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REVIEW

# Pathological Mechanisms and Molecular Imaging Advances in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders globally, where early diagnosis plays a pivotal role in delaying disease progression and improving patient outcomes. In recent years, the rapid, multidisciplinary advances in molecular imaging and emerging technologies have significantly advanced our understanding of AD pathogenesis, early diagnosis, and intervention strategies. Imaging tools such as positron emission tomography (PET) and magnetic resonance imaging (MRI), alongside emerging technologies like retinal imaging, nanosensors, and quantum dots (QDs), are continuously enhancing AD diagnostic pathways. Studies on the gut microbiome and extracellular vesicles (EVs) offer novel insights into AD pathogenesis. Furthermore, AI-driven multimodal data fusion techniques hold great promise for improving diagnostic accuracy. Future research will increasingly focus on multi-target synergistic intervention strategies, standardization of multimodal imaging, and the integration of AI with molecular diagnostics and treatment to enable early detection and personalized precision therapy for AD.

**Keywords:** Alzheimer's disease, molecular imaging, gut microbiome, magnetic resonance imaging, positron emission tomography

## Introduction

According to WHO statistics, life expectancy is increasing globally, with most individuals now expected to live beyond 60 years. The number and percentage of elderly individuals are increasing in all countries, shifting the demographic center of gravity toward older populations. The aging population also brings about a rapid increase in aging-related diseases, bringing a heavy burden to society and families. And one of the more common ones is dementia. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50%-75% of cases. The prevalence of AD increased with age and increased significantly after age 80.[1] AD is a neurodegenerative disorder characterized by progressive cognitive decline. In 2018, AD International estimated that approximately 50 million people worldwide were affected by dementia, highlighting the growing importance of AD research.

Clinically, AD is categorized into three stages based on cognitive impairment: the asymptomatic stage with biomarkers (preclinical AD), the prodromal stage with mild cognitive impairment (MCI) and/or mild behavioral changes, and the dementia stage characterized by dysfunction. This progression is continuous and progressive. Currently, there is no clinical method to reverse AD fully. Moreover, patients typically do not exhibit clinical symptoms in the early stages. Once symptoms appear, it indicates the disease has reached a stage difficult to reverse.[2]

Given the progressive and irreversible nature of AD, early diagnosis plays a vital role in optimizing patient outcomes. For patients, timely diagnosis increases the likelihood of delaying disease progression through pharmacological intervention. It also enables physicians to make comprehensive assessments and formulate individualized treatment plans. For family members, early intervention can reduce long-term caregiving burdens and medical expenses. By 2050, 71% of

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people with dementia are expected to be living in low- and middle-income countries,[3] so early diagnosis will reduce the financial burden.

The diagnosis of AD involves multiple branches of medicine, and the mainstream direction is to detect and diagnose biomarkers, including imaging biomarkers and fluid biomarkers. This review begins with the pathophysiological mechanisms of AD and proceeds to discuss diagnostic techniques that are grounded in the disease's pathology and physiological changes. Molecular imaging techniques, such as positron emission tomography (PET), can detect neurodegeneration through characteristic changes in biomarkers like β-amyloid (Aβ), Tau proteins, and energy metabolism. Additionally, magnetic resonance imaging (MRI) is used to assess structural and functional brain changes in AD. Genetic testing related to the apolipoprotein E (*APOE*) locus, retinal imaging, and electroencephalography are increasingly applied in clinical practice. The integration of these advanced technologies is expected to enable earlier and more accurate identification and intervention of AD.

## Pathophysiology of AD

The pathogenesis of AD is not a linear sequence of events but rather a complex interplay of interdependent mechanisms. Multiple interrelated mechanisms contribute to a cycle that accelerates disease progression (Figure 1). Microscopic examination reveals that the hallmark pathological features of AD include neuritic plaques composed of $A\beta_{42}$ and neurofibrillary tangles (NFTs) consisting of highly phosphorylated Tau. These proteins play a critical role in disrupting neural connectivity, ultimately leading to neuronal death and brain tissue damage. Additionally, neurodegeneration, along with synaptic and neuronal loss, is observed.

### Amyloid Accumulation

The amyloid hypothesis is the most widely accepted theory of AD pathogenesis, proposing that Aβ deposition is the initiating event in the disease cascade. Aβ is produced from amyloid precursor protein (APP) through sequential cleavage by β and γ secretases.[4] Aβ plaques accumulate in various brain regions and are primarily composed of $A\beta_{40}$ and $A\beta_{42}$, two metabolic by-products of APP.[5] These plaques are recognized by the brain as foreign substances. They activate microglia and induce cytokine release, initiating inflammatory and immune responses that ultimately lead to neuronal death and neurodegeneration.[6] Aβ aggregates are assembled from Aβ monomers into a variety of unstable oligomeric species, collectively termed (oAβ). This amyloid plaque is not only neurotoxic in its own right but also alters kinase/phosphatase activity. In the early stages of disease progression, Aβ enhances the activity of several kinases, including glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK-5).[7,8] GSK-3β plays a central role in Tau phosphorylation by targeting multiple serine/threonine residues. This exacerbates Tau-induced neurotoxicity.[7] Hyperphosphorylated Tau, dissociated from microtubules, has a higher propensity to form NFTs.[9] Additionally, N-methyl-D-aspartate receptor (NMDAR) subunits which are critical regulators of synaptic function in AD, can co-immunoprecipitate with oAβ. Aβ evokes immediate cellular $Ca^{2+}$ influx through the activation of NMDARs in primary neurons.[10]

Aβ promotes Tau pathology and, in conjunction with Tau, accelerates the progression of AD.[11] Tau is considered a key factor triggering downstream effects in the pathogenesis of AD.[12] Tau and Aβ disrupt mitochondrial calcium homeostasis, leading to mitochondrial dysfunction and reduced neuronal viability.[13] In turn, mitochondrial dysfunction promotes Aβ accumulation, NFT formation, and neurodegeneration.[14] The synergistic effects of Aβ and Tau also affect microglia and astrocytes.[15] Activated microglia and reactive astrocytes initiate neuroinflammatory cascades, thereby accelerating neurodegeneration. Ultimately, this leads to blood-brain barrier (BBB) disruption and cognitive decline.[16]

### Neurofibrillary Degeneration

In 1988, scientists isolated Tau from plaques in the brains of AD patients, suggesting for the first time that Tau proteins may be responsible for AD.[17] Tau is a soluble microtubule-associated protein predominantly expressed in neurons. Under normal physiological conditions, Tau localizes to axons and binds microtubules to maintain cytoskeletal stability. Under pathological conditions, Tau becomes hyperphosphorylated due to aberrant kinase activity, resulting in its detachment from microtubules and the formation of insoluble aggregates. These aggregates further form NFTs. Both 3R and 4R Tau

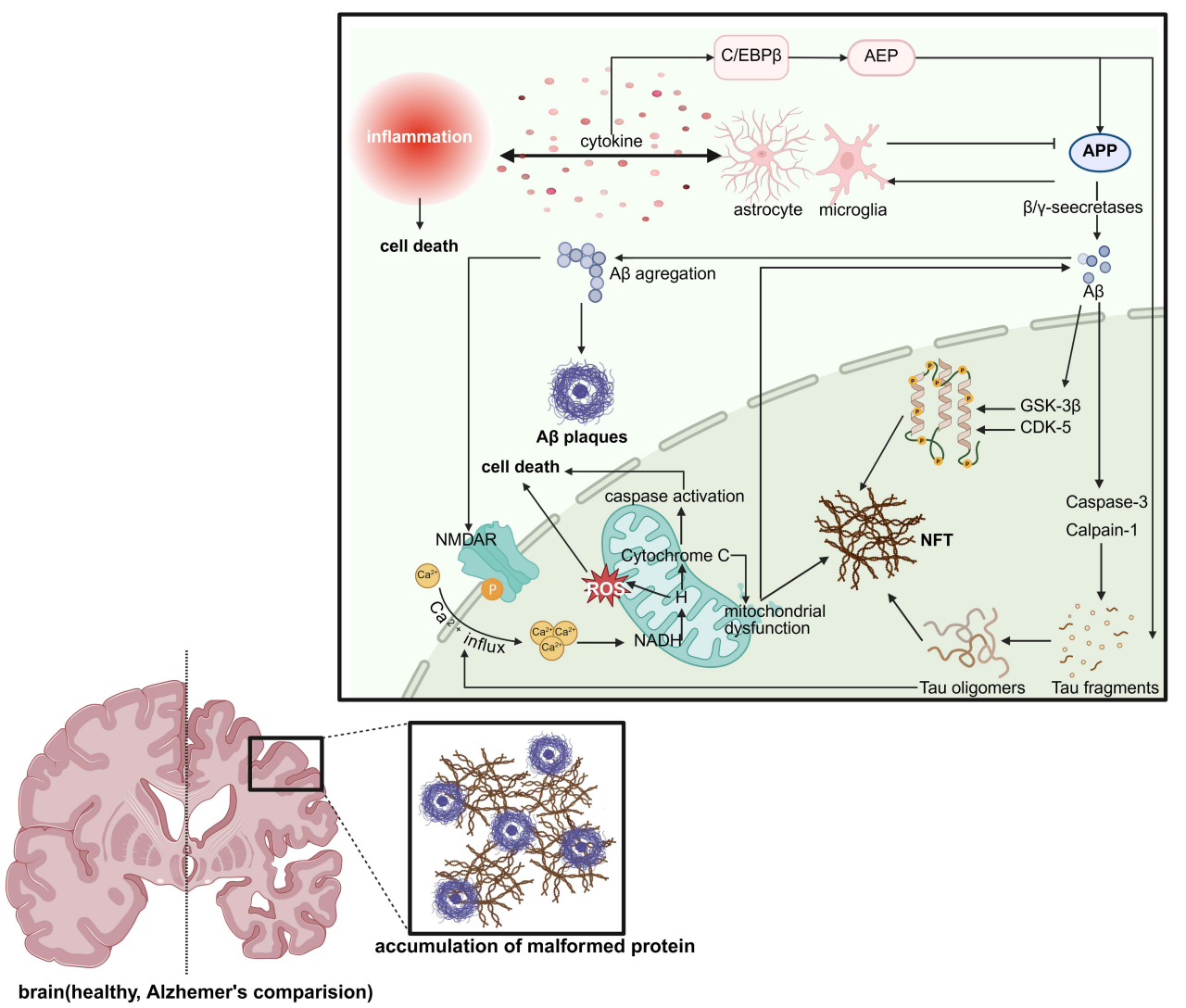


**Figure 1** Pathophysiology of Alzheimer's disease.
**Notes**: *Created in BioRender. Liu, C. (2025) https://BioRender.com/l42z565.*

isoforms are present in AD, and their dysregulated expression is closely linked to disease progression.[18] Moreover, pathological Tau can be internalized by healthy neurons through mechanisms such as endocytosis and receptor-mediated uptake, thereby perpetuating a vicious cycle of AD progression.[19] Additionally, hyperphosphorylated Tau is intrinsically neurotoxic and mediates Aβ-induced toxicity, with Aβ neurotoxicity being largely dependent on the presence of Tau.[20] Tau protein is currently a key biomarker and therapeutic target in AD diagnosis and treatment. Total tau (t-Tau) and phosphorylated tau (p-Tau) levels in colony-stimulating factor (CSF) are accurate biomarkers for tracking progression from MCI to advanced dementia.[21] Before the appearance of pathologic Aβ plaques, plasma p-Tau231 and p-Tau217 showed significant differences in capturing brain Aβ better altered.[22]

## Synaptic Dysfunction and Neurotransmitter Imbalance

The cholinergic hypothesis posits that cholinergic nerve inactivation contributes to cognitive decline in AD patients. The cholinergic system plays a fundamental role in regulating memory and attention. These cognitive functions rely on intact synaptic structures and functions. Damage to basal forebrain cholinergic neurons that innervate the cortex can result in attention deficits, contributing to the characteristic decline in learning and memory observed in AD patients.[23]

Significantly reduced levels of acetylcholine have been found in the cortical cerebrospinal fluid of AD patients,[24] and loss of synapses associated with cognition can be found in postmortem brain tissue of patients.[25] In the basal nucleus of Meynert, nicotinic acetylcholine receptors density is significantly reduced,[26] accompanied by a marked depletion of choline acetyltransferase (ChAT). The reduction in ChAT has been reported to correlate with the severity of dementia.[27] These findings indicate that cholinergic inactivation is a key contributor to memory deficits in AD.

AD is also increasingly recognized as a synaptic disorder.[28] Experimental data indicate that synapses in AD patients exhibit a reduced number, altered shapes, and changes in the expression of proteins.[29,30] And varying degrees of loss and alteration of markers on the synaptic surface are observed.[31] Disruption of synapses leads to disruption of neuronal network activity. This disruption affects both excitatory and inhibitory synapses.[32] Disruption of the excitation-inhibition (E/I) balance may induce seizures with epileptiform symptoms, which aligns with the significantly higher incidence of epilepsy in AD patients compared to the general population.[33,34]

## Neuroinflammation

Neuroinflammation is also recognized to be one of the key components in the pathogenesis of AD, and it has been proved that neuroinflammation can be an indicator of early detection of AD.[35] Activated microglia, cytokines, and pathological astrocytes have been observed in the brains of AD patients.[36,37]

Microglia are brain-resident phagocytes that contribute to central nervous system (CNS) development and play essential roles in neuronal regulation and connectivity. Due to the presence of the BBB, microglia are the main cells in the brain that accomplish peripheral immune activity. In response to harmful stimuli, microglia mediate an acute immune response. For example, if Aβ protein is deposited in the brain, microglia can reduce the accumulation of Aβ protein by increasing clearance or phagocytosis. However, activated microglia exist in both anti-inflammatory and pro-inflammatory states. Therefore, if the adverse stimulation exists for a long time and cannot be solved, the immune function of microglia will lead to increased damage. Chronic microglial activation dysregulates neuroinflammatory responses, leading to neuronal atrophy, synaptic loss, Aβ production, and neurotoxic effects.[38,39] Several immune cytokines, including tumor necrosis factor-α (TNF-α), interleukins (IL), and type I interferon, are closely linked to various AD processes.[40,41] Interferon-induced transmembrane protein 3 (IFITM3) has been shown to enhance γ-secretase activity, increasing Aβ deposition, which leads to further Aβ secretion in response to chronic inflammation.[42] At the same time, the accumulated Aβ will further activate microglia,[43] stimulate the release of pro-inflammatory factors, and interfere with the synthesis of anti-inflammatory factors to induce neuroinflammation and neurodegeneration.[44,45] Researchers also suggest that AD is primarily caused by reduced clearance of Aβ, rather than by its overproduction.[46]

## Gut Microbiome Disruption

The gut microbiome refers to the microbial community residing in the human gut, comprising bacteria, fungi, and phages. It is now hypothesized that dysbiosis of the gut microbiome may influence pathophysiologic changes in AD. This effect is not unidirectional but bidirectional. The bidirectional "microbiota-gut-brain" axis is widely recognized. The CNS connects to the gut via sympathetic and parasympathetic nerves. The gut can be connected to the brain through enteroendocrine, short-chain fatty acids, and neurotransmitters. First, dysregulation of the gut microbiome can lead to the development of an inflammatory response. These pro-inflammatory substances not only increase intestinal epithelial permeability, facilitating their translocation into the circulatory system, but also cross the BBB to activate microglia and astrocytes in the brain.[47] Among the inflammatory cytokines, C/EBPβ acts as a transcription factor for Aβ activation. It promotes the expression of asparagine endopeptidase (AEP), which cleaves APP and Tau, facilitating the formation of Aβ and NFTs.[48] Bacterial DNA, particularly from Escherichia coli and Porphyromonas gingivalis, which are significantly correlated with AD, also promoted Tau aggregation to some extent.[49] Notably, recent studies have shown that transplanting fecal microbiota from healthy wild-type mice into transgenic AD mice leads to significant improvements in Aβ plaque deposition and NFT formation.[50] Collectively, these findings suggest that disruption of the gut microbiome may contribute to the pathogenesis of AD.

## Oxidative Stress

Mitochondrial dysfunction and oxidative stress (OS) have long been implicated in the early pathogenesis of AD. A key contributor is the reduction in cytochrome c oxidase levels, which impairs mitochondrial function. This mitochondrial dysfunction is exacerbated by OS-induced hyperactivation of GSK-3, leading to disruption of mitochondrial membrane permeability and excessive production of reactive oxygen species (ROS). Metal ions, especially copper, may bind to Aβ plaque and produce ROS. The resulting ROS not only oxidize modified Aβ peptides and hinder their clearance, but also damage lipids and proteins in neuronal membranes, thereby increasing membrane permeability and vulnerability.[51] In parallel, Aβ plaques impair calcium ion storage in the endoplasmic reticulum, resulting in elevated cytosolic calcium levels. This rise in calcium depletes cellular glutathione stores and further accelerates intracellular ROS accumulation.[52] Additionally, overactivation of NMDARs enhances calcium influx, promoting the formation of both ROS and reactive nitrogen species (RNS).[53] Aβ peptides can directly activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, triggering the synthesis of free radicals and intensifying oxidative damage.[54]

# Molecular Imaging Techniques for AD Detection

Molecular imaging plays a key role in the early diagnosis and monitoring of AD by visualizing pathological biomarkers (Figure 2).

## Application of PET Imaging in AD Detection

PET imaging belongs to the category of molecular imaging and functional imaging. It is founded on advancements in basic research and the development of specific imaging agents. It has been used to study various aspects such as neuronal synaptic function, Aβ deposition, Tau proteins, as well as various neurotransmitter and receptor changes in a visual imaging manner. And patients with AD exhibit pathological changes 2–15 years before the onset of overt clinical symptoms.[55] Therefore, PET imaging is currently employed for the early clinical diagnosis of AD. PET imaging is very helpful in atypical/unspecified cases (81.1% of the cases) and in patients with MCI (88.2% of the cases).[56] Additionally, PET can assist in excluding other disease types. Studies indicate that FDG-PET demonstrates high sensitivity (96.7%) at a Clinical Dementia Rating (CDR) of 1. However, MRI and CT findings in AD are not specific.[57] PET imaging can be classified into various types based on the clinical applications of different PET imaging agents.

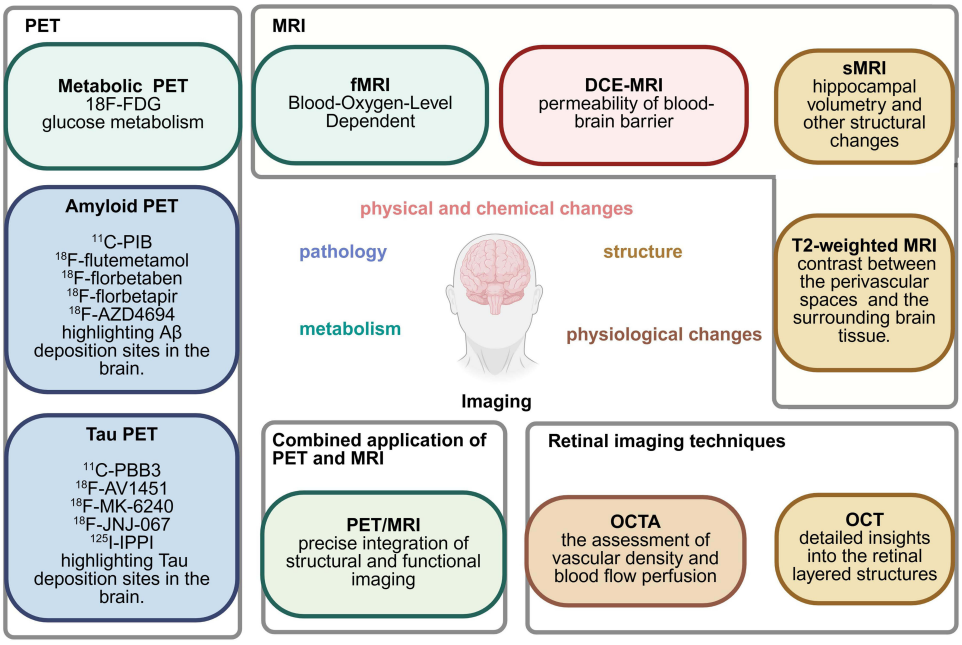


**Figure 2** Molecular imaging techniques for AD detection.
**Notes**: *Created in BioRender. Liu, C. (2025) https://BioRender.com/f41q369.*


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## Aβ Class

According to the pathophysiology of AD described above, Aβ plaques are formed and deposited in different regions of the brain. Among them, $A\beta_{42}$ shows a greater tendency to aggregate and can be detected in the brains of AD patients.[58] The Aβ PET imaging agent (amyloid imaging agent) is based on this pathogenesis in AD patients. This technique enables non-invasive in vivo detection of amyloid plaques. It demonstrates high sensitivity (69%–95%) and specificity (83%–89%) in detecting amyloid pathology in patients with neuropathologically confirmed AD.[59] Amyloid PET can also detect amyloid pathology in clinically atypical variants of AD, such as posterior cortical atrophy, frontal variant AD, or logopenic variant primary progressive aphasia.[60] Currently, $^{11}$C-Pittsburgh Compound B ($^{11}$C-PiB) and $^{18}$F-flutemetamol are commonly used in clinical diagnosis. In addition, $^{18}$F-florbetaben (NCT02681172), $^{18}$F-florbetapir, and $^{18}$F-AZD4694 are also being actively tested and gradually promoted in the clinics.[61–64]

$^{11}$C-PiB is a derivative of the Aβ stain thioflavin T, exhibiting high affinity and specificity for Aβ.[65] $^{11}$C-PiB PET can diagnose early amyloid deposition and early AD patients earlier and more specifically.[66] However, the short half-life of $^{11}$C, approximately 20 minutes. This leads to a serious obstacle to the widespread dissemination of $^{11}$C-PiB PET in routine clinics.

To overcome the limitations of short-lived radionuclides, $^{18}$F isotope was developed and subsequently approved by the US Food and Drug Administration (FDA). With a half-life of approximately 110 minutes, $^{18}$F offers a practical alternative to $^{11}$C, extending the imaging window and improving clinical usability. $^{18}$F-flutemetamol, a fluorinated analog of thioflavin T and a derivative of the widely studied $^{11}$C-PiB, demonstrates high specificity and sensitivity in detecting Aβ plaque distribution in AD patients. These findings have been confirmed through postmortem pathological verification.[67] However, both $^{11}$C-PiB and $^{18}$F-flutemetamol exhibit off-target signals in white matter during PET imaging. Notably, the white matter uptake of both tracers increases with age, but $^{18}$F-flutemetamol shows a higher degree of white matter retention compared to $^{11}$C-PiB.[68] Recent studies suggest that in younger individuals without cognitive impairment, $^{18}$F-flutemetamol may provide better imaging performance due to its stronger contrast between gray and white matter, thereby reducing the likelihood of false positives. Conversely, in cognitively unimpaired older adults, $^{11}$C-PiB may outperform $^{18}$F-flutemetamol because of its superior sensitivity in detecting subtle or near-threshold cortical Aβ deposits, particularly in higher-order cortical regions.[69]

Amyloid imaging agents share a common limitation: different amyloid-positive diseases may exhibit similar deposition patterns, making it difficult for PET imaging to differentiate among disease types.[70] Additionally, $A\beta_{40}$ is primarily confined to neuritic plaques.[71] But amyloid PET has weak binding affinity for $A\beta_{40}$. And it cannot quantify the reduction in Aβ levels over time, further diminishing its diagnostic value.[72] Notably, Aβ burden does not clearly correlate with the clinical manifestations of AD.[73] In summary, these limitations reduce the utility of amyloid imaging for monitoring disease progression.

## Tau Protein Class

In addition to Aβ, NFTs are a pathological hallmark that exists in the brains of AD patients. Tau imaging can distinguish between early and late NFT pathology by assessing the varying rates of Tau deposition at different stages. Older adults without AD may sometimes yield positive results on Amyloid PET scans, potentially leading to false-positive interpretations. The use of Tau imaging—either independently or in conjunction with amyloid imaging—can significantly improve diagnostic precision by confirming the presence of neurodegenerative lesions, thereby reducing false-positive rates.[74,75] In contrast, Tau PET imaging has demonstrated slightly higher accuracy than amyloid PET, both in detecting disease presence and in predicting the progression of AD.[76,77] In addition, data suggest that Tau-associated radioligand is specific for PHF-Tau deposition.[78] Therefore, it can be utilized to differentiate AD from other Tauopathies.[74] Owing to its diagnostic value, Tau PET imaging has become a focal point of AD research in recent years and has made significant advancements.

First-generation radioactive ligands, such as $^{11}$C-PBB3 and $^{18}$F-AV1451, have been developed, with $^{18}$F-AV1451 being the most widely used. Studies have demonstrated that $^{18}$F-AV1451 exhibits specific binding in AD-related brain regions (eg, amygdala, entorhinal cortex, parahippocampus, fusiform, etc). However, its early diagnostic capability is limited, as $^{18}$F-AV1451 does not effectively distinguish MCI from cognitively normal individuals.[79] To enhance the

selectivity for various Tau protofibril subtypes and reduce off-target binding, second-generation PET radioligands have been developed. Among the most advanced are $^{18}$F-MK-6240.[80,81] In a cross-sectional study of $^{18}$F-MK-6240, both $^{18}$F-MK-6240 and $^{18}$F-AV1451 showed statistically significant differences when comparing cognitively unimpaired amyloid negative ($A\beta^-$ CU) and $A\beta^+$ CU. The group separation was more pronounced with $^{18}$F-MK-6240. This suggests that $^{18}$F-MK-6240 may be more effective in detecting early Tau accumulation.[82] In addition to fluorine-based ligands, radioactive iodine derivatives such as $^{125}$I are increasingly being utilized in in vitro studies of NFTs. Notably, the novel radioligand $^{125}$I-IPPI has demonstrated high binding affinity to Tau, with no reported obvious off-target binding.[83,84]

In summary, Tau PET shows strong potential for diagnosing, staging, and predicting AD. However, its broader clinical application is limited by off-target binding and low sensitivity. Ongoing efforts aim to improve its clinical utility by developing second-generation Tau imaging agents. Table 1 presents PET imaging agents used for detecting AD, including those targeting Aβ and Tau proteins.

### Energy Metabolism Class ($^{18}$F-FDG)

Cerebral glucose metabolism is a key indicator of synaptic activity and neuronal density. One hallmark of AD is a reduction in glucose metabolism within the brain, which reflects the functional loss of neurons.[94] To evaluate the cerebral metabolic rate of glucose (CMRgl), the radiotracer $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is widely used in PET imaging. $^{18}$F-FDG is a radiolabeled glucose analog that substitutes for glucose in metabolic pathways, allowing clinicians to visualize and quantify regional brain metabolism. As such, $^{18}$F-FDG PET provides a reliable biomarker for assessing intracellular glucose utilization. The prevailing hypothesis suggests that metabolic disturbances in the AD brain occur prior to the onset of clinical symptoms and overt pathological changes. Therefore, $^{18}$F-FDG PET is particularly valuable for early diagnosis. Compared to structural imaging methods like MRI, $^{18}$F-FDG PET offers superior sensitivity for detecting early functional changes. PET imaging features in AD patients include hypometabolism in the frontal cortex, posterior cingulate cortex, parietal cortex, and temporal cortex regions.[95] Notably, patterns of hypometabolism vary among different AD subtypes.[96] Therefore, $^{18}$F-FDG PET can be used for the identification of AD subtypes. In distinguishing AD from non-AD dementias, $^{18}$F-FDG PET has demonstrated a sensitivity of 0.86 and a specificity of 0.88, also highlighting its diagnostic reliability.[97] $^{18}$F-FDG PET remains the primary modality for functional brain imaging in the detection and diagnosis of AD.

$^{18}$F-FDG PET also has shortcomings. It has high sensitivity, but its specificity is significantly lower.[98] In addition, there remains controversy over whether elevated blood glucose levels alter the distribution of $^{18}$F-FDG in the brains of cognitively normal individuals, potentially influencing the diagnostic interpretation of AD.[99,100] Currently, research is underway on emerging imaging agents for mitochondrial dysfunction in the parahippocampus in early-stage AD.[101]

## Application of MRI in AD Detection

MRI, characterized by its high spatial resolution, non-invasiveness, and lack of radiation exposure, can detect patterns of brain damage and abnormalities.[102] It plays a crucial role in elucidating the neuropathological mechanisms of AD and MCI, aiding in the differentiation of AD from other brain disorders, and predicting the progression from MCI to AD.[103] Currently, MRI encompasses various modalities; this paper focuses on structural MRI (sMRI), functional MRI (fMRI), vascular imaging using MRI, and the combined application of PET/MRI.

### Structural MRI (sMRI)

sMRI provides detailed images of brain anatomy, allowing precise observation of morphological and volumetric changes across various regions. This capability is crucial for identifying structural alterations associated with AD.

In AD, significant structural changes occur, notably hippocampal atrophy, which manifests in the disease's early stages. Reduction in hippocampal volume correlates closely with cognitive decline, with atrophy rates differing between AD patients and healthy individuals. Neocortical atrophy in AD follows a specific pattern, spreading from the medial temporal lobe to other regions, distinct from atrophy patterns observed in normal aging. Atrophy of the entorhinal cortex is evident in both AD and MCI patients and is closely linked to cognitive decline. Subcortical structures

**Table 1** Examples of PET Imaging Agents

| Tracer | Study Population | Main Findings | Researcher |
|---|---|---|---|
| $^{11}$C-PiB (Aβ) | 40 probable AD dementia (ProAD) patients<br>20 possible AD dementia (PosAD) patients<br>25 MCI patients | $^{11}$C-PiB PET improved diagnostic accuracy in cases with high diagnostic uncertainty after MRI and SPECT. | Omachi Y (2015)[85] |
| $^{18}$F-florbetapir (Aβ) | 10 AD patients<br>8 FTD patients<br>10 healthy controls | $^{18}$F-florbetapir effectively differentiates AD patients from frontotemporal dementia (FTD) patients and healthy controls. | Kobylecki C (2015)[86] |
| $^{18}$F-florbetaben (Aβ) | 45 MCI patients | $^{18}$F-florbetaben-positive individuals demonstrate a higher progression rate to AD over 2- and 4-year follow-ups, supporting the identification of prodromal AD in MCI patients and enabling timely intervention. | Ong KT (2015)[87] |
| $^{18}$F-flutemetamol (Aβ) | 131 MCI patients<br>41 AD patients<br>20 dementia NOS patients<br>5 SCD patients<br>10 non-AD patients | $^{18}$F-flutemetamol PET positivity rates varied among clinical groups, facilitating the differentiation of cognitive impairment subtypes and informing diagnostic decisions in patients with MCI. | Leuzy A (2019)[88] |
| $^{11}$C-PBB3 (Tau) | 7 AD patients<br>7 healthy controls | Significant differences were detected between AD patients and healthy controls in the cerebral cortex (including the hippocampal formation). | Kimura Y (2015)[89] |
| AV-1451 (Tau) | 13 AD patients<br>84 healthy controls | AV-1451 PET imaging demonstrated significant elevations in Tau protein in the entorhinal cortex, lateral occipital cortex, inferior temporal cortex, and amygdala in preclinical AD, highlighting the importance of these regions in early AD diagnosis. | Mishra S (2017)[90] |
| AV-1451 (Tau) | 364 participants<br>203 AD patients<br>161 MCI patients | An advanced AD flortaucipir pattern was associated with increased risk of clinical progression over 18 months. This indicates the value of PET in managing and assessing clinical progression in patients with cognitive impairment. | Lu M (2021)[91] |
| $^{18}$F-MK-6240 (Tau) | 6 AD patients<br>4 healthy controls | All but one AD/MCI participant exhibited increased MK-6240 retention in brain regions associated with AD-related NFT deposition, particularly in the medial temporal lobe. Late-stage AD patients also demonstrated tracer retention in neocortical regions. | Lohith TG (2019)[92] |
| [$^{18}$F]-JNJ-067 (Tau) | 17 participants<br>5 MCI patients<br>5 AD patients<br>3 PSP patients<br>4 healthy controls | Significant [$^{18}$F]-JNJ-067 binding was detected in AD participants. However, the lack of significant differences between amyloid-negative HCs and amyloid-positive MCI participants suggest this tracer has limited sensitivity in early clinical and preclinical cohorts. | Baker SL (2021)[93] |


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—including the amygdala, thalamus, basal ganglia, and basal forebrain—also exhibit varying degrees of atrophy, each correlating with cognitive decline and disease progression.[104]

sMRI effectively demonstrates brain atrophy characteristics in AD patients, plays a role in the early diagnosis of AD by detecting atrophy in specific brain regions such as the hippocampus and medial temporal lobe in people with MCI.[105] When combined with appropriate analytical methods and classification algorithms, sMRI can accurately distinguish patients with AD, MCI, and healthy controls. One study demonstrated that sMRI exhibits exceptional performance in differentiating AD from healthy controls and MCI patients, achieving precise classification. In both AD vs healthy control and AD vs MCI models, the area under the curve (AUC) reached 1.00, indicating that the sMRI model can accurately distinguish AD patients from both groups.[106]

Since sMRI can track structural brain changes over time, it is valuable for monitoring disease progression and developing individualized disease progression models. Additionally, analyzing sMRI data from AD patients at various stages helps elucidate patterns of brain structural changes during disease progression, providing insights into AD's pathological mechanisms. For instance, integrating deep learning algorithms with sMRI data can uncover neurodegenerative patterns in AD, including spatial and spatiotemporal connectivity. Studies indicate that neurodegenerative brain regions exhibit stable spatial connectivity over longitudinal studies. sMRI serves as a critical imaging tool for investigating these patterns, enhancing our understanding of AD's pathological mechanisms.[107]

However, sMRI has notable limitations: its diagnostic accuracy is limited, with low sensitivity and specificity for key regions like the hippocampus and medial temporal lobe.[105] It lacks molecular specificity, unable to directly detect AD's histological hallmarks like Aβ proteins and NFTs. Additionally, it requires specialized expertise, leading to high measurement variability.[108]

In summary, sMRI effectively captures AD-related structural brain changes, aiding early detection, differential diagnosis, progression monitoring, and pathological research. However, its limitations restrict its standalone utility. Still, when combined with other biomarkers or advanced analytical tools, it remains valuable for advancing AD understanding and clinical management.

### Functional MRI

Functional MRI (fMRI) indirectly reflects neuronal activity by detecting changes in hemodynamic dynamics when the brain is active, it can non-invasively acquire brain function information of humans in cognitive, behavioral and other states with a certain spatial and temporal resolution across the whole brain,[109] aiding in the identification of functional abnormalities in AD patients.

Cognitive tasks, such as memory encoding, elicit changes in brain activity in AD patients. For example, during the process of encoding new information, hippocampal activity is reduced in AD patients. Conversely, increased activity may be detected in other regions, such as the prefrontal cortex, which is considered an attempted compensatory mechanism employed by other neural networks when the hippocampus is impaired.[110]

During resting-state fMRI, AD patients show reduced connectivity within the default mode network (DMN), encompassing the posterior cingulate cortex, precuneus, and medial prefrontal cortex. In patients with MCI, such connectivity abnormalities are mainly manifested as reduced functional connectivity between the posterior cingulate cortex and the anterior cingulate cortex, with a lesser degree than in AD patients.[111] A study leveraged machine learning to capitalize on these resting-state fMRI patterns, training models to distinguish AD, MCI, and other groups. Among these patterns, reduced DMN connectivity in AD patients is a feature that differentiates AD from healthy controls. Machine learning algorithms effectively classified these conditions, highlighting the potential of resting-state fMRI to assist in the differential diagnosis of AD.[112]

However, fMRI has several limitations in its application. It does not directly capture neural activity but reflects it indirectly through changes in blood flow, which increases the difficulty of interpreting signals. Its temporal resolution is relatively low, and as a single imaging modality, it struggles to explicitly link specific abnormalities in functional connectivity to a particular disease, similar changes may also occur in other disorders, resulting in a deficiency in establishing disease-specific associations.[113] These factors collectively restrict its application in disease research.

Nonetheless, its ability to detect early functional changes in AD and MCI remains valuable. Combining it with other modalities may further enhance its clinical utility.

### Vascular Detection Using MRI

AD is a complex neurodegenerative disorder, with its pathogenesis closely linked to vascular factors. MRI plays a fundamental role in vascular assessment in AD, primarily by detecting perivascular spaces (PVS) and evaluating the integrity of BBB.

#### MRI Detection of PVS

PVS are fluid-filled spaces surrounding cerebral blood vessels, and their enlargement can be detected on T2-weighted MRI images. Enlarged PVS serves as a marker for cerebral small vessel disease and amyloid pathology. In cerebral amyloid angiopathy (CAA), PVS severity in the centrum semiovale (CSO) exceeds non-CAA cases, with distinct patterns in the basal ganglia observed both in vivo and postmortem.[114] Research suggests that an increased PVS burden is linked to a progressive rise in dementia risk. Higher PVS grades in the CSO are associated with an elevated risk of dementia and AD.[115] Emerging diffusion techniques like diffusion tensor imaging along the perivascular spaces (DTI-ALPS), enable assessment of fluid movement within PVS, with a lower DTI-ALPS index linked to AD dementia and reduced cognitive function.[116] Automated segmentation of PVS yields continuous measures, capturing spatial distribution and shape complexity of PVS, which offers more detailed and objective information beyond the classification provided by visual scoring.[117] These MRI-based methods for detecting PVS, from basic observation to advanced techniques, aid in understanding AD-related mechanisms and improve detection.

#### MRI Detection of the BBB

BBB dysfunction is a key pathological feature of AD, which occurs in the early stage of the disease, even before the accumulation of pathological proteins, and precedes neurodegeneration. Therefore, monitoring BBB abnormalities provides an important basis for the early detection of AD.[118] A recent study has utilized the non-invasive diffusion-prepared pseudo-continuous arterial spin labeling (DP-pCASL) MRI technique to measure the water exchange rate (Kw) across the BBB. This technique, which differentiates magnetically tagged water signals from different compartments, has shown potential in sensitively detecting BBB functionality. Results revealed decreased Kw in multiple brain regions across the AD continuum, suggest that MRI-detected Kw alterations could serve as an indicator for tracking BBB dysfunction in AD, contributing to early identification and disease monitoring.[119]

## Combined Application of PET and MRI

PET/MRI is an emerging imaging technology that combines the anatomical and quantitative advantages of MRI with the physiological information obtained from PET.[120] This hybrid approach reduces radiation exposure and enables one-stop examinations, streamlining clinical workflows. In AD research, PET/MRI captures subtle regional brain alterations, enhances early detection (including preclinical and MCI stages), and improves differential diagnosis by quantifying hippocampal/thalamic metabolic activity and predicting MCI-to-AD progression.[121] Despite its advantages, PET/MRI has limitations, including insufficient accuracy in early attenuation correction, image artifacts, inadequate sensitivity to prodromal diseases, and low equipment popularity. Looking ahead, deep learning will facilitate correction and low-dose imaging, wider anti-amyloid therapies will expand its primary care use, it is expected to become the standard imaging technique for neurodegenerative diseases by 2030.[122]

## Application of Retinal Imaging Technology in AD Detection

The retina and brain originate from the same tissue during embryonic development. As a component of the CNS, the retina exhibits structural and functional similarities to the brain, encompassing neurons, glial cells, and blood barriers. This similarity provides an anatomical and physiological basis for the association between the two, allowing the retina to serve as a window that contributes to a better understanding of processes such as healthy aging and neurodegeneration in

the CNS.[123] Therefore, retinal imaging has great potential as a non-invasive, convenient, and relatively low-cost test for early diagnosis and disease monitoring of AD.

## Pathological Features of AD in the Retina

AD manifests in the retina through structural, functional, and vascular alterations. Structurally, retinal nerve fiber layer (RNFL) thinning is prominent in advanced AD, particularly in the superior and inferior quadrants, likely reflecting the vulnerability of extramacular large ganglion cell axons.[124] MCI patients also exhibit RNFL and ganglion cell-inner plexiform layer (GC-IPL) thinning, with macular parameters showing stronger correlations with cognitive decline than peripapillary metrics.[125,126] Functionally, AD patients display visual deficits (reduced contrast sensitivity, impaired motion perception) and circadian rhythm disturbances linked to melanopsin-containing retinal ganglion cell (mRGC) loss, alongside abnormal pupillary light responses.[127] Vascularly, AD-associated retinal changes include venular narrowing, increased tortuosity, reduced fractal dimensions, and choroidal thinning, indicative of microvascular dysfunction.[128,129]

## Common Retinal Imaging Techniques

The most widely used retinal imaging techniques today include optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA).

OCT is a high-resolution imaging technique that employs low-coherence light interference to generate cross-sectional retinal scans. It offers detailed insights into the retinal layered structures, including the RNFL, ganglion cell layer (GCL), inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, and retinal pigment epithelium. In AD research, OCT is primarily employed to assess retinal thinning, particularly reductions in RNFL and GCL thickness, which may be linked to neuronal damage and neurodegeneration in AD patients.[130]

OCTA, an extension of OCT technology, is a vascular imaging modality that enables three-dimensional visualization of the retinal and choroidal microvasculature. It facilitates the assessment of vascular density and blood flow perfusion. OCTA enables the detection of retinal vascular abnormalities, including reduced vascular density and morphological alterations.[131] OCTA quantifies radial peripapillary capillary network perfusion by evaluating parameters such as capillary perfusion density (CPD) and capillary flow index (CFI), providing novel insights for AD research. Studies indicate that CPD and CFI measurements obtained via OCTA in the peripapillary region of AD patients demonstrate high repeatability, supporting the reliability of OCTA in assessing peripapillary vascular perfusion.[132]

OCT and OCTA provide valuable structural and vascular insights in AD, revealing retinal thinning and microvascular changes. Their non-invasive nature and repeatable measurements support their potential as biomarkers, though further validation is needed.

## Advantages and Limitations of Retinal Imaging in AD Diagnosis

Retinal imaging provides multiple benefits for AD diagnosis. It is non-invasive, as techniques like OCT, OCTA, and fundus photography impose a minimal physical burden on patients. These examinations are rapid, relatively simple to perform, and well-tolerated, making retinal imaging suitable for large-scale population screening and regular monitoring of high-risk AD groups. This facilitates the early detection of individuals with AD or those at risk. Additionally, retinal imaging holds the potential for early detection. Structural and functional retinal changes may precede the onset of clinical AD symptoms,[133] enhancing the potential of retinal imaging techniques for early detection. OCT can detect retinal thinning in patients with early-stage memory impairment, reflecting neurodegenerative changes in the AD brain and aiding early diagnosis.[134] However, diagnostic accuracy is confounded by age-related retinal thinning, genetic variability, and comorbidities (such as glaucoma, diabetes), which obscure AD-specific interpretations.[135,136] Technical heterogeneity across OCT/OCTA devices further limits cross-study comparability.[129] Moreover, retinal degeneration is not exclusive to AD but also occurs in other neurodegenerative and aging-related conditions, including age-related macular degeneration, diabetes, hypertension, and glaucoma. This overlap in clinical features reduces the diagnostic specificity of retinal imaging techniques for AD.[137,138] While retinal imaging offers a promising non-invasive method for AD detection, its diagnostic accuracy is constrained by overlapping pathologies, technical variability, and other

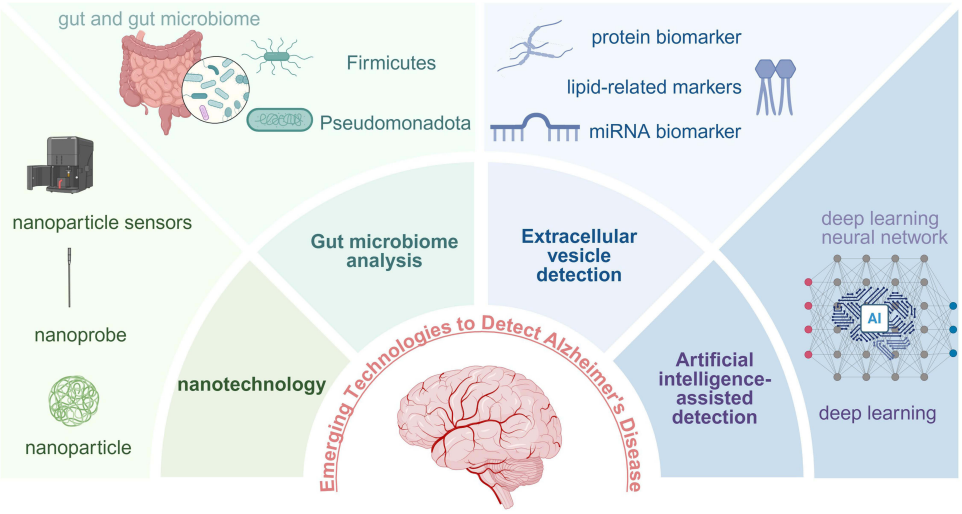


**Figure 3** Emerging technologies to detect Alzheimer's disease.
**Notes**: *Created in BioRender. Liu, C. (2025)* https://BioRender.com/q14r466.

factors. Further optimization is required to improve its clinical utility. While retinal imaging offers a promising non-invasive method for AD detection, its diagnostic accuracy is constrained by overlapping pathologies, technical variability, and other factors. Further optimization is required to improve its clinical utility.

## Emerging Detection Technologies

Advancements in biomarker-based diagnostic tools are revolutionizing the detection of AD. Emerging technologies prioritize early detection, enhanced accuracy, and greater accessibility (Figure 3).

### Nanotechnology

Traditional AD detection methods primarily utilize PET and MRI to detect Aβ deposition, pathological Tau proteins, and neurodegeneration. However, these conventional approaches have limitations. For instance, PET imaging is associated with high costs, the need for IV access for radiotracer administration, radiation exposure, and limited accessibility.[139] MRI have limited sensitivity to the earliest stages of AD.[140] In this context, nanotechnology has emerged as a promising approach for AD detection, offering potential solutions to overcome the limitations of existing methods and enhance early diagnosis.

#### Nanoparticle Sensors

Nanoparticle-based sensors utilize unique electrical and optical properties for biomarker detection. Electrochemical sensors employ nanomaterials to improve electron transfer between biomolecules and electrodes, enhancing sensitivity. For example, nanomaterials such as gold nanoparticles (AuNPs) and graphene oxide, with high surface area-to-volume ratio and excellent electrical, thermal, and catalytic properties, significantly amplify signals, provide a larger surface area for bioreceptor immobilization, accelerate electron transfer, thereby enhancing detection sensitivity to enable accurate detection of low-abundance exosomal miRNAs and support early diagnosis of neurodegenerative diseases.[141] Optical sensors exploit light-biomarker interactions for label-free, real-time detection, and combining them with nanoparticles—their main advantage is the ability to modify optical properties—can enhance sensitivity, specificity, reduce screening time, aiding early AD biomarker detection.[142]

#### Nanoprobes

Nanoprobes exhibit unique physicochemical properties such as high surface area, tunable surface chemistry, and biocompatibility, enabling highly sensitive detection of AD biomarkers. Furthermore, nanoprobe-based detection methods are non-invasive, reducing patient discomfort and lowering detection costs. Magnetic Nanoprobes play a crucial role

in AD detection. Research indicates that iron can selectively deposit in the core of Aβ plaques in the form of crystalline magnetic nanoparticles, exhibiting superparamagnetic properties that can be used for AD diagnosis.[143] For example, curcumin-conjugated superparamagnetic iron oxide nanoparticles coated with polyethylene glycol-polylactic acid can cross BBB to detect Aβ plaques. Anti-Aβ functionalized SPIONs can specifically attach to Aβ plaques, and Aβ antibody-functionalized magnetic nitrogen-doped graphene exhibits strong selectivity for Aβ, enabling electrochemical detection.[144]

### Nanoparticles

QDs have unique properties to overcome conventional dyes and imaging limitations. They enable early AD detection by tracking in vivo Aβ aggregation states, and detect biomarkers like APOE accurately.[145] Moreover, their tunable optics and versatile surface chemistry facilitate precise bioimaging, aiding in identifying pathological hallmarks. However, limitations persist: heavy metal-based QDs raise biocompatibility concerns with proinflammatory effects; BBB penetration remains a critical barrier; and clinical translation is hindered by the need for rigorous trials to validate safety and efficacy in humans.[146] Future efforts need to enhance QDs' biocompatibility, BBB penetration, and clinical translation to unlock their AD diagnostic potential.

AuNPs are extensively employed in biosensing due to their exceptional optical and electronic properties, tunable morphology and size, facile synthesis, high chemical stability, excellent conductivity, catalytic activity, and ease of functionalization.[147] Applications include electrochemical immunosensors for Aβ42 detection and plasmonic biosensors for simultaneous detection of multiple AD biomarkers.[148]

## Gut Microbiome

Based on the pathophysiologic changes in AD patients, it is known that alterations in the gut microbiome may lead to abnormalities in intestinal function or microbial content, which ultimately affects the onset and progression of AD through the "microbiota-gut-brain" axis. Gut microbiome-derived biomarkers have been considered for neurodegenerative diseases, such as multiple sclerosis, with proven differential diagnostic capabilities.[149] Therefore, it is thought that analyzing the alterations in gut microbes in AD patients may assist in determining whether a patient has AD.

### Gut Microbiome Analysis

Several studies have suggested that the composition of the gut microbiome can be an indicator of preclinical AD. Ferreiro and colleagues analyzed no significant differences in overall Bacteroidota to Firmicutes ratios between healthy and preclinical AD individuals compared to healthy and symptomatic AD individuals.[150] In contrast, Liu et al conducted a study involving 97 participants (33 AD, 32 amnestic mild cognitive impairment [aMCI], and 32 cognitively normal controls), sequencing to characterize the gut bacterial community. They found that microbial diversity was significantly reduced in AD patients, with a notably lower relative abundance of Firmicutes compared to controls. Additionally, Pseudomonadota (formerly known as Proteobacteria) was highly enriched in the AD group relative to healthy controls.[151] Similarly, Pan et al found that the relative abundance of Bacteroidota was lower in individuals with MCI compared to healthy controls, while Fusobacteria was significantly more abundant in the MCI group.[152] A related meta-analysis also identified trends in gut microbiome composition among AD patients, showing that the abundance of Bacteroides species varies across regions (higher in the US cohort, lower in the Chinese cohort).[153] Taken together, these findings indicate that gut microbiome composition is altered in individuals with AD.[154] As such, analyzing the structure of the gut microbiota may aid in the diagnosis or early detection of AD.

Beyond compositional shifts, the secretory products of gut bacteria are also altered in AD. Various metabolites, such as Arachidonic, show a progressive increase as the disease progresses.[155] Similar alterations in microbial metabolites are considered promising biomarker candidates for AD diagnosis.

### Shortcomings and Prospects of Detecting Gut Microbiome

Although gut microbiome testing meets the criteria for AD screening, being both sensitive and noninvasive. It also faces several limitations. Analyzing and interpreting the composition of the gut microbiome is time-consuming. And the

microbiome is highly dynamic and influenced by various confounding factors such as health status, lifestyle, and dietary habits, which can affect the reliability of test results. Additionally, there is currently no unified standard for evaluating gut microbiome profiles in relation to AD. Different diagnostic frameworks may yield varying assessments of disease severity based on microbiome composition. Therefore, a standardized research protocol for this screening method is still needed. Research in the field of gut microbiology has primarily focused on bacterial communities, while the roles of mycobiome and virome remain relatively underexplored. Moreover, current advancements in gut microbiome research have emphasized therapeutic applications—such as probiotics, prebiotics, and fecal microbiota transplantation—rather than the development of diagnostic tools.[154]

## Extracellular Vesicle Detection

Extracellular vesicles (EVs), including apoptotic bodies, microvesicles and exosomes, carry biomolecules like proteins and RNAs to modulate cellular activity.[156] In recent years, the potential of EVs in AD diagnosis has attracted much attention, especially as biomarkers.

### Aβ Metabolism and Tau Phosphorylation-Related Proteins

EVs derived from neurons and glial cells transport proteins implicated in Aβ metabolism, including APP, β-secretase (BACE1), and γ-secretase complex components such as presenilin-1 and presenilin-2.[157] Dysregulation of these proteins contributes to neurotoxic Aβ accumulation, and alterations in their levels within EVs may serve as potential biomarkers for AD diagnosis and disease progression monitoring. For instance, studies on CSF-derived EVs in AD patients have reported significant alterations in the levels of proteins such as Heat shock protein A1A (HSPA1A), and Prostaglandin F2 receptor negative regulator (PTGFRN) throughout disease progression.[158] EVs also contain proteins involved in Tau phosphorylation, including Tau kinases such as GSK-3β and CDK-5, and phosphatases such as protein phosphatase 2A. Aberrant Tau phosphorylation is a hallmark of AD and serves as a predictive marker for cognitive decline and a metric for assessing treatment efficacy.[159]

### miRNA Biomarkers and Lipid-Related Biomarkers

EVs protect miRNAs from degradation, enhancing their stability and clinical relevance.[160] A study reported that the number of AD dementia-related miRNAs in EVs was nearly twice that in serum. Moreover, EV-derived miRNAs exhibited a stronger correlation with medial temporal lobe atrophy, a neuroimaging biomarker of AD pathology, underscoring their diagnostic superiority.[161] Lipidomic analysis of brain-derived EVs (BDEVs) reveals AD-associated dysregulation, including altered glycerophospholipids, sphingolipids, and reduced docosahexaenoic acid. Compared to bulk lipid analysis of the frontal cortex, BDEVs offer superior sensitivity in detecting lipid dysregulation associated with AD, suggesting their utility for early AD diagnosis through peripheral blood studies.[162]

### Other Protein Biomarkers

EVs contain neuroinflammatory proteins (IL-1β, TNF-α, CCL2, CXCL10), synaptic dysfunction-associated proteins (synaptic vesicle proteins, neurotransmitter receptors, synaptic scaffold proteins), and neuronal injury markers (neuron-specific enolase, neurofilament light chain, and ubiquitin carboxy-terminal hydrolase L1). Increased levels of these EV-associated biomarkers correlate with disease severity and cognitive decline in AD patients, highlighting their potential utility in monitoring disease progression and therapeutic response.[163]

### Advantages and Challenges of Extracellular Vesicle Detection in AD Diagnosis

Extracellular vesicle detection offers significant advantages in AD diagnosis: their lipid bilayer ensures cargo stability against enzymatic degradation, improving reliability. EVs carry molecules reflecting AD-specific neuropathology, providing mechanistic insights. Early biomarker changes in EVs enable potential early-stage detection for timely intervention. However, standardization issues in isolation methods and variability in biomarker specificity hinder clinical translation, necessitating further research.[164]

## Artificial Intelligence-Assisted Detection

Artificial intelligence (AI) has greatly enhanced the efficiency and accuracy of detecting AD. AI technologies, such as machine learning and deep learning, enable the analysis of neuroimaging data from CT, MRI, and PET to detect early pathological features of AD, offering robust support for early diagnosis and treatment.[165]

### AI Technologies for AD Detection

Machine learning and deep learning play pivotal roles in AD detection and diagnosis. Researchers employ deep learning models for diagnosis, prognosis prediction, and forecasting patient health outcomes following pharmacological interventions. For instance, deep learning can automatically extract features from neuroimaging data, assisting radiologists in accurate diagnosis. Various models such as convolutional neural network, recurrent neural network, and transfer learning are applied to process multimodal data like PET and MRI, enabling AD detection, segmentation, and severity grading. Compared with traditional methods, it reduces the subjectivity and time consumption of manual feature extraction, improving diagnostic efficiency and accuracy, providing new directions and technical support for AD diagnosis.[166]

Deep learning techniques offer notable advantages in processing complex three-dimensional data and are extensively utilized in AD research. For example, integrating 3D convolutional neural network with PET imaging achieves 96% accuracy in AD versus normal control classification and 84.2% accuracy in MCI converter versus non-converter classification.[167] Other deep learning architectures, including artificial neural networks and recurrent neural networks, have also been employed to predict AD progression.

### Advantages and Challenges of AI in AD Detection

AI overcomes limitations of manual detection by autonomously extracting features from neuroimaging data, improving early diagnosis. Moreover, AI models, particularly deep learning-based algorithms, efficiently process large-scale neuroimaging data to detect complex pathological patterns.[168] It enhances accuracy by detecting complex patterns and quantifying biomarkers like amyloid plaques. AI also enables precise image segmentation, aiding quantitative analysis of disease-related changes thereby providing objective and accurate data for AD diagnosis, monitoring, and treatment evaluation.[169,170]

Despite its potential, AI encounters challenges in AD detection. These include disease heterogeneity, subtle early symptoms overlapping with other conditions, scarce longitudinal data, ethical issues like informed consent, data privacy concerns, difficulties in clinical integration, and limited diverse training datasets, necessitating further clinical validation studies.[171]

# Conclusion and Future Perspectives

In recent years, advances in biomedical research have deepened our understanding of AD across multiple critical domains, including pathophysiological mechanisms, imaging modalities, and emerging diagnostic technologies. Pathologically, AD is driven by a complex interplay of mechanisms, including Aβ aggregation, hyperphosphorylated Tau-mediated NFT formation, synaptic dysfunction, neuroinflammation, gut-brain axis dysregulation, and OS, each contributing to a self-perpetuating cycle of neurodegeneration. In terms of imaging, molecular and structural techniques remain foundational for early diagnosis. PET enables visualization of core biomarkers like Aβ and Tau, while MRI captures structural and functional brain changes. Complementing these, retinal imaging offers non-invasive insights into neurodegeneration via retinal structural and vascular alterations, emerging as a promising screening tool. Emerging technologies further expand diagnostic capabilities: nanotechnology enhances biomarker detection sensitivity; gut microbiome analysis reveals bidirectional microbiota-brain interactions; EVs carry AD-specific molecules for early detection; and AI integrates multimodal data to boost diagnostic accuracy.

Early diagnosis, enabled by these advancements, is clinically pivotal. Detecting AD in its preclinical or prodromal stages is paramount for implementing timely interventions, potentially delaying cognitive decline, improving patient outcomes, and enhancing patients' quality of life. Multimodal strategies, combining biomarkers, diverse imaging techniques, and novel technologies, are key to overcoming single-modality limitations and enhancing diagnostic precision. Such multimodal strategies lay the foundation for timely interventions and hold crucial clinical significance for improving AD prognosis.

Looking forward, AD research will focus on standardizing multimodal imaging protocols, developing multi-target therapeutic interventions, and deepening AI integration with molecular diagnostics. Interdisciplinary collaboration across clinical medicine, neuroscience, AI, and bioengineering will be critical to translating these innovations into personalized precision therapies. Such progress holds the potential to transform AD into a condition amenable to early, targeted intervention—offering transformative hope to millions worldwide.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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