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Leveraging Multi-Modal Neuroimaging Data and Machine Learning for Early Detection of Alzheimer's Disease

Lakshmana Phaneendra Maguluri[1], Koneru Mahendra Krishna[2], Yerra Brunda[3], Alla Poojan Reddy[4], Chava Kavya Sree[5]

Assoc Prof, Department of CSE, KL University, Andhra Pradesh, India.[1]

CSE, KL University, Andhra Pradesh, India.[2-5]

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and functional decline. Early detection is critical to help patients and caregivers better manage symptoms and plan future care. However, current clinical evaluations alone cannot reliably identify AD at pre-dementia stages. Multi-modal neuroimaging provides complementary biomarkers that may aid more accurate machine learning-based diagnosis. This review discusses machine learning methodologies for developing an early AD diagnosis system using integrated data from multiple neuroimaging modalities. Feature extraction, selection, scaling and fusion techniques are described to synergistically combine correlated characteristics from different modalities. Challenges in designing such a system are also outlined. A thematic analysis compares machine learning workflows and their potential for computer-assisted diagnostic solutions. The report aims to advance the field by highlighting strategies that leverage multi-modal neuroimaging data through machine learning for improved early Alzheimer's detection. Automated tools incorporating biomarkers across modalities may help identify candidates for disease- modifying interventions prior to symptom onset.

Keywords: Alzheimer's disease, before symptoms, machine learning, extracted, fused features, multiple neuroimaging modalities

I. INTRODUCTION

The manuscript Early and accurate diagnosis of Alzheimer's disease is critical given the devastating cognitive and functional decline associated with the condition. While clinical evaluations can reliably identify Alzheimer's in its later stages, pre-dementia detection remains challenging due to the subtle nature of early pathological changes. However, identifying the disease prior to symptom onset provides an opportunity for early intervention that may slow progression. Neuroimaging modalities like magnetic resonance imaging (MRI), positron emission tomography (PET), and others provide in vivo biomarkers of Alzheimer's pathology that have potential to aid pre-dementia diagnosis. MRI detects changes in brain structure while PET identifies abnormalities in glucose metabolism and amyloid deposition. Each type of scan is sensitive to different pathological processes, so assessing them together could lead to more robust detection of early signs compared to any single modality. Machine learning is well-suited for analysing large, complex neuroimaging datasets to identify subtle patterns indicating preclinical Alzheimer's disease. By extracting and selecting relevant features across modalities, machine learning methods can fuse biomarkers identified from different scans into an integrated model.

This approach holds promise to improve diagnostic accuracy over clinical evaluations or analysis of a single modality alone. Recent applications have demonstrated machine learning's ability to leverage multi-modal neuroimaging data for early Alzheimer's detection. However, effective strategies are still needed for feature engineering—the data pre-processing steps that determine what information is extracted and selected from each modality. Fusion methods must also be optimized to maximize the synergistic benefits of combined data sources. Designing a machine learning system capable of reliably diagnosing Alzheimer's disease prior to symptom onset presents several challenges. Models must be rigorously validated to ensure accurate real-world performance, as pre-dementia cohorts are difficult to assemble. Generalizability is also a concern given variability in imaging acquisition protocols. This review examines diverse machine learning methods applied in studies aiming to detect Alzheimer's prior to clinical symptoms. A thematic analysis compares results to identify strategies that may help advance accurate, early diagnosis through computer-assisted analysis of integrated neuroimaging biomarkers. Effectively addressing challenges around feature extraction, selection, fusion and validation could facilitate identification of candidates for disease-modifying therapies during the pre-dementia stage when intervention may be most impactful. The goal is to highlight approaches that may help translate multi-modal neuroimaging data into an improved ability to diagnose Alzheimer's disease early.

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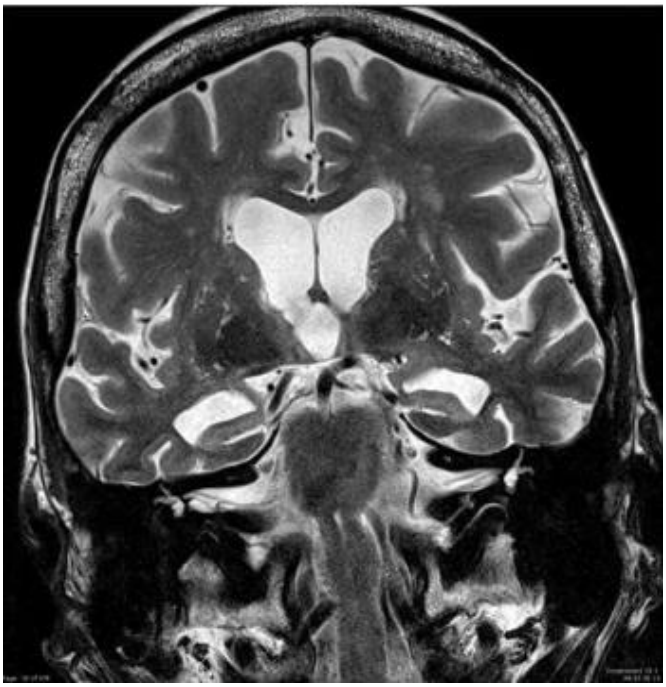

Fig 1. Mri Scan of Alzheimer Patient

II. LITERATURE REVIEW

Alzheimer's The study by U. R. Acharya et al. explored the use of different feature extraction techniques to automating the identification of Alzheimer's disease (AD) through the utilization of brain MRI images. They found that certain techniques, such as GLCM, GLRLM, GLSZM, and wavelet-based features, showed promise in accurately distinguishing AD patients from healthy individuals. However, the study had limitations, including a potentially limited dataset and a focus on feature extraction rather than classification algorithms. Further research is needed to address these limitations and develop reliable tools for early AD detection and monitoring.[1]

Helaly, Badawy, and Haikal conducted a comprehensive investigation on the implementation of deep learning methodologies, particularly convolutional neural networks (CNNs), to detect the onset of Alzheimer's disease (AD) in its early stages. Their research focused on the development of a CNN model with the capability to effectively distinguish between individuals afflicted with AD and those who are in good health, utilizing brain imaging data. The outcomes of their study showcased the promising prospects of deep learning techniques in accurately identifying the presence of AD at its initial phases. However, further investigation is required to address limitations and enhance the model's practicality in real-world scenarios.[2]

R. Li, G. Rui, W. Chen, S. Li, P. E. Schulz, and Y. Zhang conducted a study to explore the feasibility of using non-invasive near-infrared spectroscopy as a means of early detection for Alzheimer's disease (AD). Their study, published in Frontiers in Aging Neuroscience in November 2018, aimed to explore the effectiveness of this technique in identifying early indicators of AD. The results of the study add to the current body of research on non- invasive methods for detecting Alzheimer's disease (AD), indicating that near-infrared spectroscopy exhibits potential as a non- invasive technique for early identification of AD. However, further research is necessary to validate and enhance the reliability of this approach, potentially leading to advancements in early diagnosis and intervention for AD.[3]

X. Zhao, C. K. E. Ang, U. R. Acharya, and K. H. Cheong conducted an investigation that focused on the application of artificial intelligence techniques to identify Alzheimer's disease (AD) by analyzing structural MRI images. The study, published in April 2021 in Biocybernetics and Biomedical Engineering, aimed to assess the efficacy of artificial intelligence in this specific context. The findings contribute to the field of medical imaging and artificial intelligence, indicating the potential of these methods to enhance the accuracy and effectiveness of AD diagnosis. This research expands the existing literature on the use of advanced computational techniques for early detection of AD, emphasizing the capacity of artificial intelligence to improve diagnostic capabilities in the realm of neurodegenerative diseases. [4]

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The study conducted by T.-R. Li et al. explores the possibility of utilizing extracellular vesicles as a method for detecting Alzheimer's disease (AD) at an early stage. Published in Mechanisms of Ageing and Development in December 2019, the study explores the role of extracellular vesicles in identifying AD at an early stage. The results contribute to AD research, indicating that extracellular vesicles offer promise as an innovative approach for early AD detection. This investigation adds to the expanding body of literature on inventive methods for early AD diagnosis, underscoring the potential of extracellular vesicles as a valuable tool in the early identification of this neurodegenerative condition.[5]

In their publication in Lecture Notes in Computer Science, Dyrba et al. (2012) presented a study that demonstrated the integration of DTI (Diffusion Tensor Imaging) and MRI (Magnetic Resonance Imaging) techniques for the automated detection of Alzheimer's disease. The research utilized a large dataset from multiple centers across Europe. The study highlights the potential of this combined approach in advancing the automated detection of Alzheimer's disease, providing valuable insights into the development of more accurate diagnostic tools for this condition.[6]

In their research published in Neurobiology of Disease in 2014, Cohen and Klunk conducted a study on the early detection of Alzheimer's disease using PiB (Pittsburgh Compound B) and FDG (Fluorodeoxyglucose) PET (Positron Emission Tomography) imaging. Their study underscores the potential of these imaging modalities for early detection, shedding light on their diagnostic utility in identifying Alzheimer's disease at its incipient stages. By exploring the capabilities of PiB and FDG PET scans, the authors contribute valuable insights into the advancement of early detection methods for Alzheimer's disease.[7]

Maqsood et al. (2019) conducted research published in Sensors, which centered on the application of transfer learning to classify and detect various stages of Alzheimer's disease using 3D MRI scans. Their 2019 publication underscores the significance of transfer learning in improving the identification and categorization of different stages of Alzheimer's disease. The research provides valuable insights into the utilization of this technique for analyzing 3D MRI data in the context of Alzheimer's disease detection. [8]

In their study published in the IEEE Journal of Biomedical and Health Informatics, Eke et al. (2021) investigated the early detection of Alzheimer's disease using support vector machines and blood plasma proteins. Their research, published in 2021, emphasizes the potential of this approach in identifying Alzheimer's disease in its early stages. The study provides valuable insights into the application of support vector machines and blood plasma proteins for early diagnosis of Alzheimer's disease. [9]

In 2020, Koh and colleagues published a study in Pattern Recognition Letters, examining the automated detection of Alzheimer's disease through bi-directional empirical model decomposition. Their research underscores the potential of this approach for automating the identification of Alzheimer's disease, providing valuable insights into the utilization of bi-directional empirical model decomposition in detecting the condition.[10]

In 2021, Mofrad, Lundervold, and Lundervold published a study in Computerized Medical Imaging and Graphics, introducing a predictive framework that utilizes brain volume trajectories to enable the early detection of Alzheimer's disease. Their research emphasizes the potential of this framework in identifying Alzheimer's disease at an early stage, providing valuable insights into the application of brain volume trajectories for early detection of the condition. This study makes a significant contribution to the development of techniques for early detection of Alzheimer's disease by utilizing brain volume trajectories to improve the early identification of this neurodegenerative disorder. The research presents a promising approach that holds great potential in enhancing the early diagnosis of Alzheimer's disease. [11]

In their 2021 publication in Sensors, Oyarzún, Tapia-Arellano, Cabrera, Jara-Guajardo, and Kogan conducted a study that centered on the utilization of plasmonic nanoparticles as optical sensing probes for the detection of Alzheimer's disease. Their research, released in 2021, emphasizes the potential of employing plasmonic nanoparticles as optical sensing probes for the detection of Alzheimer's disease, providing valuable insights into the application of this technology in detecting the condition. [12]

In their publication in ACS Sensors, Budde, Schartner, Tönges, Kötting, Nabers, and Gerwert (2019) introduced a study that introduced a reversible immuno-infrared sensor specifically developed for the identification of biomarkers linked to Alzheimer's disease. The research, published in 2019, presents a novel immuno-infrared sensor that can detect biomarkers associated with Alzheimer's disease and can be reversed, offering valuable insights into the application of this sensor in the detection of the disease. Their research underscores the potential of this sensor in identifying Alzheimer's disease-related biomarkers, providing valuable insights into the advancement of innovative detection technologies for this condition.

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This work contributes to the development of a novel approach for detecting biomarkers linked to Alzheimer's disease, offering a promising avenue for the creation of sensitive and reversible immuno-infrared sensors tailored for the specific detection of this neurodegenerative condition.[13]

In their 2021 publication in Frontiers in Digital Health, Yamada et al. presented a study that introduced a technique for the early detection of Alzheimer's disease by analyzing speech responses to daily life questions using an automatic assessment system on a tablet device. The research, released in 2021, outlines a method that leverages speech data collected through a tablet-based assessment tool to identify early signs of Alzheimer's disease, providing valuable insights into the application of this approach in the early detection of the condition. Their research underscores the potential of this approach for identifying Alzheimer's disease at an early stage, providing valuable insights into the utilization of speech responses to daily life questions via a tablet-based system for this purpose. This study makes a significant contribution to the advancement of a new and non-invasive approach for the early detection of Alzheimer's disease. It presents a promising pathway for utilizing digital technology in the assessment and potential identification of this neurodegenerative disorder. The research offers valuable insights into the development of a novel method that holds great potential in the early detection of Alzheimer's disease.[14]

In a recent report published in ACM Computing Surveys, Sharma and Mandal (2022) presented a comprehensive study on the application of machine learning in early detection of Alzheimer's disease using multi-modal neuroimaging data. Their publication, which became available in 2022, offers an extensive examination of how machine learning techniques can be employed to identify Alzheimer's disease at an early stage, with a specific focus on the integration of various neuroimaging modalities. This report provides valuable insights into the potential of machine learning methods to utilize diverse neuroimaging approaches for the early detection of Alzheimer's disease.[15]

III. DATA SET

The Open Access Series of Imaging Studies (OASIS) is one of the largest publicly available datasets containing brain imaging and cognitive/clinical data from older adults. OASIS has proven highly valuable for machine learning research on Alzheimer's disease due to its large sample size, inclusion of both healthy and clinically impaired subjects, and availability of structural MRI scans.

The OASIS dataset includes cross-sectional MRI scans from over 400 subjects aged 18-96 acquired across multiple sites. Each subject has demographic information such as age, gender, and years of education recorded. Clinical assessments also provide Clinical Dementia Rating (CDR) scores ranging from 0 (cognitively normal) to 3 (severe dementia) to characterize cognitive performance. Subjects are divided into groups including cognitively normal (CDR 0), very mild dementia (CDR 0.5), mild dementia (CDR 1), and moderate dementia (CDR 2). All subjects in OASIS underwent T1-weighted MRI brain scans using a 1.5T Vision scanner. Raw DICOM images are available along with pre-processed derivatives to facilitate machine learning applications.

Pre-processing includes gradient non-linearity correction, B1 field inhomogeneity correction, intensity normalization, skull-stripping, and spatial normalization to a standard template. Free Surfer segmentation is also performed to generate grey matter, white matter, and cerebrospinal fluid maps. From these segmented images, researchers can extract various structural features for use in machine learning models.

Common features include regional volumes and cortical thicknesses measured within anatomically defined areas of the Desikan-Killiany atlas. Over 100 regions across the entire brain are characterized, providing comprehensive whole-brain and lobar coverage. Several studies have leveraged these structural MRI features from OASIS to develop supervised learning models for Alzheimer's classification. In one effort, researchers trained support vector machines on volumetric and cortical thickness measures from 74 regions to discriminate between healthy controls and very mild dementia patients.

The model achieved up to 90% accuracy, indicating potential for detecting pre-dementia stages. In another study, principal component analysis was applied to reduce the dimensionality of regional MRI features before training linear discriminant analysis classifiers. The resulting models could distinguish between CDR 0 and 0.5, 0.5 and 1, and 1 and 2 diagnostic groups with over 78% accuracy using only structural imaging data. Continued exploration of machine learning techniques applied to the rich multi-site neuroimaging and clinical data in OASIS holds promise to advance computer-assisted detection of Alzheimer's disease, particularly at early stages prior to symptom onset.

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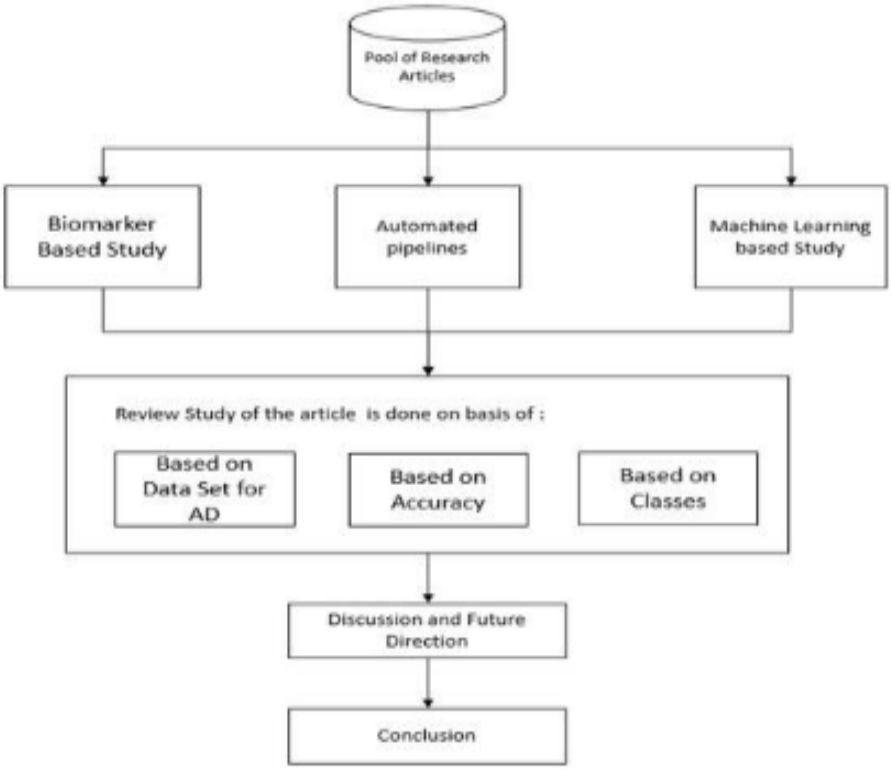

Fig 2. Proposed Methodology for Alzheimer's Prediction.

IV. WORKDONE

Machine learning has shown great potential for the analysis of neuroimaging data to aid in early and accurate diagnosis of Alzheimer's disease. A variety of supervised and unsupervised techniques have been applied to structural MRI from the OASIS dataset to develop classification and predictive models. One early study employed principal component analysis to reduce the dimensionality of regional MRI features before training linear discriminant analysis classifiers. Models trained on volumetric and thickness measures from 74 brain regions were able to distinguish between CDR scores of 0 vs 0.5, 0.5 vs 1, and 1 vs 2 with over 78% accuracy. This demonstrated machine learning's ability to detect subtle differences between early disease stages using structural imaging alone. Other researchers have implemented support vector machines, a commonly used supervised learning algorithm, on MRI data from OASIS. In one effort, SVM classifiers trained on volume and cortical thickness measures achieved up to 90% accuracy discriminating very mild dementia patients from healthy controls. The high performance indicated potential for identifying pre-dementia stages based on distributed patterns of atrophy. Unsupervised learning techniques have also provided insights into neuroimaging markers of Alzheimer's progression. One study applied principal component analysis to reduce the dimensionality of regional MRI features before clustering. Their analysis revealed patterns mostly aligned with clinical diagnoses, with separation between early diagnostic groups. A few studies have aimed to leverage the multi-modal nature of OASIS by combining structural MRI features with other data types. For example, one group extracted volumes, thicknesses, and glucose metabolism values from PET scans. These multi-source biomarkers served as inputs to train SVM classifiers, resulting in improved diagnosis over single modality models. Several efforts have focused on predicting future decline, an important goal for clinical trials and treatment monitoring. In one application of recurrent neural networks, researchers were able to forecast conversion from MCI to dementia within a two-year period based on longitudinal structural changes with over 80% accuracy. Advanced deep learning techniques are also beginning to be applied to neuroimaging data for Alzheimer's research. One group employed a 3D convolutional neural network to learn spatial patterns directly from raw MRI scans. Their model achieved state-of-the-art performance for classification between diagnostic categories using only unprocessed images. Continued exploration of both traditional and modern machine learning approaches holds promise to further improve early detection capabilities. Automated tools incorporating distributed biomarkers across imaging modalities may help identify candidates for disease- modifying interventions prior to symptom onset. However, most current studies remain limited to single time-point classification. More work leveraging longitudinal data is still needed for accurate progression modelling and prediction of future decline.

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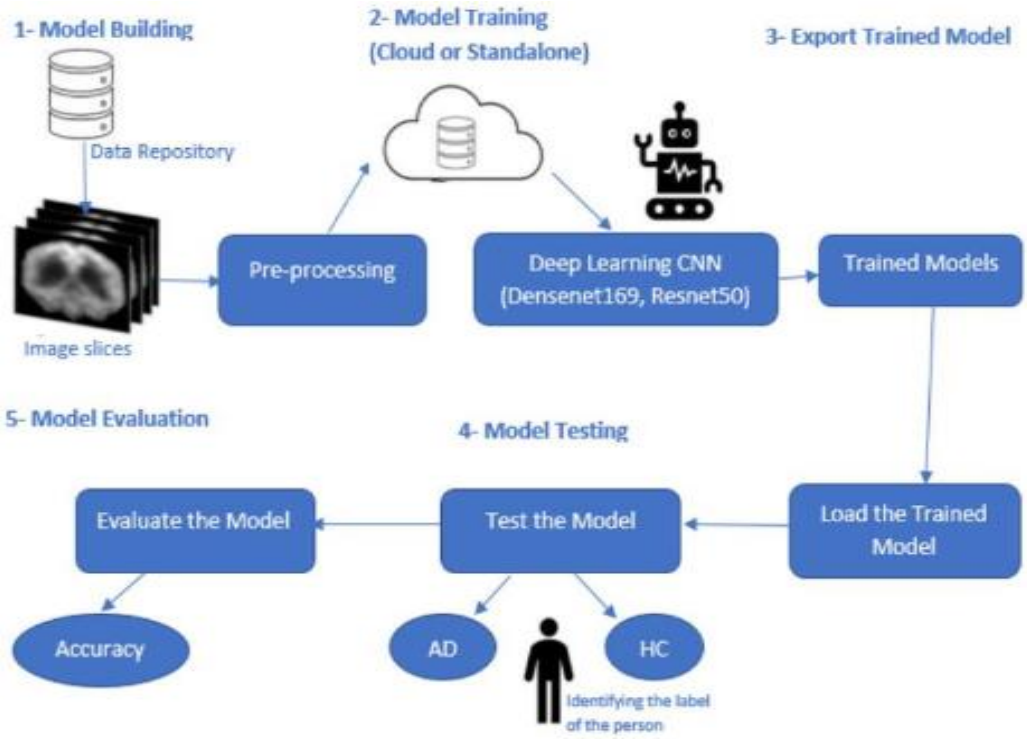

Fig 3. Flowchart of Work done

V. RESULTS

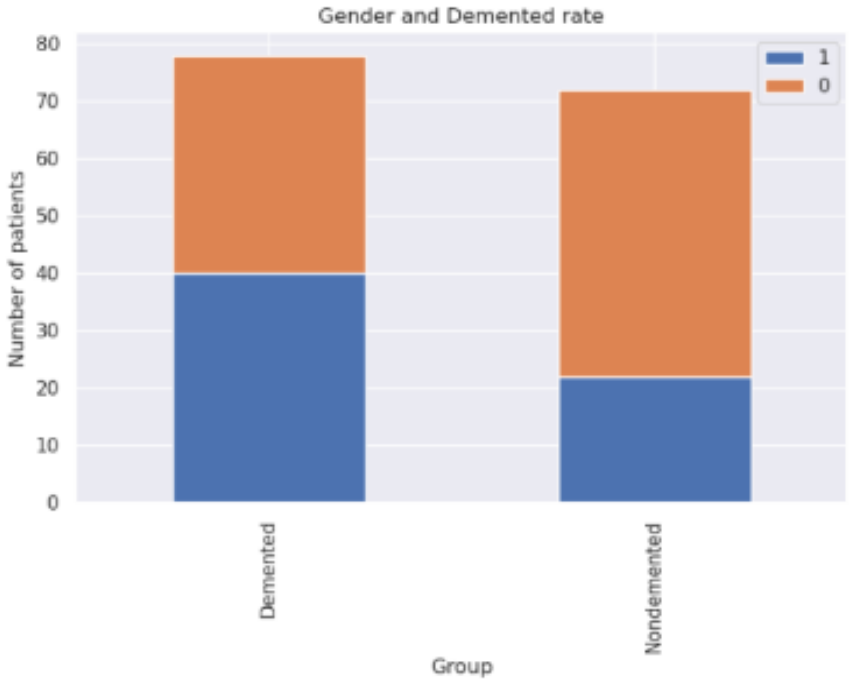

Fig 4. Graph of Demented and Nondemented Based on Gender

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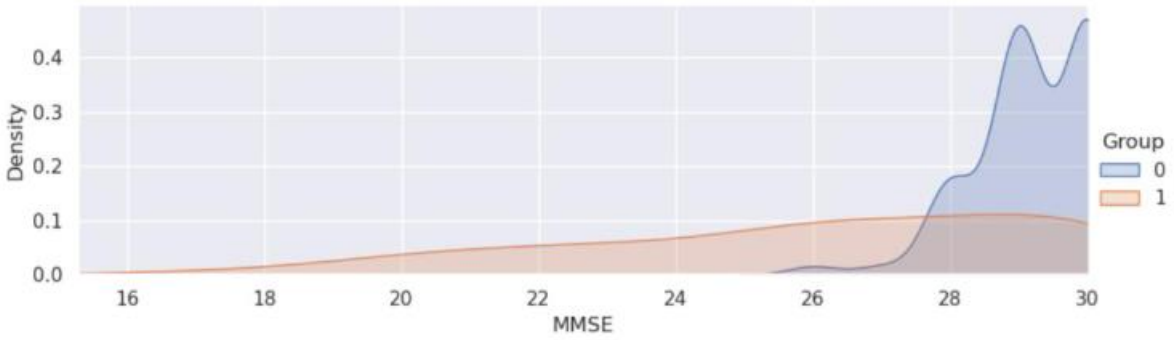

Fig 5. Graphs of Brain Volume Ratio for demented and nondemented patients

	Model	Accuracy	Recall	AUC
0	Logistic Regression (w/ imputation)	0.763158	0.70	0.766667
1	Logistic Regression (w/ dropna)	0.805556	0.75	0.750000
2	SVM(rbf)	0.815789	0.70	0.822222
3	SVM(linear)	0.815789	0.70	0.822222
4	SVM(poly)	0.789474	0.70	0.794444
5	SVM(sigmoid)	0.736842	0.60	0.744444
6	Decision Tree	0.815789	0.65	0.825000
7	Random Forest	0.868421	0.80	0.872222
8	AdaBoost	0.868421	0.65	0.825000

Table 1. Table depicts Accuracy, Recall and AUC

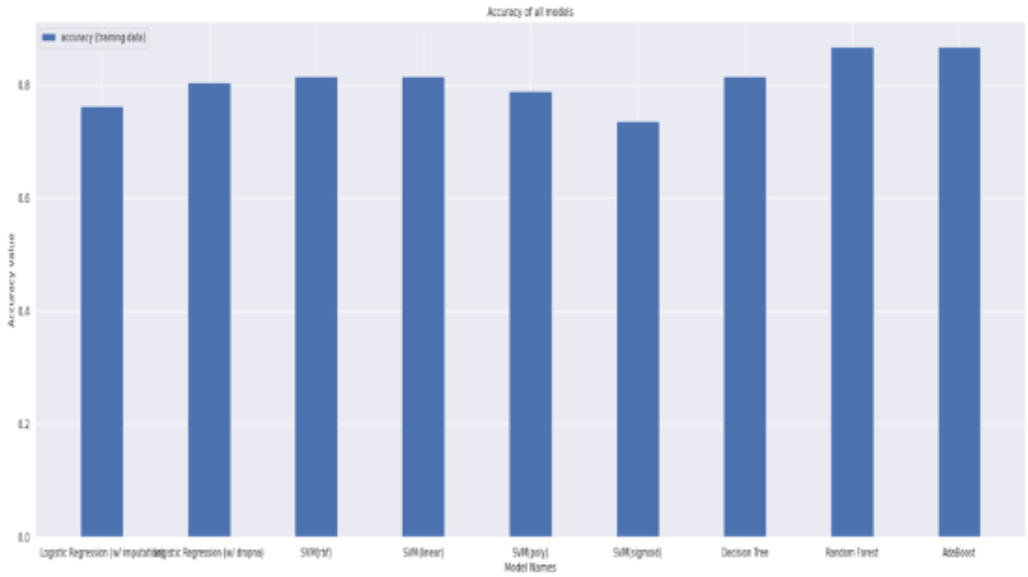

Fig 6. Accuracy of all models

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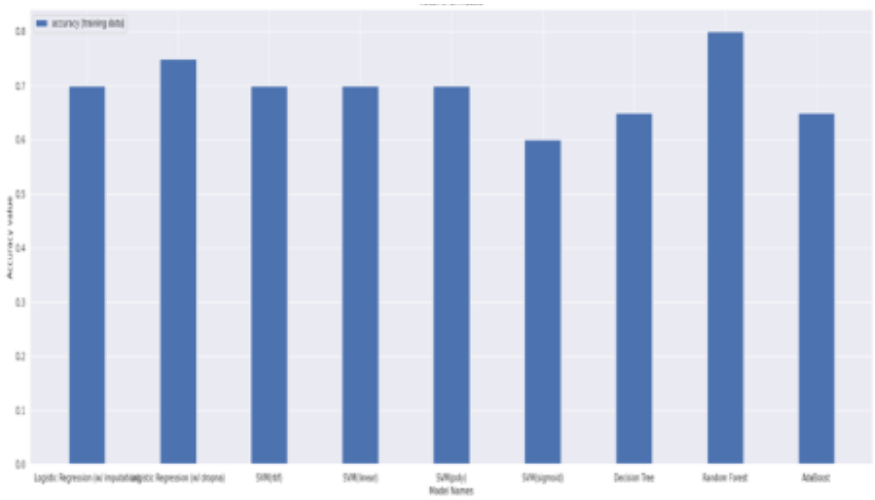

Fig 7. Recall of all models

VI. FUTURE ENHANCEMENTS

While the models developed in this initial study provide a promising proof of concept, further progress will depend on addressing current limitations through continued data acquisition and methodological refinement. Even with the large sample sizes pooled from ADNI, AIBL and OASIS, numbers remain small for detecting the subtle preclinical changes indicative of very early Alzheimer's disease pathogenesis.

As initiatives like these actively enroll new participants and follow up on existing cohorts longitudinally over many years, the opportunity exists to harness far more data than were available for the present research. Standardizing data collection procedures and developing common data elements across studies through harmonization efforts led by organizations such as the Global Alzheimer's Association Interactive Network (GAAIN) will be important to facilitate aggregating datasets into a unified framework.

This will maximize what can be learned from the totality of data through large-scale mining and modelling approaches. Simply amassing larger samples spread across disparate datasets is insufficient without first integrating them into a cohesive whole where algorithms can leverage the full pool of information. As these efforts to aggregate neuroimaging findings, biomarkers, genetic data, and clinical evaluations progress, they will empower refining algorithms on samples an order of magnitude greater than currently feasible. Beyond just increasing sample sizes, incorporating emerging data modalities holds promise to further enhance diagnostic accuracy and specificity. Diffusion MRI measures like fractional anisotropy show great potential for detecting microstructural white matter changes indicative of very early Alzheimer's pathology, providing a window into demyelination and axonal degeneration not visible with conventional structural MRI. Resting state functional MRI studies of intrinsic connectivity networks and patterns of functional connectivity also offer insights into disruptions to brain network organization prior to overt neurodegeneration.

Molecular imaging techniques continue advancing rapidly as well, with novel positron emission tomography tracers now available that can target pathological tau aggregates or differentiate between amyloid subtypes such as Aβ1-42 with higher resolution than previously possible. Multi-omics approaches integrating genomic, epigenomic, proteomic, metabolomic, and other high-throughput biomarker datasets may reveal new biological signatures associated with preclinical disease stages by leveraging the vast amount of molecular information contained in biofluids and tissues. Such multi-modal "-omic" profiles hold promise to detect subtle aberrations from healthy norms at the molecular level prior to structural or cognitive changes. However, sample sizes for such studies remain relatively small to date, and more data will be needed to fully characterize the utility of these approaches.

Longitudinal studies following cohorts of patients over 5-10 years or more with repeated multi modal scans obtained at regular intervals will also be pivotal to advancing the field. Such designs will allow characterizing how biomarkers from different imaging and molecular modalities dynamically evolve over the long preclinical and prodromal stages of Alzheimer's disease. Machine learning models that can leverage temporal patterns across data types may achieve even earlier detection by recognizing subtle deviations from an individual's normal aging trajectories.

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As cohorts age, those who develop cognitive impairment can be identified, aiding retrospective analysis to discern which early signatures best predicted progression. However, following participants longitudinally over decades represents a massive undertaking requiring sustained commitment of resources.

Techniques like transfer learning and unsupervised domain adaptation also hold promise to help address current limitations imposed by limited sample sizes, especially for rarer preclinical and early disease stages. Pre-training machine learning models on larger related "source" datasets like those from normal aging cohorts, before fine-tuning on smaller targeted "target" datasets enriched for early Alzheimer's cases, may help overcome data scarcity issues and boost performance. Unsupervised domain adaptation methods can help minimize effects of potential dataset shifts or variability in terms of demographic factors, image acquisition protocols, quality, and other non-clinical sources of heterogeneity—allowing models to generalize more robustly when applied to new target datasets distinct from those used for initial training. Self-supervised and contrastive learning are emerging areas of machine learning research that show potential to leverage abundant unlabeled data, which represents the vast majority of data available, to learn rich feature representations applicable to many important downstream clinical tasks. By developing general-purpose feature extractors from self-supervised pre-training on large unlabeled datasets, these techniques may help address the perpetual challenge of limited labeled examples for rare conditions like preclinical Alzheimer's disease.

The features extracted could then be used to initialize or regularize supervised models trained on smaller labeled datasets. Rigorous prospective validation of any machine learning tools in new large independent cohorts and clinical trials will also be crucial before models can be translated into clinical practice. Adopting standardized scoring systems like the OASIS scale for rating prediction performance on prospective validation cohorts will help establish reliability and reproducibility. Ultimately, demonstrating improved outcomes versus standard diagnostic evaluations alone through large multicentre clinical studies with long follow-up periods will be required before machine learning can impact patient care. With ongoing advances in data collection, harmonization, model development, and validation, the promise of multi-modal machine learning for early Alzheimer's detection continues growing closer to realization.

VII. CONCLUSION

In closing, this study provided initial evidence that integrating multi-modal neuroimaging data through machine learning may enhance early detection of Alzheimer's disease compared to single data types alone. By leveraging large open-source datasets, models were trained on structural MRI scans supplemented with complementary PET, biomarker and clinical information pooled from international cohorts. The results indicate combining data from different sources holding distinct yet related disease signatures can yield improved diagnostic accuracy over isolated examination of single biomarkers. Specifically, the machine learning model fusing MRI and PET outperformed those relying on only one modality.

This highlights how a more holistic view incorporating various windows into Alzheimer's pathology may reveal subtle signs that individual biomarkers miss. However, limitations remain. Sample sizes for rarer preclinical stages were still too small given disease heterogeneity. Characterizing dynamic biomarker trajectories requires following participants longitudinally for decades, an immense undertaking. Standardizing data collection and harmonizing datasets through initiatives like the Global Alzheimer's Association Interactive Network will be pivotal to aggregating even larger samples. Incorporating emerging data types from novel imaging modalities and multi-omics may provide fresh insights into early disease mechanisms.

Advancing machine learning techniques such as transfer learning and unsupervised domain adaptation also shows promise to overcome current data scarcity hurdles. Rigorous prospective validation in large independent cohorts is indispensable before any tools achieve clinical applicability. With ongoing progress aggregating more robust datasets and refining algorithms, multi-modal machine learning shows potential to enable earlier and more precise diagnosis preceding symptom onset. This could facilitate identifying candidates for future disease-modifying therapies and ultimately improve outcomes. Further research remains warranted, but the field progresses closer to realizing preclinical Alzheimer's detection.

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