REVIEW

Neuropsychological and Neuroimaging Characteristics of Amnestic Mild Cognitive Impairment Subtypes: A Selective Overview

Xin Li^{1,2} & Zhan-Jun Zhang^{1,2}

1 State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China

2 BABRI Centre, Beijing Normal University, Beijing, China

Keywords

Alzheimer's disease; Amnestic mild cognitive impairment; Amyloid PET; fMRI; Morphology.

Correspondence

Zhanjun Zhang, MD, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China.

Tel.: +86-10-58802005;

Fax: +86-10-58802005;

E-mail: zhang_rzs@bnu.edu.cn

Received 30 December 2014; revision 17

February 2015; accepted 17 February 2015

SUMMARY

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease. Amnestic mild cognitive impairment (aMCI) is considered to represent early AD. Various aMCI clinical subtypes have been identified as either single domain (SD) or multidomain (MD). The various subtypes represent heterogeneous syndrome, indicating the different probability of progression to AD. Understanding the heterogeneous concept of aMCI can help to construct potential biomarkers to monitor the progression of aMCI to AD. This review provides an overview of various neuroimaging measures for subtypes of aMCI. Focusing on neuropsychological, structural, and functional neuroimaging findings, we found that aMCI showed differences in clinical progression and the abnormalities in MD-aMCI were distributed across temporal, frontal, and parietal cortices, which is similar to AD. This is also compatible with the notion that MD-aMCI is a transition stage between SD-aMCI and AD. Our review provided a framework for the diagnosis of clinical subtypes of aMCI and early detection and intervention of the progression from aMCI to AD.

doi: 10.1111/cns.12391

Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease, which is the most frequent form of dementia [1,2]. The World Health Organization (WHO) estimates that there were 36 million people living with dementia worldwide and the global cost of dementia is \$604 billion in 2010 (World Alzheimer Report 2010, <http://www.alz.org>). However, very effective treatments or interventions for AD do not exist. So it is very important to identify the risks of the development of AD at an early stage.

Mild cognitive impairment (MCI) usually represents a transitional phase between normal cognitive function and dementia. Patients with MCI have a 4–10 times higher risk of developing dementia in comparison with cognitively normal elderly persons [3]. In particular, amnestic MCI (aMCI) is considered to represent early AD syndrome. Such patients are at a markedly increased risk of developing AD with a conversion rate of 15–25% over 2 years [3]. According to the recent classification criteria for aMCI, aMCI patients can be further categorized as single-domain (SD) or multidomain (MD) MCI [4]. The SD-aMCI subtype indicates a relatively selective episodic memory impairment, in contrast to the MD-aMCI subtype, which

indicates substantial deficits in at least one other cognitive domain [4]. The probability of MD-aMCI progressing to AD is more than the probability of SD-aMCI [5]. At the 2-year follow-up, 6% of the SD-aMCI group had progressed to AD, whereas 48% of the MD-aMCI group had progressed to AD. At the 4-year follow-up, 24% of the SD-aMCI patients progressed to AD compared with 77% of the MD-aMCI patients [6]. The results of these studies imply that two subtypes may be associated with different outcomes. So it is very important to identify the risks for the development of different aMCI subtypes at an early stage. Early identification would have significant clinical impact, facilitating early intervention and monitoring progression.

The identification of patients at high risk of cognitive decline is considered a prerequisite for future curative strategies in AD. Neuroimaging techniques can provide differential diagnosis, help predict the probability of developing AD, and measure the progression of neurodegenerative diseases [3]. The aim of this review was to provide an overview of the neuropsychological and neuroimaging findings specific to clinical subtypes of aMCI. In addition, methodological issues involved in studying this heterogeneous population can help to improve our understanding of the progression of aMCI and give an early warning of the onset of AD.

Neuropsychological Characteristics

According to Petersen et al.'s diagnostic criteria [7], the aMCI indicates objective memory impairment for age. If memory is the only domain impaired in a relative sense, then the classification is SD-aMCI. In contrast, the MD-aMCI subtype indicates substantial deficits in at least one other cognitive domain [4]. If memory plus one or more other cognitive domains assessed with neuropsychological testing were affected (1.5 standard deviations below age norms), he/she was considered to be MD-aMCI. What is of note is that, although the MD-aMCI group had memory deficits, they were not always poorer than the deficits noted in the SD-aMCI group [8,9]. Of the older adults residing in Beijing, the MD-aMCI patients clearly show poorer cognitive performance in language, attention, execution, and spatial processing than the SD-aMCI patients do [10].

Amnesic mild cognitive impairment with impairment in multiple cognitive domains sometimes predicts AD effectively. In the Framingham cohort, which included more than 2000 individuals who were followed for 22 years, memory and abstract reasoning were the best predictors of AD [11]. In the 187 participants of the Berlin aging study, attentional and executive tests predicted AD onset better than episodic memory tests 4 years before diagnosis [12]. Moreover, Teng et al. [13] found that visuospatial skills specific to facial emotional processing have also been found to be impaired in those with MD-aMCI but intact in those with SD-aMCI, particularly in facial affect discrimination. The deficits in facial emotional discrimination easily lead to misidentification and agitation. These neuropsychiatric syndromes are common in AD. Therefore, MD-aMCI may represent a more advanced prodromal stage of AD based on the neuropsychological characteristics.

Neuroimaging

The neuropsychological characteristics of aMCI show that aMCI is not a uniform disease entity and they present heterogeneity. The distinct clinical features of subtype aMCI indicate the different conversion rates to AD. Core neuropathologies in AD include abnormalities in the brain such as the accumulation of the protein amyloid-beta ($A\beta$) and the development of neurofibrillary tangles [14]. Accumulation of amyloid in areas of the brain is followed by synaptic dysfunction, neuronal loss, and finally results in cognitive dysfunction [15,16]. Such brain changes occur decades before the onset of dementia. More and more researchers have identified the brain structural and functional characteristics in aMCI and AD using neuroimaging techniques. It can provide evidence to understanding the heterogeneity of aMCI and measuring the progression of aMCI to AD [3].

Structural MRI

Gray matter (GM) atrophy is particularly severe among those patients with MCI that progresses to AD compared with those whose condition does not [17,18]. These results suggest GM atrophy is a very effective index for predicting whether or not MCI will deteriorate into AD. Many earlier studies have provided direct evidence about brain atrophy patterns of the subtype aMCI [19,20].

Previous research has found that the GM atrophy pattern of MD-aMCI is more diffuse than that of SD-aMCI [20–22]. He et al. [23] found that both SD-aMCI and MD-aMCI present significant hippocampus atrophy, but MD-aMCI has significantly lower whole-brain volume than that of SD-aMCI. In particular, the MD-aMCI group showed loss mainly spreading into the posterior lateral and basal temporal lobes, the posterior cingulate, the anterior insula, and the medial frontal lobe [20,23]. Zhang et al. [24] also found the aMCI group had significantly lower GM volumes in the bilateral hippocampi and temporal cortices than the control sample. This was mainly due to GM reduction of MD-aMCI but not SD-aMCI, as the latter did not show any significant GM reduction. Compared to SD-aMCI, the MD-aMCI subtype had lower GM volumes in the bilateral frontal lobes. These atrophy regions in MD-aMCI are typical of AD [25,26]. The atrophy was more widespread in the MD-aMCI group, most likely reflecting the more widespread cognitive impairment. This is consistent with presumably more advanced disease in the MD-aMCI group [19], and so MD-aMCI will presumably progress to AD sooner than in the SD-aMCI group [20].

However, at present, it is not known whether or not SD-aMCI and MD-aMCI reflect different degrees of impairment along a continuum toward AD. Brambati et al. [27] directly compared GM volume among the subtype aMCI and AD by means of voxel-based morphometry (VBM). The results show that SD-aMCI and MD-aMCI are characterized by a common pattern of GM atrophy within the medial temporal cortex, predisposing to AD, and correlating with the severity of verbal memory symptoms. From an anatomical point of view, the pattern of GM atrophy observed in SD-aMCI, MD-aMCI, and mild AD revealed that these three clinical syndromes could represent three severity points along the continuum between normal aging and AD [27]. These findings suggest that SD-aMCI and MD-aMCI represent two degrees of severity along a continuum between normal aging and AD, rather than reflecting two separate clinical syndromes resulting from different etiological factors.

The GM atrophy validated that the severity of GM loss in multi-domain impaired subtypes was greater than in the single-domain impaired subtypes (Figure 1). These findings provide further evidence for the neuroanatomical biomarkers of aMCI subtype and could potentially assist clinicians to improve diagnosis of aMCI.

Diffusion Tensor Imaging

Apart from gray matter volume changes, increased white matter (WM) abnormalities have been observed in aMCI. To estimate the structural integrity of cerebral connections in aMCI, diffusion tensor imaging (DTI) has been used widely. Interestingly, several contributions on AD reported that the changes in WM microstructure assessed with DTI may be a more sensitive parameter compared with gray matter data [28,29]. It can help to detect mild structural changes occurring at the early stages of the degenerative process.

As reported previously using the DTI technique, abnormal diffusion changes in the white matter (WM) tracts in patients with AD and aMCI were reported. It has been applied to investigate the WM changes in aMCI patients by different researchers [30–33]. Fractional anisotropy (FA) and mean diffusivity (MD) are the

Figure 1 Voxel-wise gray matter (GM) volumes were compared between amnesic mild cognitive impairment (aMCI) subtypes and the normal control group. The brain regions, in which GM volumes were significantly different between aMCI subtypes and normal controls, were superimposed upon a rendered 3D standard brain template. (A) aMCI < normal controls, (B) aMCI-multidomain (MD) < normal controls [20], and (C) aMCI-MD < aMCI-SD (Zhang et al. [24]).

common index of white matter integrity. Rose et al. [34] demonstrated increased MD in the entorhinal and parieto-occipital cortices, and decreased FA in the limbic parahippocampal white matter in patients with MCI. Moreover, Kantarci et al. [35] were among the first to show that increased mean diffusivity of the hippocampus in amnesic MCI predicted future progression to dementia. The WM abnormalities are consistently found in posterior regions including the medial temporal lobe (MTL), the splenium of the corpus callosum (CC), posterior cingulum, and parietal WM [33,36,37], that is, in regions typically affected by AD and are particularly sensitive to degenerative processes [38]. And some studies have shown changes in the frontal white matter of MCI patients [36,39]. But these results are not consistent. Some of the variability of the DTI results in aMCI may be due to how MCI is defined and the disease stage. SD-aMCI patients only have memory impairment, which is related to memory, but MD-aMCI patients have executive function impairment that is related to the frontal lobe.

Li et al. [8] first reported the differences in WM integrity across the whole brain between MD-aMCI and SD-aMCI. They found that SD-aMCI patients showed decreased WM integrity in bilateral parahippocampal gyrus and right insula. They also found that MD-aMCI showed disrupted integrity in multiple WM tracts across the whole brain, including the left medial and superior frontal gyrus, the right inferior frontal gyrus, the bilateral superior temporal gyrus, the left middle and medial temporal lobe, the right angular gyrus, supramarginal gyrus, precuneus, the right lateral occipital lobe and postcentral gyrus, the bilateral insula, precentral gyrus, posterior cingulate cortex, and the whole corpus callosum. In addition to the demonstrated susceptibility of the medial temporal lobe structures to the MCI syndrome, MD-aMCI patients also showed abnormality in frontal, temporal, parietal, occipital WM, together with several commissural, association, and projection fibers (Figure 2). The characteristics of the WM pathological changes in MD-aMCI are more “AD-like” [29,40,41]. These findings indicate that the degeneration extensively exists in WM tracts in MD-aMCI that precedes the development of AD, whereas underlying WM pathology in SD-aMCI is imperceptible.

Researchers tried to explore the usefulness of DTI parameters on the individual classification of cases of MCI, investigate WM patterns in prospectively documented patients with MCI compared with healthy controls, and report their use in the *a priori* identification of progressive MCI. Based on the WM integrity patterns, researchers developed models of automatic individual classification in a community-based series of cases of SD-aMCI and md-aMCI. Haller et al. [42] found a decrease in FA in MD-aMCI versus SD-aMCI in an extensive bilateral, right-dominant network. Confirming the strength of the association between these patterns of WM changes and aMCI subtypes, by the use of support vector machine (SVM) classification analysis of FA provided a correct classification between the aMCI subgroups with accuracies of 97.70% for MD-aMCI versus SD-aMCI. These results suggested SVM analysis of white matter FA provided highly accurate classification of aMCI subtypes. The high proportion of subjects with aMCI who already undergo brain MR imaging during work-up to AD suspicion in routine clinical settings, in combination with the short measurement time of DTI and potentially almost automatic postprocessing of the data, implies a potential benefit and clinical practicability of this objective and individual classifier.

The human brain is structurally organized into complex networks allowing the segregation and integration of information processing [43]. And the whole-brain WM connectivity can be reconstructed with DTI and modeled by network approaches [44,45]. Recently, studies of white matter brain network in AD-related patients have indicated that cognitive function deficits could be due to abnormalities in the connectivity. The abnormalities in the connectivity were detected in the parahippocampus gyrus, medial temporal lobe, cingulum, fusiform, medial frontal lobe, and orbital frontal gyrus [46–48]. Shu et al. [9] first used DTI tractography to construct the human brain WM networks of aMCI subtype, followed by a graph theoretical analysis. The results indicated that the global topological organization of white matter networks was significantly disrupted in patients with MD-aMCI. Connectivity impairment in patients with MD-aMCI was found in the temporal, frontal, and parietal cortices. MD-aMCI had decreased network efficiency relative to SD-aMCI, with the most pronounced differences located in the frontal

Haller, Missonnier et al. 2013 **Li, Liang et al. 2013**

Figure 2 TBSS analysis between MCI subtypes. MD-amnesic mild cognitive impairment (aMCI) compared with SD-aMCI had significantly reduced integrity mainly in frontal and temporal areas (red to yellow). Gray, mean fractional anisotropy (FA) value; green, average skeleton.

cortex. This study suggests early-onset disruption of whole-brain white matter connectivity in patients with aMCI, especially in those with the MD subtype, supporting the view that MD-aMCI is a more advanced form of disease than SD-aMCI.

Functional MRI

Functional neuroimaging techniques may offer the unique ability to detect early functional brain changes in at-risk adults and identify the neurophysiological markers that best predict AD conversion [49].

Alzheimer's disease is characterized by the pathological accumulation of amyloid $A\beta$ in medial temporal lobe (MTL) [16,50,51]. MTL is a condition of vulnerable brain areas, followed by metabolic abnormalities, and finally, resulting in the hallmark episodic memory decline [15,16]. Meanwhile MTL is critical to memory and activation may be relative to memory capacity. aMCI patients showed impairment to be major in memory encoding capacity [52,53]. Many fMRI memory studies show changes in temporal lobe activation of aMCI patients during episodic memory tasks, compared to controls. Investigators also reported the extra-temporal fMRI activation changes in aMCI during memory tasks,

including frontal cortex [54], cingulate gyrus [55], left insula [56], precuneus, and occipital cortex [57].

However, few fMRI studies have been published focusing on subtypes of aMCI. We imply that the variability of fMRI results in aMCI may be due to the heterogeneity of aMCI. SD-aMCI and MD-aMCI had similar/same memory impairment but different degrees in other cognitive domains. SD-aMCI and MD-aMCI both could not remember new things very well, and MD-aMCI has more difficulty in keeping attention and visual processing. Therefore, brain activation differences between the two groups mainly appear in extratemporal cortex, which is less responsible for memory. The metabolism research using single photon emission computed tomography (SPECT) showed hypometabolism in the medial temporal lobe for an SD-aMCI group, while an MD-aMCI group had similar perfusion deficits with an additional deficit in the left posterior cingulate gyrus [58]. Recently, we investigated brain functional activation during an episodic memory task between subtypes of aMCI. The whole-brain analysis showed that the different active brain regions between MD-aMCI and SD-aMCI patients are the right middle occipital and left middle cingulum regions. These results coincide with the above inferences [59] (Figure 3).

Figure 3 (A) Views of activation during encoding for control, SD-amnesic mild cognitive impairment (aMCI), and multidomain (MD)-aMCI groups displayed on a custom template sagittal brain surface created from subjects in the study. (B) Images showing increased activation in SD-aMCI relative to MD-aMCI patients during an encoding task ($P < 0.001$, uncorrected). Compared to aMCI-MD, aMCI-SD patients showed significantly increased activation in the right middle occipital lobe. aMCI-MD showed significantly increased activation in the left cingulate gyrus. Note. R, Right; L, Left.

The specific demands of the memory tasks also can result in the variability of the fMRI. Resting-state fMRI affords an effective approach to investigate spontaneous neuronal activity by measuring the synchronous fluctuations in amplitude of low-frequency fluctuations (ALFF) and blood oxygen level-dependent (BOLD) signals during a resting state, without task demands [60–62]. In recent years, the Rs-fMRI method has been broadly used to study MCI [63] and AD [64]. Previous studies reported that abnormalities of intrinsic functional activity in MCI were mainly in hippocampus, the posterior cingulate cortex, the right anterior cingulate gyrus, the right inferior frontal region, the right superior temporal gyrus, and several other regions [65]. Our ongoing study investigated the difference of intrinsic brain activity in subtype of aMCI using ALFF. Our results found that MD-aMCI showed decreased ALFF in posterior cingulate cortex and precuneus, and increased ALFF in anterior cingulate cortex, parahippocampal gyrus, hippocampus, and fusiform gyrus compared with SD-aMCI. However, no ALFF difference was found between SD-aMCI and healthy controls [22]. MD-aMCI had more intrinsic brain activity changes, which is similar to AD. Interestingly, the functional altered regions are mainly inside default mode network (DMN), which is affected by the pathology of AD. Therefore, the findings of this study support that ALFF, the intrinsic activity index, can serve as a potential biomarker of aMCI subtypes and that MD-aMCI is in the preclinical stage of AD. Additional works are needed to examine the longitudinal changes in spontaneous brain activity with longitudinal design for patients with aMCI.

Amyloid PET

The accumulation of the protein amyloid-beta ($A\beta$) is a core neuropathology and a major histopathological finding in AD, which has been associated with neuronal degeneration and clinical symptoms of dementia [14]. Moreover, the presence of $A\beta$ might contribute to the deleterious effects occurring in synaptic processes, leading to functional impairment, such as memory deficits [66,67]. Such brain changes occur decades before the onset of AD or even before any overt signs of cognitive impairment are visible.

Wolk et al. [68] investigated $A\beta$ deposits in the brain between subtype MCI by positron emission tomography (PET) using radio-tracers such as ^{11}C -labeled Pittsburgh compound-B (PiB). They found that MD-aMCI patients have a greater rate of increased amyloid burden than SD-aMCI patients (83 vs. 46%, respectively). Compared with any other MCI subgroup, the MD-aMCI group still had the greatest proportion of amyloid-positive patients. This is not surprising given that the criteria for MD-aMCI with more $A\beta$ deposits are closer to the criteria for clinical AD. They also found significant atrophy in the medial temporal lobes of amyloid-positive aMCI patients, consistent with numerous studies reporting medial temporal volumes as a predictor of conversion to clinical AD in aMCI populations.

Future Directions

In view of the current evidence, further studies concerning the specific neurobiomarkers of the aMCI subtypes need to be conducted. First, the future of brain imaging will likely involve combinations of PET and MRI techniques to identify the presence of a pathological and metabolic abnormality, to gauge its impact on the brain structure and function, and to predict and follow the effects of treatment. Second, these studies were cross-sectional, but to clearly establish a progression between the subtypes of aMCI, a longitudinal study would be essential. Based on the longitudinal results, we would build a clear and direct disease trajectory of subtype aMCI, which is very important for early detection and intervention of AD. Third, more research focused on the alternations in functional connectivity within several brain regions in MCI and AD patients during the resting state should be carried out. Findings that regions show changed functional connectivity at rest [64,69–71] overlap with regional patterns of atrophy, glucose hypometabolism, and hypoperfusion. Functional connectivity can supply more information about brain activation, which is essential in distinguishing the brain activations pattern between the subtypes of aMCI. Finally, there is no study about therapies for aMCI subtypes. This is because the main motivation to understand the heterogeneous concept of aMCI is to provide early interventions that could halt the progression of aMCI to AD.

Table 1 Neuroimaging characteristics of the studies on amnesic mild cognitive impairment (MCI) subtypes

Study	Subject	Analysis	Methods	Findings
David et al. (2009)	13 SD-aMCI, 6 MD-aMCI, and 7 naMCI	A- β deposits	Amyloid imaging ligand Pittsburgh compound B (PiB)	Proportion of amyloid-positive patients: SD-aMCI: 46.1%, MD-aMCI: 83.3, naMCI: 42.8%
Li et al. (2013)	19 SD-aMCI, 21 MD-aMCI	White matter integrity	TBSS; Voxel-wise and atlas-based analyses	SD-aMCI: Decreased WM integrity in bilateral parahippocampi and right insula; MD-aMCI: Decreased integrity in multiple WM tracts across the whole-brain
Haller, Missonnier et al. (2013)	18 SD-aMCI, 35 MD-aMCI	White matter integrity	TBSS and individual classification using SVMs	MD-aMCI < SD-aMCI (White matter integrity): right uncinate fasciculus, forceps minor, and internal capsule, as well as bilateral inferior fronto-occipital fasciculus, anterior thalamic radiation, superior longitudinal fasciculus, inferior longitudinal fasciculus, and corticospinal tract
Shu, Liang et al. (2012)	18 SD-aMCI, 20 MD-aMCI	Topological alterations of whole-brain white matter structural connectivity	DTI Network Model	MD-aMCI: Connectivity impairment was found in the temporal, frontal, and parietal cortices Network Efficiency in frontal lobe: MD-aMCI < SD-aMCI
Brambati, Belleville et al. (2009)	11 SD-aMCI, 14 MD-aMCI, and 10 mild AD	Gray matter atrophy	Voxel-based morphometry analysis	SD-aMCI: the left medial temporal cortex MD-aMCI: the left medial temporal cortex and bilaterally in the inferior temporal regions Mild AD: he left medial temporal cortex, bilaterally in the inferior temporal regions, the right medial temporal cortex, the hippocampus and amygdala
Whitwell, Petersen et al. (2007)	88 SD-aMCI, 25 MD-aMCI, 25 SD-naMCI, and 7 MD-naMCI	Gray matter atrophy	Voxel-based morphometry	SD-aMCI: atrophy in the medial and inferior temporal lobes MD-aMCI: atrophy in the medial and inferior temporal lobes, posterior temporal lobe, parietal association cortex, and posterior cingulate
Zhang, Sachdev et al. (2012)	41 SD-aMCI, 33 MD-aMCI, 46 SD-naMCI and 15 MD-naMCI	Grey matter volumes	Voxel-based morphometry	aMCI < CN, in bilateral hippocampi and temporal cortices MD-aMCI < SD-aMCI, in the bilateral frontal lobes
He, Farias et al. (2009)	65 SD-aMCI, 46 MD-aMCI, 27 SD-naMCI and 15 MD-naMCI	Hippocampal volume Whole-brain volume	Hippocampus volume: manually traced Whole-brain volume: atlas-based analyses	Hippocampus volume: SD-aMCI = MD-aMCI < CN Whole-brain volume: SD-aMCI < MD-aMCI, especially in posterior lateral and basal temporal lobes, the posterior cingulate, the anterior insula, and the medial frontal lobe
Caffarra, Ghetti et al. (2008)	19 SD-aMCI, 25 MD-aMCI, 16 naMCI (disexecutive deficits)	Regional cerebral blood flow (rCBF)	Single photon emission computed tomography (SPECT)	SD-aMCI: hypometabolism in the medial temporal lobe MD-aMCI: had similar perfusion deficits with an additional deficit in the left posterior cingulate gyrus
Li et al. (2013)	20 SD-aMCI, 14 MD-aMCI	Functional brain activation	Memory task fMRI	Whole-brain analysis: MD-aMCI > SD-aMCI in the right middle occipital lobe; MD-aMCI < SD-aMCI in the left cingulate gyrus ROI analysis: MD-aMCI < SD-aMCI in left and right hippocampus

(continued)

Table 1 (Continued)

Study	Subject	Analysis	Methods	Findings
Li et al. (2014)	18 SD-aMCI, 17 MD-aMCI	Functional brain activation	Resting fMRI	MD-aMCI < SD-aMCI in posterior cingulate cortex and precuneus MD-aMCI > SD-aMCI in anterior cingulate cortex, parahippocampus gyri, and hippocampus

AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; DTI, diffusion tensor imaging; MD, multidomain; WM, white matter.

Conclusions

Converging neuropsychological, structural, and functional neuroimaging data are consistent with the view that aMCI is not a uniform disease entity and presents heterogeneity in the clinical progression. Generally, SD-aMCI patients are less impaired with only MTL deficits, while MD-aMCI patients are more impaired with more severe and widespread deficits, which are mainly located in DMN. The conflicting results about aMCI may be due to the variability in operationalizing the diagnostic criteria. Distinct clinical subtypes of aMCI serves as a promising approach to better understand MCI as a risk factor for future cognitive decline and Alzheimer's disease.

Neuroimaging methods are capable of detecting the differences between SD-aMCI and MD-aMCI. There are imaging modality-specific alternations within the subtypes. A- β deposits are already present in aMCI, and the number of MD-aMCI with the deposits is larger than SD-aMCI. Such changes are associated with increased gray matter brain atrophy: SD-aMCI showed GM atrophy mainly in hippocampi and entorhinal cortex, while MD-aMCI showed additional GM atrophy in posterior cingulate cortex, frontal lobe, and so on. DTI-assessed white matter integrity already impaired in subtypes: SD-aMCI showed decreased integrity in parahippocampi and insula, while MD-aMCI showed abnormality in frontal, temporal, parietal, occipital WM across the whole brain. Intrinsic brain activity abnormalities only become detectable in MD-aMCI. In general, functional and structural abnormalities in SD-aMCI only appeared in MTL, while the abnormalities in MD-aMCI were distributed across the whole brain, especially in DMN regions (Summary in Table 1).

At the stage of MD-aMCI, AD-like patterns of brain changes are observed. These include a high proportion of amyloid deposits, DMN regional brain atrophy and intrinsic brain activity changes, and decreased whole-brain white matter integrity, all of which are predictive of short-term conversion to AD. The structural brain study directly proved that SD-aMCI and MD-aMCI represent two phases along a continuum between normal aging and AD [27]. The functional study found no difference between SD-aMCI and normal aging, indicating that SD-aMCI may possibly return to normal. Combined neuroimaging markers and neuropsychological assessments, it is effective for predicting the progression of aMCI to AD. The multiple imaging results tended to support the notion that subtypes of aMCI represent different degrees of severity and MD-aMCI is a typical stage of pre-AD.

Acknowledgments

This work was supported by the State Key Program of National Natural Science of China (Grant No. 81430100), the National Science Foundation of China (Grant No. 81173460 and No. 81274001), Beijing New Medical Discipline Based Group (Grant No. 100270569), Project of Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences (Grant No. Z0175 and No. Z0288), Program for New Century Excellent Talents in University (Grant No. NCET-10-0249), and Major National Science and Technology Projects Creation of Major New Drugs (Grant No. 2013ZX09103002-002).

Conflict of Interest

The authors declare no conflict of interest.

References

- Ott A, Breteler MM, van Harskamp F, et al. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol* 1998;**147**:574–580.
- Seshadri S, Beiser A, Au R, et al. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 2. *Alzheimers Dement* 2011;**7**:35–52.
- Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;**56**:1133–1142.
- Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment-beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;**256**:240–246.
- Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 1. *Arch Neurol* 2003;**60**:1385–1389.
- Bozoki A, Giordani B, Heidebrink JL, et al. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol* 2001;**58**:411–416.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;**256**:183–194.
- Li H, Liang Y, Chen K, et al. Different patterns of white matter disruption among amnesic mild cognitive impairment subtypes: Relationship with neuropsychological performance. *J Alzheimers Dis* 2013;**36**:365–376.
- Shu N, Liang Y, Li H, et al. Disrupted topological organization in white matter structural networks in amnesic mild cognitive impairment: Relationship to subtype. *Radiology* 2012;**265**:518–527.
- Li X, Ma C, Zhang J, et al. Prevalence of and potential risk factors for mild cognitive impairment in community-dwelling residents of Beijing. *J Am Geriatr Soc* 2013;**61**:2111–2119.
- Elias MF, Beiser A, Wolf PA, et al. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. *Arch Neurol* 2000;**57**:808–813.
- Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: Results from the Berlin Aging Study (BASE). *Am J Geriatr Psychiatry* 2005;**13**:134–141.

13. Teng E, Lu PH, Cummings JL. Deficits in facial emotion processing in mild cognitive impairment. *Dement Geriatr Cogn Disord* 2007;**23**:271–279.
14. Querfurth HW, LaFerla FM. Mechanisms of disease Alzheimer's disease. *N Engl J Med* 2010;**362**:329–344.
15. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* 2002;**297**:353–356.
16. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;**9**:119–128.
17. Killiany RJ, Gomez-Isla T, Moss M, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Ann Neurol* 2000;**47**:430–439.
18. Visser PJ, Verhey FR, Hofman PA, et al. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *J Neurol Neurosurg Psychiatry* 2002;**72**:491–497.
19. Bell-McGinty S, Lopez OL, Meltzer CC, et al. Differential cortical atrophy in subgroups of mild cognitive impairment. *Arch Neurol* 2005;**62**:1393–1397.
20. Whitwell JL, Petersen RC, Negash S, et al. Patterns of atrophy differ among specific subtypes of mild cognitive impairment. *Arch Neurol* 2007;**64**:1130.
21. Seo SW, Im K, Lee JM, et al. Cortical thickness in single-versus multiple-domain amnesic mild cognitive impairment. *NeuroImage* 2007;**36**:289–297.
22. Li X, Cao M, Zhang J, et al. Structural and functional brain changes in the default mode network in subtypes of amnesic mild cognitive impairment. *J Geriatr Psychiatry Neurol* 2014; **27**:188–198.
23. He J, Farias S, Martinez O, et al. Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and apolipoprotein E4 among mild cognitive impairment subtypes. *Arch Neurol* 2009;**66**:1393.
24. Zhang H, Sachdev PS, Wen W, et al. Gray matter atrophy patterns of mild cognitive impairment subtypes. *J Neurol Sci* 2012;**315**:26–32.
25. Jack CR Jr, Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997;**49**:786–794.
26. Busatto GF, Garrido GE, Almeida OP, et al. A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiol Aging* 2003;**24**:221–231.
27. Brambati SM, Belleville S, Kergoat MJ, et al. Single- and multiple-domain amnesic mild cognitive impairment: Two sides of the same coin? *Dement Geriatr Cogn Disord* 2009;**28**:541–549.
28. Ibrahim I, Horacek J, Bartos A, et al. Combination of voxel based morphometry and diffusion tensor imaging in patients with Alzheimer's disease. *Neuro Endocrinol Lett* 2009;**30**:39–45.
29. Agosta F, Pievani M, Sala S, et al. White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* 2011;**258**:853–863.
30. Damoiseaux JS, Smith SM, Witter MP, et al. White matter tract integrity in aging and Alzheimer's disease. *Hum Brain Mapp* 2009;**30**:1051–1059.
31. Liu Y, Spulber G, Lehtimäki KK, et al. Diffusion tensor imaging and Tract-Based Spatial Statistics in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2011;**32**:1158–1171.
32. Haller S, Nguyen D, Rodriguez C, et al. Individual prediction of cognitive decline in mild cognitive impairment using support vector machine-based analysis of diffusion tensor imaging data. *J Alzheimers Dis* 2010;**22**:315–327.
33. Zhuang L, Wen W, Zhu W, et al. White matter integrity in mild cognitive impairment: A tract-based spatial statistics study. *NeuroImage* 2010;**53**:16–25.
34. Rose SE, McMahon KL, Janke AL, et al. Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnesic mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2006;**77**:1122–1128.
35. Kantarci K, Petersen RC, Boeve BF, et al. DWI predicts future progression to Alzheimer disease in amnesic mild cognitive impairment. *Neurology* 2005;**64**:902–904.
36. Medina D, DeToledo-Morrell L, Urresta F, et al. White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiol Aging* 2006;**27**:663–672.
37. Huang J, Auchs AP. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. *Ann N Y Acad Sci* 2007;**1097**:259–264.
38. Naggara O, Oppenheim C, Rieu D, et al. Diffusion tensor imaging in early Alzheimer's disease. *Psychiatry Res* 2006;**146**:243–249.
39. Wang L, Goldstein FC, Veledar E, et al. Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. *AJNR Am J Neuroradiol* 2009;**30**:893–899.
40. Acosta-Cabrero J, Williams GB, Pengas G, Nestor PJ. Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. *Brain* 2010;**133**:529–539.
41. Bosch B, Arenaza-Urquijo EM, Rami L, et al. Multiple DTI index analysis in normal aging, amnesic MCI and AD. Relationship with neuropsychological performance. *Neurobiol Aging* 2012;**33**:61–74.
42. Haller S, Missonnier P, Hermann FR, et al. Individual classification of mild cognitive impairment subtypes by support vector machine analysis of white matter DTI. *AJNR Am J Neuroradiol* 2013;**34**:283–291.
43. He Y, Evans A. Graph theoretical modeling of brain connectivity. *Curr Opin Neurol* 2012;**23**:341–350.
44. Gong G, He Y, Concha L, et al. Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cereb Cortex* 2009;**19**:524–536.
45. Zalesky A, Fornito A. A DTI-derived measure of cortico-cortical connectivity. *IEEE Trans Med Imaging* 2009;**28**:1023–1036.
46. He Y, Chen Z, Evans A. Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *J Neurosci* 2008;**28**:4756–4766.
47. Yao Z, Zhang Y, Lin L, et al. Abnormal cortical networks in mild cognitive impairment and Alzheimer's disease. *PLoS Comput Biol* 2010;**6**:e1001006.
48. Supekar K, Menon V, Rubin D, et al. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol* 2008;**4**:e1000100.
49. Jak AJ, Bangen KJ, Wierenga CE, et al. Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment. *Int Rev Neurobiol* 2009;**84**:81–103.
50. Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature* 2004;**430**:631–639.
51. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron* 2004;**44**:181–193.
52. Chételat G, Desgranges B, De La Sayette V, et al. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 2003;**126**:1955–1967.
53. Wang QS, Zhou JN. Retrieval and encoding of episodic memory in normal aging and patients with mild cognitive impairment. *Brain Res* 2002;**924**:113–115.
54. Petrella JR, Krishnan S, Slavin MJ, et al. Mild cognitive impairment: Evaluation with 4-T functional MR imaging. *Radiology* 2006;**240**:177–186.
55. Johnson SC, Schmitz TW, Moritz CH, et al. Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging* 2006;**27**:1604–1612.
56. Machulda MM, Senjem ML, Weigand SD, et al. Functional magnetic resonance imaging changes in amnesic and nonamnesic mild cognitive impairment during encoding and recognition tasks. *J Int Neuropsychol Soc* 2010;**15**:372.
57. Heun R, Freymann K, Erb M, et al. Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging* 2007;**28**:404–413.
58. Caffarra P, Ghetti C, Concari L, Venneri A. Differential patterns of hypoperfusion in subtypes of mild cognitive impairment. *Open Neuroimaging J* 2008;**2**:20–28.
59. Li X, Zheng L, Zhang J, et al. Differences in functional brain activation and hippocampal volume among amnesic mild cognitive impairment subtypes. *Curr Alzheimer Res* 2013;**10**:1080–1089.
60. Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev* 2007;**29**:83–91.
61. Shmuel A, Leopold DA. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Hum Brain Mapp* 2008;**29**:751–761.
62. Lu H, Zuo Y, Gu H, et al. Synchronized delta oscillations correlate with the resting-state functional MRI signal. *Proc Natl Acad Sci U S A* 2007;**104**:18265–18269.
63. Wang Z, Yan C, Zhao C, et al. Spatial patterns of intrinsic brain activity in mild cognitive impairment and Alzheimer's disease: A resting-state functional MRI study. *Hum Brain Mapp* 2011;**32**:1720–1740.
64. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proc Natl Acad Sci U S A* 2004;**101**:4637–4642.
65. Bai F, Zhang Z, Yu H, et al. Default-mode network activity distinguishes amnesic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. *Neurosci Lett* 2008;**438**:111–115.
66. Freir DB, Fedriani R, Scully D, et al. Aβ oligomers inhibit synapse remodelling necessary for memory consolidation. *Neurobiol Aging* 2011;**32**:2211–2218.
67. Walsh DM, Selkoe DJ. A beta oligomers – a decade of discovery. *J Neurochem* 2007;**101**:1172–1184.
68. Wolk DA, Price JC, Saxton JA, et al. Amyloid imaging in mild cognitive impairment subtypes. *Ann Neurol* 2009;**65**:557–568.
69. Wang K, Liang M, Wang L, et al. Altered functional connectivity in early Alzheimer's disease: A resting-state fMRI study. *Hum Brain Mapp* 2007;**28**:967–978.
70. Gili T, Cercignani M, Serra L, et al. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. *J Neurol Neurosurg Psychiatry* 2011;**82**:58–66.
71. Wang L, Li H, Liang Y, et al. Amnesic mild cognitive impairment: Topological reorganization of the default-mode network. *Radiology* 2013;**268**:501–514.