

Recent research about mild cognitive impairment in China

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Summary: The rapid aging of the Chinese population has spurred interest in research about the cause and prevention of dementia and its precursor, mild cognitive impairment (MCI). This review summarizes the last decade of research in China about MCI. Extensive research about the epidemiology, neuropsychological characteristics, diagnosis, genetic etiology, neuroimaging and electrophysiological changes, and treatment of MCI has provided some new insights but few breakthroughs. Further advances in the prevention and treatment of MCI will require a greater emphasis on multi-disciplinary prospective studies with large, representative samples that use standardized methods to assess and monitor changes in cognitive functioning over time.

Key words: mild cognitive impairment, dementia, research methodology, China

1. Definition and diagnostic criteria of mild cognitive impairment

The concept of mild cognitive impairment (MCI) was first proposed by Reisberg^[1] in 1982. It was subsequently described as memory loss without associated decline in cognitive functioning or daily functioning that does not meet diagnostic criteria for dementia. Most Chinese researchers use the following definition for MCI^[2]: a clinical condition between natural aging and mild dementia characterized by memory loss with or without mild cognitive dysfunction which does not affect the individual's social and daily functioning and that is not explained by other nervous system conditions, mental disorders, or other known medical diseases.

For many years there was no operational criteria for the diagnosis of MCI. Then in 1999 Petersen and colleagues^[3] proposed diagnostic criteria for MCI which were subsequently accepted by most researchers in China. In 2006 Chinese experts revised and updated the diagnostic criteria for MCI as follows^[4]: (a) main complaint is memory loss which can be confirmed by a family member or associate; (b) cognitive functioning in other domains is relatively unaffected or only mildly affected; (c) daily life is not affected; (d) criteria for the diagnosis of dementia have not been met; (e) symptoms are not due to other diseases; and (f) the score on the global deterioration scale (GDS) is between two and three, the Clinical Dementia Rating (CDR) score is 0.5, the memory test score is at least 1.5 standard deviations lower than the average score of individuals of the same age and level of education, and the mini-mental status examination (MMSE) score is higher than 24 or the Mattis Dementia Rating Scale (DRS) score is at least 123.

Most researchers in China agree that MCI can be grouped into two categories: amnesic mild cognitive impairment (aMCI) and non-amnesic mild cognitive impairment (naMCI). These two categories of MCI are sometimes further classified into four subcategories: amnesic single cognitive domain impairment, amnesic multi-cognitive domain impairment, non-amnesic single cognitive domain impairment and non-amnesic multi-cognitive domain impairment.^[4] A study at the Shanghai Mental Health Centre also classified MCI based on the presumed underlying etiology into the following four types: MCI caused by Alzheimer's Disease (AD), MCI caused by Vascular Dementia (VD), MCI caused by natural aging and MCI due to other (rare) causes.^[2]

2. Epidemiology

The reported prevalence of MCI in Europe and North America varies from 2.8 to 17.5%.^[5-7] The prevalence of MCI in different regions in China varied between 5.4 and 25.0% (11.6% in Beijing in 2004^[8]; 15.4% in Guizhou Province in 2005^[9]; 5.4% in Taiyuan City in 2006^[10]; 9.89% in Xinjiang Province in 2007^[11]; 6.3% in Guangzhou City in 2010^[12]; and 25.0% in Shaanxi Province in 2011^[13]). The variation in prevalence by location may be partly attributed to differences in the ages covered in the surveys, diagnostic criteria, evaluation tools, levels of education and life styles. Cognitive functioning declines with age among most elderly people, and it declines even faster among individuals with MCI. A survey conducted among elderly people living in Beijing found that the prevalence of MCI was 3.3% among persons 60 to 65 years of age, 11.0% in persons 65 to 70 years of age, 12.5% in persons 75 to 80 years of age, and 17.2%

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in persons over 80 years of age.^[8] Findings about the relationship of gender to MCI have been inconsistent. Tang and colleagues^[8] found no significant difference in the prevalence of MCI between males and females, while other studies found a higher prevalence among females.^[2] There is, however, a strong association between MCI and level of education; higher levels of education are associated with a lower prevalence of MCI. One study reported a 11.0% prevalence of MCI among individuals with a primary school education, 7.8% among those with a secondary school education, 6.7% among those with a high school education, and 5.5% among those with a college education.^[14]

One study conducted in 2000 in Hangzhou City (Zhejiang Province) followed up 18 individuals with MCI and found that all of them progressed to dementia within four years.^[15] A large epidemiological survey in Beijing found that 7.0% of individuals with MCI developed Alzheimer's Disease (AD) within a year while only 1.1% of persons of the same age without MCI developed AD.^[16] A study conducted in Taiyuan City (Shanxi Province) found that the average incidence of dementia was 6.5% for each person-year among elderly individuals with MCI, compared to 1.2% for each person-year among elderly individuals without MCI, which yields a Risk Ratio of 5.27.^[17] Xiao and colleagues^[18] followed up individuals with MCI for three years and found that 27.7% developed dementia, compared to 0.7% in the control group. A long-term follow-up study of individuals with MCI by Zhu and colleagues^[19] reported that 16.5% developed dementia within five years and 42.1% developed dementia within ten years.

3. Risk Factors

MCI develops slowly over several years, so it is associated with a wide range of environmental, psychosocial, and biological factors including diet, life style, personality traits and other physical diseases. Studies conducted in China have found that good diet and a healthy life style are associated with a relatively low prevalence of MCI. An extroverted personality, high levels of independence, high levels of self-discipline, a good family environment and positive (optimistic) attitudes can prevent or postpone the occurrence of MCI.^[20-22]

One study in China reported that 52.8% of individuals with MCI have physical illnesses including hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and Parkinson's disease.^[22] These physical diseases are risk factors for MCI and for the deterioration of cognitive functioning. Studies in China report that individuals with hypertension are at a higher risk for MCI than those without hypertension.^[23] Other studies have found that Type 2 diabetes mellitus (T2DM), obesity, and poor control of blood lipids are also associated with impairment in cognitive function.^[24] The elevated level of blood lipid in patients with hyperlipidemia causes damages to the endothelium of

the cerebral arteries and accelerates atherosclerosis; these processes slow cerebral blood flow and retard cerebral metabolism and, thus, increase the risk of cognitive impairment. Individuals with diabetes are more than four times more likely to have MCI compared to those without diabetes.^[25] Insulin resistance (IR) and a high blood level of insulin are also independent risk factors for MCI.^[26] Recently, researchers from other countries have proposed the concept of non-high-density lipoprotein (HDL)-cholesterol, an umbrella term for all cholesterol that can cause atherosclerosis; a study in China found that non-HDL-cholesterol was correlated with cognitive functioning among patients with T2DM and could help predict whether or not an individual with T2DM had MCI.^[27]

Vascular factors account for approximately 23% of MCI among elderly people.^[28] Different types of vascular conditions and different types of cognitive impairments are included under the composite label 'vascular cognitive impairments' (VCI).^[28,29] Recently, cognitive function impairment caused by transient ischemic attacks (TIAs) has attracted researchers' attention. One study in China found that compared to those with less severe carotid artery stenosis, individuals with severe carotid artery stenosis (>70%), have more serious impairments in cognitive functioning and have a higher prevalence of transient ischemic attacks (TIAs).^[30] Moreover, individuals with TIAs who have severe carotid artery stenosis had more severe cognitive impairment and were more likely to have MCI than those without severe carotid artery stenosis.^[30]

Degenerative diseases of the brain also affect cognitive functioning among the elderly. Two examples are leukoaraiosis, which is associated with MCI, and Binswanger disease, which is associated with moderate cognitive impairment and dementia.^[31] Another example is Parkinson's disease (PD). The severity of PD is correlated with the severity of cognitive impairment; even during the early stages of PD there is an elevated prevalence of MCI – typically the single domain variant of MCI.^[32]

In summary, advanced age, unhealthy life styles, hypertension, cardiovascular and cerebrovascular diseases, hypercholesterolemia and diabetes are common correlates of MCI. Early interventions targeted at these risk factors may provide a venue to prevent MCI or to delay the progress of cognitive impairment.

4. Genetic and biochemical factors

The causative pathways that result in MCI remain unclear. Studies on MCI in China have assessed the role of genetics, oxidative stress, and inflammation.

Many studies report that only some individuals with MCI progress to full-blown dementia, so a lot of research attention has focused on factors that may increase or decrease the risk of conversion from MCI to dementia. Several researchers have investigated the relationship

between ApoE, ApoE ϵ 4 and cognitive functioning. Wang and colleagues^[33] found that the frequency of the ϵ 4 allele was ten fold higher among individuals with MCI compared to the frequency among individuals without MCI. They also found that combining the ApoE test with the results of a neuropsychological battery can greatly increase the sensitivity and specificity of predicting subsequent AD among individuals with current MCI. Chen and colleagues^[34] followed up 2207 elderly people with normal cognitive functioning for three years in Guizhou Province and found that the ApoE ϵ 4 genotype was associated with a higher risk of MCI (including both aMCI and naMCI) and that the ApoE ϵ 3 genotype was a protective factor for naMCI.

Other researchers have focused on different genes. Fu and colleagues^[35] found that the CYP46A1 gene, which encodes cholesterol 24-hydroxylase, is associated with a decline in cognitive functioning. Shi^[36] found that low density lipoprotein receptor-related protein one (LRP1) is related to aMCI. Researchers in other countries report that β -amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) are related to early-onset AD,^[37] but there have been few studies on these genes in China. Despite the lack of major breakthroughs about the genetic basis of MCI and AD, genetic studies may eventually lead to a biologically based subclassification of these conditions (that are currently defined by phenomenology) and, thus, help in the effort to prevent the occurrence of MCI and to prevent the progression of MCI to AD.

Inflammatory mediators and oxidative stress are important components in the causal mechanism of cognitive impairment.^[38] Super-oxide dismutase (SOD) is the key enzyme in eliminating superoxide anion so its activity represents the ability to clear oxygen radicals. Conversely, the level of blood malondialdehyde (MDA) reflects the level of cell damage caused by free radicals. Research indicates that compared to persons without MCI, those with MCI have significantly lower levels of blood SOD and significantly higher levels of blood MDA; these findings confirm the association between oxidative stress and cognitive impairment. Moreover, other studies^[39] have shown that the level of acetylcholinesterase (AChE) is higher among individuals with MCI compared to controls, which suggests that the functioning of the central cholinergic system is also associated with the occurrence of MCI.^[39] And high sensitivity C-reactive protein (hs-CRP) has also been found to be related to MCI.^[40] Recently, researchers from other countries have reported that changes in the functioning of peripheral lymphocytes is associated with changes in the immunological functioning of the brain among patients with AD.^[41] Chinese researchers discovered that decreased levels of T-helper lymphocytes can serve as an indicator of the level of impairment of cognitive functioning.^[42] Other research^[43] has shown that the glycogen synthase kinase-3 enzyme (GSK-3) in peripheral lymphocytes is more active among individuals with MCI or AD.

Huang's research team^[44] in Beijing Xuanwu Hospital was the first to show that the blood level of vascular endothelial growth factor (VEGF) is decreased among patients with AD or MCI, and that the decline was greater among patients with AD than among those with MCI. Chinese researchers also reported that the blood level brain-derived neurotrophic factor (BDNF) is significantly lower among individuals with aMCI than among controls.^[45] Other research in China^[46] has found that the serum level of matrix metalloproteinase-9 (MMP-9) is higher among older individuals with metabolic syndrome who have concurrent MCI than in those who have metabolic syndrome without MCI, suggesting a relationship between serum MMP-9 and the development and severity of MCI in individuals who have metabolic syndrome.

5. Diagnosis

The diagnosis of MCI is quite difficult, particularly at the early stages of the condition. It often relies on a combination of neuropsychological testing, brain imaging and brain electrophysiological assessment.

5.1 Neuropsychological evaluation

Neuropsychological assessment is the cornerstone of screening for cognitive impairment. Chinese researchers have adapted several widely used screening tools from the West. The mini-mental status examination (MMSE) is one of the most commonly used evaluation tools for cognitive functioning,^[47] but the results are influenced by age and cultural factors. The decline of cognitive function identified by MMSE is not specific – it can be influenced by diseases, level of consciousness and mental state – so MMSE results need to be interpreted in light of a clinical evaluation of the individual.^[48] The Montreal Cognitive Assessment (MoCA) is a simple and highly sensitive cognitive screening tool^[49] covering multiple important cognitive domains that provides a comprehensive evaluation of cognitive functioning. It has been widely used in clinical work in China; using the cutoff score of 26 for MCI, it has a sensitivity between 95 and 97% and a specificity between 75 to 76%.^[50-52] However, Guo and colleagues^[53] found that MoCA was not as sensitive when screening for naMCI, and other authors^[52-54] consider the proposed cutoff score controversial because several items are education-dependent; different cutoff scores for different education groups have not, as yet, been determined.

In 1999, Xiao and colleagues^[55] administered a comprehensive battery of neuropsychological tests to people with and without MCI, including vocabulary learning, vocabulary fluency, classification, marking, visual reasoning, the trails test and the spatial structural test. In all of these tests the results for individuals with MCI were significantly poorer than those in healthy control subjects. More recently the auditory verbal memory test (AVMT) and the repeated associative

memory test of Paired Associative Learning Test (PALT) have been found useful for the early detection of MCI.^[56] Thus the use of multiple neuropsychological tests in screening for MCI can decrease the rate of false negatives and help in the sub-classification of MCI (though it may also increase the rate of false positives). Currently, Chinese researchers recommend a two-step screening strategy for MCI: (1) use the MMSE and the MoCA to identify possible cases of MCI; (2) administer a scale that assesses individuals' overall health and the history of their cognitive problems along with the Activities of Daily Living Scale (ADL) and the Global Deterioration Scale (GDS) to identify individuals who are screened positive for MCI.^[57]

5.2 Neuroimaging

Brain histopathology is the current gold standard for assessing the occurrence and severity of AD.^[58] Braak and Braak^[59] proposed a predictive model of the progressive stages of AD based on the distribution of neurofibrillary tangles (NFT) and neuropil threads found in brain autopsies. Although these specific patterns have not been visualized using neuroimaging techniques, neuroimaging can be used to find structural and functional markers of this histopathology. For example, hippocampal atrophy measured by MRI and CT has been shown to correlate with regional NFT counts.^[60,61] Thus, brain imaging can potentially be useful both in the diagnosis of MCI and in the assessment of the progression of MCI towards full-blown dementia. With the goal of diagnosing MCI and differentiating it from other conditions, over the last several years researchers in China have been developing brain imaging techniques that are non-invasive, high-definition and multi-angled.

Previously, brain volume measurements were typically assessed using structural Magnetic Resonance Imaging (MRI), but these methods have more recently been replaced by voxel-based morphometric assessments of brain volume. In 2000, Xiao and colleagues^[62] reported that grey matter volume reduction and lateral ventricle enlargement could be ancillary indicators of MCI and early AD, but their follow-up study^[63] did not find 3D MRI useful in predicting whether MCI would progress to dementia. Subsequent studies among individuals with early MCI reported pathological changes in the hippocampus, the medial temporal lobe and the entorhinal cortex.^[64,65] Most Western researchers believe that the annual rate of hippocampus atrophy predicts the progression from MCI to dementia,^[66] but there has not yet been any large-scale prospective study in China to test this hypothesis.

Compared to structural MRI, functional MRI (fMRI) can detect real-time functional changes in different brain regions. Yang and colleagues^[67] used fMRI to study the difference in the blood-oxygen-level-dependent (BOLD) signal between individuals with and without MCI during complicated cognitive tasks; individuals with MCI had lower bilateral hippocampus activation than controls

during both rule deduction tasks and rule application tasks. Another study by the same researchers^[68] found that functional changes in the dorsolateral prefrontal cortex is a marker of MCI that occurs earlier than any structural or morphological changes in the brain. Research by Wang and colleagues^[69] found that, compared to controls, individuals with MCI have weaker activation in the parahippocampal region of the medial temporal lobe, the bilateral prefrontal cortex, the right lateral temporal lobe, and the fusiform gyrus; this result indicates that individuals with MCI have deficits in neurological functioning related to memory encoding, storage and retrieval.

Diffusion-weighted imaging (DWI) MRI measures the diffusion of water molecules inside and outside of brain cells, so it can be used to examine changes in the microstructures of the brain. Using this method, the fractional anisotropy (FA) value and the apparent diffusion coefficient (ADC) value of the left lateral temporal lobe and the genu and splenium of the corpus callosum were found to be significantly different between individuals with and without MCI. The ADC values of the right lateral frontal lobe and the bilateral centrum semiovale were also found to be significantly different between individuals with and without MCI. When cognitive functioning declines the FA value decreases and the ADC value increases.^[70] White matter impairment, an increasingly recognized contributor to cognitive decline (in addition to neurofibrillary tangles and senile plaques),^[71] can also be identified using DWI MRI. A study^[72] found abnormal FA of the white matter of the parietal lobe in people with early stage cognitive impairment; this suggests that abnormal white matter in the region is a marker for loss of connectivity and, thus, may play a role in the progression to dementia. Individuals with MCI are more likely than those without MCI to have medium, severe or overall white matter lesions (WML);^[73] moreover, individuals with MCI with medium or more severe WML displayed more cognitive impairments in more domains than those who only had mild WML. In individuals with MCI, WML impair the functioning of the frontal lobe, the limbic cortex, the thalamus-cortex pathway and the striatum-cortex pathway. Some Chinese researchers suggest that the mean diffusivity (MD) value of the splenium of the geniculate nucleus can be used as a biomarker to differentiate aMCI from AD.^[74]

A research study that used diffusion tensor imaging (DTI) to compare white matter changes in aMCI and various types of dementia provided further evidence that aMCI is a prodromal phase of AD.^[71] Among individuals with AD, white matter changes occurred in the anterior and posterior cerebral white matter, including the genu and the splenium of the corpus callosum. In individuals with MCI, white matter changes were observed in the left anterior periventricular area and in the genu of the corpus callosum (which connects cortical and subcortical areas between the two hemispheres). Another study^[75] used DTI to compare

white matter disruptions in aMCI with single- and multiple-domain cognitive deficits; individuals with multiple-domain aMCI had widespread white matter degeneration that was not seen in those with single-domain aMCI-SD; thus providing a potential biomarker to differentiate the two subtypes of aMCI. However, longitudinal studies using this methodology are needed to investigate potential progression from single-domain aMCI to multiple-domain aMCI.

Researchers in China have also started using proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) in clinical studies of MCI. Ding and colleagues^[76] found that the N-acetylaspartate/creatine (NAA/Cr) ratio was significantly lower in neurons and axons in the bilateral medial temporal lobes among individuals with MCI and mild AD compared to controls, suggesting a reduction and atrophy of neurons in the medial temporal lobes of individuals with MCI and mild AD. They also found that the NAA/Myo-inositol (NAA/Mi) ratio was significantly lower in individuals with MCI and mild AD compared to controls. Moreover, the Mi/Cr and NAA/MI ratios in the left temporal lobe were significantly different from those in individuals with MCI compared to those with mild AD. Taken together these results indicate that $^1\text{H-MRS}$ can serve as a useful tool to help diagnose MCI and mild AD. Another study^[77] used $^1\text{H-MRS}$ to compare aMCI and vascular cognitive impairment with no dementia (VCIND); after assessing the concentrations and ratios of several brain metabolites they found that individuals with aMCI had a markedly reduced NAA/Mi ratio in the bilateral posterior cingulate gyrus and in the white matter of the occipital lobe while individuals with VCIND had a significantly lower NAA/Choline (Cho) ratio in the bilateral white matter of the frontal lobe and in the left occipital lobe.

Research using positron emission tomography (PET) has found that individuals with MCI have a reduced cortical metabolic rate in the left lateral orbital gyrus, the right lateral temporal medial gyrus, and the right lateral putamen, suggesting that these regions are related to cognitive functioning.^[78] Guo and colleagues^[79] used PET dynamic imaging to compare brain retention of the amyloid tracer $^{11}\text{C-PIB}$ in individuals with MCI, individuals with AD and healthy controls; they found that one subgroup of individuals with MCI had similar PIB retention results to those of the control group and another MCI subgroup had similar results to those of the AD group. This suggests that $^{11}\text{C-PIB}$ PET imaging could be used to predict whether or not MCI will progress to AD, but longitudinal studies are needed to test this hypothesis.

Chinese researchers have only recently started using single-photon emission computed tomography (SPECT) to study MCI. One SPECT study^[80] used the radioactive ratio (RAR) in the left and right lateral parietal lobes to categorize patients with MCI into two subgroups: MCI24 and MCI216. Compared to healthy controls, the MCI216 subgroup displayed significantly lower blood perfusion in the left thalamus and significantly higher

blood perfusion in the bilateral temporal inferior gyrus and the right temporal superior gyrus. The study found different patterns in blood perfusion between the MCI subgroups but there were only four individuals in the MCI24 subgroup so it was not possible to compare the severity and long-term outcome of the two subtypes. Future longitudinal studies with larger sample sizes are needed to provide further evidence about the clinical relevance of these subtypes. Another study by Gao and colleagues^[81] found that low blood perfusion in the bilateral temporoparietal lobe was a prominent characteristic in patients with AD, but not in patients with MCI. At the 2-year follow-up, 5 of the 15 individuals with MCI had progressed to AD; baseline blood perfusion in the cingulate gyrus was the only measure that was associated with progression to AD (it was significantly lower in the group that progressed to AD) – this is another potential biomarker for subsequent dementia in individuals with MCI.

Most neuroimaging studies in China use a cross-sectional design to differentiate individuals with MCI from normal controls or from patients with AD. There have been several positive findings related to the early diagnosis of MCI and the progression of MCI to AD, but sample sizes are generally small and few of the studies compare neuroimaging with other less expensive assessment tools (e.g., neuropsychological testing and brain electrophysiology). Longitudinal studies with larger sample sizes that compare the sensitivity and specificity of different screening strategies are needed.

5.3 Brain electrophysiology

Brain electrophysiology takes little time and requires less cooperation from patients than other assessment methods, so it has great potential for application as a diagnostic procedure of MCI in China. Auditory brainstem response (ABR) elicited during electrophysiological testing is one potential method that can reflect pathological changes in the brain. A study in China^[82] comparing the ABR of healthy controls, individuals with MCI and patients with AD found that the AD group had significantly prolonged absolute latency of wave III (from the polysensory zone [Pz]) and significantly decreased absolute amplitude of wave III (from Pz) and wave V (from Pz); and the MCI group had significantly decreased absolute amplitude of wave V (from Pz) compared to the control group.^[82] Wave III is associated with the superior olivary complex and wave V is associated with the inferior colliculus,^[82,83] so the differences between groups in these waveforms suggest impairments in these areas. Xiao and colleagues^[84] found that individuals with MCI displayed significantly lower absolute amplitude of ABR wave V and lower amplitude of the P300 wave to target stimuli than healthy elderly controls. These findings suggest that the absolute latency and amplitude of the ABR wave V, the contingent negative variation (CNV) reaction time and the amplitude of the target P300 wave have diagnostic value for early AD.

Event-related potential (ERP) is strongly correlated to cognitive functioning and to the severity of dementia; it can provide a quantitative assessment of the degree of impairment in cognitive functioning.^[85] P300, a type of ERP, is not affected by culture, language or literacy, so it is easy to elicit co-operation from subjects during the examination.^[86] Thus, it provides a relatively fast way to quantitatively measure cognitive functioning. The latency of target P300 (P3) to visual stimuli is negatively correlated with MMSE scores: the longer the P3 latency, the lower the MMSE scores and the more severe the cognitive impairment.^[87] The P3a, which has been associated with brain activity related to involuntary attention, shows reduced amplitude in individuals with MCI,^[88] suggesting decreased involuntary attention to novelty and decreased reaction time in voluntary attention to simple tasks. Thus, ERP responses to different performance tasks is another method for studying MCI that may eventually identify biomarkers that can objectively distinguish MCI from early AD

Mismatch negativity (MMN), an ERP provoked by an odd stimulus in a series of repetitive stimuli,^[89] may also be useful in the assessment of cognitive impairment in elderly individuals. Prolonged MMN latency and reduced MMN amplitude is found among individuals with AD but not among individuals with MCI.^[90] Wang and colleagues^[91] found an increased power index in individuals with MCI (compared to controls) at each frequency band and at every brain region during tasks that require working memory. Moreover, the more difficult the task the greater the number of brain regions that showed a strong negative correlation between the power index and MMSE score; this suggests a compensatory mechanism in which the same cognitive task requires more effort in individuals with MCI.

In summary, brain electrophysiology has been widely used as a supplementary method to assist in the diagnosis of MCI. However, as is the case for neuroimaging studies, large-scale prospective studies are needed to confirm the utility of the potential biomarkers that have been identified in cross sectional or case-control studies.

6. Treatment

Both pharmacological and non-pharmacological clinical trials for MCI have been conducted. Results from some clinical trials support the use of pro-cognitive AD medications in treating MCI,^[92,93] but there is, as yet, no evidence on the long-term efficacy of these medications.^[94] Li and colleagues^[92] found that treating individuals with MCI with donepezil increased the NAA/Cr ratio in the dorsal left frontal lobe and the left temporal lobe (as assessed by ¹H-MRS). Another study^[93] comparing combined treatment with donepezil and ginkgo leaf extract to monotherapy with ginkgo leaf extract in individuals with MCI found that the combined treatment led to higher MMSE scores, a lower rate of abnormal EEG, and shorter P300 latency.^[93] Other medications

that have shown some promise in the treatment of MCI include galantamine, chitosan phosphatidylcholine, oligosaccharide-phosphatidylinositol, small molecule activating peptide, and vitamin C.^[95,96] Chitosan phosphatidylcholine can improve facial recognition in individuals with MCI, and can significantly improve their ability to process conflicting spatial information.^[97] And Nicergoline, a medication that can ameliorate cognitive deficits, has been found to significantly improve memory quotients of individuals with MCI.^[98]

Researchers in China have also carried out non-pharmacological clinical trials in individuals with MCI. For example, a study found that long-term repetitive transcranial magnetic stimulation (rTMS) with multiple treatment courses can delay the progression of memory impairment in individuals with MCI.^[99] Regular courses of rTMS can also postpone the onset of the slowing of EEG waves associated with brain aging. Cognitive training – including comprehensive visual training, comprehensive auditory training, eye movement training and memory training – has been found to improve cognitive functioning in individuals with MCI, and is used widely in clinical practice.^[100,101]

Multiple syndromes described in Traditional Chinese Medicine (TCM) have also been used to guide the clinical treatment of individuals with MCI using TCM medications. Common TCM syndromes include the following: deficiency of the kidney and spleen, deficiency of *qi* (i.e., life force) and blood, phlegm turbidity invading the head, static blood blocking the meridian and collaterals, and *yin* deficiency with *yang* hyperactivity.^[102] Based on the TCM conceptualization of the underlying cause of each individual case of MCI, TCM treatment methods aim to invigorate the spleen, kidneys and *qi*. Research studies report that the combination of TCM and western medicines to treat MCI is better than using western medicine alone.^[103] The adjunctive use of acupuncture to treat MCI has also been reported to improve the clinical results of western medicine.^[104,105] However, the quality of these studies is generally low and the sample sizes are small, so it is premature to provide clinical guidelines about the use of TCM in the treatment of MCI.^[106] Research studies in large samples of representative subjects that are rigorously conducted and assessed by evaluators who are blind to the treatment status of the participants are needed.

7. Conclusions

Mild cognitive impairment (MCI) has many interacting causes. Some individuals with this condition progress to full-blown dementia and others do not; the factors that distinguish these two subgroups of MCI remain obscure. The median age of the Chinese population has increased rapidly over recent decades, so the importance of preventing dementia (and, thus, the enormous public health burden imposed by dementia) has stimulated a huge upsurge in research about dementia and its

precursors, particularly MCI. Research by Chinese investigators about the epidemiology, neuropsychology, etiology, diagnosis, treatment, and prevention of MCI has provided some new insights but few breakthroughs.

Weaknesses in the design and organization of many of the studies conducted in China have seriously undermined their potential value. Most epidemiological studies are cross-sectional – not longitudinal – so it is not possible to monitor the onset and development of cognitive impairment in individual subjects. Most studies about the diagnosis and subclassification of MCI are also cross-sectional so it is impossible to determine the utility of the subgroups of MCI that are identified. Genetic and neuroimaging studies have identified several potentially important biomarkers, but the studies are rarely duplicated and there is little attempt to integrate these findings with neuropsychological research or with treatment research. And most clinical studies (particular studies in TCM) have small samples from a single non-representative institution, follow subjects for a relatively short period, do not use internationally recognized assessment tools, and do not have blind evaluators assessing the final outcome.

Resolving these issues will require a substantial overhaul of the organization of research about dementia and MCI in China. Proposed studies with samples sizes that are not adequate to test the study hypothesis should not be funded. Funding should focus on multidisciplinary longitudinal studies rather than

on cross-sectional single-discipline studies; this would make it possible to characterize the natural evolution of different proposed subtypes of MCI. Diagnostic studies need to be community-based so they capture the full range of cognitive impairment. Funding streams must be made available to conduct replication studies and follow-up studies of potentially useful biomarkers. Treatment studies should be multi-centered, include large, representative samples of different types of subjects, follow the subjects for a minimum of one year, and, wherever possible, have blind evaluation of outcomes. Finally, all studies should adhere to the basic scientific principle of using standardized methods of assessment so that all findings can be easily replicated by independent investigators.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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中国轻度认知功能损害的研究进展

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摘要: 中国人口的迅速老龄化促进了对老年痴呆及其前体(轻度认知功能损害, MCI)的病因和预防的研究。本文综述了过去十年中国有关 MCI 的研究。有关 MCI 的流行病学、神经心理特征、诊断学、遗传病因学、神经影像学和电生理变化以及治疗方面的广泛研究已提供了一些新的见解, 但很少有突破结果。对于 MCI

的预防与治疗, 未来的发展方向则更注重具有代表性的大样本多学科前瞻性研究, 并使用标准化方法来评估和监测认知功能随着时间的推移而产生的变化。

关键词: 轻度认知功能损害, 痴呆, 研究方法学, 中国

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