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SURVEY

# A Review on Machine Learning Approaches for Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment Based on Brain MRI

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**ABSTRACT** Alzheimer's disease is a progressive disease for which researchers have yet to discover the main cause, but believe it probably involves a combination of age-related changes in the brain, genetic, environmental and lifestyle factors. Alzheimer's is an irreversible disease that still has no cure. Therefore, its early diagnosis is very important to prevent its progression. Developing Machine Learning algorithms in healthcare, especially in brain disorders such as Alzheimer's disease, provides new opportunities for early diagnosis and recognition of important biomarkers. This paper presents an overview of advanced studies based on Machine Learning techniques for diagnosing Alzheimer's disease and different stages of mild cognitive impairment based on magnetic resonance imaging (MRI) images in the last 10 years. Also, this paper comprehensively describes the commonly efficient Machine Learning algorithms in each stage of magnetic resonance imaging processing used in the papers, which can facilitate the comparison of algorithms with each other and provide insight into the impact of each technique on classification performance. This review can be a valuable resource to gain a new perspective on the various research methods used in recent studies on Alzheimer's disease.

**INDEX TERMS** Alzheimer's disease, image processing techniques, machine learning, mild cognitive impairment, MRI.

## I. INTRODUCTION

One of the most important organs of the human body is the brain, which controls several vital tasks. It is also responsible for thinking, problem-solving, decision-making, and memory. Memory refers to the psychological processes for storage and retrieval of information over time, which plays an important role in creating our personality and identity [1]. Memory may be affected by various factors including; stroke, brain disorders, and dementia that cause its function to be disturbed. Dementia is an umbrella term for describing various neurological conditions, and any decline in cognition that gradually deteriorates brain function that is significant enough to interfere with independent, daily functioning [2]. Every 3 seconds, a person in the world suffers from dementia [3]. According to the World Health Organization (WHO) and World Alzheimer Report 2015, the number of people who have dementia worldwide is estimated at 55 million which will reach about 75 million by 2030 and more than 131.5 million by 2050 [4], [5]. In Fig. 1, the number of people suffering from dementia worldwide and the prediction of this number in the future are shown.

Alzheimer's disease (AD) is the most common type of dementia, accounting for 60%-80% of cases. AD is a brain disorder that affects people aged 65 and over and is the fifth leading cause of death among people over this age [7]. This is a progressive, degenerative brain disorder that leads to nerve cell death, tissue loss, memory problems, and cognitive problems that is different from the normal decline in cognitive function that may occur with aging. The early stage of AD is

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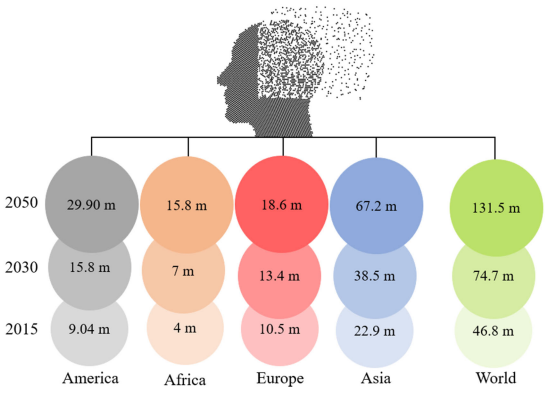


**FIGURE 1.** People with dementia around the world, along with forecasts for 2030 and 2050 (content based on "Dementia statistics, Alzheimer's disease international" [6]).

called mild cognitive impairment (MCI), which progresses gradually. Although not all MCI patients get converted into AD [8], MCI is useful in predicting AD, with about 15% of MCI patients converting to AD every year [9]. AD is considered a multifactorial disease but the scientists proposed the beta-amyloid ($A\beta$) neuritic plaques and neurofibrillary tangles (called Tau proteins) as the main causes [10]. By the gradual accumulation of $A\beta$ between neurons and Tau proteins inside of the neurons, the communication between brain cells and nerve message transmission within nerve cells are disturbed, respectively [11], [12]. So, the normal neurons begin to function less effectively and gradually lose their ability to communicate and finally die, which results in overall shrinkage of the brain tissue. The death of neurons particularly in the hippocampus region restricts the ability to form new memories. The hippocampus is the region in the brain that is responsible for forming memories. It is the first region in the brain that is affected by AD and gets atrophy [13]. Also, AD can impact different types of brain tissues such as gray matter (GM), cerebrospinal fluid (CSF), and white matter (WM) or different brain regions such as lateral ventricles (LV) and medial temporal lobe (MTL).

Scientists have shown that abnormal accumulation of proteins and tangles begins 10-20 years before the onset of overt symptoms [14], [15], [16]. Therefore, as there is no certain treatment for AD, the detection of these abnormalities and early diagnosis of it is strongly important and can prevent the speed of its progression. AD can diagnosed by different methods: cognitive tests, non-imaging methods such as electroencephalogram (EEG), and neuroimaging methods such as magnetic resonance imaging (MRI). The cognitive tests are the primary methods which are taken from the patients by doctors or experts and based on their scores, the stage of patients has been determined. The non-imaging and imaging methods are the processes that can help doctors or radiologists to eliminate other conditions that may cause similar symptoms of mental decline such as stroke and head injury. Additionally, the structural and functional variation of neuroimaging caused by AD can be identified from the multiple modality neuroimages like MRI and positron emission tomography (PET) [17].

In general, humans are not able to detect abnormal patterns correctly in the early stage or recognize the special characteristics related to them simply and with more accuracy [18]. So, computer-aided designed (CAD) systems can provide better diagnostic suggestions by analyzing these patterns or any special changes in the brain efficiently. Various diagnostic approaches utilize CAD systems to streamline assessment, enhance accuracy, and aid healthcare professionals in medical diagnosis. The diagnostic process for AD demands comprehensive expertise to differentiate AD from normal cognitive (NC) aging by analyzing these different patterns or tissues. In CAD systems in recent decades, Machine Learning (ML) algorithms have played a crucial role in the field of AD prediction or diagnosis [19]. The implementation of these new processing techniques based on signal or image applications and novel biomarkers can contribute to understanding AD and finding a cure [20]. ML process constitutes a subset of artificial intelligence (AI) characterized by its ability to access data and commence with data observation to look for patterns and construct efficient models for making decisions regarding new data in the future. The fundamental objective of ML algorithms is to facilitate automated or semi-automated learning within computer systems, thereby assisting medical professionals in arriving at optimal decisions.

The AD diagnosis process requires considerable knowledge and comprehension to distinguish AD patients from healthy persons through the analysis of the visible variations of brain regions. Among different diagnosis and modalities methods, most of the AD diagnosis systems relied on structural MRI to extract the variety of features by determining either the volume of interest (VOI) or region of interest (ROI) from different areas or tissues of the brain [18]. However, relying on several features extracted from one or more brain regions is not sufficient to accurately classify and differentiate groups. Therefore, it is necessary to combine different types of imaging features and clinical information to enhance the accuracy of AD diagnosis. The purpose of this review is to describe the different techniques in the studies of AD and different stages of MCI based on MRI image processing and ML algorithms in recent years. This review explains in detail the algorithms used in numerous papers and expresses the efficient techniques in each stage of the ML process to provide informative insights for evaluating the impact of each technique on classification performance. In this paper, the ML pipelines used in the papers generally consist of the following steps: data collection, preprocessing, feature extraction, classification, and evaluation of the model performance measurements.

## II. ALZHEIMER'S DISEASE DIAGNOSIS METHODS

This section describes the diagnostic methods used in AD in three subsections. The first part describes the

clinical examination method. The second section explains common non-imaging methods. Finally, the third section presents common imaging modalities for the diagnosis of AD.

### A. CLINICAL EXAMINATION

Dementia evaluation as a standard protocol includes a detailed history of the patient and a comprehensive clinical examination of the patient in terms of neurological, psychological, and cognitive functions. Additionally, other evaluations such as blood analysis, laboratory factors such as serum folic acid, thyroid stimulating hormone, and serum level of vitamin B12 are also measured. Interviews with relatives or other informants provide valuable insights. Neuroradiological evaluations are also employed as part of the diagnostic process [21], [22]. It is imperative to manage other potential physical and mental disorders, such as hypothyroidism or depression, which could contribute to cognitive impairment before confirming a diagnosis of dementia [23]. Neuropsychological assessment is another examination that is a very common practical method used in clinics. This examination involves a thorough evaluation of key cognitive domains, including memory, executive functions, language, attention, and visuospatial skills. One of the widely accepted neuropsychological tests is the mini-mental state examination (MMSE) which is the best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research, and community settings [24]. MMSE is a 30-question test that can generally be administered in less than 10 minutes and consists of attention and orientation, memory, registration, recall, calculation, language, and the ability to draw a complex polygon [25]. The maximum score of this test is 30 and any score of 24 or more indicates normal cognition. Below this, scores can indicate severe ($\leq$ 9 points), moderate (10–18 points), or mild (19–23 points) cognitive impairment.

### B. NON-IMAGING METHODS

Magnetic resonance imaging (MEG) and electroencephalography (EEG) are two non-imaging techniques that show brain dynamic changes in a non-invasive way with a good temporal resolution [26]. MEG records the brain activity using the magnetic fields caused by the electrical activity of neurons [27], [28]. This method can provide a high spatial and temporal resolution [27], [28], [29]. EEG is a low-cost, non-invasive, and portable technology that records the electrical activity of neurons in the brain. Compared to MEG, this technology has shown highly promising results in the diagnosis of brain disorders using the computational analysis of EEG signals [30], which can be used as a potential marker for the assessment of AD and MCI [31]. EEG frequency spectrum is used more as a main characteristic for determining the abnormality pattern in AD patients and compare with healthy persons. EEG frequency spectrum is commonly partitioned into distinct frequency bands, each associated with specific physiological states. These bands include: the delta wave (0.5-4 Hz) predominantly observed during deep sleep; theta waves (4)-8 Hz), usually observed during rest and sleep; alpha wave (8-12 Hz), which is recognized during awareness without attention and concentration; beta waves (12-30 Hz), detected during normal consciousness and active focus; and finally, the gamma wave (30-100 Hz), which indicates high brain activity often associated with problem-solving and high cognitive performance [32]. Previous EEG studies encompassing both MCI and AD patients consistently reveal brain signal alterations compared to healthy cohorts. These alterations typically involve decreased alpha and beta rhythms activity alongside increased delta and theta oscillations [33], [34], [35], [36], [37]. These changes are regarded as promising neural biomarkers for early AD detection, given their strong correlations with patients' cognitive function. Moreover, reduced complexity and coherence in EEG recordings, along with decreased ratios of theta/gamma and high alpha/low alpha, have been identified as potential diagnostic biomarkers for AD [37], [38], [39], [40], [41].

### C. IMAGING METHODS

Although EEG is a widely used non-imaging diagnostic tool, it can be complicated to use and is easily disturbed by noise [42]. For this reason, extracting valuable information for AD diagnosis directly from EEG data can be challenging. In addition, since AD, MCI, and other brain disorders cause similar symptoms and biomarkers in the brain signals, their differentiation from each other makes the process of diagnosis difficult in clinical studies. So, utilizing the imaging methods can provide useful information and help us to detect these changes in the brain. Many recent developments in biomarkers for AD diagnosis through neuroimaging techniques demonstrate significant versatility by targeting various anatomical and physiological mechanisms. These mechanisms include structural decline and texture changes, such as volumetric and grayscale information derived from MRI scans, network correlations assessed through functional MRI (fMRI) activity, and the presence of pathological aggregates like beta-amyloid and tau proteins, and functional changes identified through PET imaging [43]. As structural and molecular imaging contributes to a better understanding of the pathophysiology of neurodegenerative dementias [44], MRI and PET imaging modalities have been used more for clinical and research applications related to AD. In 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans of MCI and AD patients, there is low uptake of the regional cerebral metabolic rate for glucose (CMRgl) in the posterior cingulate, precuneus, temporal-parietal, and frontal cortices compared with the normal person. Also, there is increasing atrophy in the medial

temporal, especially the hippocampus and cerebral cortex, and ventricular enlargement in the MRI images of MCI and AD patients.

#### 1) 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

A PET scan is a nuclear medicine imaging method that can measure the metabolic or biochemical function of body tissues and organs using radioactive tracers depending on the specific target [45]. In AD studies, the popular radiotracers; F18-fludeoxyglucose, beta-amyloid, and tau protein are used to evaluate the metabolic activity of the brain, the amount of accumulation of beta-amyloid and tau proteins, respectively [46]. FDG-PET has been proven to be promising for detecting functional brain changes in AD and identifying changes in early AD. Many studies have been published evaluating the value of FDG-PET in AD for the last 3 decades [47]. This radiotracer allows us to measure the rate of consumption of glucose or glucose uptake in the brain. In AD patients, in each area of the brain that is affected by the disease, the nerve cells die gradually because of the lack of communication with each other and finally, the metabolism activity in that area decreases. Therefore by conducting PET imaging based on FDG radiotracer, we can observe less metabolism in the AD brain compared to the normal brain [48].

#### 2) MAGNETIC RESONANCE IMAGING

As mentioned above, MRI is one of the most popular imaging technologies in medical diagnosis. This modality is a non-invasive imaging method that uses the body's inherent magnetic properties to produce accurate images of the body and provide 3D anatomical images. The performance of MRI imaging is based on the nuclei of hydrogen atoms in the body due to its abundance in water and fat [49]. Many diseases are associated with increased water content. For this reason, MRI can be considered as a sensitive tool to identify these changes and diagnose the disease. Many diseases are associated with increased water content. For this reason, MRI can be considered as a sensitive tool to identify these changes and diagnose the disease. However, an accurate recognition of the causes of disease and realizing the related changes has challenges for instance infections and tumors may show similar symptoms and variations in some cases. Nevertheless, the combination of correct information extraction and image analysis by a radiologist often leads to the correct diagnosis. With structural changes caused by dendritic and neuronal losses in the AD brain [50], MRI exploits the ability to detect hydrogen nuclei within the affected regions, thereby facilitating the evaluation of disease progression. The primary advantage of MRI lies in its widespread availability to employ in AD research that can produce high-resolution T1-weighted MRI images for measuring the area structural changes which serve as a crucial indicator for the clinical diagnosis of AD [46].

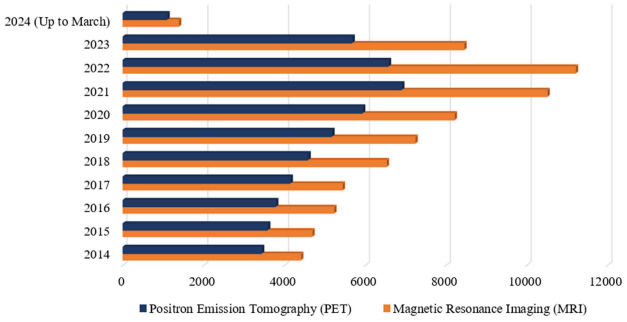


**FIGURE 2.** The number of published papers between 2015-2024 (up to March) based on the Google Scholar website for the subject "Alzheimer's disease and mild cognitive impairment diagnosis using Machine Learning and PET/MRI."

To compare the quantity of research conducted using PET and MRI based on Machine Learning algorithms for Alzheimer's disease and mild cognitive impairment diagnosis, an exploration was carried out on the Google Scholar website by this subject "Alzheimer's disease and mild cognitive impairment diagnosis using Machine Learning and PET/MRI". The number of papers published between 2015 to 2024 (up to March) was examined and the result has been shown in Fig. 2. As depicted in Fig. 2, more papers emphasized MRI in AD diagnosis research.

Hence, due to the extensive research and widespread application of MRI in brain studies, particularly in AD and MCI, this paper aims to concentrate on reviewing and evaluating articles about the diagnosis of AD and MCI focusing on MRI, and extraction of efficient information and features from images using ML-based algorithms.

##### *a: MAGNETIC RESONANCE IMAGING-FEATURES RELATED TO ALZHEIMER'S DISEASE*

MRI imaging has a high potential for diagnosing brain injuries, tumors, and lesions. In addition, it helps to eliminate symptoms similar to AD caused by other causes or disorders [51]. The MRI images contain more anatomical detail with significant gray/white matter contrast than other images. High-resolution MRI images obtained in both cross-sectional and longitudinal studies enable the assessment of structural changes associated with AD, including; cerebral and hippocampal atrophy, entorhinal and prefrontal cortex volume decline, ventricular dilation [43], [46], and texture alterations such as changes in pixel grayscale averages in special regions, throughout the progression of disease over time. Therefore, manual analysis or semi-automated/automated algorithms are applied to images to segment these interested regions and provide reliable classification results with high diagnostic accuracy that correlate well with the underlying pathology [52]. The main advantages of MRI lie in its widespread availability in AD research as well as its ability to produce high-resolution T1-weighted MRI images for evaluating the structural brain changes that serve as a crucial indicator for the clinical diagnosis of AD [46].

## III. MACHINE LEARNING ALGORITHMS IN AD STUDIES

Computer-aided diagnosis systems utilize artificial intelligence (AI) algorithms in medical sciences in various fields such as disease diagnosis/prediction, discovery of biomarkers, identifying potential risks about drugs, the possibility of remote patient treatment, and improving communication between doctors and patients [53]. With advancements in artificial intelligence technology in the 21st century, an increasing number of researchers are leveraging AI for medical image analysis [42]. Machine Learning (ML) as a subset of artificial intelligence, comprises a variety of pre-developed algorithms that can be applied to datasets to extract informative insights, among which, many classical Machine Learning algorithms are valuable for diagnosing AD [54]. The primary aim of these algorithms in medical diagnosis applications is to permit the computers to learn and help doctors to make the best decision on new cases or data. Today, researchers are looking for the automatic or semi-automatic detection of valuable biomarkers based on ML to diagnose and classify people with AD and healthy people in a short time and more accurately. Machine Learning algorithm stages include: data acquisition, preprocessing, segmentation, feature extraction, feature selection, and classification. Finally, the designed or trained model is evaluated by some measurement criteria. In Fig. 3, a typical Machine Learning algorithm workflow in medical image analysis is shown. The application of ML algorithms in the processing of medical images and signal processing generally follows the same workflow. It is noteworthy, that the specific methods used to extract efficient information from different data in these two approaches are different and Machine Learning steps can be designed depending on the input data. Additionally, the data acquisition and the subject examination in these approaches can be different which requires their related processes. For instance, in some papers based on EEG signals, the stimulus has been utilized and the brain response to that has been analyzed for evaluating the brain disorder [37].

ML methods depend on the size and representativeness of the data, and a large database is generally needed to improve the Machine Learning methods outcomes [55]. A large database for research can be a limiting factor, particularly in research for the study of brain images, which is often based on small datasets. In small databases, very complex diagnostic models tend to be overfitting. Overfitting is a fundamental issue in Machine Learning models that occurs when a model learns the details and noise in the training data to the extent that it essentially memorizes them. Consequently, an overfitted model has good performance on the training data and poor performance on test or new data. This poor performance on new data arises because the model has not generalized well and was not able to effectively recognize the targeted patterns among the training set. Since most research is based on small databases, it can be argued that many researchers have overfitting problems [55]. The applied pre-processing and segmentation methods, extraction of different features, the type of used classifiers, and the model evaluation metrics are the factors that can help prevent the overfitting of the model. In this section, each step of the ML algorithms in medical image processing used in AD and MCI diagnosis is discussed, and the efficient methods in each step are explained. Tables 1, 2, 3, and 4 summarize the MRI image processing based on ML algorithms presented in the papers for the diagnosis of AD and MCI in the last 10 years. Some papers based on deep learning algorithms are also included in the tables to enable comparison with other ML methods.

The papers discussed in detail in the tables were selected to show different methods in ML algorithms at each stage of MRI image processing. We demonstrate a comprehensive comparison by including a variety of approaches. The selection criteria included relevance to AD and different stages of MCI diagnosis, publication within the last 10 years, and the use of ML techniques in MRI processing. Databases such as PubMed, IEEE Xplore, and Google Scholar have been evaluated, with search terms including 'Alzheimer's disease', 'mild cognitive impairment,' 'machine learning,' 'MRI,' and 'image processing.' Inclusion and exclusion criteria were based on the impact of the studies in advancing the field.

### A. DATA ACQUISITION

The first phase of medical image processing based on Machine Learning algorithms in AD studies is data acquisition. Data acquisition is the process of collecting data that can be achieved directly from the patients/participants in hospitals or clinics, or indirectly downloading data by using valid online websites. These clinical trial data can include different modalities of imaging and various information such as: the patient's medical history, the patient's personal information (age, weight, educational history, etc.), cognitive exam scores, and blood tests. There are some public datasets available in different domains that can be accessed for the training and validation of proposed ML models. In AD research, prominent neuroimaging datasets such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Open Access Series of Imaging Studies (OASIS) are frequently utilized. The ADNI and OASIS databases are comprehensive datasets including different stages of mild cognitive impairment, Alzheimer's disease, and normal aging, that can provide various analyses for different study purposes. These databases cover a wide range of valuable information including imaging data, genetics, and cognitive assessments. Additionally, they provide the possibility of longitudinal data studies which can allow the researchers to evaluate the progression of the disease over time and examine the brain changes. Other advantages that distinguish these databases from others and are widely used in Alzheimer's research include public availability, easy access to data, large sample sizes, and support for diverse research goals. More

**TABLE 1. The summary of papers on the diagnosis of AD and MCI using applied ML algorithms and MRI imaging (preprocessing, segmentation, and feature extraction).**

| Author and published year | Aim | Modality | Preprocessing and Segmentation | Feature Extraction |
|---|---|---|---|---|
| Shukla et al (2024) | AD (DIG) | MRI | Elimination of artifacts (N4 biased correlation) + Image alignment + Infinity handling + Data type conversation + Image normalization | Statistical features of cortical regions and subcortical + Feature selection based on K-Best |
| Lin et al (2023) | AD (PRE) | MRI | Missing value handling | MRI features + Feature normalization |
| Goel et al (2023) | AD (DIG) | MRI, PET | Image realignment + Image normalization + Image registration | Significant slice extraction using GLCM, WT, MRI and PET features |
| Irfan et al (2023) | AD (PRE) | MRI | Skull stripping + Spatial normalization + Image smoothing | MRI features |
| Liu et al (2022) | AD (DIG) | MRI | Slice timing + Head movement correction + Image resampling + GM and WM segmentation | MRI features |
| Fan et al (2021) | AD (DIG) | MRI | Skull removal + Image down-sampling + Image clipping + Image intensity normalization | Structural and MRI features |
| Khan et al (2021) | AD (DIG & PRE) | MRI | Image normalization + Finding the boundary between WM and GM + Applying the triangular mesh consisting of vertices in each hemisphere around the WM + Analysis of cortical curvature of the parcellation unit | Cortical features, WM features, and intrinsic curvature of the brain regions + Sequential feature selection technique + Features normalization |
| Li et al (2020) | AD (PRE) | Baseline and follow-up volu-metric MRI | Regional brain segmentation | Hippocampus features, entorhinal cortex features, middle temporal cortex features, fusiform gyros features + Regional volumes normalization + Feature dimension reduction based on the principal analysis by conditional expectation (PACE) |
| Kruthika et al (2019) | AD (PRE) | MRI | Head motion correction + Compensation for a slice-dependent time shift + Image smoothing + Image normalization | Volume measurements includes; cerebral cortex and white-matter, 3rd and 4th ventricle, inferior lateral ventricle, lateral ventricles, cerebellum cortex, caudate, putamen, pallidum, cerebellum white-matter, hippocampus and the amygdala with normalizing by head size - intracranial volume and also extraction of right and left thickness features as follows: superior temporal, middle temporal, inferior temporal, entorhinal, temporal pole, lateral orbitofrontal, para hippocampal, medial orbito- frontal, pars orbitalis, superior frontal, rostral middle frontal, inferior parietal, supramarginal, caudal middle frontal, postcentral, precuneus, pars opercularis, pars triangularis, precentral, paracentral, frontal pole, superior parietal, transverse temporal, posterior, anterior, isthmus and caudal cingulate, etc + Feature selection based on particle swarm optimization (PSO) |
| Basaia et al (2019) | AD & MCI (DIG) | MRI | Image normalization + Image registration + WM, GM, and CSF segmentation | Region volume + MRI features |
| Kruthika et al (2019) | AD (DIG) | MRI | Image configuration includes; bias, noise, and global intensity normalization + Skull-stripping + Image normalization + Diluted and enhanced intensity | MRI features |
| Ge et al (2019) | AD (DIG) | MRI | GM, WM, and CSF segmentation | GM, WM, CSF features + Feature fusion + Feature reduction based on XGBoost |
| Gupta et al (2019) | AD (DIG & PRE) | Follow-up 3D sMRI (3 years) | Correction of the inhomogeneity artifacts + Segmentation of the Hippocampus, GM, WM, cortical and subcortical regions | Voxel-based morphometry features of GM and WM, hippocampus volume (HV), cortical and subcortical volumetric features + Feature selection based on the high-level features + Features normalization |
| Oh et al (2019) | AD (DIG) | MRI | Bias-field inhomogeneities correction + Spatial normalization + Image registration + Image smoothing + Segmentation of brain/skull, GM, WM, CSF, and other regions | MRI features |
| Wang et al (2019) | AD (PRE) | MRI | Anterior commissure-posterior commissure correction + Inhomogeneity correction + Skull stripping + Removing the cerebellum + Image registration + GM, WM, and CSF segmentation | Extraction of volumes from the regions + Feature normalization |

Abbreviations; DIG = diagnosis, PRE = predictive, GLCM = gray level co-occurrence matrix, WT = wavelet transform.

**TABLE 2. The summary of papers on the diagnosis of AD and MCI using applied ML algorithms and MRI imaging (preprocessing, segmentation, and feature extraction) (TABLE 1. Continued).**

| Author and published year | Aim | Modality | Preprocessing and Segmentation | Extracted Features |
|---|---|---|---|---|
| Zhang et al (2019) | AD (DIG) | MRI | Regions segmentation | Voxel-based morphometry parameters such as; ventricle volume, whole brain volume, entorhinal volume, fusiform volume, middle temporal lobe volume, and intracranial volume + Hippocampus texture features + Feature selection for clinical characteristic based on the Chi-square test |
| Saravanakumar et al (2019) | AD (DIG) | MRI | Regions segmentation | Voxel-based morphometry features of GM + Feature dimension reduction based on PCA |
| Lahmiri et al (2019) | AD (DIG) | MRI | GM and WM segmentation + Estimation of the pial and GM/WM boundary surfaces (surface generation process) | Cerebral cortex + Cortical thickness + Gyrification index of each hemisphere + Estimation of the 3D fractal dimension (FD) for the cortical surfaces + the Alzheimer's disease assessment scale (ADAS) cognitive test scores |
| Zhu et al (2019) | AD (DIG) | MRI | Anterior commissure-posterior commissure correction + Inhomogeneity correction + Skull-stripping + Removing the cerebellum + GM, WM, and CSF segmentation + Image registration | GM features + Feature selection based on "task-specific" and "self-representation" |
| Bansal et al (2018) | Detect dementia | MRI | Filling up the missing entries by using the average values | MMSE scores + Patient information + Clinical dementia rating + Atlas scaling factor + Estimation of the total intracranial volume + Whole-brain volume normalization + Feature dimension reduction based on CFSSubsetEval + Evaluation of the individual predictive ability of all the features with the degree of redundancy among them |
| Jha (2018) | AD (DIG) | MRI | Image resizing | Dual-tree complex wavelet transforms (DTCWT) coefficient + Feature dimension reduction based on PCA + Applying LDA for the linear projection of features to detach two or more classes |
| Lu et al (2018) | AD (PRE) | MRI, FDG PET | GM and WM segmentation + Subdividing of each region into smaller regions of varying sizes and patches (patch segmentation) + Skull stripping | Feature normalization + Mean intensity of each patch (understanding the metabolism activity) + Volume of each patch (understanding the brain structure) + GM and WM features |
| Islam et al (2018) | AD (DIG) | MRI | N/A | MRI features + Batch normalization + Rectified linear unit |
| Sampath et al (2018) | AD (DIG) | MRI | Noise removal + Elimination of the blur image + Regions segmentation | GLCM texture features + Statistical features + Feature selection based on the hybrid wrapper filtering |
| Long et al (2017) | AD (PRE) | MRI | Segmentation of six subcortical structures including caudate, putamen, globus pallidus, hippocampus, amygdala, and thalamus + Segmentation of five cerebral cortical regions including frontal, parietal, occipital, temporal, and cingulate + GM and WM segmentation + Intensity normalization, Skull stripping + Image realignment + Tissue partition + Surface reconstruction and inflation + Spherical mapping to standard coordinate system and parcellation of cerebral cortex + Image registration | Morphological features + MMSE scores |
| Cai et al (2017) | AD (PRE) | MRI | Skull stripping + Cortical sulci segmentation + GM, WM, and CSF segmentation + Calculation of the medial surface of the cortical folds + Reconstruction of the sulcal structure | Global sulcal index (g-SI) + Average sulcal width for each of five sulci; the superior frontal, intra-parietal, superior temporal, central, and sylvian fissure + Cortical thickness + Cortical volume + Subcortical volume + Feature selection based on information gain (IG) |
| Suk et al (2017) | AD (DIG) | MRI | Anterior commissure-posterior commissure correction + Skull-stripping + Cerebellum removal + Image resampling + Intensity inhomogeneity correction + GM, WM, and CSF segmentation + Image registration + Spatial normalization of the GM densities | GM tissue volumes + Extraction features from segmented regions + Clinical scores + Feature selection based on multiple sparse regression model |
| Raut et al (2017) | AD (DIG) | MRI | Noise reduction + Image normalization + Hippocampus segmentation | GLCM texture features + Shape features + Clinical scores |
| Hon et al (2017) | AD (DIG) | MRI | Image resizing | MRI features |
| Saraf et al (2016) | AD (DIG) | MRI | Removing non-brain tissues + GM, WM, and CSF segmentation + Image registration + Image smoothing + Image resizing | MRI features |
| Farzan et al (2015) | AD (DIG) | MRI | Skull stripping + Image registration to avoid rescaling artifacts + GM, WM, and CSF segmentation + Finding the boundary points of these regions + Image normalization | Statistical analysis + Segmented regions features + Brain volume with percentage of brain volume changes (PBVC) + Feature normalization + Feature selection based on PCA |

Abbreviations; DIG = diagnosis, PRE = predictive, GLCM = gray level co-occurrence matrix, PCA = principal components analysis, LDA = linear discriminant analysis.

**TABLE 3. The summary of papers on the diagnosis of AD and MCI using applied ML algorithms and MRI imaging (classification, validation methods, results, and database).**

| Author and published year | Classification | Validation Method | Accuracy percentage (The best result in the papers) | Database |
|---|---|---|---|---|
| Shukla (2024) | LR + DT + SVM, RF, gradient boosting (GB), Ensemble learning | 5-Fold CV | AD vs NC = 99, AD vs MCI = 85.50, NC vs MCI = 96 (Ensemble_LR_SVM), AD vs NC vs MCI = 82 (RF) | AD = NC = MCI = 200 (ADNI) |
| Lin (2023) | ANN | Train/ Test/ Validation | Demented vs Non-demented = 89.7 | Demented (at initial visit) = 64, Non-demented = 72 (OASIS) |
| Goel et al (2023) | Random vector functional link (RVFL) | Train/ Test/ Validation | AD vs MCI vs NC = 95.89 | AD = NC = MCI = 210 (ADNI) |
| Irfan et al (2023) | CNN | Train/ Test/ Validation | AD vs MCI vs NC = 92.21 | 2182 images (AD = 453, MCI = 981, NC = 748) (ADNI) |
| Liu et al (2022) | Multi-scale convolutional neural network-MSNCet (based on ResNet) | 5-Fold CV | NC vs AD = 98.96, AD vs MCI = 95.37, NC vs MCI = 92.60 | AD = 160, MCI = 200, NC = 160 (ADNI) |
| Fan et al (2021) | U-Net | 5-Fold CV | AD vs NC = 95.71, EMCI vs LMCI = 90.14, AD vs LMCI = 90.05, NC vs EMCI = 87.98, AD vs NC vs EMCI vs LMCI = 86.47 | 118 subjects for training (ADNI), 23 subjects for Testing (Australian Imaging Biomarkers and Lifestyle Study of Ageing-AIBL) including AD = 33, NC = 52, EMCI = 56, LMCI = 40, and for testing AD = 10, NC = 13) |
| Khan et al (2021) | Twin SVM (TSVM), Least square TSVM (LSTSVM), Robust energy least square TSVM (RELS-TSVM) | 5,10-Fold CV | AD vs NC=100, AD vs MCI=100, MCI vs NC = 100 (LSTSVM) | AD = 50, MCI = 50, NC = 50 (ADNI) |
| Li et al (2020) | Logistic classification | Train/ Test/ Validation | 3 years prediction MCI to AD = 75%, | cMCI (mild cognitive impairment converters) = 272, ncMCI (mild cognitive impairment non-converters) = 529 (the number of data changed to 801 because of; missing data for 66 subjects and reverting 5 subjects from AD to MCI) + 127 subjects (cMCI = 30, ncMCI = 97) for testing (ADNI) |
| Kruthika et al (2019) | NB, KNN, SVM | 5-Fold CV | AD vs NC vs MCI = 96.31 (all classifiers) | AD = 178, MCI = 160, NC = 137 (ADNI) |
| Basaia et al (2019) | CNN | 10-Fold CV | AD vs NC=99.2 (ADNI), cMCI vs NC = 87.7 (ADNI+"Milan database), sMCI vs NC=76.4 (ADNI+"Milan database), cMCI vs AD = 75.8 (ADNI+"Milan database), sMCI vs AD = 86.3 (ADNI+"Milan database), cMCI vs sMCI=75.17 (ADNI) | AD=294, cMCI (converted to AD)=253, NC=352, sMCI (stable MCI) = 510 + AD = 124, MCI = 50, NC = 55 (ADNI + "Milan" dataset, respectively) |
| Kruthika et al (2019) | 3D-CapsNets and NCN with 3D-autoencoder | Train/ Test/ Validation | AD vs NC = 98.42 | AD = 75, MCI = 75, NC = 75 (ADNI) |
| Ge et al (2019) | 3D multi-scale convolutional networks | Train/ Test/ Validation | AD vs NC = 98.29 on average (random partition), AD vs NC = 89.51 on average (subject-separated partition) | AD = 198 subjects (600 images), NC = 139 subjects (598 images) (ADNI) |
| Gupta et al (2019) | KNN, SVM, Random forest (using NRCD database to validation method and using ADNI database to compare classifier) | Train/ Test/ Validation | AD vs NC = 93.06, aAD vs mAD = 97.36, NC vs mAD = 94.73 (SVM classifier) | AD = 81, aAD = 35 (MCI non-converted to AD in 36 months), mAD = 39 (MCI converted to AD in 36 months), NC = 171 (National Research Center for Dementia in Korea-NRCD) |
| Oh et al (2019) | Convolutional autoencoder (CAE) based on unsupervised learning + Supervised learning (AD vs NC) + Transfer learning (pMCI vs sMCI) | 5-Fold CV | AD vs NC=86.60, NC vs pMCI = 77.37, NC vs sMCI = 63.04, pMCI vs sMCI = 73.95, AD vs pMCI = 60.97, AD vs sMCI = 75.06 | AD = 198, NC = 230, pMCI (Progressive MCI) = 166, sMCI (stable MCI) = 101 (ADNI) |
| Wang et al (2019) | Generative adversarial network (GAN), SVM-Linear, SVM-RBF, SVM-Polynomial, Neural network | Train/ Test/ Validation | MCI conversion prediction = 80.91 (GAN) | cMCI (converted to AD) = 101, ncMCI (non-converted to AD) = 115 (ADNI) + 1419 images for training the GAN model |

Abbreviations; LR = linear regression, DT = decision tree, SVM = support vector machine, RF = random forest, CV = cross-validation, ADNI = alzheimer's disease neuroimaging initiative, ANN = artificial neural network, CNN = convolutional neural network, OASIS = open access series of imaging studies, KNN = K-nearest neighbors, NB = naive bayes.

**TABLE 4. The summary of papers on the diagnosis of AD and MCI using applied ML algorithms and MRI imaging (classification, validation methods, results, and database) (TABLE 3. Continued).**

| Author and published year | Classifiation | Validation Method | Accuracy percentage (The best result in the papers) | Database |
|---|---|---|---|---|
| Zhang et al (2019) | Extreme learning machine (ELM), SVM, Gaussian process regression (GPR), Partial least square (PLS) | 10-Fold CV | AD vs NC = 96 (ELM) | AD = 58, NC = 94 (ADNI) |
| Saravanakumar et al (2019) | Genetic algorithm (GA) based adaBoos, PCA adaboost, PCA-greedy adaBoost | Train/ Test/ Validation | AD vs MCI vs NC = 0.92 (PCA-GA Adaboost) | N/A |
| Lahmiri et al (2019) | LDA, KNN, NB, SVM | 10-Fold CV | AD vs NC = 100 (SVM based on the ADAS cognitive test scores & cortical metric) | AD=35, NC=35 (ADNI) |
| Zhu et al (2019) | SVM | 10-Fold CV | AD vs NC = 90.3, NC vs MCI = 72.2, sMCI vs pMCI = 71.3 | AD = 186, sMCI (subjects didn't convert to AD in both 24 months and 36 months) = 124, pMCI (subjects converted from MCI to AD in 24 months) = 118, ncMCI (subjects did not convert in 24 months but converted in 36 months) = 49, uMCI (subjects were MCI at the baseline but were never converted to AD at any available time points among 0 – 96 months) = 102, NC = 226, MCI = 393 (ADNI) |
| Bansal (2018) | NB, J48, RF, Multi-Layer perceptron (MLP) | Train/ Test/ Validation | Non-demented vs Demented older adult = 99.52 (j48 based on the Cross-sectional MRI images), Non-demented vs Demented older adult = 99.20 (j48 based on the longitudinal MRI images) | Cross-sectional MRI=416, Longitudinal MRI data = 373 (ADNI) |
| Jha (2018) | Extreme learning machine (ELM) | 5-Fold CV | AD vs NC = 90.26 (ADNI), AD vs NC = 95.72 (OASIS) | AD = 86, NC = 86 (ADNI), AD = 28, NC = 98 (OASIS) |
| Lu et al (2018) | Multimodal and multiscale deep neural network (MMDNN) with stacked-autoencoder (SAE) | 10-Fold CV | MCI subjects convert to AD in 3 years = 82.93 | sNC (stable cognitively normal) = 360, sMCI (stable MCI) = 409, pNC (progressive NC means progressed to clinical diagnosis of probable AD) = 18, pMCI (Progressive MCI) = 217, sAD(stable AD means subjects with a clinical diagnosis of probably AD) = 238 (ADNI) |
| Islam et al (2018) | DNN | Train/ Test/ Validation | AD vs NC = 93.18 | 3 or 4 images for each 416 subjects (OASIS) |
| Sampath et al (2018) | N-fold cross validation process | N-Fold CV | AD vs NC = 99.26 | N/A (ADNI) |
| Long et al (2017) | Linear SVM | 10-Fold CV | AD vs NC = 96.5, pMCI vs NC = 91.74, sMCI vs pMCI = 88.99 | AD = 65, sMCI (stable MCI)=132, pMCI (progressive MCI) = 95, NC = 135 (ADNI) |
| Cai et al (2017) | NB, SVM, LR | Monte carlo cross-validation (MCCV) | AD vs NC = 90.9 (SVM) | AD = 75, NC = 75 (OASIS) |
| Suk et al (2017) | Deep-ESRNet (multi-output linear regression-MOLR, Joint linear and logistic regression-JLLR + SVM) | 10-Fold CV | AD vs NC = 91.02 (Deep-ESRNet+JLLR), MCI vs NC = 74.20 (MOLR+DeepESRNet), pMCI vs sMCI = 74.82 (Deep-ESRNet+JLLR) | AD = 186, sMCI (stable MCI) = 226, pMCI (progressive MCI) = 167, NC = 226 (ADNI) |
| Raut (2017) | ANN based on error back propagation (EBP) | Train/ Test/ Validation | N/A | 100 MRI images (OASIS) |
| Hon (2017) | Transfer learning based on VGG16 and Inception V4 | 5-fold CV | AD vs NC = 96.25 | AD = 100, HC = 100 subjects (picking the most informative 32 images from the axial plane of each scan, so 3200 images from each group for the training set) (OASIS) |
| Saraf et al (2016) | CNN based on Adopted LeNet and Adopted GoogleNet | Train/ Test/ Validation | AD vs NC = 98.84 | AD = 211, NC = 91 (ADNI) |
| Farzan et al (2015) | K-mean, Fuzzy clustering method (FCM), Linear SVM, SVM with radial based function (RBF) | leave-one-out cross-validation (LOOCV) | AD vs NC = 91.7 (SVM-RBF) | AD = 30, NC = 30 (ADNI) |

Abbreviations; SVM = support vector machine, CV = cross-validation, ADNI = alzheimer's disease neuroimaging initiative, PCA = principal components analysis, LDA = linear discriminant analysis, KNN = k-nearest neighbors, NB = naive bayes, RF = random forest, OASIS = open access series of imaging studies, LR = linear regression, CNN = convolutional neural network (TABLE 3. Continued).

information details of these databases have been shown in Table 5 and described in the following sections.

#### 1) THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database [56], was established in 2003. This database includes MRI and PET images along with other biological data such as clinical and neuropsychological evaluations such as cognitive tests, genetics, CSF, and blood biomarkers to evaluate the progress of Alzheimer's disease and different stages of cognitive impairment. This database presents research initiated by the ADNI1, ADNI-GO, ADNI2, and ADNI-3 studies, which are collaborative endeavors between public and private institutions and provide a platform for research in different subdomains.

#### 2) THE OPEN ACCESS SERIES OF IMAGING STUDIES

The Open Access Imaging Study Set (OASIS) dataset [57], provides a multimodal cross-sectional/longitudinal neuroimaging and processed imaging dataset, which involves a wide range of clinical, cognitive, genetics and biomarker information. This accessible platform is employed as a valuable resource to use in neuroimaging, clinical, and cognitive research about both normal aging and cognitive decline. This database includes different releases; OASIS-Cross-sectional, OASIS-Longitudinal, OASIS1, OASIS-2, OASIS3, and OASIS-4 that can be utilized for AD research, advanced data analytics, neuroanatomical atlases, and advanced segmentation algorithms, depending on the type of database used.

### B. PREPROCESSING

Image preprocessing is preparing the raw images for subsequent analysis steps training the ML models. The implementation of preprocessing methods varies according to the modality and data acquisition protocols as well as the study purpose. In neuroimaging analysis, this step plays an important role in disease diagnosis by recognizing the significant missing values, artifacts, and noise such as defects and outliers. By applying the preprocessing techniques, the unwanted regions, extra information, and errors are removed or have less effect on the model to be able to make a decision correctly. Also, this step can improve the quality of the images and provide the image with enhanced contrast for identifying the object of interest accurately. Some of the most commonly used techniques in the preprocessing phase of MRI image analysis include: image denoising [58], [59], biased correlation [60], [61], [62], image alignment [60], [63], missing value and data handling [60], [64], image intensity normalization [19], [60], [61], [63], [65], [66], [67], [68], [69], [70], [71], image registration [62], [63], [67], [68], [69], [72], [73], [74], [75], skull stripping [63], [65], [66], [68], [72], [73], [74], [76], [77], [78], image smoothing [19], [61], [62], [75], [78], image resampling [65], [74], [79], head motion correction [61], [79], anterior commissure-posterior commissure correction [72], [73], [74], intensity inhomogeneity correction [72], [73], [74], [80], image resizing [75], [81], [82], and contrast or intensity enhancement [66]. Among the techniques mentioned, image denoising and skull stripping have been widely used in AD studies.

#### 1) IMAGE DENOISING

Medical images mainly contain various types of noise, which reduce the quality of the images. These artifacts can diminish the quality of the diagnosis procedure and accurate discovery of disease-related biomarkers [83]. The aim of using denoising techniques by applying filters after data acquisition is to remove or reduce the noise to improve the quality of images. Several variants of filters have been developed for the specific types of noise across various medical imaging modalities [84]. Generally, these filters perform low-pass filtering by reducing the disparity between pixel values through the averaging of nearby pixels. Employing a low-pass filter tends to preserve the low-frequency information within an image while attenuating the high-frequency information. Median and Gaussian filters are common preprocessing methods to improve image quality in neuroimages and AD studies, which can reduce noise while preserving high-value information in images.

#### 2) SKULL STRIPPING

Skull striping is a method that can separate the brain from non-brain tissue, outside the skull or unwanted areas such as the neck. This method improves the accuracy of diagnosis in various brain diseases and facilitates the segmentation of the brain for further analysis. Skull-stripping techniques based upon deformable models mainly evolve and deform an active contour to conform to the brain surface, which is recognized by selected image features [85]. The efficacy of skull stripping may be influenced by various factors, such as imaging artifacts, imaging protocols, and MRI scanners that can significantly impact the quality of skull stripping outcomes [86].

### C. SEGMENTATION

The process of partitioning an image into regions with similar properties such as gray level intensity, texture, brightness, and contrast is called image segmentation [87]. The aim of applying image segmentation techniques in medical imaging is to subdivide the objects in an image to identify the regions of interest such as abnormalities tissues for further analysis including obtaining anatomical information, extracting shape characteristics i.e., volume or size, surgical plans, recognizing the stage of disease, treatment planning prior to radiation therapy, etc. In brain studies, the reliability of radiologists' assessment of brain diseases hinges on the quality of brain segmentation [88]. So, this step has a pivotal role in the entire diagnostic process.

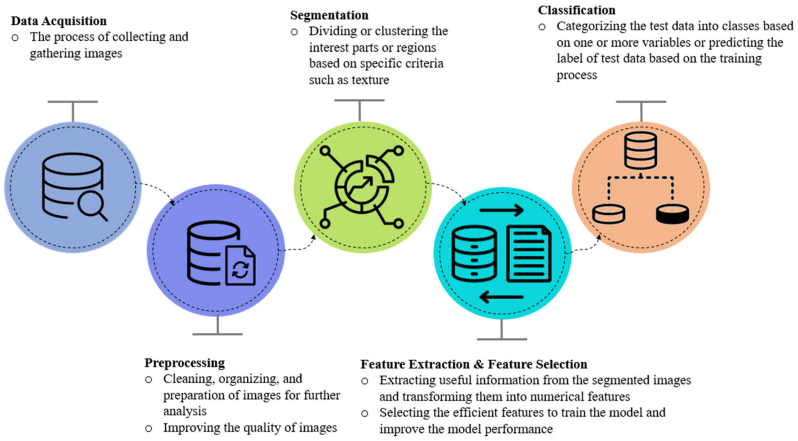


**FIGURE 3.** Machine learning algorithms workflow in medical image analysis.

**TABLE 5.** The more information details about the common databases used in Alzheimer's studies.

| Database-study characteristics | Primary goal | Cohorts/Number of subjects |
|---|---|---|
| ADNI-1 | Advancing the biomarkers as outcome measures for clinical trials | 200 elderly controls + 400 MCI + 200 AD |
| ADNI-GO (Grand Opportunities) | Exploring biomarkers in early AD stages | Existing ADNI-1 + 200 early MCI |
| ADNI-2 | Exploring the biomarkers for predictors of cognitive decline and as outcome measures | Existing ADNI-1 and ADNI-GO + 150 elderly controls + 100 EMCI + 150 LMCI + 150 AD |
| ADNI-3 | Investigation of the use of PET-tau and functional imaging techniques in clinical trials | Existing ADNI-1, ADNI-GO, ADNI-2 + 133 elderly controls + 151 MCI + 87 AD |
| OASIS-1 | Studying the cross-sectional MRI in young, middle-aged, non-demented, and demented older adults | 416 subjects with 434 MR sessions: 100 demented + 316 non-demented |
| OASIS-2 | Studying the longitudinal MRI in non-demented and demented older adults | 151 subjects with 373 MRI: 64 demented + 77 non-demented + 10 converted from non-demented to demented over time |
| OASIS-3 | Studying the longitudinal multimodal neuroimaging, clinical, and cognitive data for normal aging and Alzheimer's disease | 1377 subjects with 2842 MRI, 2157 PET, and 1472 CT: 755 CN adults + 622 various stages of cognitive decline |
| OASIS-4 | Studying MRI, clinical, cognitive, and biomarker data for individuals who presented with memory complaints | 663 subjects with 676 MRI |

In the case of AD studies based on brain MRI, the image segmentation method primarily involves partitioning brain tissue into distinct components, including WM, GM, CSF, and hippocampus area. These regions represent the important areas in the brain impacted by AD. As Alzheimer's progresses, there are significant changes in GM volume reduction [89], changes in WM [90], tissue pattern changes in CSF [91] and atrophy in the hippocampus [92]. Therefore, the identification and recognition of these changes and tissues can be effective biomarkers in the diagnosis of Alzheimer's disease. By applying image processing techniques, the regions of interest can be segmented, and quantitative characteristics, shape, volume, or morphological features can be extracted from each of the desired regions in MRI images [88]. Threshold-based algorithms, region-based algorithms, and clustering-based methods are common traditional segmentation techniques that are widely used in AD studies due to their demonstrated effectiveness and performance. Threshold-based algorithms, region-based algorithms, and clustering-based methods are the popular traditional segmentation techniques extensively employed in AD studies due to their demonstrated effectiveness and performance.

### D. FEATURE EXTRACTION AND FEATURE SELECTION

Feature extraction is a process that recognizes effective features and useful information form raw data. This process helps to the training procedure of Machine Learning models in identifying efficient characteristics and removing irrelevant properties. In MRI image analysis, a range of useful features are extracted from the segmented regions that include informative insights. These features encompass statistical features [19], [59], [60], [68], hippocampus volume [61], [63], [71], [80], [93], [94], lateral ventricle volume [61], [93], temporal lobe volume [61], [63], [77], [93], [94], cortical thickness [60], [63], [70], [77], [80], [95], tissue pattern

changes [96], gray and white volumes [62], [63], [67], [68], [70], [72], [73], [74], [75], [76], [77], [79], [80], [95], [97], [98], CSF volume [62], [67], [68], [72], [73], [74], [75], [77], [98], sulcal measurement [77], cerebral cortex [61], [63], [95], etc. that can represent the structural changes and pattern properties. Texture analysis and morphometric analysis are two sets of features that have shown significant potential for classifying patients with AD. These features contain details and valuable information about different brain tissues and brain regions. In the following sections, more detailed explanations of these two types of features are provided.

After the extraction of features from the data or segmented regions, feature selection techniques are applied to reduce the dimensions of the feature matrix. The purpose of this technique is to select effective features containing the most information that can construct the robust learning models. Principal component analysis (PCA) is a statistical method for feature selection that is widely used in medical image processing and data science. This technique is a method for extracting important variables (principal components) from the large feature matrix of a data set [99]. These components represent linear combinations of the main variables that account for the maximum variance observed in all variables. Thus, the PCA method represents an approximation of the data set using a small number of these principal components that can be used to train Machine Learning models to reduce overfitting issues [99], [100].

#### 1) TEXTURE IMAGE ANALYSIS

In MRI images of patients with AD, changes in image intensity due to the deposition of Amyloid-beta, Tau proteins, or other physiological alterations may appear as specific textural patterns before neuronal death occurs [96]. Texture analysis facilitates the realization of changes in MRI images that might not be visually apparent among image pixels and provides detailed information about brain tissues for the prediction of AD. Texture analysis approaches are highly diverse and depending on the methods employed for extracting texture features, can be categorized into four main groups; statistical, structural, model-based, and transform-based.

One of the most commonly cited methods for analyzing brain tissues involves the first and second-order statistical-based TA approach. Statistical texture analysis techniques measure the distribution and relationships of gray-level intensity in the image [96]. First-order statistical TA, explores the image intensity values within the region of interest via a histogram [101], and calculates parameters such as mean, standard deviation, skewness, and kurtosis. Second-order statistical methods measure the spatial relationship and stochastic properties of pixel intensity values in an image. Among various methods to analyze second-order statistics, the gray-level co-occurrence matrix (GLCM) is the most commonly used in medical image processing, particularly in Alzheimer's studies. The GLCM is a method that quantifies texture by analyzing the gray-level distribution of pairs of pixels within a specified distance and orientation in the image, with particular intensity values arranged in defined spatial relationships [102].

#### 2) MORPHOMETRIC IMAGE ANALYSIS

Morphometric image analysis combines principles of geometry and histology. Morphometrics is a method of quantitative analysis of the size and shape of geometrical features of objects or regions [103] that can be applied to an entire image or region of interest. Among the different types of morphometric analysis, voxel-based morphometry (VBM) is one of the most widely used methods in brain research and Alzheimer's disease studies, which has shown significant performance.

VMB is a computational technique based on statistical parametric mapping that allows the investigation of focal differences in brain tissue anatomy through a voxel-wise comparison of multiple brain images that allows a comparison of the volume or density of the brain tissue between patient and control groups. In this technique, the whole brain volume or its subparts as the regions of interest such as GM, WM, and CSF is measured. This method involves spatially normalizing all these anatomical images to a common stereotactic space [104], in order to eliminate individual differences in brain anatomy. Then the smoothing and statistical analysis is performed on a voxel-by-voxel basis to assess group differences. VBM enables the detection of changes in gray matter before overt cortical atrophy becomes evident [105]. This capability for early detection of brain structural changes may offer opportunities for early interventions to mitigate progression before overt cortical atrophy sets in, especially in AD studies.

### E. CLASSIFICATION

The classification procedure refers to recognize or predict a label or category of a new sample based on training data. Classification can be categorized into several types: supervised, unsupervised, semi-supervised, and reinforcement learning. One of the most widely algorithm used in medical applications is supervised learning models. These models have shown significant performance in various applications, such as disease diagnosis, realizing biomarkers, and disease progression. This algorithm uses the labeled data set to train its model for prediction or classification process. K-nearest neighborhood (KNN), support vector machine (SVM), decision trees (DT), random forest (RF), and artificial neural networks (ANN) are a few types of supervised classifiers that are mainly implemented in neuroimaging. For distinguishing healthy individuals and persons with different stages of cognitive impairment and Alzheimer's, SVM and RF classifiers have shown remarkable accuracy compared to other methods.

#### 1) SUPPORT VECTOR MACHINE

Support Vector Machines (SVM) map the training set of samples to points in multidimensional space to find the hyperplane with the maximum margin between different data types. In general, the goal of the SVM algorithm is to find an optimal hyperplane or a set of hyperplanes in a high-dimensional space. These hypermaps are selected based on the largest distance to the nearest data point of each class to create a suitable separation between the data. The hyperplane is defined in (1).

$$F(i) = \beta + \omega_i T_i. \tag{1}$$

where $\beta$ refers to the threshold value, $\omega_i$ represents the weight vector, $T_i$ denotes the scalar offset, and $i$ denotes the samples from the training set that are near the hyperplane, known as the support vectors [19].

The SVM algorithm is used in the classification and regression process as well as different approaches in the diagnosis process [70]. The advantage of these algorithms lies in their flexibility for linear and nonlinear-based discriminatory analyses. While SVM algorithms can be powerful tools for classification tasks in Alzheimer's research, their lack of interpretability and challenges with large samples provide some disadvantages that need to be combined with other techniques to address these limitations. The combination of these SVM algorithms and feature selection methods can be particularly suitable for analyzing high-dimensional datasets with a small sample size [106], which is one of the important issues in medical research.

#### 2) RANDOM FOREST

Random forests (RF) are an ensemble learning technique based on a large number of decision tree algorithms, which operate as a recursive division of data into subsets based on the most important feature in each node of the tree. The goal of the decision tree algorithm is to find the feature that maximizes the information gain or minimizes the impurity after the split. The equation for calculating the entropy in the decision tree algorithm is shown in (2).

$$E(S) = \sum_{i=1}^{n} -P_i \log_2 P_i \tag{2}$$

where $E(S)$ denotes the entropy of the feature for the sample set $S$, $n$ refers to the number of different probabilities being considered, and $P_i$ represents the probability of an input feature.

Each tree in the random forest algorithms is built independently and relies on a random vector sampled from the input data, with all trees in the forest having the same distribution [107]. In the process of classifying a new instance, each decision tree generates a classification for the input data, which random forest aggregates and selects the most or averaged voted prediction as the final result. Research shows that RF algorithms can enable a large number of weak-correlated classifiers to form a strong classifier [108]. While random forest algorithms provide significant performance in many situations, they have some disadvantages such as potential biases in feature importance and sensitivity to noise that cause some limitations in Alzheimer's research. In general, these are being widely used in the prediction and classification of diseases related to the brain and cancer that have the potential to be strong predictors for both small sample sizes and high-dimensional data.

In this paper, the diagnosis of Alzheimer's and mild cognitive impairment using MRI image processing based on traditional ML algorithms has been emphasized. It is noteworthy that deep learning models are a subgroup of machine learning that can analyze data and recognize patterns in the brain to solve complicated decision-making tasks. Among deep learning models, convolutional neural networks (CNNs) and Recurrent Neural Networks (RNNs) have recently demonstrated significant results in Alzheimer's detection. CNNs can automatically learn to extract relevant features from images which is crucial in MRI image processing and analyze subtle changes in the brain that may indicate the early stages of Alzheimer's disease [18]. It is notable that its lack of interpretability, especially in clinical environments where understanding the logic behind the diagnosis is important, is one of its limitations. Also, this model requires large amounts of labeled data and powerful hardware to train effectively. RNNs are a class of neural network architecture used to handle sequential data and temporal dependencies. This makes RNNs particularly well-suited for tasks involving time series data, especially data analysis in brain MRI longitudinal studies which is important for understanding the progression of Alzheimer's over time and creating accurate modeling for predicting future stages of the disease. Despite the advantages of RNN, this model has training complexity and requires large amounts of sequential data and powerful computational resources to train effectively.

### F. EVALUATION OF ML MODEL PERFORMANCE

For the evaluation of Machine Learning models' performance, quantitative measurement methods are used. These metrics provide insights into the model's operational efficacy and facilitate comparisons among various models or algorithms. In medical applications, scrutinizing the Machine Learning model is crucial to assess its predictive potential, capacity for generalization, ability to recognize, and overall quality functionality for patient care. Accuracy, Sensitivity, and Specificity are the three main metrics used to evaluate the classification model for data-accurate prediction and classification purposes for disease analysis that have great potential to figure out how the designed model works efficiently. The classification accuracy that is described in (3), is the ratio of the number of correct predictions to the total number of input samples. The sensitivity that is described in (4), corresponds to the detection of positive samples

correctly with respect to all the positive data. The specificity that is described in (5), corresponds to the detection of negative samples correctly with respect to all the negative data [109]. The formulas are following:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}. \tag{3}$$

$$Sensitivity = \frac{TP}{TP + FN}. \tag{4}$$

$$Specificity = \frac{TN}{TN + FP}. \tag{5}$$

In the above expressions, the labels of patient and healthy persons are considered positive and negative, respectively. Also, the labels are determined: TP for true positive (the number of persons correctly identified as patients), FN for false negative (the number of persons incorrectly identified as healthy), FP for false positive (the number of persons incorrectly identified as patients), and TN for true negatives (the number of persons correctly identified as healthy).

Papers have utilized various methods for evaluating their proposed models. As shown in Tables 3 and 4, the *accuracy* metric has been chosen because it was consistently reported across all these reviewed papers and serves as a crucial indicator of a model's performance. *accuracy* is a comprehensive criterion for assessing the performance of the proposed model that can measure the ability of the system to correctly identify all cases, including both patients and healthy individuals. Although the size of the database used varies between reviewed papers, this consistency in the use of accuracy allows us to make a better comparison between the different proposed Machine Learning models and evaluate their effectiveness in identifying Alzheimer's disease and different stages of mild cognitive impairment. Also, this helps us to identify the most useful algorithm for designing the Machine Learning model and recognize the efficient features for classifying different groups that can be an effective guideline for us for future studies and clinical applications by highlighting important biomarkers for diagnosing Alzheimer's disease and mild cognitive impairment.

## IV. TOWARD THE DEVELOPMENT OF MACHINE LEARNING ALGORITHMS RELATED TO AD BASED ON MRI

The increasing adoption of ML algorithms in healthcare especially in Alzheimer's offers expanded opportunities for early diagnosis and treatment that can become more reliable guidance for professionals, gradually. The application of technologies based on AI and ML can help doctors accurately diagnose these symptoms. Based on the published articles, many researchers are looking to combine different models to train their algorithms. The significant growth of data collection in these years has provided the platform for the implementation of such algorithms. AD and cognitive impairment are associated with changing atrophy patterns in different brain regions. Brain MRI scans with high-resolution imaging and the implementation of advanced image processing methods facilitate the discovery of these patterns and new variation spectrum caused by the disease in different brain regions, especially the hippocampus area. The 2D and 3D images that MRIs provide for Alzheimer's, make it easy for physicians to detect abnormalities in the brain. Consequently, MRI-based segmentation and image analysis are emerging as promising tools in AD research. Multi-view learning which analyzes the data from various views of the MRI images, the combination of different extracted features from the brain, and the ensembling of different classifiers have received attention in the past few years.

## V. CONCLUSION

Alzheimer's disease is the most common type of dementia that has grown significantly in recent years. Researchers believe that the cause of this disease does not rely on only one factor, and multiple factors such as genetics, lifestyle, and environment are likely to be influential. This disease affects all regions of the brain and leads to disturbances in brain function and symptoms such as changes in behavior and personality. Therefore, it is difficult for physicians to diagnose these symptoms correctly, especially in the early stages. Among AD diagnosis methods based on neuroimaging modality, MRI is more frequently utilized than other diagnosis technologies. MRI is a non-invasive imaging modality that provides detailed information about the soft tissue of the brain and it is a promising tool for the detection of abnormality pattern changes related to diseases including AD. There exists no definitive treatment currently for this disease. Consequently, the early and effective diagnosis of Alzheimer's and MCI plays a critical and pivotal role in arresting their progression and slowing the advancement of the disease stages. The development of Machine Learning algorithms in healthcare especially in Alzheimer's opens up new opportunities for early diagnosis that provide physicians with increasingly reliable guidance over time.

This paper presented a state-of-the-art review of studies that used ML techniques for the diagnosis of AD and different stages of MCI based on MRI images in the last 10 years. Different Alzheimer's diagnosis methods including clinical examination, non-imaging, and imaging modalities as well as popular used techniques in each method such as mini mental state examination, EEG brain signal, PET, and MRI scans have been described. Each step of MRI analysis using Machine Learning algorithms with several popular techniques applied in each step that had great achievements in the AD studies is discussed in this paper. These techniques include; useful preprocessing techniques for preparing the images for further analysis such as skull stripping and image denoising, segmentation of desired regions, the most efficient extracted features from the brain

that cover highly valuable information such as texture and morphological characteristics, and also the classifiers that have high-performance for differentiating the patient and healthy with famous evaluating metrics for measurements their functions. Achieving an ML model with high accuracy necessitates a large dataset of medical images for training. Nonetheless, attaining such a large dataset is often difficult in medical applications. The ADNI and OASIS are common and public datasets in AD studies involving MRI, PET, clinical testing, and neuropsychological assessment that can provide this facility for researchers to combine different approaches for the progression of MCI and early AD. Research in Alzheimer's is progressing towards extracting various brain features, including structural, pattern, or texture information. Combining these different features, investigating the multi-viewing data, and ensembling different classifiers or learning models have been shown an enhance the accuracy of ML algorithms that have been significantly studied in the papers recently. This review can be a valuable source for obtaining comprehensive information on the advanced image processing of brain MRI using Machine Learning algorithms implemented in recent research on AD and different stages of MCI. Since the accurate diagnosis of AD and distinction with MCI persons have many challenges, the purpose of this review is to describe the detailed algorithms used in numerous papers and also to express the efficient techniques in each stage of the ML process to provide informative insights for evaluating the impact of each technique on classification performance. Future research could extend the current review and examine different brain features in other imaging modalities not covered in the present study.

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