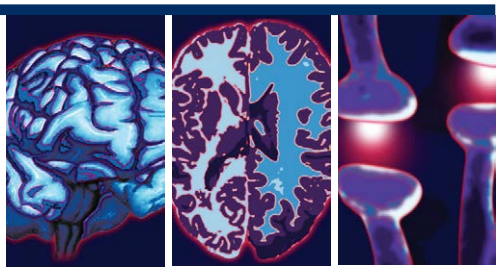
Review



Neuroimaging Advances in Preclinical Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is considered as a continuously pathological continuum. The AD pathophysiological process begins decades before the emergence of clinical symptoms. Recently, due to the advanced neuroimaging techniques and biochemical tests, various biomarkers are gradually identified, providing the ability to detect the evidence of AD pathology in the preclinical stage and further intervene the process of disease. Multimodal magnetic resonance imaging (MRI), with relatively non-invasive and economic benefits, is of great values to promote the clinical application. Therefore, researches involving brain structural and functional alterations in preclinical AD are summarized in this review.

Keywords

Alzheimer's disease, Preclinical, Magnetic resonance Imaging, Neuroimaging

Introduction

Alzheimer's disease (AD), characterized by progressive deficits in memory and other cognitive fields, has a long asymptomatic phase during which AD-related pathophysiological abnormalities, such as amyloid-β (Aβ) deposition, neurofibrillary tangles (NFTs) formation and proliferation of glial cells, have been apparent [1,2]. Given lack of effective treatments and failure of numerous clinical trials at the stage of dementia, the preclinical phase of AD may provide a crucial opportunity for postponing and even preventing the process of the disease.

Due to the absence of specific clinical phenotypes and a lower sensitivity of the current neuropsychological scales in identifying potential individuals in presymptomatic AD, the application of pathological biomarkers stemmed from cerebrospinal fluid (CSF) and positron emission tomography (PET) is of great importance to achieve accurate diagnosis *in vivo* before the appearance of AD clinical symptoms. Reduced levels of Aβ42 combined with raised concentrations of tau in CSF and alternative Aβ and tau deposition in brain detected by PET imaging would provide relatively objective information reflecting AD-related pathology [3,4]. However, the above-mentioned biomarkers have some defects in utility because of their invasiveness and radioactivity. Recently, the advances of multiple neuroimaging techniques, such as structural MRI (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI), have

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offered a promising prospect that allows non-invasively investigating abnormalities of brain structure and spontaneous functional activities in early AD [5]. Additionally, previous studies have investigated that AD is a disconnection syndrome with multiple etiologies and complex mechanisms [6,7]. Therefore, a system-level research based on brain anatomical and functional connectome is beneficial to gain an insight into the changes of whole-brain connectivities [8]. Here, we will introduce the conceptual framework of preclinical AD over the past decade. Then, we further elucidate specific neuroimaging properties in the presymptomatic stage of AD.

■ Criteria for preclinical AD

Dubois *et al.* initially proposed the definition of preclinical AD in 2007, which means a long asymptomatic phase from the appearance of brain pathophysiological changes to the onset of subtle clinical symptoms [9]. Individuals with the evidence of Alzheimer's pathologies have high likelihood to develop clinical AD. Subsequently, in 2010, the international working group (IWG) further distinguished two preclinical states of AD, including the presymptomatic state and the asymptomatic at risk state [10]. The term "presymptomatic state" is designated for carriers with an autosomal dominant monogenic AD mutation who will inevitably present AD clinical symptoms during their lifetime. Whereas, cognitively normal individuals with at least one biomarker reflecting pathophysiological features of AD only have the potential to trigger the characteristic clinical phenotype, which is implicated as individuals in asymptomatic at risk state. Additionally, in 2014, researchers further elaborated on the research diagnostic guide for preclinical AD in the revised IWG-2 criteria [4]. It is noteworthy that aforementioned criteria for preclinical AD require the absence of AD clinical symptoms.

Another *classification of preclinical AD* stages *aims at stratifying patients on the basis of multiple biomarkers. Based on the classic biomarker model initially proposed by* Jack *[11], National Institute on Aging-Alzheimer's Association (NIA-AA) has defined three different preclinical states: cognitively normal subjects with amyloidosis (stage 1), amyloidosis with evidence of neurodegeneration (stage 2), and amyloidosis, neurodegeneration and subtle cognitive decline (stage 3) [1]. This criterion emphasizes that tauopathy is a sign of "downstream" neurodegeneration and* Aβ deposition without the emergence of neurodegeneration is sufficient to make a definite diagnosis of AD. *In contrast, numerous studies have shown that* Aβ load is not in parallels with brain anatomic changes and dysfunction. Moreover, several postmortem studies have confirmed that some individuals with the evidence of Aβ deposition may not display cognitive decline before their death. *Therefore, the IWG-2 criteria have further highlighted the coexistence of decreased* Aβ and increased total-tau or phosphorylated-tau in CSF for confirming AD pathology [2].

Recently, the AD biomarker model has been gradually challenged [2,12]. Some researchers consider that this model is just suitable for familial AD, while sporadic AD may not abide by the time sequence of various biomarkers [13]. In order to portray the preclinical phase accurately, Dubois *et al.* redefined the concept of preclinical AD on the basis of the risk dichotomy to progress to clinical AD [2]. Current studies have indicated that the combination of amyloid and tau pathology may be most suitable in stratifying individuals with the highest risk of conversion to AD [14], while individuals exhibit an isolated brain amyloidopathy or tauopathy have relatively lower risk. Taken together, whatever the stage (preclinical, mild cognitive impairment or dementia), the co-occurrence of Aβ and tau could confirm the final diagnosis of AD.

■ Brain structural imaging

■ Structural MRI

Structural MRI, as a promising neuroimaging technique, has the potential to distinguish individuals with a high likelihood of conversion to AD, monitoring the disease progression and further evaluate the effectiveness of therapeutic intervention [15]. Brain structural abnormalities, characterized by local brain atrophy and disrupted global structural connectivity, have been previously shown in patients with AD. Using structural MRI, numerous studies have reported a significant volume reduction of the medial temporal region, parietal lobe, and posterior cingulate both in AD and MCI [15-17]. Current researches also validate the similarity of spatial distribution in structural changes occurring decades before the onset of AD symptoms [18-21]. The earliest preclinical changes appear to be the entorhinal cortex approximately 8-10 years prior to the clinical symptom onset, followed by the hippocampus and amygdala, indicating that the medial temporal lobe is likely to be the

earliest site attacked by Alzheimer's pathologies [22-24]. In support of this proposal, based on voxel-based morphometry (VBM) and shape analysis of MRI, Tondelli M *et al.* also confirmed the significant atrophy at baseline in the right medial temporal lobe for those individuals later diagnosed as AD [19]. It is inconsistent with findings in another study that local frontoparietal regions may be initially affected by emerging β-amyloid pathology while effects in the temporal cortex appear later [25]. These discrepancies of abnormal brain regions among different studies are partly explainable by different sample size and analysis strategies used. Additionally, brain structural changes may be affected by the interaction between amyloidosis and tauopathology. For instance, Fortea J *et al.* proposed that cortical atrophy only occurs in subjects with both Aβ (+) and phosphorylated-tau (+) [26]. Cognitively healthy individuals only with the evidence of amyloidosis have reduced atrophy rates in cortical thickness while those with decreased CSF Aβ values and raised CSF tau levels simultaneously present accelerated atrophy in medial temporal structures, depicting a biphasic trajectory of brain structural changes in preclinical AD [27].

Besides regional brain structural changes associated with worse cognitive performance in specific domains, discrete neuroanatomical networks have widespread interruption of information integration within and between brain regions. Currently, researchers have demonstrated the relationship between disruptions of gray matter network and AD-related pathology in cognitively normal adults. Tijms, *et al.* found that lower Aβ42 levels in the CSF could be linearly associated with lower connectivity density at whole brain level, nonlinearly with lower clustering and higher path length values, indicating a reduced efficiency of network organization in preclinical AD [28].

■ Diffusion tensor imaging

Diffusion MRI or DTI is another neuroimaging technique mirroring the white matter degradation [29]. Previous studies have manifested widespread white matter disruptions represented by decreased fractional anisotropy (FA), increased mean diffusivity (MD) and increased radial diffusivity (RD) in AD and MCI patients [30-32]. The existence of white matter microstructural changes has also been confirmed in the presymptomatic AD. Molinuevo *et al.* revealed that cognitively normal individuals with positive Aβ42 had increased axial diffusivity (A×D) in several white matter fiber tracts, such as corpus callosum, corona radiate, superior longitudinal fasciculus, etc., while other diffusion MRI indexes, including fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) have no differences [33]. This study demonstrated the subtle loss of axonal myelination with widely preserved white matter integrity in preclinical AD.

Converging evidences have shown that emerging amyloidosis alone is not sufficient to disrupt the brain structural connectivity, while individuals with the evidence of neurodegeneration are able to present alterations of the white matter connectome even without the amyloid pathology [34]. Furthermore, for individuals with both amyloid pathology and neurodegeneration (A+N+), abnormalities in structural network topology are more significant. Previous studies reported that MCI (A+N+) subjects exhibited distinct brain structural connectivity patterns which is in line with those alterations in patients with AD [35]. Similarly, employing DTI combined with graph theory, cognitively normal individuals with A+N+ showed obvious abnormalities in topological properties characterized by longer paths, lower efficiency, increased clustering and modularity compared with subjects only with neurodegenerative evidence [36]. We list changed brain structural patterns of preclinical AD in **Table 1**.

■ Brain functional imaging

Functional MRI (fMRI), one of the most common imaging techniques, allows to reveal brain functional activities based on the principle of blood oxygenation level dependent (BOLD) [37]. Task-related fMRI can reflect the activation of local brain regions when subjects execute special tasks and accept external stimulus, whereas resting-state fMRI indirectly mirrors neural activity via exploring spontaneously low-frequency amplitude at rest state. Accumulation of Aβ in the brain might bring about the synaptic dysfunction, leading to functional disconnection and abnormal information communication among multiple brain regions [38]. The progressive disruption in brain area connectivity contributes to subsequent cognitive decline, which is even prior to brain structural changes, such as neuronal apoptosis and atrophy [39,40].

■ Task-related functional MRI

Previous studies have investigated that patients

Table 1: Summary of brain structural changes for preclinical AD based on sMRI and DTI.

Study	Techniques	Subjects	Sample	Measures	During	Main results
Tondelli, et al. [19]	sMRI	CN[1]	148	Volume	10 years	1.Structural brain changes occur years before the onset of clinical symptoms; 2. Subjects later developing AD have significant atrophy at baseline in the right medial temporal lobe.
Pegueroles, et al. [27]	sMRI	CN	98	Cortical thickness	2 years	It is a biphasic trajectory of changes in brain structure in preclinical AD.
Soldan, et al. [24]	sMRI	CN	245	Volume, thickness	18 years	Not only baseline hippocampus but also entorhinal cortex measures are associated with the time to progress from normal cognition to cognitive impairment independently of cognitive reserve and ApoE-ε4 genotype.
Younes, et al. [22]	sMRI	CN	349	Volume, surface area	up to 18 years	During preclinical AD, changes in the shape of the entorhinal cortex precede those in the hippocampus and the amygdala.
Miller, et al. [20]	sMRI	CN	349	Volume, thickness	up to 17 years	1. Structural markers of the amygdala, hippocampus and entorhinal cortex are significantly different between controls and those with preclinical AD; 2. Entorhinal cortex is more affected in the early onset of the disease than the other structures
Miller, et al. [23]	sMRI	CN; preclinical AD; symptomatic AD	230; 50; 20	Volumes, surface area and thickness	up to 17 years	1. The earliest changes within the medial temporal is in entorhinal cortex; 2. There is selectivity of neurodegeneration in early AD.
Mattsson, et al. [25]	sMRI	CN; AD	47; 15	Volumes	4 year	Early Aβ pathology may have mild effects on local frontoparietal regions while effects in temporal regions appear later and accelerate.
Fortea, et al. [26]	sMRI	CN	145	Cortical thickness	/	Pathological cortical thickening is associated with low CSF Aβ, followed by atrophy once CSF p-tau becomes abnormal.
Schroeder, et al. [21]	sMRI	CN	69	Cortical thickness, volumes, shape, surface area	/	Localized shape measures (hippocampal) and cortical thickness (entorhinal cortical region) may be potential biomarkers of presymptomatic AD.
Tijms, et al. [28]	sMRI	CN	185	Degree, clustering coefficient, and path length	/	Lower Aβ42 levels can be related to the disruptions of gray matter networks and these relationships were specific to regions, such as medial temporal lobe, precuneus and the middle frontal gyrus.
Besson, et al. [18]	sMRI; FDG-PET	CN	54	Volume	/	1. MRI and FDG-PET biomarkers should be used in combination, offering an additive contribution; 2. Aβ and tau-related pathological processes may interact but not necessarily appear in a systematic sequence.
Jack, et al. [60]	sMRI; amyloid PET	CN	1246	Hippocampal volume	/	1.Memory loss and hippocampal atrophy occur at earlier ages than amyloid deposition; 2. Brain structural and cognitive decline are associated with aging but not Aβ deposition.
Pereira, et al. [36]	DTI	CN	357	Paths, efficiency, clustering, modularity	2 years	1. CN with neurodegeneration showed a disrupted network topology characterized by longer paths, lower efficiency, increased clustering and modularity; 2. CN with both amyloid pathology and neurodegeneration showed more significant abnormalities in all global network measures.
Molinuevo, et al. [33]	DTI	CN	19 (Aβ42+); 19 (Aβ42-)	Axial diffusivity (AxD)	/	Subtle axonal disruptions occurred in preclinical AD, whereas white matter integrity is still widely preserved.
Kantarci, et al. [34]	DTI	CN; MCI	570; 131	Fractional anisotropy (FA)	/	Amyloid load alone does not influence white matter integrity without coexistent gray matter neurodegeneration in preclinical AD.

[1]CN: cognitively normal;

"/" means: the study is not longitudinal.

with MCI had increased functional activities within medial temporal lobe in compensating for brain structural damages [41-43]. One latest research has also verified the consistent functional activation in hippocampus during the memory encoding task for amyloid-positive asymptomatic subjects [44]. Longitudinally, raised hippocampus activity at baseline is likely to promote Aβ accumulation in brain cortices, followed by further cognitive decline, indicating the close correlation between hippocampus functional activation and AD-related pathology [45]. Furthermore, entorhinal cortex, one of the key components in default mode network (DMN), exhibits pathological aggregation of tau earlier than that in hippocampus and may present the earliest functional alterations [46]. Currently, it has been demonstrated that hippocampal activations and entorhinal deactivations are modulated during an episodic memory task. Nevertheless, amyloid-positive older adults with normal cognition have reduced ability to modulate activity in entorhinal cortex, but not hippocampus, signifying that entorhinal cortex may be the first brain area attacked by Aβ among the DMN regions [46]. This is consistent with findings mentioned earlier via structural MRI. In addition, normally, frontotemporal network connectivity is increased with aging during an incidental episodic encoding task in compensating for the reduced regional activity, further maintaining the performance of episodic memory. However, for subjects with Aβ deposition, they display no changes of functional connectivity in frontotemporal network, but increased regional activities, which is not associated with cognition improvement [47]. From the above observations, Aβ deposition will affect neuronal activity when memory encoding task is executed.

Besides DMN, frontoparietal control regions, associated with cognitive control or working memory, also have the Aβ accumulation even in the elderly [48,49]. Oh *et al.* found hyperactivation in frontoparietal control regions during the process of working memory, suggesting that Aβ-related hyperactivation is not specific to the episodic memory system but occurs in frontoparietal control regions as well [48]. Furthermore, another study revealed that functional activity in frontoparietal control regions is related to the difficulty of tasks. For higher cognitive control load, Aβ-positive elderly showed reduced task-switching activation in the right inferior frontal cortex [49].

■ Resting-state functional MRI

Patients with AD have shown functional disconnection within DMN regions, such as decreased functional connectivity between precuneus and left hippocampus [50]. Recently, cognitively normal elderly with Aβ load have presented the changed functional connectivity between regions within the DMN before the appearance of cognitive decline and behavioral symptoms. Sheline *et al.* have confirmed that those with brain amyloid deposition have significantly reduced functional connectivity linking precuneus to hippocampus, parahippocampus, anterior cingulate, etc., but increased functional connectivity with visual cortex, which is in line with the changed functional patterns of AD patients [51]. These consequences offer sufficient evidences that Aβ toxicity can be detected early via resting state fMRI. Another study has revealed that Aβ deposition is closely related to the decreased functional connectivity of perihinal cortex in the medial temporal lobe, but has no relationship with cognitive impairment and brain atrophy, indicating that abnormalities of functional connectivity within medial temporal lobe may be the earliest biomarker of preclinical AD before the occurrence of brain structural changes [52]. The mechanism that DMN is specifically targeted by Aβ may be the hyperactivation of DMN regions. The primary components of DMN, including medial prefrontal cortex, posterior cingulate, precuneus, inferior parietal lobe, etc., have higher functional connectivity with other brain regions. These key brain regions, also called hubs, play a crucial role in integrating the global brain information process and their consistent neural activities may intrigue or accelerate the accumulation of Aβ [53-55]. Additionally, functional disconnection within DMN regions are associated with the level of Aβ. Compared with subjects who deposit less Aβ in the brain, cognitively normal adults with more Aβ deposition have significantly decreased functional connectivity [39].

Besides DMN, there are several other brain networks involving sensorimotor and complex cognitive function, such as dorsal attention network (DAN), frontoparietal control network (FPCN), salience network (SN), etc [56]. Changed functional connectivity within these brain networks have been confirmed, indicating that AD-related pathology not only disrupts DMN regions, but attacks other brain networks. Elman *et al.* found the decreased functional connectivity in the right FPCN and

DAN for Aβ-positive asymptomatic elderly, demonstrating that Aβ-related dysfunction involves in multiple brain networks [57]. However, functional connectivity is not limited within a special network. Relatively pivotal brain hub regions have built widespread functional connectivities with other networks for achieving effective information communication. Therefore, patients with AD present disruptions both in with-network local connectivity and between-network global connectivity, which is similar to the altered patterns in the preclinical stage of AD. Drzezga *et al.* also showed that cognitively normal adults had reduced functional connectivity between posterior cingulated/precuneus and global brain regions and simultaneously decreased metabolism in those regions, which is consistent with MCI patients with the evidence of Aβ deposition in the brain and further confirmed the relationship between changed functional connectivity and brain hypometabolism [58]. Based on the independent component analysis (ICA), an approach of extracting distributed sets of brain regions with correlated fluctuating activity, Elman *et al.* found the existence of functional connectivity among multiple brain networks affected by the level of Aβ in the brain [57]. Increased global Aβ contributed to the raised functional connectivity between the anterior PFCN and DMN regions, but decreased relationship between anterior-ventral SN and precuneus/DMN. Moreover, Aβ accumulation is also associated with the reduced network efficiency in the cerebrum-cerebellum system [58,59]. Finally, functional activities for preclinical AD are summarized in **Table 2**. We also clarify the relationship among each neuroimaging modality in **Figure 1**.

Future Directions

Recently, almost all of clinical trials involved in drugs targeting Aβ have ended up with failure. Due to the vast loss of neuron and widespread

Table 2: Summary of brain functional changes for preclinical AD based on Fmri.

Study	Techniques	Subjects	Sample	Task/Resting	Main results
Edelman, et al. [44]	fMRI	CN	21PIB (+); 23PIB (-)	Face-name memory-encoding task	Aβ deposition is associated with increased medial temporal lobe activation during memory encoding in preclinical AD.
Leal, et al. [45]	fMRI	CN	45	Memory task	Increased hippocampal activation is related to subsequent Aβ deposition and cognitive decline.
Huijbers, et al. [46]	fMRI	CN	79	Episodic memory task	Neocortical Aβ deposition is linked to neuronal dysfunction specifically in entorhinal cortex.
Oh & Jagust, [47]	fMRI	CN	36 elderly; 15 young subjects	Incidental episodic encoding task	Frontotemporal network connectivity during memory encoding is increased in aging without Aβ deposition in compensating for reduced regional activity, but disrupted by Aβ.
Oh, et al., [48]	fMRI	CN	57 elderly; 42 young subjects	Working memory (WM) task	Aβ-related hyperactivation is not specific to the episodic memory system but occurs in the frontoparietal control regions as well.
Oh, et al, [49]	fMRI	CN	62 elderly; 43 young subjects	Executive contextual task	Aβ deposition is associated with decreased right prefrontal activation during task switching.
Sheline, et al. [51]	fMRI	CN; AD	68; 35	Resting state	1. Aβ deposition disrupt resting state default mode network connectivity in preclinical AD; 2. Early manifestation of Aβ toxicity can be detected using resting state fMRI.
Song, et al. [52]	fMRI	CN	56	Resting state	1. Aβ load is related to disrupted intrinsic functional connectivity of the perirhinal cortex; 2. Dysfunction in the medial temporal lobe may represent a very early sign of preclinical AD and may predict future memory loss.
Hedden, et al. [39]	fMRI	CN	38	Resting state	*CN with high amyloid burden display significantly reduced functional correlations within the default network relative to CN with low amyloid burden.*
Elman, et al. [57]	fMRI	CN	92	Resting state	1. Besides DMN, changes of within-network functional connectivity occur in multiple networks; 2. Between-network functional connectivity changes are also apparent.
Drzezga, et al. [58]	fMRI; sMRI; FDG-PET	CN; MCI	24; 13	Resting state	Functional disconnection and hypometabolism display spatially overlap and may represent early functional changes involving Aβ deposition before the onset of AD clinical symptoms.
Steininger, et al. [59]	fMRI	CN	15	Resting state	Amyloidosis in CN will disrupt brain network efficiency within the cerebro-cerebellar system.

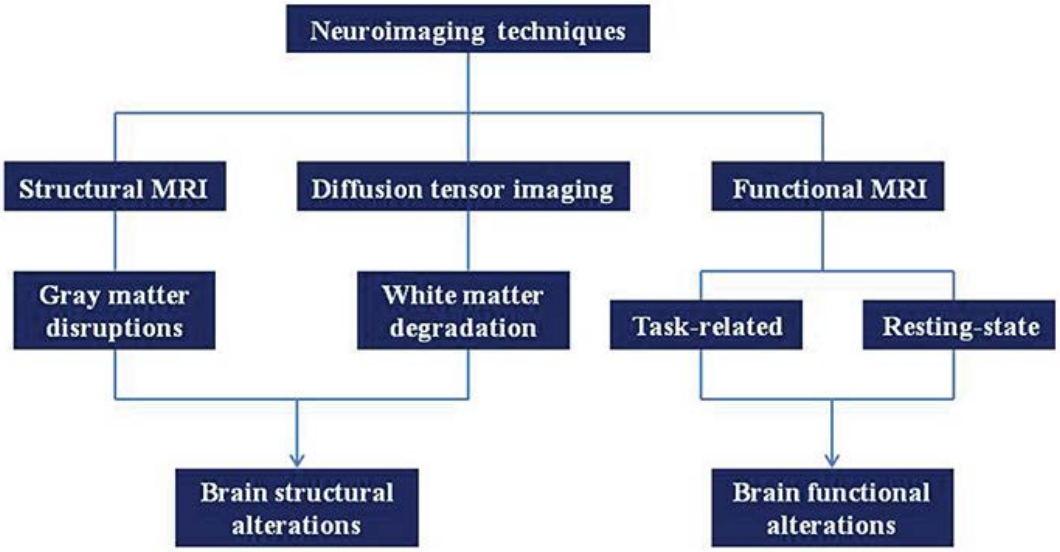

Figure 1: Neuroimaging Modality.

brain atrophy at the stage of dementia, therapeutic intervention focusing on patients with mild or moderate AD are less effective. Therefore, the proposition of term "preclinical AD" has a great potential to markedly prompt series of studies involving the secondary prevention of AD, further providing essential theoretical basis for achieving early diagnosis and preventing the process of AD. The long symptom-free phase of AD is also a crucial stage for fully understanding the brain information integration and the earliest neural alterations before cognitive decline.

At present, AD is regarded as a complex symptom with the interaction between characteristic genetic mutations and environmental changes. Multiple factors, such as age, sex, education, *ApoE* genotype, etc., would modulate the ultimate clinical profiles of AD [60,61]. In the future, the effects of those established risk factors (e.g. aging, low educational level, obesity) on memory, brain structure and Aβ load are supposed to be considered in preclinical AD studies. Additionally, the combination of various biomarkers derived from multimodal neuroimaging techniques and biochemical methods may contribute to identify high-risk individuals with great possibility of conversion to AD from those without clinical symptoms. Meanwhile, based on big data and machine learning methods, employing patterns of structural and functional information in classification is required to improve the diagnostic precision of AD in the asymptomatic stage.

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