Review

Application of modern neuroimaging technology in the diagnosis and study of Alzheimer's disease

https://doi.org/10.4103/1673-5374.286957

Received: January 23, 2020

Peer review started: February 14, 2020

Accepted: March 28, 2020

Published online: August 10, 2020

Hong-Mei Zeng[1, 2], Hua-Bo Han[3], Qi-Fang Zhang[4], Hua Bai[1, 2, 5, *]

Abstract

Neurological abnormalities identified via neuroimaging are common in patients with Alzheimer's disease. However, it is not yet possible to easily detect these abnormalities using head computed tomography in the early stages of the disease. In this review, we evaluated the ways in which modern imaging techniques such as positron emission computed tomography, single photon emission tomography, magnetic resonance spectrum imaging, structural magnetic resonance imaging, magnetic resonance diffusion tensor imaging, magnetic resonance perfusion weighted imaging, magnetic resonance sensitive weighted imaging, and functional magnetic resonance imaging have revealed specific changes not only in brain structure, but also in brain function in Alzheimer's disease patients. The reviewed literature indicated that decreased fluorodeoxyglucose metabolism in the temporal and parietal lobes of Alzheimer's disease patients is frequently observed via positron emission computed tomography. Furthermore, patients with Alzheimer's disease often show a decreased N-acetylaspartic acid/creatine ratio and an increased myoinositol/creatine ratio revealed via magnetic resonance imaging. Atrophy of the entorhinal cortex, hippocampus, and posterior cingulate gyrus can be detected early using structural magnetic resonance imaging. Magnetic resonance sensitive weighted imaging can show small bleeds and abnormal iron metabolism. Task-related functional magnetic resonance imaging can display brain function activity through cerebral blood oxygenation. Resting functional magnetic resonance imaging can display the functional connection between brain neural networks. These are helpful for the differential diagnosis and experimental study of Alzheimer's disease, and are valuable for exploring the pathogenesis of Alzheimer's disease.

Key Words: Alzheimer's disease; behavior; brain; cognitive impairment; fluorodeoxyglucose; memory; neurological function; structural magnetic resonance imaging; translocator protein

Introduction

Alzheimer's disease (AD) is a type of dementia characterized by progressive cognitive dysfunction and abnormal mental behavior. In the very early stage, patients with AD may only have abnormalities in nervous system function without abnormalities in brain structure (Bosco et al., 2017; Kamagata et al., 2020). In the middle and late stages, abnormalities in brain structure usually occur, but traditional neuroimaging techniques are insufficient for making specific diagnoses (Bakhta et al., 2019). Examination of AD patients using modern neuroimaging techniques, such as positron emission computed tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), structural magnetic resonance imaging (sMRI), magnetic resonance diffusion tensor imaging (MR-DTI), magnetic resonance perfusion weighted imaging (MR-PWI), susceptibility weighted imaging (SWI), and functional magnetic resonance imaging (fMRI), has not only revealed specific changes in brain structure, but also new findings regarding brain function (Dubois et al., 2018). In this article, we review valuable advances in the use of these new neuroimaging techniques in clinical or animal studies of AD.

Retrieval Strategy

We examined studies reporting on the use of neuroimaging technologies in the clinical diagnosis of AD and experimental AD studies published between 2008 and 2020. The following search terms were used for electronic retrieval of articles from the Medline database: imaging term (MeSH) AND (Alzheimer's disease, brain term (MeSH) OR nerve, term (MeSH)/clinical diagnosis OR experimental study term (MeSH)). The results were further screened by title and abstract to include only articles describing clinical diagnoses and basic research in patients with AD and mild cognitive impairment. Reviews were

[1]Department of Neurology, Third Affiliated Hospital of Guizhou Medical University, Duyun, Guizhou Province, China; [2]Department of Neurology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou Province, China; [3]Department of Radiology, Third Affiliated Hospital of Guizhou Medical University, Duyun, Guizhou Province, China; [4]Key Laboratory of Endemic and Ethnic Diseases of Ministry of Education, and Key Laboratory of Medical Molecular Biology, Guizhou Medical University, Guiyang, Guizhou Province, China; [5]Medical Experiment Center, Third Affiliated Hospital of Guizhou Medical University, Duyun, Guizhou Province, China

*__Correspondence to:__ Hua Bai, MD, PhD, 842031616@qq.com.

https://orcid.org/0000-0002-5617-0215 (Hua Bai)

Funding: *This work was supported by the Science and Technology Support Plan of Guizhou Province of China, No. QianKeHe-Zhicheng [2020]4Y129 (to HB); the Scientific Research Foundation of Guizhou Health Committee of China, No. gzwkj2017-1-022 (to HB); the Scientific Research Project of Guizhou Traditional Chinese Medicine Bureau of China, No. QZYY-2018-044 (to HB).*

How to cite this article: *Zeng HM, Han HB, Zhang QF, Bai H (2021) Application of modern neuroimaging technology in the diagnosis and study of Alzheimer's disease. Neural Regen Res 16(1):73-79.*

excluded.

In addition, electronic retrieval of articles from the Medline database was conducted to examine specific neuroimaging techniques used in the clinical diagnosis and study of AD. We included literature published prior to March 2020 with the following retrieval terms: PET, SPECT, MRS, sMRI, MR-DTI, MR-PWI, MR-SWI, and fMRI. To ensure that the articles concerned the diagnosis of AD and AD research, we included the following terms: local cerebral blood flow (rCBF), fluorodeoxyglucose (FDG), translocator protein (TSPO), N-acetyl aspartate (NAA), inositol, creatine, cerebral microbleeding, apparent diffusion coefficient, and low-frequency fluctuating signal.

Limitations of Traditional Neuroimaging Techniques in the Diagnosis of Alzheimer's Disease

Cranial X-ray examination, computed tomography (CT), and ordinary magnetic resonance imaging (MRI) are traditional neuroimaging techniques. Skull X-ray examination is of great diagnostic value for abnormal changes in bone tissue in the head. In particular, this technique can be used to evaluate the development and aging of the skull and ascertain the presence of bone hyperplasia, osteoporosis, degeneration, corrosion, damage, and calcification (Kim et al., 2020). However, abnormal changes in brain tissue and other central nervous tissue cannot be distinguished via head X-ray examination, and so this technique is of little value in the diagnosis of AD. Cranial CT scans usually show no abnormal findings in patients in the early stages of AD, while patients in the middle and advanced stages may exhibit white matter osteoporosis, cortical atrophy, widened sulci, ventricular dilatation, and cerebral atrophy (Bai et al., 2014; Kim et al., 2020). However, CT scans of the head cannot clearly distinguish hippocampal atrophy from mild cerebral atrophy, thus limiting the diagnostic value of this technique for assessing AD patients (Bai et al., 2014; Wong et al., 2020). Ordinary head MRI can be conducted using T1- or T2-weighted images. MRI scans conducted on the axial, sagittal, and coronal planes can enable clear distinction of gray matter from white matter. Using MRI, mild hippocampal atrophy can be clearly distinguished from medial temporal lobe atrophy. Furthermore, the size and volume of brain nuclei can be roughly determined, which is of certain value when using imaging to diagnose AD. However, the specificity and sensitivity of data obtained using head MRI are low with respect to the diagnosis of AD, and do not reveal much in terms of physiological and biochemical changes associated with AD (Preische et al., 2019).

Single-Photon Emission Computed Tomography and Positron Emission Computed Tomography in the Diagnosis of Alzheimer's Disease

SPECT and PET are both nuclear medicine imaging techniques. Both use radionuclide imaging to enable examination of brain function and metabolism, which is of great value for the early diagnosis of AD and clinical AD research (Chiba et al., 2019). SPECT combines radionuclide imaging with three-dimensional CT imaging to reveal radionuclide distribution and brain blood flow in different brain regions. The current conventional approach is to intravenously inject the single-photon radionuclide 99m technetium-biscysteine into the patient prior to scanning. Then, the SPECT detectors rotate rapidly around the longitudinal axis of the patient's head to receive photons emitted in multiple directions. Photons that contact the sodium iodide on the probe generate flash signals, which are detected. After electrochemical processing, optical signal conversion, and quantitative computational analyses, the reconstructed images can be used to judge rCBF and make predications regarding brain dysfunction (Walker, et al., 2016). The typical abnormality observed in AD patients is a symmetrical decrease in rCBF in both the temporal and parietal lobes. Rossini et al. (2019) proposed that cerebral blood perfusion detected by SPECT could be used to infer the progress of neurodegenerative disease. They found that compared with patients with mild cognitive impairment, patients with subjective cognitive impairment had lower rCBF in the left medial temporal region of the cerebral hemisphere and were more likely to develop AD. When examining the correlation between clock drawing task results and decreased rCBF revealed via SPECT in mild cognitive impairment patients, Duro et al. (2019) found a significantly positive correlation between total clock drawing task score and rCBF in the left temporal lobe or putamen nucleus. This suggests that there is likely to be a strong correlation between rCBF in key brain regions, revealed via SPECT, and clock drawing task score individuals with mild cognitive impairment or AD.

Common PET brain imaging techniques include glucose metabolism imaging, receptor transporter and neurotransmitter imaging, and cerebral perfusion imaging (Okazawa et al., 2020). The basic principle of PET imaging is the labeling of substances essential for human metabolism, such as glucose or nucleic acid, with short-lived positron emitting radionuclides (such as ^{18}F and ^{11}C) (Okazawa et al., 2020). The most commonly used substance is ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG). This is then injected intravenously into the body and circulates through the brain (Okazawa et al., 2020). PET system detectors are used to detect positron signals emitted from substances such as ^{18}F-FDG, and CT and image reconstruction are performed to analyze possible metabolic abnormalities and pathological sites in the local brain (Bosco et al., 2017). The commonly used imaging agents for PET are non-toxic and have minimal side effects, and PET is a non-invasive method (Doecke et al., 2020). PET is highly sensitive, capable of rapid imaging of human pathophysiological processes, and can measure the concentration of bioactive substances at very low levels in the tissues of interest (Doecke et al., 2020). PET can be used to quantitatively analyze a variety of physiological and pharmacological parameters *in vivo* and find dysfunction in local tissue before disease-induced structural changes occur (Doecke et al., 2020). **Table 1** summarizes the application of various neuroimaging techniques in the diagnosis and study of AD.

The differential diagnosis of dementia by PET appears to be more accurate and practical than other existing methods. Vascular dementia is typically characterized in PET studies by a decrease in the brain's multifocal, asymmetric metabolism of FDG. In PET, frontotemporal dementia usually manifests as decreased metabolism of FDG in the frontotemporal lobe. PET usually shows reduced FDG metabolism in one or both temporal and parietal lobes in AD patients (Deleye et al., 2017). Gordon et al. (2018) used PET to examine the metabolism of ^{11}C Pittsburgh compound B (^{11}C PIB) in 346 patients and that of ^{18}F-FDG in 352 patients. They found a significant decrease in the glucose metabolic rate, an increase in amyloid β protein (Aβ) deposition, and a thinning of the cerebral cortex in patients with autosomal dominant hereditary AD. Furthermore, the decrease in glucose metabolic rate appeared to have taken place about 19 years before the apparent onset of AD. At present, Aβ-PET imaging technology has been used to diagnose AD according to Aβ deposition in the brains of suspected AD patients, with high specificity and sensitivity. Nakamura et al. (2018) found that immunoprecipitation and mass spectrometry for the determination of high-performance plasma Aβ biomarkers were better synchronized in the diagnosis of AD than Aβ-PET imaging for the detection of Aβ deposits. Honig et al. conducted a phase 3 double-blind placebo controlled clinical trial in which participants in each group were examined by brain PET or tested for $A\beta_{1-42}$ protein in the cerebrospinal fluid.

Table 1 | **Application of various neuroimaging techniques in AD diagnosis**

	Type of examination	Content of examination	Main uses
Common neuroimaging techniques	CT, MRI, sMRI	Brain structure	sMRI used in the clinical diagnosis of AD
Imaging techniques related to nuclear medicine	SPECT, PET	Cerebral blood flow and functional metabolism of brain tissue	Early diagnosis and study of AD
fMRI in a narrow sense	Task-related fMRI and resting-state fMRI	Brain activity and neural network function	Clinical trials for AD
Other fMRI techniques	MRS, MR-DTI, MR-PWI, MR-SWI	Neurotransmitters, pathological changes, cerebral blood flow, and iron content	Diagnosis, differential diagnosis and study of AD

AD: Alzheimer's disease; CT: computed tomography; fMRI: functional magnetic resonance imaging; MR-DTI: magnetic resonance diffusion tensor imaging; MRI: magnetic resonance imaging; MR-PWI: magnetic resonance perfusion weighted imaging; MRS: magnetic resonance spectroscopy; MR-SWI: magnetic resonance susceptibility weighted imaging; PET: positron emission computed tomography; sMRI: structural magnetic resonance imaging; SPECT: single-photon emission computed tomography.

Patients with mild AD were randomly assigned to receive 400 mg of solanezumab intravenously every 4 weeks for 76 weeks. Analysis with the ADAS-cog14, which is an AD assessment scale, showed no improvement in cognitive function (Honig et al., 2018).

The TSPO is a protein located on the outer membrane of mitochondria, with a molecular weight of 18 kDa. Sridharan et al. (2017) showed that TSPO levels were proportional to the activation of microglia and astrocytes. After microglial activation, TSPO can polymerize to form multiple binding sites, and it is strongly associated with neuronal inflammation in the pathogenesis of AD (Sridharan et al., 2017). Several researchers have used TSPO-PET technology to study neuroinflammation, and were able to diagnose AD in the early stage. The TSPO-PET imaging tracers that have been developed or used are [^{11}C]PBR28, [^{18}F]DPPA-714, [^{18}F]-FEPPA, [^{11}C]DAA1106, [^{11}C]DPPA-713, and [^{18}F]GE-180 (Sridharan et al., 2017). Kreisl et al. used [^{11}C]PBR28 to study TSPO binding in individuals with AD, mild cognitive impairment, and in normal controls (Kreisl et al., 2013). Compared with those with mild cognitive impairment or the control group, tracer uptake was significantly increased in the prefrontal, lower parietal, temporal, and occipital cortical regions in the patients with AD, suggesting higher neurogenic inflammation in these regions. The authors concluded that TSPO binding may be a pathological feature of the transition from mild cognitive impairment to AD (Kreisl et al., 2013).

Yasuno et al. (2012) used the [^{11}C]DAA1106 tracer in individuals with AD, mild cognitive impairment, and in healthy subjects in a 5-year follow-up study with TSPO-PET imaging. They found that all of the mild cognitive impairment patients with dementia exhibited a significant increase in the corresponding intake of [^{11}C]DAA1106 compared with the control group. This suggests that the progression from mild cognitive impairment to AD requires the involvement of neuroinflammation, and supports the important role of neuroinflammation in the pathogenesis of AD, as well as the potential future role of TSPO-PET as a biomarker for AD progression. Further research is required to understand the biological significance of TSPO expression in glial cell phenotypes, although one study reported on the dangers of glial hyperplasia and its role in the pathogenesis of AD (Yasuno et al., 2012). Indeed, in the differential diagnosis of AD from other types of dementia, both SPECT and PET can be used together to analyze the structure and function of the brain.

Application of Magnetic Resonance Spectroscopy Imaging Technology in the Diagnosis and Study of Alzheimer's Disease

MRS is an imaging technique in which the magnetic resonance principle and chemical shift phenomena are used to develop and quantitatively analyze specific nuclei and related compounds. This technique has the advantages of high resolution, no bony artifacts, no ionizing radiation damage, multidirectional and multiparameter imaging, and the ability to display brain structures without the use of contrast agents (Chen et al., 2019). Owing to differences in chemical shifts, chemical compounds can be differentiated according to their differences on the MRS spectral peak line. In MRS, the area of the formant is proportional to the number of resonance nuclei, enabling observation of the concentration of the compound (Kreisl, et al., 2016). Furthermore, in MRS, there are five resonance spectrum peaks in the normal human brain: NAA, choline complex (Cho), myoinositol (MI), creatine (Cr), and glutamate. The NAA peak is the highest, and the corresponding NAA concentration in the normal brain is about 12 mM. A decrease in the NAA peak during MRS can be a sign of loss or damage to neurons in the brain. Cho is a precursor of acetylcholine and phosphatidylcholine. It can be a neurotransmitter or a component of cell membranes. Cho is strongly associated with cognitive function, ion transport, and transmitter metabolism. MI exists only in glial cells, and increases in glial damage areas. The concentration of Cr in gray matter is higher than that in white matter. It is a high-energy phosphate reserve substance converted by ATP/ADP, and Cr levels increase when energy metabolism declines *in vivo*, which can be a marker of cell integrity. Glutamate is an excitatory amino acid that increases during brain ischemia and hypoxia (Suzuki et al., 2019). The following schematic diagram summarizes the application of MRS imaging technology in the diagnosis and study of AD (**Figure 1**).

Variously, researchers believe that infarction, hemorrhage, tumor, degeneration, deformity, and brain infection can be diagnosed using MRS (Schneider 2017). Furthermore, many studies have found selective metabolic abnormalities in different brain regions in AD patients (Care et al., 2015; Zhang, et al., 2015). In the early stage of AD onset, when there is no significant abnormality in hippocampal volume, MRS can reveal spectral abnormalities. For instance, Care et al. (2015) reported that the NAA/Cr ratio decreased when the MI/Cr ratio increased. Furthermore, they found that this decreased NAA/Cr ratio in the hippocampus indicated a greater loss of nerve cells in this region, which could be an indicator of the progression from mild cognitive impairment to AD. Thus, they proposed that a MI/Cr ratio of 0.7 indicates probable AD. The increase of Cho during MRS is considered to signal the presence of senile plaques in the brain, but changes in Cho sometimes lack regularity (Zhang et al., 2015). Studies have shown that in addition to decreased NAA levels in the hippocampus, AD patients also exhibit decreased NAA levels in the posterior cingulate gyrus, anterior cingulate gyrus, and neocortex compared with controls (Zimny et al., 2011; Bateman et al., 2012). Furthermore, MI is significantly increased in the hippocampus, occipital lobe, parietal lobe, posterior cingulate cortex, and other brain regions in AD patients. Reduced NAA has been associated with decreased performance on specific cognitive tests, including delayed recall of words and delayed practice for learned word lists. These results are consistent with the progressive pathology of AD and the deterioration of neural function (Foy et al., 2011), and support the hypothesis that increased early neurocongestion and decreased neural function may contribute to the development of AD. Targosz-Gajniak et al. (2013) proposed that MI/Cr level could be used to predict the development of AD with high sensitivity and specificity, and that it could distinguish amnestic-mild cognitive

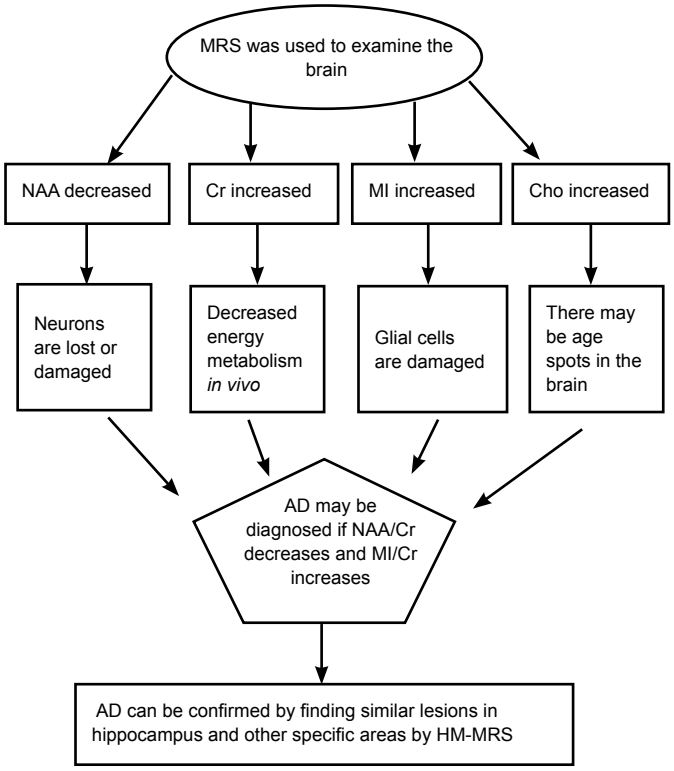

Figure 1 | **Application of MRS imaging in the diagnosis and study of AD.** Patients could be confirmed to have AD if NAA/Cr decreased and MI/Cr increased in the hippocampus, medial temporal lobe, posterior cingulate gyrus, and other parts of the brain according to high magnetic field MRS. AD: Alzheimer's disease; Cho: choline complex; Cr: creatine; HM-MRS: high magnetic field magnetic resonance spectroscopy; MI: myoinositol; MRS: magnetic resonance spectroscopy; NAA: N-acetyl aspartate.

impairment from non-amnestic-mild cognitive impairment. The role of NAA/Cr as a marker of neural functional integrity is supported by numerous studies reporting that reduced NAA/Cr is a feature of mild cognitive impairment and AD. The abnormal changes in the hippocampus and entorhinal cortex determined by MRS are strongly associated with the progression of AD, and these changes are consistent with the results of ordinary MRI and PET (Kantarci et al., 2007). Zhu et al. (2019) used MRS to measure NAA/Cr, Cho/Cr, and MI/Cr ratios in the left hippocampus and frontal lobe, and analyzed the genotype of apolipoprotein E using a high-resolution curve method. The results showed that an apolipoprotein E allele could predict MRS changes in the gene locus in AD patients, indicating that the combination of apolipoprotein E genotyping and MRS detection might have clinical value in the early diagnosis of AD.

In the clinical diagnosis of AD, the importance of biomarkers and brain imaging data is increasing. The recent use of high magnetic field (3.0 tesla and above) MRS significantly improved the signal-to-noise ratio and spectral resolution, thus making brain imaging data more reliable. Under a high magnetic field, all metabolites show greater dispersion, and so the peaks with similar chemical shift values can be more reliably quantized (Voevodskaya et al., 2016). Some metabolites that are not easily quantified at low magnetic fields can be quantified at high magnetic fields. These include glutamic acid, glutamine, p-aminobutyric acid, glutathione, glucose, taurine, and lactic acid (Voevodskaya et al., 2016). Glutamate is an excitatory neurotransmitter that can reflect the loss of glutamate neurons or decreases in synaptic function. Aminobutyric acid is an inhibitory neurotransmitter used to regulate the activity of neurons and astrocytes. Lactic acid is a product of anaerobic glycolytic metabolism and is usually detected in brain diseases under hypoxic conditions (Kantarci et al., 2009). A high magnetic field MRS study comparing the hippocampus and posterior cingulate gyrus of patients with AD and mild cognitive impairment showed significant decreases in NAA/Cr, MI/Cr, and MI/NAA in the hippocampus of AD patients. Furthermore, an increase in MI that occurred early in mild cognitive impairment patients could not be used to distinguish mild cognitive impairment from AD (Kantarci et al., 2009). The characteristic aggregation of extracellular amyloid plaques and intracellular neurofibrillary tangles usually begins in the entorhinal and medial temporal lobes and gradually spreads throughout the neocortex. Decreased NAA levels in the medial temporal lobe, posterior cingulate gyrus, and major cortical lobes may represent the strongest manifestation of MRS in AD patients, reflecting the loss of neurons and neurological dysfunction associated with the disease. A decrease in NAA and an increase in MI were observed prior to significant medial temporal lobe atrophy. Changes in multiple neurochemical substances in local brain regions evaluated using MRS are not limited to increases or decreases in measured values, but can be accurately quantified (Shen et al., 2018).

Data obtained using MRS may provide new links between neurobiochemistry and neuropathology. Further research is necessary to understand the pathological basis of MRS data, and translate the advantages of high magnetic field research into enhanced diagnostic decision-making. High magnetic field MRS is expected to reveal the metabolite profile of AD, and has significant advantages in improving the signal-to-noise ratio and spectral resolution, improving the reliability of quantization, and detecting a wide range of nerve metabolites. Because high magnetic field MRS revealed a decreased NAA/Cr ratio and increased MI/Cr ratio in the hippocampus, entorhinal cortex, medial temporal lobe, posterior cingulate gyrus, and other parts of the brain, these changes may represent strong evidence for a diagnosis of AD, and can be confirmed as AD via additional imaging.

Application of Other Magnetic Resonance Imaging Techniques in Alzheimer's Disease Diagnosis and Experimental Studies

While traditional imaging techniques have played a limited role in the diagnosis of AD, modern imaging technologies have become more dominant in the diagnosis of AD, and have additional functions as components of efficacy evaluations, prognosis judgments, and drug development. In addition to the SPECT, PET, and MRS methods introduced above, MRI-PWI, SWI, MR-DTI, fMRI, and sMRI are also used in the early diagnosis and experimental study of AD.

MR-PWI comprises two technologies: the dynamic susceptibility contrast technique and arterial spin labeling. Dynamic susceptibility contrast examination can be used to calculate relative cerebral blood flow volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time, which is of unique value for the diagnosis and study of cerebrovascular diseases, as well as the pathogenesis of AD. Eskildsen et al. (2017) used dynamic susceptibility contrast technology to study brain microcirculation in patients with AD and mild cognitive impairment. They found an increase in regions with relative temporal heterogeneity in AD patients with low perfusion and capillary transport, and a positive correlation between high-intensity relative temporal heterogeneity and white matter-related symptoms in AD patients. Furthermore, they reported that the lesion sites in AD patients involved the temporal lobe, parietal lobe, and frontal lobe. The arterial spin labeling technique marks the protons in the arteries with an inverted pulse. The marked protons diffuse into the blood and tissues, causing changes in the magnetization vector that are proportional to the amount of perfusion, allowing arterial spin labeling to quantify rCBV (Eskildsen et al., 2017). MRI usually shows a weakened signal in the parietal and temporal occipital

areas in AD patients, and the degree of decreased blood flow in the corresponding areas is associated with the severity of clinical symptoms. Furthermore, rCBV in the temporal and parietal lobes is decreased in AD patients, and the sensitivity and specificity of rCBV in distinguishing AD from controls are both about 90% (Zhang, 2016; Basselerie et al., 2017; Eskildsen et al., 2017). SWI is a type of three-dimensional imaging that utilizes the difference in magnetic sensitivity between different tissues to produce an image contrast. It is a contrast-enhanced MRI technology with a high signal-to-noise ratio and high resolution. It was originally called high-resolution oxygen-dependent venous imaging (Basselerie et al., 2017). The original images of two component pairs are obtained at the beginning of an SWI inspection to generate a magnetic distance diagram and a phase diagram. While conventional MRI produces a single magnetic distance map, SWI fuses the magnetic distance map with the phase map to form a unique image contrast. Then, a variety of image processing schemes are conducted with the data sets to generate a more positive magnetic moment diagram, a filtering phase diagram, a minimum signal projection conversion diagram, and finally a magnetically sensitive weighted imaging diagram (Basselerie et al., 2017). SWI is more sensitive than conventional gradient echo sequences to microhemorrhages, and is highly valuable in the diagnosis of cerebral hemorrhage, brain trauma, brain tumors, cerebrovascular malformations, and neurodegenerative diseases (Park et al., 2019). The relationship between cerebral microbleeding and AD is unclear. Basselerie et al. (2017) used MRI to evaluate SWI sequences, enabling the detection of CBM in individuals with AD, mild cognitive impairment, and elderly controls. They found that cerebral microbleeding was more common in the AD and mild cognitive impairment groups than in the control group. Thus, cerebral microbleeding could serve as a potential imaging marker for AD progression. Because the pathological changes associated with AD are not only related to abnormal iron deposition, but also may be positively correlated with the severity of dementia, brain iron content could facilitate the diagnosis of AD and assessments of the severity of AD. Previous studies have demonstrated that SWI imaging can also effectively detect iron deposition in the brain (Zhang, 2016; Basselerie et al., 2017). Furthermore, a linear relationship has been identified between the phase value of SWI and the content of iron in the brain (Park et al., 2019). The phase value of the left hippocampus was more evident than that of the right hippocampus in AD patients (Basselerie et al., 2017). When SWI was used to measure the iron content in the brain, deposition was significantly increased in AD patients (Park et al., 2019).

MR-DTI is a brain functional imaging technology developed on the basis of diffusion-weighted imaging. This technique can be effectively used to observe and track changes in white matter fibers, and is mainly used to examine white matter, track brain development, assess brain cognitive function, and characterize brain diseases. DTI can apply diffusion gradients in multiple linear directions, and can thus be used to quantitatively analyze diffusion differences of water molecules in different directions and to observe the microstructure and path of nerve fibers (Kantarci et al., 2017). Kuchtova et al. (2018) found abnormalities in the subcallosum and the parafrontal gyrus of AD patients using DTI. They hypothesized that this hippocampal atrophy was an adaptation to the loss of hippocampal projections through the cranial vault. In addition, patients with atypical AD show cortical atrophy via MRI, low metabolism via PET, and white matter degeneration via DTI. Several investigators assessed multimode neuroimaging data from atypical AD patients and found that Tau protein had a strong local negative correlation with FDG metabolism in the occipital and frontal lobes (Kuchtova et al., 2018). Tau proteins in the frontoparietal region were negatively correlated with the volume of the temporoparietal gray matter nucleus (Sintini et al., 2019). Some studies found that during the development of mild cognitive impairment to AD, the main pathological abnormalities in white matter fibers were demyelination, while DTI showed increased apparent diffusion coefficients and mean diffusivity, and decreased fractional anisotropy (Sintini et al., 2019; Spotomo et al., 2019). In AD patients, increased apparent diffusion coefficients were mainly found in the white matter of the hippocampus, temporal lobe, and parietal lobe, which is generally consistent with the pathological process of AD. Abnormal mean diffusivity and fractional anisotropy values reflected the neuropathological features of myelin loss, axonal damage, and oligodendrocyte reduction. Because the comprehensive analysis enabled by DTI can reveal the state of the white matter structure network, it can be used to indirectly evaluate intelligence and cognitive function (Spotomo et al., 2019).

While regular MRI scans can analyze abnormalities in brain structure at a three-dimensional level, sMRI scans measure the shape and structure of brain tissue, allowing detailed analyses and accurate calculations regarding the volume of various brain components. sMRI technology is divided into transverse measurements and longitudinal measurements (Cao et al., 2020). The longitudinal measurement method is divided into the boundary change integral method and the pixel measurement method. The pixel measurement method can be used to comprehensively and objectively analyze volume changes in different brain regions, and can describe the characteristics of local brain regions as well as differences in brain tissue composition. In patients with AD, sMRI usually first reveals atrophy of the entorhinal cortex, hippocampus, and posterior cingulate gyrus. An evidence-based medical analysis showed that atrophy of the frontal and parietal lobes was more significant in an AD group than in a mild cognitive impairment group, and that bilateral hippocampal volume decreased by about 24% in the AD group compared with the normal group (Cao et al., 2020). Gupta et al. (2019) proposed a machine-learning-based framework to distinguish patients with AD from those with mild cognitive impairment. The framework combines four different biomarkers: fluorescent FDG-PET, sMRI, cerebrospinal fluid protein levels, and apolipoprotein E genotyping. The researchers obtained four biomarkers from 158 subjects using the baseline data set from the AD neuroimaging program. For each image, 246 areas of interest were extracted using the Brainnetome template image and the NiftyReg toolkit. These characteristics were then combined with three cerebrospinal fluid proteins and two apolipoprotein E genotype characteristics obtained from the neuroimaging project website using early fusion techniques. The sMRI test was used as a biomarker for analysis.

'Generalized fMRI' usually refers to all MRI examinations except for ordinary MRI and sMRI. In a narrow sense, fMRI includes task-related fMRI and resting fMRI. Task-related fMRI mainly observes changes in brain activity, which are strongly associated with the blood oxygen level-dependent (BOLD) effect, also known as BOLD-fMRI. BOLD-fMRI is an imaging technique that uses changes in the ratio of oxygenated hemoglobin to deoxyhemoglobin in local blood in the brain activity region to modulate the T2-weighted imaging of local brain tissue, thus presenting the function of local brain tissue activity (Selkoe et al., 2019). BOLD-fMRI can be used to locate functional areas in the brain and differentiate dementia diagnoses. Both patients with mild cognitive impairment and AD have been found to have structural and functional abnormalities in the temporal lobe and hippocampus, which are strongly associated with apolipoprotein E allele abnormality (Teipel et al., 2015; Zhang, 2016; Selkoe et al., 2019). Resting fMRI is mainly used to check the function of the connection between neural networks, based on BOLD

resting-state brain function detection with a low-frequency fluctuating signal. The methods for analyzing the correlation connection include seed correlation analysis, independent component analysis, and small-world network model analysis. When resting fMRI was used to examine memory task activity in AD patients, the researchers not only observed decreased activation of the medial temporal lobe, but also inactive integration of the default network (Feis et al., 2019). Seed-correlation analysis indicated that the normal human brain has a solid functional connection between the middle and back nodes of the default network, while the functional connection in AD patients is severely damaged, especially the functional connection between the posterior cingulate gyrus and the hippocampus (Rijpma et al., 2018).

In addition, resting fMRI indicated a decrease in regional homogeneity in the posterior cingulate gyrus and anterior cuneiform lobe of AD patients, and an increase in regional homogeneity in the left fusiform gyrus and right lingual gyrus. These changes suggest that damage to neural networks in the brains of AD patients may be compensated for by other brain functions (Ossenkoppele et al., 2018). At present, experimental studies of AD mainly employ various types of fMRI examinations, especially studies on the pathogenesis of AD and evaluations of AD treatments. Thus, fMRI not only has clinical significance for the diagnosis and differential diagnosis of AD, but also has scientific value for research regarding the effects of therapeutic interventions and studies on the pathogenesis of AD. The detailed structure of the brain is strongly associated with the complex functions of the brain. The various modern neuroimaging techniques have advantages and disadvantages in the diagnosis and study of AD (**Table 2**).

Table 2 | **Comparison of advantages and disadvantages of modern neuroimaging technology in AD diagnoses**

	Test indicators	Technical features (advantages)	Technical shortcomings
SPECT	rCBF	Inferring brain function by analyzing cerebral blood flow	Indirect estimation of brain function
PET	^{18}F-FDG, ^{11}C-PiB, TSPO	Quantitative analysis of various metabolites, high sensitivity	High cost, developer required
MRS	NAA, Cho, MI, Cr, Glu	Display brain structure and function without developer	Poor specificity in diagnosis of AD
MR-PWI	rCBV, rCBF, MTT	High sensitivity for early diagnosis of cerebral infarction	AD exclusion only
MR-SWI	CMB, iron content	Show tiny bleeding and abnormal iron metabolism	Only for differential diagnosis of AD
MR-DTI	ADC, MD, FA	It is sensitive to leukoencephalopathy and cognitive abnormality and can be used to distinguish MCI and AD	No indication of cortical function
sMRI	Brain morphology and atrophy detected by BSI or VBM	Accurate judgment of brain atrophy and abnormal brain structure	Show structure only
Tr-fMRI	O-Hb, D-Hb	Display brain function through cerebral blood oxygenation	For scientific research, less clinical use
R-fMRI	LFFS, ReHo	Display functional connections between brain neural networks	For scientific research, less clinical use

^{11}C-PiB: ^{11}C Pittsburgh compound B; ^{18}F-FDG: ^{18}F-labeled fluorodeoxyglucose; AD: Alzheimer's disease; ADC: apparent diffusion coefficient; BSI: boundary shift integral; Cho: choline complex; CMB: cerebral microbleeding; Cr: creatine; D-Hb: deoxyhemoglobin; FA: fractional anisotropy; Glu: glutamate; LFFS: low-frequency fluctuating signal; MCI: mild cognitive impairment; MD: mean diffusivity; MI: myoinositol; MR-DTI: magnetic resonance diffusion tensor imaging; MR-PWI: magnetic resonance perfusion weighted imaging; MRS: magnetic resonance spectroscopy; MR-SWI: magnetic resonance susceptibility weighted imaging; MTT: mean transit time; NAA: N-acetyl aspartate; O-Hb: oxygenated hemoglobin; PET: positron emission computed tomography; rCBF: regional cerebral blood flow; rCBV: relative cerebral blood flow volume; ReHo: regional homogeneity; R-fMRI: resting functional magnetic resonance imaging; sMRI: structural magnetic resonance imaging; SPECT: single-photon emission computed tomography; Tr-fMRI: task-related functional magnetic resonance imaging; TSPO: translocator protein; VBM: voxel-based morphometry.

Conclusion

Modern imaging technology has improved the ease and accuracy of the detection of cognitive impairments and the differential diagnosis of AD. When examined using PET, AD patients often present decreased FDG metabolism in the temporal and parietal lobes, which can facilitate the differential diagnosis of AD from the perspective of nerve function. However, this kind of examination requires special developer, and the examination cost is relatively high. MRS tests, which do not require the use of a developer, can reveal both brain structure and function. AD can be diagnosed according to a decreased NAA/Cr ratio and increased MI/Cr ratio, especially in high magnetic field MRS. Atrophy of the entorhinal cortex, hippocampus, and posterior cingulate gyrus can be detected early by sMRI, which is of great value in imaging diagnoses of AD. It is an accurate measure of brain atrophy and structural abnormalities. MR-PWI is mainly used for the early diagnosis of cerebral infarction and exclusion of AD. MR-SWI can show microhemorrhages and abnormal iron metabolism, which is helpful for the differential diagnosis and experimental study of AD. Task-related fMRI can show functional brain activity through cerebral blood oxygenation, which is helpful for the diagnosis of AD and observation of the effects of therapeutic treatments. Resting fMRI can show the functional connections between neural networks in the brain, which is of certain value for studying the mechanisms of AD. Each of the above neuroimaging techniques has advantages and disadvantages, and should be used selectively according to the examination purpose. Different types of imaging anomalies associated with AD generally follow certain rules during the onset of AD. The detection of these anomalies can be used for both experimental studies and clinical diagnosis. Through clinical analysis and experimental exploration, expert consensus with evidence-based medical data will be more widely used in the diagnosis and study of AD.

Author contributions: *Literature retrieval and analysis: HMZ and HB; discussion and analysis: HB, HBH and QFZ; first draft of the manuscript: HB. All authors approved the final version of the paper.*
Conflicts of interest: *The authors declare that there are no conflicts of interest associated with this manuscript.*
Financial support: *This work was supported by the Science and Technology Support Plan of Guizhou Province of China, No. QianKeHe-Zhicheng [2020]4Y129 (to HB); the Scientific Research Foundation of Guizhou Health Committee of China, No. gzwkj2017-1-022 (to HB); the Scientific Research Project of Guizhou Traditional Chinese Medicine Bureau of China, No. QZYY-2018-044 (to HB). The funding sources had no role in study conception and design, data analysis or interpretation, paper writing or deciding to submit this paper for publication.*

Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewers: *Paulina Carriba, Cardiff University, UK; Stavros I. Dimitriadis, Cardiff University School of Psychology, UK.*
Additional file: *Open peer review reports 1 and 2.*

References

Bai H, Tan X, Li Q (2014) MRI and EEG characteristics of Alzheimer's disease and vascular dementia. Zhongguo Kangfu Lilun yu Shijian 20:1057-1059.

Bakhta K, Cecillon E, Lacombe E, Lamy M, Leboucher E, Philippe J (2019) Alzheimer's disease and neurodegenerative diseases in France. Lancet 394:466-467.

Basselerie H, Bracoud L, Zeestraten E, Bouguen E, Kiyasova V, Pueyo M, Cognard C, Dumas H, Gramada R, Ousset PJ, Vellas B, Bonneville F (2017) Incident cerebral microbleeds detected by susceptibility weight-imaging help to identify patients with mild cognitive impairment progressing to Alzheimer's Disease. J Alzheimers Dis 60:253-262.

Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367:795-804.

Bosco P, Redolfi A, Bocchetta M, Ferrari C, Mega A, Galluzzi S, Austin M, Chincarini A, Collins DL, Duchesne S, Maréchal B, Roche A, Sensi F, Wolz R, Alegret M, Assal F, Balasa M, Bastin C, Bougea A, Emek-Savaş DD, et al. (2017) The impact of automated hippocampal volumetry on diagnostic confidence in patients with suspected Alzheimer's disease: a European Alzheimer's disease consortium study. Alzheimers Dement 13:1013-1023.

Cao R, Wang X, Gao Y, Li T, Zhang H, Hussain W, Xie Y, Wang J, Wang B, Xiang J (2020) Abnormal anatomical rich-club organization and structural-functional coupling in mild cognitive impairment and alzheimer's disease. Front Neurol 11:53.

Carelli V, Musumeci O, Caporali L, Zanna C, La Morgia C, Del Dotto V, Porcelli AM, Rugolo M, Valentino ML, Lommarini L, Maresca A, Barboni P, Carbonelli M, Trombetta C, Valente EM, Patergnani S, Giorgi C, Pinton P, Rizzo G, Tonon C, et al. (2015) Syndromic parkinsonism and dementia associated with OPA1 missense mutations. Ann Neurol 78:21-38.

Chen Q, Boeve BF, Tosakulwong N, Lesnick T, Brushaber D, Dheel C, Fields J, Forsberg L, Gavrilova R, Gearhart D, Haley D, Gunter JL, Graff-Radford J, Jones D, Knopman D, Graff-Radford N, Kraft R, Lapid M, Rademaker R, Syrjanen J, et al. (2019) Frontal lobe 1H MR spectroscopy in asymptomatic and symptomatic MAPT mutation carriers. Neurology 93:e758-765.

Chiba Y, Fujishiro H, Iseki E, Kasanuki K, Sato K (2019) The cingulate island sign on FDG-PET vs. IMP-SPECT to assess mild cognitive impairment in Alzheimer's disease vs. dementia with lewy bodies. J Neuroimaging 29:712-720.

Deleye S, Waldron AM, Verhaeghe J, Bottelbergs A, Wyffels L, Van Broeck B, Langlois X, Schmidt M, Stroobants S, Staelens S (2017) Evaluation of small-animal PET outcome measures to detect disease modification induced by BACE inhibition in a transgenic mouse model of Alzheimer disease. J Nucl Med 58:1977-1983.

Doecke JD, Ward L, Burnham SC, Villemagne VL, Li QX, Collins S, Fowler CJ, Manuilova E, Widmann M, Rainey-Smith SR, Martins RN, Masters CL, AIBL Research Group (2020) Elecsys CSF biomarker immunoassays demonstrate concordance with amyloid-PET imaging. Alzheimers Res Ther 12:36.

Dubois B, Epelbaum S, Nyasse F, Bakardjian H, Gagliardi G, Uspenskaya O, Houot M, Lista S, Cacciamani F, Potier MC, Bertrand A, Lamari F, Benali H, Mangin JF, Colliot O, Genthon R, Habert MO, Hanpel H, INSIGHT-preAD study group (2018) Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. Lancet Neurol 17:335-346.

Duro D, Cerveira P, Santiago B, Cunha MJ, Pedroso de Lima JM, Botelho MA, Santan I (2019) Clock drawing test in mild cognitive impairment: correlation with cerebral perfusion in single-photon emission computed tomography. Neuropsychology 33: 617-632.

Eskildsen SF, Gyldensted L, Nagenthiraja K, Nielsen RB, Hansen MB, Dalby RB, Frandsen J, Rodell A, Gyldensted C, Jespersen SN, Lund TE, Mouridsen K, Brændgaard H, Østergaard L (2017) Increased cortical capillary transit time heterogeneity in Alzheimer's disease: a DSC-MRI perfusion study. Neurobiol Aging 50:107-118.

Feis RA, Bouts MJRJ, Dopper EGP, Filippini N, Heise V, Trachtenberg AJ, van Swieten JC, van Buchem MA, van der Grond J, Mackay CE, Rombouts SARB (2019) Multimodal MRI of grey matter, white matter, and functional connectivity in cognitively healthy mutation carriers at risk for frontotemporal dementia and Alzheimer's disease. BMC Neurol 19:343.

Foy CM, Daly EM, Glover A, O'Gorman R, Simmons A, Murphy DG, Lovestone S (2011) Hippocampal proton MR spectroscopy in early Alzheimer's disease and mild cognitive impairment. Brain Topogr 24:316-322.

Gordon BA, Blazeg TM, Su Y, Hari-Raj A, Dincer A, Flores S, Christensen J, McDade E, Wang G, Xiong C, Cairns NJ, Hassenstab J, Marcus DS, Fagan AM, Jack CR Jr, Hornbeck RC, Paumier KL, Ances BM, Berman AM, Cash BM, et al. (2018) Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. Lancet Neurol 17:241-250.

Gupta Y, Lama RK, Kwon GR, Alzheimer's Disease Neuroimaging Initiative (2019) Prediction and classification of Alzheimer's disease based on combined features from apolipoprotein-e genotype, cerebrospinal fluid, MR, and FDG-PET imaging biomarkers. Front Comput Neurosci 13:72.

Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ, et al. (2018) Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 378:321-330.

Kamagata K, Andica C, Hatano T, Ogawa T, Takeshige-Amano H, Ogaki K, Akashi T, Hagiwara A, Fujita S, Aoki S (2020) Advanced diffusion magnetic resonance imaging in patients with Alzheimer's and Parkinson's diseases. Neural Regen Res 15:1590-1600.

Kantarci K, Murray ME, Schwarz CG, Reid RI, Przybelski SA, Lesnick T, Zuk SM, Raman MR, Senjem ML, Gunter JL, Boeve BF, Knopman DS, Parisi JE, Petersen RC, Jack CR Jr, Dickson DW (2017) White-matter integrity on DTI and the pathologic staging of Alzheimer's disease. Neurobiol Aging 56:172-179.

Kantarci K, Weigand SD, Petersen RC, Boeve BF, Knopman DS, Gunter J, Reyes D, Shiung M, O'Brien PC, Smith GE, Ivnik RJ, Tangalos EG, Jack CR Jr (2007) Longitudinal 1H-MRS changes in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 28:1330-1339.

Kantarci K, Weigand SD, Przybelski SA, Shiung MM,Whitwell JK, Negash S, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr (2009) Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. Neurology 72:1519-1525.

Kim Y, Jiang X, Giancardo L, Pena D, Bukhbinder AS, Amran AY, Schulz PE, Alzheimer's DiseaseNeuroimaging Initiative (2020) multimodal phenotyping of Alzheimer's disease with longitudinal magnetic resonance imagingand cognitive function data. Sci Rep 26:5527.

Kreisl WC, Lyoo CH,Liow JS,Wei M, Snow J, Page E, Jenko KJ, Morse CL, Zoghbi SS, Pike VW, Turner RS, Innis RB (2016) C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging 44:53-61.

Kreisl WC, Lyoo CH, McGwier M, Snow J, Jenko KJ, Kimura N, Corona W, Morse CL, Zoghbi SS, Pike VW, McMahon FJ, Turner RS, Innis RB, Biomarkers Consortium PET Radioligand Project Team (2013) In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. Brain 136:2228-2238.

Kuchtova B, Wurst Z, Mrzilkova J, Lbrahim I, Tintera J, Bartos A, Musil V, Kieslich K, Zach P (2018) Compensatory shift of subcallosal area and paraterminal gyrus white matter parameters on DTI in patients with Alzheimer disease. Curr Alzheimer Res 15:590-599.

Nakamura A, Kaneko N, Villemaqne VL, Kato T, Doecke J, Doré V, Fowler C, Li QX, Martins R, Rowe C, Tomita T, Matsuzaki K, Ishii K, Ishii K, Arahata Y, Iwamoto S, Ito K, Tanaka K, Masters CL, Yanagisawa K (2018) High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 554:249-254.

Okazawa H, Ikawa M, Jung M, Maruyama R, Tsujikawa T, Mori T, Rahman MGM, Makino A, Kiyono Y, Kosaka H (2020) Multimodal analysis using [11C]PiB-PET/MRI for functional evaluation of patients with Alzheimer's disease. EJNMMI Res 10:30.

Ossenkoppele R, Rabinovici GD, Smith R, Cho H, Schöll M, Strandberg O, Palmqvist S, Mattsson N, Janelidze S, Santillo A, Ohlsson T, Jögi J, Tsai R, La Joie R, Kramer J, Boxer AL, Gorno-Tempini ML, Miller BL, Choi JY, Ryu YH, Lyoo CH, Hansson O (2018) Discriminative accuracy of [18F] flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. JAMA 320:1151-1162.

Park M, Moon Y, Han SH,Moon WJ (2019) Motor cortex hypointensity on susceptibility-weighted imaging: a potential imaging marker of iron accumulation in patients with cognitive impairment. Neuroradiology 61:675-683.

Preische O, Schultz SA, Apel A, Kuhle J, Kaeser SA, Barro C, Gräber S, Kuder-Buletta E, LaFougere C, Laske C, Vöglein J, Levin J, Masters CL, Martins R, Schofield PR, Rossor MN, Graff-Radford NR, Salloway S, Ghetti B, Ringman JM, et al. (2019) Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med 25:277-283.

Rijpma A, van der Graaf M, Meulenbroek O, Olde Rikkert MGM, Heerschap A (2018) Altered brain high-energy phosphate metabolism in mild Alzheimer's disease: a 3-dimensional 31P MR spectroscopic imaging study. Neuroimage Clin 18:254-261.

Rossini F, Zauner H, Bergmann J, Kronbichler M, Spindler I, Golaszewski S, Trinka E, Staffen W (2019) HMPAO-SPECT can discriminate between patients with subjective cognitive complaints with and without cognitive deficits and those with mild cognitive impairment. Curr Alzheimer Res 16:843-851.

Schneider L (2017) Alzheimer's disease and other dementias: update on research. Lancet Neurol 16:4-5.

Selkoe DJ (2019) Early network dysfunction in Alzheimer's disease. Science 365:540-541.

Shen Z, Lei J, Li X, Wang Z, Bao X, Wang R (2018) Multifaceted assessment of the APP/PS1 mouse model for Alzheimer's disease: applying MRS, DTI, and ASL. Brain Res 1698:114-120.

Sintini I, Schwarz CG, Martin PR, Graff-Radford J, Machulda MM, Senjem ML, Reid RI, Spychalla AJ, Drubach DA, Lowe VJ, Jack CR Jr, Josephs KA, Whitwell JL (2019) Regional multimodal relationships betweentau, hypometabolism, atrophy, and fractional anisotropy in atypical Alzheimer's disease. Hum Brain Mapp 40:1618-1631.

Spotorno N, Hall S, Irwin DJ, Rumetshofer T, Acosta-Cabronero J, Deik AF, Spindler MA, Lee EB, Trojanowski JQ, Van Westen D, Nilsson M, Grossman M, Nestor PJ, McMillan CT, Hansson O (2019) diffusion tensor MRI to distinguish progressive supranuclear palsy from α-synucleinopathies. Radiology 293:646-653.

Sridharan S, Lepelletier F. X, Trigg W, Banister S, Reekie T, Kassiou M, Gerhard A, Hinz R and Boutin H (2017) Comparative evaluation of three TSPO PET radiotracers in a LPS-induced model of mild neuroinflflammation in rats. Mol Imaging Biol 19:77-89.

Suzuki K, Suzuki S, Ishii Y, Fujita H, Matsubara T, Okamura M, Sakuramato H, Hirata K (2019) Serum insulin-like growth factor-1 levels in neurodegenerative diseases. Acta Neurol Scand 139:563-567.

Targosz-Gajniak MG, Siuda JS, Wicher MM, Banasik TJ, Bujak MA, Auqusciak-Duma AM, Opala G (2013) Magnetic resonance spectroscopy as a predictor of conversion of mild cognitive impairment to dementia. J Neurol Sci 335:58-63.

Teipel S, Drzezga A, Grothe MJ, Barthel H, Chetelat G, Schuff N, Skudlarski P, Cavedo E, Frisoni GB, Hoffmann W, Thyrian JR, Fox C, Minoshima S, Sabri O, Fellgiebel A (2015) Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection. Lancet Neurol 14:1037-1053.

Voevodskaya O, Sundgren PC, Strandberg O, Zetterberg H, Minthon L, Blennow K, Wahlund LO, Westman E, Hansson O, Swedish BioFINDER study group (2016) Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease. Neurology 86:1754-1761.

Walker Z, Moreno E, Thomas A, Inglis F, Tabet N, Stevens T, Whitfield T, Aarsland D, Rainer M, Padovani A, DaTSCAN DLB Phase 4 Study Group (2016) Evolution of clinical features in possible DLB depending on FP-CIT SPECT result. Neurology 87:1045-1051.

Wong D, Atiya S, Fogarty J, Montero-Odasso M, Pasternak SH, Brymer C, Borrie MJ, Bartha R(2020) Reduced hippocampal glutamate and posterior cingulate n-acetyl aspartate in mild cognitive impairment and Alzheimer's disease is associated with episodic memory performance and white matter integrity in the cingulum: a pilot study. J Alzheimers Dis 73:1385-1405.

Yasuno F, Kosaka J, Ota M, Higuchi M, Ito H, Fujimura Y, Nozaki S, Takahashi S, Mizukami K, Asada T, Suhara T (2012) Increased binding of peripheral benzodiazepine receptor in mild cognitive impairment dementia converters measured by positron emission tomography with [(11)C] DAA1106. Psychiatry Res 203:67-74.

Zhang B, Ferman TJ, Boeve BF, Smith GE, Maroney-Smith M, Spychalla AJ, Knopman DS, Jack CR Jr, Petersen RC, Kantarci K (2015) MRS in mild cognitive impairment: early differentiation of dementia with Lewy bodies and Alzheimer's disease. J Neuroimaging 25:269-274.

Zhang J (2016) How far is arterial spin labeling MRI from a clinical reality? Insights from arterial spin labeling comparative studies in Alzheimer's disease and other neurological disorders. J Magn Reson Imaging 43:1020-1045.

Zhu XQ, Zhou X, Zhao W, Zhang YM, Liu FJ, Cao J, Sun ZW (2019) Effect of apolipoprotein E genotype on MR spectrum of amnestic mild cognitive impairment and Alzheimer's disease. Zhonghua Yi Xue Za Zhi 99:1156-1161.

Zimny A, Szewczyk P, Trypka E, Wojtynska R, Noga L, Leszek J, Sasiadek M (2011) Multimodal imaging in diagnosis of Alzheimer's disease and amnestic mild cognitive impairment: value of magnetic resonance spectroscopy, perfusion, and diffusion tensor imaging of the posterior cingulate region. J Alzheimers Dis 27:591-601.

P-Reviewers: Carriba P, Dimitriadis SI; C-Editor: Zhao M; S-Editors: Wang J, Li CH; L-Editors: Koke S, Stow A, Qiu Y, Song LP; T-Editor: Jia Y