Machine Learning Approaches for Early Prediction of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting more than 55 million individuals all around the world. However, effective measures are still rare, and many challenges exist, including the ambiguity of cause, multifactor interactions, lack of effective indicators for early stages, and low clinical trial success rate. As a result, recent researchers divert their attention from treatment to the early diagnosis of AD, to take precautions before the onset of AD. Traditional prediction methods, such as biomarker analysis and neuroimaging tests, have limitations in sensitivity and comprehensiveness. Recent advancements in machine learning, particularly deep learning and explainability techniques, have presented new ways to improve the accuracy and practicality of early prediction of AD. Researchers explore the integration of multimodal data fusion, self-supervised learning frameworks, and interpretable models in AD prediction. While significant progress has been made, model interpretability and clinical acceptance remain. The paper first reviews and analyses traditional methods to recognize AD and then explores the potential of emerging technologies in enhancing early AD prediction, providing insights into future research directions, such as the development of more robust and transparent machine learning models.

1 INTRODUCTION

AD, the most common cause of neurodegenerative disease, affecting more than 55 million people's normal lives in 2020, and the number is expected to double every 20 years, becoming a huge challenge for the whole world (Dementia Statistics | Alzheimer's Disease International (ADI), n.d.). Although a large amount of funds has been invested into studying therapy for AD, there are still very limited methods.

Early identification has a positive effect on patients with AD. From the normal state to the severe dementia state, it will take 15 to 20 years of the mild cognitive impairment stage, where the symptoms are not obvious at first and some preventive measures can be adopted to promote potential patients' fitness (Scheltens et al., 2021). Researchers have found that some activities, including learning new things like language and participating in an active socially integrated lifestyle, would highly improve patients' cognitive performance (Fratiglioni et al., 2004). Identifying patients at the Mild Cognitive Impairment (MCI) stage, particularly early MCI, can help delay the onset of AD (Velazquez et al., 2021).

For this reason, accurate and effective prediction methods are urgently needed to decline symptoms and delay the onset of AD. Traditional methods are biomarker analysis. To be specific, proteomics and longitudinal data from the ADNI database are widely used to predict AD risk based on novel plasma protein biomarkers including amyloid-beta protein (Aβ) (Youssef et al., 2025). Recently, with the current machine learning methods, especially artificial intelligence, and electroencephalogram (EEG) prevailing around the world, many researchers have begun to combine them to have a more accurate prediction from another perspective (Kishore et al., 2021).

This paper will discuss current popular forecasting methods in detail, compare their performance, and explore possible ways to improve early prediction of AD.

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2 OVERVIEW OF AD

2.1 Pathophysiological Features

Several researches have been done to explore the cause of AD, and till now some pathophysiological features have been discovered. Key pathophysiology features are Aβ plaques, and neurofibrillary tangles (NFTs). Accumulation of Aβ peptide causes an increase in intracellular reactive oxygen species (ROS) and free radicals that are related to a deficient antioxidant defense system. Besides, NFTs are composed of hyperphosphorylated tau(p-tau) proteins, and the accumulation of abnormal tau proteins within neurons will lead to neural damage (Navigatore Fonzo et al., 2021). Both Aβ peptide and NFTs will cause protein oxidation, lipid peroxidation, and oxidation of DNA and RNA, ultimately leading to some clinical symptoms (Navigatore Fonzo et al., 2021).

2.2 Clinical Features

Clinical symptoms mainly include cognitive impairment and motor or language impairment, embodying memory loss, confusion, and difficulty with language and problem-solving skills. These symptoms typically worsen over time and can significantly impact a person's ability to perform daily activities (Alzheimer's Disease - Symptoms and Causes, n.d.). In addition to the cognitive symptoms of AD, there is growing evidence to suggest that AD may also have systemic effects on the body. Based on a sample of 4156 participants with plasma Aβ sample collected between 2002 and 2005, researchers used multivariable linear regression models to explore the cross-sectional relation of plasma Aβ with echocardiographic measures and discovered that high levels of Aβ40 were related to worse cardiac function and higher risk of new-onset HF in the general population, revealing an association between AD and cardiac disease (Zhu et al., 2023). The outcome further demonstrated the clinical appearance of AD. From this perspective, finding a better way to early recognize AD and taking necessary measures is of great importance.

3 TRADITIONAL PREDICTION METHODS

3.1 Biomarker Test

Traditional prediction methods can be divided into three categories: biomarkers tests, neuroimaging tests, and cognitive and behavioral assessments. In the case of clinical treatment, doctors often integrate these methods to assess the degree of AD.

The biomarker test is one of the predominant methods. The resources of biomarkers include blood, cerebrospinal fluid, and genetic biomarkers, each contributing to different parts of the identification.

For blood-based biomarkers tests, researchers assess p-tau protein and amyloid-β42/40 (Aβ42/40) in the blood (Schwinne et al., 2023). Using blood to identify AD is a simple and useful prediction method, especially in the region where the resources are limited. This non-invasive approach provides a wider range of clinical applications and accelerates clinical trials for AD. But challenges still exist, including the strong need of acceptable performance compared with other diagnostic assessments such as amyloid positron emission tomography (PET) and cerebrospinal fluid biomarkers (Schindler et al., 2024).

Another biomarker resource is cerebrospinal fluid (CSF). It is another resource to detect Aβ and p-tau. However, acquiring samples from cerebrospinal is an invasive process, which leads to higher risk and disinclination from patients. Besides, because of the low concentration of Aβ and p-tau, the recognition can be easily influenced by other diseases like chronic kidney disease (Hunter et al., 2025).

3.2 Neuroimaging Test

Neuroimaging relies on modern imaging techniques, such as functional Magnetic Resonance Imaging (fMRI), structural MRI (sMRI), and PET. sMRI can identify morphological data like brain region volume, cortical thickness, and integrity of white matter. In clinical practice, sMRI is often used to test the atrophy of the hippocampus, where the abnormal data would suggest the risk of developing AD and the accuracy is higher than 90% (Khvostikov et al., 2018). Besides, compared with other methods, sMRI is nonradiative and simpler to operate. It is a widely used brain imaging method in clinical practice and is effective in detecting structural lesions of the brain and evaluating the degree of brain atrophy. So, it

could be used as a routine means for AD imaging and monitoring (Zhang et al., 2023).

The imaging of fMRI depends on the blood oxygen level-dependent (BOLD) effect, which refers to local hemodynamic changes during brain activity. Patients with AD will have abnormal connections between functional networks in their brain such as the default mode network (DMN) in the mild stage (Velazquez et al., 2019). fMRI measures indicators such as the strength of functional connections between different brain regions in these networks, thereby predicts the level of functional abnormalities (Chen et al., 2023). Not only does fMRI have high temporal and spatial resolution, but it does also not require the injection of radioactive drugs. Thus, it is extremely suitable for studying early brain changes and exploring the pathophysiological mechanism of the disease. However, the result analysis is relatively complex and can be easily affected by multiple factors, including head motion artifacts during scanning, physiological noise from cardiac and respiratory cycles, variations in preprocessing pipelines (normalization and motion correction methods), gaps between statistical analysis approaches, individual difference in neurovascular coupling, magnetic field instability, and confounding effects from medications (Handwerker et al., 2012; Hutchison et al., 2013; Bergamino et al., 2024). Additionally, factors like task design, baseline cerebral blood flow, and even subjects' mental states may further introduce variability, requiring strict quality control and standardized protocols to minimize these influences.

Apart from sMRI and fMRI, PET is also effective in predicting AD. By testing the uptake of radioactive tracers in various regions of the brain, PET is often used to show the distribution and metabolism of specific biomolecules in the brain, such as glucose metabolism, neurotransmitter receptor distribution, and deposition of specific proteins (Zhang et al., 2023). Therefore, PET can specifically monitor changes in metabolism in the brain at the molecular level and has unique advantages for the early diagnosis of AD, performing high sensitivity and specificity in detecting amyloid deposition. However, the challenges are that the cost of examination is a bit high, and there is a need for radioactive drugs, which will put the patients at certain radiation risk.

3.3 Cognitive and Behavioral Assessment

Cognitive and behavioral assessment is widely used as a diagnosis method. Test indexes usually include memory, language ability, attention and executive function, and neuropsychiatric symptoms (Scarmeas et al., 2007). More often than not, cognitive and behavioral assessment is a very basic method to diagnose AD, but it is not effective and accurate enough, and it is difficult to achieve the purpose of prediction.

4 EMERGING TECHNOLOGIES IN EARLY PREDICTION OF AD

Traditional methods above provide various means for prediction and diagnosis. Recent studies focus on integrating these means, while utilizing machine learning models to enhance the prediction level of AD, offering more opportunities and saving more time to reduce the symptoms of AD patients (Velazquez et al., 2019). Those emerging techniques are mostly based on machine learning, following the workflow of data analysis to enhance the accuracy and efficiency of prediction.

Generally, the process of machine learning can be divided into several steps: 1) data preparation; 2) training sets generation; 3) algorithm training, evaluation, and selection; and 4) deployment and monitoring (Velazquez et al., 2019).

4.1 Multimodal Data Fusion: Enhancing Predictive Comprehensiveness

Traditional methods, no matter whether biomarkers test or neuroimaging method, mainly depend on single indicators, leading to insufficient sensitivity due to limited data dimensions, while current machine learning methods can build more comprehensive predictive models by integrating multi-source data, including sMRI, PET, blood biomarkers, and clinical variables (Table 1). The table below compares traditional methods and machine learning methods in terms of data source, feature extraction, and applicable scenarios for AD research. Traditional methods often rely on single source data and manual feature screening, mainly serving as a supplement for diagnosis. In contrast, machine learning methods use multimodal data and automatically capture complex relationships, being more suitable for early screening and dynamic monitoring of the disease.

In addition, multimodal data can also enhance the

stability of prediction. When predicting AD, data from different modalities may be affected by various factors, resulting in poor stability of the prediction results. Multimodal data fusion can integrate data from multiple dimensions to reduce the noise and bias of single-modality data, thereby enhancing the stability of the prediction model (Qiu et al., 2022).

Table 1: Comparison between Traditional Methods and Machine Learning Methods.

Dimension	Traditional Methods	Machine Learning Methods
Data Source	Single (e.g CSF, sMRI)	Multimodal (imaging, genetic, clinical, behavioral data)
Feature Extraction	Manual screening	Automatically capture high-dimensional non-linear relationships
Application Scenarios	Diagnosis assistance	Early screening and dynamic monitoring

4.2 Deep Learning Models: Enhance Feature Learning Capabilities

Recent advancements in deep learning models have great impacts on the field of medical image analysis, particularly in the early prediction of AD. Among these innovations, self-supervised learning, especially contrastive learning frameworks, has become a powerful approach to enhance feature extraction of brain imaging data.

4.3 Self-Supervised Learning for Robust Feature Extraction

Self-supervised learning (SSL) can leverage large amounts of unlabeled medical imaging data to gain robust and generalizable features. Unlike traditional supervised learning, which relies on labeled data, SSL can pre-train models on unlabeled brain MRI or PET scans to capture more intrinsic and structural features of AD (Kwak et al., 2023).

SSL can effectively identify subtle pathological changes, including Aβ degeneration, even in the early stages of AD. This pre-trained model is extremely suitable for unlabeled datasets to achieve superior performance in AD prediction (Fedorov et al., 2021). It is particularly useful in the real world, where labeled data is often limited due to the high cost and complexity of obtaining expert annotations.

4.4 Contrastive Learning for Multi-Modal Feature Fusion

Contrastive learning, a specific model of SSL, supports multi-modal feature fusion. It can integrate complementary information from different imaging modalities (e.g., MRI, PET), and clinical data (e.g., cognitive scores, and genetic markers). By learning representations among the data sources, contrastive learning model will get a more comprehensive view of AD pathology, advancing the accuracy of early prediction (Kwak et al., 2023).

4.5 Comparison with Traditional Approaches

Compared with traditional deep learning approaches, like convolutional neural networks (CNNs), SSL-based models have some advantages: i) SSL reduces the reliance on labeled data, which is often rare in clinical situation; ii) by leveraging unlabeled data, SSL models can extract more robust and generalizable features, advancing their performance on different patient populations; iii) the integration of multimodal data in SSL models provides a more comprehensive view of AD pathology, enabling earlier and more accurate predictions (Fedorov et al., 2021; Khatri & Kwon, 2023; Kwak et al., 2023).

4.6 Explainability and Clinical Acceptance: Bridging the Gap between Machine Learning and Clinical Practice

Traditional methods for AD prediction are often limited because they strongly rely on human expertise and are short of flexibility in complex scenarios. However, although machine learning models, particularly deep learning models, have better performance, their "black box" nature often reduces clinical trust. To address this, researchers have created explainability tools, such as SHAP (Shaply Additive Explanation) analysis, to reveal the processes when making decisions (Yi et al., 2023).

SHAP analysis quantifies the contribution of each input feature to the model's predictions to provide insights into the decision-making process. In early AD prediction, SHAP can reveal how specific brain regions (e.g., hippocampus, and amygdala) influence the model's diagnosis. SHAP analysis not only maintains high performance in predicting AD, but also resolves the defects in transparency, leading to

wider application in clinical practice. Moreover, models equipped with SHAP demonstrate higher clinical acceptance, particularly in scenarios requiring high accuracy and ability (Vimbi et al., 2024).

4.7 Future Outlook

To further improve the effectiveness and accuracy of AD prediction, future directions might include: 1) developing more robust feature extraction modules to analyze various medical imaging data; 2) exploring more transparent explainability tools to enhance clinical trust; and 3) advancing multi-modal data fusion to achieve a more comprehensive understanding of AD biomarkers. These innovations will drive the development of more accurate, flexible, and clinically effective tools for early AD prediction, ultimately improving patients' outcomes and advancing precise medicine in neurology.

5 CONCLUSION

This paper reviews prevailing methods to predict AD, from traditional approaches including biomarkers tests, neuroimaging tests, and cognitive and behavioral assessment to emerging machine learning methods. In general, traditional approaches focus on pathological characteristics from different dimensions, to give out a precise diagnosis of AD at its mild stage instead of effectively predicting AD before its onset. To reach the purpose of early prediction, researchers integrated different dimensions and, with a large dataset, utilized machine learning methods to sufficiently analyze the probability of acquiring AD. By integrating diverse data sources, such as MRI, PET, and clinical biomarkers, machine learning models have been proven to have better performance in capturing subtle pathological changes associated with AD. Among the emerging methods, self-supervised learning frameworks, particularly contrastive learning, have shown strong potential in leveraging unlabeled data to enhance feature extraction and model generalization to another level. Additionally, this paper also discussed explainability tools, such as SHAP analysis, which bridge the gap between machine learning models and clinical practice by providing transparent insights into model decisions.

After summarizing and evaluating current approaches, this paper indicates existing challenges and gives out important directions for advancement. Further research needs to focus on the robustness and generalizability of models, particularly in diverse and different populations. This could be achieved by developing more powerful and interpretable models that can handle multimodal and various data, reducing reliance on high-quality labeled datasets. Additionally, addressing ethical and private concerns, such as ensuring data anonymization and fostering trust in AI systems, will be crucial for the deployment of these technologies in clinical settings. Finally, fostering interdisciplinary collaborations between machine learning experts, neurologists, and ethicists will be essential to bridge the gap between theoretical advancements and practical clinical applications. By addressing these challenges, we can unlock the full potential of machine learning in AD prediction, ultimately improving patient outcomes and advancing precision medicine in neurology.

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