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·Review·

Advances in longitudinal studies of amnestic mild cognitive impairment and Alzheimer's disease based on multi-modal MRI techniques

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Amnestic mild cognitive impairment (aMCI) is a prodromal stage of Alzheimer's disease (AD), and 75%–80% of aMCI patients finally develop AD. So, early identification of patients with aMCI or AD is of great significance for prevention and intervention. According to cross-sectional studies, it is known that the hippocampus, posterior cingulate cortex, and corpus callosum are key areas in studies based on structural MRI (sMRI), functional MRI (fMRI), and diffusion tensor imaging (DTI) respectively. Recently, longitudinal studies using each MRI modality have demonstrated that the neuroimaging abnormalities generally involve the posterior brain regions at the very beginning and then gradually affect the anterior areas during the progression of aMCI to AD. However, it is not known whether follow-up studies based on multi-modal neuroimaging techniques (e.g., sMRI, fMRI, and DTI) can help build effective MRI models that can be directly applied to the screening and diagnosis of aMCI and AD. Thus, in the future, large-scale multi-center follow-up studies are urgently needed, not only to build an MRI diagnostic model that can be used on a single person, but also to evaluate the variability and stability of the model in the general population. In this review, we present longitudinal studies using each MRI modality separately, and then discuss the future directions in this field.

Keywords: magnetic resonance imaging; amnestic mild cognitive impairment; Alzheimer's disease; multi-modality; longitudinal studies

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder in the elderly population; it has a high morbidity, and AD patients usually complain of memory impairment and serious decline of the abilities of daily living. There is still no effective therapy for AD in the late stages, and certain drugs are only effective in the early stages. Thus, in the very early stages of AD, it is important to determine the risk factors for conversion and determine which group of patients with aMCI will develop AD. MRI techniques have certain advantages, such as ready availability and high reliability, relatively fine spatial and temporal resolution, safety as noninvasive imaging tools that make multiple repeated scans available, and the possibility of early detection of abnormal structures and functions over the course of a longitudinal study. These characteristics make them valuable tools in research on AD-related imaging biomarkers. Here, we review follow-up studies of aMCI and AD using multi-modal MRI techniques, with the aim of providing a scientific basis for further investigations on neuroimaging diagnostic models. In the following sections, patients with aMCI or MCI who progressed to AD within a research program are referred to as aMCI-P or MCI-P, and those who did not convert to AD and remained stable during the entire observed clinical course are referred to as aMCI-S or MCI-S.

Longitudinal Studies of Structural Magnetic Resonance Imaging (sMRI)

sMRI was the first MRI technique applied in AD diagnostic research. Nowadays, gray-matter atrophy, white-matter lesions, and whole-brain atrophy are thought to be related to an early diagnosis of AD.

Studies on Gray-Matter Atrophy

The decline in temporal lobe volume of AD patients has been shown to predict incipient dementia six years prior to the emergence of clinical dementia[1]. The aMCI-P group showed gray-matter loss mainly in the bilateral medial and inferior temporal lobes, the temporoparietal neocortex, and the frontal lobes, compared to normal controls (NCs). When compared with the aMCI-S group, the aMCI-P group showed greater loss in the medial and inferior temporal lobes, the temporoparietal neocortex, posterior cingulate cortex (PCC), precuneus, anterior cingulate, and frontal lobes. These results demonstrated that the MRI patterns of atrophy at baseline have the ability to predict the subsequent clinical course in aMCI patients[2]. Further, gray-matter atrophy was most evident in the medial temporal lobes in the early stages of the disease. With the progression of memory decline, the regions of atrophy spread forward to the parietal, frontal, and lateral occipital cortex, followed by the anterior cingulate cortex[3].

Gray-matter loss in certain brain areas is relevant to the conversion of MCI to dementia, such as medial temporal lobe atrophy. In the process of conversion, using a standardized rating scale, visual assessment of medial temporal lobe atrophy on sMRI is an effective and independent biomarker in relatively young MCI patients[4]. This was further confirmed in a follow-up study by Prasad *et al.*[5]. At baseline, the clinical dementia rating scores correlated with the thickness of the temporal and parietal lobes. Compared to the MCI-S group, the MCI-P group showed significant thinning of the temporal and parietal cortex in prodromal AD; this predicted the progression to mild AD with a sensitivity of 83%[6]. Plant *et al.* considered the anterior cingulate gyrus and the orbitofrontal cortex as the most valuable regions for the prediction of MCI conversion to AD, and their data showed that the best prediction accuracy is 75%[7]. Other studies suggested that volume loss in the entorhinal cortex and hippocampus appear before the onset of dementia[8]. In an sMRI follow-up study by Killiany *et al.*, the entorhinal cortex, both sides of the superior temporal sulcus, and the anterior cingulate were selected as the predictors of conversion. And the results showed that the discrimination between the NC group and the MCI patients who did not progress to probable AD (the "questionables") was 85%, and between the “questionables” and “converters” was 75%[9].

Atrophy rates present the progression of AD from the perspective of development, while the degree of volume loss in a region is a result of dynamic changes in brain structures from NC to aMCI to AD. In the study of McDonald *et al.*, AD patients had greater atrophy rates in the medial, mediolateral, and superior temporal cortex, superior parietal lobe, and PCC[3], compared to both MCI and NC groups. Meanwhile, another follow-up study implied that the volume loss of the hippocampus is the most powerful predictor of conversion to AD in MCI patients. The hippocampal loss rate is the best biomarker to discriminate MCI from NC rather than volume atrophy of the hippocampus, and the rate of whole-brain atrophy discriminates AD from MCI[10]. In addition, the rate of hippocampal atrophy was greater in the MCI-P than in the MCI-S group, and was correlated with the Mini-Mental State Examination and Clinical Dementia Rating scores[11]. These findings suggest that hippocampal loss rates map well with cognitive decline in MCI, and therefore are predictors of progression[11].

Nowadays, researchers are trying to find more precise indicators for predictions and descriptions of the disease process by applying emerging evaluation indexes. Results from a 10-year longitudinal study proposed that, instead of the average rate of hippocampal atrophy, there is a higher risk of developing incident dementia per standard deviation with a faster rate of hippocampal volume reduction (left hippocampus equals to right), and this new marker can forecast dementia onset[12]. Most recently, Leung *et al.*[13] assessed the acceleration rates in NC, MCI, and AD participants, using sMRI data at 0, 6, 12, 18, 24, and 36 months. The results showed that MCI patients had an average acceleration of 0.22%/year^2 in hippocampal atrophy rates, and *post hoc* analysis suggested that MCI patients who converted to a clinical diagnosis of AD (MCI-P) within 3 years of baseline were the primary cause of the accelerated hippocampal loss (acceleration 0.50%/year^2, double the average)[13].

Abnormal sMRI changes also occur in other brain

regions. For example, the precuneus and parahippocampal gyrus, AD-vulnerable regions, in cognitively normal individuals with a maternal AD history had increased gray-matter volume loss, which may be relevant to an enhanced risk for developing AD[14]. In a large cohort study involving 511 participants, den Heijer *et al.* found that atrophy of the hippocampus and amygdala on sMRI in NCs was strongly associated with dementia within a 6-year follow-up, even in people without subjective memory complaints at the beginning of the study[15].

Because of the dynamics of gray-matter atrophy on sMRI, and its inconsistency with the clinical course, investigators have combined other measures with sMRI to comprehensively explain the research findings. By using neuropsychological rating scales to asses the changes in cognitive function of participants, Mungas *et al.* showed that the main determinant of memory decline is the volume of the hippocampus, whereas the decline of executive function is influenced by multiple factors such as hippocampal and cortical atrophy[16]. In addition, older age, greater hippocampal atrophy, and apolipoprotein E epsilon 4, which accelerate the subsequent atrophy rates of the hippocampus[17], together with brain glucose metabolism and hippocampal volume assessed by positron emission tomography (PET)[18], are all closely associated with MCI patients at high risk for AD and promise to be surrogate biological markers.

Studies on White-Matter Lesions

White-matter lesions on sMRI are very common in the elderly[19]. Lesions in nearly 30% of subjects worsened during a 5-year follow-up, and these changes were associated with worse cognitive performance[19]. A recently-published report confirmed that the incidence of white matter hyperintensity (WMH) is independent of cognitive decline, while an insidious and continuously-evolving WMH is significantly associated with episodic memory and executive malfunction, and has clinically-relevant cognitive consequences[20]. However, in a very early study, Garde *et al.* indicated that WMH is not the major factor of cognitive dysfunction in healthy octogenarians[21]. The selection of participants for sMRI research on white matter must be done cautiously, especially with regard to the age factor.

Previous studies have shown that punctuate lesions in the white matter are generally nonischemic enlarged perivascular spaces. But early confluent white-matter injuries become real ischemic infarctions with the progression of microvascular disease[22]. Further longitudinal research demonstrated that punctuate white matter lesions are not ischemic infarctions, are thus benign and do not progress, but early confluent white matter injuries are real ischemic infarctions, do progress, and are thus malignant[23]. Many investigators believe that MRI abnormalities due to small-vessel disease in the brain, such as lacunar infarction and WMH, are related to cognitive impairment[19, 24, 25]. Besides, they are associated with a higher risk of developing AD[24], and play an important role in predicting the likelihood of MCI conversion to AD[5].

However, there are also different views. A study in 2008 showed that WMH is only associated with the risk of individuals in the NC group who progress to MCI, but is irrelevant to the conversion of MCI to various types of dementia. Instead, the parenchymal infarctions in MCI patients were considered to be a predictor of conversion to AD[26]. DeCarli *et al.* demonstrated that the neuropsychological measures of memory and executive function at baseline are associated with the risk of developing dementia, while the apolipoprotein E genotype, cerebrovascular risk factors, stroke, lacunar infarctions, and extensive WMH do not predict the conversion of MCI patients[27]. This study suggested that the neuropsychological scales fully reflect the cognitive decline in MCI patients and forecast their conversion. However, DeCarli's study did not assess the influence of gray-matter atrophy, a key factor in predicting conversion, and therefore their results need further confirmation.

Studies on Whole-Brain Atrophy

A 6-year follow-up study showed that, compared with those in a cognitively-normal state, the baseline brain volume was 17% smaller in persons diagnosed with dementia within 2 to 3 years after MRI scanning and still 5% smaller in those who received a clinical diagnosis of dementia 6 years after scanning[15]. Ventricular expansion was faster in persons who eventually converted to MCI, and a more rapid expansion appeared 2 years prior to the onset of clinical symptoms[28]. Brain atrophy rates increase as aMCI progresses to AD. Younger participants usually had a greater atrophy rate than older ones with aMCI-S and aMCI-P[29]. These variations of preclinical atrophy rates imply that there are specific optimal time-windows for dementia prevention and interventional therapies. The key

point of treatment is the early detection and diagnosis of aMCI and AD.

Hippocampal volume loss, as well as whole-brain and ventricular atrophy rates, has been regarded as the major risk of progression in MCI patients. Given similar degrees of hippocampal atrophy, MCI patients with greater annual percentage changes in ventricular and whole-brain volume are at an increased risk of conversion to AD[30]. This view was further confirmed by Sluimer *et al.*[31], who demonstrated that AD patients had the highest whole-brain atrophy rates (−1.9% per year), and MCI patients (–1.2% per year) had higher whole-brain atrophy rates than patients with subjective complaints (–0.7% per year) and controls (–0.5% per year). Also, whole-brain atrophy rates were strongly associated with the annual change of Mini-Mental State Examination scores. In participants free of dementia, a greater whole-brain atrophy rate was associated with an enhanced risk of developing dementia[31]. In summary, whole-brain atrophy rates are deemed to be more powerful than brain volume loss at baseline in predicting cognitive impairment and conversion to AD[25, 32, 33].

The sMRI technique can be used in other aspects of whole-brain atrophy research. Antemortem sMRI deficits have a strong association with postmortem neurofibrillary tangles. For example, the rate of enlargement of ventricular volume can be used to monitor disease progression or indirectly assess the response to clinical treatments targeting neurofibrillary tangles and senile plaques[34]. The structural abnormality index (STAND) score developed from an algorithm by Vemuri *et al.*, accurately reflects the severity of neuropathology and may be potentially used as an independent marker for *in vivo* pathological staging and the early diagnosis of AD as well[35].

Longitudinal Studies with Functional MRI

The recently-developed fMRI technique is mainly used for studies of brain functions. It can be divided into two types, resting-state fMRI and task-based fMRI, depending on the state of participants during the scanns. fMRI further contributes to the presentation of dynamic changes in functional brain activity in follow-up studies. However, there are relatively fewer longitudinal studies of fMRI than sMRI.

Studies with Resting-state Functional MRI

In a recent study[36], AD patients showed decreased functional connectivity (FC) within the default mode network (DMN) in the precuneus and PCC compared with NCs, independent of gray-matter atrophy. The values of regional FC in individuals with MCI fell between those of the AD and NC groups. In addition, the reduced FC within the DMN was clinically relevant to cognitive dysfunction[36]. In another longitudinal study, aMCI patients generally presented a higher FC in the PCC/precuneus at baseline, but with progression of the disease, these connections decreased evidently at follow-up compared to NCs. Furthermore, abnormal FC in the PCC/precuneus of aMCI patients was positively associated with the dysfunction of episodic memory at both baseline and follow-up[37]. In addition, Wang *et al.* recently reported similar findings[38]. In their study, a lower FC between the PCC and other regions in the DMN was observed in MCI patients. After a 3-year follow-up, the superior and middle frontal gyri displayed further reductions in connectivity to the PCC in MCI patients, albeit with an enhanced FC to the PCC in medial prefrontal and anterior cingulate cortex. In addition, the PCC connectivity with some areas was markedly correlated with the Mini-Mental State Examination and California Verbal Learning Test scores. Based on the above findings, it was suggested that mechanisms of impairment and compensation exist simultaneously in the progression of MCI patients[38]. Some researchers believe that dysfunction in the DMN may help to diagnose and monitor progression in aMCI patients. Hippocampal subregions and the PCC are recognized as key factors in the decline of episodic memory in aMCI, and longitudinal changes of FC in these regions make it possible to distinguish aMCI-P from aMCI-S patients with a sensitivity of 83.3% and specificity of 83.3% (for NCs the sensitivity was 83.3% and the specificity was 91.7%). This implies that abnormal FC in hippocampal subregional networks make a difference in the early detection of AD and prediction of aMCI patients[39]. Damoiseaux *et al.*[40] revealed the dynamic changes of FC in the DMN by separately investigating the FC in three default mode subnetworks in different brain regions. Compared with NCs, AD patients at baseline showed decreased connectivity in the posterior DMN and increased connectivity in the anterior and ventral DMNs. At follow-up, FC decreased in all the three subnetworks in AD patients[40].

While the above studies were all focused on FC in the DMN, Bai *et al.* studied the functional changes in the

cerebellum of individuals with aMCI. They demonstrated higher values for the amplitude of low-frequency fluctuation in the posterior cerebellar lobe in aMCI patients compared with NCs, while in the follow-up study, there was a greater reduction of FC to the posterior cerebellar lobe in aMCI patients. These results suggest that, compared with regional activity measures in aMCI patients, the FC of the cerebellum may be a more sensitive marker of functional disturbance. While the cerebellum is partly relevant to the mechanisms of aMCI, further studies are needed to reach a more precise and comprehensive conclusion[41].

Studies of Task-based Functional MRI

In the progression of MCI to AD, changes of brain function have been observed. Longitudinal research with the fMRI technique may provide a reliable physiological imaging biomarker of brain activation over time, and is useful for identifying the MCI individuals at highest risk of conversion. Vannini *et al.*[42] detected altered brain functions before the onset of clinical symptoms in the MCI-P group. Compared with relatively stable MCI patients and NCs, the patients in the MCI-P group displayed increased parietal activation, which could reflect neuronal deficits due to accumulating AD pathology and may serve as a biomarker for predicting cognitive decline in patients with MCI[42]. Other studies found that the hippocampus is the only region associated with cognitive dysfunction, and is the key point in identifying MCI patients with a higher risk for AD[43]. O'Brien *et al.*[44] found that the participants who were normal at baseline but whose Clinical Dementia Rating declined faster over the 2-year follow-up showed the highest memory-task-correlated hippocampal activation at baseline and the greatest reduction of hippocampal activation at 2-year follow-up[43, 44].

Studies on deactivation in the DMN demonstrated that the anterior frontal lobes, precuneus, and PCC are the main regions involved. AD patients usually had the lowest deactivation, followed by MCI patients with less deactivation than NCs. Some longitudinal studies proposed deactivation in the posteromedial cortex as an indicator for detecting MCI patients at greatest risk of AD[45, 46]. By using goodness-of-fit (GOF) indices of DMN expression (obtained by comparing DMN connectivity maps with a template DMN map constructed from NCs), Petrella *et al.*[47] found that the baseline GOF indices were associated with changes of the Clinical Dementia Rating scores in the entire course of follow-up. GOF indices were shown to be effective in distinguishing MCI patients who converted to AD during a 2- to 3-year follow-up period; the indices were highest in NC, then MCI, and lowest in AD[47].

These findings from fMRI studies are consistent with the view that MCI is a transitional stage between NC and clinical AD. And the altered functional changes in the DMN may be important and potential early biomarkers in the diagnosis and prediction of MCI.

Longitudinal Studies with Diffusion Tensor Imaging

Fractional anisotropy (FA) and mean diffusivity (MD) are the primary indices of DTI to determine the integrity and lesions of white-matter tracts. White-matter injuries generally appear as decreased FA values and increased MD values. The histological information gained by DTI *in vivo* may help monitor disease progression and explore the pathogenesis of cognitive dysfunction[48].

Scola *et al.* proposed a notion that there are subtle brain diffusivity changes in prodromal AD, predominantly in the posterior parts of the brain, and these gradually spread towards the anterior portions over the course of the disease, finally involving the frontal lobe. The severity of microstructure injuries within and beyond the medial temporal lobe in aMCI subjects is correlated with a rapid conversion to AD[49]. A recent study by Teipel *et al.*[50] suggested that microstructural changes in subcortical fiber tracts are not only related to aging but also to neurodegeneration in the early stages of AD. In that study, it was found that FA reductions occurred in the corpus callosum, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and cingulate bundle in NCs in 13–16 months of follow-up, while MCI patients showed significantly decreased FA in the anterior corpus callosum. These changes matched the pattern of gray and white matter atrophy involving the prefrontal, cingulate, and parietal lobes[50]. Further follow-up studies showed that FA and radial diffusivity changes in the fornix, corpus callosum, and cingulum led to early identification of MCI patients who progressed to AD in a relatively short time[51]. Nowrangi *et al.* analyzed DTI data (i.e. FA and MD) and clinical assessments at baseline and at 3, 6, and 12 months in three groups (NC, MCI, and AD).

Compared with MCI or NC, AD patients showed increased MD values and decreased FA values in the fornix and splenium. Longitudinal results suggested that MD changes within groups were more evident than FA changes: in both the MCI and AD groups, MD values increased in the inferior and anterior cingulum and the fornix. Therefore, they concluded that MD is a better predictor of change than FA, and more importantly, evident increases of fornix MD in MCI patients imply an early progression of AD[52]. A previous follow-up study using sMRI and DTI measured hippocampal MD and volumes in aMCI subjects. The aMCI-P group had a slightly increased left hippocampal MD at baseline compared with the aMCI-S group, while their hippocampal volumes and cognitive examinations did not differ. This result suggested that longitudinal hippocampal diffusivity is superior to hippocampal volume for the prediction of progression to AD in aMCI patients during a 1–2-year period[53]. A relatively short-term (3 months) longitudinal study confirmed Fellgiebel's conclusion. In this study, researchers observed changes in the DTI indices when there were no differences in clinical cognitive function and sMRI. Compared to NCs, AD patients had a decreased FA at baseline and after 3 months in the fornix and anterior portion of the cingulum. AD patients had a lower FA than MCI patients in these regions and the splenium at 0 and 3 months. And a lower FA in the fornix and anterior cingulum corresponded to poorer cognitive performance. The fornix, a primary outflow tract of the hippocampus, could be a key indicator of aMCI progression[54]. Through a 2-year follow-up, Charlton *et al.* also regarded DTI as a better technique than sMRI; it is more sensitive to age-related white-matter changes even over short time periods[55]. But in another longitudinal investigation lasting for 2.5 years[56], researchers found that sMRI and DTI are both powerful in predicting the progression and transition from aMCI to AD. Fornix FA and MD and hippocampal volumes were all very good predictors of conversion with accuracy >90%[56]. These findings need further confirmation in a larger study[56].

Perspectives

The Alzheimer's Disease Neuroimaging Initiative (ANDI), carried out in 2004, was aimed at searching for more suitable biomarkers in predicting the clinical development of AD by combining various techniques, such as MRI, PET, and cerebrospinal fluid (CSF) examinations. Research from the ADNI database demonstrated that MRI is superior to CSF biomarkers in tracking the stages of clinical disease and predicting future decline[57-60]. Other studies from different databases also reached similar conclusions, confirming that MRI is a better indicator of early AD and predictor of MCI progression than metabolic abnormalities[61], PET[62], and CSF biomarkers[63]. MRI has been widely used in both clinical and scientific studies with high security, good stability, and easy patient acceptance. Advances in this field would surely promote the development of multi-modal MRI techniques in different diseases of different systems.

However, many technical problems of MRI still exist, especially in its routine application in clinical aMCI and AD screening, diagnosis, and prediction of outcome. These problems include a lack of standardized MRI acquisition methods, spatial distortions of MRI data, relatively labor-intensive MRI data analysis that is prone to interoperator variability, and a lack of normal ranges for MRI measures[64], which have a poor effect on the early detection of disease and outcome prediction. We have reason to believe that progress in MRI-relevant biomarkers from longitudinal multi-center studies, such as the ADNI, could help to address the above-mentioned critical challenges. Standardized image acquisition and analysis processes could also be set up, and the results from these large-scale follow-up studies could be more comparable and more easily generalized.

So far, there have been no MRI models that can be applied directly to the clinical screening and diagnosis of aMCI and AD. Investigators have found the key roles of some critical brain regions (e.g. the hippocampus and prefrontal lobes) in memory impairment. Future studies should be conducted to integrate various modalities such as sMRI, fMRI, and PET to provide more accurate and comprehensive information for the early diagnosis of AD[65], and by doing so to elevate the reliability and validity of diagnosis[66, 67]. We will fully understand the structural and functional changes of brain disorders and disease, assisted by imaging functional networks and other new techniques, to find more appropriate methods for the clinical application of MRI technology. Currently, MRI techniques have provided objective and powerful evidence for identifying aMCI converters in the prodromal stages of AD and assistance

in early intervention and treatment of diagnosed patients. With further studies and development of technology, these neuroimaging biomarkers will eventually be confirmed and applied clinically for the benefit of mankind.

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