Advancing Early Detection of Alzheimer's Disease with Machine Learning & Neuroimaging Modalities

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***Abstract*— Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the rapid degeneration of brain cells, which severely impairs memory, cognitive function, and overall independence, ultimately leading to a steep decline in quality of life. Therefore, accurate and early diagnosis evaluations are essential for effective treatment and management. This survey paper examines the role of machine learning (ML) algorithms in relations to predicting Alzheimer's disease, with a significant emphasis on the use of magnetic resonance imaging (MRI) scans as the main imaging modality. MRI data is well known for its detailed insights into the structural changes of the brain to view the differentiation between healthy individuals and "abnormal" patients exhibiting varying stages of Alzheimer's disease. The survey particularly focuses on two medical biomarkers widely utilized in AD research: amyloid-beta plagues and neurofibrillary tangles, both of which are mainly linked to the progression of AD. The survey addresses the recent innovations in ML-based models towards the early prediction of Alzheimer's disease, the prevalence of amyloid-beta accumulation and neurofibrillary tangles with the use of MRI data scans and highlights any recently identified biomarkers that can push the boundaries for the future of AD research. Overall, this survey aims to highlight the significant impact of combining machine learning and MRI data to advance the efforts in the early detection and improve diagnostic accuracy of AD, while providing an outline of key research goals that current and future researchers should prioritize to continue enhancing the capabilities of detecting AD.**

Keywords—Alzheimer's disease (AD), neurogenerative disorders, machine learning, early diagnosis, structural brain changes, amyloid-beta plaques, neurofibrillary tangles

I. INTRODUCTION

A. Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in the world and is the leading cause of dementia in contemporary society, which affects millions of individuals every single year [1]. AD is mainly characterized by its progressive cognitive decline, such as memory loss, impairment of language, and physical disorientation; it significantly impacts the daily lives of patients and places a significant amount of physical, emotional, and financial stress onto the caregivers and existing healthcare systems [2]. According to the World Health Organization, more than 55 million people live with dementia worldwide, and 10 million new cases arise annually [3]. Additionally, studies estimate that AD is projected to affect more than 100 million people by 2050, highlighting the critical need for breakthrough research efforts on a global scale [4]. The biomarkers of

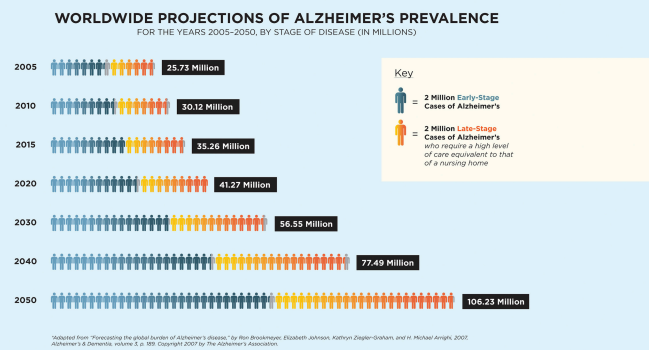

Figure 1: Projections of Alzheimer's disease throughout the world from 2005 to 2050; the blue color indicating early-stage cases of AD; the orange color indicates late stages of AD, requiring care equivalent to that of a nursing home [12].

AD include the accumulation of amyloid-beta plaques and neurofibrillary tangles [5], which disrupt communication between neurons in the brain, leading to synaptic degeneration and eventually neuronal death. These physical changes are particularly seen in brain regions such as the hippocampus, which plays a central role in the formation of memories; the continual growth of these changes will eventually lead to widespread brain atrophy [6]. In a clinical sense, AD progresses through several distinguished stages, ranging from mild cognitive impairment (MCI) [7] to extreme dementia, to the extent where patients require full-time supervision over simple daily tasks. The risks for AD encompass a variety of fields, including genetic, environmental, and individual lifestyle fields [8]. However, age remains as the most significant risk factor to all individuals, and other factors such as poor diet and physical inactivity influence a higher risk for individuals. The risk is significantly worse for older individuals, as the chances of AD double every five years after the age of 65 [9], and coexisting conditions such as cardiovascular diseases and diabetes show the intermixing of conditions within the progression of the disease. In the contemporary era, the most difficult challenge regarding AD diagnosis is preclinical detection in the early stages; traditional methods, such as patient history and basic cognitive tests are currently insufficient for early AD detection. Pharmacological treatments such as NMDA receptor antagonists are also used to improve communications between neurons, and non-pharmacological approaches such as cognitive training and exercise have shown slight benefits in delaying symptoms [10]. However, recent research has found neuroimaging modalities such as structural MRI, functional MRI, and PET scans to be beneficial in

identifying biomarkers associated with AD, enabling researchers to identify changes in the brain years before any current symptoms appear in individuals. Despite breakthroughs in AD research, there is no main cure for AD, and the priority shifts towards looking for non-invasive methods of disease detection [11].

B. Machine Learning

Machine learning (ML), a major subfield of artificial intelligence (AI), offers the ability to analyze insightful patterns inside complex datasets based on the training data provided. Unlike traditional statistical methods, ML algorithms can adapt from new data, as well as provide classifications and predictions that are difficult to produce with standard methods. ML offers several different types of learning methods, including supervised, unsupervised, and reinforcement learning, each offering their own capabilities for certain types of data and purposes [13]. Supervised learning uses labeled datasets to train models, which makes it ideal for classification tasks regarding disease detection. In contrast, unsupervised learning identifies hidden patterns with unlabeled datasets, and reinforcement learning focuses on optimizing decision-making with the use of feedback mechanisms. ML also has the capability to process multimodal and high-dimensional data, which is essential in healthcare, as their data is involved in neuroimaging and medical records. Some applications of ML that are used in relation to health include predictive modeling, disease classification, and biomarker identifications. For example, popular techniques such as support vector machines (SVM) and conventional neural networks (CNN) have been the most used for detecting outliers and analyzing images, especially in AD research. SVMs can be trained to classify individuals into distinguished categories of AD, simply based on the features that are extracted from the neuroimaging data. In terms of early diagnosis, SVMs are particularly useful since they are able to identify small changes in brain activity that are not observable to the human eye. With the use of feature selection, SVMs can reduce the overall dimensionality so that the only certain biomarkers are prioritized to ensure accurate and efficient results. Additionally, SVMs can apply towards multiple neuroimaging modalities simultaneously as a way to increase the accuracy of AD predictions. On the other hand, CNNs are a type of deep learning algorithm which particularly focus on image recognition tasks, which are useful in relation to AD has it can be used to analyze patterns in images of brain structures; since these images contain structural and functional information related to the brain, CNNs are able to identify signs of hippocampal shrinkage, accumulation of amyloid plagues, tau tangles, and abnormal distribution patterns, all which help identify AD within individuals [14]. The strength of CNNs rely on their strength in adapting to learn features implicitly, which are essential for medical imaging tasks. However, for ML to be successfully applied, it must go through rigorous model training, validation testing, and several trials to avoid flaws such as overfitting and a lack of generalizability. The combination of ML algorithms and existing neuroimaging techniques provide current researchers the direction towards a method for early AD diagnosis. The main purpose of ML in relation to AD diagnosis is to be able to develop a path for the future identification of individuals that are susceptible as well as creating new forms of therapeutic treatments that succeed the current traditional methods today.

C. Neuroimaging Modalities

There are several neuroimaging modalities that have emerged from recent AD research, each offering unique capabilities for identifying and predicting disease progression. These modalities utilize advanced imaging techniques to capture structure, functional, and metabolic changes inside the brain, providing critical insights into the underlying mechanisms of AD. Among the main ones used in modern research, magnetic resonance imaging (MRI) stands out as the most widely used neuroimaging modality for predicting the progression from MCI to AD. A study observes that out of a total of 56 distinct journals, structural MRI (sMRI) accounted for 48.2% of the modalities utilized [15]. The popularity of sMRI is due to its high spatial resolution, allowing researchers to identify early neurotomical changes associated with AD, including hippocampal volume reduction and entorhinal cortical thinning [16]. sMRI utilizes magnetic fields and radio waves in order to produce high-resolution images of brain structures, enabling researchers to detect abnormalities such as cortical volume reduction. By adjusting contrast settings, sMRI is able to distinguish between white and gray matter, offering detailed insights into tissue associated with AD [17]. In order to enhance these modalities, some models integrated sMRI with cognitive assessments such as the Mini-Mental State Exam (MMSE) and the Alzheimer's Disease Assessment Scale (ADAS). Demographic factors such as age, sex, and certain genotypes have been combined into sMRI-based models in order to enhance the overall accuracy in identifying MCI and AD patients. Despite the advantages of MRI in the research field, there are also weaknesses that prevent an optimal solution, such as high costs and lack of mobility. There are also other sub-levels of MRI modalities, such as functional MRI (fMRI), which use similar principles to MRI but particularly focus more on providing high spatial and temporal resolution, as well as long-term analysis of brain activity [18]. fMRI is relatively new in the field of biomarkers for AD. One of its advantages is that it is a non-invasive imaging technique that does not require radiation exposure allowing for multiple trials for longitudinal studies [19]. fMRI also provides insight on the brain regions that centralize on memory formation, as well as certain behavioral events; however, the amount of data based on fMRI is very limited in its

outcome and has been used in highly exclusive centers [19].

The second main modality used in AD research is position emission tomography (PET) imaging, which focuses on capturing any early metabolic and amyloid-related changes inside the brain in high resolution with the use of radioactive tracers. Unlike structural imaging modalities such as sMRI, PET focuses more on the functional processes and the biochemical abnormalities associated with AD [20]. One of the main applications of PET imaging in relation to AD is the detection of glucose metabolism deficits; with the use of fluorodeoxyglucose PET (FDG-PET), researchers are able to measure the amount of glucose inside the brain, providing an indirect insight into neuronal activity. Regions with reduced glucose metabolism are the focus, with the most common regions being the temporoparietal cortex and posterior cingulate, indicating symptoms of cognitive decline [20]. As a way to achieve better predictions related to cognitive deterioration, one study uses a deep learning method to combine FDG-PET with 18F-florbetapir (AV-45) PET, a radiopharmaceutical tracer used to detect amyloid-beta plaques in the brain, which is a known indicator of AD seen in individuals [21]. Other combined approaches include integrating PET data with neuropsychological tests, such as ADAS scores and general demographic information, to improve the efficiency in identification for at-risk individual [22]. Another sub-level of the PET modality is denoted as Tau PET, which highly specializes in mapping the spread of tau pathology from the medial temporal lobe to the neocortical regions as AD progresses. These advantages can be seen as a more reliable method than the amyloid PET previously mentioned [23]. Despite these advantages, PET imaging is uncommon in modern AD research due to its higher cost and its overall complexity compared to the MRI modality.

Electroencephalography (EEG) is another neuroimaging modality recognized for its non-invasive and cost-effective characteristics [24]; it has mainly been used to detect neural biomarkers related to MCI and AD, focusing on the analysis of decreased alpha and beta rhythms activity, as well as increased delta and theta oscillations. These wave changes in the brain are well-established and correlate well with the presence of AD. However, EEG is less frequently utilized in research studies focused on early AD diagnosis predictions. One of the major limitations is since over 95% of EEG studies that have been conducted over the past thirty years have only involved less than 100 participants, which makes the findings of these studies less useful. Also, the several types of dementia, such as frontotemporal dementia and vascular cognitive impairments, creates a further need to validate the EEG findings with the user of larger datasets that include the different types of dementia. Addressing these flaws along with overcoming the knowledge gap will require long-term research efforts in the future.

II. DATASETS

Before reviewing the integration of machine learning algorithms in relation to early diagnosis AD prediction, it is important to recognize the main datasets used in modern research. In terms of AD research, the most widely known public dataset belongs to the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. The ADNI dataset is fully comprehensive, offering a longitudinal collection of imaging, biomarker, and genetic data that delves in structural, functional, and molecular brain imaging types. In the ADNI dataset, individuals are classified among multiple categories, including cognitively unimpaired (CN), mild cognitive impairment (MCI), and Alzheimer's disease (AD). In our survey, the ADNI's MRI dataset is a core component that is used in the research articles as it contains thousands of high-resolution MRI scans that are collected over several intervals (e.g., 6 months, 1 year, 18 months, 2 years, 3 years), which allows researchers to observe the progression of the disease over time. The scans highlight certain brain regions that have been mainly affected by AD, including the hippocampus and entorhinal cortex [25].

The OASIS dataset is widely used among research articles related to machine learning algorithms for early detection in AD; however, we will particularly focus on the MRI scans of individuals that the OASIS dataset includes. There are three main versions in relation to MRI, each with unique characteristics that support cross-sectional and longitudinal research into AD progression. OASIS-1 is cross-sectional collection of 416 subjects aged 18 to 96, with around 3-4 individual T1-weighted MRI scans were obtained in one scan session for each subject. Both women and men are included in this version, with 100 of the subjects over the age of 60 that are clinically diagnosed with mild to moderate AD. Additionally, there is a reliability dataset comprised of 20 non-demented subjects who were re-scanned 90 days after their initial scan sessions to track disease progression. OASIS-2 is a longitudinal collection of 150 subjects aged 60 to 96, with 2-3 visits for each subject spaced one year apart for a total of 373 imaging sessions. In each session, 3-4 individual T1-weighted MRI scans were included, like OASIS-1. Among all the subjects, 72 were non-demented, with 51 individuals diagnosed with mild to moderate Alzheimer's disease. 14 subjects were initially classified to be non-demented but were later diagnosed to be classified as demented in subsequent visits. This makes OASIS-2 valuable in terms of tracking the structural brain changes over time for AD. OASIS-3 is the most recent and comprehensive version, which includes a compilation of data from 1,378 subjects collected over the course of 30 years. This dataset includes a total of 2,842 MRI sessions, with 755 cognitively normal adults and 622 individuals with varying stages of cognitive

impairment. In terms of other features, OASIS-3 includes cognitive testing data, clinical assessments, and PET, although this survey will primarily focus on the distinct types of MRI data [26].

One relatively less popular dataset is the Alzheimer's Disease Sequencing Project (ADSP), a large-scale research initiative focused on discovering the genetic factors that contribute to AD and other overlapping neurodegenerative disorders. The ADSP has several objectives: identifying genetic risk factors contributing to increased risk of developing AD, identifying new genomic variants contributing to protection against developing AD, and providing insight to why individuals with known risk factor variants escape from fully developing AD. These goals are studied across multi-ethnic populations in order to identify any new pathways for disease prevention and requires a large number of participants needed to capture information of all variants. The ADSP contains a Discovery dataset, which contains whole-genome sequencing data on 584 subjects from 113 families, as well as pedigree data for over 4000 subjects. The Replication dataset is the most recent from ADSP, which includes a combination of genotyping and sequencing approaches from at least 30,000 subjects taken from the years 2016-2021 [27].

III. RESULTS

The application of machine learning in AD diagnosis had ramped up in recent years, driven by the urgent need for early and accurate detection as the number of diagnosed patients is rapidly advancing without an ideal cure. ML algorithms, utilizing multiple imaging modalities including sMRI, fMRI, and the combination of other cognitive metrics, offer immense potential to uncover patterns and biomarkers that are an order of magnitude above traditional methods that are set in place. This section will provide an overview of several distinct studies that employ various ML techniques, with SVMs and CNNs being some of many to predict certain AD features and early diagnosis predictions.

To start, Behesti et al. [28] introduce a novel feature-selection approach that combines feature ranking and genetic algorithms (GAs) to optimize feature subsets with a computer-aided diagnosis (CAD) system, balancing the strong discriminative ability with reduced dimensionality. The classifier used was based off an SVM algorithm, a supervised learning algorithm that was integrated with a linear kernel to evaluate AD classification as well as MCI-to-AD conversion. The dataset used includes a total of 458 participants from the ADNI dataset based on sMRI data from the brain, and it is evaluated using a 10-fold cross validation, which allows every data point to be part of both the training and test data. By utilizing the Fisher criterion into the GA's objective function, this approach can effectively identify the most significant features to predict the progression of MCI as well as the classification of AD. This approach can manage higher-dimensional datasets while highlighting the use of voxel-based morphometry (VBM) when analyzing gray matter atrophy patterns seen in individuals. These patterns are important as they can influence the difference between stable and more progressive MCI states. In terms of results, the accuracy of the proposed system for classifying between those with AD and healthy controls (HC) and sMCI/pMCI with the use of sMRI data was 93.01% and 75%, highlighting that the performance of the proposed approach is comparable with literature reviews using state-of-the-art techniques using MRI data.

Dimitriadis et al. [29] developed a Random Forest (RF)-based framework to automate the classification of AD, MCI, converting MCI (cMCI), and HC simultaneously using sMRI data. The study utilizes the ADNI dataset, focusing on 400 subjects, with 60 subjects in each of the four classification groups, representing different levels of cognitive impairment among the individuals. The dataset was then divided into a balanced training set of 240 subjects, with 60 subjects selected from each group to train the proposed model. The remaining 160 subjects (40 from each group) were used for validation testing. The sMRI images went through preprocessing with the use of FreeSurfer to extract features, and additional data, including Mini-Mental State Examination (MMSE) scores and demographic information, were integrated to enhance the feature set. Features such as cortical thickness, cortical surface area, gray matter density, hippocampal shape, and subcortical structure volumes were extracted from the T1-weighted MRI scans after preprocessing. Feature selection was based off the Gini impurity index, which exclusively selects the most relevant features for classification. The overall framework achieved a 61.9% classification accuracy overall on the blind testing dataset, but it is important to note that it marks the first attempt in AD research to simultaneously classify four groups using single-modality MRI data. This approach is a useful benchmark for future implementations that focus on multimodal biomarkers, such as PET imaging and genetic markers.

Lahmiri and Boukadoum's study [30] uses brain MRI data with a particular focus on fractal analysis and ML to differentiate between HC and AD-affected brains. Conventional approaches such as segmentation or specific regions of interest were avoided; instead, the study utilizes the full 2D MRI images and transforms them into 1D signals with the use of row concatenation. With the use of multi-scale analysis (MSA), six generalized Hurst's exponents were extracted. The ML algorithm used is based off an SVM classifier with a fourth-order polynomial kernel, due to its ability to model complex and non-linear decision boundaries efficiently. The training and testing process was based off a leave-one-out cross validation method, and the validation dataset was based off 93 MRI images (51 HC, 42 AD). The results of the proposed approach reached a correct classification rate (CCR) of 99.18%, a perfect

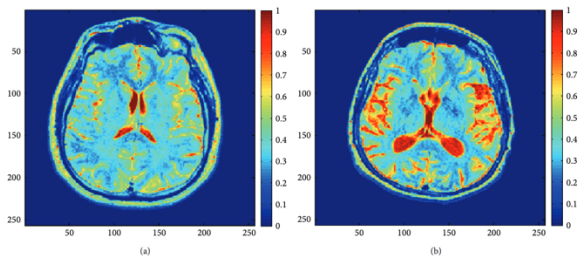

Figure 2: Healthy image (a) and AD image (b) in double color format [30]

sensitivity score of 100%, and a high specificity of 98.20%. In terms of computational efficiency, the MSA reduce the overall processing time to 5.64 seconds, which is a major improvement from their previous value of 400 seconds. While other studies used over 1,000 features, this approach maintained the simplicity by choosing only six features overall. The results indicate that this fractal-based proposal can be an efficient diagnostic for AD screen, as it offers superior accuracy, simple implementation, and a fast computational processing time. Figure 2 shares an example of a healthy and AD-affected brain MRI image on the left and right, respectively.

Moradi et al. [31] developed a ML framework to predict the progression of MCI to AD using data from the ADNI dataset, based on baseline T1-weighted MRI preprocessed data images, and used voxel-based morphometry to extract gray matter density maps, and strengthened with cognitive tests such as the ADAS-cog, MMSE, Functional Activities Questionnaire (FAQ), and Clinical Dementia Rating—Sum of Boxes (CDR-SB). This study included 231 HC, 200 AD patients, 100 stable MCI (sMCI) patients who eventually progressed to AD within the span of 1-3 years, and 130 unclassified MCI. (uMCI) patients without sufficient recordings of following up**.** A new MRI biomarker was based on a semi-supervised Low-Density Separation (LDS) approach, which utilized unlabeled data to rectify decision boundaries, as well as an integration of a Random Forest (RF) model using MRI-based biomarkers, age, and other cognitive metrics. In terms of results, the LDS classifier achieved a performance under an AUC of 0.7661, while the integrated RF model improved performance up to 0.9020. The study observes that removing age-related effects from MRI significantly improves the overall prediction of AD in both young pMCI and old sMCI subjects and hypothesize that this is due to the misidentification of age-related atrophy and pMCI. In the cross-validation runs, the cross-validation was properly nested, making these AUC values a promising candidate for the early prediction of AD conversion compared to other MRI-based SVM algorithms.

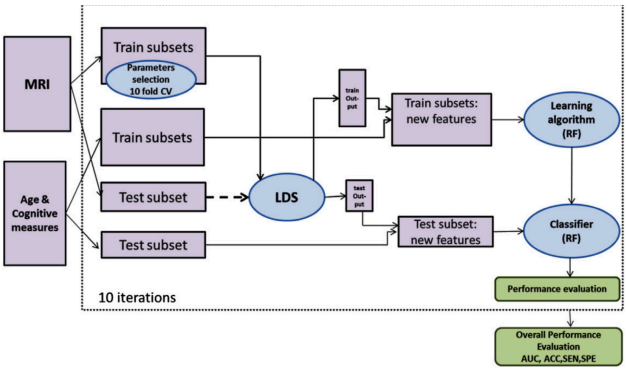

Figure 3: Workflow for the aggregate biomarker and its cross-validation based evaluation [31]

Schouten et al. [32] conducted a comprehensive study to classify AD with a powerful non-invasive method known as diffusion magnetic resonance imaging (dMRI), with a particular specialization on white matter integrity. The study combines two major datasets from the Prospective Registry on Dementia (PRODEM) and the Austrian Stroke Prevention Family Study (ASPFS), including a total of 77 AD patients and 173 HC ranging from 47-83 years old. With the use of a Siemens Magneto TrioTim 3T scanner, the study was able to capture diffusion-weighted MRI images in 12 distinct directions as well as anatomical T1-weighted images. Several ML algorithms were utilized to analyze the performance metrics related to diffusion tensor imaging, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (DA), and radial diffusivity (DR). Feature extraction was mainly processed with the use of tract-based spatial statistics (TBSS), as well as the use of independent component analysis (ICA), an unsupervised learning method that does not require class labels of individuals. Based on the Harvard-Oxford anatomical brain atlas, the combination of the cortical regions in the left and right hemisphere regions as well as the ones in the subcortical atlas totaled to 110 grey anatomical regions for analysis. When using TBSS, classification results include an AUC between 0.888 and 0.902, with the highest performance metrics achieved with DR. On the other hand, the ICA-clustered measures achieved the highest AUC value of 0.920. These results demonstrate the usefulness of diffusion MRI in terms of classifying AD, with FA-ICA having the highest single-measure performance metric. The integration of ML algorithms into feature reduction and classification methods show major potential, and this is highlighted here with the use of diffusion MRI, a great starting point to the variety of procedures currently utilized in the healthcare domain.

Abdulkadir et al. [33] proposes the influence of hardware variability on the performance of an automated machine classifier used for AD detection with the use of sMRI data. The classifier is based off the SVM algorithm, a high-dimensional pattern

classification method whose primary goal is to distinguish between cognitively normal (CN) individuals and those who have AD. The reasoning for sMRI as the main imaging modality was due to its sensitivity to gray matter atrophy patterns, and this is the main observation for identifying AD. The primary dataset used in the study is based on ADNI, and a total of 417 participants and 518 distinct MRI sessions were used, including 226 CN and 191 AD individuals. The classification method utilized in the study integrates the SVM algorithm with a linear kernel. The key features of the algorithm were mainly extracted with a series of preprocessing steps involving segmentation, spatial normalization, and the modulation of T1-weighted MRI scans. Two validation methods were performed to evaluate the models implemented in the study, including leave-one-sample-out cross-validation (LOO-CV) as well as an independent validation test set. The hardware used for evaluation include manufacturers such as Siemens, Philips, GE, as well as different field strengths and coil systems. The results of the study achieved a maximum accuracy of 84.2%, observing that heterogenous hardware sources have minimal effect regarding classification accuracy. This observation demonstrates that implementing a variety of data from different hardware sources is possible and allows the potential size of training datasets used for AD diagnosis to be increased without any quantitative reduction in classification accuracy. However, it is important to note that changing field strengths were found to introduce additional variance, and two scanners with the identical hardware settings may not provide the same results, influencing the classification accuracy.

Jain et al. [34] implements the use of conventional neural networks (CNNs) in order to classify between AD, MCI, and CN individuals using sMRI data. The reasoning for CNNs over other networks such as ANNs is that they operate over volumes, use parameter sharing, and include local connectivity, all which benefit towards AD classification. However, the struggles of using CNNs and other deep learning architectures is the requirement of large training datasets, which is a main problem in the medical imaging field as it is difficult and expensive to acquire an abundant amount of data sufficient to make a well-known contribution towards the research field **[35]**. Due to the super sensitivity of hyper-parameters that deep learning requires, as well as the number of computational resources it requires to operate, researchers have implemented an alternative approach known as transfer learning **[36].** Therefore, the main objective proposed by the study is to integrate transfer learning with a VGG16, a 16-layer network that is one of the first architectures of its kind to explore network depth by pushing 16 layers and small convolution filters. While training a CNN as big as the VGG16 could take weeks, while a pre-trained model only takes a few hours. The study builds upon earlier works that were based on ML algorithms to classify AD **[31]** and it extends these models by implementing deep learning techniques and utilizing transfer learning to address the limited data available in the current domain of research. To enhance the overall classification accuracy while also addressing the limited access of medical imaging data available. This study relies on the ADNI dataset, separating a total of 150 subjects divided evenly across the three categories of individuals. T1-weighted sMRI scans were obtained from each subject, and then preprocessed to analyze features of motion correction, intensity normalization, and skull stripping. In terms of dimensionality reduction, the 3D sMRI images were sliced into 2D images, and the most qualitative images was selected based on certain entropy values. Overall, the dataset balances out to around 1,600 distinct slices for each category and were resized to a compatible format to feed into the CNN algorithm.

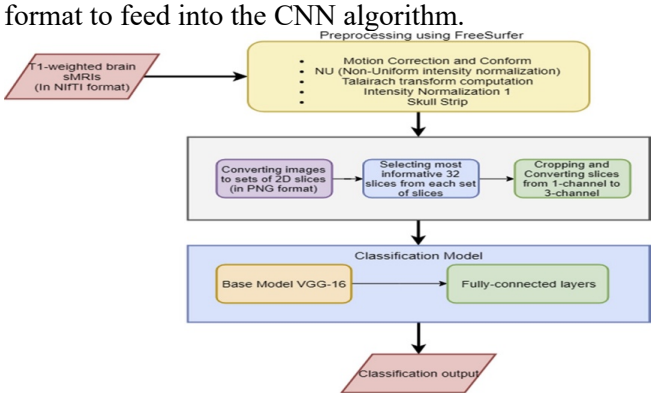

Figure 4: Overall scheme of the method used to implement the proposed classification model with the use of T1-weighted brain sMRIs and the integration of the VGG-16. [34]

Experimental results display that the model is effective in three-way classification, achieving a peak accuracy of 95.73% on the validation set. The model is also excellent in binary classifications, achieving accuracies of 99.14%, 99.30% and 99.22% for AD vs. CN, AD vs. MCI, and MCI vs. CN classifications respectively. These results highlight the success of using deep learning methods for AD classification, and other neural networks are suggested to be used for evaluation.

Alam et al. [37] focuses on developing an advanced ML approach for the early classification of AD and MCI individuals, emphasizing the importance of early diagnosis given the rapid progression of AD and its deteriorating lifestyle impact towards behavior and memory. This study uses sMRI due to its non-invasive characteristics and its ability to detect structural changes in the brain that can distinguish AD patients from HC. The study proposes an innovative hybrid approach integrates the concept of advanced wavelet

transforms and machine learning to enhance the accuracy of AD classification compared to traditional methods. The approach consists of several components, starting with the extraction of discriminative features with the use of the dual-tree complex wavelet transform (DTCWCT); with its directionally selective and shift-invariant properties, it is chosen over traditional wavelet transforms due to its higher quality in pointing out singularities inside MRI images. Previous studies have also shown higher performances using DTCWT feature-based AD disease detection compared to DWT-based features. The next step involves using Principal Component Analysis (PCA) as a technique transform data from higher to lower dimensional spaces. However, since PCA does not account for the variability of features between classes, Linear Discriminant Analysis (LDA) is applied to order to maximize the separation between classes and enhance AD classification. The final step involves the Twin Support Vector Machine (TSVM), which is a special variant of SVMSs that perform classification with the construction of two nonparallel hyperplanes; previous studies [38] have already shown TSVM to be highly effective in terms of classification. The sMRI is brought from both the ADNI and OASIS datasets, two of the most widely used datasets in relation to AD research. The data from the ADNI dataset includes 172 subjects divided evenly between 86 HC and AD individuals, while the OASIS dataset contains 95 subjects, divided into 44 HC and 51 AD patients with varying stages of AD. The axial slices of the MRI scans were preprocessed and resized before extracting the DTCWT coefficients.

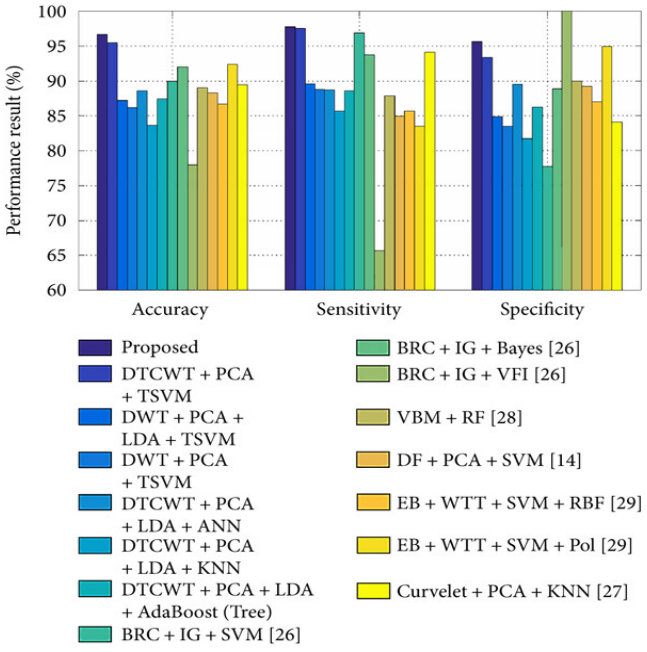

Figure 5: Experimental results between proposed design compared to other state-of-the-art models, including accuracy, sensitivity, and specificity performance metrics [37]

The proposed hybrid approach was tested on both ADNI and OASIS datasets, and varying PC values were used to find the optimal performance of classification. The study also applied 5-fold cross validation (CV) to the OASIS dataset and 10-fold CV to the ADNI dataset. The overall classification performance was measured in terms of accuracy, sensitivity, and specificity, and competes well against twelve other state-of-the-art methods in the form of a bar chart as seen in Figure 5 above. The proposed method in the OASIS is seen to yield a peak accuracy of 96.68%, sensitivity of 97.72%, specificity of 95.61%. These performance metrics are very promising in terms of AD classification and provide an innovative solution in addressing the modern challenges of AD diagnosis.

Cai et al. [39] explore the development of a deep learning framework to classify AD, MCI, and CN states as a three-way classification with the use of sMRI data, with the primary challenge addressing the domain shift between different MRI scanners and their potential variability in performance. This approach considers both the marginal and conditional distributions simultaneously, while improving the overall performance when feature alignment is successful. Current domain adaptation techniques are able to accomplish feature alignment by applying limitations on data that belong to other domains, allowing the classifier to apply the source domain onto the target domain with great generalization effects. Studies show the rise of domain adaptation methods among researchers in the medical imaging field due to its high performance [40]. Another feature that may benefit the adaptation techniques is prototype learning, which provides valuable insight into the relationship between the different classes and the latent space involved, as well as being a robust method when handling few-shot learning. The study introduces the Prototype-Guided Multi-Scale Domain Adaptation (PMDA) framework, which is comprised of MRI multi-scale feature extraction, prototype learning, and an adversarial domain adaptation module. The study is based off the ADNI dataset, comprising of sMRI data at two distinct magnetic field strengths: 3T, indicated as the source domain, and 1.5T, indicated as the target domain. The total study comprises of 896 MRI scans and consists of 272 AD, 312 MCI, and 312 CN individuals. Starting off with the first part of the PMDA, the MRI multi-scale feature extraction is computed with the use of 3D convolutional layers and self-attention mechanisms to capture all features in the brain. In the second part of the PMDA framework, prototype learning is used to help align the features from different domains while minimizing any inter-domain divergence and maximizing the amount of intra-class density. In the last part of the PMDA framework, the adversarial domain

adaptation is based on a co-training strategy that uses dual discriminators to further align the source and target domains together, removing any issues due to overfitting. Experimental results demonstrate that high performance of the PMDA in three different binary classification tasks, achieving accuracies of 92.11%, 76.01%, and 82.37% in AD vs. CN, AD vs. MCI, and MCI vs. CN respectively. These performance metrics surpassed state-of-the-art supervised domain adaptation methods including Domain-Adversarial Neural Networks (DANN), Conditional Domain Adversarial Networks (CDAN), and even supervised learning models such as 3DResNet50. Overall, the PMDA is a great framework that demonstrates the use of CNNs in combination with feature extraction, prototype learning, and adaptation techniques to create a highly effective classifier for multiple stages of AD.

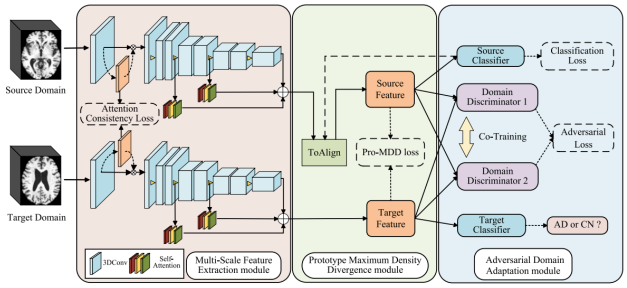

Figure 6: Illustration of the proposed Prototype-Guided Multi-Scale Domain Adaptation (PMDA) framework for MRI-based AD diagnosis [39]

Kong et al. [41] explore the application of a multi-modal ML framework to enhance the early detection of AD. The study observes the three-dimensional convolutional neural network (3D-CNN) as one of the recent innovations applied with MRI to perform binary and ternary disease classifications, as seen in [42]. Using a combination of MRI and PET modal images, the study expands on this research by developing a 3D-CNN with a combination of both PET and MRI images, followed by feature enhancement as well as multi-modal feature fusion to categorize AD. Rather than individual images, the gray matter region in the MRI images are extracted and fed into the PET image where image fusion occurs. Then, a fully connected neural network (NN) can classify across the three different categorizations as seen in Figure 6. The model essentially separates each imaging modality with dedicated CNN branches and extracts features unique to their modality; then, these features are fused with the concept of feature concatenation and weighted averaging to capture synergistic patterns across the main modalities. Once the fused features

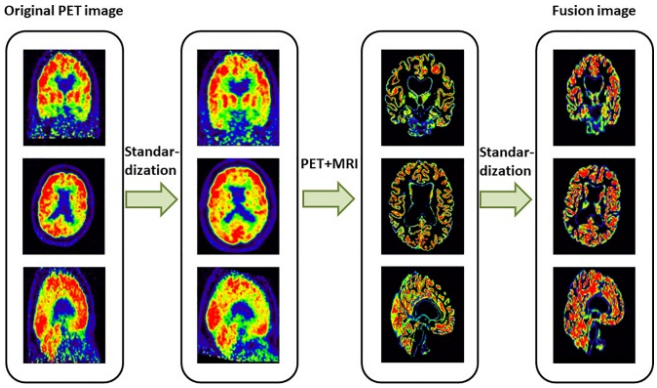

Figure 5: PET image processing method. The pictures from left to right are the original PET image; the registered PET image; the GM part cropped from the MRI is mapped into the PET image; the final registered fused image [41]

pass through the fully connected layers, a softmax layer is used to assign diagnostic labels (AD, MCI, and CN). The dataset for the study was obtained with the ADNI public dataset, comprising a total 740 3D images, divided evenly with 370 FDG-PET modality scans and 370 sMRI images. These fused images allow for richer modal features as well as the capability to represent stronger qualitative data with minimized noise. A sparse autoencoder is also added to the 3D-CNN architecture to allow the network to learn the authentic characteristics of the sample, as well as offer dimensionality reduction. In terms of results comparing other studies that use 3D-CNN architectures for classifying AD, the proposed image fusion framework achieved the highest performance, with an accuracy of 93.21%, a sensitivity of 91.43% and a specificity of 95.42%. Similar results can be seen for the classification of MCI and AD by very large margins. In the final multi-modal task, the proposed image fusion framework also achieved the highest performance with an accuracy of 87.67%.

Xu et al. [43] presents a fresh approach to detecting the progressing of AD with the use of magnetoencephalography (MEG)-derived brain networks. MEG is non-invasive and low-cost compared to PET scans and offers excellent temporal resolution that is able to capture subtle brain changes during the early stages of AD and in between the transitions of pMCI, MCI, and sMCI. MEG is also able to capture the fields produced by intraneuronal currents more directly than other metabolic responses, and a MEG-based biomarker could provide a more reliable indicator for evaluating synaptic dysfunction during the progression of AD. A deep-learning framework was built, particularly around Gaussian embedding in order to characterize the early stages of AD with the use of eyes-closed resting-state MEG data. The dataset is comprised of 76 MCI patients and 53 age-matched NC patients, as well as demographic information and cognitive tests such as age, gender, education level, and MMSE score.

For each patient, three to five minutes of resting-state MEG data were acquired while the participants were actively awake with their eyes closed. In this configuration, MEG data was recorded with an Elekta Vectorview system, which is pre-processed with a Maxfilter software to reduce noise with the sue of spatiotemporal filters. In relation to machine learning classifiers, the proposed model, known as the Multiple Graph Gaussian Embedding Model (MG2G), uses embeddings as features to average the classification accuracy of ten distinct classifiers built into the sci-kit learn library. Each of these classifiers were also trained on a 5-fold cross validation strategy to distinguish between NC, sMCI, and pMCI patients. In terms of results, the model achieved an accuracy of 61% for three-way classification; in terms of binary classification, the model achieved accuracies of 79%, 78%, and 82% for NC vs. sMCI, sMCI vs. pMCI, and NC vs. pMCI respectively. These performance metrics surpassed the baseline models for all four different tasks, highlighting the model's efficiency in yielding qualitative features that are seen in early AD stages.

IV. CONCLUSIONS

The integration of ML frameworks with emerging neuroimaging modalities of the contemporary era is a transformative era since new solutions for discovering new early detections for AD are being found. In this study, various machine learning methods, neuroimaging modalities, and datasets were all addressed with a primary objective to address the modern challenges of early and accurate AD diagnosis. After observation, the findings demonstrate that ML algorithms can provide valuable insights towards finding patterns and biomarkers that traditional methods would fail to observe or even have the possibility to find, which offers a slight relief towards the future of the global AD epidemic. Several ML algorithms, including SVMS, RF classifiers, and CNNs, were able to shine a new light on the traditional perspective of analyzing the structure and functionality of the brain. All the ML algorithms show outstanding qualities in being able to classify the distinct stages of AD, including MCI, pMCI, sMCI, AD, and differentiating between HC individuals. The types of neuroimaging modalities, including sMRI, dMRI, fMRI, PET, EEG, and MEG were all shown to be beneficial in their integration with the ML frameworks. The most popular neuroimaging modality was sMRI, which is widely known for its ability to detect hippocampal shrinkage, cortical thinning, gray matter atrophy, and other features that indicate AD progression. Other modalities such as DMRI and PET imaging focus more into white matter integrity and amyloid-beta plaque accumulation. Based on the studies mentioned above, the ADNI, OASIS, and ADSP all played a central role due to its public accessibility and large quantizable data allowed for researchers to access. However, researchers are still limited in terms of hardware variability and sample diversity, which calls for more research in relation to domain adaptation techniques and more standardized data collections. Further improvements could be made with the addition of more case studies, prioritizing efficiency, and scalability for practical applications, and applying a larger dataset to incorporate more than the current dataset limitations. Overall, these ML integrations offer transformative ideas for a more insightful understanding on the functionalities of AD and the variety of ways to prevent and regress the symptoms for MCI and AD-affected individuals.

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