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A Review on the Techniques for Early Diagnosis of Alzheimer's Disease

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ABSTRACT: *Alzheimer's disease is a neurological condition in which there is rapid deterioration of the brain and it affects around 50 million people globally. The most obvious sign of Alzheimer's is dementia which is primarily an affliction of old age. Majority of the people presenting with dementia in old age are Alzheimer's patients. The symptoms of Alzheimer's disease are debilitating and have the ability to utterly disrupt a person's normal life. It is only discovered after this terrible disease has destroyed all neurons, thus there is little chance to cure it or reverse the adverse effects. There are two types of techniques for detecting Alzheimer's disease: invasive and non-invasive techniques. Invasive method obtains data from the patient by drawing a small amount of blood or performing a lumbar puncture, whereas non-invasive method collects data using imaging techniques like MRI and CT scan. Invasive technique, on the other hand, is thought to be a more accurate indicator of Alzheimer's disease than non-invasive technique since it provides strong biomarkers. Once Alzheimer's disease has progressed to its final stage, it is incurable. Treatment is only viable when the disease is in its initial stages. Future treatments for Alzheimer's disease will focus on the causative maladies of neurofibrillary tangles (p-tau) and senile plaques (A). The pathological traits connected to debilitating disease, special protein, b proteins, are critical for future therapeutics.*

Keywords: Alzheimer's disease, techniques, diagnosis, neurological condition, symptoms.

INTRODUCTION

Dementia affects more than 50 million individuals globally. Two million people are affected by Alzheimer's disease, and it is predicted that by 2050, more than 134 billion people will have it. Alzheimer's disease is one of the most highly prevalent types of dementia contributing to 70 percent of overall cases of memory that primarily affects people in their old age (Valenzuela et al., 2020). It is accompanied by neuronal degradation over time, commonly known as neurodegenerative

disease. One of the most evident symptoms linked with the diagnosis of Alzheimer's disease is memory loss as a result of cognitive region deterioration in the brain. Other symptoms include abrupt changes in mood, behavioral issues, unusual thoughts of being lost, difficulty in executing daily activities, and trouble in speaking, walking, and writing (Wisniewski and Goñi, 2015; Sanabria et al., 2017; Weller and Budson, 2018; DeTure and Dickson, 2019; de Oliveira et al., 2020; Fernández Montenegro et al., 2020; Tait et al., 2020).

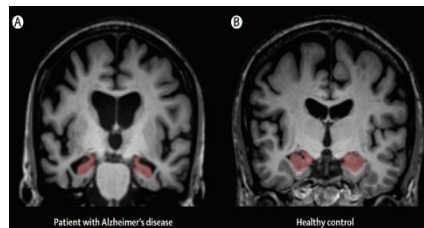


Fig. 1. Alzheimer's disease, comparison with normal brain
("Alzheimer's disease", 2022)

The symptoms of Alzheimer's disease are debilitating and have the ability to utterly disrupt a person's normal life. This disease causes irreparable harm because when a neuron dies due to AD, it cannot be replaced by a new neuron. Therefore, it is crucial to recognize Alzheimer's disease early on, when neurological damage has barely begun, so that it can be treated before it destroys all of the brain's neurons. Early detection of this condition is difficult as

these necessitate costly diagnostic approaches. It costs more than 800 billion dollars all across the world. To battle Alzheimer's disease, it is necessary to develop such diagnostic tools and techniques that are both inexpensive and precise (Fernández Montenegro et al., 2020).

There are two types of techniques for detecting Alzheimer's disease: invasive and noninvasive techniques. Invasive method obtains data from the patient's

interior by drawing a small amount of blood or performing a lumbar puncture, whereas noninvasive method collects data using imaging techniques like MRI and CT scan. Invasive technique, on the other hand, is thought to be a more accurate indicator of Alzheimer's disease than non-invasive technique since it provides strong biomarkers.

Alzheimer's disease can only be diagnosed after it has affected more than 50% of neurons and has progressed to the point where therapy is no longer possible. There is a need to develop biomarkers, procedures, and instruments that can detect Alzheimer's disease at an early stage (Li et al., 2021). The presence of a biomarker for this particular disease will be a blessing if it shows abnormal concentrations that can confirm the disease within the patient. CSF and Plasma IncRNA BACE1 AS are two such possible indicators. However, CSF-based biomarkers that dwell in the brain can offer pathology and metabolism data much more precisely, thus they are preferable over plasma biomarkers (Li et al., 2021). In Alzheimer's disease, pathological cognitive aggregation occurs when extracellular amyloid beta plaques form from amyloid protein deposition, and hyper phosphorylated tau neurofibrillary tangles (NFTs) develop from tau protein

aggregation (Weller and Budson, 2018; Wisniewski and Goñi, 2015). The aggregation of these proteins can damage neurons and are also responsible for cognitive declination. Potential biomarkers, hallmark amyloid plaques, neurofibrillary tangles, and clinical presentation are required for Alzheimer's disease diagnosis. The estimated prevalence of Alzheimer's disease is 10% higher in those over the age of 65 and 40% higher in those over the age of 80 (DeTure and Dickson, 2019). Strategies like exercise, can help to prevent the disease from developing. Exercise has been shown to increase cognitive functioning as well as reduce the progression of cognitive decline. However, individuals who are already with Alzheimer's disease do not have positive findings (Frederiksen et al., 2019; Tarumi et al., 2019).

In the past, only the brain tissue of the dead was being used to diagnose Alzheimer's disease. As a result of the recent clinical advancements, CSF (cerebrospinal fluid) and PET (positron emission tomography) biomarkers can now be used to diagnose Alzheimer's disease in patients while they are still alive (Weller and Budson, 2018). There is no cure for dementia. However, early detection can aid in providing needed support, proper medicine, and, to the

extent possible, maintaining intellectual, social, and physical activities. Early identification of Alzheimer's disease (AD) is thought to be critical for enhancing patients' and their family's quality of life. This study is based on the systemic review of all available literature about Alzheimer's disease's current available effective therapies and also future implications.

Present Available treatments

Once Alzheimer's disease has progressed to its final stage, it is incurable. Treatment is only viable in the initial stages of the disease. Cholinesterase inhibitors, rivastigmine, memantine, and galantamine are a few recommended medications that could be used to treat Alzheimer's. The speed of intellectual decent and the progression of chronic disease remain constant; therefore, these medications merely serve to enhance the patient's life quality (Weller and Budson, 2018). These medications might also help in retaining memory and alertness of AD patient. Alongside these medicines, healthy diet and some exercise might also lower the risk of developing AD. Furthermore, supplements containing omega-3 fatty acids, such as fish oil, may potentially help the patient's condition with AD.

CSF AB42: p tau ration and biomarkers of amyloid PET scans are the best

diagnostic tests for Alzheimer's disease. After receiving a radiolabeled tracer agent, a PET scan is performed to detect the amyloid (A) peptides deposition into plaques. PET scanning offers a 96% sensitivity and a 100% specificity. Although pet scanning can provide a definitive sign of Alzheimer's disease, it is quite expensive, and it is not a feasible diagnostic method for some people. CSF, tau protein, and hyperphosphorylated tau peptide (p-tau) examinations are some of the less expensive but extremely intrusive procedures for detecting Alzheimer's disease. These approaches have an accuracy of up to 85%. One of the less intrusive procedures that can open up new avenues is serum assay by simple blood test, identifying the amount of circulating protein involved in the disease (Weller and Budson, 2018).

Future treatment

Future treatments for Alzheimer's disease will focus on the causative maladies of neurofibrillary tangles (p-tau) and senile plaques (A). The pathological traits connected to this disease, special protein, b proteins, are critical for future therapeutics. There is a limited amount of evidence of studies that were successful on a smaller scale but unsuccessful on a larger size. Aside from that, there is a silver lining for

biologists and researchers in that a greater understanding of the etiologic abnormalities associated with Alzheimer's disease could lead to the development of better and less expensive diagnosis and therapies for this neurodegenerative ailment (Ashton et al., 2018).

1. Simple blood test

Diagnosing Alzheimer's disease necessitates either costly brain imaging or intravenous CSF analysis. CSF analysis is simple and inexpensive to undertake. Therefore, for running bigger clinical Alzheimer's disease experiments with reduced screening mistakes, a blood test is preferable since it is less painful, less expensive, and more accurate (Nabers et al., 2019). In this condition, proteins and amyloid beta proteins aggregate to form pathogenic entities. Amyloid beta and tau protein aggregates generate massive clumps and tangles in the body. These masses shrink brain and induce cellular damage, resulting in memory loss, behavioral issues, and other problems (Prasad, 2020).

A minimally invasive blood test can help pave the way for Alzheimer's disease identification because it begins around 10-15 years before the illness's symptomatic appearance. Therefore, at an initial screening stage, a minimally

intrusive, safe, and reliable blood test is recommended to pinpoint any significant risk of developing Alzheimer's disease because a simple blood draw can successfully determine improper folding of tau and amyloid beta protein (Nabers et al., 2019; Yoon et al., 2021).

2. Eye-tracking technology

The visual processes are affected by Alzheimer's disease in a variety of ways. By examining the measurement time to reaction to a stimulation, eye movement can also provide information about a person's mental state. As a result, reflexes and eye movement can quickly assess an individual's mental state and visual memory (Ganasegeran et al., 2021). The fixation time, refixations, and movement angle of Alzheimer's sufferers and healthy people are compared using eye movement tracking equipment. This technology is most effective for detecting MCI (mild cognitive impairment). In mild cognitive impairment, patients experience troubles with cognition, including problems with thinking and memory. Mild cognitive impairment is further subdivided into amnesia mild cognitive impairment (aMCI) and non-amnesia mild cognitive impairment (naMCI). People with amnesia mild cognitive impairment (naMCI) are more likely to acquire

condition that subjects with non-amnesia mild cognitive deficits. Such people that are at a higher risk of acquiring such condition can be easily identified using eye tracking equipment. The comorbidities of eye movement serve as a diagnostic marker for the early diagnosis of disease and can successfully provide information of those MCI patients who are prone to developing AD. This would act as a supporting element in tracking the evolution of the sickness and, ultimately, assessing the severity as well as effectiveness of the therapeutic interventions. Eye tracking technology is extremely important as an earlier diagnosis of Alzheimer's disease would enable effective treatments, when available, to be administered before pathological changes to the brain can spread and be permanent (Wilcockson et al., 2019; Tadokoro et al., 2021).

3. EEG microstate Analysis

One of the viable platforms for measuring brain dynamic changes is electroencephalogram – EEG for imaging of microstates. Any information linked to cognitive impairment can be simply defined using EEG microstates. It has the potential to be a non-invasive and relatively inexpensive biomarker for the early detection of a variety of neurological

illnesses, including dementia and Alzheimer's disease, on a shorter time frame. Another invasive approach for cognitive screening for early diagnosis of Alzheimer's disease is EEG microstates. An impaired microstate class, and its increased duration may be a sign of Alzheimer's disease. In the presence of Lempel–Ziv complex to the microstate transition process, Alzheimer disease is even easier to diagnose. Based on the current effectiveness of EEG microstate for early diagnosis of Alzheimer's disease, it has the potential to be a useful and cost-effective tool for diagnosis and drug development in the future (Tait et al., 2020).

4. Biomarker

The term "biomarker" refers to a biological trait used in clinical research and trials to assess the presence or progression of disease, as well as the treatment effects. The word is defined by the World Health Organization as any measurement that reflects an interaction between a biological system and a possible hazard, which might be chemical, physical, or biological (Davda and Corkill, 2020).

4.1. Plasma phospho-tau (P-tau) Biomarker

The primary detection factors of Alzheimer's disease include cerebrospinal fluid (CSF), amyloid-42

(A42), total tau (T-tau), and phosphorylated tau (P-tau). These biomarkers have the ability to accurately distinguish AD patients from non-AD patients. They also allow for precise tracking of a patient's Alzheimer's disease progression. They can be used to forecast the progression of Alzheimer's disease in people with cognitive impairment (Nordberg, 2015; Janelidze et al., 2020).

4.2. Blood biomarker

A microfluidic platform for detecting ADAM10 in CSF and plasma has been developed using electrochemical immunosensors. It's a very simple, sensitive, and low-cost method with a high accuracy rate. Throughout the disease, there was an increase in protein levels, and D μ P accuracy in discriminating people is noted. ADAM10 has been shown to be an alternate technique for the early diagnosis and monitoring of AD when detected with the D μ P (Ashton et al., 2018; Tadokoro et al., 2021).

4.3. RNA sequencing bio marker

Although the effects of Alzheimer's disease are irreversible, RNA sequencing can help to slow down the progression of the disease. This method can also be used to predict the risk of Alzheimer's disease (Shigemizu et al., 2020).

4.4. Retinal biomarkers

New imaging tools for quantifying retinal structural and vascular markers for cognitive impairment and dementia include optical coherence tomography (OCT), OCT angiography, fundus photography, and dynamic vessel analyzer (DVA). These retinal changes may prove to be helpful biomarkers for screening and monitoring dementia progression in clinical practice if more research is needed (Czakó et al., 2020).

5. (DNS), a longitudinal cognitive test

The Digital Neuro Signature (DNS) developed by Altoida generates stronger test-retest reliability in intra-individual assessments, as well as more accuracy in detecting impaired cognition. The ability of DNS-intra individual variability to predict conversion from mild cognitive impairment to Alzheimer's disease is discovered (Meier et al., 2021).

6. Depth wise separable convolutional neural networks

The DSC algorithm, which is based on the OASIS magnetic resonance imaging dataset, is particularly effective at detecting Alzheimer's disease. In order to increase model performance, transfer learning is used. The model parameters of the suggested technique are lowered by 87.94% and the computing cost is

reduced by 84.25% when compared to Convolutional Neural Network. It shows promise in terms of detecting Alzheimer's disease on mobile embedded devices with modest computational resources (Ju et al., 2017).

7. Biomedical Device

A non-invasive biomedical device for the early detection of moderate cognitive impairment, which can progress to Alzheimer's disease if left untreated. The design of this biomedical equipment is based on Event Related Potential (ERP) principles, in which the individual is provided auditory stimulation and then stimulated brain waves are acquired from the parietal lobes of the P3 and P4 region. This stimulated signal is then amplified and filtered before being recoded as sound waves at an 880x gain. MATLAB then evaluates the stimulated signal, providing final data that aid in the diagnosis of MCI (Ahmed and Al-Neami, 2021).

Apart from the invasive/non-invasive classification, Alzheimer's detection methods can also be classified as non-cognitive and cognitive tests. Cognitive tests encompass the methods that assess the patients' cognition; these procedures are non-invasive as well as easy to

implement. On the other hand, non-cognitive tests include all other methods that were used to detect and diagnose dementia.

8. Non-Cognitive AD Screening Methods

8.1. Neuroimaging Techniques

Currently, neuroimaging techniques are successful noninvasive tools of AD diagnosis. MRI, PET, AND CT scan are few neuro imaging techniques which are useful to detect disease-related alterations in patients' brains. Diffusion Tensor Imaging (DTI) and Fluid-attenuated Inversion Recovery (FLAIR) techniques, which are types of MRI techniques used to detect alterations in white and grey matter in the brain, have been shown to have a positive relationship with this neurodegenerative condition (Agüera - Ortiz et al., 2017).

8.2. Behavioral Analysis

Behavioral analysis is another low-cost, non-invasive approach for diagnosing Alzheimer's disease. Sensors are used in this technology to capture a person's regular activities as well as unusual attitudes and behaviors. This approach is quite effective, with a detection rate of up to 75% (Fernández Montenegro et al., 2020).

8.3. Emotional analysis

Another potential indicator for Alzheimer's disease detection is social declination. As a result, special attention is given to recognize the patient's emotions as they become more intense over time in Alzheimer's patients. Emotion is important in subjects like psychology and neuroscience since it can reveal a lot about a person's physical and mental health. Different technologies, including facial movement, EEG, and eye tracking

technique, can be used to recognize and record a patient's emotions (Fernández Montenegro et al., 2020).

9. Cognitive Tests

Complex attention, executive function, perceptual motor, language, learning and memory, and social recognition are six areas of neurocognition that are significantly damaged by Alzheimer's disease, according to the American Psychiatric Association (Fernández Montenegro et al., 2020) (Table 1).

Table 1: Details of different parameters of cognitive tests

Complex Attention	Ability to maintain sustained, divided, and selective attention
Executive Function	Ability to plan, make decisions, working memory, feedback response, overpowering habits, and flexible thinking
Perceptual Motor	Ability to recognize figures based on their shape or color (face detection or hand-eye coordination).
Language	Ability of comprehension and articulation
Learning and memory	Immediate, recent, and very long-term memory
Social Recognition	Ability to recognize and understand other people's feelings

10.1. Methods Based on Problem-Solving Tasks

A person with Alzheimer's illness experiences trouble solving tasks and answering questions. In Alzheimer's patients, these issues are common. The MMSE (Mini mental state examination

method) is a frequently used approach for early diagnosis by healthcare professionals. However, the mini cog test is chosen over the MMSE exam because it is challenging for patients with IQs less than 20 (Yang et al., 2016; Mitchell, 2017).

10.2. Methods Based on Visual or Auditory Tasks

Aside from the cognitive tests mentioned above, various other tests based on performing auditory and visual activities are considered beneficial in detecting an early Alzheimer's disease.

For example, images are shown to the patient in the VAT (Visual Association Test), and in DLT (Dichotic Listening Test) sound is memorized to patient first and then prevalence of right ear is detected. These tests have a high level of precision (Table 2).

Table 2: A detail of methods based on visual or auditory tasks

	Technique/Method	Device	Precision / accuracy	Cost
Cognitive Screening	Visual tasks	Images	Low	Moderate
	Problem solving tasks	Simple objects, pen, and paper	High	Low
	Emotional tasks	Images, EEG	High	Low
	Listening tasks	Headphones	Low	Low
	Virtual environments	VR Device (head mounted)	High	Moderate
Non-Cognitive Screening	Neuroimaging technique	MRI, CT scan, PET	High	High
	Behavioral analysis	Sensor connected with patient body or in home)	Low	Moderate
	Visual analysis	Eye tracking device	Moderate	Moderate

3. Evaluation Techniques and Metrics for AD Diagnosis Strategies based on Artificial Intelligence

AD diagnosis is not only limited to cognitive and non-cognitive test.

Classifications based on machine learning and score, and threshold approaches are a few viable strategies for AD diagnosis. Artificial intelligence's emergence opens up possibilities for screening procedures for

Alzheimer's disease and dementia risk prediction (AI). Artificial intelligence can improve risk prediction and reliability, and it is a cost-effective method that is available to everyone. As a result, it wouldn't be an exaggeration to argue that artificial intelligence has the potential to transform the healthcare industry 10. In machine learning classification, binary and multi class is used to compare gait data from healthy individuals and Alzheimer patients. While in one class classification, AD diagnosis is performed automatically. AD diagnosis is also possible by comparing OCC and Multiclass classifiers to classify auditory data (Aztria et al., 2016).

Screening methods based on Virtual Environment

The virtual environment, which includes machine learning technologies such as eye tracking and speech recognition, allows for assessment via a game platform that incorporates behavioral activities is another non-invasive effective method for detecting Alzheimer's disease. This 15-minute test can provide information regarding impaired symptoms. Virtual environment is deemed promising for neurophysiological testing due to advancements in computer technologies. As a result, this noninvasive technology

has become an important digital biomarker in healthcare as a medical test for Alzheimer's disease detection. The table below shows a variety of virtual environment applications in Alzheimer's disease (García-Betances et al., 2015; Chong et al., 2017; Fernández Montenegro et al., 2020).

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