Journal of Positive School Psychology http://journalppw.com
2022, Vol. 6, No. 8, 5616-5634

Alzheimer's Diseases Detection By Using MRI Brain Images: A Survey:

Zahraa Sh. Aaraji [1] △, Hawraa H. Abbas [2], Ameer Asady [3]

[1] *College of Engineering, Electrical and Electronic department, University of Kerbala, Kerbala, 65001, Iraq,* *zahraa.sh@s.uokerbala.edu.iq*
[2] *College of Engineering , Electrical and Electronic department, University of Kerbala, Kerbala, 65001, Iraq ,* *hawraa.h@uokerbala.edu.iq*
3 *College of Engineering, Electrical and Electronic department, University of Kerbala, Kerbala, 65001, Iraq* *ameerasady9@gmail.com*

Abstract:

Alzheimer's disease (AD) is one of the most common public health issues the world is facing today. This disease has a high prevalence primarily in the elderly accompanying memory loss and cognitive decline. At present, there is no specific treatment for this disease. Early and accurate diagnosis of AD become a challenging task which many authors have developed numerous computerized automatic diagnosis systems utilizing neuroimaging and other clinical data. These studies have identified the importance of structural differences in brain regions such as the entorhinal cortex, hippocampi, and other brain areas between Alzheimer-affected brain and a healthy brain. Magnetic Resonance Imaging (MRI) scanners have proven the potentiality to study AD-related brain structural variations, consequently, structural MR imaging techniques have been exploited as a significant diagnostic tool when reporting a cognitive decline. The researchers showed promising results not only for excluding non-neurodegeneration causes, but rather to accurately identify AD neurodegenerations. Machine Learning (ML) and subfield deep learning (DL) has become prominent techniques for detecting AD at their early stages. Here, brief literature of the previously adopted AD diagnosis techniques will be reviewed, including traditional diagnosis methods, and advancing to the relevant modern employment of DL in AD diagnosis.

INDEX TERMS: Alzheimer's disease, Beta Amyloids (Aβ), neuroimaging, Structural MRI, Deep Learning, convolution neural network.

I INTRODUCTION:

Dementia is a broader term of brain disease that causes a decline in the person's ability to think, remember, and affects his behavioral abilities in his daily life. Dementia ranges in severity from the mildest stage, when it just begins to affect a person's ability to function, to the most severe stage, when the person is completely reliant on others for his most basic daily activities [1] .

The most common type of dementia is Alzheimer's disease (AD**)**, an age-related neurodegenerative disorder that affects the brain, resulting in cells' death and overall brain volume loss. This leads to cognitive mental problems such as memory loss and confusion; which is one of the most prominent characteristics in Alzheimer's patients [2].

Beta amyloids and tau tangles, abnormal protein deposits in the brain, cause AD by damaging brain cells in the memory and mental functions areas. When more neurons die, entire brain areas shrink, resulting in cognitive function issues, which are the primary symptoms of AD [3]. As the disease

progresses The Damage becomes more diffuse, and the brain shrinks significantly. Because beta-amyloid grows up over time, it will take more than ten years for a patient to notice any symptoms of the disease [4]. According to scientists, the causes seem to be related to a combination of environmental and genetic factors. The most common factors associated with the risk of developing AD are age and some environmental risk factors including smoking, strokes, heart disease, depression, arthritis, and diabetes. A study on over 3000 cases defined a score for a healthy lifestyle including nonsmoking, physical activity, low alcohol consumption, high quality dietary, and engagement in cognitive activities. The study concluded that a high score healthy lifestyle is associated with a lower risk factor of AD [5]. Figure 1 explains the protein deposits in AD compared to a healthy brain.

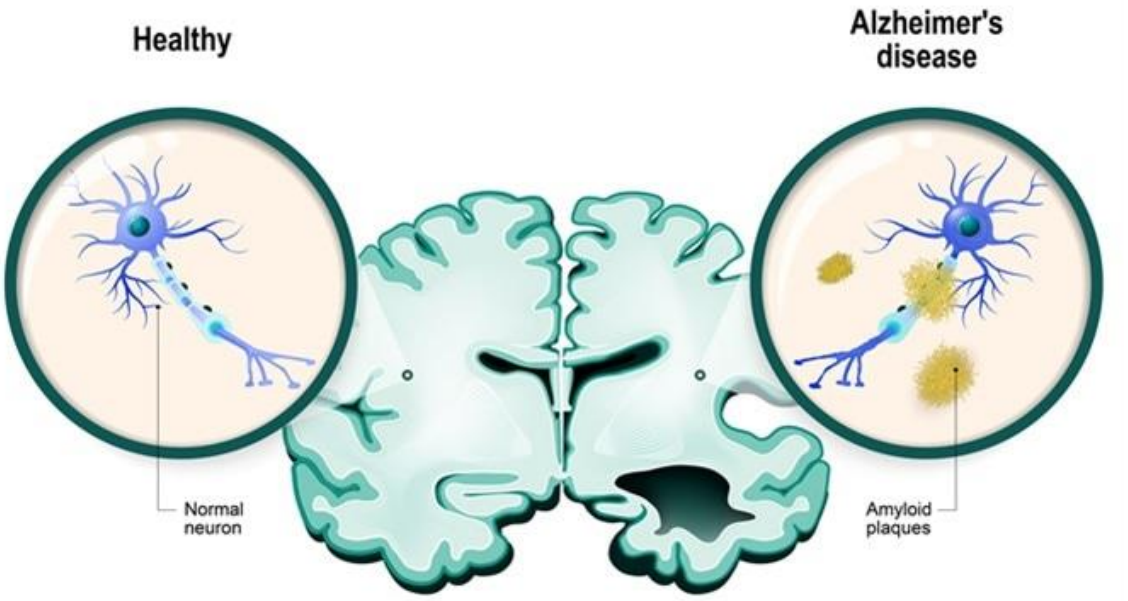


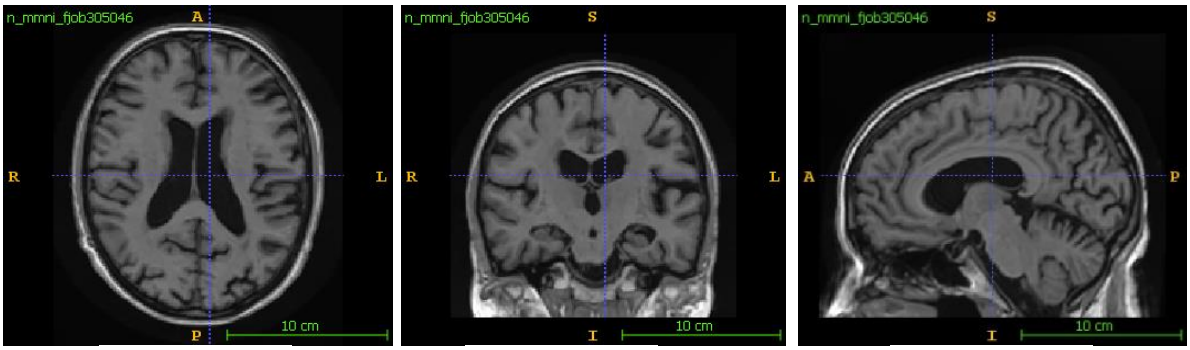
Figure 1 Comparison between a Normal brain and AD brain showing amyloid plaques.

The number of reported AD cases, which contributes more than 60% to all dementia cases, is elevating. AD is considered the sixth leading cause of death in the United States and the fifth-leading cause of death in adults older than 65 years [6]. Based on the updated key facts posted on the World Health Organization (WHO) website, around 50 million people have a form of dementia, with nearly 10 million new cases are reported each year [7]. In 2018, more than 122,000 people died from AD, an increase of 146% from the year 2000 .an estimated 6.3 million American adults over 65 years are living with AD In 2021, with the number expected to more than double by the year 2050 to approximately 14 million individuals. The total healthcare costs for the treatment of AD are expected to be $355 billion in 2021, the costs expected to rise to more than $1.1 trillion by 2050 [5] [6].

Because of AD affected brain suffers from degradation for as long as a decade or more before showing any evident symptoms. This fact encouraged researchers to start a detailed investigation on the progression of the disease through the visualized pathological variations that emerged across the demented brain using different types of imaging techniques. These investigations aimed to predict the disease's presence before showing its advanced symptoms. Early and accurate detection helps to slow down the disease progression and reduce the costs of treatment because it enables people with dementia and their families to better prepare for the progression of the disease

Advanced neuroimaging techniques, such as magnetic resonance imaging (MRI), Computed Tomography (CT), and positron emission tomography (PET), have been developed and used to identify structural and molecular biomarkers

associated with AD, this techniques coupled with advanced computational machine learning methods, have led to accurate prediction of the presence of the disease. MRI is a technique that creates a detailed 3D image of the brain employing magnetic fields and radio waves. Brain MR Images can identify structural atrophic changes in the brain [8] . Figure 2 shows the three MRI planes (taken from the ADNI* datasets).



Axial **Coronal** **Sagittal**

Figure 2: three views of a 3D T1-weighted MR image Axial, Coronal and Sagittal.

Machine Learning (ML) has become one of the most exceptional technologies in the last decade. ML is the act of the computer doing a task without being explicitly programmed. Consequently; Machine Learning (ML) has been widely used in different medical fields. On the other hand, Deep Learning (DL) techniques are a broader family of ML has emerged as one of the most promising tools for AD diagnosis. Discriminative features of the disease can be extracted automatically from raw data using DL models. The most advanced DL architectures are designed to work with real-world images for image segmentation, Image regression and classification, and other visual imagery analysis. These models require a large amount of training data such as brain MR images to learn the patterns and features embedded in these images. The benefit of DL models is that learned features are directly extracted from input images, eliminating the need for manually generated features [9], [10]. In this study, the relevant studies that examine AD and use MRI data, ML and DL techniques with various AD datasets are reviewed.

This paper is organized as follows: AD structural biomarkers are described in section 2, MRI as neuroimaging techniques of AD are introduced in Section 3, the datasets used in AD diagnosis are described in Section4, Section 5, offers a brief review of different classification methods that have been reported in the literature from ML towards DL for this problem In Section 6, the conclusion is presented.

2 ALZHEIMER'S DISEASE BIOMARKERS:

Biomarkers, also known as "biological markers", are medical key features that can accurately measure a biological state of a disease. There are numerous of AD biomarkers: genetic, biochemical and neuroimaging biomarkers that related to structure and other to the function of the brain [11] [12] . In this study the structural biomarkers captures by structural MRI are discuss briefly.

2.1 Brain Atrophy:

The brain consists of 3 main tissues visible in a MR image:

1. White Matter (WM), high voxel intensity (white color).
2. Gray Matter (GM), medium voxel intensity (gray color).
3. Cerebrospinal Fluid (CSF), low voxel intensity (black color).

Neurodegeneration in both GM and WM tissues occur as an outcome of normal aging, while brain atrophy rate in GM and WM is increased in AD neurodegeneration [13]–[16]. As AD progresses, more brain cells die and the brain volume is significantly reduced. In Structural MRI, the brain

neurodegeneration and volume loss are crystal clear, but it is challenging to differentiate normal aging from AD. Figure below shows a healthy brain compared to a brain with AD.

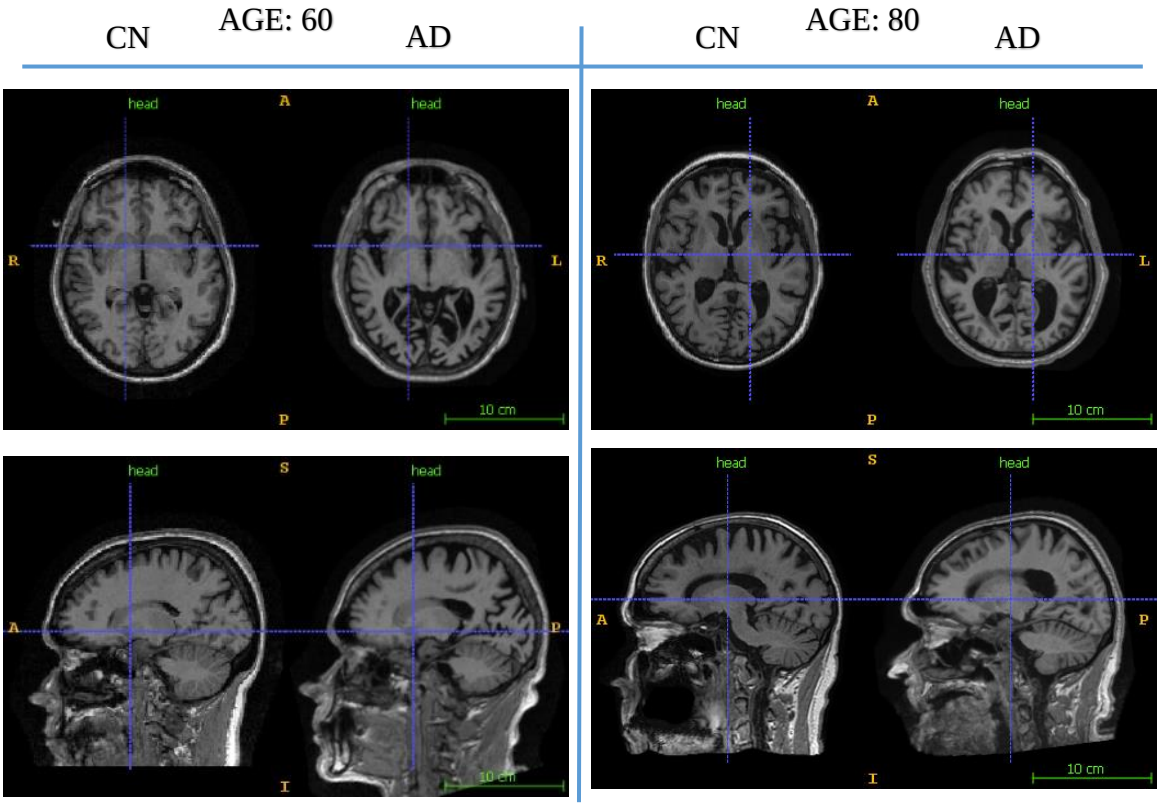


Figure 3 Brain atrophy comparison in normal aging against AD.

2.2 Hippocampal Atrophy:

Memory impairment symptoms is a must when diagnosing AD, the hippocampus is the brain area that plays a key role in forming new memories. Several studies show that the hippocampus, and the entorhinal cortex region are the most vulnerable Regions of Interest (ROIs) with respect to AD pathology. In particular, hippocampal atrophy is known to occur early in the course of AD on a spatial scale large enough to be detectable with structural MR images, also the hippocampal volume loss plays a key role in distinguishing very mild AD from healthy Aging [13], [14].

Other subcortical regions, especially in the Medial Temporal Lobe (MTL) also suffer from atrophy, but at lower rates than the hippocampal atrophy. Basically, AD progression causes more neurodegeneration across different brain regions, researchers are still studying the patterns that differentiate AD from normal aging and other medical diseases that causes brain atrophy

2.3 Ventricular Enlargement:

The ventricles are four interconnected cavities distributed throughout the brain that produce and hold the CSF within. They found that when ventricles enlarge, the surrounding brain tissue dies. Lateral ventricular enlargement remains one of the most robust brain abnormalities biomarkers in AD, and even though ventricles enlarge with normal aging, several studies have shown the correlation between the enlargement of ventricles and progression of AD [16]. Figure 4 show hippocampus atrophy (colored in light red) and lateral ventricles enlargement (colored in light blue) in AD patient compared to a CN subject both at age 80 years old.

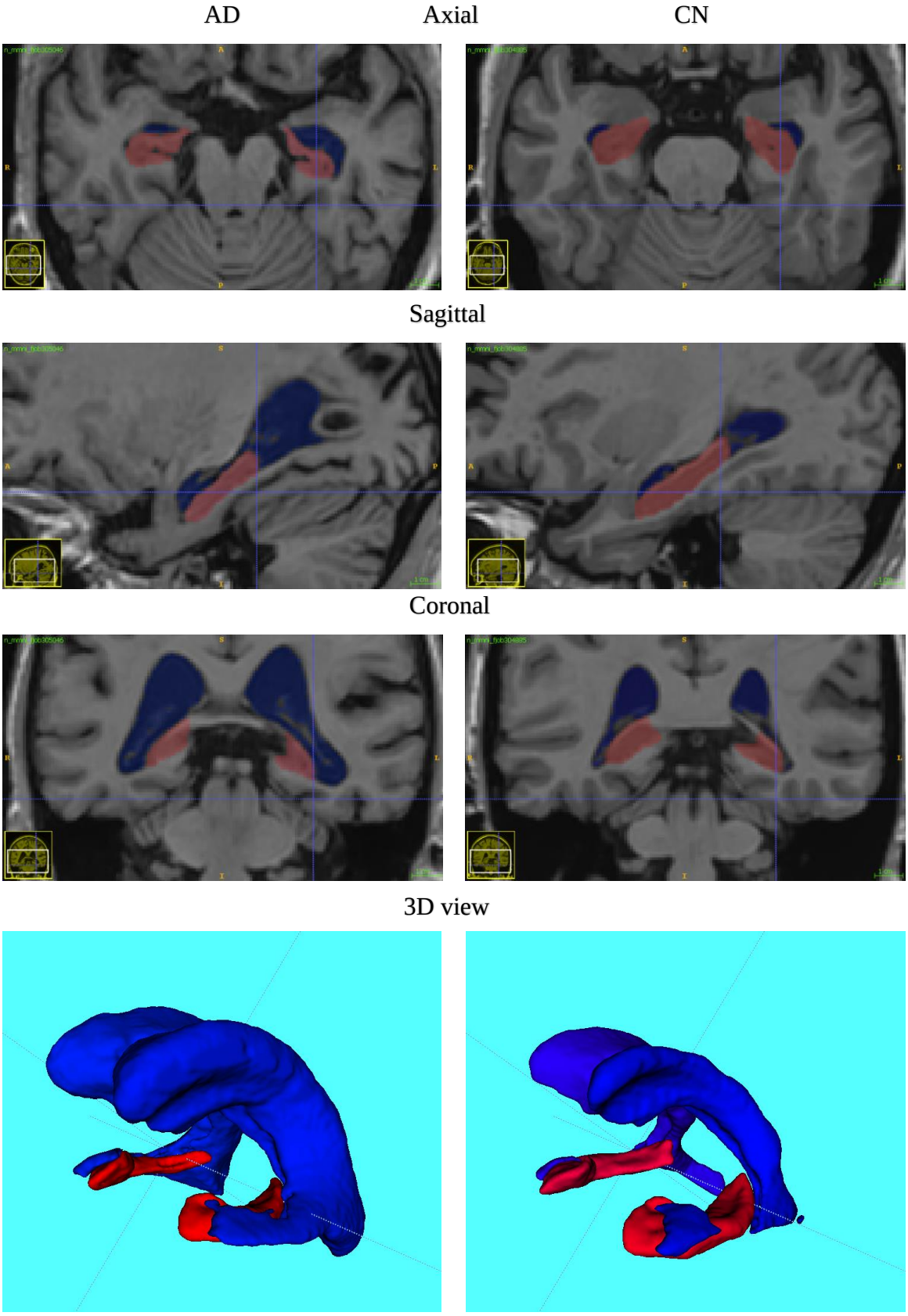


Figure 4 Hippocampal atrophy and Ventricular enlargement between normal aging and AD

3 NEUROIMAGING TECHNIQUES:

Studies have shown the strength of imaging biomarkers as a crucial information about AD, they concluded that the use of neuroimaging techniques have the ability to detect pathological brain changes. There are two types of imaging techniques: structural imaging and functional imaging. Structural imaging provides information on the structure of the brain, including neurons, synapses, glial cells, and other structures. Functional imaging provides information about the brain's activities. Both functional and structural imaging techniques have been exploited as a significant diagnostic tool when reporting cognitive decline, they showed promising results not only for excluding non-neurodegeneration causes, but rather to accurately identify AD neurodegenerations [8], [12], [17], [18].

Commonly used modalities include structural MRI and Computed Tomography (CT) to detect AD-related structural changes, while functional MRI and Positron Emission Tomography (PET) are being used to detect functional abnormalities in the brain. This study will focuses on the structural MRI as a neuroimaging technique and discuss the studies which exploited to AD classification.

3.1.1 Magnetic Resonance Imaging

MRI was first used in 1977 as an imaging technique in radiology to obtain two- and three-dimensional images of the body. MRI functions without the damaging X-Ray used in CT scans or the ionizing radiation used in PET, MRI depends merely on magnetic fields, magnetic field gradients and radio waves. MRI produces high contrast images of tissues such as bones, muscles, brain tissues, fat and body fluids. MRI is based principally upon sensitivity to the existence and properties of water, specifically the Hydrogen atoms, which makes up 70% to 90% of most body tissues. Most diseases alter water amount and properties within the human body making MRI scanners a truly powerful diagnostic tool [13], [19], [20].

The most important Hydrogen properties are Proton Density (PD), and two characteristics called T1 and T2 relaxation times. PD is the amount of hydrogen atoms in a volume; for example, CSF and blood have higher PD than bone. Relaxation times describe how long it takes for a tissue to get back to its original state after being altered by MR. These three terms basically define how an MRI scanner determines the contrast for different tissue types. Figure below explains the difference between a PD-, T1- and T2-weighted MR images of the brain.

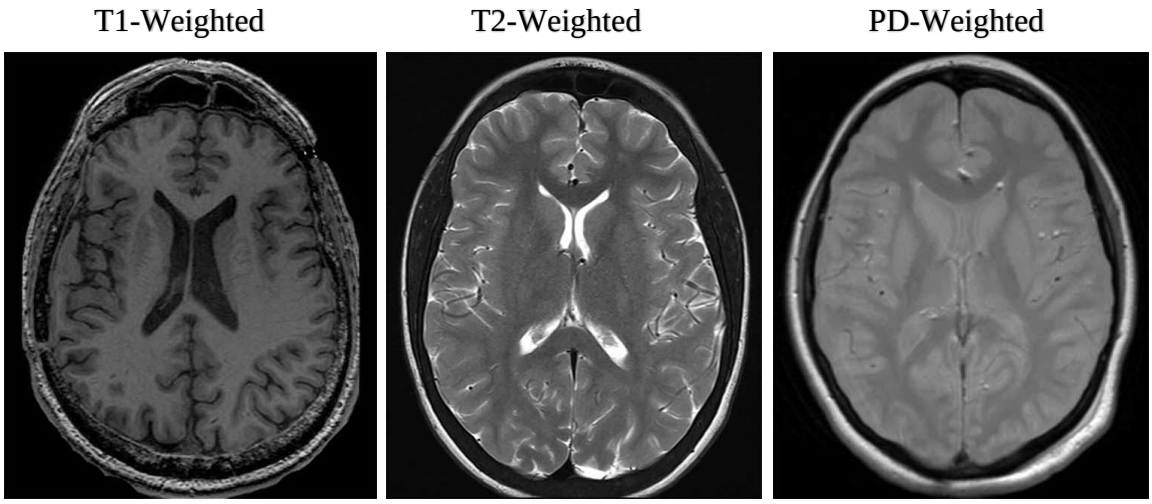


Figure 5 different weighting in MRI scans

As shown in the figure above, the high tissue contrast offered by T1-weighted MRI enables accurate structural neuroimaging analysis. Different weighting in MRI scans have its own weaknesses and strengths, but T1-weighted shows excellent contrast between different brain tissues. Thus, it is commonly

used as a diagnostic tool whenever the brain structure evaluation is needed.

Structural MRI provides high resolution 3D image as a series of 2D slices, instead of a 2D pixel, a single element in a 3D image is called a Voxel. Unlike pixels, voxel can be seen from 3 different views; Axial, Sagittal and Coronal.

4 DATASETS:

This section explains the dataset that often utilized in AD classification.

4.1 Alzheimer Disease Neuroimaging Initiative (ADNI):

ADNI database (adni.loni.usc.edu) was the first source of brain MR images and the clinical data used in evaluating the proposed method. ADNI has been running since 2004, and funds will last until 2021. In several studies ADNI was previously utilised to categories AD and understand the transformation to AD. The primary goal of ADNI is to test whether serial MRI, PET scans, other biological markers, clinical and neuropsychological assessment can track and diagnose the early stages of AD progression. The dataset also contains metadata for each brain scan, including gender, age, education, and diagnosis. Determination of sensitive and specific markers of early AD progression intends to aid researchers and clinicians in developing new treatments, monitoring their effectiveness, and lessening the time and cost of clinical trials.

In the ADNI1 dataset, there are 2033 MRI session distribution in three diagnostic groups: AD, CN, and MCI. AD group refers to the patients with Alzheimer's diagnosis, CN group refers to normal cognitive status subjects that show no sign of AD. MCI group references patients that can take care of their daily activities with mild damage in other cognitive areas.

4.2 Open Access Series of Imaging Studies (OASIS):

OASIS is an open-sourced project that aims to make neuroimaging datasets freely available for the scientific community. The information provided by OASIS covers a wide demographic, with thousands of people showing both normal aging and AD. The OASIS project provides three large datasets with scan data from 1664 patients, including 2975 MRI sessions and 1608 PET sessions. OASIS-1, OASIS-2, and OASIS-3 are the three datasets provided. The data provided by OASIS was partitioned and sorted into Yes and No instances based on medical diagnostics linked to each patient that data was collected from. No-instances were classified as those patients who had received a diagnosis of ”Cognitively Normal” and the rest of the patients were classified as Yes-instances. These datasets are widely used by researchers in many works to studies the dementia in older adult.

4.3 National health and aging trends study:

In response to the growing number of cases, the Alzheimer's disease Centers funded by the National Institute on Aging established the National Alzheimer's Coordinating Center (NACC) in 1999, with the goal of facilitating research initiatives. The Alzheimer's Disease Genetics Consortium and the National Centralized Repository for Alzheimer's disease and Related Dementias, in collaboration with NACC, provided invaluable resources for the exploratory and explanatory phases of the research.

5 LITERATURE REVIEW:

This section introduces a brief overview of various automated MRI classification techniques. First, traditional feature extraction and classification methods based on classical ML techniques are discussed in detail. Then, this section migrates to explore different DL models utilized in automatic MRI classification for AD diagnosis.

5.1 General Overview of Manual Methods:

According to features extraction methods from brain MR images, the methods summarized below are old-fashioned manual feature extraction methods.

(Laakso et al. [21], 1995) used atlases of the human brain to define the boundaries of both amygdala, hippocampus, and the frontal lobe. Measured volumes was normalized by dividing on the whole brain volume. They performed Analysis of

Variance (ANOVA) to differentiate between (32) AD-probable patients and (16) normal controls. ANOVA is a statistical method to find the relation between a category and a numerical variable.

(Frisoni et al. [22], 1996) performed linear measurements like diameters, heights, widths, and distances of many brain structures. They performed discriminant analysis to identify measures independently contributing to discrimination of (46) AD patients from (31) healthy subjects. They concluded that linear measures of hippocampal atrophy contributed the most to the diagnosis of AD.

(Wolf et al. [23], 2001) exploited the hippocampal head, body, and total volumetric measures to predict the cognitive dysfunction according to Clinical Dementia Rating (CDR) of (39) subjects. They conclude that hippocampal atrophy is sensitive to detect subjects at risk for AD.

The before mentioned studies and the like suffered from three major points:

- No big cohorts were available at the time, leading to small study populations with several subjects less than (100). Due to this, comparison with these studies is not applicable.
- Manual boundary definition and measurement techniques require a great deal of time and experience, making them inefficient in the diagnostic field.
- Manual feature selection is impractical because of the human error and inability to be unbiased.

5.2 Automated Feature Extraction and Classical ML Classification techniques:

Researchers had to discover new methodologies to automate feature extraction within an MR image. In recent years, many automated and semi-automated feature extraction techniques have been developed and enhanced for analyzing structural MR images. Software packages such as FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), FSL (http://fsl.fmrib.ox.ac.uk/), and Statistical Parametric Mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm/) provide powerful tools for analyzing MRI data. These extracted features can be classified based on their type. Voxel-based features represent statistics of voxel distributions on major brain tissues such as WM, GM, and CSF [24].

(Frisoni et al. [25], 2002), and (Karas et al. [26], 2003) used SPM99 to segment the brain into GM, WM, and CSF density maps. Then, segmented GM maps are registered to a template, smoothed out, and voxel-by-voxel statistically compared in-between groups to visualize GM atrophy between AD patients and CN subjects. Both studies concluded that the significant GM loss occurred in the medial temporal lobe structures, especially in the hippocampal regions.

(Klöppel et al. [27], 2008) used the newer version SPM5 to process the MR images and produce GM density maps. They utilized SVM to automatically define significant GM voxels contributing to the discrimination of (67) AD patients from (91) CN subjects. Their study concluded that supervised ML techniques can aid the clinical diagnosis of AD using MR images.

Studies that utilized full GM density maps suffered from [28], [29]:

- Extremely high dimensionality, number of features is the number of voxels within a density map.
- Extremely prone to registration error since these methods compares voxel-by-voxel for a discrimination task.

Other studies performed dimensionality reduction to decrease the number of features using various techniques.

(Vemuri et al. [30], 2008) down-sampled GM density maps from an isotropic voxel size of ($1mm^3$) to ($8mm^3$) by simple averaging. This step reduced the GM maps by (8) times, lowering its voxel count. Vemuri et al. performed an additional feature selection step by ensuring a condition of large margins when using a linear SVM classifier. This study was performed on (190) AD patients and (190) CN subjects. It concluded that the use of SVM with feature reduction and selection can generalize well to new data.

(Baglat et al.[31],2020) Applied different machine learning techniques such as Logistic Regression, Random Forest, Decision Tree, AdaBoost, and SVM for the earlier diagnosis and Classification of Alzheimer's disease using Open Access Series of Imaging Studies (OASIS) dataset, in which a significant performance was achieved using Random Forest classifier.

(Toshkhujaev et al. [32] , 2020) Achieved an accuracy of 91.57% on ADNI dataset. The author used MALPEM tool for the segmentation of the 138 ROIs, the time consumed for segmenting one subject by this tool is between 8 and 10 hours. The author also supplemented these features by age, gender and education.

(Casanova et al. [33], 2011) applied a large-scale regularization approach to select only GM and WM maps' voxels with significant contribution to the discrimination output. They utilized Penalized Logistic Regression to identify voxels with significant atrophy in (49) AD and (49) CN subjects. Casanova et al. concluded that even WM regions carry useful information regarding the diagnosis of AD.

(Khedher et al. [34], 2014) extracted the density maps of GM, WM, and CSF using SPM8. Then, they exploited two feature reduction methods: Principal Component Analysis (PCA) and Partial Least Squares (PLS), to reduce the dimensionality of the density maps. Khedher et al. tested the two feature reduction methods with two SVM classifiers: linear and Radial Basis Function (RBF). Training of the resulting classification methods was performed on (188) AD, (401) MCI, and (229) CN subjects. The PLS method reached a peak accuracy rate and outperformed the PCA method.

(Beheshti et al. [35], 2017) uniquely employed the Genetic Algorithm to select features based on their discriminative contribution. First, they obtained GM density maps using SPM8. Then, they segmented these GM maps to 3D regions of significant GM volume reduction and extracted voxel values from those volumes of Interest (VOI). Further feature reduction was performed using the Genetic algorithm, and the classification was carried out using SVM on (160) AD and (162) CN subjects. The genetic algorithm was able to select the optimal features with maximum discriminative and minimum quantity.

These studies were the first to automate the feature extraction and selection methodologies. Although these feature selection methods were voxel-wise that cannot represent fully detailed patterns. Except (Vemuri et al., 2008) who did average down-sampling to GM density maps, the rest suffered from the same issue of being prone to registration error.

Other studies segmented the brains into several anatomical Regions of Interest (ROI) using various parcellation approaches. Different methods of feature extraction were performed on the anatomical ROIs to acquire the feature vectors. These features are called ROI-based features.

(Fan et al. [36], 2008) pursues a voxel-based morphometric analysis using an atlas warping approach to generate regional tissue density maps that reflect the regional distribution of brain tissue. The segmented GM maps were aligned to a brain template to find regional differences and volumetric measurements. They also constructed SVM classifiers using these volume measurements. This study included (56) AD, (88) MCI, and (66) CN subjects. One major conclusion of this study is that two thirds of the MCI patients of this cohort are closer to AD than they are to CN individuals.

(Magnin et al. [37], 2009) used an anatomically labeled template of the brain that includes the whole-brain gray matter for the parcellation process. They registered the MR images of (16) AD and (22) CN subjects to the labeled template to find the best correspondence between the anatomical regions of the images and the template. This registration process provided (90) ROIs that were used to compute the intensity histogram of each ROI as a feature. They evaluated the new automated method with a SVM classifier.

While these studies used different regions to detect patterns of AD, other studies utilized pre-defined regions like the hippocampal complex for the classification of AD.

(Colliot et al. [38], 2008) performed an automated segmentation of the hippocampus and amygdala simultaneously based on competitive region-growing between these two structures. A bounding box was manually defined around the amygdala-hippocampal complex. Classification of (25) AD, (24) MCI, and (25) CN subjects were done using ROC curves statistical analysis of the measured volumes. They found that MCI subjects who later converted to AD had (20%) less hippocampal volume.

(Shen et al. [39], 2012) investigated the hippocampal shape variation using several Statistical Shape Models (SSM). SSMs' dimensionality was reduced using PCA, and their discriminative ability was tested using SVM classifiers. They concluded that while volume alone provides significant discrimination ability, the shape of the hippocampus can provide valuable information for the diagnosis of AD.

(Ahmed et al. [40], 2014) Used two biomarkers, they extracted visual features from the most common region affected by AD (hippocampal area) and calculated the surrounding CSF amount to discriminate between AD, CN, and MCI using the Bag-of-Visual Features extraction technique. They proposed a late fusion scheme for the classification of both biomarkers using SVM with RBF kernel.

Although they achieved high classification results, these traditional feature extraction and machine learning techniques still suffer from these limitations [41], [42]:

These techniques are time-consuming and require a great deal of experience in the medical imaging field for an accurate diagnosis.

They require intensive processing steps before manual or automated feature extraction and selection.

- Highly prone to the processing errors like registration, normalization, segmentation, etc.
- Extracting low-level features using classical ML algorithms could fail to achieve the best results.
- Traditional ML approaches have relatively lower performance with larger amounts of input data.

5.3 DL Methods:

A logical next step is to let the computer learn and extract features that optimally represent the data for the problem task at hand. This concept lies at the basis of many DL algorithms: networks composed of many layers that transform input data (e.g., MR images) to outputs (e.g., disease present/absent) while learning increasingly higher-level (deeper) features.

DL is a relatively new machine learning methodology that has made significant advances in medical imaging recently. Because of their high performances in image classification, CNNs have gained a lot of attention as the most widely used DL architectures. DL architectures, unlike traditional machine learning algorithms, allow for the automatic abstraction of low-level to high-level latent feature representations (e.g., dots, lines, and edges for low-level features, and circles, cubes, and many other shapes and objects for high-level features). As a result, it's reasonable to assume that DL relies less on image pre-processing and necessitates less prior knowledge of other complex procedures like feature selection. [38]–[45].

(Suk and Shen [46]) were the first to apply a DNN architecture with an input layer, three hidden layers, and an output layer. They segmented MRI images into three regions: gray matter, white matter, and CSF, and then divided them into 93 ROIs. The compressed features of the computed GM volumes from the segmented ROIs were learned using the DNN architecture. They used an SVM classifier to evaluate the learned features for subject classification after feature extraction and selection. While Suk and Shen used a DL architecture, they did not directly use the DNN architecture to analyze the MR images, but a mere feature selection method.

In machine learning techniques the Pre-processing, feature extraction, and selection necessitate a great deal of user's experience because it has a significant impact on classification performance. DL approaches were used to

distinguish AD using original neuroimaging data without any feature selection procedures. When using DL architecture, pre-processing is optional, however it does to reduce DL complexity. The use of whole-brain or image patches necessitates an extremely large number of parameters, dementing extremely high computational power in DL approaches. The rise of Graphical Processing Units (GPU) for parallel computing and the advancement of computational power sped up the training of deeper DL architectures. This advancement paved the way for the use of brain MR images as an input to deep learning networks for feature extraction, selection, and classification.

(Valliani and Soni [47], 2017) utilized the pre-trained ResNet-18 network [48] for the classification of (188) AD, (243) MCI, and (229) CN subjects. The ResNet-18 model was trained on millions of natural images, hence the "pre-trained" term. To initialize the kernels of the convolution layers, they used the already learned weights on the pre-trained. Input data were a single image of the median axial slice skull-stripped and registered. The last two fully connected layers were trained from scratch to output both multi-class and AD vs. CN prediction results.

(Puente-Castro et al. [48], 2020) used the same pre-trained ResNet model but replaced the classification layer with an SVM classifier. They employed a single sagittal slice from the 3D brain MRI images for the classification task.

While these studies used a single slice from the 3D MR images as inputs, these inputs suffered from extreme information loss resulting in low classification accuracy. This loss is because one slice cannot represent the full details of the brain and the patterns of the disease.

(Qiu et al. [49], 2018) used the pre-trained VGGNet-11 for the classification task of (303) CN and (83) MCI subjects. Only (3) slices from the 3D MR images were used as Input to the network. They froze all convolution layers and kept the last fully-connected layers for the training. They trained three models for each slice, and the output prediction was fused using a series of voting approaches. Their result confirms that using more image slices increases the prediction accuracy.

(Pan et al. [50], 2020) implemented (123) homogeneous 2D CNNs with six convolution layers and two fully connected layers for a set of slices consisting of (40) sagittal slices, (50) coronal slices, and (33) axial slices The outputs of multiple trained 2D CNN classifiers were then combined to create the final classifier ensemble, which was used to predict classification results. The authors were able to examine most brain regions that contribute to the differentiation of AD vs. CN subjects using the proposed method.

Even using all the 2D slices as input to the DL network, 2D convolution cannot find patterns along the 3rd dimension. Researchers tried to solve this by constructing DL models that can take the (3) views of MR images as inputs.

(Islam and Zhang [51], 2018) proposed an ensemble of (3) homogeneous deep CNN architectures with dense connections. These dense connections have a regularizing effect that reduces overfitting in the network. Each one of the networks takes one of the three views: Axial, Sagittal, and Coronal, as input images. Islam and Zhang compared their model to the two pre-trained models; ResNet and Inception.

(Lin et al. [52], 2018) performed a different approach, they assembled 2.5D image patches of several selected regions from the 3D MR images. They achieved the 2.5D patches by combining the three views into an RGB image (each slice has three channels). Output features were boosted by an extra (325) features extracted using FreeSurfer software. Lin et al. introduced PCA to select the most redundant CNN- and FreeSurfer-based features within the feature vector. Their results show that CNN architectures can extract discriminative features of the hippocampus for prediction by learning the morphology changes between (188) AD and (229) CN subjects. And FreeSurfer provides extra structural brain image features to boost the prediction performance.

Most authors focused on 3D networks to address the problem of insufficient information in the 2D slice-level approach. Despite their higher computational cost, these models perform better at

extracting discriminative features from the 3D brain in MR images.

(Cheng et al. [53], 2017) presented a combination of multiple 3D CNNs, built on different local image patches to transform the local brain regions into more compact high-level features. Each CNN architecture consists of (4) convolution layers and one fully connected layer to classify (199) AD from (229) subjects. Their experimental results show that the combination of multiple CNNs can improve classification performance. (Li et al. [54], 2018) proposed a classification method based on multiple cluster CNN architectures with dense connections. K-means clustering is used to group patches with similar spatial structures into several clusters, and each CNN architecture extracts the patch-level features for each cluster. Local patch-level features are ensemble to form the final global classification results. Li et al. evaluated their method on (199) AD, (229) CN, and (403) MCI subjects.

Other studies focused on brain regions with significant morphological variations such as the hippocampal complex as input patches for their CNN architecture.

(Adreghal et al. [55], 2017) constructed a 2D CNN architecture with only (2) convolution layers and one fully connected layer. The input layer receives small patches of hippocampal ROI only. They extracted the ROI patches using the Automated Anatomical Labelling (AAL) atlas with a bounding box over the resulted hippocampus mask. They concluded that despite using a small ROI patch from the MR images, they achieved encouraging accuracy results.

(Liu et al. [56], 2020) presented a multi-model DL framework based on CNN architectures for the automatic hippocampal segmentation and AD classification using structural MRI data. The proposed DL framework consists of two DL models. One model is a deep CNNs for learning hippocampus segmentation, which generates a binary segmentation mask of the hippocampus. The second model is a 3D CNN with dense connections that receives a 3D ROI patch covering the hippocampus extracted based on the centroid of the first model's segmentation mask. Finally, Liu et al. added a fully-connected layer and a SoftMax layer to combine the learned features from both models for final disease classification. The proposed framework outputs both the disease status and the hippocampal segmentation result for (97) AD, (233) MCI, and (119) CN subjects.

(Katabathula et al. [57], 2021) proposed a lightweight DL model for AD classification using combined segmented hippocampus features extracted by two CNNs with dense connections and global shape representations obtained by the LB spectrum. The CNN-based feature extraction was performed separately on both the left and right hippocampi on structural MR images. They demonstrated that the combination of CNN-based features and global shape features improved AD classification performance.

The benefit of using small image patches as CNN inputs reduces the computational power requirements to train such CNN networks. That is because an input image with fewer pixels requires fewer convolutions, pooling, and other operations. Fewer operations mean that the network training requires less memory size to hold the activation maps of a single iteration. Patch-level networks' drawback is that they lack the continuity of the whole image resulting in discontinuous patterns in-between neighboring patches.

(Korolev et al. [58], 2017) proposed two deep 3D CNN architectures for the classification of brain MRI scans. First architecture is similar to the VGGNet, while the second architecture matches the ResNet architecture. Both CNNs implement 3D convolution and pooling layers instead of 2D ones. Both networks showed similar results for the classification of (50) AD, (43) Late MCI, (77) Early MCI, and (61) CN subjects. (Yagis et al. [59], 2020) presented a deep 3D CNN similar to the VGGNet model for the classification of AD patients. The network accepts images without any pre-processing steps to output the disease state.

(Ebrahimi et al. [60], 2020) implemented and compared several deep models and configurations, including 2D and 3D state-of-the-art CNNs. They designed a 3D pre-trained ResNet by repetition of learned 2D learnable parameters along the 3rd dimension. This 3D ResNet achieved better classification results compared to other CNN

architectures. They explained this by the fact that 2D kernels are not optimized to record the spatial information of the 3D MR images due to the non-existence of the 3rd dimension.

(Zhang et al. [61], 2021) used 3D ResNet architecture for classifying AD vs. CN and progressive MCI (pMCI) vs. stable MCI (sMCI). They utilized the Self-Attention residual mechanism to capture long-range dependencies and reduce computational inefficiency due to repeated convolutional operations. They also implemented gradient-based localization class activation mapping (Grad-CAM) to visualize and explain the prediction of AD. Results have shown that the classification performance of models with the self-attention mechanism is significantly higher than models without it.

The increase of studies in DL related to AD classification can be attributed to its ease of use. In traditional ML techniques, obtaining the AD-related features is necessary, but these features become increasingly hard to find as the complexity of data increases. DL simplicity comes from the fact that the user does not have to decide which features are efficient; the DL hidden layers were decide.

6 DISCUSION:

AD diagnosis at an early stage occupies a significant role in reducing its symptoms and decelerating Cognitive Deterioration. Hence the computer-aided systems for early and accurate AD diagnosis became critical. In recent years, many studies focused on extracting the AD-related feature from SMRI images for the classification task of AD and CN using many techniques applied on MRI data with various AD datasets. In this study, brief literature on the previously adopted AD diagnosis techniques will be reviewed beginning with traditional diagnosis methods and advancing to the relevant modern employment of DL in AD classification.

In the method that relies on machine learning techniques, the number of subject participants in the experimental was limited this lead to limitations in the achieved results. In this study, only methods with more than 150 subjects per class are selected to compare their results. The table below shows a comparison between state-of-art ML methods to discriminate AD from CN subjects based on MR images.

Method	AD vs. CN
Baglat et al. [31]	86.8%
Ahmed et al.[40]	87.00%
Shen et al.[39]	88.00%
Khedher et al. [34]	88.49%
Vemuri et al. [30]	89.30%
Toshkhujaev et al. [32]	91.57%

Table 1: shows results comparison between the state-of-art methods.

In general, several studies that adopted traditional ML techniques suffered from three problems that lead to limitations in final accuracy:

- Such techniques are time-consuming and require a great deal of experience in medical imaging to produce an accurate diagnosis.
- These techniques also require intensive pre-processing steps to facilitate feature extraction and selection, which can be error-prone.
- Extracting low-level features using classical ML algorithms from multiple

imaging modalities may fail to achieve the best results.

In recent years, a large number of studies depended on more advanced DL techniques, although these studies achieved high accuracy compared with ML techniques but also suffered from limitations due to their inputting data way. Some DL studies utilized whole-brain MR original images as input to automate feature extraction and classification across the brain. However, these methods have several limitations:

- One or more 2D slices of a 3D brain MRI were used in several studies. They had low classification accuracy because they ignored other brain regions not included in the chosen 2D slices, which resulted in information loss.
- A number of studies used all 2D slices of a 3D brain MRI. Given that MRI scans are 3D images and that 2D image slices have a spatial relationship, 2D interpretation of the 3D world suffers from information loss.
- Several studies have proposed 3D DL architectures for extracting features from 3D brain MRIs; however, due to the high dimensionality of these studies, they are prone to over-fitting.
- Using Whole-brain MR original images leads to ignoring the regional and local pathological information that is critical to the diagnosis of AD

Other studies that depend on DL have focused on feature classification extracted from segmented ROIs such as the cortical and subcortical regions, including the hippocampi, GM, and CSF. Such methodologies can result in good classification accuracy. The limitation of these studies is that they neglect possible pathological variation across the whole brain regions. Connectivity between brain regions contributes to the classification accuracy of the brain MR images.

Several studies reviewed most papers that proposed to use CNN models for AD classification using anatomical MRI. Due to many differences between these papers, like participant selection, image pre-processing steps, and validation procedures, it is impractical to compare classification performance across studies. Furthermore, because the frameworks for these studies are not publicly available and implementation details are missing, they are difficult to replicate. Finally, due to insufficient or unclear procedures, some papers may report biased results [41]–[45], [62]. Table (2) shows comparison between the state-of-art DL-based methods; reported in the literature.

Method	Data input	AD vs. CN	AD vs. MCI	CN vs. MCI	Multi-class
Valliani and Soni [47]	2D Slice-level	81.30%			56.80%
Puente-Castro et al.[48]	2D Slice-level	81.46%			
Qiu et al.[49]	2D Slice-level		83.10%		
Pan et al. [50]	2D Slice-level	84.00%		79.00%	
Islam and Zhang [51]	2D Slice-level	93.18%			
Lin et al. [52]	2.5D Slice-level	88.79%	81.40%		

Cheng et al. [53]	3D Patch-level	87.15%			
Li et al.[54]	3D Patch-level	89.50%		73.80%	
Adreghal et al. [55]	3D ROI-level	82.80%	62.50%	66.00%	
Liu et al. [56]	3D ROI-level	88.90%		76.20%	
Katabathula et al. [57]	3D ROI-level	92.52%			
Korolev et al.[58]	3D Full MRI	88.00%	67.00%	67.00%	
Yagis et al.[59]	3D Full MRI	73.40%			
Ebrahimi et al.[60]	3D Full MRI	96.88%			
Zhang et al.[61]	3D Full MRI	91.30%			

Table 2: Comparison with state-of-the-art methods.

7 Conclusion:

Alzheimer's disease is a chronic neurodegenerative disease that causes nerve cell death and tissue loss throughout the brain. It usually begins slowly and gets worse over time. There is no cure currently available for stopping or reversing the disease progression, which results in the medications being focused on relieving the patients from its symptoms. The cost of these medications that expected to rise dramatically, thus necessitating individual computer-aided systems for early and accurate AD diagnosis. The effective and accurate detection of AD is important for the initiation of effective treatment. In particular, Early detection of AD is critical for therapeutic development and, ultimately, for effective patient care. This study performed a systematic review of the most important AD datasets, ML and DL diagnostic approaches of AD based on MRI neuroimaging data .this study noticed that published papers in this field tend to focus on two main areas of research: identification the AD-related structural biomarkers from MRI images, exploit the ML and DL techniques that couple with these structural biomarkers in order to discriminant AD patients, mild cognitive impairment and cognitively normal. Most of the studies in the literature are achieved high accuracies, especially which relies on DL techniques, due to their ease of use and their ability to extract high-resolution feature that is more related to the disease.

8 References:

[1] "Dementia," World Health Organization, Sep. 21, 2020.

[2] Richard A Marasco, "Current and evolving treatment strategies for the Alzheimer disease continuum," The American Journal of Managed Care, vol. 26, no. Suppl 8, Aug. 2020, doi: 10.37765/ajmc.2020.88481.

[3] "Beta-amyloid and the amyloid hypothesis," Alzheimer's Association, Apr. 2017, [Online]. Available: https://www.alz.org/national/documents/topicsheet_betaamyloid.pdf

[4] J. Weller and A. Budson, "Current understanding of Alzheimer's disease diagnosis and treatment," F1000Research,

vol. 7, p. F1000 Faculty Rev-1161, Jul. 2018, doi: 10.12688/f1000research.14506.1.

[5] K. Dhana, D. A. Evans, K. B. Rajan, D. A. Bennett, and M. C. Morris, "Healthy lifestyle and the risk of Alzheimer dementia," Neurology, vol. 95, no. 4, Jul. 2020, doi: 10.1212/WNL.0000000000009816.

[6] "<scp>2021</scp> Alzheimer's disease facts and figures," Alzheimer's & Dementia, vol. 17, no. 3, Mar. 2021, doi: 10.1002/alz.12328.

[7] "Dementia, a public health priority," World Health Organization, 2013, [Online]. Available: https://apps.who.int/iris/handle/10665/75263

[8] N. Sheikh-Bahaei, S. A. Sajjadi, R. Manavaki, and J. H. Gillard, "Imaging Biomarkers in Alzheimer's Disease: A Practical Guide for Clinicians," Journal of Alzheimer's Disease Reports, vol. 1, no. 1, Jul. 2017, doi: 10.3233/ADR-170013.

[9] D. Shen, G. Wu, and H.-I. Suk, "Deep Learning in Medical Image Analysis," Annual review of biomedical engineering, vol. 19, pp. 221–248, Jun. 2017, doi: 10.1146/annurev-bioeng-071516-044442.

[10] L. Alzubaidi et al., "Review of deep learning: concepts, CNN architectures, challenges, applications, future directions," Journal of Big Data, vol. 8, no. 1, Dec. 2021, doi: 10.1186/s40537-021-00444-8.

[11] K. Strimbu and J. A. Tavel, "What are biomarkers?," Current Opinion in HIV and AIDS, vol. 5, no. 6, Nov. 2010, doi: 10.1097/COH.0b013e32833ed177.

[12] T. Varghese, R. Sheelakumari, J. S. James, and P. Mathuranath, "A review of neuroimaging biomarkers of Alzheimer's disease," Neurology Asia, vol. 18, no. 3, pp. 239–248, 2013, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/25431627

[13] E. Bayram, J. Z. K. Caldwell, and S. J. Banks, "Current understanding of magnetic resonance imaging biomarkers and memory in Alzheimer's disease," Alzheimer's & Dementia: Translational Research & Clinical Interventions, vol. 4, no. 1, Jan. 2018, doi: 10.1016/j.trci.2018.04.007.

[14] C. R. Jack et al., "Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease," Neurology, vol. 49, no. 3, Sep. 1997, doi: 10.1212/WNL.49.3.786.

[15] P. Vemuri et al., "MRI and CSF biomarkers in normal, MCI, and AD subjects: Diagnostic discrimination and cognitive correlations," Neurology, vol. 73, no. 4, Jul. 2009, doi: 10.1212/WNL.0b013e3181af79e5.

[16] S. M. Nestor et al., "Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database," Brain, vol. 131, no. 9, Aug. 2008, doi: 10.1093/brain/awn146.

[17] K. A. Johnson, N. C. Fox, R. A. Sperling, and W. E. Klunk, "Brain Imaging in Alzheimer Disease," Cold Spring Harbor Perspectives in Medicine, vol. 2, no. 4, Apr. 2012, doi: 10.1101/cshperspect.a006213.

[18] J.-P. Soucy et al., "Clinical applications of neuroimaging in patients with Alzheimer's disease: a review from the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012," Alzheimer's Research & Therapy, vol. 5, no. S1, Jul. 2013, doi: 10.1186/alzrt199.

[19] V. P. B. Grover, J. M. Tognarelli, M. M. E. Crossey, I. J. Cox, S. D. Taylor-Robinson, and M. J. W. McPhail, "Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians," Journal of Clinical and Experimental Hepatology, vol. 5, no. 3, Sep. 2015, doi: 10.1016/j.jceh.2015.08.001.

[20] D. W. McRobbie, E. A. Moore, M. J. Graves, and M. R. Prince, "MR: What's the attraction?," in MRI From Picture to Proton, Cambridge: Cambridge University Press, 2006, pp. 1–8. doi: 10.1017/CBO9780511545405.001.

[21] M. P. Laakso et al., "Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: Correlation with memory functions," Journal of Neural Transmission - Parkinson's Disease and Dementia Section, vol. 9, no. 1, Feb. 1995, doi: 10.1007/BF02252964.

[22] G. B. Frisoni, A. Beltramello, C. Weiss, C. Geroldi, A. Bianchetti, and M. Trabucchi, "Linear measures of atrophy in mild Alzheimer disease.," American Journal of Neuroradiology, vol. 17, no. 5, p. 913, May 1996, [Online]. Available: http://www.ajnr.org/content/17/5/913.abstract

[23] H. Wolf et al., "Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly," Neurobiology of Aging, vol. 22, no. 2, Mar. 2001, doi: 10.1016/S0197-4580(00)00238-4.

[24] F. Falahati, E. Westman, and A. Simmons, "Multivariate Data Analysis and Machine Learning in Alzheimer's Disease with a Focus on Structural Magnetic Resonance Imaging," Journal of Alzheimer's Disease, vol. 41, no. 3, Jul. 2014, doi: 10.3233/JAD-131928.

[25] G. B. Frisoni, "Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry," Journal of Neurology, Neurosurgery & Psychiatry, vol. 73, no. 6, Dec. 2002, doi: 10.1136/jnnp.73.6.657.

[26] G. B. Karas et al., "A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry," NeuroImage, vol. 18, no. 4, Apr. 2003, doi: 10.1016/S1053-8119(03)00041-7.

[27] S. Kloppel et al., "Automatic classification of MR scans in Alzheimer's disease," Brain, vol. 131, no. 3, Feb. 2008, doi: 10.1093/brain/awm319.

[28] S. Rathore, M. Habes, M. A. Iftikhar, A. Shacklett, and C. Davatzikos, "A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages," NeuroImage, vol. 155, Jul. 2017, doi: 10.1016/j.neuroimage.2017.03.057.

[29] C. Zheng, Y. Xia, Y. Pan, and J. Chen, "Automated identification of dementia using medical imaging: a survey from a pattern classification perspective," Brain Informatics, vol. 3, no. 1, Mar. 2016, doi: 10.1007/s40708-015-0027-x.

[30] P. Vemuri et al., "Alzheimer's disease diagnosis in individual subjects using structural MR images: Validation studies," NeuroImage, vol. 39, no. 3, Feb. 2008, doi: 10.1016/j.neuroimage.2007.09.073.

[31] P. Baglat, A. W. Salehi, A. Gupta, and G. Gupta, "Multiple Machine Learning Models for Detection of Alzheimer's Disease Using OASIS Dataset," 2020, doi: 10.1007/978-3-030-64849-7_54.

[32] S. Toshkhujaev et al., "Classification of Alzheimer's Disease and Mild Cognitive Impairment Based on Cortical and Subcortical Features from MRI T1 Brain Images Utilizing Four Different Types of Datasets," Journal of Healthcare Engineering, vol. 2020, p. 3743171, 2020, doi: 10.1155/2020/3743171.

[33] R. Casanova et al., "High Dimensional Classification of Structural MRI Alzheimer?s Disease Data Based on Large Scale Regularization," Frontiers in Neuroinformatics, vol. 5, 2011, doi: 10.3389/fninf.2011.00022.

[34] L. Khedher, J. Ramírez, J. M. Górriz, A. Brahim, and F. Segovia, "Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented MRI images," Neurocomputing, vol. 151, Mar. 2015, doi: 10.1016/j.neucom.2014.09.072.

[35] I. Beheshti, H. Demirel, and H. Matsuda, "Classification of Alzheimer's disease and prediction of mild cognitive impairment-to-Alzheimer's conversion from structural

magnetic resource imaging using feature ranking and a genetic algorithm," Computers in Biology and Medicine, vol. 83, Apr. 2017, doi: 10.1016/j.compbiomed.2017.02.011.

[36] Y. Fan, N. Batmanghelich, C. M. Clark, and C. Davatzikos, "Spatial patterns of brain atrophy in MCI patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline," NeuroImage, vol. 39, no. 4, Feb. 2008, doi: 10.1016/j.neuroimage.2007.10.031.

[37] B. Magnin et al., "Support vector machine-based classification of Alzheimer's disease from whole-brain anatomical MRI," Neuroradiology, vol. 51, no. 2, Feb. 2009, doi: 10.1007/s00234-008-0463-x.

[38] O. Colliot et al., "Discrimination between Alzheimer Disease, Mild Cognitive Impairment, and Normal Aging by Using Automated Segmentation of the Hippocampus," Radiology, vol. 248, no. 1, Jul. 2008, doi: 10.1148/radiol.2481070876.

[39] K. Shen, J. Fripp, F. Mériaudeau, G. Chételat, O. Salvado, and P. Bourgeat, "Detecting global and local hippocampal shape changes in Alzheimer's disease using statistical shape models," NeuroImage, vol. 59, no. 3, Feb. 2012, doi: 10.1016/j.neuroimage.2011.10.014.

[40] O. ben Ahmed, J. Benois-Pineau, M. Allard, C. ben Amar, and G. Catheline, "Classification of Alzheimer's disease subjects from MRI using hippocampal visual features," Multimedia Tools and Applications, vol. 74, no. 4, Feb. 2015, doi: 10.1007/s11042-014-2123-y.

[41] G. Litjens et al., "A survey on deep learning in medical image analysis," Medical Image Analysis, vol. 42, Dec. 2017, doi: 10.1016/j.media.2017.07.005.

[42] N. Yamanakkanavar, J. Y. Choi, and B. Lee, "MRI Segmentation and Classification of Human Brain Using Deep Learning for Diagnosis of Alzheimer's Disease: A Survey," Sensors, vol. 20, no. 11, Jun. 2020, doi: 10.3390/s20113243.

[43] A. A.-A. Valliani, D. Ranti, and E. K. Oermann, "Deep Learning and Neurology: A Systematic Review," Neurology and Therapy, vol. 8, no. 2, Dec. 2019, doi: 10.1007/s40120-019-00153-8.

[44] J.-G. Lee et al., "Deep Learning in Medical Imaging: General Overview," Korean Journal of Radiology, vol. 18, no. 4, 2017, doi: 10.3348/kjr.2017.18.4.570.

[45] T. Jo, K. Nho, and A. J. Saykin, "Deep Learning in Alzheimer's Disease: Diagnostic Classification and Prognostic Prediction Using Neuroimaging Data," Frontiers in Aging Neuroscience, vol. 11, Aug. 2019, doi: 10.3389/fnagi.2019.00220.

[46] H.-I. Suk and D. Shen, "Deep learning-based feature representation for AD/MCI classification," Medical image computing and computer-assisted intervention : MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention, vol. 16, no. Pt 2, pp. 583–590, 2013, doi: 10.1007/978-3-642-40763-5_72.

[47] A. Valliani and A. Soni, "Deep Residual Nets for Improved Alzheimer's Diagnosis," in Proceedings of the 8th ACM International Conference on Bioinformatics, Computational Biology,and Health Informatics, 2017, p. 615. doi: 10.1145/3107411.3108224.

[48] A. Puente-Castro, E. Fernández-Blanco, A. Pazos, and C. Munteanu, "Automatic assessment of Alzheimer's disease diagnosis based on deep learning techniques," Computers in biology and medicine, vol. 120, p. 103764, 2020.

[49] S. Qiu, G. H. Chang, M. Panagia, D. M. Gopal, R. Au, and V. B. Kolachalama, "Fusion of deep learning models of MRI scans, Mini-Mental State Examination, and logical memory test enhances diagnosis of mild cognitive impairment," Alzheimer's & dementia (Amsterdam, Netherlands), vol. 10,

pp. 737–749, Sep. 2018, doi: 10.1016/j.dadm.2018.08.013.

[50] D. Pan, A. Zeng, L. Jia, Y. Huang, T. Frizzell, and X. Song, "Early Detection of Alzheimer's Disease Using Magnetic Resonance Imaging: A Novel Approach Combining Convolutional Neural Networks and Ensemble Learning," Frontiers in Neuroscience, vol. 14, p. 259, 2020, doi: 10.3389/fnins.2020.00259.

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

[52] W. Lin et al., "Convolutional Neural Networks-Based MRI Image Analysis for the Alzheimer's Disease Prediction From Mild Cognitive Impairment," Frontiers in Neuroscience, vol. 12, p. 777, 2018, doi: 10.3389/fnins.2018.00777.

[53] D. Cheng, M. Liu, J. Fu, and Y. Wang, "Classification of MR brain images by combination of multi-CNNs for AD diagnosis," Jul. 2017. doi: 10.1117/12.2281808.

[54] F. Li and M. Liu, "Alzheimer's disease diagnosis based on multiple cluster dense convolutional networks," Computerized Medical Imaging and Graphics, vol. 70, pp. 101–110, 2018, doi: https://doi.org/10.1016/j.compmedimag.2018.09.009.

[55] K. Aderghal, M. Boissenin, J. Benois-Pineau, G. Catheline, and K. Afdel, "Classification of sMRI for AD Diagnosis with Convolutional Neuronal Networks: A Pilot 2-D+ $$\epsilon $$ Study on ADNI," 2017. doi: 10.1007/978-3-319-51811-4_56.

[56] 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, 2020, doi: https://doi.org/10.1016/j.neuroimage.2019.116459.

[57] S. Katabathula, Q. Wang, and R. Xu, "Predict Alzheimer's disease using hippocampus MRI data: a lightweight 3D deep convolutional network model with visual and global shape representations," Alzheimer's Research & Therapy, vol. 13, no. 1, p. 104, 2021, doi: 10.1186/s13195-021-00837-0.

[58] S. Korolev, A. Safiullin, M. Belyaev, and Y. Dodonova, "Residual and plain convolutional neural networks for 3D brain MRI classification," 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017), pp. 835–838, 2017.

[59] E. Yagis, L. Citi, S. Diciotti, C. Marzi, S. W. Atnafu, and A. G. S. de Herrera, "3D Convolutional Neural Networks for Diagnosis of Alzheimer's Disease via Structural MRI," in 2020 IEEE 33rd International Symposium on Computer-Based Medical Systems (CBMS), 2020, pp. 65–70. doi: 10.1109/CBMS49503.2020.00020.

[60] A. Ebrahimi, S. Luo, and A. D. N. Initiative, "Convolutional neural networks for Alzheimer's disease detection on MRI images," Journal of Medical Imaging, vol. 8, no. 2, pp. 1–18, Apr. 2021, doi: 10.1117/1.JMI.8.2.024503.

[61] X. Zhang, L. Han, W. Zhu, L. Sun, and D. Zhang, "An Explainable 3D Residual Self-Attention Deep Neural Network FOR Joint Atrophy Localization and Alzheimer's Disease Diagnosis using Structural MRI," IEEE journal of biomedical and health informatics, vol. PP, 2021.

[62] J. Wen et al., "Convolutional neural networks for classification of Alzheimer's disease: Overview and reproducible evaluation," Medical Image Analysis, vol. 63, Jul. 2020, doi: 10.1016/j.media.2020.101694.