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Review

Neuroimaging modalities in the detection of Alzheimer's disease-associated biomarkers

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia. Neuropathological changes in AD patients occur up to 10–20 years before the emergence of clinical symptoms. Specific diagnosis and appropriate intervention strategies are crucial during the phase of mild cognitive impairment (MCI) and AD. The detection of biomarkers has emerged as a promising tool for tracking the efficacy of potential therapies, making an early disease diagnosis, and prejudging treatment prognosis. Specifically, multiple neuroimaging modalities, including magnetic resonance imaging (MRI), positron emission tomography, optical imaging, and single photon emission-computed tomography, have provided a few potential biomarkers for clinical application. The MRI modalities described in this review include structural MRI, functional MRI, diffusion tensor imaging, magnetic resonance spectroscopy, and arterial spin labelling. These techniques allow the detection of presymptomatic diagnostic biomarkers in the brains of cognitively normal elderly people and might also be used to monitor AD disease progression after the onset of clinical symptoms. This review highlights potential biomarkers, merits, and demerits of different neuroimaging modalities and their clinical value in MCI and AD patients. Further studies are necessary to explore more biomarkers and overcome the limitations of multiple neuroimaging modalities for inclusion in diagnostic criteria for AD.

Keywords: Alzheimer's disease; biomarker; neuroimaging modality; diagnosis

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, has no known pharmaceutical cure and is a common progressive brain disease. AD is defined as a cognitive disorder and characterized by systematic dementia symptoms, such as memory, learning, language, executive function, visuospatial function, and behavioural changes or impairment (Korczyn, 2011). The World Health Organization estimates that over 30 million people worldwide suffer from AD, and the rate of AD incidence is accelerating with the increasing ageing of the world's population at present (Giridharan *et al.*, 2022). In addition, the global AD epidemic is estimated to affect more than 100 million individuals by 2050 (van Oostveen and de Lange, 2021). AD will become a major challenge to public health and ultimately have an increased social burden (Liu *et al.*, 2022).

Neuropathological changes occur up to 10–20 years before the emergence of clinical symptoms of AD (Blennow *et al.*, 2006). The prodromal phase of AD is defined as mild cognitive impairment (MCI), which is characterized by declines in performance in one or more cognitive domains with the preservation of functional independence (Petersen, 2004). The initial pathological change in AD and MCI patients is neurotoxic amyloid-β (Aβ) deposition. In the brain, abnormal processing of Aβ by β-secretase and subsequently γ-secretase contributes to the formation of senile plaques, which in turn results in the destruction of neurons. This pathological process is exacerbated by the activity of reactive oxygen species. Eventually, Aβ-induced neurotoxicity leads to impaired learning, a progressive degradation of mental state, and behavioural abnormalities (Alam and Sharma, 2019; Ausó *et al.*, 2020). Likewise, hyperphosphorylation results in neurofibrillary tangles (NFTs) containing abnormal hyperphosphorylated tau aggregates, leading to neuronal loss, neurotoxicity, brain atrophy, and cognitive decline (Ausó *et al.*, 2020). Patients with AD currently go to the hospital for evaluation late in the course of the disease and miss the stage of early intervention/delay of disease development. Moreover, there are currently no effective clinical drugs for the treatment of AD, and early diagnosis and intervention can help to delay the development of AD and prolong the healthy years of patients. Neuroimaging modalities can detect various aspects of brain changes. Therefore, it is necessary to search for neuroimaging biomarkers to achieve the goal of early detection and intervention of diseases (Blennow *et al.*, 2015). Specific and sensitive testing strategies are crucial for the detection and accurate diagnosis of AD in the preclinical or early phase (Henry *et al.*, 2013).

Nowadays, biomarkers could objectively reflect the specific structural and molecular level changes in the body and have become a hot topic in clinical trials and scientific research in AD. In 2018, the NIA-AA proposed the AT(N) classification system, which categorized different biomarkers (imaging and biofluids). Biomarkers are grouped into the categories of β amyloid deposition (A), pathologic tau (T), and neurodegeneration (N) [AT(N)] for the definition of AD, but biomarkers for MCI are not mentioned (Table 1). The NIA-AA recommends the consideration of biomarkers about amyloid positron emission tomography (PET) positivity,

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Table 1: AT(N): biomarker grouping.

A stands for aggregated Aβ or associated pathologic state biomarkers	T stands for aggregated tau or associated pathologic state biomarkers	N stands for neurodegeneration or neuronal injury biomarkers
amyloid PET positivity	tau-PET positivity	brain atrophy shown by structural MRI
CSF Aβ42 or Aβ42/Aβ40 ratio decrease	CSF phosphorylated tau increase	reduced metabolism on FDG-PET
		increased total tau in the CSF

A β: β amyloid; CSF: cerebrospinal fluid

Tau-PET positivity, reduced metabolism on fluoro-deoxyglucose (FDG)-PET, brain abnormalities on quantitative structural magnetic resonance imaging (MRI) for AD diagnosis (Jack *et al.*, 2018). It is emphasized that the AT(N) system is flexible in that new biomarkers can be added to the three existing AT(N) groups, and new biomarker groups beyond AT(N) can be added when they become available. The NIA-AA indicated that the AT(N) classification system is a research framework that still needs to be thoroughly examined and modified before being adopted in general clinical practice.

Although the NIA-AA recommends the consideration of some biomarkers for the definition of AD, there are some limitations in AD diagnosis. PET has the limitation of high cost. Furthermore, it cannot be ignored that high-dose PET radiation is harmful for people's health. Cerebrospinal fluid assays are invasive, carry the risk of infection and side effects, and are not routine examinations in the clinic (Sperling *et al.*, 2011). Therefore, there is still a need to develop novel imaging techniques for detecting relevant biomarkers in the future. The detection of biomarkers should be non-invasive, low-cost, and routine in the clinic. More sensitive measures are necessary to detect early dysfunction and structural and functional disconnection (Kim *et al.*, 2022a). Other techniques, including functional MRI (fMRI), diffusion tensor imaging (DTI), arterial spin labelling (ASL), and magnetic resonance spectroscopy (MRS), single photon emission-computed tomography (SPECT), and near-infrared fluorescence (NIRF) probes represent the potential possibility of identifying AD and discriminating AD from other dementia diseases, such as vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Thus, a comprehensive analysis of the available neuroimaging modalities is necessary for identifying MCI and AD and differentiating AD from other diseases. In this review, a systematic literature search for articles was conducted in the PubMed, EMBASE. We searched articles published in English from January 2000 through the end of April 2023. We used the following search terms as text for the search in the electronic databases: 'Alzheimer', 'mild cognitive impairment', 'MCI', 'AD', 'biomarker', 'MRI', 'magnetic resonance imaging', 'PET', 'positron emission tomography,' 'SPECT', 'single photon emission-computed tomography', 'NIRF probes', 'near-infrared fluorescence probes', 'structural MRI', 'sMRI', 'fMRI', 'MRS', 'ASL', 'DTI', 'functional MRI', 'functional magnetic resonance imaging', 'magnetic resonance spectroscopy', 'arterial spin labelling', 'diffusion tensor imaging', and 'neuroimaging'.

Herein, we review multiple neuroimaging modalities (structural MRI, fMRI, MRS, ASL, DTI, PET, SPECT, and NIRF probes) combined with potential biomarkers in MCI and AD, present their merits and demerits, discuss their clinical value, and show limitations in current clinical trials. The influencing factors cannot be ignored in the design of clinical trials, such as age, sex, and years of education. Some limitations should also be considered in the design of clinical trials in the future, such as lack of large-scale and longitudinal studies. Whereas only traditional structural modalities are currently recommended for the diagnosis of AD in clinical practice, further research is necessary to overcome the limitations of these modalities to meet their future inclusion in diagnostic criteria for AD.

MRI

Due to its relatively economical and convenient properties, MRI plays a vital role in the clinical diagnosis of AD as a noninvasive clinical test (Chandra *et al.*, 2019). MRI techniques, such as structural MRI, fMRI, MRS, DTI, and ASL, remain effective in the detection of AD (Li *et al.*, 2022a; McKhann *et al.*, 2011; Rankin *et al.*, 2006). Each MRI technique has its pros and cons in the detection of AD. Doctors and researchers should be familiar with the characteristics of different MR techniques when considering their clinical applications. Next, we discuss various biomarkers in multiple MRI modalities (structural MRI, fMRI, MRS, ASL, and DTI), and the different brain/connection regions affected across modalities for MCI and AD (Table 2).

Structural MRI

Structural MRI is used to reveal brain atrophy and other static tissue abnormalities. The progression of brain atrophy follows Braak stages (Braak and Braak, 1991). NIA-AA diagnostic recommendations refer to atrophy of critical brain regions (i.e. the parahippocampal gyrus, hippocampus, posterior association cortex, amygdala, and subcortical nuclei) using quantitative structural MRI in AD (Sperling *et al.*, 2011).

Some studies have reported that atrophy was found in both the cerebral cortex and subcortical regions in MCI patients using quantitative structural MRI. In cerebral cortex atrophy, a meta-analysis reported significant grey matter (GM) loss in the entorhinal cortex in the MCI group in comparison to the cognitively normal (CN) group (Lombardi *et al.*, 2020). Entorhinal cortex atrophy is considered a good biomarker and might be used to differentiate MCI individuals from CN participants (Zhou *et al.*, 2016). Moreover, entorhinal cortex atrophy, the location of the earliest lesions in AD, prediction of the conversion from MCI to AD in patients (Leandrou *et al.*, 2018). In subcortical atrophy, GM volumetric loss occurs in the hippocampus in MCI patients in comparison to a CN group (Vasavada *et al.*, 2015). Hippocampal atrophy in MCI patients is associated with declarative memory deficits (Schröder and Pantel, 2016). Hippocampal atrophy can be detected in CN elderly individuals up to 3 years before MCI diagnosis and may be a promising biomarker for presymptomatic disease. In addition, hippocampal atrophy can predict whether MCI patients would progress to AD during a 3-year follow-up (Miao *et al.*, 2022).

A large number of studies have reported atrophy in the cerebral cortex, subcortical regions, and cerebellum in AD. In cerebral cortex atrophy, a meta-analysis reported significant GM loss in the entorhinal cortex in AD (Li *et al.*, 2022b). The entorhinal cortex is the brain region that exhibits the earliest histological alterations in AD, including the formation of NFTs and cell death (Igarashi, 2023). GM loss in the frontal, parietal, and temporal lobes is found in AD patients in comparison to CN individuals (Duarte *et al.*, 2006). Considerable attention has been focused on understanding

Table 2: The: different brain/connection regions affected across modalities.

MRI modalities	MCI	AD
Structural MRI	Entorhinal cortex Hippocampus	Entorhinal cortex Frontal, parietal, and temporal lobes Hippocampus Amygdala Olfactory bulb Cerebellum
Task-based fMRI	Medial temporal lobe, posterior cingulate gyrus/precuneus during memory task Functional connectivity in the hippocampus, parahippocampus, and fusiform areas during the encoding task of novel picture-word pairs	Medial temporal lobe, posterior cingulate gyrus/praecuneus during memory task Cerebellum, premotor, and supplementary motor regions during motor task Parieto-occipital, parietal, left inferior temporal gyrus, and premotor cortical areas during visuospatial tasks Functional connectivity in the right supramarginal gyrus during the auditory task
Resting-state fMRI	DMN VN Fontoparietal control network Dorsal attention network	DMN VN Fontoparietal control network Ventral attention networks Dorsal attention network
MRS	Cingulate region Hippocampus	Cingulate region Hippocampus
ASL	Bilateral and medial temporoparietal regions, posterior cingulate cortex, and inferior prefrontal cortex	The parietal, temporal, and occipital cortex areas, hippocampus, posterior cingulate, basal ganglia, thalamus
DTI	The corpus callosum, temporal brain region, corona radiata, and superior longitudinal fasciculus	The frontal lobe, corpus callosum, fornix, cingulate gyrus, cingulate bundle, uncinate fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fascicles, inferior longitudinal fasciculus, and medial temporal lobe

brain cortical changes associated with cognitive and behavioural problems during AD progression (Hu *et al.*, 2023).

In subcortical atrophy, volumetric loss occurs in the hippocampus, amygdala, and olfactory bulb in AD patients using quantitative structural MRI (Cavedo *et al.*, 2011; Li *et al.*, 2011; Yu *et al.*, 2015). Brain atrophy is observed in the hippocampus in the early course of AD (Li *et al.*, 2011; Platero *et al.*, 2019). The presence of diffuse hippocampal atrophy is associated with deficits in memory and executive functioning in AD patients (Oosterman *et al.*, 2012). It also differentiates AD from Parkinson's disease with dementia (PDD) and DLB (Delli Pizzi *et al.*, 2016; Tam *et al.*, 2005). In addition, a meta-analysis reported a significant volumetric reduction in the amygdala in the AD group in comparison to the CN group (Zacková *et al.*, 2021). Atrophy of the amygdala is associated with neuropsychiatric symptomatology and cognitive dysfunction in AD (Poulin *et al.*, 2011). Furthermore, a volumetric reduction in the olfactory bulb is present in AD patients (Chen *et al.*, 2018; Petekkaya *et al.*, 2020; Yu *et al.*, 2015). Of note, olfactory bulb is damaged in very early (i.e. Braak's stage 0 or 1) stages (Kovács *et al.*, 2001).

Studies of cerebellar atrophy have also been reported in AD patients. The cerebellum is affected in the late clinical stage of AD (Tabatabaei-Jafari *et al.*, 2017). Cerebellar atrophy may be secondary to the progression of AD pathology in the cerebrum rather than the cerebellum itself (Colloby *et al.*, 2014).

In summary, quantitative structural MRI is a popular neuroimaging technique with good soft tissue contrast and high spatial resolution, which are important features for AD detection. Structural MRI also provides excellent anatomical detail of magnetic resonance images, which can provide reliable classification results with high diagnostic accuracy that correlate with the underlying pathology (Frisoni *et al.*, 2010). Structural MRI studies have generally shown robust volumetric declines in both the hippocampus and entorhinal cortex in MCI and AD patients and atrophy of other brain regions in AD patients. According to Braak stage theory, the earliest neurodegeneration always occurs in the entorhinal cortex and spreads from there to the hippocampus. NFTs start to aggregate in the hippocampus. The disease spreads from the hippocampus to the entire temporal lobe, eventually reaching the cortex and other regions of the brain (Braak and Braak, 1991). Moreover, quantitative structural MRI combined with biomarkers is a promising method for the discrimination of MCI and AD from the CN group and in the prediction of MCI conversion to AD in clinical trials. In particular, structural MRI is important in identifying gross structural lesions, differentiating AD from PDD and DLB with hippocampal atrophy. Thus, structural MRI studies should focus on differentiating AD from other forms of dementia, such as VaD and FTD, in the future. In fact, structural MRI cannot assess functional changes in the brain, so the combination with other measurements might enhance the accuracy of AD detection. Despite the widespread use of quantification software in research, the adoption of many quantification software packages in clinical practice is rare. This is probably due to limited availability and the time needed for use of those packages as well as the questionable external validity of research results (Brisson *et al.*, 2020). Future efforts aimed at more fully translating research results into clinical practice will improve the diagnostic ability of quantitative structural MRI, allowing for more reliable identification of patients in early stages of AD.

fMRI

fMRI detects changes in the haemodynamics of brain vessels to indirectly measure neural activation. The haemodynamic response is thought to reflect brain region activation based on the number of oxyhaemoglobins and deoxyhaemoglobins present (Gore, 2003). fMRI is used to image the activation of brain areas, and altered brain activation has been found in some regions in patients with AD. fMRI includes task-based fMRI (t-fMRI) and resting-state fMRI (rs-fMRI).

t-fMRI is an advanced technique for evaluating brain mapping given a specific assigned task (motor, visual, neuropsychological, etc.) and functional activity alterations (Forouzannezhad *et al.*, 2019). These task-based studies in MCI and AD patients investigate functional alterations during a particular activity, such as tasks of memory (Yetkin *et al.*, 2006), vision (Rombouts *et al.*, 2000), and motor performance.

The most prevalent and well-known symptoms of AD and amnestic MCI are cognitive deficits, specifically memory problems. Moreover, an amnesic syndrome is typically the earliest symptom of AD (Dickerson and Sperling, 2008). The medial temporal lobe (MTL) memory system is a site of very early pathology in AD, and significant pathology is present in the MTL memory system at the MCI stage (Dickerson and Sperling, 2008). Both hyperactivation and hypoactivation of the MTL during memory tasks have been reported in MCI patients (Hampstead *et al.*, 2011; Jin *et al.*, 2012; Lenzi *et al.*, 2011). The discrepancy of MCI patients in MTL may be caused by different activation patterns in MTL structures and hippocampal subregions in comparison to CN individuals (Yassa *et al.*, 2010). This difference may also be due to the mixed sample of MCI and AD patients included in the studies (Celone *et al.*, 2006). These findings indicate that future studies may focus on sample inclusion, avoiding mixed samples of MCI and AD patients. Furthermore, some studies have shown reduced posterior cingulate gyrus/precuneus activation and hyperactivation in frontal regions, including the precentral gyrus, in MCI patients in comparison to CN individuals during memory tasks (Hampstead *et al.*, 2011; Jin *et al.*, 2012; Terry *et al.*, 2015). In AD, MTL hypoactivation, reduced posterior cingulate gyrus/praecuneus deactivation and frontal hyperactivation are approximately consistent findings during memory tasks (Canário *et al.*, 2022; Jonin *et al.*, 2022; Parra *et al.*, 2013; Petrella *et al.*, 2007; Pihlajamäki and Sperling, 2009; Yetkin *et al.*, 2006).

In addition, there is increasing evidence for motor dysfunction early in AD, even preceding cognitive deterioration (Agosta *et al.*, 2010; Albers *et al.*, 2015; Della Sala *et al.*, 2004; Kueper *et al.*, 2017; Parra *et al.*, 2013). Despite the prevalence of motor symptoms in MCI and AD patients, their underlying neural mechanisms are not very explicit (Koppelmans *et al.*, 2022). The motor performance of MCI patients has mainly been explored by other techniques, such as functional near-infrared spectroscopy (Holtzer and Izzetoglu, 2020; Liu *et al.*, 2021c). Decreases in activation are displayed in the cerebellum, premotor, and supplementary motor regions for patients with early-stage AD during a motor task by t-fMRI (Koppelmans *et al.*, 2022; Vidoni *et al.*, 2012). As such, future studies could further focus on motor dysfunction in MCI using t-fMRI and explore potential biomarkers for being early predictors of MCI and AD that augment the diagnostic process.

Moreover, there have been a few neuroimaging studies that have explored the neural basis of visuospatial deficits in AD. Based on studies thus far, no significant hyperactivation or hypoactivation has been found in visuospatial processing tasks in MCI patients by using t-fMRI (Faraco *et al.*, 2013; Jacobs *et al.*, 2015; Papma *et al.*, 2012). Reduced activation detected by t-fMRI occurs mainly in the parieto-occipital, parietal, left inferior temporal gyrus, and premotor cortical areas in AD patients when compared to the CN group during visuospatial tasks (Bokde *et al.*, 2010; Thiyagesh *et al.*, 2009). These specific functional deficits in AD provide important evidence for an underlying pathophysiological basis for the symptom of visuospatial disorientation.

In addition to activation, t-fMRI can be used to explore the functional connectivity between different brain regions to represent/reflect the level of functional communication between brain regions in MCI and AD (van den Heuvel and Hulshoff Pol, 2010). Enhanced functional connectivity is found in the hippocampus, parahippocampus, and fusiform areas in MCI patients during the encoding task of novel picture-word pairs (Hämäläinen *et al.*, 2007). In addition, auditory stimulation was applied to control and patients with AD to investigate functional neuroanatomy alterations in an auditory scenario. Increased functional connectivity in the right supramarginal gyrus is also found in AD patients in comparison to CN individuals using the auditory task by t-fMRI (Golden *et al.*, 2015).

Functional connectivity is studied not only by t-fMRI but also by rs-fMRI in MCI and AD patients. rs-fMRI examines spontaneous and synchronous blood oxygenation level-dependent low-frequency fluctuations in the absence of the participant performing an explicit task during scanning. In addition, rs-fMRI provides insight into functional connectivity among structures in intrinsic networks implicated in the MCI and AD spectrum (Lv *et al.*, 2018). Disrupted functional connectivity is mainly observed in the default mode network (DMN) and visual network (VN), which are involved in cognitive executive processes and visual memory (Forouzannezhad *et al.*, 2019). A group of 'attentional networks' are also disrupted in MCI and AD patients by using rs-fMRI, including the frontoparietal (FPN), the dorsal attention (DAN), and the ventral attention (VAN) networks. The early clinical manifestation of AD is usually memory impairment. However, attention, as the initial stage of cognition, is often not easily perceived.

The DMN is the main network under investigation in rs-fMRI in MCI and AD. Decreased functional connectivity in the DMN has been reported in many studies. This pattern of DMN dysfunction has been displayed in the MCI group with limited increases compared with the CN group between DMN structures, indicative of a prodromal compensatory mechanism (DeMayo *et al.*, 2023a; Niu *et al.*, 2018; Zhang *et al.*, 2020; Zheng *et al.*, 2017). Brain structures implicated in the DMN mostly include the posterior cingulate cortex (PCC), precuneus cortex, medial prefrontal and lateral temporal cortices and hippocampus (Forouzannezhad *et al.*, 2019). Reduced functional connectivity in AD is shown between MTL structures, such as the hippocampus and entorhinal cortex, and the PCC by rs-fMRI (Greicius *et al.*, 2004; Mohammadian *et al.*, 2023; Yu *et al.*, 2017; Zheng *et al.*, 2017). This evidence indicates the significance of the MTL in the DMN as an indicator of AD. Levels of PCC connectivity in the DMN to other DMN structures are associated with neuropsychological impairment (Celebi *et al.*, 2016). Furthermore, there was an increase in anterior DMN regions (frontal lobe) and a decrease in posterior DMN regions (precuneus cortex) in early AD. Two to four years later, all brain regions showed marked declines in connectivity. This evidence might support the notion that early mechanistic compensation occurs within the DMN, but eventually global neurodegeneration occurs (Damoiseaux *et al.*, 2012).

In addition to the DMN, the VN of the brain is affected by AD progression. Decreasing functional connectivity is shown between the left and right gyri and inferior temporal gyrus, which are in-

volved in visual cognition in MCI. Functional connectivity reduction in these areas might lead to visual processing deficits, such as failure to recognize faces (Cai *et al.*, 2015). The results may explain why AD or MCI patients are unable to recognize familiar faces. Furthermore, the inhibited activity of the right inferior temporal cortex in patients with AD represents the breakdown of the VN caused by the long-term visual memory decline of AD patients (Jin *et al.*, 2020; Zhong *et al.*, 2014).

Moreover, this pattern of DAN dysfunction has been displayed in the MCI group compared with the CN group between DMN structures. Recent studies have indicated that functional alterations in the DAN could be used as a sensitive marker to forecast the progression from MCI to AD (Pini *et al.*, 2022; Wu *et al.*, 2022; Wu *et al.*, 2023). AD-related decrease of DAN functional connectivity was mainly reported when mean mini-mental state exam score was lower than 14 (Brier *et al.*, 2012; Zhao *et al.*, 2022). The DAN appears to be involved in the endogenous goal-driven attention orienting (top-down) process, which is responsible for the preparation and selection for stimuli and responses (Qi *et al.*, 2020). Interventional approaches of transcranial magnetic stimulation and exercise are reported about modulating functional connectivity in DAN (Kazemi *et al.*, 2020). Furthermore, early intervention treatments in DAN may be potential directions for MCI and AD patients.

FPN was also significantly reduced in MCI and AD in comparison to CN individuals using rs-fMRI (Cruzat *et al.*, 2023; Li *et al.*, 2015; Pini *et al.*, 2022). The FPN is involved in top-down attentional control and allocation of available neural resources to critical cognitive processes and motor planning and motor execution. Reduced connectivity in FPN may lead to the dysfunction of logic, regulating behaviour, learning, and complex planning abilities (Zhao *et al.*, 2019).

Recent studies have reported that effects on the VAN are inconsistent in AD patients by using rs-fMRI. Decreased VAN functional connectivity was observed in AD patients compared with the CN individuals (Qian *et al.*, 2015). The limited effects on VAN connectivity were also reported in the present investigation of AD, which might suggest that the VAN was stable and less susceptible to the impact of the AD (Kurth *et al.*, 2019; Li *et al.*, 2012; Zhang *et al.*, 2015). The VAN is involved in an exogenous stimuli-driven attention reorienting (bottom-up) process which is activated when detecting the salient targets (Yeo *et al.*, 2011). There is a need for further research to investigate VAN in AD in the future.

Overall, the fMRI modality is used to measure brain activity and functional connectivity. Growing evidence suggests that brain activity and functional connectivity are consistent with cognitive function and neural processes. Brain functional changes might accompany or even precede detectable structural alterations (Qiu, 2022; Reas *et al.*, 2020). t-fMRI can be used to examine alterations in functional connectivity and brain activation during tasks such as memory, vision, and motor performance in MCI and AD patients. In addition, t-fMRI is a promising technique to distinguish patients with AD and those with behavioural variant FTD with motor and cognitive tasks (Rucco *et al.*, 2017). Thus, future fMRI studies in AD are needed to investigate the possibility of differentiating AD from other forms of dementia, such as PDD, DLB, VaD, and FTD, in the future. rs-fMRI can provide useful information about the functional connectivity of brain networks in MCI and AD patients, such as the DMN, VN, FPN, DAN, and VAN. However, other networks of the brain, such as the control network, salience network, and sensorimotor networks, might be explored in AD in the future. fMRI data are indeed intensive to collect, clean, preprocess, and analyse (Kim *et al.*, 2022a). Data collection and analysis techniques are another critical area for further development. Moreover, technical factors are important in assessing fMRI; small amounts of head movement that are not easily detected and multiple different methods of data analysis may confound the results. Subsequent studies can compare different techniques to obtain stable and sensitive parameters and combinations of parameters and sites for detecting microstructural changes. With advances in fMRI techniques, fMRI may have potential in practical clinical use in the future.

MRS

MRS is an advanced method for the measurement of neurochemicals in either a single voxel or multiple voxels (Lee *et al.*, 2017). MRS assesses the level of brain metabolites, and its parameters are expressed as concentrations or ratios, such as glutamate + glutamine (Glx), N-acetylaspartate (NAA), glutamate and NAA/creatine (Cr), glutamate/myo-inositol (mI), and NAA/mI ratios.

MRS can measure chemical concentrations in the brain (Kantarci *et al.*, 2000). Since 1992, a decrease in NAA neuronal metabolites has been demonstrated using MRS performed on autopsy brain samples of AD patients with respect to levels detected in the CN group. The observed decrease in NAA is linked to the number of senile plaques and NFTs in the brain (Klunk *et al.*, 1992). The reduction in NAA or NAA/Cr has been considered a marker of neuroaxonal density and viability (Kantarci *et al.*, 2000).

In MCI, NAA/Cr ratios are lowered in the left hippocampus and PCC (Oeltzschner *et al.*, 2019; Zhu *et al.*, 2015). When examining region-specific changes in AD, lower NAA and NAA/Cr are found in the PCC (Fayed *et al.*, 2014), and lower mI/Cr is found in the anterior cingulate gyrus and posterior cingulate gyrus (Guo *et al.*, 2016). A meta-analysis reported that NAA decreased in the posterior cingulate and hippocampus in AD patients, while mI and mI/Cr were increased in the posterior cingulate. Moreover, a sustained decrease was observed in the NAA/mI of the posterior cingulate in AD patients (Liu *et al.*, 2021a). Furthermore, the NAA/mI ratios in the PCC gradually decline during the transition from MCI to AD and are also deemed a valid discriminator of AD patients (Mitolo *et al.*, 2019). Clinically, decreased NAA is a predictive marker of phenoconversion to both dementia and cognitive dysfunction. In addition, the increased mI may affect the phosphorylation of membrane proteins or cause changes in phospholipid metabolism, affecting the formation of Aβ (Falini *et al.*, 2005; Kantarci, 2013). NAA/mI and NAA/Cr ratios distinguish AD from VaD, and glutamate/Cr ratios differentiate DLB from AD (Su *et al.*, 2016; Weiss *et al.*, 2003).

Glx, a product of the amination of glutamate, is transferred to neurons from glial cells after the exocytotic release of glutamate into the synaptic space. The glutamate concentration and the glutamate/mI ratio are lower in patients with MCI than in the CN in the PCC (Zeydan *et al.*, 2017). As free amino acids, both are involved in metabolism, neuronal function, plasticity, and excitotoxicity (Antuono *et al.*, 2001). Recently, Glx has been considered a promising marker for AD. Glx concentrations are reduced in the hippocampus and cingulate region (Shiino *et al.*, 2012). In addition, the Glx/Cr ratio is reduced in AD patients in the anterior cingulate cortex and right hippocampus (Huang *et al.*, 2017). Aβ induces several changes in nerve cells, including synaptic activity and loss of neuronal viability, leading to a reduction in glutamate levels. Moreover, the decrease in glutamate content affects A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), which play a key role in cognition and synaptic function. Moreover,

this decrease in AMPARs may be the reason for the decrease in cognitive function and the loss of synapses in AD. Glu and Glx/Cr may be seen as signs of cognitive deterioration in AD patients (Liu *et al.*, 2010).

In summary, MRS can be used to explore potential associations between the level of metabolites and pathological changes in MCI and AD patients. In addition, MRS is important in differentiating AD from VaD and DLB. The advantages of MRS are the substantially lower cost and the fact that it can be added to structural MRI sequences to extract additional information. MRS acquisition differs from a single-voxel technique, in which signals from a previously selected voxel are acquired, and multivoxel spectroscopy, in which many voxels are simultaneously obtained. Single-voxel spectroscopy has the advantage that the quantification of metabolites is accurate and scan times are short, but only one brain region can be examined at a time. Multivoxel spectroscopy allows simultaneous acquisition of data from numerous brain regions with the limitation of being less precise, and it demands a longer imaging time (Maul *et al.*, 2020). In general, MRS quantifies metabolites by evaluating metabolite concentrations in a few select brain anatomical regions but not the whole brain (DeMayo *et al.*, 2023b). To evaluate the potential benefits for early AD detection, diagnosis, and treatment, large-scale, preferably longitudinal studies are necessary under standardized conditions in the future.

ASL

To the extent that regional metabolism and perfusion are coupled, ASL labels water molecules in arterial blood as an endogenous tracer for perfusion (Chao *et al.*, 2010). In ASL, water molecules proximal to the area of interest in the arterial blood are magnetically labelled.

Cerebral blood flow (CBF) is the rate at which arterial blood is delivered to the capillary bed in brain tissue and is generally quantified in millilitres of blood per 100 grams of tissue per minute (Brown *et al.*, 2007). CBF is generally considered to be a proxy measure for brain functional activity. As the activity of neurons changes, so does the demand for oxygen, and the changing demand for energy moderates the CBF. CBF can be measured with a standard MRI sequence and compared to an unlabelled image as a control (Zhang *et al.*, 2017). In this way, changes in the neurovascular system can be detected by ASL imaging.

In MCI, decreases in CBF are found in the bilateral and medial temporoparietal regions, PCC, and inferior prefrontal cortex (Dolui *et al.*, 2020), whereas increases in CBF are found in the hippocampus, amygdala, right inferior frontal and insular region, and basal ganglia (Dai *et al.*, 2009; Duan *et al.*, 2020). Regarding disease-related outcomes, regional hypoperfusion is related to progression from MCI to AD, in addition to functional and cognitive deterioration (Chao *et al.*, 2010). In addition, notable hypoperfusion is present in the parietal, temporal, and occipital cortex areas, hippocampus, posterior cingulate, basal ganglia, thalamus, and frontal region in AD (Alexopoulos *et al.*, 2012; Duan *et al.*, 2020; Huang *et al.*, 2018; Huang *et al.*, 2019; Li *et al.*, 2020; Mak *et al.*, 2014; Riederer *et al.*, 2018; Zou *et al.*, 2014). A meta-analysis revealed that CBF measured via ASL showed impairment in AD compared with the control group in subregions of the MTL. The CBF difference was significant in the hippocampus between the AD and CN groups (Kapasouri *et al.*, 2022). Reduced CBF coexists with increased CBF, which is a response to pathologic damage in the early stages of the neurodegenerative process. In particular, CBF is elevated in AD patients in the hippocampus, which suggests a compensatory increase in neural activity. In addition, the CBF-impaired regions in AD are colocalized with two brain resting-state networks: the DMN and the salience network. The regions of CBF changes showed great spatial overlap with the AD pathologically affected regions (Anchisi *et al.*, 2005). Moreover, measures of perfusion on ASL imaging may also differentiate AD from VaD, DLB, and FTD (Binnewijzend *et al.*, 2014; Gao *et al.*, 2013; Mao *et al.*, 2023).

In summary, ASL is a perfusion MRI modality that is relatively inexpensive and easy to perform; furthermore, it could be added to conventional brain MRI, requiring 5 minutes of additional scan time. Moreover, ASL can provide CBF quantification and can be performed repeatedly (Alsaedi *et al.*, 2018). Growing evidence supports the utility of ASL to measure CBF in AD and differentiate AD patients from CN individuals. ASL is also a helpful technique in differentiating AD from VaD, DLB, and FTD. Hypoperfusion through ASL overlaps with hypometabolism patterns acquired via FDG-PET in AD patients. In addition, ASL is useful to explore overlapping pathogenetic mechanisms in AD (Grade *et al.*, 2015). The noninvasive and inexpensive nature of the ASL measurements and the extraction of additional quantitative and vascular information might make the use of ASL in AD an attractive alternative to FDG-PET. The limitation of ASL in clinical practice is its low signal-to-noise ratio, which results in reduced image quality (Alsaedi *et al.*, 2018). With improvements in experimental design and hardware, ASL could be a promising tool for exploring early detection, pathogenetic mechanisms, and diagnosis of AD.

DTI

DTI is one of the most effective MR techniques for the investigation of brain anatomy and measures the thermal motion of water molecules (Beaulieu and Allen, 1994). DTI can acquire data for a wide variety of microstructures, which is vital for identifying disruption of those microstructures due to disease and the fibre tracks of white matter (WM) (Buckner *et al.*, 2009).

The primary metrics of DTI include the average rate of water molecule diffusivity, mean diffusivity (MD), and the variability associated with diffusion, fractional anisotropy (FA) (Madden *et al.*, 2012). FA is used to represent the motional anisotropy of water molecules and is sensitive to the integrity of WM, whereas MD is a scalar measure of the directionally averaged diffusion magnitude and is used to assess the microstructural properties of broad brain structures, including grey matter (Maeda *et al.*, 2021).

MCI patients show extensive and serious abnormal diffusion measures in the corpus callosum, temporal brain region, corona radiata, and superior longitudinal fasciculus (Brueggen *et al.*, 2019; Li *et al.*, 2016). In addition, the integrity of several WM fibres, including the bilateral anterior thalamic radiation, corticospinal tract and left hippocampal cingulum, forceps minor, left cingulum (cingulate gyrus), and left inferior fronto-occipital fasciculus, was damaged in MCI patients (Luo *et al.*, 2019; Shao *et al.*, 2019). The selective impairment of WM is probably associated with the pathologically proven distribution of NFTs and amyloid plaques in the cortex and interconnection among WM fibres (Head *et al.*, 2004). MD increases in the basal forebrain are related to an increased risk of progression from MCI to AD (Brueggen *et al.*, 2015). Moreover, Brueggen *et al.*, Li *et al.*, and a meta-analysis reported that decreased FA in patients with AD was identified in the left frontal lobe, corpus callosum, fornix, cingulate gyrus, cingulate bundle, uncinate fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fascicles, inferior longitudinal fasciculus, and MTL, including the hippocampus and cingulum, in AD patients

(Chen *et al.*, 2023; Kumar *et al.*, 2022; Qin *et al.*, 2021). MD is significantly higher in the splenium of the corpus callosum and parietal lobe WM in AD patients than in those in healthy controls (Duan *et al.*, 2006). MD and FA abnormalities are associated with executive and memory dysfunction (Hirni *et al.*, 2013; Sjöbeck *et al.*, 2010). Diffusivity metrics also differentiate AD from other dementias, such as DLB and FTD (Firbank *et al.*, 2016; Schumacher *et al.*, 2023; Zhang *et al.*, 2009). Furthermore, combined with the WM dispersion characteristics provided by DTI and artificial intelligence technology, current research has made breakthroughs in the assisted recognition of AD (Chen *et al.*, 2022).

Overall, DTI can be used to describe the microstructure of WM through its tensor model. The diffusion features and structural connectomics of specific brain regions may provide useful information for assisted early recognition of AD. DTI might reveal the structural impairment and dysfunction of WM in AD patients through the combination of macroscopic network activity and microscopic neural structure, which could provide a theoretical basis for understanding the abnormal neural mechanisms underlying AD and intervention treatment. DTI can be used to describe the microstructure of WM but has limited value in describing GM atrophy, cortical variation, and brain functional network activation (Wang *et al.*, 2022). Therefore, it is necessary to further combine fMRI, structural MRI, and ASL with other neuroimaging modalities in the study of AD neural mechanisms in the future and investigate whether there is a relationship between structural and functional connections and their influence on the progressive pathology of AD. Traditional DTI has limitations in resolving intravoxel complexities such as crossing, fibre bending, and twisting. High angular resolution diffusion imaging has appeared to address this limitation by sampling the diffusion signal along many gradient directions. It may offer an improved approach to biomarker discovery (Lenglet *et al.*, 2009). The new technique should be considered to overcome existing barriers in clinical trials in the future. Finally, most AD WM abnormality studies based on DTI are cross-sectional studies (Chen *et al.*, 2023). This experimental design may miss individual differences and longitudinal progression in the progressive progression of AD. In the future, longitudinal studies will further focus on early biomarkers for the transformation prediction of MCI individuals into AD.

PET

PET imaging measures metabolic changes by using different radioactive tracers for each intended target (Ruan and Sun, 2023). PET imaging involves the coincident detection of gamma rays released from positron annihilation events originating from radioactive tracers (Omami *et al.*, 2014). Owing to the higher diagnostic accuracy of PET for AD in both diagnostic and research contexts, PET has been used as an imaging method in various therapeutic and prognostic studies. The neuropathologic features of AD include intracellular NFTs consisting of hyperphosphorylated microtubule-associated Tau protein and extracellular senile plaques composed of Aβ peptides (Scheltens *et al.*, 2016). The NIA-AA recommends the consideration of biomarkers about amyloid PET positivity, Tau-PET positivity, and reduced metabolism on FDG-PET for AD diagnosis (Table 1).

Amyloid PET binds amyloid-β fibrils in senile plaques. Currently, carbon-11 Pittsburgh compound B ([^{11}C]PiB) is the most extensively studied in the amyloid radiopharmaceuticals (Johnson *et al.*, 2013). In MCI patients, increased [^{11}C]PiB uptake has been reported in comparison to AD patients (Forsberg *et al.*, 2008). In addition, [^{11}C]PiB uptake is predictive of progression to AD (Lim *et al.*, 2014). It has been reported that [^{18}F]florbetapir-positive scans were predictive for progressive deterioration of cognitive states in MCI and AD patients, compared with those with a negative scan (Doraiswamy *et al.*, 2014). Furthermore, [^{18}F]flutemetamol and [^{18}F]florbetaben have been approved by the U.S. Food and Drug Administration (Tripathi and Murray, 2022). [^{18}F]flutemetamol has shown the ability to discriminate patients with AD from elderly healthy (Hatashita *et al.*, 2019). In addition, [^{18}F]florbetaben is a derivative of polyethylene glycol stilbene and has shown high specificity for Aβ with probable AD patients (Barthel *et al.*, 2011a, 2011b). Diffuse cortical amyloid tracer binding is predominant in frontal and posterior cingulate with a relative sparing of medial temporal cortex, sensorimotor, and occipital cortex in AD (Okamura *et al.*, 2018).

Tau PET binds paired helical filaments-tau in NFTs, neuropil threads, and dystrophic neurites. The earliest radiotracer to target tau was [^{18}F]-labelled THK-523 *in vivo* but unfortunately, a very high retention in WM precludes its use in research (Villemagne *et al.*, 2014). Additionally, several [^{18}F]-labelled arylquinoline derivatives were developed as candidate tau PET radiotracers such as [^{18}F]THK-5105 and [^{18}F]-THK-5117 (Harada *et al.*, 2015). [^{18}F]THK5351, has shown faster uptake and washout kinetics and lower WM uptake compared with [^{18}F]THK5117 in AD patients, as well as lower cortical retention in MCI compared with AD (Lockhart *et al.*, 2016). In addition, [^{18}F]AV-1451 showed distribution of tau pathology according to Braak stages (Marquié *et al.*, 2017). Furthermore, 18F-AV-1451 uptake was found in the cortex in MCI, while the uptake was confined in the hippocampus in Aβ negative healthy participants (Pontecorvo *et al.*, 2017). There are a few newer radio tracers such as [^{18}F]RO-948, [^{18}F]JNJ64349311, [^{18}F]PI-2620, and [^{18}F]GTP1 that have been used for tau imaging (Leuzy *et al.*, 2019; Sanabria Bohórquez *et al.*, 2019). Tau tracer binding is obviously higher in the temporo-parietal cortex, and lower in subcortical regions in AD (Lagarde *et al.*, 2019). A close relationship is observed with tau pathology and severity of cognitive impairment and hence may be used as a prognostic biomarker for AD (Villemagne *et al.*, 2018).

FDG-PET relies on the detection of hypometabolism in different brain regions corresponding to sites of neurodegeneration. The reliance of the brain on glucose for its activity allows FDG, a glucose analogue, to be used to measure glucose transporter-mediated uptake, following which activity is trapped in the cells after phosphorylation. Glucose uptake is inversely proportional to neuronal dysfunction (Nasrallah and Dubroff, 2013). FDG-PET measures glucose metabolism in different brain regions and represents a metabolic marker in the preclinical detection and early diagnosis of dementia. Metabolic changes commonly occur before detectable structural changes take place in the brain (Sanchez-Catasus *et al.*, 2017). Hypometabolism in FDG-PET images is considered a biomarker of AD. FDG-PET is used in the differential diagnosis of AD and evaluation of MCI conversion to AD (Rice and Bisdas, 2017). Cerebral glucose hypometabolism has been consistently demonstrated in the posterior cingulate gyrus, MTL, frontal cortices, and/or parieto-temporal regions of typical AD patients. Similarly, moderate hypometabolism has been detected in the basal ganglia, cerebellum, visual cortices, and sensorimotor thalamus (Tripathi and Murray, 2022).

In summary, PET has been used as a biomarker in various prognostic and therapeutic studies and studies related to AD. The high diagnostic accuracy of PET imaging has also been considered in diagnostic and research criteria for AD. FDG-PET plays an important role in the diagnosis and prognosis of AD. Amyloid PET is becoming more common in clinical practice. Amyloid PET has been used

in clinical trials of novel drugs that help reduce the formation of Aβ but has not yet achieved favourable outcomes. Failure of anti-amyloid therapies for AD leads to a paradigm shift towards tau as a therapeutic target (Tripathi and Murray, 2022). Tau PET may offer new insights and be of great help in the differential diagnosis and treatment selection of AD patients. In addition, PET is a costly, invasive, and inconvenient technique that also requires exposure to ionizing radiation, limiting its clinical application (Acuff *et al.*, 2020). Despite these differences, PET imaging has the potential to improve the diagnostic specificity and targeted therapy of AD.

SPECT

SPECT, a nuclear medicine imaging modality, involves injecting a gamma-emitter radiotracer into the patient and obtaining tomographic images of its distribution. Thus, it can be used to detect both cellular and chemical changes linked to a disease. The absorption of the radiotracer relies on the biochemical behaviour of the tracer *in vivo* (Catafau, 2001).

SPECT evaluates regional CBF and is correlated with metabolic changes (O'Brien *et al.*, 2014). The presence of hypoperfusion in SPECT in the posterior parietal cortex, posterior cingulate, and in MCI patients has been consistently associated with an increased risk of progression to AD (Quaranta *et al.*, 2018). Typically, AD is represented on SPECT images by hypometabolism in the temporal, posterior parietal, and PCC with either normal appearance of the sensorimotor cortex and the primary visual, thalamus, brainstem, cerebellum, and basal ganglia or the presence of bilateral hypoperfusion (Ferrando and Damian, 2021).

In summary, SPECT is currently one of the most widely available imaging techniques for the study of brain function with lower cost than PET (Ritt, 2022). Regional CBF imaging using SPECT may provide useful information about brain perfusion in the diagnosis of AD. SPECT is valued for its high specificity and sensitivity in differentiating AD from CN individuals (Kong *et al.*, 2023). 123I-ioflupane (DaTscan™) SPECT has been approved in the European Union and the USA to evaluate PDD patients (Kemp *et al.*, 2011). Therefore, SPECT is a promising tool for exploring the early detection and diagnosis of AD.

Fluorescence Molecular Tomography

Presently, definitive and accurate AD diagnosis still relies on clinical findings from postmortem analysis of AD patients' brains (Murphy and LeVine, 2010; Valotassiou *et al.*, 2018). In addition, nuclear imaging modalities have some disadvantages, such as high cost, poor resolution, long testing times, and unavoidable exposure to radioactivity (Xu *et al.*, 2016). Optical imaging modalities, particularly NIRF imaging, may provide a non-invasive *in vivo* method to visualize the real-time status of the AD brains more accurately at the biomolecular level (Liu *et al.*, 2021b; López-Cuenca *et al.*, 2021). Importantly, small molecule NIR probes are used to detect Tau protein, β-amyloid, and other biomarkers (Rai *et al.*, 2022). Optical imaging applications can simultaneously record and analyse both the spatial and functional dynamics of pathological injuries (Liu *et al.*, 2021b).

Great progress has been made for AD probes. However, there are some challenges for small molecular fluorescence AD probes *in vivo*. (i) There is a lack of NIRF probes for the accurate identification of different pathological states of Aβ, which should be addressed by further molecular design. (ii) Most reported probes only target one or two associated biomarkers. However, it is vital to use different probes that detect corresponding targets from the same resource. (iii) Although dual diagnostic and therapeutic AD probes were reported with *in vitro* data, an *in vivo* study is missing (Liu *et al.*, 2022).

In summary, AD probes yield sharp fluorescence signal enhancement on binding to AD biomarkers, leading to clear images of biomarkers with a high signal-to-background ratio. The AD probes are designed to penetrate the blood–brain barrier and target AD biomarkers for the precise diagnosis of early-stage AD. AD probes have multiple other functions, such as therapeutic integration and multimodal imaging, and various optimal characteristics, such as a variety of optical properties and dual responsiveness (Rai *et al.*, 2022). AD probes should be considered in novel molecular design strategies for the precise diagnosis and treatment of AD at an early stage.

Discussion

General summary

We have reviewed the literature concerning neuroimaging modalities, generally including MRI (structural MRI, t-fMRI, rs-fMRI, MRS, ASL, and DTI), PET, SPECT, and optical imaging, in MCI and AD patients. Different neuroimaging modalities with various biomarkers have already provided useful information in terms of diagnosing AD during the preclinical stage, tracking its progression, and differentiating AD from other forms of dementia. In structural MRI studies, there are promising biomarkers in both MCI and AD patients, such as hippocampal atrophy and entorhinal cortex atrophy. Hippocampal atrophy can predict whether MCI patients would progress to AD and can be used to differentiate AD from PDD and DLB. Entorhinal cortex atrophy that provides prediction for the conversion from MCI patients to AD. Other biomarkers in the cerebral cortex detected by using structural MRI (e.g. GM loss in the frontal, parietal and temporal lobes), subcortical regions (e.g. atrophy of the amygdala and olfactory bulb), and cerebellum (e.g. cerebellar atrophy) also have potential in AD patients. In fMRI studies, t-fMRI is used to investigate functional alterations during tasks of memory, vision, and motor performance in MCI and AD patients. Some contradictory results were found regarding brain activation of the MTL during memory tasks in MCI patients. This difference may be due to the mixed sample of MCI and AD patients, and there is a need for further research to overcome the limitations of the inclusion criteria in the future. Additionally, reduced posterior cingulate gyrus/precuneus deactivation and frontal hyperactivation are approximately consistent findings during memory tasks in MCI and AD patients. t-fMRI and rs-fMRI studies in this review demonstrate disruptions in brain functional connectivity patterns in AD and MCI patients compared to CN group. Changes in both structural and functional network organization in AD are linked to the patterns of amyloid-β and tau accumulation and spread, providing insights into the neurobiological mechanisms of AD. Furthermore, the detection of gene-related connectome changes might be helpful in the early diagnosis of AD and facilitate the development of personalized therapeutic strategies that are effective in the early stages of AD (Yu *et al.*, 2021b). In MRS studies, the concentration or ratios of brain metabolites, such as Glx, NAA, glutamate, and ratios of NAA/Cr, glutamate/mI, and NAA/mI, were found to be promising biomarkers. In ASL studies, changes in CBF were found in different brain regions in MCI and AD patients by using ASL, which differentiates AD from VaD, DLB, and FTD. In DTI studies, WM damage was found in MCI and AD patients by using DTI. Additionally, recent research has made breakthroughs in combining DTI and artificial

Table 3: The: summary of biomarkers in AD in different neuroimaging modalities.

Biomarker	Category	Representative neuroimaging modalities	Shortcomings	Main findings in MCI	Main findings in AD
Brain activation	Brain activity	Task-based fMRI	Being intensive to collect, clean, preprocess, and analyse data	Hyper- and hypo-activation in the task-related region during tasks of memory	Hyper- and hypo-activation in the task-related region during tasks of memory, vision, and motor performance
Functional connectivity	Brain networks	Resting-state fMRI	Being intensive to collect, clean, preprocess, and analyse data	Altered functional connectivity in DMN, VN, FPN, and DAN	Altered functional connectivity in DMN, VN, FPN, DAN, and VAN
		Task-based fMRI	Being intensive to collect, clean, preprocess, and analyse data	Altered functional connectivity in the task-related region during the encoding task of novel picture-word pairs	Altered functional connectivity in the right supramarginal gyrus during the auditory task
Volumetric reduction	Anatomical structure	Structural MRI	Rare use of quantification software in clinical practice	Atrophy in partial cerebral cortex, subcortical regions	Atrophy in partial cerebral cortex, subcortical regions, and cerebellum
CBF fluorescence	Anatomical structure	ASL	Low image quality	Regional hypoperfusion and hypertransfusion	Regional hypoperfusion and hypertransfusion
		SPECT	Low diagnostic accuracy	Regional hypoperfusion	Regional hypoperfusion
WM damage	Anatomical structure	DTI	Low image quality, imprecise quantitative measures	WM integrity impairment	WM integrity impairment
Aβ deposition and Tau	Pathogenic protein	Amyloid PET	High cost, harmful radiation	Altered amyloid tracer binding in brain regions	Altered amyloid tracer binding in brain regions
		Tau PET	High cost, harmful radiation	Altered Tau tracer binding in brain regions	Altered Tau tracer binding in brain regions
		NIRF probes	Lack of clinical trials	/	Detection of Tau protein, β-amyloid
Glx, NAA, NAA/Cr, Glutamate, glutamate/mI	Brain metabolite	MRS	Being unable to evaluate the whole brain	Decreased level and ratios of brain metabolites	Decreased level and ratios of brain metabolites
Glucose metabolism	Metabolic marker	FDG-PET	High cost, harmful radiation	Reduced cerebral glucose metabolism	Reduced cerebral glucose metabolism

intelligence technology in the assisted recognition of AD. In addition to MRI, biomarkers in other neuroimaging modalities have shown potential in identifying MCI and AD. PET plays an important role in the diagnosis and prognosis of AD. The limitation of high cost may be solved with social development and improvement of medical insurance. Moreover, SPECT is mainly used for the diagnosis of PDD at present, and studies on the diagnosis of AD using SPECT are scarce. More clinical trials are necessary to investigate the diagnosis of AD using SPECT. Preclinical studies indicate that NIRF imaging is an advanced modality in AD. It is necessary to explore NIRF imaging in clinical trials in AD in the future. The clinical value of these biomarkers in different neuroimaging modalities needs to be further demonstrated and has the potential to be included in the AT(N) classification system in the future. Furthermore, other new biomarkers should be discovered and explored in different neuroimaging modalities.

The relationships among different markers

There are various biomarkers that can be detected by different neuroimaging methods, as mentioned before. Different biomarkers belong to one category. Biomarkers of brain structures (i.e. hippocampal atrophy, frontal, parietal, and temporal lobe atrophy), WM damage, and CBF are all classified as anatomical structures, which are measured in structural MRI, DTI, ASL, and SPECT, respectively. Moreover, multiple neuroimaging modalities are used to measure the same biomarker, and a neuroimaging method can measure different biomarkers. PET and NIRF probes are all representative neuroimaging methods for measuring pathogenic proteins (Aβ deposition and tau), and PET can also be used for measuring the level of glucose metabolism. Brain activation and functional connectivity are generally measured by using t-fMRI. Moreover, functional connectivity is measured by using not only t-fMRI but also rs-fMRI (Table 3). The NIA-AA recommends the consideration of biomarkers about amyloid PET positivity, Tau-PET positivity, reduced metabolism on FDG-PET, brain abnormalities on structural MRI for AD diagnosis (Table 1). Asia Expert Opinion in 2021 recommends that the brain networks impairment on fMRI and the WM integrity impairment on DTI are promising biomarkers for AD diagnosis (Kandiah *et al.*, 2022). In other prospective biomarkers, regional hypoperfusion and hypertransfusion on ASL or SPECT, decreased level and ratios of brain metabolites in MRS, hyper- and hypo-activation in the task-related region on t-fMRI are also promising biomarkers for AD diagnosis.

Across all these biomarkers, investigators should consider specificity to the disease process, histological validation, practical feasibility in a clinical research setting, sensitivity to detect abnormalities, and relationship to cognitive/clinical outcomes. However, there is not a single neuroimaging technique that meets

all these criteria and provides a sufficiently rich understanding of pathological processes. Different imaging modalities with biomarkers may offer complementary information and rich information that could be used for tracking and staging within individuals. Combining neuroimaging modalities with composite neuroimaging biomarkers is a new open field, and multicentre clinical trials are needed to further explore composite neuroimaging biomarkers in the future (Márquez and Yassa, 2019).

Advantages and disadvantages of neuroimaging modalities

There are various neuroimaging modalities in this review. Each imaging modality has its own advantages and limitations. The major advantage of MRI is its widespread availability in AD research. MRI scans provide detailed anatomical information (Márquez and Yassa, 2019). However, there are still some limitations to be addressed on different MRI modalities. (i) fMRI data are indeed intensive to collect, clean, pre-process, and analyse. MRS quantifies metabolites by evaluating metabolite concentrations in a few select brain anatomical regions but not the whole brain. The limitation of ASL in clinical practice is its low signal-to-noise ratio, which results in reduced image quality. In addition, Traditional DTI has limitations in resolving intravoxel complexities such as crossing, fibre bending, and twisting. (ii) Methods to further improve the effect of high field intensity MRI on the human body should be further studied (Yu *et al.*, 2021a). Compared with MRI, PET, and SPECT can visualize neurotransmitters and brain receptors and determine specific biomolecule concentrations in the picomolar range if developed to have higher sensitivity (Bois *et al.*, 2008; Cheng *et al.*, 2012). Notably, previous studies reported that PET had insurmountable limitations due to its high cost, the short half-lives of the radioactive atomic species and scarcity of the required isotopes (Bertoncini and Celej, 2011). Compared to PET, SPECT has a relatively low signal-to-noise ratio and background interference (Yang *et al.*, 2020). Optical imaging has become a reliable approach for fast data acquisition, wide availability, and the real-time detection of Aβ with high sensitivity and high resolution (Kaminski Schierle *et al.*, 2011; Maeda *et al.*, 2007). Despite tremendous progress in small molecular fluorescence AD probes, there are still some limitations for AD imaging and therapy *in vivo*. For example, NIR fluorescence probes that combine NIR fluorescence imaging with other conventional phototherapies for the accurate identification of different pathological states of Aβ *in vivo* have not yet been developed (Ma *et al.*, 2018; Ozawa *et al.*, 2021; Suzuki *et al.*, 2019).

Influenced factors

There is growing evidence about neuroimaging biomarkers in AD. However, the influencing factors may be ignored in the design of clinical trials. The influencing factors of age and sex have been reported in clinical trials in AD. Age remains the greatest risk factor for AD and is thus a fundamental driver for the development of this disease (Masters *et al.*, 2015). An accelerated decrease was found in hippocampal volume at the baseline age of 55–60 years, and an accelerated decline was found in cortical thickness and hippocampal volume at the baseline age of 65–70 years. Accelerated declines in hippocampal volume continue after 70 years (Luo *et al.*, 2022). Between 2015 and 2030, the number of people in the world aged 60 years or over is projected to grow by 56%, and by 2050, the global aged population is projected to more than double. The increasing ageing at the global population level has led to a high increase in the prevalence of AD (Riedel *et al.*, 2016). In an AD Neuroimaging Initiative study, brain atrophy rates were ~1–1.5% faster in women than in men in a 1-year follow-up evaluation (Hua *et al.*, 2010). A meta-analysis reported that men had higher GM densities than women in several brain regions, including the hippocampus, amygdala, putamen, and insular cortex (Ruigrok *et al.*, 2014). Men with AD show lower connectivity strength than women within several brain network properties (Li *et al.*, 2021). A study of AD patients reported that striatal Aβ accumulation was faster in women than in men (Kim *et al.*, 2022b). A higher prevalence and incidence of AD is found in women than in men. The greater risk of AD in females may be attributed to their greater longevity of, on average, 4.5 years. Women may have intrinsic susceptibilities to the disease, including hypertension, menopause, pregnancy disorders, hormone therapy, and gynaecological surgeries (Cui *et al.*, 2023). Tau depositions significantly increased in females in some brain regions in Aβ positive patients (Zhang *et al.*, 2022). Epidemiological studies have reported that higher education years are associated with a reduced risk of incident AD, suggesting that education may provide protection against the onset of AD (Cho *et al.*, 2015; Scarmeas *et al.*, 2006). This protective effect of education is supported by the cognitive reserve hypothesis. Cognitive reserve refers to the ability of the brain to compensate for damage by using pre-existing cognitive processing approaches or by recruiting compensatory approaches (Scarmeas and Stern, 2004). Therefore, an individual with higher education years might cope better with an equivalent level of pathology than an individual with lower education years, which in turn, delay the clinical expression of AD (Dumurgier *et al.*, 2010). Once AD clinically manifests, brain pathology is already advanced in AD patients with higher education, more so than those with lower education. Therefore, the influencing factors of age, sex, and years of education should be considered in the design of clinical trials for AD.

Limitations in the design of clinical trials

Based on the reported findings about neuroimaging modalities, we found some limitations in the design of clinical trials. First, a limitation of neuroimaging modalities is their use in mostly cross-sectional studies. AD is a progressive disease in nature, which requires longitudinal data about early biomarkers for the prediction of transformation from MCI to AD. Next, those studies in this review were generally performed in small cohorts including 10–100 participants. Thus, multicentre and large-scale trials are necessary in the future. In brief, large-scale and longitudinal studies are worth conducting with optimized and standardized neuroimaging modalities to elucidate the pathogenesis and facilitate the early diagnosis of AD in the future.

In conclusion, different imaging modalities have shown substantial utility in identifying biomarkers of AD pathology. These, in turn, could be used to improve diagnostic accuracy and develop novel molecular-based treatment interventions. While only traditional structural modalities are currently recommended for the diagnosis of AD in clinical practice, further research is necessary to overcome the limitations of more advanced modalities. Advancements in these modalities should warrant their future inclusion in diagnostic criteria for AD.

Author Contributions

Qian Li designed the study; Chun Dang, YanchaoWang and Yaoheng Lu performed the research; and all authors drafted the article or revised it for important intellectual content.

Conflict of Interest

The authors declare no conflict of interest.

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