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REVIEW

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Research on magnetic resonance imaging in diagnosis of Alzheimer's disease

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Abstract

As a common disease in the elderly, the diagnosis of Alzheimer's disease (AD) is of great significance to the treatment and prognosis of the patients. Studies have found that magnetic resonance imaging plays an important role in the early diagnosis of Alzheimer's disease. This article tries to review the application of magnetic resonance imaging in the diagnosis and differential diagnosis of Alzheimer's disease.

Keywords Alzheimer's disease (AD), Diagnosis, Structural magnetic resonance imaging (sMRI), Functional magnetic imaging (fMRI)

Alzheimer's disease (AD) is a common disease in the elderly. With the development of population ageing, the prevalence of AD is increasing gradually. Alzheimer's disease (AD) is a central nervous system degenerative disorder characterized by progressive cognitive impairment and behavioral impairment that occurs in the elderly and pre-elderly. The clinical manifestations included memory impairment, aphasia, aphasia, agnosia, impairment of visuospatial ability, impairment of abstract thinking and calculation, personality and behavior changes, etc. AD is the most common type of dementia in the elderly, accounting for about 50% −70% of dementia in the elderly. Therefore, early clinical diagnosis of AD is very important to delay the progression of the disease.

Regarding the pathogenesis of AD, there are multiple theories, including the β-amyloid protein (Aβ) waterfall theory, the tau protein theory, oxidative stress mechanism, inflammatory mechanism, etc. In recent years, some scholars have also proposed the neurovascular theory, which may be helpful for MRI diagnosis of AD. This theory believes that disorders of cerebrovascular function lead to neuronal cell dysfunction and reduced Aβclearance, leading to cognitive impairment. In recent years, magnetic resonance imaging plays an increasingly important role in the diagnosis of AD. Magnetic resonance imaging (MRI) was divided into structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI). SMRI included T-1 magnetic resonance imaging (T-1WI), T-2 magnetic resonance imaging (T-2WI) and diffusion-weighted imaging (DMRI) fMRI includes resting fMRI, task fMRI and so on. Magnetic resonance imaging (MRI) can image from cross-section, sagittal plane, coronal plane and so on, so it has a high resolution to the brain tissue structure, can obtain the brain accurate detail and the rich tissue vein characteristic [1], therefore, magnetic resonance imaging (MRI) has become the main means of clinical examination and prediction diagnosis of many brain diseases, and is widely used in the field of brain disease diagnosis [2–4]. In this paper, we try to review the research progress of magnetic resonance imaging in the diagnosis of AD.

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Application of MRI in the diagnosis of AD

Application of sMRI in the diagnosis of AD

sMRI is a non-invasive method that can be used to visualize, quantify and detect structural changes induced by AD in vivo. Volumetric measurements of gray matter–GM–RRB–GM) and white matter (WM), as well as estimates of cortical thickness, can be extracted and reliably used for the classification of AD [5]. In recent years, more and more scholars have focused on the early diagnosis of AD, focusing on the analysis of different modality neuroimaging or biomarkers to assist the diagnosis of AD [6–8]. Mild cognitive impairment (MCI), a precursor to Alzheimer's disease, is one of the most challenging neurodegeneration; it can be divided into early mild cognitive impairment (EMCI) and late mild cognitive impairment (LMCI). It is well known that MCI has a high risk of developing AD, so identifying MCI is key to early detection and diagnosis of AD [9]. With the development of computer and medical imaging technology, prediction of MCI transformation and classification of AD, MCI, and normal control (NC) can be made by combining imaging data such as MRI, positron emission computed tomography, and machine learning methods [10, 11]. In recent years, with the identification of AD biomarkers, many studies have suggested that structural changes in gray matter atrophy can be evident in MCI and AD patients [12]. Visser et al. [13] also found that patients with MCI had medial temporal lobe atrophy and memory impairment, and memory impairment features were more predictive of dementia than medial temporal lobe features; and the combination of the two can improve the prediction accuracy of AD.

It is well known that brain atrophy is a common phenomenon in patients with MCI and AD due to the loss of nerve cells and synapses. The extent of brain atrophy can be effectively measured by the volume of gray matter (GM-RRB). Some literature has confirmed the loss of gray matter in global and local brain regions in patients with MCI and AD [14–16]. Through follow-up of patients with NC or MCI, as well as measurements of hippocampal, amygdala, or temporal lobe gray matter volume, previous studies have reported that physical brain atrophy occurs with age in older adults [17, 18]. Butto et al. [19] showed reduced temporal gray matter in AD patients by voxel-based morphometry (VBM). Therefore, gray matter volume has been used as an anatomical feature to effectively assist in the early prediction of AD. Schmitter et al. [20] improved classification accuracy in AD versus MCI, early AD versus late AD, respectively, by classifying gray matter volumes in certain brain structures. Suk et al. [21] demonstrated a greatly improved classification accuracy for AD based on MRI and PET by combining gray matter volume with mean intensity and CSF. These structural changes are reflected in the contraction or thinning of the cerebral cortex and atrophy of the hippocampus by the SMRI. Many studies [22] have focused on analyzing shrinkage patterns and extracting features from spatial domain SMRI images for application in the field of AD diagnosis. Zhang y et al. [23] based on the texture features of SMRI gray-matter images and hippocampal structural features, proposed a depth learning approach for AD diagnosis based on regional attention of gray-matter slices, more accurate diagnosis of Alzheimer's disease can be achieved by focusing more effective features on gray matter coronal images.

These results suggest that SMRI hippocampal texture features are effective in the diagnosis of AD. Although SMRI can clearly show the anatomic changes of brain tissue in the early stage of AD, however, because of the complex anatomy of the lesion and the low specificity of the lesion, SMRI is not the first choice for the diagnosis of early AD.

In recent years, with the development of MRI technology, the application of diffusion imaging technology in AD is increasing gradually, these include diffusion tensor imaging (DTI-RRB), neurite directional dispersion and density imaging (NODDI), diffusion peak imaging (DKI) and free-water diffusion MRI. In AD, DTI mainly observed changes in white matter regions of the brain, and most of the findings focused on the increase in mean diffusion rate (MD) in the hippocampus. Compared with DTI, the DKI technique employs a non-gauss model that is closer to water molecular diffusion, accurately reflects subtle changes in the white and gray matter of the brain in AD patients, and the anisotropic fraction (FA) is restricted to an anisotropic environment, the kurtosis parameter can be used to evaluate the state of water diffusion in both isotropic and anisotropic environments. Because of the lack of specificity of the peak parameters of DKI, the mechanism of some pathological changes cannot be explained clearly, while the neurite density index (Ndi) of NODDI can explain the mechanism behind the changes of parameters such as FA, and the effects of different pathological stages of AD on FA and Md. In addition, NODDI studies the diffusion and atrophy of the cortex in the gray matter, and NODDI imaging parameters are strongly associated with performance on neuropsychological tests. Free-water diffusion imaging uses a double-tensor model different from the above three imaging techniques, which accurately reflects the changes of water diffusion and solves the partial volume effect of cerebrospinal fluid. Compared with DTI, free-water diffusion imaging produces less image deviation and is more consistent with the measured signal. At the same time, the scanning time of free-water diffusion

imaging is significantly shorter than that of NODDI and other complex diffusion imaging techniques. Agostinho D et al. [24] achieved classification of AD disease by binding of sMRI to DTI and additionally found that there were some recessive unknown alterations on WM that were associated with amyloid pathology. It can be further studied and used to develop a new classification framework for AD. It can also improve our understanding of the disease Pathophysiology at WM level.

In conclusion, the application of diffusion-weighted imaging to subcortical nuclei, including the striatum and thalamus, will help to further evaluate AD progression in the clinic, the application of MRI in AD will be deepened by combining the diffusion imaging technique with clinical biological markers, improving the specificity of the technique and further expanding the pathological sample size. In the future, diffusion-weighted imaging will play an increasingly important role in the early diagnosis, differential diagnosis and therapeutic monitoring of AD.

fMRI in the diagnosis of AD

Because local brain lesions are often accompanied by changes in blood flow and metabolic activity in the early stages, and brain structure often changes only in the later stages of the disease, functional imaging techniques have greater potential in identifying early pathological changes in the disease [25].Currently, fMRI is an emerging method for the study of brain diseases, based on oxygen-dependent blood magnetic resonance imaging that measure changes in hemodynamics caused by neuronal activity. Because of its non-invasive, accurate localization of brain function and no risk of repeated examination of patients, it has been widely concerned by researchers, especially in the evaluation of patients with cognitive impairment of memory (Fig. 1). At present, the research of AD by fMRI is mainly divided into two parts: resting state functional magnetic resonance imaging (rs-fMRI) and task state functional magnetic resonance imaging (ts-fMRI). Rs-fMRI is used to collect brain signals while the patient is at rest. It does not need to cooperate with

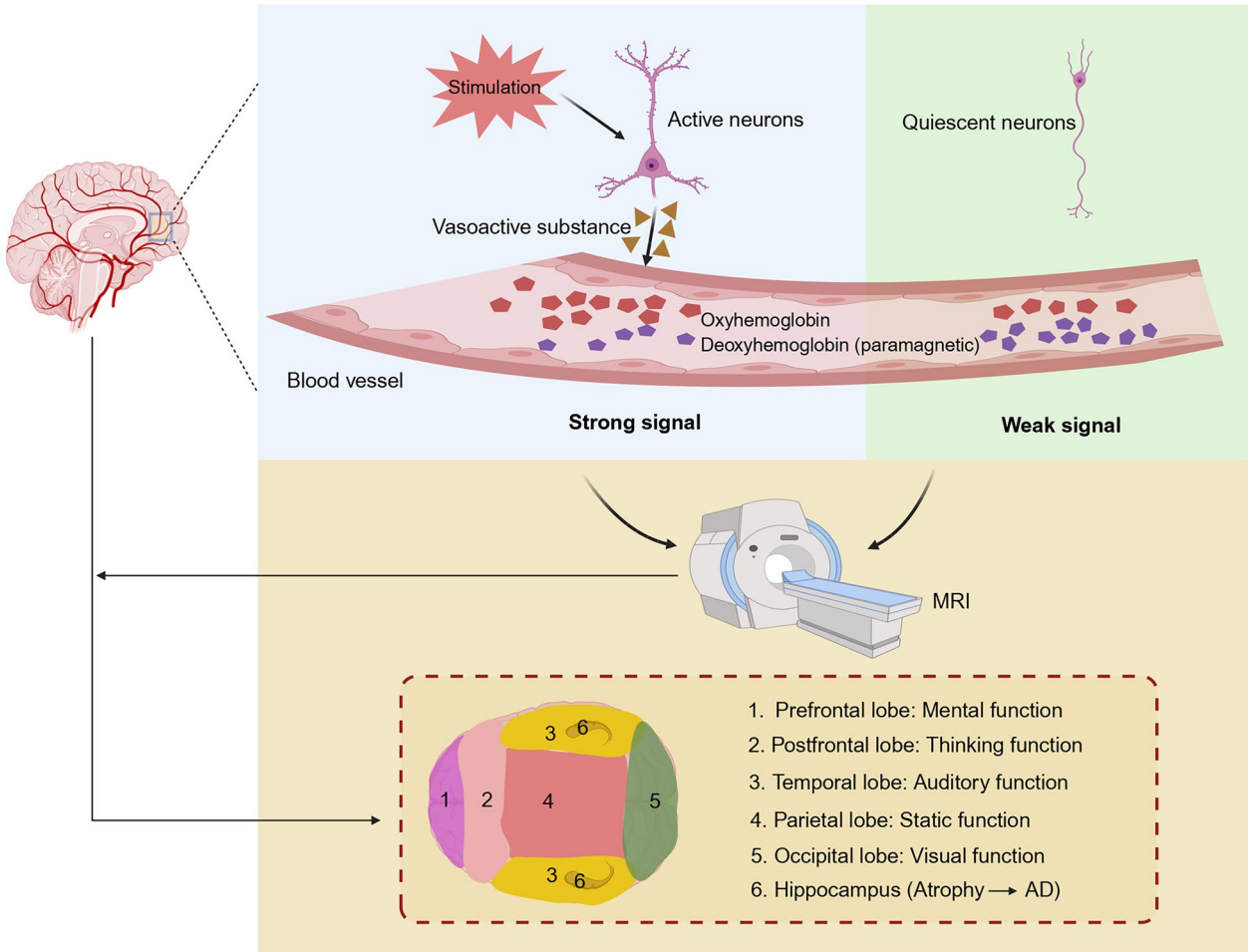

Fig. 1 MRI imaging principles

other complicated tasks. Ts-fMRI is superior to ts-fMRI in the study of neural activity in specific regions of brain network, and the experimental design is more flexible.

It is generally believed that only local neuropathological changes occur in the stage of subjective cognitive decline (SCD) in AD, whereas the correlation between rs-fMRI indices of SCD and classical pathological biomarkers suggests that rs-fMRI may be a potential imaging marker to identify SCD [26]. A large cross-ethnic cohort study [27] showed that both Chinese and German patients with SCD had an increase in SFC between the hippocampus and the right insula, which was positively correlated with the SCD-plus score. It is concluded that the increase of SFC in the hippocampus of SCD can be used as a reliable basis to reflect the decline of cognitive ability. Another ReHo Study [28] also showed that the hippocampus and parahippocampal gyrus of SCD patients were higher than those of healthy controls (health control, HC) and negatively correlated with multiple cognitive functions such as memory, language, space, and attention in SCD, it is suggested that the decreased function of hippocampus and parahippocampal gyrus may be a high risk factor for the development of dementia. In general, the characteristic changes of rs-fMRI suggest that some important brain areas are damaged early in AD, mainly located in anterior cuneiform/posterior cingulate gyrus, inferior parietal lobule and hippocampus. However, although rs-fMRI has shown strong applicability in clinical research, the technique relies to a certain extent on data post-processing methods, the results of the study may be different because of the different post-treatment methods. Therefore, the recent development of processing technology has great prospect for improving the efficiency of rs-fMRI in early diagnosis of AD. For example, Gonneaud et al [29]. used rs-fMRI data, biomarker a β, high-risk factor for AD Apoe E4 and artificial intelligence algorithms to construct predictive models of brain age, a characteristic pattern was found to accelerate aging-related changes in brain function prior to the onset of AD symptoms.

In terms of functional measurement, ts-fMRI has a strong advantage. It can reflect the active areas of the brain during the task by observing the changes in blood oxygen levels produced during the task, to achieve the purpose of observation of specific functional processing areas of the brain. However, there are quite a lot of noise effects in ts-fMRI experiment, except for the head-moving noise and machine noise, which are also encountered in the rest state, the emotion recognition task has additional noise effects on subjects' psychophysiological conditions (such as heart rate) and eye movement (such as pupil size change), it is necessary to collect this information and to take it into account in statistical models for a detailed interpretation of the data. Researchers from Queen Mary College, University of London [30], studied this question using task-state fMRI, which allows patients with frontotemporal dementia syndrome to watch videos of natural, dynamic expressions, data on subjects' fMRI and autonomic nerve activity were recorded in an attempt to discuss this issue by comparing the data performance of the patient group with that of an age-matched healthy control group. These findings open a window on the brain functional mechanisms underlying the complex socio-emotional phenotype in patients with frontotemporal dementia and have important implications for the development of new physiological biomarkers.

The application of MRI in the differential diagnosis of AD

Vascular dementia (VD)

VD refers to dementia caused by brain damage caused by cerebrovascular disease, which is the second common dementia after AD. VD usually involves the frontal lobe, temporal lobe and limbic system, or the lesion damages enough brain tissue, it results in severe impairment of higher cognitive functions such as memory, attention, executive function and language. The disease usually requires long-term continuous treatment, usually active drug treatment, the patient with mild disease, the general prognosis is good, if patients with severe disease, the prognosis is poor. The clinical diagnosis of AD and VD is mainly based on neuropsychological test and medical history, which cannot fully show the morphology and changes of brain tissue, so it cannot be clearly distinguished. There is considerable overlap in the clinical symptoms and neuroimaging features of the two diseases, which makes distinguishing them challenging [31]. Accurate diagnosis of AD and VD is essential to determine the optimal treatment regimen for patients [32]. The clinical diagnosis of AD and VD is mainly based on neuropsychological test and history, which cannot fully show the morphological changes of brain tissue, so it cannot be clearly distinguished. Conventional diagnostic MRI biomarkers may have clinical applications in this area. Imaging biomarkers from SMRI will be an important first step in multimodal analysis [33]. The specific imaging features of AD were as follows: the clinical diagnosis of AD was symmetrical extensive brain atrophy, obvious atrophy of temporal lobe and parietal lobe, especially the volume atrophy of hippocampus, without infarction, while VD was characterized by infarction, the lesions of large vessels mainly occurred in frontal lobe and temporal lobe, and most of them were single. The lesions of small vessels mainly invaded bilateral basal ganglia, thalamus and paraventricular ganglia, and showed extensive white matter damage. This suggests that central nervous system

magnetic resonance imaging may differentiate between AD and VD based on changes in brain metabolism and hippocampal atrophy.

In the study by Zheng, H et al. [34] using brain structural volume features from SMRI, the authors achieved 84% accuracy in classifying AD and VD subjects using SVM; hippocampal volume was found to be the most important feature in differential diagnosis. He Huan et al. [35] studied the regional homogeneity (ReHo) and functional connectivity shown by fMRI in VD patients and found that the damage of frontal–subcortical circuit may be related to the damage of cognitive function. This study found that the REHO value of the VD group was lower than that of the control group, which further confirmed that the decreased striatal function may be related to the decreased learning and cognition of the rats The decrease of ReHo in the striatum of VD rats affected the signal transmission of dopamine, and then affected the cognitive function. Lee et al. [36] found that the REHO values of the right dorsolateral entorhinal cortex and the right neocortex in VD rats were significantly higher than those in the control group, suggesting that the dorsolateral entorhinal cortex is a key link in the water maze learning task, the increase of ReHo may be related to the poor learning ability of VD rats, and it is necessary to compensate for the lack of ability to encode spatial information by improving the function of lateral medial olfactory cortex The increase of ReHo in neocortex may also be a compensatory response. In conclusion, the local REHO values in VD rat model were different from those in the control group. The changes in bilateral striatum, right dorsolateral entorhinal cortex and right neocortex may be related to the decline of cognitive function.

Dementia with Lewy body (DLB)

DLB is a group of patients whose clinical and pathological features overlap between Parkinson's disease and Alzheimer's disease, and are characterized by fluctuating cognitive impairment, visual hallucinations, and Parkinson's syndrome, a neurodegenerative disease characterized by Lewy bodies (diffuse distribution of cortical and subcortical gray matter nuclei). Most scholars believe that the disease has constituted an independent disease, mostly seen in the elderly, men slightly more than women. DLB is the major neurodegenerative pathology affecting cognitive function in the elderly after AD. It begins after age 50 and accounts for 20% of dementia patients [37]. However, DLB is often misdiagnosed clinically because of its common clinical and pathological features with AD. This imaging feature of DLB on MRI is described in detail below.

The most prominent SMRI features of DLB are the midbrain involvement with atrophy of the cholinergic neurotransmitter system, the Meynert basal ganglia, and atrophy of the gray matter in the dorsal and central pons, suggesting an abnormality of the cholinergic neurotransmitter system in DLB, it may be related to the pathological properties of synaptophysin in DLB midbrain [38]. Blanc, F et al. [39] by SMRI, a visual analysis of patients with premorbid symptoms of AD and DLB showed that DLB had isolated atrophy of the anterior superior insula, whereas AD had atrophy of the hippocampus and insula. Nemoto K et al. [40] found that both DLB and AD patients had significant volume reductions in the temporal midpole and hippocampal regions, except that the area of reduction around these regions was more diffuse in AD patients than in DLB patients, that is, in comparison with AD patients, the atrophy of the middle temporal lobe and hippocampus was milder in DLB. Therefore, MRI can help us differentiate AD from DLB in clinic.

fMRI features of DLB: resting fMRI studies have demonstrated enhanced connectivity activity in the prewedge and attention-related brain regions, putamen to frontal lobe, and temporal to parietal lobe, whereas connectivity activity in the prefrontal and visual cortexes decreased in patients with DLB [41]. Using the parameters of color, face recognition and motion, task-based fMRI showed that the functional activity of the superior temporal gyrus was enhanced, and there was no significant difference in the activity of visual regions 1, 2 and 3 between the normal subjects and the normal subjects, however, functional activity is decreased in the higher visual cortex (v 5/middle temporal lobe), which is the main visual-motor response area [42]. These studies suggest that the higher cortical areas of the occipital lobe in DLB are involved, while the primary cortical function is preserved. Whether the visual hallucination and visual spatial impairment of DLB are related to the functional abnormality of the higher visual cortex remains to be verified by more research evidence.

In conclusion, the primary objective of MRI examination is to eliminate the possibility of brain lesions (brain tumors, bleeding sequelae) inducing DLB. And the presence of ischemic vasculopathy should not prevent the diagnosis of DLB, as these may be common. Focal atrophy does not explicitly guide the diagnosis of DLB, even though hippocampal atrophy is usually discrete or even absent, and insular atrophy may be of interest in patients with MCI [43].

Parkinson's disease dementia (PDD)

Parkinson's disease (PDD) is the most common neurodegenerative disease after AD, with an incidence of 1% in the elderly. In recent years, more and more attention has been paid to the non-motor symptoms related to Parkinson's disease, including cognitive impairment,

mental disorders, depression, autonomic dysfunction and sleep disorders. The literature reports that 20% −57% of the patients with Parkinson's disease have mild cognitive impairment within 3–5 years after diagnosis, which is mainly manifested as executive dysfunction and gradually develops into dementia, and there are other cognitive domain impairment, such as visuospatial disorders, language and memory disorders. Mild cognitive impairment is considered an effective early warning of cognitive decline to PDD [38]. With the aggravation of motor symptoms in Parkinson's disease (PDD), the deterioration of cognitive function often becomes a risk factor for psychiatric symptoms and leads to hospitalization. With the development of neuroimaging technology and the development of dementia drugs, the imaging diagnosis and treatment of PDD have been greatly improved in recent years, especially in MRI. This is reflected in the following.

Application in PDD with the development of MRI imaging technology, MRI imaging of gray matter and white matter is clear, which provides an important non-invasive means to observe cognitive dysfunction-related diseases. Beyer et al. [44] observed MRI data in patients with AD, DLB, and PDD and in normal older adults, with similar dementia severity in all dementia patients. It was found that the cortical atrophy of temporal, parietal and occipital lobes was more severe in DLB patients than in PDD patients. Compared with PDD, the gray matter of bilateral temporal lobe and amygdala in AD patients showed atrophy. Compared with DLB, the atrophy of temporal and frontal lobes was more obvious in AD Group. It is therefore suggested that cortical atrophy is more severe in DLB patients than in PDD despite similar dementia severity, suggesting that different mechanisms in the brain are involved in the development of both dementia syndromes. It is further supported that DLB and PDD are two distinct disease entities, more like two subtypes of Lewy body disease.

Hattori et al. [45] used diffusion tensor imaging (DTI) to observe the relationship between white matter damage and cognitive function of Parkinson's disease (PD) and DLB patients, and compared the changes of white matter, gray matter and cerebral perfusion. The results showed that the partial anisotropy (FA) in certain areas of the brain, especially in the white matter of the biparietal lobe, was significantly correlated with the Mini-mental State Examination (MMSE) in patients of PDD. In addition, patients with PDD and DLB had extensive gray matter atrophy. All patients had posterior hypoperfusion in the occipital and parietal lobes. This result suggests that white matter damage underlies PDD cognitive impairment, which is consistent with changes in brain function (hypoperfusion), first in white matter and second in gray matter atrophy.

The Lee et al. [46] study also selected 19 patients with probable PDD and 18 patients with probable DLB, who were analyzed on a voxel-based basis by means of standard neuropsychological tests and FA values determined on DTI. All patients had similar dementia severity and similar demographic characteristics. Results of DLB patients had lower visual recognition memory, semantic fluency and ideomotor behavior than PDD patients ($P < 0.05$). Compared with the control group, the FA values in bilateral frontal lobe, left temporal lobe and left parietal white matter were significantly decreased in PDD patients. The decrease in FA in DLB was similar to that in PDD, but the white matter abnormalities were more severe and extended to the bi-insular lobe, posterior cingulate gyrus, and bilateral vision-related regions. In direct comparison, FA values in DLB patients decreased significantly in posterior temporal lobe, posterior cingulate gyrus, and bilateral visual fibers extending to occipital lobe. Some scholars observed the FA value and mean diffusion rate of white matter in PDD patients and age-matched controls, and found that there were extensive white matter lesions in PDD patients, furthermore, white matter lesions in frontal lobe are associated with executive dysfunction.

Huntington's disease, HD

HD is an autosomal dominant Neurodegeneration, and HTT is the causative gene. HD causes extensive degeneration of neurons in the striatum. As the disease progresses, it gradually affects other parts of the brain, such as the frontal and temporal lobes, and when the patient dies, the brain loses 25 percent of its volume. The main clinical manifestations are dance-like movements, cognitive impairment and mental and behavioral abnormalities. A typical HD patient often begins with choreography, which, combined with a family history, can be easily identified in the early stages. However, some patients with atypical HD have the symptoms of unsteady walking, walking stiffness, slow movement and cognitive decline, and some patients do not have chorea for a long time, such patients are often misdiagnosed as leukodystrophy, hereditary ataxia, hereditary spastic paraplegia and so on. Genetic testing is important for identifying these patients. At present, there are no specific therapeutic drugs for HD, and new drugs are being developed continuously. In order to accurately evaluate the therapeutic effect of new drugs in clinical trials, it is very important to identify appropriate biomarkers. Compared with the low sensitivity of the clinical scale and the relatively invasive detection of protein in vivo, the imaging biomarkers found by MRI imaging data are more sensitive, convenient and safe. In HD patients, the cells are in a critical state for a period of time before their neurons

die. Symptoms and cognitive difficulties in HD patients reflect a decline in neuronal function rather than a loss of neuronal number. Thus, MRI is more sensitive than morphological studies to the early stages of the disease [47].The imaging features of HD on MRI are discussed in detail as follows.

Preferential atrophy and dysfunction of the striatum are the most prominent neuropathology in postmortem brain samples from Huntington's disease. Pérot JB, et al. [48] utilizing multimodal MRI schemes, a combination of anatomical, diffusion-weighted, gluCEST, and MT imaging confirmed that MRI-measured striatal atrophy is currently the best biomarker for disease progression in Huntington's disease carriers. However, although there is a good correlation between striatal atrophy and disease severity, atrophy provides only limited information about the pathogenesis of Huntington's disease, and it may be a long-term consequence of subtle biological changes that occurred many years before the macro changes occurred. In addition, volume changes may occur in several other brain structures simultaneously, such as cortical and subcortical areas and white matter (VM), which suggests that VM changes may be one of the early features of the disease; and may constitute a key biomarker, especially in the pre-symptomatic phase of the disease.

In summary, neuroimaging (such as MRI) can clearly show changes in the basal ganglia of the brain in HD patients, with atrophy of the striatum and cortex being the most common manifestation. Brain functional imaging is also helpful to improve our understanding of cognitive deficits in HD patients. Some functional imaging studies have shown a link between striatal dysfunction and cognitive performance, complementing structural changes in the brain.

The above applications of MRI in the diagnosis of AD are summarized in Table 1.

Research progress in MRI combined with other techniques for diagnosing AD

The value of synthetic MRI combined with three-dimensional arterial spin labeling (3D-ASL) in the diagnosis of Alzheimer's disease

With the development of MRI in recent years, synthetic magnetic resonance imaging (SynMRI) has provided new ideas for the diagnosis of AD. Synthetic MRI can obtain five quantitative relaxation images in one scan, including T1, T2, longitudinal relaxation rate (R1), transverse relaxation rate (R2) and PD, as well as eight contrast-weighted images, including proton density weighted image (PDWI) and short-time inversion recovery (STIR) image [49].These quantitative values can be post-processed and analyzed for the whole brain [50]0.3D-ASL is a non-invasive blood perfusion imaging technology that generates images by using magnetically labeled water molecules as endogenous tracers. It does not require the destruction of the blood–brain barrier and can stimulate microscopic changes in tissue blood perfusion and microvascular density [51].Synthetic MRI combined with 3D-ASL is a non-invasive technology for quantitative cerebral blood flow (CBF) and has been increasingly used in neuroscience research to evaluate. In ASL MRI, arterial blood is labeled with radiofrequency pulses near the imaging plane. After the labeled spins are perfused into the brain tissue, a perfusion-weighted MRI image is

Table 1 AD and related differential diagnosis

	Mainly involved parts	Main manifestations of MRI	Diagnostic indicators/auxiliary means
AD	Hippocampus	Symmetrical widespread cerebral atrophy, Significant atrophy of the temporal and parietal lobes, the hippocampus especially shrinks	Changes in blood flow and metabolic activity, and measurement of hippocampal atrophy volume
VD	Frontal lobe, temporal lobe, and limbic system	Large vessel lesions mainly occur in the frontal and temporal lobes, mostly single, while small vessel lesions mainly invade the basal ganglia, thalamus, and paraventricular ganglia on both sides, mainly manifested as extensive damage to the white matter	ReHo decreases
DLB	Midbrain	The midbrain is most affected, with atrophy of the cholinergic neurotransmitter system, the nucleus basalis of Meynert, and gray matter atrophy in the mid-dorsal pons, as well as cortical atrophy in the temporal, parietal, and occipital lobes	Measuring cortical thickness
PDD	Bifrontal lobes, left temporal lobe, and left parietal lobe	Extensive white matter lesions, with less atrophy in the bilateral frontal lobes, left temporal lobe, and left parietal cortex than in DLB	Decreased FA in the biparietal white matter, MMSE scores (visual recognition memory, semantic fluency, and ideomotor behavior were higher than those in DLB)
HD	Brain striatum	Preferential atrophy and dysfunction of the striatum, cortical and subcortical regions, and white matter volume changes	Genetic testing

obtained [52]. In summary, synthetic MRI combined with 3D-ASL can assess the severity of AD patients by comparing the differences in relaxation values and cerebral blood flow between AD patients and healthy controls, thereby achieving early detection, early intervention, and improving patients' quality of life and prognosis.

On the other hand, AD is the main cause of dementia. Dementia is characterized by a decline in cognitive thinking ability and independence, and the hippocampus plays a vital role in cognition and memory. It is also the first site affected by neurofibrillary tangles (NFTs). The newer synthetic MRI and 3D-ASL technologies can quantitatively measure T1, T2, PD values and CBF values of the bilateral hippocampus [53],providing an opportunity for early diagnosis of AD and evaluation of the severity of the disease. However, this inspection method also has certain limitations:1. arterial transit time may vary among subjects, especially for AD patients, causing potential inaccuracy of CBF measurement; 2.studies have found that vascular risk factors such as diabetes and hypertension can also affect experimental results [54]; 3. in addition, limitations associated with ASL technology must also be considered, including its sensitivity to transit time effects and relatively low spatial and temporal resolution [55].

Neurological imaging of olfactory function in patients with early AD

The key to the prevention and treatment of AD lies in early detection and early diagnosis, and olfactory dysfunction often occurs in the early stages of AD. Therefore, the rational use of olfactory function assessment methods to detect AD early and treat it is of great significance for delaying the progression of AD. Olfactory function evaluation can be carried out by studying the imaging technology indicators of the olfactory system to objectively evaluate the olfactory function [56, 57].

After olfactory stimulation, fMRI is used to detect the activation of olfactory centers at all levels, which can objectively evaluate olfactory function. SOBEL et al. [58] first found that when normal people are stimulated by olfaction, the primary olfactory cortex shows a transient signal enhancement after inhalation of gas, and then an adaptive response within 30 to 40 s. Wang et al. [59] studied AD patients and found that the fMRI signal of olfactory stimulation in the primary olfactory cortex of AD patients was reduced compared with the normal control group. This conclusion was further confirmed by VASA-VADA et al. [60], who found that the signal reduction was correlated with atrophy of the primary olfactory cortex of the brain [61]. In the fMRI test results, individual differences are often large, so it is currently difficult to give an exact range of changes to diagnose the difference between AD and normal. Some researchers believe that combining other types of imaging data and using data groups of different AD stages for analysis can better identify early AD [62].

Of course, olfactory function combined with MRI also has certain limitations, such as:1.several other neurodegenerative diseases, such as Lewy body dementia and Parkinson's disease, also exhibit odor identification dysfunction and cognitive impairment; 2. some of the AD patients were taking regular or irregular treatment with cholinesterase inhibitors, which may influence the results; 3. the study found that odor recognition dysfunction combined with odor threshold and discrimination can provide a deeper understanding of the relationship between AD and the olfactory spectrum [63].

In summary, the degree of olfactory dysfunction can predict the transition from mild cognitive impairment to AD and help predict AD at an early stage. In clinical primary prevention, the use of objective and effective olfactory detection methods may provide an opportunity for timely and targeted intervention measures to reduce the accompanying dementia incidence and public health burden.

MRI and clinical biomarkers of AD

AD is one of the most widespread neurodegenerative dementias. It is characterized by a progressive and irreversible loss of brain function, which adversely affects: (a) memory, (b) thinking, (c) language, (d) judgment, and (e) behavioral skills. Several neuroimaging techniques using MRI can also be used for neurological assessment. Gebre RK et al. [64] identified scenarios where plasma biomarkers were significantly better at predicting cognition and where their usefulness was lower through a set of experiments. Overall, plasma biomarkers' performance was in line with brain health and cardiovascular measures. Ismail, Leon, et al. [65] have linked MBI to lower amyloid beta 42/40 and Ghahremani et al. higher levels of phosphorylated tau-181. Cassidy et al. [66] also indicated a potential link between MBI and reduced integrity of the locus coeruleus. Gao G, et al. [67] have found that most glycoproteins are potential drug targets and biomarkers for disease diagnosis, and are closely related to Alzheimer's disease. This research will ultimately improve the sensitivity and specificity of glycoproteins for clinical disease detection through in-depth study of the glycan structure of glycoproteins.

Using MRI sequences, AD is associated with (a) microstructural changes with local tau protein load and local tissue atrophy; (b) ischemia and multicellular lesions; (c) hemorrhage; (d) edema; and (e) white matter changes primarily in the frontal lobes; and (f) demyelination and axonal loss (Fig. 2). Using MRI, it has been shown that cortical atrophy in AD is caused by loss of neurons in the

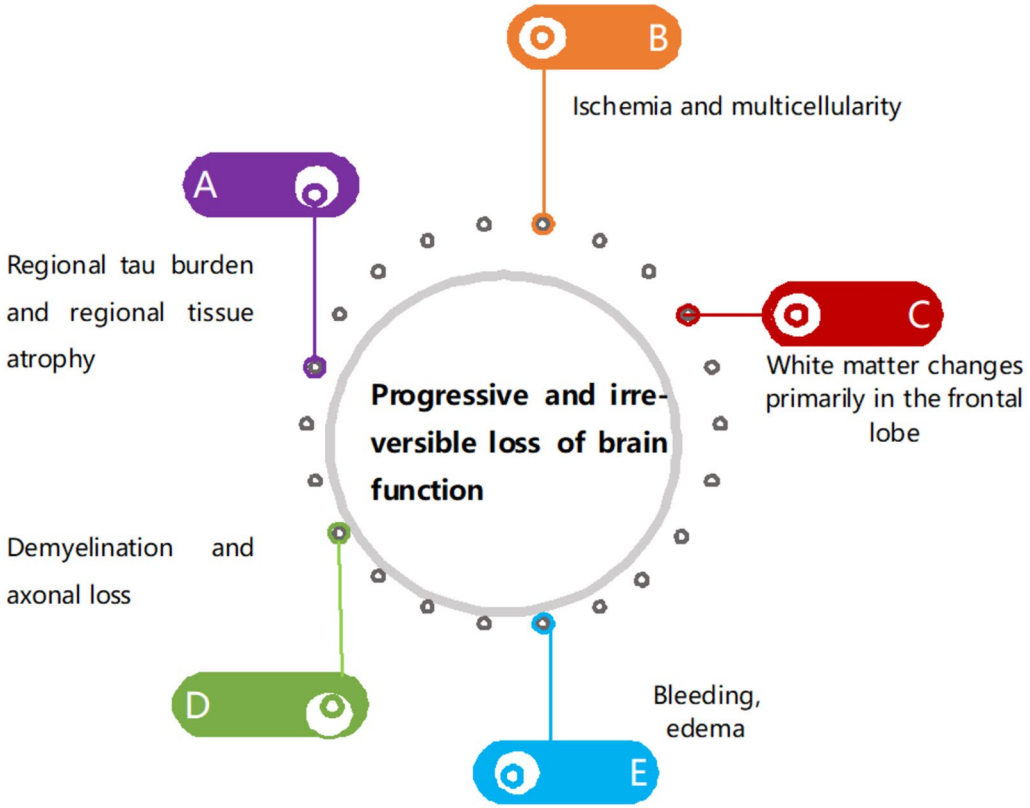

Fig. 2 Microstructural changes in AD

medial temporal and parietal lobes, spreading to limbic gray matter structures and finally to the frontal cortical regions, allowing the relationship between atrophic changes and neuronal loss to be studied, which is well established and correlates well with clinical variability [68]. Biomarker assays also have certain limitations. If biomarkers can be combined with histopathological diagnosis and Montreal Cognitive Assessment (MoCA), it may be more helpful in the diagnosis of AD patients. MoCA as the only measure of cognitive functioning without a more comprehensive cognitive assessment is a well validated screening tool with enhanced sensitivity to frontal lobe dysfunction [69].

MRI and optogenetics of AD

Studies have confirmed that optogenetics is of great significance in the diagnosis and treatment of patients with Alzheimer's disease. In 2016, Roy's team successfully restored memory in mice using optogenetics [70]. In the study, the researchers implanted light-sensitive proteins into the hippocampus of mice with memory loss. In response to light, memory cells in the hippocampus of the mice were activated. The next day, without light, the mice lost their memory again. Another study used optogenetics stimulation therapy to repair eciipn-ca1pv synaptic degeneration damage and effectively treat memory damage caused by Alzheimer's disease [71]. At the same time, an important research achievement in Alzheimer's disease is the treatment of cognitive dysfunction with near-infrared bioluminescence [72]. In summary, due to the minimally invasive nature and high precision of optogenetics, optogenetics has broad application prospects in clinical treatment. Many irreversible diseases, especially neurodegenerative changes, can be addressed through optogenetics. This provides new ideas for MRI combined with optogenetics in the diagnosis and treatment of Alzheimer's disease. But due to economic and other factors, optogenetics is mainly used in mouse experiments. There are few clinical trials of optogenetics. Therefore, it will take a long time to prove that optogenetics can be widely used in humans [73].

AD is a common disease of the elderly, and its incidence rate is gradually increasing every year with the aging of the population. The course of the disease is relatively slow, and the changes in the condition are relatively hidden, making diagnosis difficult and complex. With the continuous expansion of modern biological and medical testing capabilities and fields, magnetic

resonance diffusion tensor imaging technology has become a new technology in the field of magnetic resonance imaging research for diagnosing AD. It can be used to detect subtle changes in white matter nerve fiber bundles and identify microstructural changes in AD in the early stages, thereby enabling early identification, disease assessment, differential diagnosis and prediction of AD patients.

Currently, studies have proven hyperpolarization techniques significantly enhance the sensitivity of magnetic resonance (MR) and thus present fascinating new directions for research and applications with in vivo MR imaging and spectroscopy (MRI/S). Hyperpolarized 13C MRI/S, in particular, enables real-time noninvasive assessment of metabolic processes and holds great promise for a diverse range of clinical applications spanning fields like oncology, neurology, and cardiology, with a potential for improving early diagnosis of disease, patient stratification, and therapy response assessment. Despite its potential, technical challenges remain for achieving clinical translation. Perhaps combined with the already widely established and available MRI infrastructure, hyperpolarized MRI could be rapidly expanded to a wider range of uses. This will hopefully encourage larger-scale preclinical and clinical studies that are urgently needed to determine the usefulness of this tool and explore its full potential [74].

Over the past century, AD imaging diagnostic technology has been increasingly advanced. At the same time, the boundaries of science have been continuously extended to research fields such as synthetic MRI, olfaction, clinical biomarkers and optogenetics for diagnosing AD. Both old and new fields are bearing fruit. These new research technologies and applications provide more ideas and ways for humans to explore AD diagnostic methods. I believe that with the continuous innovation and application of modern medicine and bioengineering technology, medical workers in the future will be able to diagnose AD better and earlier, so as to achieve the ultimate goal of early prevention and early treatment of AD.

Author contributions
Guohua Zhao and Haixia Zhang wrote the draft. Yuzhen Xu and Xiuli Chu revised it.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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