IJIRCCE

e-ISSN: 2320-9801 | p-ISSN: 2320-9798

INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN COMPUTER & COMMUNICATION ENGINEERING

Volume 12, Issue 4, April 2024

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

Impact Factor: 8.379

International Journal of Innovative Research in Computer and Communication Engineering

| e-ISSN: 2320-9801, p-ISSN: 2320-9798| www.ijircce.com | |Impact Factor: 8.379 | Monthly Peer Reviewed & Referred Journal |

|| Volume 12, Issue 4, April 2024 ||

| DOI: 10.15680/IJIRCCE.2024.1204246 |

Alzheimer's Diseases Detection by using Deep Learning

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ABSTRACT: The accurate diagnosis of Alzheimer's disease (AD) plays an important role in patient treatment,especially at thedisease'searlystages,becauseriskawarenessallowsthepatientstoundergopreventive measures even before the occurrence of irreversible brain damage. Although many recent studies have used computers to diagnose AD, most machine detection methods are limited by congenital observations. AD can bediagnosed-butnotpredicted-at its earlys tages,as prediction is only applicablebe for the disease manifests itself. Deep Learning (DL) has become a common technique for the early diagnosis of AD. Here, we briefly review some of the important literature on AD and explore how DL can help researchers diagnose the disease at its early stages.

KEYWORDS: Alzheimer's disease, deep learning, early stage detection and diagnosis.

I. INTRODUCTION

Translational applications of computational neuroscientific approaches have been proven exceptionally beneficial in comprehensive mental health trials[1].This multidisciplinary field of study can help model the biological processes governing the healthy and diseased states of the human brain and map these processes into observable clinical presentations. In the past decade, the rapid increase in high-volume biomedical datasets (neuroimaging and related biological data), concurrent with the advances in machine learning (ML), has opened new avenues for the diagnosis and prognosis of neurodegenerative and neuropsychiatric disorders [2]. From a computational perspective, this recent advancement has spawned the development of tools that incorporate several patient-specific observations into predictions and improve the clinical outcomes of patients suffering from such disorders [3], [4]. The ultimate purpose of these neuroscientific approaches is to enhance the initial exposure and complete the treatment plan of individuals in high risk of Alzheimer's disease (AD) and AD-related cognitive decline [5], [6].

For the reasons mentioned above, recent studies have focused on establishing exceptionally capable approaches that use ML systems to enhance the examination of AD. The use of automatic systems capable of differentiating pathological cases from normal cases based on their magnetic resonance imaging (MRI) scans (i.e., no past hypotheses are needed) will contribute immensely to the initial diagnosis of AD [7].

In this study, we review relevant studies that examines AD and use MRI data, ML and Deep Learning (DL) techniques with various AD datasets.

The rest of the study is organised as follows. Section II presents a brief history of AD, such as the discovery of the disease and brain imaging techniques. Section III describes the movement from ML towards DL in the AD field. Sections IV and V present a review of AD modules and datasets, respectively. The conclusion is provided in section VI.

II. RELATED WORK

ALZHIEMER'S DISEASE STORY3

The history of AD, as presented in this section, is consolidation of finding from AD publications searched in Google Scholar. Only the latest publications were considered, and selected. Our research focused on datasets used to examine AD and mild cognitive impairment MCI) [8], the forerunner of AD. The processes and techniques used by previous only the papers published between 2008 and 2019 were researchers were studied.

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A. ALZHEIMER's DISEASE

In 1910, in the eighth edition of *Clinical Psychiatry: A Text-book for Students and Physicians*, Kraepelin discussed a special group of cases with very severe cell transformations that involve too many plaques, the death of about one-third of the cerebral cortex, replacing them with specific bursts of coloured neurofibrils, and represent the most severe form of malnutrition. Kraepelin, who offered a description at a time when the clinical definition of AD was unclear [9], was the first to coin the condition as ''Alzheimer's disease''. The diagnosis of the Auguste Deter disease (the first case was introduced in 1906 by the German psychiatrist Alois Alzheimer) was somewhat ambiguous; after more than 100 years, credible descriptions for the clinical definition of AD started to surface. The descriptions of AD by Dr. Alois Alzheimer in 1907 and then by Proskin in 1909, included senile plaques and neurofibrillary sections [10]. However, when a patient's brain was clinically studied, no significant signs of arteriosclerosis were found, yet they were believed to be part of the diagnosis of the patient. In 1998, scientists from the University of Munich Germany and the Max Planck Institute of Neurobiology in Martinsried found that certain brain segments may be affected by neurofibrillary cramps and amyloid plaques [11]. Such research has since been considered the first reported case of AD; more importantly, the case meets the criteria as to how AD is defined today.

In 1997, Dr. Gerber and his colleagues from the Psychiatric Department of Max Planck Institute of Neurobiology examined histological cuts from F. Johan whose brain tissues had been well preserved for over 90 years. The research was regarded the second reported case of AD. An examination of the cuts revealed numerous amyloid plaques. The above research suggests that a mutational analysis of preserved brain tissue is practicable. On the 100th anniversary of Dr. Alzheimer's historic discovery, his findings were again confirmed. Figure 1 shows a comparison of a healthy brain and a brain affected by AD.

AD is currently ranked as the sixth leading cause of death in the US. Recent estimates indicate also that the disorder may even rank third (after heart disease and cancer) as the leading cause of the death for elderly [13]. Clearly, predicting the progression of AD at its early stages and preventing the disease from progressing are of great importance. The diagnosisofADrequiresvariousmedicaltestsandenormousmultivariate heterogeneous data. However, manual comparison, visualisation, and analysis of data are difficult and tedious due to the heterogeneous nature of medical tests. An efficient approach to accurately predict brain conditions is by classifying MRI scans, but this task is also challenging. Nonetheless, novel approaches have been proposed to diagnosis AD at its early stages through the efficient classification of brain MRI

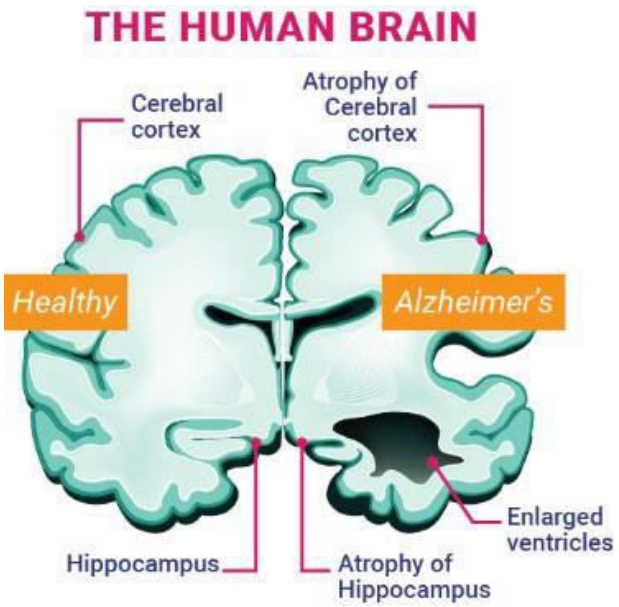

FIGURE 1. Progress of AD from MCI to severe AD [12].

International Journal of Innovative Research in Computer and Communication Engineering

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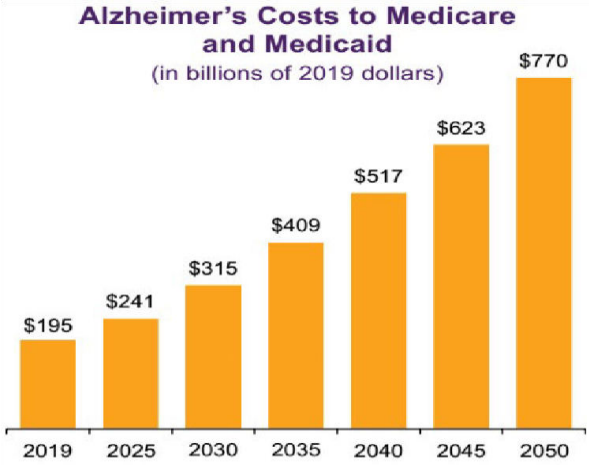

FIGURE 2. The estimation of the Alzheimer's costs of medicare and medicaid until 2050.

images and the use of label propagation with convolutional neural network (CNNs) [14]. As reported by the Alzheimer's Association in 2019, treatment for AD remain unavailable. In US alone, over five million people are affected by AD [15], [16]; amongst them, 200,000 individuals are younger than 65 years old. The report indicates that AD is expected to affect 10 million people, most of them in their 60s by 2050. This report further says that someone is affected with ADevery 67 seconds [17]. Figure2shows theestimation of Alzheimer's costs (in USD millions) of medicare and medicaid within the coming 50's years.

B. BRAIN IMAGING TECHNIQUES FORALZHEIMER's DISEASE (AD)

Brain imaging techniques can be used to non-invasively visualize the structure, function, or pharmacology of the brains [18]. The imaging techniques are generally divided into two categories: structural imaging and functional imaging [19]. Structural imaging provides information about the brain's structure, including neurons, synapses, glial cells, etc.

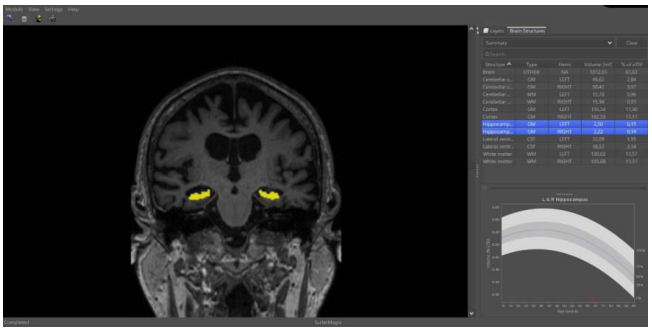

FIGURE 3. Example of structural Magnetic Resonance Imaging (MRI) [24].

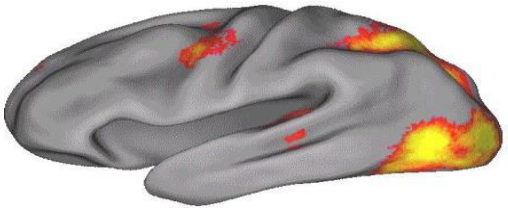

FIGURE 4. Example of functional Magnetic Resonance Imaging (fMRI) [25].

Functional imaging provides information about the activities performed by the brain [20]. The neuroimaging techniques mostly used for AD are the following:

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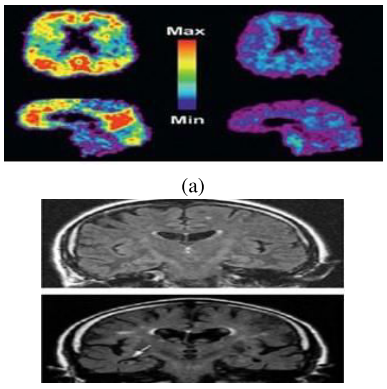
• **Magnetic Resonance Image (MRI):** This imaging technique utilises radio waves and magnetic fields to generate high-quality and high-resolution 2D and 3D images of brain structures. No harmful radiations from X-rays or radioactive tracers is generated. The most commonly used MRI for AD cases is the structural MRI, which measures brain volumes in vivo to detect brain degeneration (loss of tissue, cells, neurons, etc.). Brain degeneration is an inevitable progressive component of AD [21], [22]. Figure 3 shows an example of a structural MRI used to detect brain atrophy. Alternatively, Figure 4 shows an example of functional Magnetic Resonance Imaging (fMRI), a widely used method to measure human primary visual cortex and detect brain topography. fMRI provides useful information and data about the human brain's activity, i.e., how the brain functions. fMRI methods, such as brain imaging based on arterial Blood Oxygenation Level Dependent BOLD) contrasts and spin-labelling (ASL), are sensitive to the cerebral metabolic rate of oxygen consumption and cerebral blood flow (CBF). Figure 5a shows the brain areas of elderly subjects (AD patients; control), whilst Figure 5b shows medial temporal activation for the same control group [23].
Compared to other techniques, Single-Photon Emission Computed Tomography (SPECT) is more economical than the other techniques, but it is particularly delicate for the initial examination of changes in cerebral blood flow [27]. However, this technique remains to



(a)

(b)

FIGURE 5. a) The brain area in older controls and AD (b) MRI scan brain in Medial Temproral atrophy [26].

be one of the most popularly used procedures when analysing cerebral functions. Many studies have shown thatSPECTcanpreciselymeasurethecerebralperfusion of patients during AD examination. A recent study examined 116 patients suffering from AD. Amongst them, 67 individuals manifested other neurological issues, 26 individuals manifested nonAlzheimer's dementia and 23 individuals were categorised as age-matched controls [28]. The study was conducted to associate and examine cerebral perfusion, cognitive proteins and cerebrospinal fluid (CSF)-tau. The subjects were divided into dementia and control case groups. The Mini-Mental State Examination, the Cambridge Cognitive Examination and a functional rating scale on symptomatic dementia were used to classify cognitive functions and functional conditions. 99mTC-HMPAO SPECT scanning was associated with CSF-tau protein levels. The selected factors enhanced the examination's precision, thus rendering the study reliable. Other previous studies focused on bilateral parietal and temporal hypoperfusion amongst AD patients, andtheyfoundsignificantcorrelationsintheirneuropsychological test outcomes and SPECT conclusions [29]. The authors in [29] found that SPECT is more convenient for the examination of AD compared with the CSF-tau protein.

Figure 6 shows a raw arterial spin labelling perfusion image of a 70-year-old patient [30]. Given the intensely stall arterial transit time, the proximal part of the arterial tree is neither recommended for fit for this type of research.

• **Positron Emission Tomography (PET)**: This imaging procedure utilises radiotracers, and the brain's activities are analysed as radioactive spheres. Figure 7 shows the use of amyloid and fluorodeoxyglucose, the most commonly used tracers, for AD diagnosis. Certain actions, such as looking, listening, thinking, remembering, and working, were considered [32], [33].

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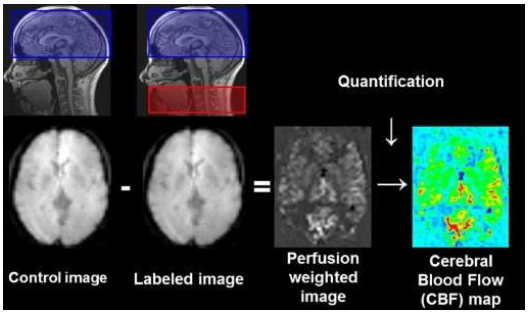

FIGURE 6. General principle of arterial spin labeling [31].

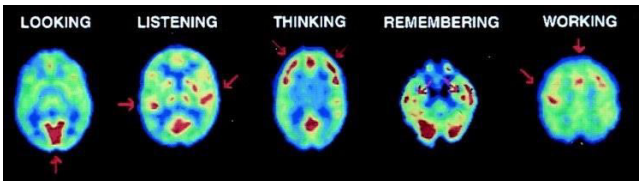

FIGURE 7. PET scan of a brain in normal condition [34].

Acetylcholinesterase was observed when the radioligands C-PMP and C-MP4A were utilised. This finding indicates a reduction in the temporal lobes of the AD subjects [35]. The same decline was observed amongst subjects with MCI, which eventually progressed to AD. The subjects with AD and neurodegenerative dementia were further classified. A-beta amyloid-specific ligands (Pittsburgh compound B 11C-PIB) were used because the subjects with AD showed improvements relative to the subjects with frontotemporal lobar degeneration (FTLD) and Parkinson's disease (PD) [36]. A temporoparietal hypoperfusion impression was observed in most of the AD subjects in PET. False-positive results, which do not offer any value to MRI, render SPECT inconvenientforclinicalpurposes;bycontrast,theuseof neuroreceptors and FP-CIT SPECT are more useful and convenient because they enable researchers to visualise discrepancies in the nigrostriatal dopaminergic neurons. FP-CITSPECTisanimagingprocedureappliedtowater diffusion analysis. This method can calculate the position, direction and anisotropy of white matter in the brain. This approach focuses on the discrepancies in the microstructural architecture of water molecules [37]. Although considerable research has been conducted to identify CSF-tau biomarker and amyloid levels, the lack of a unanimous conclusion hinders diffusion tensor imaging (DTI) from being included as reliable method for analyzing CSF biomarkers [38]. Figure 8(A) presents the DTI with coloured labels (red: left–right; green: anterior–posterior; blue: head–foot) performed with fractional anisotropy. While Figure 8(B) presents the DTI for AD performed with tractography analysis, in which regular changes in AD are observed (blue: corpus callosum; red: uncinate fasciculus; green: superior lateral fasciculus).

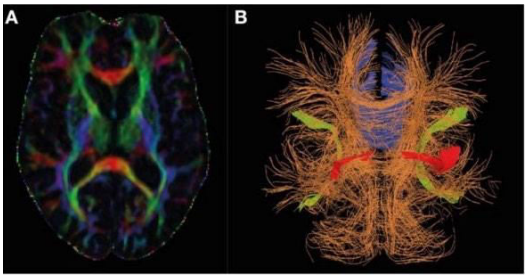

FIGURE 8. Diffusion Tensor Imaging (DTI) in AD [39].

• **MRI biomarkers of AD:** Biomarkers are regarded as the medical signs (i.e. the external manifestations of the medical statuses of patients) that can be measured precisely [40]. Biomarkers are defined in many different ways. For example, the International Program on Chemical Safety defines a biomarker as an object, an architecture or a procedure for a body that can be measured and from which the presence of a disorder can be concluded [41]. AD biomarkers have the following properties:

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1. Capable of identifying basic characteristics of AD's neuropathology;
2. Capable of certifying neuropathologically confirmed AD cases;
3. Efficient, capable of identifying initial AD and capable of differentiating AD from different forms of dementias;
4. Reliable, non-invasive, easy to implement and inexpensive.

Three kinds of biomarkers can help further describe AD: genetic, biochemical and neuroimaging biomarkers [42]. In the current study, MRI biomarkers are considered because of their enormouspotential in AD detection. Structural images from MRI can identify atrophic modifications that influence the entorhinal cortex and the hippocampus at the initial phase of MCI, which may advance to temporal and parietal lobes in AD and affect the frontal lobes at the final phases of AD. The identification of AD and neurons that are still not permanently impaired can be achieved by utilising functional MRI and DTI. These two procedures can determine functional connectivity and structural connectivity, and they add more authority and resources to biomarkers of AD; however, they still require regulation and authorisation to ensure clinical utility. These points signify that the most efficient and the most utilised MRI biomarker for AD is the structural MRI, specifically when the hippocampus volume is involved.

III. PROPOSED ALGORITHM

FROM MACHINE LEARNING TO DEEPLEARNING IN AD

ML has been used in the past decade to detect the MRI biomarkers of AD. Many ML methods are currently utilised to improve the determination and prediction of AD. A precise

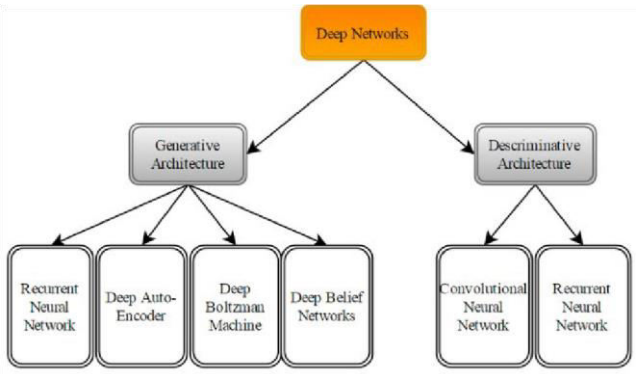

FIGURE 9. Categories of Deep Learning architectures.

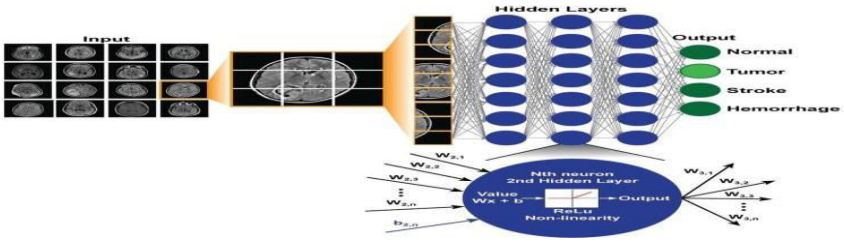

FIGURE 10. An example of Convolutional Neural Network (CNN) [48].

volume of images, multiple levels of representations are produced. The first-layer features, for instance, resemble Gabor filters or colour blobs that are often generalizable on many other image problems and datasets [56].

Deep neural networks may be used with bio-image datasets, but this approach requires enormous amounts of data, which in most cases is hard to obtain [57]. The data augmentation process is the solution to this issue, as it has the ability to develop the data by customising the initial data through the application of its own procedure. Some of the well-known procedures of data augmentation are reflecting, translating and rotating initial images to produce contrasting depictions [58]. Furthermore, different images can be obtained by customising the image's brightness, saturation and contrast [41], [42]. In addition to data augmentation, the other most commonly used method is the

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principal component analysis (PCA) jittering. In PCA jittering, some fundamental segments are added as they are multiplied by a lesser number [59], [60]. The main reason behind this process is to show only the most compatible characteristics of an image. In the latest research [61], [62], generative adversarial networks are utilised to blend images that contrast with the basic ones. This method requires the training of a distinct network [56], [57].

However, the produced images are not based on the changes in the image dataset. Other methods are therefore selected on the basis of the problem. For example, in [63], pointwise multiplications are utilised for the synthetic-aperture radar images to duplicate speckle noise. In [64], elastic deformation is adopted to reproduce the act of stretching in breast cancer treatments.

Another way of exploiting DL is to fine-tune a pre-trained DL model, such as CNNs, on a new dataset representing a new problem. This approach exploits the shallowest layers of a pre-trained CNN. Fine-tuning (or tuning) is a procedure that continues the training process on a new image dataset. This method greatly reduces the computational costs involved in the training process of new datasets, and it is suitable for relatively small datasets. Given the reduced computational costs, another benefit of using fine-tuning is providing opportunities to researchers to investigate easily the ensembles of CNNs. These ensembles can be built using more than one pre-trained CNN and many different parametric sets.

MCI from progressive MCI:

- Left hippocampus volume
- Right hippocampus volume
- Cortical thicknesses of left precuneus
- Left superior temporal sulcus
- Image data array: 3D or 4D array of image data.
- An affine array: details about the image location.
- Image metadata: describes the image.
- Uniform dataset (UDS): The data in thisdataset are gathered by evaluating the cases from the National Institute on Aging-Funded Alzheimer's Disease Centers. Evaluation is carried out annually. Each year, the cases undergo clinical examination to determine the neuropsychological testing scores. Nearly 60% of all UDS cases have the apolipoprotein E genotype. The UDS can utilise structural MRI images and data for the cases, and it can subsequently implement enhancements by focusing on the latest factors emphasising frontotemporal lobar degeneration. More work is being conducted to enable researchers to obtain different types of images and biomarkers from biospecimens (i.e. CSF).
- Neuropathology dataset: This dataset contains standardised neuropathology data from patients who died and whose bodies were autopsied.
- Minimum dataset: Prior to the establishment of UDS in 2005, cross-sectional data on cases from the Alzheimer's Disease Center were gathered through previous research.
- Second, we need to determine the main types of AD, beginning with the datasets from the Alzheimer's Disease Neuroimaging Initiative, Harvard Medical School and Max Planck Institute Leipzig (Mind–Brain–Body Dataset-LEMON).

A. ADNI

The ADNI dataset was gathered from over 40 radiology hubs, and it comprised 509 cases in total (137 AD cases, 76 MCIc cases, 134 MCInc cases and 162 CN cases) [78]. The time frame to supervise the transition to AD was 18 months. ADNI was previously utilised in many studies to categorise AD and understand the transformation to AD. The basic purpose of ADNI is to determine if serial MRI, PET other biological markers and clinical and neuropsychological estimations can be combined to calculate the advancement of MCI and initial AD.

The ADNI dataset was built on the T1-weighted structural MRIs captured at 1.5T in concordance with the ADNI acquisition protocol. The standard data of the patients were examined. Additional preprocessing was performed, including image re-orientation, cropping, skull stripping, image normalisation to the Montreal Neurological Institute standard space (MNI152 T1, 1 mm brain template) and tissue segmentation into grey and white matter probability maps. The volume of the MRI was 121 × 145 × 121 voxels. These volumes were used by the ML systems to perform the categorisation functions, such as AD against CN, MCIc against CN and MCIc against MCInc. The performances of the classifiers used for the grey matter tissue probability maps were correlated with those used for the white matter and whole-brain volume maps. Twentyfold cross-validation was used for the validation.

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The MRI dataset of the ADNI consisted of 260 patient cases (130 AD cases and 130 CN cases). Prior to this processing of this dataset, the approach of Carli *et al.* [79] was used to determine AD. The characteristics of AD, including voxel cluster and voxel volume, were retrieved and utilised in this study.

The data in the ADNI1 dataset were obtained from a repository, as suggested by Anna *et al.* The details are tabulated in Table 1. All of the data were captured at 1.5T and used to obtain the maximum data for training and testing. In ADNI1 studies, follow-ups are not generally required, as the work entails the searching of variations amongst groups of patients. However, follow-ups are required when changes in MCI patients need to be depicted. The obtained data were documented in Excel spreadsheets.

IV. SIMULATION RESULTS

HARVARD MEDICAL SCHOOL DATASET:

The Harvard Medical School dataset comprised T2-weighted brain MR images, and almost all of the selected images were from the dataset. The images all have the size of 256 × 256 pixels. The 613 images were split into two AD categories (27 images for the normal category and 513 images for the abnormal category) and then utilised for training and

TABLE 1. ADNI1 standardized data collections for 1.5T.

Collection Name	Collection Description
ADNI1:Screening 1.5T	Contains screening or baseline scans
ADNI1: Complete 1Yr 1.5T	Contains screening, 6- and 12-months scans
ADNI1: Complete 2Yr 1.5T	Contains screening, 6 months, 1 year, 18 months (MCI only) and 2 years scans
ADNI1: Annual 2Yr 1.5T	Contains screening, 1, and 2 years scans
ADNI1: Complete 3Yr 1.5T	Contains screening, 6 months, 1 year, 18 months (MCI only), 2 years, and 3 years (normal and MCI only) scans

validation [80]. The normal category contained two cases, whereas the abnormal category contained 40 cases. As shown by the current dataset, the abnormal images correspond to cerebrovascular, neoplastic, degenerative and inflammatory diseases. Embolic infarction, diffusion and acute stroke fall under the cerebrovascular disease.

MAX PLANCK INSTITUTE LEIPZIG MIND-BRAIN-BODYDATASET-LEMON

A dataset was created to examine mind, body and emotion interactions for the 2013–2015 period in Germany [81]. The mind–brain–body dataset of Max Planck Institute Leipzig comprised 228 subjects divided into two categories: young (N = 154, 25.1 ± 3.1 years, 20–35 age range, 45 females) and old (N = 74, 67.6 ± 4.7 years, 59–77 age range, 37 females) [81]. The dataset was created over two days, during which patients underwent the following major processes: MRI at 3T fMRI, quantitative T1 magnetisation-prepared rapid gradient echo (MP2RAGE), T2-weighted fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging(SWI), susceptibility mapping (QSM), diffusion-weighted imaging (DWI) and 62-channel electroencephalogram experiment at rest [82]. Blood pressure, heart rate and pulse anthropometrics were collected in all the tests. Blood samples, urine samples and respiration rate were frequently collected. By utilising the standardised clinical interview guide for DSM IV (i.e. Hamilton depression scale and the borderline symptom list) [83], the institute was also able to examine psychiatric syndromes. The whole process of identifying psychiatric syndromes required six tests and 21 questionnaires.

NATIONAL HEALTH AND AGING TRENDS STUDY

In response to the increasing number of cases, the National Institute on Aging-Funded Alzheimer's Disease Centers instituted in 1999 the National Alzheimer's Coordinating Center (NACC) whose purpose in to facilitate research initiatives [84]. NACC, in coordination with the Alzheimer's Disease Genetics Consortium and the National Centralised Repository for Alzheimer's Disease and Related Dementias, offered precious resources for the exploratory and explanatory aspects of the research work.

OPEN ACCESS SERIES OF IMAGING STUDIES(OASIS)

Dr. Randy Buckner (Howard Hughes Medical Institute) developed datasets for the Open Access Series of Imaging Studies at Harvard University, the Neuroinformatics Research Group at Washington University School of Medicine and the Biomedical Informatics Research Net-

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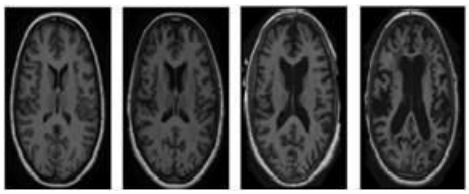

FIGURE 11. Sample images from the Open Access Series of Imaging Studies dataset [86].

work [85]. The dataset involved 416 cases of 18- to 96-yearold subjects and 100 cases of subjects older than 60 years old. Figure11showsasampleofbrainMRIimagesfromtheOpen Access Series of Imaging Studies dataset.

V. CONCLUSION AND FUTURE WORK

Overall, on the basis of high-level literature review, we found that the published papers in this area tend to focus on two main areas of research, namely, biomarkers and neuroimaging, but with increasing interest in image analysis. Although regarded thorough and extensively conducted, the work adds little knowledge to the initial detection of AD, as the majority of selected patients are already known to have AD. This study reviewed the some of the important related AD datasets and diagnose techniques and detection. This approach is feasible for early-stage neuroimaging research.

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| e-ISSN: 2320-9801, p-ISSN: 2320-9798| www.ijircce.com | |Impact Factor: 8.379 | Monthly Peer Reviewed & Referred Journal |

|| Volume 12, Issue 4, April 2024 ||

| DOI: 10.15680/IJIRCCE.2024.1204246 |

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