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Reorganization of anterior and posterior hippocampal networks associated with memory performance in mesial temporal lobe epilepsy

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H I G H L I G H T S

- Functional connectivity based on resting-state fMRI was analyzed in mesial temporal lobe epilepsy (mTLE) patients with unilateral hippocampal sclerosis.
- Left and right mTLE have differential organization of anterior and posterior hippocampal networks.
- The alterations of functional connectivity in mTLE were related to verbal memory performance.

A B S T R A C T

Objective: To investigate the pattern of functional demarcation of hippocampal network and its relationship with memory performance in mesial temporal lobe epilepsy (mTLE) with unilateral hippocampal sclerosis.
Methods: Resting state fMRI data were acquired from fifteen left mTLE patients, fourteen right mTLE patients and twenty healthy subjects. We explore the hippocampal-cortical alterations and corresponding inter-hemispheric functional connectivity (FC) across anterior and posterior hippocampal networks. The association between FC and memory performance was assessed.
Results: Left mTLE showed increased intra-hemispheric FC in anterior hippocampal networks, including left anterior hippocampal-entorhinal cortex and right anterior hippocampal-orbitofrontal cortex, and decreased inter-hemispheric FC between anterior hippocampus, entorhinal cortex and posterior cingulate cortex. Right mTLE was associated with extensive reduction in inter-hemispheric FC along the areas of anterior and posterior hippocampal networks. Intra-hemispheric FC between left anterior hippocampus and entorhinal cortex was positively correlated with verbal memory in left mTLE. Inter-hemispheric FC between posterior parahippocampal gyrus was negatively correlated with verbal memory in right mTLE.
Conclusions: Our findings suggested that left and right mTLE exhibit different neural reorganization patterns of anterior and posterior hippocampal networks associated with verbal memory.
Significance: The findings may facilitate the characterization of mTLE associated with memory deficit.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) is the prototypical refractory focal epilepsy characterized by memory deficit, warranting surgical intervention (Elger et al., 2004; Berg, 2008). Milner's and other studies found that the mesial temporal lobe structures, which encompass the hippocampus and extra-hippocampal regions, such as entorhinal cortex (EC) and

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parahippocampal cortex, were critical structures underlying human memory (Squire and Zola-Morgan, 1991). Most neuroimaging modalities in mTLE patients with HS studies demonstrated that abnormal epileptogenic hippocampus altered the structure and function of bilateral adjacent mesial temporal lobe cortex, resulting in verbal and non-verbal memory deficits (Dupont et al., 2000; Alessio et al., 2004; Bonilha et al., 2004). Furthermore, subsequent studies suggested that mTLE is a ''large-scale network disease", which also extends into broader extra-mesial temporal cortex abnormalities associated with memory function (Keller et al., 2009; Liao et al., 2011; Sidhu et al., 2013). However, based on the complexity of hippocampal formation and function, a diverse range of reorganized patterns were reported in presurgery and post-surgery studies of large-scale networks associated with pathological changes in hippocampus. A few studies reported beneficial plasticity in memory performance while others showed maladaptive plasticity (Figueiredo et al., 2008; Bonelli et al., 2010; McCormick et al., 2013, 2014).

Recently, considerable evidence derived from animal experiments and human fMRI studies indicated that the anterior and posterior portions of the hippocampus formed two functionally distinct memory circuits, each circuit delineating distinct anatomical connections to other related brain regions (Kahn et al., 2008; Fanselow and Dong, 2010; Ranganath and Ritchey, 2012). The anterior hippocampus is directly connected to the EC, temporal pole (TP) and orbitofrontal cortex (OFC) via white matter fibers, resulting in anterior hippocampal networks, which are primarily associated with verbal memory. The posterior hippocampus is connected to the posterior parahippocampal gyrus (PPHG), posterior cingulate (PCC), thalamus (THA), dorsolateral prefrontal cortex (DLPFC) and lingual gyrus (LG) associated with polysynaptic pathway, resulting in posterior hippocampal networks, which are mainly associated with non-verbal memory (Duvernoy et al., 2004; Poppenk and Moscovitch, 2011). This conceptual framework may elucidate the neural architecture of diverse memory systems in mTLE. A recent study investigated the anterior and posterior hippocampal networks in TLE and found distinct reorganized patterns of intra-hemispheric FC between anterior and posterior hippocampal networks associated with memory (Voets et al., 2014). However, this study was based on a cohort of TLE with mixed etiology. Inter-hemispheric FC is closely related to high-order memory process (Gazzaniga, 2000; Shen et al., 2015). Particularly, inter-hemispheric FC between hippocampus was predictive of the capacity to episodic memory in healthy adults, which reflects intrinsic connectivity within mesial temporal lobe memory system (Wang et al., 2010b). The alterations of inter-hemispheric FC of nodes within anterior and posterior hippocampal networks were still unclear. Importantly, studies of global cerebral networks demonstrated distinct pattern of functional connectivity in the left mTLE and right mTLE, with the left mTLE showing a more predominant impairment of FC, particularly in the left hemisphere (Pereira et al., 2010; Kucukboyaci et al., 2013). Conversely, the right mTLE showed a greater reduction in global inter-hemispheric FC than the left mTLE (Chiang et al., 2014).

We hypothesized that the left and right mTLE show differential organization of anterior and posterior hippocampal networks. Furthermore, the relationship between the anterior or posterior hippocampal networks and the specific verbal or non-verbal memory in left and right mTLE still remains unknown. Our study was based on a cohort of unilateral mTLE with hippocampal sclerosis and demonstrated the relationship between memory performance and altered intra-hemispheric and inter-hemispheric resting state FC across anterior and posterior hippocampal network. We used the resting state FC method to characterize the intra-hemispheric functional relationship between brain regions. In addition, inter-hemispheric functional interaction was also evaluated using resting-state functional homotopy, which was used to reveal processes such as memory function in previous studies (Salvador et al., 2008; Stark et al., 2008; Zuo et al., 2010).

2. Methods and materials

2.1. Subjects

Fifteen right-handed mTLE patients with left HS and fourteen right-handed mTLE patients with right HS were recruited from the Department of Neurology, Second Affiliated Hospital of Zhejiang University School of Medicine from 2014 to April 2016. The study was approved by the Ethics Committee of our hospital (Study number 2014-151). Written informed consent was obtained from each subject in this study. Each patient was diagnosed based on detailed medical history, neurological examination, scalp video-EEG monitoring with sphenoidal electrodes, and conventional MRI with strict inclusion/exclusion criteria, as described previously (Li et al., 2015). Twenty age-matched right-handed healthy volunteers with documented absence of neurological or psychiatric disorders were enrolled in this study. The detailed combinations of antiepileptic drugs (AEDs) were recorded in all mTLE patients. The AEDs taken by all patients were carbamazepine (left: 8/15; right: 10/14), clonazepam (left: 3/15; right: 1/14), lamotrigine (left: 4/15; right: 4/14), levetiracetam (left: 7/15 mTLE; right: 5/14), oxcarbazepine (left: 5/15; right: 1/14), sodium valproate (left: 4/15; right:8/14), topiramate (left: 1/15; right: 1/15).

2.2. Neuropsychological testing

All patients and healthy controls were subjected to neuropsychological evaluation including the Edinburgh Handedness Inventory; verbal paired associates and logical memory of the Wechsler Memory Scale-Revised, Chinese version (WMS-RC) to investigate verbal memory; and recognition and visual reproduction of the WMS-RC to investigate non-verbal memory. The immediate recall raw score was used as the performance measure. The total raw scores of WMS-R were transformed to memory quotient (MQ) using normative data according to age.

2.3. Imaging and data acquisition

MRI images were acquired using a 3.0 Tesla Discovery MR750 (GE Healthcare) MRI scanner with a 8-channel head coil at the Department of Radiology, the Second Affiliated Hospital of Zhejiang University School of Medicine. All the patients were scanned during the interictal periods, and instructed to maintain their eyes closed while allowing the mind to wander and relax during the scan. A three-dimensional brain volume imaging (3D-BRAVO) sequence was used to acquire structural images with the indexes as follows: repetition time (TR) = 8.208 ms, echo time (TE) = 3.220 ms, inversion time (TI) = 450 ms, Flip Angle (FA) = 12°, matrix size: 256×256, voxel size = $0.47 \times 0.47 \times 1$ mm^3, and 206 slices. A high-resolution T2-weighted structural MRI angulated perpendicular to the longitudinal axis of the hippocampus was scanned to make a definite diagnosis of hippocampal sclerosis with indexes as follows: TR = 5514 ms, TE = 176 ms, FA = 110°, matrix size: 512×512, voxel size = $0.39 \times 0.39 \times 2$ mm^3, slice thickness = 2 mm (no gap), and 30 slices. Blood oxygenation level-dependent (BOLD) signal was measured using a gradient-echo echo-planar imaging (EPI) sequence with indexes as follows: TR = 2000 ms, TE = 30 ms, FA = 77°, matrix size: 64×64, voxel size = $3.75 \times 3.75 \times 4$ mm^3, slice thickness = 4 mm (no gap), and 38 slices. A total of 205 volumes were acquired for each subject.