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Clinical study

# The associated volumes of sub-cortical structures and cognitive domain in patients of Mild Cognitive Impairment

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ABSTRACT

This study aimed to explore the relationship between sub-cortical structures alterations and the cognitive domains in Mild Cognitive Impairment (MCI) patients, expected to find identifying sub-cortical structure markers of MCI progression to dementia. A total of 67 MCI patients (8 subjects refused to follow up) were recruited, who were divided into 21 stable MCI (sMCI) and 38 progress MCI (pMCI), according to cognitive assays. FreeSurfer software was used to perform volumetric measurements of the sub-cortical structures from 3.0 T magnetic resonance scans. Data revealed that pMCI subjects had lower scores in memory, language, executive and visual spatial compared with sMCI subjects. Compared with the sMCI group, the volume of the left thalamus, bilateral hippocampus, corpus callosum posterior and corpus callosum central was smaller in pMCI subjects. Partial correlation and general linear regression analysis showed that the left hippocampus was predicted region for memory, left thalamus was predicted region for language, executive and visual spatial. These current results suggest that the volumes of sub-cortical structures in stable MCI and progress MCI patients were heterogeneous. Among these regions, the left hippocampus was predicted region for memory, left thalamus was predicted region for language, executive and visual spatial, suggesting that these structures might be important for detecting the subtle effects of MCI patients' cognitive domain or to assess the effectiveness of therapeutic intervention for MCI.



## 1. Introduction

In persons over age 65 years, 14% have sufficient cognitive impairment to warrant a diagnosis of dementia, and an equal number have mild but unequivocal cognitive impairment short of dementia [1]. Individuals with Mild Cognitive Impairment (MCI) have impaired memory and other cognitive domains compared with their contemporaries, but do not yet fulfill the criteria of dementia [2]. Petersen [3] has proposed a "multiple-domain MCI" for patients exhibiting dysfunction across a range of neuropsychological modalities, "single nonmemory cognitive domain MCI" for patients whose cognitive symptoms reflect circumscribed impairment in a nonmemory domain, and "amnestic MCI" where memory loss is the predominate reason for impairment. Amnestic MCI has been proposed as the subtype most likely to portend a diagnosis of Alzheimer's disease (AD). Despite use of different MCI diagnostic criteria, several studies all demonstrate MCI convert to

*Abbreviations:* 3D-TFE, Three-Dimensional Turbo Fast Echo; AD, Alzheimer's disease; ADL, Activities of Daily Living; AFT, Animal Fluency Test; AVLT, Auditory Verbal Learning Test; AVLT-R, Auditory Verbal Learning Test Recall; BNT, Boston Naming Test; CA, Cornu Ammonis; CDR, Clinical Dementia Rating; CDT, Clock Drawing Test; DST, Digit Span Test; DSM-V, Diagnostic and Statistical Manual of Mental Disorders-V; FOV, Field Of View; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; IADL, Instrumental Activities of Daily Living; LMT, Logical Memory Test; LMT-R, Logical Memory Test Recall; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; NSA, Number of Signal Averaged; pMCI, progress Mild Cognitive Impairment; SFT, Speech Fluency Test; sMCI, stable Mild Cognitive Impairment; TE, Echo Time; TMT, Trail Making Test; TR, Repetition Time; T2WI, T2 Weighted Imaging; VCT, Visual Coping Test; VCT-R, Visual Coping Test Recall; VST, Victoria Stroop Test; WMH, White Matter Hyperintensity.

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dementia rates that are higher than the incidence of dementia in the general population, thus lending overall validity to the notion that MCI patients are at increased risk for significant cognitive decline [2]. Roughly half of people with MCI will progress to a more severe form of cognitive decline over about 3 years [4]. But the relationship between progression from cognitive decline to dementia is less clear. Therefore, studies started to focus on identifying markers for the progression of MCI to dementia.

In clinical practice, neuropsychological tests are used to monitor MCI and dementia progression or treatment efficacy. However, although these tests unquestionably reflect an important aspect of disease progression (i.e. functional impairment), they also have several limitations such as relatively low specificity and reliability [5]. During the past few years, there has been a considerable effort to identify additional biomarkers as early indicators of pathological changes to improve the accuracy of the clinical diagnosis of possible/probable AD and the prediction of disease progression from MCI [6]. Several studies also suggested their combination with other features types, such as Magnetic Resonance Imaging (MRI)-based biomarkers, to increase early prediction accuracy [7]. Indeed, Structural MRI studies have proved useful for evaluating the prognosis of individuals with MCI and AD. Previous studies found that grey matter and cortex atrophy in brain regions such as the hippocampus, entorhinal cortex, and medial temporal cortex was observed in most patients diagnosed with MCI and early-stage AD [8,9]. Tondelli et al. found that reduced grey matter volume in medial temporal lobe regions including the hippocampal formation may precede the clinical onset of AD by 10 years [10]. The applicability of hippocampal subfield segmentation in clinical populations has gained increasing attention, with different studies providing evidence for predominant Cornu Ammonis (CA)1 and subiculum atrophy in MCI [11,12] and AD [13,14]. Cortical thickness analysis constitutes another widely accepted approach to measure gray matter atrophy in AD, and cortical thinning has been found in MCI and AD [15,16]. Advanced segmentation techniques now permit the quantification of sub-cortical volumes and provide the basis for sub-cortical structures analysis. Some sub-cortical structures, such as the amygdala, putamen, caudate, and thalamus, are affected in individuals with MCI and AD [17–19]. Although volume loss in the thalamus [20–22], putamen [21,23,24] and caudate nucleus [17,21,23] have been identified in AD, little is known about sub-cortical volumetric differences in MCI in general, and in future converters in particular.

The purpose of this study was to explore the relationship between sub-cortical structures alterations and the cognitive domains in MCI patients, expected to find identifying sub-cortical structure markers of MCI progression to dementia. These observations might be helpful for physicians to distinguish progress MCI and take earlier intervention.

## 2. Subjects and methods

### 2.1. Patients

A total 67 MCI patients, had neuropsychological screening between February 2016 and September 2016, were enrolled from the Department of Neurology of the Affiliated Drum Tower Hospital of Nanjing University Medical School in this study. The ethics committees of the Affiliated Drum Tower Hospital of Nanjing University Medical School approved the study protocol (clinical trials government identifier: NCT01364246). All patients provided written informed consent. All patients were right-handed.

All subjects were examined using a standardized protocol, including a neuropsychological screening, a whole brain MRI, a general medical, and a neurological examination that was performed by a neurologist. The clinical diagnosis of MCI was made by a multidisciplinary consensus meeting according to the MCI diagnosis criteria [6]. The criteria were as follows: 1. Concern regarding a change in cognition from the patient, knowledgeable informant, or from a skilled clinician observing the patient. 2. Objective evidence of impairment (from cognitive testing) in one or more cognitive domains, including memory, executive function, attention, language, or visual spatial skills. 3. Preservation of independence in functional abilities (although individuals may be less efficient and make more errors at performing ADL/IADL than in the past). 4. No evidence of a significant impairment in social or occupational functioning. Individuals with any cerebrovascular abnormalities, as determined by T2WI or a history of brain injury or alcoholism were excluded from the study. Subjects with visible White Matter Hyperintensity (WMH; grade 2 or more according to a reported rating scale [25]) and a history of epilepsy, encephalodysplasia were also excluded.

8 subjects refused to follow up. After 12 (11.84 ± 1.32) months, 59 subjects were reassessed cognitive function by neuropsychological testing. The 59 subjects then were divided into the following two groups on the basis of final neuropsychological screening:

1. Stable MCI (sMCI): satisfied the above MCI criteria.
2. Progress MCI (pMCI): satisfied the DSM-V dementia criteria [26].

### 2.2. Neuropsychological assessments

The cognitive function of all subjects was evaluated using a standardized neuropsychological test battery. Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) were used for Cognitive screening. Psychiatric was evaluated by the Neuropsychiatric Inventory (NPI). Emotional was assessed by the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA). Daily life ability was assessed by the Activities of Daily Living Scale (ADL).

Auditory Verbal Learning Test (AVLT) and Logical Memory Test (LMT) were used for memory domain assessment. Speech Fluency Test (SFT), Animal Fluency Test (AFT) and Boston Naming Test (BNT) were used for Language domain assessment. Attention domain was evaluated by the Digit Span Test (DST). Executive domain was evaluated by Trail Making Test (TMT) and Victoria Stroop Test (VST). Visual Coping Test (VCT) and Clock Drawing Test (CDT) were used for visual spatial ability assessment.

The raw scores of all tests were transformed to a scale ranging from 0 to 10 based on all possible scores, as per the following formula:

$$X' = ([X - Xmin]/[Xmax - Xmin]) * 10.$$

For the tests scoring the subjects' reaction times, the following formula was utilized:

$$X' = 10 - ([X - Xmin]/[Xmax - Xmin]) * 10.$$

For a better overall assessment of the performance of certain cognitive functions, the transformed scores within a cognitive domain were averaged to obtain the function scores.

### 2.3. Image acquisition and processing

Images were acquired on a 3 Tesla MR scanner (Achieva 3.0T TX dual-source parallel RF excitation and transmission technology, Philips Medical Systems, The Netherlands), with an eight-channel phased array coil. A Three-Dimensional Turbo Fast Echo (3D-TFE) T1 weighted imaging sequence with Repetition Time (TR)/Echo Time (TE) = 9.8/4.6 ms; flip angle of 8°; Number of Signal Averaged

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