



Research report

Plastic modulation of episodic memory networks in the aging brain with cognitive decline

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HIGHLIGHTS

- Self-referential processing network made critical contributions to episodic memory retrieval in aMCI.
- Self-referential processing mediate the cooperation of the episodic memory retrieval sub-networks in aMCI.
- Plastic modulation of episodic memory networks in aMCI.

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ABSTRACT

Social-cognitive processing has been posited to underlie general functions such as episodic memory. Episodic memory impairment is a recognized hallmark of amnesic mild cognitive impairment (aMCI) who is at a high risk for dementia. Three canonical networks, self-referential processing, executive control processing and salience processing, have distinct roles in episodic memory retrieval processing. It remains unclear whether and how these sub-networks of the episodic memory retrieval system would be affected in aMCI. This task-state fMRI study constructed systems-level episodic memory retrieval sub-networks in 28 aMCI and 23 controls using two computational approaches: a multiple region-of-interest based approach and a voxel-level functional connectivity-based approach, respectively. These approaches produced the remarkably similar findings that the self-referential processing network made critical contributions to episodic memory retrieval in aMCI. More conspicuous alterations in self-referential processing of the episodic memory retrieval network were identified in aMCI. In order to complete a given episodic memory retrieval task, increases in cooperation between the self-referential processing network and other sub-networks were mobilized in aMCI. Self-referential processing mediate the cooperation of the episodic memory retrieval sub-networks as it may help to achieve neural plasticity and may contribute to the prevention and treatment of dementia.

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1. Introduction

Social cognition has been posited to underlie general functions such as episodic memory [1]. Amnesic mild cognitive impairment (aMCI) cases are believed to represent high annual transition rates to Alzheimer's disease (AD) [2], and episodic memory impairment is a recognized hallmark of AD spectrum that worsens progressively and has undisputed clinical significance for patients [3]. Episodic memory refers to the ability to encode, retain and retrieve information related to personal events and experiences occurring at specific times and places [4].

Global decline in episodic memory retrieval or recognition is a central feature of aMCI [5]. Episodic memory tasks have been studied extensively with fMRI to identify hippocampal dysfunction during memory retrieval in aMCI subjects [6–11]. Our previous fMRI study further explored aMCI and showed significantly lower hippocampal functional connectivity in a network involving the prefrontal lobe, temporal lobe, parietal lobe, and cerebellum and higher functional connectivity to more diffuse areas of the brain than normal aging control subjects [12]. There is growing evidence that memory processing involves other cortical systems that contribute in a somewhat hierarchical manner, resulting in progressively complex representations that are integrated and associated with bound memory traces probably stored in the medial temporal lobe [13]. Moreover, a recent meta-analysis indicated that three canonical brain networks, self-referential processing (i.e., default mode network, DMN, which is associated

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with greater activity during “Remember” than during “Know” responses), executive control processing (i.e., dorsal network, which is associated with greater activity levels for “Know” than for “Remember” responses) and salience processing (i.e., ventral network, which is associated with increasing familiarity), had dissociating roles in episodic memory retrieval [14]. This study supported the three sub-networks as components of networks that respond in concert rather than regions activated in isolation [15]. However, it remains unclear whether and how the sub-networks of the episodic memory retrieval system would be affected in aMCI.

There has been increasing evidence demonstrating that neural plasticity in persons at risk for developing AD improves compensatory mechanisms and partly restores the affected functions [16]. In the resting-state neural networks, bidirectional modification of functional integrity in cerebro-cerebellar networks associated with a pre-existing neural reserve through the adjusted connectivity between different networks was observed in dementia [17]. Our previous combination of resting-state and task-state fMRI studies also suggested that these mobilized and redistributed resources of the DMN appeared to replace task-positive network function to some degree to complete a given task in aMCI subjects [18]. Converging evidence has implicated episodic memory encoding [19] and working memory encoding [20] to be associated with early plasticity within hippocampal circuits. These investigations may provide new clues to examine the pathophysiology of neurodegenerative diseases and to determine the progression of aMCI into AD and have implications for understanding memory function in diseased brain states. Despite these insights, uncertainty remains concerning the plasticity of the episodic memory retrieval sub-networks underlying aMCI.

In this task-state fMRI study, we constructed systems-level episodic memory retrieval sub-networks using two computational approaches, a multiple region-of-interest based approach and a voxel-level functional connectivity based approach, which would be used to show (i) more conspicuous alterations in self-referential processing of the episodic memory retrieval network will be identified in subjects with aMCI, and (ii) increases in cooperation between the self-referential processing network and other sub-networks will be mobilized in aMCI.

2. Methods

2.1. Participants

The Research Ethics Committee of the Affiliated Zhong-Da Hospital of Southeast University approved the experimental protocols, and informed consent was obtained from all subjects. Briefly, 28 aMCI subjects and 23 healthy controls were recruited. The recruitment of aMCI subjects included single domain (only memory impairment) and multiple domains (memory impairment plus impairment in at least one other cognitive domain). All aMCI subjects were included in the study according to Petersen et al. [21] and others' recommendations [22]: (i) subjective memory impairment corroborated by the subject and an informant; (ii) objective memory performance documented by an AVLT-delayed recall score less than or equal to 1.5 SD of age- and education-adjusted norms (cut-off of ≤ 4 correct responses on 12 items for patients with ≥ 8 years of education); (iii) MMSE score of 24 or higher; (iv) CDR of 0.5; (v) no or minimal impairment in daily activities; and (vi) absence of dementia or insufficient dementia to meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's criteria. In addition, the controls were required to have a CDR of 0, an MMSE score ≥ 26 , and an

AVLT-delayed recall score >4 for subjects with 8 or more years of education.

2.2. Exclusion criteria

Participants with a history of known stroke, alcoholism, head injury, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric illness, major medical illness, or severe vision or hearing loss were not included in this study.

2.3. fMRI paradigm of episodic memory retrieval task

The details of the present paradigm of episodic memory tasks have been described by others' AD studies [7] and our previous aMCI studies [12]. First, a training session was carried out 45 min prior to the scanning session, and a second training session was performed 15 min prior to the scanning session. Each training session consisted of 5 different pictures with neutral mood, each picture presented repeatedly 15 times in a pseudorandom order. Every picture was presented for 2800 ms with a 200 ms interstimulus interval. Each scanning session consisted of 90 exposures, including 45 'old' pictures that appeared in pseudorandom order as one, two, three, four or five consecutive items and 45 'new' pictures that were presented once each, also in pseudorandom order. During scanning, the participants had to judge whether the presented picture was 'old' or 'new'. To indicate their choice, they used a two-button fiber optic box held in the right hand: the index finger was used to respond to 'old' pictures and the middle finger to respond to 'new' pictures. The Presentation application recorded these button responses (reaction time and accuracy).

2.4. Data acquisition

The subjects were scanned using a General Electric 1.5T scanner (General Electric Medical Systems, USA) with a homogeneous birdcage head coil. Conventional axial Fast Relaxation Fast Spin Echo sequence (FRFSE) T2 weighted anatomic MR images were obtained to rule out cerebral infarction or other lesions: repetition time (TR)=3500 ms, echo time (TE)=103 ms, flip angle (FA)=90°, acquisition matrix=320 × 192, field of view (FOV)=240 mm × 240 mm, thickness=6.0 mm, gap=0 mm and no. of excitations=2.0. Task-state scans involved the acquisition of 30 contiguous axial slices using a gradient-recalled echo-planar imaging pulse sequence: TR=3000 ms, TE=40 ms, FA=90°, acquisition matrix=64 × 64, FOV=240 × 240 mm, thickness=4.0 mm, gap=0 mm and 3.75 × 3.75 mm² in-plane resolution and NEX=1.0. The scanning session generated 92 vol over a duration of 4 min and 36 s. The first 6 s contained word cues to ready the participants.

2.5. Data pre-processing

Data analyses were performed with SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>). The first two volumes of the scanning session were discarded to allow for T1 equilibration effects. The remaining images were corrected for timing differences and motion effects. Participants with head motion more than 2.5 mm maximum displacement in any direction or 2.5° of angular motion during the scan was excluded. Then, the resulting images were spatially normalized into the SPM5 Montreal Neurological Institute echo-planar imaging template using the default settings and resampling to 3 × 3 × 3 mm³ voxels that were smoothed with a Gaussian kernel of 8 × 8 × 8 mm.

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