Behavioural Brain Research 288 (2015) 94–102

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

State-based functional connectivity changes associate with cognitive decline in amnestic mild cognitive impairment subjects

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HIGHLIGHTS

- Neural basis of episodic memory (EM) network is different when situation switched.
- AMCI patients showed different constructs of EM network from rest to task states.
- State-based altered connectivity can predict cognitive decline in aMCI patients.

ARTICLE INFO

Article history:
Received 14 January 2015
Received in revised form 4 April 2015
Accepted 9 April 2015
Available online 20 April 2015

Keywords:
Episodic memory
Functional connectivity
Neural network
Functional magnetic resonance imaging
Amnestic mild cognitive impairment

ABSTRACT

Episodic memory (EM) dysfunction is a central characteristic of amnestic mild cognitive impairment (aMCI) subjects, and has a high risk of converting to Alzheimer's disease (AD). However, it is unknown how the EM network is modulated when a situation is switched. Twenty-six aMCI and twenty-two cognitively normal (CN) subjects were enrolled in this study. All of the subjects completed multi-dimensional neuropsychological tests and underwent functional magnetic resonance imaging scans during a resting-state and an episodic memory retrieval task state. The EM network was constructed using a seed-based functional connectivity (FC) approach. AMCI subjects showed poorer cognitive performances in the episodic memory and executive function. We demonstrated that connectivity of the left posterior parahippocampal gyrus (LpPHG) connected to the left ventral medial prefrontal cortex and the right postcentral gyrus (RPCG) was significantly decreased in aMCI subjects compared to CN subjects. Meanwhile, there was increased connectivity of the LpPHG to the right dorsal medial prefrontal cortex (RDMPFC), RPCG, left inferior parietal cortex, and bilateral superior parietal lobe in all of the subjects that changed from a resting-state to a task-state. Interestingly, the changed LpPHG-RDMPFC connectivity strength was significantly correlated with EM scores and executive function in the aMCI subjects. As a result, general brain regions are functionally organized and integrated into the EM network, and this strongly suggests that more cognitive resources are mobilized to meet the challenge of cognitive demand in the task state. These findings extend our understanding of the underlying mechanisms of EM deficits in aMCI subjects.

1. Introduction

Episodic memory (EM) impairment is the predominant cognitive dysfunction and primary clinical feature of amnestic mild cognitive impairment (aMCI) [1], and has a high risk of progressing to Alzheimer's disease (AD) [2,3]. This deficit of the episodic memory system typically results in the inability to learn new information (encoding) and recall recently learned information (retrieval) [4]. Numerous studies with functional neuroimaging approaches have described how the preservation of memories can relate to encoding and retrieval discrimination, and these studies have also demonstrated that there are distinct neural circuits that are separately involved in the process of encoding and retrieval of episodic memory [5,6]. Although the fundamental and selective role of the hippocampus in episodic memory across mammalian species has been addressed, little is known about the potential effects of other structures, such as the parahippocampal gyrus (PHG), on the large-scale distributed episodic memory system. Also, abnormalities of functional coupling depends on these well-integrated networks, which are primarily reflected by intrinsic functional connectivity, and are the neural basis of impaired cognition at resting or task-dependent state in subjects with aMCI [7–9]. As such, several

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http://dx.doi.org/10.1016/j.bbr.2015.04.013
0166-4328/

questions remain. What is the functional pattern of neural activity associated with the core anatomical structure, such as PHG, within the episodic memory system? How is the information integration of the episodic memory system under different conditions manipulated, and how are these changes related to cognitive performance?

The PHG, as a key node of the episodic memory retrieval network [10–12], is essential for transferring the contextual-related new information between the cortex and the hippocampus [13,14], indicating that the PHG region may play a gating mechanism for transferring information from the hippocampus to the neocortex during memory retrieval [15,16]. Importantly, task-dependent fMRI studies have shown that enhanced activity in the PHG region was closely associated with successful retrieval [17], and reduced activity in the left PHG was reported when MCI and AD patients performed episodic memory retrieval tasks [7,18–20], and this resulted in dysfunction of the retrieval of the episodic memory system when the PHG region was damaged [21]. Furthermore, subregions of the PHG play different roles in memory processing. Most of the caudal portion of the PHG was occupied by retrieval conditions [22]. The posterior PHG (pPHG) is more functionally connected to memory and is involved in retrieval based on processing and analyzing spatial details of contexts [23,24]. Meanwhile, the left pPHG (LpPHG) is associated with successful spatial retrieval, rather than familiarity, during the viewing of objects and faces [25–29]. Taken together, these findings highly suggest the importance of the PHG, especially in the LpPHG region, during the episodic memory retrieval task. However, it is still unknown whether the alteration of PHG network is associated with cognitive function when situations are changed. Thus, we proposed the network-based hypothesis that the changed functional connectivity of the LpPHG network from resting-state to episodic memory retrieval task state can predict the cognitive decline in aMCI subjects.

Therefore, in the current study we investigated: (1) whether there are differences in functional connectivity of the LpPHG network in CN subjects compared to aMCI subjects at rest and task state; (2) the correlation between the cognitive performances and altered functional connectivity of the LpPHG network in aMCI subjects.

2. Methods and materials

2.1. Subjects

Thirty aMCI subjects (age range 65–83 years, mean 72.35 ± 5.08 years) and 25 cognitively normal (CN) subjects (age range 65–79 years, mean 72.82 ± 3.47 years) were recruited into this study. All of the subjects were enrolled through community health screening activities and newspaper advertisements (all were Han Chinese and right handed) in Nanjing, China. The study protocol was approved by the Research Ethics Committee of the Affiliated Zhongda Hospital, Southeast University, and written informed consent was obtained from all participants. Four aMCI and three CN subjects were excluded because of incomplete image scanning during fMRI runs, yielding a total of 26 aMCI and 22 controls for final analysis.

The diagnostic criteria used to identify aMCI subjects were those reported by Petersen et al. [30–32], including: (1) subjective memory impairment complained by subject and an informant; (2) objective memory performances documented by the Auditory Verbal Memory Test-Delayed Recall (AVMT-DR) score that is ≤1.5 standard deviation (SD) of age-adjusted and education-adjusted norms (the cutoff was ≤4 correct responses on 12 items for 8 years of education) [33]; (3) normal general cognitive functioning as evaluated by a Mini-Mental State Exam (MMSE) score of 24 or higher [34]; (4) a Clinical Dementia Rating (CDR) of 0.5, with at least a 0.5 in the memory domain [35]; (5) none or minimal impairment in activities of daily living; (6) absence of dementia or an insufficient level to meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for AD [36]. Participants were excluded if they had a past history of known stroke (modified Hachinski score >4) [37], alcoholism, head injury, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric illness (excluded by clinical assessment and case history), major medical illness (e.g., cancer, anemia, thyroid dysfunction), or severe visual or hearing loss, as well as contraindications for MRI scanning. In addition, none of the aMCI subjects were on cognitive enhancing therapies. Control subjects were required to have a Clinical Dementia Rating of 0, an MMSE score ≥26, and an AVMT-DR >4 for those with 8 or more years of education. All subjects underwent comprehensive neuropsychological assessments, including AVMT-DR, Rey–Osterrieth Complex Figure Test (CFT) and CFT Delayed Recall (CFT-DR), Trail Making Tests (TMT) A and B, Digit Span Test (DST), Symbol Digit Modalities Test (SDMT), and Clock Drawing Test (CDT), which covered memory, executive function, perceptual speed, and visual-spatial cognitive domains. The included and excluded assessments were performed by an experienced neuropsychiatrist who conducted a structured interview with the subjects and their informants.

2.2. Resting-state functional magnetic resonance imaging (R-fMRI)

All participants were scanned by a General Electric 1.5 Tesla scanner (General Electric Medical Systems, USA) with a homogeneous birdcage head coil. High resolution spoiled gradient-recalled echo (SPGR) 3D axial images were acquired for anatomical reference. The parameters were: repetition time (TR) = 9.9 ms, echo time (TE) = 2.1 ms, flip angle (FA) = 15°, acquisition matrix = 256 × 192, field of view (FOV) = 240 mm × 240 mm, thickness = 1.0 mm, gap = 0 mm, number of excitations (NEX) = 1.0. Axial resting-state (no cognitive tasks were performed, eyes closed, and ears occluded) functional connectivity fMRI (R-fMRI) datasets were obtained in 7 min and 6 s with a gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence, and 142 volumes were acquired in total. The R-fMRI imaging parameters were: TR = 3000 ms, TE = 40 ms, FA = 90°, acquisition matrix = 64 × 64, FOV = 240 mm × 240 mm, thickness = 4.0 mm, gap = 0 mm, and 3.75 mm × 3.75 mm in-plane resolution; NEX = 1.0.

2.3. Task-activated functional magnetic resonance imaging (T-fMRI)

The associative episodic retrieval task was obtained from the International Affective Picture System [38]. The task involved serial presentation of color photographs with neutral mood, consisting of two identical training sessions prior to the scan and one scanning session. The first training session occurred 45 min prior to the scanning session, and the second training session lasted 15 min. Each session lasted 135 s. Participants were asked to view and remember the training pictures. The duration of the scanning session was 4 min and 36 s, and the first 6 s contained word cues to prepare for the participants. Every picture was presented for 2800 ms with a 200 ms interval time between the pictures. The scanning session consisted of 90 exposures, including 45 "old" pictures (presented in the training sessions) that appeared pseudo-randomly as one, two, three, four, or five consecutive items and 45 "new" pictures (not presented in the training sessions) that were presented only once, pseudo-randomly. The "old" pictures were also intermixed pseudo-randomly with the "new" pictures. A two-bottom fiber-optic box held in the right hand was used to record participants' judgment as to whether the presented picture was "old" or "new". The index