Alzheimer's Diseases Detection by Using Deep Learning Algorithms: A Mini-Review

SUHAD AL-SHOUKRY[1,2]**, TAHA H. RASSEM**[1]**, (Senior Member, IEEE), AND NASRIN M. MAKBOL**[3]

[1]Faculty of Computing, College of Computing and Applied Sciences, Universiti Malaysia Pahang, Kuantan 26300, Malaysia
[2]Najaf Technical Institute, Al-Furat Al-Awsat Technical University, Najaf 54003, Iraq
[3]College of Computer Science and Engineering, Hodeidah University, Hodeidah, Yemen

Corresponding author: Taha H. Rassem (tahahussein@ump.edu.my)

ABSTRACT The accurate diagnosis of Alzheimer's disease (AD) plays an important role in patient treatment, especially at the disease's early stages, because risk awareness allows the patients to undergo preventive 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 be diagnosed-but not predicted-at its early stages, as prediction is only applicable before 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.

INDEX TERMS 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. ALZHIEMER'S DISEASE STORY

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 only the papers published between 2008 and 2019 were

The associate editor coordinating the review of this manuscript and approving it for publication was Minho Jo.

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 researchers were studied.

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 diagnosis of AD requires various medical tests and enormous multivariate 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
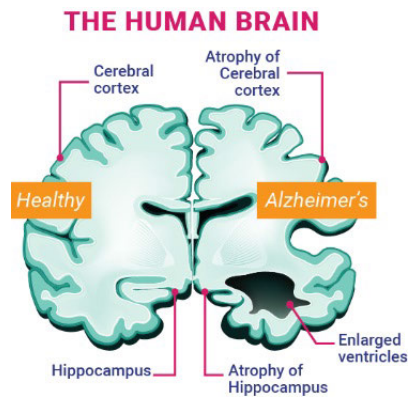

FIGURE 1. Progress of AD from MCI to severe AD [12].
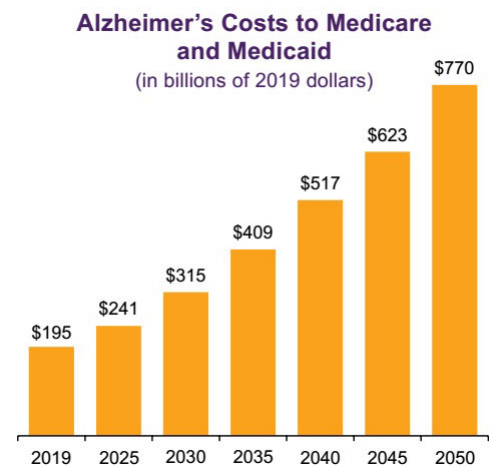

FIGURE 2. The estimation of the Alzheimer's costs of medicare and medicaid until 2050.

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 AD every 67 seconds [17]. Figure 2 shows the estimation of Alzheimer's costs (in USD millions) of medicare and medicaid within the coming 50's years.

B. BRAIN IMAGING TECHNIQUES FOR ALZHEIMER'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.
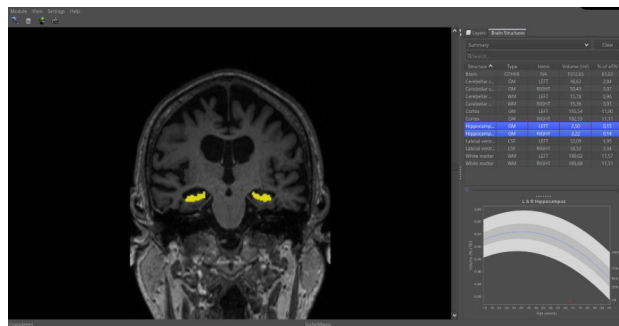
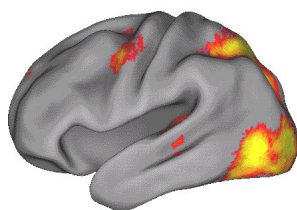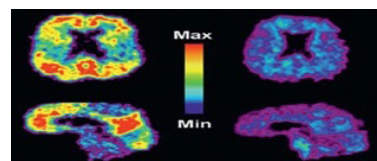**FIGURE 3.** Example of structural Magnetic Resonance Imaging (MRI) [24].

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

FIGURE 5. a) The brain area in older controls and AD (b) MRI scan brain in Medial Temproral atrophy [26].
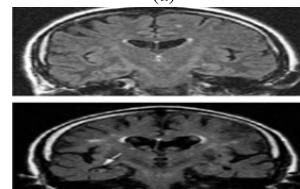
Functional imaging provides information about the activities performed by the brain [20]. The neuroimaging techniques mostly used for AD are the following:

- **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 be one of the most popularly used procedures when analysing cerebral functions. Many studies have shown that SPECT can precisely measure the cerebral perfusion 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 non-Alzheimer'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, and they found significant correlations in their neuropsychological 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].
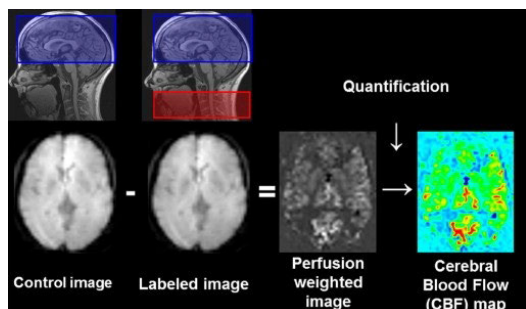
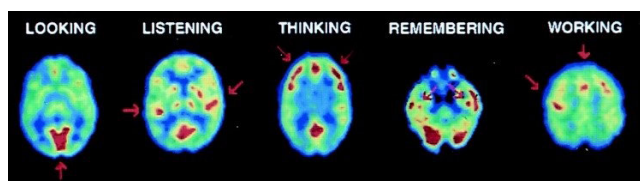**FIGURE 6.** General principle of arterial spin labeling [31].

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 inconvenient for clinical purposes; by contrast, the use of neuroreceptors and FP-CIT SPECT are more useful and convenient because they enable researchers to visualise discrepancies in the nigrostriatal dopaminergic neurons. FP-CIT SPECT is an imaging procedure applied to water 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).
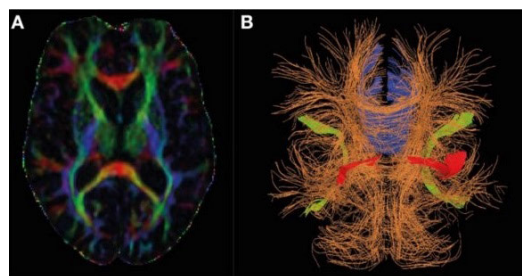

FIGURE 8. Diffusion Tensor Imaging (DTI) in AD [39].

- **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:

  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 enormous potential 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. FROM MACHINE LEARNING TO DEEP LEARNING 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
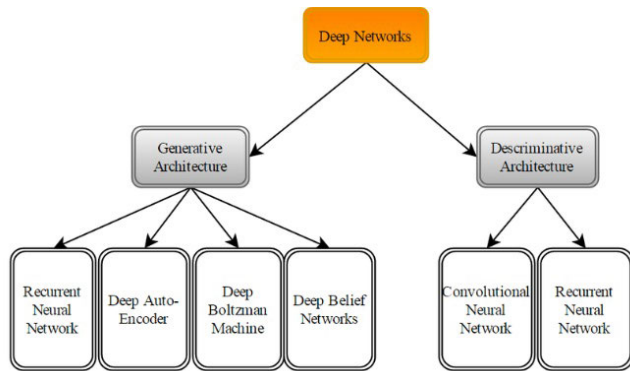
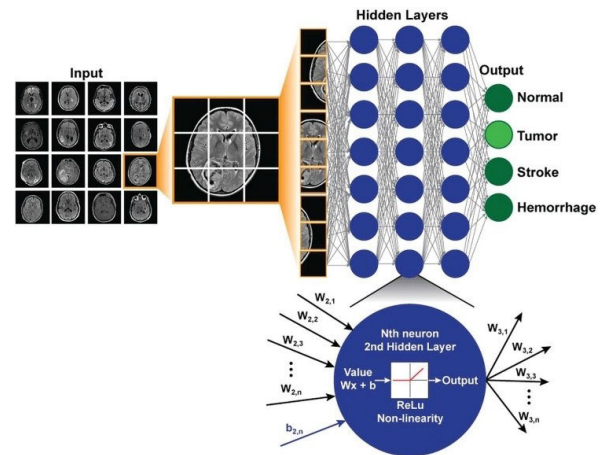**FIGURE 9.** Categories of Deep Learning architectures.

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

categorisation of stable MCI versus progressive MCI was achieved by Haller *et al.* by analysing 35 cases of normal controls and 67 cases of MCI with a support vector machine (SVM) [43]. Segmentation has been emphasised in most ML processes for bio-image classification, whereas the retrieval of strong texture descriptions has generally been neglected. Nonetheless, in many cases, retrieving compelling characteristics from a complete image can obviate the need for image segmentation [44]. Most of the early research used classic texture descriptors, such as Gabor filters and Haralick texture features [45], [46]. DL has been described as 'a new area of ML research, which has been introduced with the objective of moving ML closer to one of its original goals: artificial intelligence'

The DL structure typically involves more than two levels of abstraction and representation to help understand text, sound and image data [47]. DL can be classified into two sections, namely, generative architecture and discriminative architecture, as shown in Figure 9. Generative architecture can be subdivided into the four sections of Recurrent Neural Network (RNN), Deep Auto-Encoder (DAE), Deep Boltzmann Machine (DBM) and Deep Belief Networks (DBN), whilst discriminative architecture can be divided into Convolutional Neural Network (CNN) and RNN.

Many researchers in the recent past have identified the scale-invariant feature transform and the local binary patterns as the modern texture descriptors for bio-image analysis [49]–[51]. As these descriptors are developed by humans to retrieve features from images, they are termed handcrafted features. A key point in the use of these descriptors is to pinpoint a portion of an image by using a vector, after which the handcrafted texture is retrieved. As a type of classifier, the SVM then receives the descriptions retrieved by the handcrafted procedure [52]. The most suitable descriptors retrieve descriptions from a dataset, and many of the most commonly used and compact descriptors use DL to accomplish the desired goal [53], [54]. For this purpose, the CNN is used to retrieve the descriptions from the images, as shown in Figure 10. CNNs act especially as a generic characteristics retriever [55]. Once a deep network is trained on a large

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 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.

Other studies have employed CNNs merely as feature extractors [57]. The classification is undertaken using either SVM with a polynomial or linear kernels and logistic regression extreme ML random forest or XGBoost and logistic regression (decision trees) or SVM with various kernel [65]. The results retrieved from CNN classification and those from other classifiers that merely considered features extracted by CNN were compared by Shmulev and Belyaev [66]; they concluded that the latter operates more efficiently than the former. CNNs can be used on pre-extracted features instead of applied directly to image data. This case is especially true when the CNN is directly applied to the outputs of various regression models or when clinical scores are compared with other hyperparameters and MRI-based features.

Additionally, CNNs can be applied to non-Euclidean spaces, such as patients' graphs or cortical surface images. Other architectures can also be applied to anatomical MRIs. Various studies have employed different versions of the multilayer perceptron, which consists of a probabilistic neural network or a stack of FC layers. Both supervised (deep polynomial networks) and unsupervised (deep Boltzmann machine and AE) structures have been employed by other studies to extract high-level representations of the features, whereas SVMs are primarily used for classification [67].

Extensive preprocessing, which usually occurs in non-CNN architectures, are applied to imaging features, such as texture, shapes or cortical thickness and regional features. Besides, embedding or feature selection is frequently required to further reduce dimensionalities. However, DL-based classification approaches are not restricted to cross-sectional anatomical MRIs only. Longitudinal studies can utilise information obtained from different time points whilst studying the same subject.

Nho *et al.* [68] implemented an SVM with kernels that allowed for the switching of amnestic MCI to AD whilst removing the other subtypes of the prodromal phase of AD. A 90.5% cross-validation efficiency was achieved in their AD and NC analyses. In addition, they achieved 72.3% efficiency in anticipating the progression of MCI to AD. Two processes were used for the retrieval of characteristics:

- FreeSurfer: a brain segmentation and cortical parcellation software tool.
- SPM5: a statistical parametric mapping tool.

They also reported that the best prediction of MCI progressing to AD can be achieved for features varying from 24 to 26. In addition, they found that the thickness of the left entorhinal cortical is the most crucial determinant; the other two crucial determinants are right hippocampal volume and apolipoprotein Eε4 status. Hippocampal volume was used by Costafreda *et al.* [69] to predict MCI cases that were likely to

progress to AD. Their work comprised 103 MCI cases from AddNeuroMed. They used FreeSurfer for the preprocessing of data and SVM for the classification of data by using a non-linear Gaussian radial basis kernel. They implemented their model after training it on full AD and NC samples. Within a year, they achieved an efficiency of 85% for AD and 80% for NC. They concluded that the consolidation of entorhinal atrophy can improve prognostic performance via hippocampal modifications.

Their critical review of several SVM-based research showed that SVM is a widely utilised method to distinguish between AD cases and cognitively normal cases and between stable forms and progressive forms of MCI [12]. Structural and functional neuroimaging techniques were also used for diagnosis, progression prediction and treatment prognosis. Coupé*et al.* [70] determined five important characteristics to effectively distinguish stable MCI from progressive MCI:

- Left hippocampus volume
- Right hippocampus volume
- Cortical thicknesses of left precuneus
- Left superior temporal sulcus
- Right anterior part of the parahippocampal

Their work reported 72% efficiency for the ADNI data.

Wolf *et al.* [71] sampled 138 AD patients, 225 CN cases and 358 MCI patients to distinguish and predict AD. They used data from ADNI and practiced on the brain imaging. They also used neural networks and logistic regression to distinguish AD cases from CN cases. Comprehensive brain characteristics were chosen as the parameters. Crucial characteristics, such as volume or thickness, were identified instead of simply focusing on certain areas of the brain.

- Left middle temporal gyrus
- Left hippocampus
- Volume of the right entorhinal cortex
- Left interior lateral ventricle
- Right inferior parietal lobe

In 2018, Liu *et al.* [72] suggested the use of cascaded CNNs because of their ability to progressively analyse different levels and characteristics of MRI and PET brain images. No expertise was required, as no image segmentation was involved in preprocessing the data. This feature generally serves as the advantage of this approach over the other methods. In the other methods, the features are retrieved and then fitted to the model. Their study involved 100 NC cases, 93 AD patients and 204 MCI patients based on the ADNI data. A 93.26% efficiency was achieved.

Kruthika *et al.* [73] proposed a content-based image retrieval system that relied on 3D Capsules Network (CapsNets), i.e. a 3D CNN, and a pre-trained 3D auto-encoder technology to detect AD at its initial stages. They stated that 3D CapsNets are capable of performing rapid imaging. However, unlike the deep CNN, their method can only improve the detection. They achieved an accuracy of 98.42% in distinguishing AD. Basaia *et al.* [74] examined subjects from an organisation in which 407 healthy controls

and 418 AD, 280 progressive MCI and 533 stable MCI cases were involved. They used CNNs and practiced on the 3D T1-weighted images. Their dataset was ADNI. They investigated CNN activity to classify AD, progressive MCI and stable MCI. 75% accuracy was obtained when CNNs were used to segregate the progressive MCI patients from the stable MCI patients. Payan and Montana [75] developed an algorithm that used MRI scans to evaluate the condition of a particular patient. They used a total of 2,265 cases, and they selected the ADNI dataset for their work.

Hosseini-Asl *et al.* [76] suggested the use of DSA-3D-CNN, which they found to be more precise than the other modern predictors in evaluating AD based on the MRI scans. By distinguishing the AD, MCI and NC cases, they showed that the retrieval of features can be enhanced in 3D-CNN. Seven metrics were utilised by the brain extraction tool for the analysis. They used the FMRIB software library. Apart from describing the process of using the data, this library contains tools to facilitate MRI, fMRI and DTI brain imaging data. PET was used to classify head MRIs into brain and non-brain images by removing non-brain tissues (an important aspect of any analysis). Preprocessing was not needed in BET, and the process was not time-consuming.

IV. MODULES DATASETS TYPES FOR AD

This section explains the dataset modules and the types of AD. The widely utilised types of data are the neuroimaging file formats. First, the AD dataset module loads the scans, then the image data from the Neuroimaging Informatics Technology Initiative (NIfTI) are utilised [77]. NiBabel (one of the classic packages of Python) is configured by using pip. The NiBabel images are composed of the following:

- 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 this dataset 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 $121 \times 145 \times 121$ 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.

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.

B. 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.

### C. MAX PLANCK INSTITUTE LEIPZIG MIND-BRAIN-BODY DATASET-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.

D. 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.

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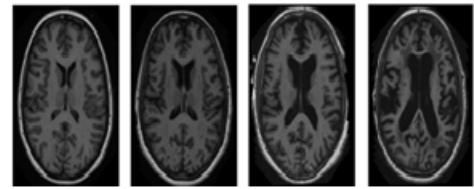
FIGURE 11. Sample images from the Open Access Series of Imaging Studies dataset [86].

work [85]. The dataset involved 416 cases of 18- to 96-year-old subjects and 100 cases of subjects older than 60 years old. Figure 11 shows a sample of brain MRI images from the Open Access Series of Imaging Studies dataset.

V. CONCLUSION

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.

REFERENCES

[1] E. Bullmore and O. Sporns, "Complex brain networks: Graph theoretical analysis of structural and functional systems," *Nature Rev. Neurosci.*, vol. 10, no. 3, pp. 186–198, Mar. 2009.

[2] S. Eickhoff, T. E. Nichols, J. D. Van Horn, and J. A. Turner, "Sharing the wealth: Neuroimaging data repositories," *NeuroImage*, vol. 124, pp. 1065–1068, Jan. 2016.

[3] N. Bhagwat, "Prognostic applications for Alzheimer's disease using magnetic resonance imaging and machine-learning," Ph.D. dissertation, Graduate Dept. Inst. Biomater. Biomed. Eng., Univ. Toronto, Toronto, ON, Canada, 2018.

[4] J. Yao, "Development of a multimodal framework for cardiac computed tomography gating," Ph.D. dissertation, School Elect. Comput. Eng., Georgia Inst. Technol., Atlanta, GA, USA, 2018.

[5] S. Ahmed, K. Y. Choi, J. J. Lee, B. C. Kim, G.-R. Kwon, K. H. Lee, and H. Y. Jung, "Ensembles of patch-based classifiers for diagnosis of Alzheimer diseases," *IEEE Access*, vol. 7, pp. 73373–73383, 2019.

[6] A. Chaddad, C. Desrosiers, and T. Niazi, "Deep radiomic analysis of MRI related to Alzheimer's disease," *IEEE Access*, vol. 6, pp. 58213–58221, 2018.

[7] K. F. Hunter, M. Northwood, V. Haggar, and F. Bates, *Management of Fecal Incontinence for the Advanced Practice Nurse*. Springer, 2018, pp. 127–148.

[8] J.-Y. Han, L. M. Besser, C. Xiong, W. A. Kukull, and J. C. Morris, "Cholinesterase inhibitors may not benefit mild cognitive impairment and mild Alzheimer disease dementia," *Alzheimer Disease Associated Disorders*, vol. 33, no. 2, pp. 87–94, 2019.

[9] I. P. Vatanabe, P. R. Manzine, and M. R. Cominetti, "Historic concepts of dementia and Alzheimer's disease: From ancient times to the present," *Revue Neurologique*, vol. 176, no. 3, pp. 140–147, Mar. 2020.

[10] E. R. Adlard and R. J. Sundberg, "The chemical century: Molecular manipulation and its impact on the 20th century," *Chromatographia*, vol. 80, no. 10, p. 1599, Oct. 2017.

[11] L. Keuck, "History as a biomedical matter: Recent reassessments of the first cases of Alzheimer's disease," *Hist. Philosophy Life Sci.*, vol. 40, no. 1, p. 10, Mar. 2018.

[12] C. Saraiva, C. Praça, R. Ferreira, T. Santos, L. Ferreira, and L. Bernardino, "Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases," *J. Controlled Release*, vol. 235, pp. 34–47, Aug. 2016.

[13] H. K. Koh and A. K. Parekh, "Toward a united states of health: Implications of understanding the US burden of disease," *JAMA*, vol. 319, no. 14, pp. 1438–1440, Apr. 2018.

[14] D. Jin, J. Xu, K. Zhao, F. Hu, Z. Yang, B. Liu, T. Jiang, and Y. Liu, "Attention-based 3D convolutional network for Alzheimer's disease diagnosis and biomarkers exploration," in *Proc. IEEE 16th Int. Symp. Biomed. Imag. (ISBI)*, Apr. 2019, pp. 1047–1051.

[15] R. H. Blank, *End-of-Life Decision Making for Alzheimer's Disease Across Cultures*. Singapore: Springer, 2019, pp. 121–136.

[16] J. McCleery, L. Flicker, E. Richard, and T. J. Quinn, "The national institute on aging and Alzheimer's association research framework: A commentary from the cochrane dementia and cognitive improvement group," *Alzheimer's Dementia*, vol. 15, no. 1, pp. 179–181, Jan. 2019.

[17] N. R. S. Kimura, M. A. T. Baptista, R. L. Santos, M. da Gloria Portugal, A. Johannenssen, M. L. Barca, K. Engedal, J. Laks, J. P. Simões, V. M. Rodrigues, and M. C. N. Dourado, "Caregivers' perspectives of quality of life of people with young- and late-onset Alzheimer disease," *J. Geriatric Psychiatry Neurol.*, vol. 31, no. 2, pp. 76–83, Mar. 2018.

[18] N. L. Hill and J. Mogle, "Alzheimer's disease risk factors as mediators of subjective memory impairment and objective memory decline: Protocol for a construct-level replication analysis," *BMC Geriatrics*, vol. 18, no. 1, Dec. 2018.

[19] D. D. Nolte, J. J. Turek, and K. Jeong, "Method and apparatus for motility contrast imaging," U.S. 20 150 062 592 A1, Oct. 16, 2018.

[20] S. J. Makaretz, M. Quimby, J. Collins, N. Makris, S. McGinnis, A. Schultz, N. Vasdev, K. A. Johnson, and B. C. Dickerson, "Flortaucipir tau PET imaging in semantic variant primary progressive aphasia," *J. Neurol., Neurosurg. Psychiatry*, vol. 89, no. 10, pp. 1024–1031, Oct. 2018.

[21] M. Waser, T. Benke, P. Dal-Bianco, H. Garn, J. A. Mosbacher, G. Ransmayr, R. Schmidt, S. Seiler, H. B. D. Sorensen, and P. J. Jennum, "Neuroimaging markers of global cognition in early Alzheimer's disease: A magnetic resonance imaging-electroencephalography study," *Brain Behav.*, vol. 9, no. 1, Jan. 2019, Art. no. e01197.

[22] K. Trojachanec, I. Kitanovski, I. Dimitrovski, and S. Loshkovska, "Longitudinal brain MRI retrieval for Alzheimer's disease using different temporal information," *IEEE Access*, vol. 6, pp. 9703–9712, 2018.

[23] S. A. Engel, D. E. Rumelhart, B. A. Wandell, A. T. Lee, G. H. Glover, E.-J. Chichilnisky, and M. N. Shadlen, "fMRI of human visual cortex," *Nature*, vol. 369, no. 6481, p. 525, 1994.

[24] R. Cuingnet, E. Gerardin, J. Tessieras, G. Auzias, S. Lehéricy, M.-O. Habert, M. Chupin, H. Benali, and O. Colliot, "Automatic classification of patients with Alzheimer's disease from structural MRI: A comparison of ten methods using the ADNI database," *NeuroImage*, vol. 56, no. 2, pp. 766–781, May 2011.

[25] I. Lajoie, S. Nugent, C. Debacker, K. Dyson, F. B. Tancredi, A. Badhwar, S. Belleville, Y. Deschaintre, P. Bellec, J. Doyon, C. Bocti, S. Gauthier, D. Arnold, M.-J. Kergoat, H. Chertkow, O. Monchi, and R. D. Hoge, "Application of calibrated fMRI in Alzheimer's disease," *NeuroImage, Clin.*, vol. 15, pp. 348–358, Jan. 2017.

[26] E. J. W. Van Someren, J. M. Oostermanm, B. Van Harten, R. L. Vogels, A. A. Gouw, H. C. Weinstein, P. Poggesi, and E. J. A. Scherder, "Medial temporal lobe atrophy relates more strongly to sleep-wake rhythm fragmentation than to age or any other known risk," *Neurobiol. Learn. Memory*, vol. 160, pp. 132–138, Apr. 2019.

[27] M. Sagnou, B. Mavroidi, A. Shegani, M. Paravatou-Petsotas, C. Raptopoulou, V. Psycharis, I. Pirmettis, M. S. Papadopoulos, and M. Pelecanou, "Remarkable brain penetration of cyclopentadienyl M(CO)$_3^+$ (M = ^{99m}Tc, Re) derivatives of benzothiazole and benzimidazole paves the way for their application as diagnostic, with single-photon-emission computed tomography (spect), and therapeutic agents for Alzheimer's disease," *J. Med. Chem.*, vol. 62, no. 5, pp. 2638–2650, 2019.

[28] I. Begcevic, D. Brinc, M. Brown, E. Martinez-Morillo, O. Goldhardt, T. Grimmer, V. Magdolen, I. Batruch, and E. P. Diamandis, "Brain-related proteins as potential CSF biomarkers of Alzheimer's disease: A targeted mass spectrometry approach," *J. Proteomics*, vol. 182, pp. 12–20, Jun. 2018.

[29] N. A. Johnson, G.-H. Jahng, M. W. Weiner, B. L. Miller, H. C. Chui, W. J. Jagust, M. L. Gorno-Tempini, and N. Schuff, "Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: Initial experience," *Radiology*, vol. 234, no. 3, pp. 851–859, Mar. 2005.

[30] Y. Li, S. Dolui, D.-F. Xie, and Z. Wang, "Priors-guided slice-wise adaptive outlier cleaning for arterial spin labeling perfusion MRI," *J. Neurosci. Methods*, vol. 307, pp. 248–253, Sep. 2018.

[31] J.-C. Ferré, E. Bannier, H. Raoult, G. Mineur, B. Carsin-Nicol, and J.-Y. Gauvrit, "Arterial spin labeling (ASL) perfusion: Techniques and clinical use," *Diagnostic Intervent. Imag.*, vol. 94, no. 12, pp. 1211–1223, Dec. 2013.

[32] A. Drzezga, D. Altomare, C. Festari, J. Arbizu, S. Orini, K. Herholz, P. Nestor, F. Agosta, F. Bouwman, F. Nobili, Z. Walker, G. B. Frisoni, and M. Boccardi, "Diagnostic utility of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in asymptomatic subjects at increased risk for Alzheimer's disease," *Eur. J. Nucl. Med. Mol. Imag.*, vol. 45, no. 9, pp. 1487–1496, 2018.

[33] V. L. Villemagne, V. Doré, S. C. Burnham, C. L. Masters, and C. C. Rowe, "Imaging tau and amyloid-β proteinopathies in Alzheimer disease and other conditions," *Nature Rev. Neurol.*, vol. 14, no. 4, pp. 225–236, Apr. 2018.

[34] A. D. Cohen and W. E. Klunk, "Early detection of Alzheimer's disease using PiB and FDG PET," *Neurobiol. Disease*, vol. 72, pp. 117–122, Dec. 2014.

[35] R. Ducksbury, T. Whitfield, and Z. Walker, "SPECT/PET findings in Lewy body dementia," in *PET and SPECT in Neurology*. Berlin, Germany: Springer, 2014, pp. 373–415.

[36] D. A. Wolk, Z. Zhang, S. Boudhar, C. M. Clark, M. J. Pontecorvo, and S. E. Arnold, "Amyloid imaging in Alzheimer's disease: Comparison of florbetapir and pittsburgh compound-B positron emission tomography," *J. Neurol., Neurosurg. Psychiatry*, vol. 83, no. 9, pp. 923–926, Sep. 2012.

[37] M. J. Knight, A. Wearn, E. Coulthard, and R. A. Kauppinen, "T2 relaxometry and diffusion tensor indices of the hippocampus and entorhinal cortex improve sensitivity and specificity of MRI to detect amnestic mild cognitive impairment and Alzheimer's disease dementia," *J. Magn. Reson. Imag.*, vol. 49, no. 2, pp. 445–455, Feb. 2019.

[38] A. Kumar, S. Singh, A. Chaurasiya, and A. Singh, "Implication of preclinical biomarkers in identification of mild cognitive impairment (MCI) and Alzheimer's disease: Promises and future challenges," *Res. Rep.*, vol. 2, pp. 1–16, May 2018.

[39] M. J. Knight, B. McCann, R. A. Kauppinen, and E. J. Coulthard, "Magnetic resonance imaging to detect early molecular and cellular changes in Alzheimer's disease," *Frontiers Aging Neurosci.*, vol. 8, pp. 1–9, Jun. 2016.

[40] L. Mosconi, M. Walters, J. Sterling, C. Quinn, P. McHugh, R. E. Andrews, D. C. Matthews, C. Ganzer, R. S. Osorio, R. S. Isaacson, M. J. De Leon, and A. Convit, "Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer's disease: A cross-sectional study of middle-aged adults from the broader New York city area," *BMJ Open*, vol. 8, no. 3, Mar. 2018, Art. no. e019362.

[41] M. Mussap, A. Noto, F. Cibecchini, and V. Fanos, "The importance of biomarkers in neonatology," *Seminars Fetal Neonatal Med.*, vol. 18, no. 1, pp. 56–64, Feb. 2013.

[42] A. Cedazo-Minguez and B. Winblad, "Biomarkers for Alzheimer's disease and other forms of dementia: Clinical needs, limitations and future aspects," *Exp. Gerontol.*, vol. 45, no. 1, pp. 5–14, Jan. 2010.

[43] S. Haller, D. Nguyen, C. Rodriguez, J. Emch, G. Gold, A. Bartsch, K. O. Lovblad, and P. Giannakopoulos, "Individual prediction of cognitive decline in mild cognitive impairment using support vector machine-based analysis of diffusion tensor imaging data," *J. Alzheimer's Disease*, vol. 22, no. 1, pp. 315–327, Sep. 2010.

[44] M. Gamarra, A. Mitre-Ortiz, and H. Escalante, "Automatic cell image segmentation using genetic algorithms," in *Proc. 22th Symp. Image, Signal Process. Artif. Vis. (STSIVA)*, Apr. 2019, pp. 1–5.

[45] I. Fogel and D. Sagi, "Gabor filters as texture discriminator," *Biol. Cybern.*, vol. 61, no. 2, pp. 103–113, Jun. 1989.

[46] R. M. Haralick, K. Shanmugam, and I. Dinstein, "Textural features for image classification," *IEEE Trans. Syst., Man, Cybern.*, vol. SMC-3, no. 6, pp. 610–621, Nov. 1973.

[47] L. Deng *et al.*, "Deep learning: Methods and applications," *Found. Trends Signal Process.*, vol. 7, nos. 3–4, pp. 197–387, Jun. 2014.

[48] S. Vieira, W. H. L. Pinaya, and A. Mechelli, "Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications," *Neurosci. Biobehav. Rev.*, vol. 74, pp. 58–75, Mar. 2017.

[49] L. Nanni, S. Brahnam, S. Ghidoni, E. Menegatti, and T. Barrier, "A comparison of methods for extracting information from the co-occurrence matrix for subcellular classification," *Expert Syst. Appl.*, vol. 40, no. 18, pp. 7457–7467, Dec. 2013.

[50] Y. Xu, J.-Y. Zhu, E. I.-C. Chang, M. Lai, and Z. Tu, "Weakly supervised histopathology cancer image segmentation and classification," *Med. Image Anal.*, vol. 18, no. 3, pp. 591–604, Apr. 2014.

[51] J. Barker, A. Hoogi, A. Depeursinge, and D. L. Rubin, "Automated classification of brain tumor type in whole-slide digital pathology images using local representative tiles," *Med. Image Anal.*, vol. 30, pp. 60–71, May 2016.

[52] N. Cristianini and J. Shawe-Taylor, *An Introduction to Support Vector Machines and Other Kernel-Based Learning Methods.* Cambridge, U.K.: Cambridge Univ. Press, 2000.

[53] J. Schmidhuber, "Deep learning in neural networks: An overview," *Neural Netw.*, vol. 61, pp. 85–117, Jan. 2015.

[54] C. Feng, A. Elazab, P. Yang, T. Wang, F. Zhou, H. Hu, X. Xiao, and B. Lei, "Deep learning framework for Alzheimer's disease diagnosis via 3D-CNN and FSBi-LSTM," *IEEE Access*, vol. 7, pp. 63605–63618, 2019.

[55] Y. LeCun, Y. Bengio, and G. Hinton, "Deep learning," *Nature*, vol. 521, pp. 436–444, May 2015.

[56] J. Yosinski, J. Clune, Y. Bengio, and H. Lipson, "How transferable are features in deep neural networks?" in *Proc. 27th Int. Conf. Neural Inf. Process. Syst. (NIPS)*, vol. 2. Cambridge, MA, USA: MIT Press, 2014, pp. 3320–3328.

[57] S. Sarraf and G. Tofighi, "Classificatioof Alzheimer's disease using fMRI data and deep learning convolutional neural networks," 2016, *arXiv:1603.08631*. [Online]. Available: http://arxiv.org/abs/1603.08631

[58] Y. Li, C. Huang, L. Ding, Z. Li, Y. Pan, and X. Gao, "Deep learning in bioinformatics: Introduction, application, and perspective in the big data era," *Methods*, vol. 166, pp. 4–21, Aug. 2019.

[59] A. Krizhevsky, I. Sutskever, and G. E. Hinton, "ImageNet classification with deep convolutional neural networks," *Commun. ACM*, vol. 60, no. 6, pp. 84–90, May 2017.

[60] J. Shijie, W. Ping, J. Peiyi, and H. Siping, "Research on data augmentation for image classification based on convolution neural networks," in *Proc. Chin. Autom. Congr. (CAC)*, Oct. 2017, pp. 4165–4170.

[61] M. Frid-Adar, I. Diamant, E. Klang, M. Amitai, J. Goldberger, and H. Greenspan, "GAN-based synthetic medical image augmentation for increased CNN performance in liver lesion classification," *Neurocomputing*, vol. 321, pp. 321–331, Dec. 2018.

[62] D. Zhao, D. Zhu, J. Lu, Y. Luo, and G. Zhang, "Synthetic medical images using F&BGAN for improved lung nodules classification by multi-scale VGG16," *Symmetry*, vol. 10, no. 10, p. 519, 2018.

[63] J. Ding, B. Chen, H. Liu, and M. Huang, "Convolutional neural network with data augmentation for SAR target recognition," *IEEE Geosci. Remote Sens. Lett.*, vol. 13, no. 3, pp. 364–368, Jan. 2016.

[64] E. Castro, J. S. Cardoso, and J. C. Pereira, "Elastic deformations for data augmentation in breast cancer mass detection," in *Proc. IEEE EMBS Int. Conf. Biomed. Health Informat. (BHI)*, Mar. 2018, pp. 230–234.

[65] T. Shen, J. Jiang, Y. Li, P. Wu, C. Zuo, and Z. Yan, "Decision supporting model for one-year conversion probability from MCI to AD using CNN and SVM," in *Proc. 40th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Jul. 2018, pp. 738–741.

[66] Y. Shmulev and M. Belyaev, "Predicting conversion of mild cognitive impairments to Alzheimer's disease and exploring impact of neuroimaging," in *Graphs in Biomedical Image Analysis and Integrating Medical Imaging and Non-Imaging Modalities*, D. Stoyanov, Z. Taylor, E. Ferrante, A. V. Dalca, A. Martel, L. Maier-Hein, S. Parisot, A. Sotiras, B. Papiez, M. R. Sabuncu, and L. Shen, Eds. Cham, Switzerland: Springer, 2018, pp. 83–91.

[67] H.-I. Suk, S.-W. Lee, and D. Shen, "Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis," *NeuroImage*, vol. 101, pp. 569–582, Nov. 2014.

[68] K. Nho, L. Shen, S. Kim, S. L. Risacher, J. D. West, T. Foroud, C. R. Jack, M. W. Weiner, and A. J. Saykin, "Automatic prediction of conversion from mild cognitive impairment to probable Alzheimer's disease using structural magnetic resonance imaging," in *Proc. AMIA Annu. Symp.*, Nov. 2010, pp. 542–546.

[69] S. G. Costafreda, I. D. Dinov, Z. Tu, Y. Shi, C.-Y. Liu, I. Kloszewska, P. Mecocci, H. Soininen, M. Tsolaki, M. Tsolaki, B. Vellas, L. Wahlund, C. Spenger, A. Toga, S. Lovestone, and A. Simmons, "Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment," *NeuroImage*, vol. 56, no. 1, pp. 212–219, May 2011.

[70] P. Coupé, S. F. Eskildsen, J. V. Manjón, V. S. Fonov, and D. L. Collins, "Simultaneous segmentation and grading of anatomical structures for patient's classification: Application to Alzheimer's disease," *NeuroImage*, vol. 59, no. 4, pp. 3736–3747, Feb. 2012.

[71] R. Wolz, V. Julkunen, J. Koikkalainen, E. Niskanen, D. P. Zhang, D. Rueckert, H. Soininen, J. Lötjönen, "Multi-method analysis of MRI images in early diagnostics of Alzheimer's disease," *PLoS ONE*, vol. 6, no. 10, 2011, Art. no. e25446.

[72] M. Liu, D. Cheng, K. Wang, and Y. Wang, "Multi-modality cascaded convolutional neural networks for Alzheimer's disease diagnosis," *Neuroinformatics*, vol. 16, nos. 3–4, pp. 295–308, Oct. 2018.

[73] K. R. Kruthika, Rajeswari, and H. D. Maheshappa, "Multistage classifier-based approach for Alzheimer's disease prediction and retrieval," *Informat. Med. Unlocked*, vol. 14, pp. 34–42, 2019.

[74] S. Basaia, F. Agosta, L. Wagner, E. Canu, G. Magnani, R. Santangelo, and M. Filippi, "Automated classification of Alzheimer's disease and mild cognitive impairment using a single MRI and deep neural networks," *NeuroImage, Clin.*, vol. 21, Jan. 2019, Art. no. 101645.

[75] A. Payan and G. Montana, "Predicting Alzheimer's disease: A neuroimaging study with 3D convolutional neural networks," in *Proc. 4th Int. Conf. Pattern Recognit. Appl. Methods (ICPRAM)*, vol. 2, Feb. 2015, pp. 1–6.

[76] M. Ghazal, "Alzheimer rsquo s disease diagnostics by a 3D deeply supervised adaptable convolutional network," *Frontiers Biosci.*, vol. 23, no. 2, pp. 584–596, 2018.

[77] M. Larobina and L. Murino, "Medical image file formats," *J. Digit. Imag.*, vol. 27, no. 2, pp. 200–206, Apr. 2014.

[78] L. Vermunt, A. J. L. van Paasen, C. E. Teunissen, P. Scheltens, P. J. Visser, and B. M. Tijms, "Alzheimer disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal," *Neurology*, vol. 92, no. 23, pp. e2699–e2705, Jun. 2019.

[79] F. De Carli, F. Nobili, M. Pagani, M. Bauckneht, F. Massa, M. Grazzini, C. Jonsson, E. Peira, S. Morbelli, and D. Arnaldi, "Accuracy and generalization capability of an automatic method for the detection of typical brain hypometabolism in prodromal Alzheimer disease," *Eur. J. Nucl. Med. Mol. Imag.*, vol. 46, no. 2, pp. 334–347, Feb. 2019.

[80] R. Yiou and D. Goodenough, "Applying problem-based learning to the teaching of anatomy: The example of harvard medical school," *Surgical Radiologic Anatomy*, vol. 28, no. 2, pp. 189–194, May 2006.

[81] N. Mendes *et al.*, "A functional connectome phenotyping dataset including cognitive state and personality measures," *Sci. Data*, vol. 6, p. 180307, 2019.

[82] A. Babayan *et al.*, "A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults," *Sci. Data*, vol. 6, Feb. 2019, Art. no. 180308.

[83] R. Drill, O. Nakash, J. A. DeFife, and D. Westen, "Assessment of clinical information: Comparison of the validity of a structured clinical interview (the SCID) and the clinical diagnostic interview," *J. Nervous Mental Disease*, vol. 203, no. 6, pp. 459–462, Jun. 2015.

[84] D. Beekly, K. Schwabe-Fry, G. Thomas, C. S. DeCarli, O. T. Carmichael, and W. A. Kukull, "The national Alzheimer's coordinating center: Development of the MRI, PET and CSF biomarker databases," *Alzheimer's Dementia*, vol. 13, no. 7, p. P157, Jul. 2017.

[85] D. S. Marcus, T. H. Wang, J. Parker, J. G. Csernansky, J. C. Morris, and R. L. Buckner, "Open access series of imaging studies (OASIS): Cross-sectional MRI data in young, middle aged, nondemented, and demented older adults," *J. Cognit. Neurosci.*, vol. 19, no. 9, pp. 1498–1507, Sep. 2007.

[86] H. Matsuda, "MRI morphometry in Alzheimer's disease," *Ageing Res. Rev.*, vol. 30, pp. 17–24, Sep. 2016.

SUHAD AL-SHOUKRY received the B.Sc. degree from the Faculty of Computer Science, University of Babylon, Iraq, in 1996, and the master's degree in information technology from the Faculty of Science and Information Technology, Universiti Kebangsaan Malaysia (UKM), in 2015. She is currently pursuing the Ph.D. degree with the Faculty of Computing, College of Computing and Applied Science, Universiti Malaysia Pahang (UMP). She is also an Assistant Lecturer with Al-Furat Al-Awsat Technical University, kufa, Najaf, Iraq. Her research interests include image processing and computer-aided diagnosis.

TAHA H. RASSEM (Senior Member, IEEE) received the B.Sc. degree in computer engineering from the University of Technology, Baghdad, Iraq, in 2001, the M.Tech. degree in computer science from the University of Hyderabad, Hyderabad, India in 2007, and the Ph.D. degree in computer engineering-image processing from the School of Electrical and Electronic Engineering, Universiti Sains Malaysia, in 2014. He was an Assistant Lecturer with the Computer Engineering Department, School of Computer Science and Engineering, Hodeidah University, Hodeidah, Yemen, from 2001 to 2005. He is currently a Senior Lecturer with the Graphics and Multimedia Program, Faculty of Computing, Universiti Malaysia Pahang (UMP). He has published many research articles with many ISI and Scopus indexed journal. He was a committee member with many of the international conferences. His research interests include image classification, object recognition, deep learning, natural language processing, and computer vision. He is a Senior Member of IAENG, a Senior Member of ASR, and a member of MBOT.

NASRIN M. MAKBOL received the B.Sc. degree in computer science from the University of Technology, Baghdad, Iraq, in 2001, the M.Tech. degree in computer science from the University of Hyderabad, Hyderabad, India, in 2007, and the Ph.D. degree in computer engineering-distributed signal processing from Universiti Sains Malaysia, in 2015. She was a Postdoctoral Fellow with the School of Electrical and Electronic Engineering, Universiti Sains Malaysia. She is currently an Assistant Professor with the College of Computer Science and Engineering, Hodeidah University. Her research interests include digital watermarking and image processing.

• • •