2019, doi: 10.1016/j.cogsys.2018.12.015.

[26] E. Hosseini-Asl, R. Keynto, and A. El-Baz, “Alzheimer’s Disease Diagnostics by Adaptation of 3D Convolutional Network,” in 2016 IEEE International Conference on Image Processing (ICIP), Sep. 2016, pp. 126–130. doi: 10.1109/ICIP.2016.7532332.

[27] J. Liu, M. Li, Y. Luo, S. Yang, W. Li, and Y. Bi, “Alzheimer’s disease detection using depthwise separable convolutional neural networks,”

Comput. Methods Programs Biomed., vol. 203, p. 106032, May 2021, doi: 10.1016/j.cmpb.2021.106032.

[28] M. Liu et al., “A multi-model deep convolutional neural network for automatic hippocampus segmentation and classification in Alzheimer’s disease,” NeuroImage, vol. 208, p. 116459, Mar. 2020, doi: 10.1016/j.neuroimage.2019.116459.

[29] Z. Xu, H. Deng, J. Liu, and Y. Yang, “Diagnosis of Alzheimer’s Disease Based on the Modified Tresnet,” Electronics, vol. 10, no. 16, Art. no. 16, Jan. 2021, doi: 10.3390/electronics10161908.

[30] V. Ramineni and G.-R. Kwon, “Diagnosis of Alzheimer’s Disease using Wrapper Feature Selection Method,” Smart Media J., vol. 12, no. 3, pp. 30–37, 2023, doi: 10.30693/SMJ.2023.12.3.30.

[31] M. Y. Kamil, “A deep learning framework to detect Covid-19 disease via chest X-ray and CT scan images,” Int. J. Electr. Comput. Eng. IJECE, vol. 11, no. 1, Art. no. 1, Feb. 2021, doi: 10.11591/ijece.v11i1.pp844-850.

[32] K. He, X. Zhang, S. Ren, and J. Sun, “Deep Residual Learning for Image Recognition.” arXiv, Dec. 10, 2015. Accessed: Oct. 16, 2023. [Online]. Available: http://arxiv.org/abs/1512.03385

[33] “A Basic Introduction to Separable Convolutions | by Chi-Feng Wang | Towards Data Science.” Accessed: Nov. 21, 2023. [Online]. Available:

https://towardsdatascience.com/a-basic-introduction-to-separable-convolutions-b99ec3102728

[34] S. H. Nozadi, S. Kadoury, and null The Alzheimer's Disease Neuroimaging Initiative, "Classification of Alzheimer's and MCI Patients from Semantically Parcelled PET Images: A Comparison between AV45 and FDG-PET," Int. J. Biomed. Imaging, vol. 2018, p. 1247430, 2018, doi: 10.1155/2018/1247430.

[35] M. Khajehnejad, F. H. Saatlou, and H. Mohammadzade, "Alzheimer's Disease Early Diagnosis Using Manifold-Based Semi-Supervised Learning," Brain Sci., vol. 7, no. 8, p. 109, Aug. 2017, doi: 10.3390/brainsci7080109.

[36] I. Tolstikhin et al., "MLP-Mixer: An all-MLP Architecture for Vision." arXiv, Jun. 11, 2021. doi: 10.48550/arXiv.2105.01601.

[37] E. Hosseini-Asl, R. Keynton, and A. El-Baz, "Alzheimer's disease diagnostics by adaptation of 3D convolutional network," in 2016 IEEE International Conference on Image Processing (ICIP), Sep. 2016, pp. 126–130. doi: 10.1109/ICIP.2016.7532332.

[38] S. Basaia et al., "Automated classification of Alzheimer's disease and mild cognitive impairment using a single MRI and deep neural networks," NeuroImage Clin., vol. 21, p. 101645, 2019, doi: 10.1016/j.nicl.2018.101645.

[39] N. Goenka and S. Tiwari, “AlzVNet: A volumetric convolutional neural network for multiclass classification of Alzheimer’s disease through multiple neuroimaging computational approaches,” Biomed. Signal Process. Control, vol. 74, p. 103500, Apr. 2022, doi: 10.1016/j.bspc.2022.103500.

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