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Artificial Intelligence for Alzheimer's Disease Detection: Enhancing Biomarker Analysis and Diagnostic Precision †

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment. Early and accurate detection of AD is crucial for timely intervention and effective treatment. Biomarkers such as amyloid-beta and tau proteins, genetic markers like the APOE genotype, and neuroimaging findings are essential for AD diagnosis and prognosis, but their complex interactions require advanced analytical tools. AI has emerged as a transformative tool in healthcare, offering advanced computational techniques to analyze complex biomarker data with enhanced precision. This review paper explores the advancements in diagnosing Alzheimer's disease (AD) using artificial intelligence (AI) techniques. In the paper, we discuss the importance of diagnosing AD accurately and the potential benefits of using AI techniques for the early and accurate detection of AD. We emphasize the significance of AI in optimizing biomarker analysis for AD detection, discussing the challenges in their implementation and future implications. AI technologies can transform AD detection by significantly improving diagnostic imaging techniques, identifying key biomarkers, and standardizing the analysis of complex neuroimaging data. In the paper, we also highlight the critical role of AI in addressing challenges associated with integrating new technologies into clinical practice and providing effective solutions for consistent and reliable AD detection techniques.

Keywords: Alzheimer's disease detection; artificial intelligence; biomarker analysis; neurodegenerative disorders; early diagnosis; neuroimaging; machine learning

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1. Introduction

1.1. Overview of Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disorder and the most prevalent cause of dementia accounting for an estimated 60–80% of cases [2]. AD often initiates with a Mild Cognitive Impairment (MCI) stage characterized primarily by memory loss, followed by a gradual decline that encompasses behavioral issues and reduced self-care. The disease develops very slowly and the resulting changes are irreversible. Prodrome diagnosis of AD, especially in MCI state, is especially crucial so that one can take therapeutic measures and delay the disease progression. MCI is a transitional stage between normal cognitive aging and more serious conditions like dementia. MCI includes several types: amnestic MCI (aMCI), primarily affecting memory; early MCI (eMCI), characterized by subtle cognitive changes; late MCI (lMCI), involving more pronounced deficits; and non-amnestic MCI, which impacts other cognitive functions. Additionally, Subjective Cognitive Decline (SMC) refers to self-reported cognitive concerns without measurable impairment. Understanding these distinctions is crucial for diagnosis and prognosis, informing treatment strategies [31]. Pathological abnormalities, such as amyloid plaques can form 10–20 years prior to cognitive dysfunction and significant nerve cell loss [5]. It affects the central nervous system (CNS) through the excessive accumulation of protein fragment β-amyloid and an abnormal form of the protein tau plaques [1]. This accumulation is followed by neurodegeneration which causes structural changes and a loss of functional connectivity and damage to other brain cells. Additionally, there are alterations in reactive processes, including neuroinflammation and changes in plasticity, which are associated with oxidative stress and mitochondrial dysfunction [1]. Another brain change linked to Alzheimer's disease is atrophy, characterized by a reduction in brain volume due to neurodegeneration and other factors [2]. Figure 1 [37] illustrates the AD progression in brain. Detecting AD at its onset enables timely intervention with medications and lifestyle adjustments that may slow progression and enhance quality of life and prevent fatality. It also aids in planning for future care, differentiates AD from other cognitive disorders, and allows access to support resources and clinical trials [3–5].

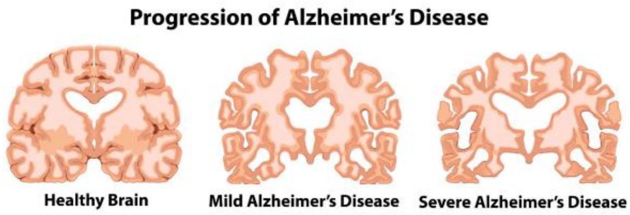

Figure 1. Illustration of AD progression, including the healthy brain, mild AD, and severe AD [37].

1.2. Role of Biomarkers in AD

Biomarkers can be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" [15]. Biomarkers play a critical role in the diagnosis, prognosis, and management of AD. They provide measurable indicators of biological processes, enabling early detection and monitoring of disease progression. The development of early and reliable diagnostic markers is essential for detecting the disease sooner, enabling preventive actions to prevent further neuronal damage [3–5].

1.3. AI in Healthcare

AI has emerged as a transformative tool in healthcare, offering innovative computational techniques to analyze complex biomarker data with enhanced precision. It has demonstrated a significant potential in enhancing the detection and diagnosis of AD by identifying intricate patterns in large datasets and analyze large volumes of genetic, imaging, and clinical data generated during neurodegenerative disease research [13]. AI techniques like deep learning and natural language processing have transformed healthcare, leveraging datasets such as ADNI, NACC, and OASIS. ADNI enables predictive modeling in Alzheimer's disease through neuroimaging and biomarker data, while NACC and OASIS provide extensive clinical and imaging resources for studying neurodegenerative diseases. These tools enhance diagnosis and personalized treatment strategies. AI can optimize biomarker analysis, enhance neuroimaging techniques, and provide more consistent and reliable diagnostic solutions. The rapid increase in computational power, along with advancements AI has opened up new possibilities for analyzing complex medical data, such as neuroimaging scans and biomarker profiles [14]. In this review, we discuss about the AI techniques that can be utilized to enhance the biomarker analysis and improve the diagnostic precision of AD.

2. Biomarkers in AD

Neuroimaging techniques including imaging modalities like Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans, play a crucial role in detecting structural brain changes and visualizing pathological features like amyloid-β plaques and tau tangles [1,3,5]. These techniques help identify characteristic patterns of brain atrophy and protein accumulation associated with AD [18]. CSF analysis can also reveal biomarkers related to AD pathology, providing further evidence to support a diagnosis [1,9]. Blood-based biomarkers are being developed to provide a less invasive diagnostic option [3,4]. Genetic testing, such as for the APOE ε4 variant, can indicate an increased risk of AD but is not used in isolation for diagnostic purposes. A summary of traditional biomarkers is given in Table 1 [1,3,11,18].

Table 1. Summary of various traditional biomarkers that are used for AD detection. Created by author and reference taken form [1,3,11,18].

Category	Biomarker	Description	Key Feature
MRI	Grey Matter Volume	Measures the volume of grey matter in the brain, indicating atrophy	Reflects structural changes in neurodegeneration
PET	Amyloid Beta Deposition	Visualizes amyloid-beta plaques and tau tangles using radiotracers	Direct detection of pathology.
Cerebrospinal Fluid (CSF) Biomarkers	Amyloid-Beta (Aβ42)	Indicates amyloid plaque deposition in the brain	Measured using ELISA or mass spectrometry.
	Total Tau (t-tau)	Measures levels of total tau protein in CSF	Reflects neuronal damage and degeneration.
	Phosphorylated Tau (p-tau)	Measures levels of phosphorylated tau protein in CSF	Indicates neurofibrillary degeneration.
Blood-Based Biomarkers	Amyloid-Beta (Aβ42 and Aβ40)	Measures levels of amyloid-beta in blood plasma	Reflects amyloid plaque deposition
	Tau Proteins (t-tau and p-tau)	Measures levels of tau proteins in blood plasma	Indicates Tau pathology
	Neurofilament Light Chain (NFL)	Measures levels of NFL in blood plasma	Reflects neurodegeneration
Genetic Biomarkers	APOE Genotype (APOE ε4)	Identifies presence of APOE ε4 allele, associated with increased genetic risk for AD	DNA sequencing or genotyping assays, including PCR-based methods are used

3. Recent Advances in AI Techniques for Biomarker Analysis

Machine Learning involves creating algorithms and statistical models that let computers learn from experience and become better at completing tasks. Deep Learning can perform classification tasks on images, text, or sound by using large datasets and multilayered neural networks. DL models consist of multiple layers of neurons which are trained on large datasets of images to learn patterns and features that are useful for image analysis. DL models can automatically learn relevant features from the data [12,14]. Transfer Learning is another algorithm which is used in AD detection where a model developed for a specific task is adapted for a different but related task. Instead of training a new model, which requires substantial data and computational resources, transfer learning leverages the knowledge gained from a pre-trained model. Figure 2 illustrates the algorithms used for diagnosis of AD.

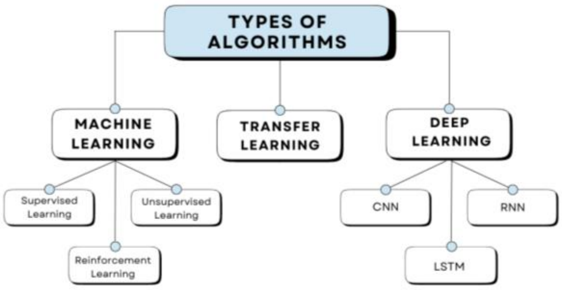

Figure 2. Different types of algorithms used for diagnosing Alzheimer's Disease [14].

3.1. AI in Imaging Biomarkers

Magnetic resonance imaging (MRI) and positron emission tomography (PET) are two medical imaging techniques that are widely used for the early detection of AD [24]. A review of neuroimaging approaches and AI methods for early detection has been covered in [14]. In [20], prospective F-FDG PET brain scans have been employed to train a 48-layer deep convolutional neural network named InceptionV3. Mehmood et al. [21] employed MRI images with a pre-trained VGG convolutional neural network, achieving high accuracy in distinguishing AD patients from healthy controls. A computational method for diagnosing AD from brain MRI scans proposed in [28] is a combination of Gaussian mixture model (GMM) and a convolutional neural network (CNN) for tissue segmentation. It also employs extreme gradient boosting (XGBoost) with a support vector machine (SVM) for classifying Alzheimer's disease based on the segmented tissues. Popuri [29] proposed a novel biomarker using MRI-based features to measure neurodegeneration. Choi et al. [30] developed a CNN system that accurately predicts cognitive decline in MCI patients using PET images. The model achieved 84.2% accuracy in predicting MCI to AD conversion.

3.2. AI in Cerebrospinal Fluid(CSF) Biomarkers

CSF biomarkers are promising for Alzheimer's diagnosis but involve an invasive lumbar puncture, which can be uncomfortable and carries some risk. The test's cost and availability may also limit its use [23]. Diagnostic guidelines include CSF levels of amyloid-beta, total tau protein, p-tau [31]. The study [15] discusses the use of automated platforms for assessing core AD biomarkers in CSF. The study compares two large cohorts of patients with various neurological disorders and applies unsupervised Gaussian mixture models to classify patients based on their CSF biomarker profiles. The findings suggest that automated assays and unsupervised machine learning approaches can help in the biochemical profiling of neurological disorders and improve diagnostic protocols.

3.3. AI in Blood-Based Biomarkers

Brain-derived biomarkers are generally found in lower concentrations in blood compared to CSF primarily due to the blood-brain barrier, which restricts the free movement of substances between the central nervous system and the bloodstream. Advances have been made to enhance the analytical sensitivity of these methods [14]. It has been discovered that combining blood bio-marker detection with imaging markers may help enhance the accuracy of AD diagnosis [25]. Blood-based data is emerging as a promising non-invasive biomarker for Alzheimer's Disease. Generated through omics techniques, this data is complex, high-dimensional, and voluminous, making manual analysis difficult. The study [26], explores the use of AI to identify small sets of blood transcripts that can differentiate between healthy individuals and those with AD. The combination of DL models with imaging from blood samples to investigate AD has been suggested in [27] where the authors concluded that a robust deep learning pipeline, which incorporates positive and bias control models along with visualization techniques, is valuable for validating the results of deep learning models.

3.4. AI in Genetic Biomarkers

By integrating genetic data with other types of omics information, such as transcriptomics and proteomics, AI provides a comprehensive view of the biological pathways involved in AD, enabling the identification of novel genetic biomarkers associated with early disease onset [12]. APOE ε4 is a key genetic biomarker for Alzheimer's disease (AD), with its risk association varying by genotype. Individuals with two ε4 alleles (ε4/ε4) have a significantly higher risk than those with one ε4 allele combined with an ε3 allele (ε4/ε3). Additionally, the presence of the ε2 allele (ε2/ε4 or ε2/ε3) appears to confer some protective effects against AD. Understanding these combinations is crucial for risk assessment and research. By processing genetic data in real time, AI improves the detection of early biomarkers and supports personalized treatment strategies, thereby advancing the early diagnosis and management of AD [6]. This integration of AI and genetic biomarkers enhances the accuracy of early diagnosis and supports the development of personalized treatment strategies by identifying individuals at higher risk [6,14].

4. Enhancing Diagnostic Precision and Advances in AD Monitoring Using AI

The data produced by non-invasive methods is highly complex due to noise, large volume, high dimensionality, and variability [14]. Analyzing thousands of MRI or PET images presents a level of computational complexity that simple methods cannot handle [12]. Blood screening data includes omics measurements with an exceptionally high number of samples and features. This complexity makes it challenging to analyze and interpret using traditional statistical methods. AI techniques can help to identify patterns in data and generate predictive models that can assist in the early detection and accurate AD.

Table 2. Summary of various AI techniques that can be used for Biomarker Analysis.

Category	Biomarker	Technique	References
MRI	Grey Matter Volume	VGG (CNN); Segmentation: GMM and CNN Model Classification: XGBoost and SVM; Novel Biomarker based on MRI;	[14,21,28,29,38]
PET	Amyloid Beta Deposition	(InceptionV3) CNN; Ensemble Model; Imaging Analysis using CNN	[14,20,30]
Cerebrospinal Fluid (CSF) Biomarkers	Amyloid-Beta ($A\beta 42$)	Gaussian Mixture Models Automated Assays and Unsupervised Learning	[15]
	Total Tau (t-tau)	Gaussian Mixture Models Automated Assays and Unsupervised Learning	[15]
	Phosphorylated Tau (p-tau)	Gaussian Mixture Models Automated Assays and Unsupervised Learning	[15]
Blood-Based Biomarkers	Amyloid-Beta ($A\beta 42$ and $A\beta 40$)	CNN on imaging blood samples VGG-16 and Inceptionv3	[14,25–27]
	Tau Proteins (t-tau and p-tau)	CNN on imaging blood samples VGG-16 and Inceptionv3	[14,25–27]
	Neurofilament Light Chain (NFL)	Regression models, Neural networks, and Ensemble methods	[14,25–27,38]

Genetic Biomarkers	APOE Genotype (APOE ε4)	CNN, Supervised Learning Methods	[6,12,14]

5. Conclusions

The advent of artificial intelligence (AI) and deep learning (DL) is set to revolutionize Alzheimer's disease (AD) detection by enhancing biomarker analysis and diagnostic precision. Early and accurate diagnosis of AD is essential for improving patient quality of life through timely preventative measures. To achieve this, there is a growing need to identify and utilize AI-based biomarkers that can detect early cognitive deviations indicative of AD. As non-invasive technologies advance and more data is generated, the role of AI will become increasingly pivotal. AI technologies, have demonstrated a significant potential in enhancing the detection and diagnosis of AD by identifying intricate patterns in large datasets that may elude traditional analysis methods. By combining these computational tools with non-invasive as well invasive biomarker approaches, we can expect significant improvements in the early detection and diagnosis of AD.

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