



Asymmetry in cross-hippocampal connectivity in unilateral mesial temporal lobe epilepsy

Hong Li^{a,1}, Wenliang Fan^{a,1}, Jie Yang^b, Shuyan Song^c, Yuan Liu^a, Ping Lei^a,
Lochan Shrestha^a, Grace Mella^a, Wei Chen^{d,e,**}, Haibo Xu^{a,f,*}

^a Department of Radiology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

^b Department of Communication Sciences and Disorders, Massachusetts General Hospital Institute of Health Professions, Boston, MA, USA

^c School of Life Science and Technology, Key Laboratory of Image Processing and Intelligent Control of Education Ministry of China, Huazhong University of Science and Technology, Wuhan 430074, China

^d Department of Radiology, Tongji Hospital, Tongji University School of Medicine, Shanghai 200065, China

^e Radiology and Medical Imaging Center, The First People's Hospital of Yibin, Sichuan 644000, China

^f Department of Radiology, Zhongnan Hospital of Wuhan University, Wuhan 430071, China

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ABSTRACT

Mesial temporal lobe epilepsy (mTLE) is mostly characterized by hippocampal sclerosis (HS) changes. Although considerable progress has been made in understanding the altered functional network of mTLE patients, whether one side of the abnormal hippocampal (HP) structure will affect the other healthy side of the hippocampal network is still unclear. Here, we used a seed-based method to explore the commonly alternative hippocampal network in mTLE patients by comparing the bilateral hippocampal network of unilateral mTLE patients with healthy control participants. We observed that both sides of the hippocampal network in unilateral mTLE patients were changed independent of the affected or “healthy” side, which may suggest a common plasticity network for both sides of hippocampal sclerosis mesial temporal lobe epilepsy patients. Furthermore, using the HP as the ROI, we found that the functional connectivity of the intra-HP in the left mTLE-HS group was moderately positively correlated with the duration of the disease, while a strong negative correlation between functional connectivity of the intra-HP and duration were detected in the right mTLE-HS group, which suggested that it was easier for the right HP than the left HP to communicate with the contralateral HP according to the progression of mTLE disease because the hippocampus plays different roles in the communication and compensatory mechanism associated with the contralateral side of the hemisphere. We hope that this potential relevance may help us to better characterize mTLE with hippocampal sclerosis and ultimately assist in providing a better diagnosis and more accurate invasive treatments of mTLE.

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1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common form of focal epilepsy in adults, and hippocampal sclerosis (HS)

* Corresponding author at: Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China.

** Corresponding author at: Department of Radiology, Tongji Hospital, Tongji University School of Medicine, No. 389 Xincun Road, Shanghai 200065, China.

E-mail addresses: 248026233@qq.com (H. Li), fanwenliang168@163.com (W. Fan), kingsleyang@gmail.com (J. Yang), song_shuyan@163.com (S. Song), 309105825@qq.com (Y. Liu), leiping_rosemary@126.com (P. Lei), lochan.shrestha@yahoo.com (L. Shrestha), gracegloriam@gmail.com (G. Mella), q1530831809@qq.com (W. Chen), xuhaibo1120@hotmail.com (H. Xu).

¹ These authors contributed equally as joint first authors to this work.

is the most common cause of refractory mesial temporal lobe epilepsy, which requires surgical treatment (Berg, 2008). Conventional MRI (cMRI) revealed a structural abnormality in the hippocampus and other brain regions of mTLE-HS patients due to hippocampal sclerosis (Wieser, 2004), and this structural damage has been reported to be associated with the duration of the disease and memory impairments (Alessio et al., 2004; Morgan et al., 2015). Advanced MRI techniques, task-oriented fMRI and resting-state functional connectivity MRI (rs-fcMRI) have recently been widely used to examine how the impairment in the hippocampus, respectively, influences itself and HP-cortical neural connectivity in mTLE patients. For example, McCormick et al. observed reduced connectivity from the posterior cingulate cortex (PCC) to the epileptogenic hippocampus and increased PCC connectivity to the contralateral hippocampus (McCormick et al., 2013). Overall, converging evidence indicates reduced connectivity with the epileptogenic

Table 1
Summary of the demographic and clinical data.

Demographic	Control (n = 13)	Left mTLE (n = 11)	Right mTLE (n = 11)	P-value
Age (mean \pm SD, year)	26.8 \pm 7.0	25.5 \pm 9.3	23.5 \pm 9.8	0.663 ^a
Gender	7M, 6F	7M, 4F	9M, 2F	0.350 ^b
Epilepsy duration (year)	N/A	9.4 \pm 8.2	5.2 \pm 3.5	0.134 ^c
Seizure frequency (times/month)	N/A	1.1 \pm 0.7	1.3 \pm 1.4	0.647 ^c
Seizures type (subjects)	N/A	CPS: 11; SGT: 9; SPS: 2	CPS: 11; SGT: 8; SPS: 2	N/A

CPS, complex partial seizures; SGT, secondary generalized tonic–clonic seizure; SPS, simple partial seizure; F, females; M, males.

^a p-Value was obtained using ANOVA (two tailed).

^b p-Value was obtained using a Pearson χ^2 test (two-tailed), with a continuity correlation for $n < 5$.

^c p-Value was obtained using the independent-sample *t*-test (two-tailed).

hemisphere of mTLE-HS patients and increased connectivity to the contralesional hemisphere (usually the healthy side) (Addis et al., 2007; Bettus et al., 2009; Campo et al., 2013). Researchers have also identified imaging biomarkers of functional connectivity (FC) that may serve as clinical indicators of disease severity. Morgan's series of studies found that an increase in duration (>10 years) of mTLE-HS has a linear relationship with increased hippocampal connectivity (Morgan et al., 2011); the FC between the right hippocampus and ventral lateral nucleus of the right thalamus can distinguish seizure-free patients with left and right mTLE-HS with high sensitivity and specificity (Morgan et al., 2012). The PCC connectivity to the epileptogenic and contralateral hippocampus in association with presurgical and postsurgical memory function proved to be a superior index for explaining the variance in memory change following surgery (McCormick et al., 2013).

There have been some studies on hippocampal networks in TLE patients using intracranial electroencephalography (Bettus et al., 2008; Schevon et al., 2007). However, these studies were limited to the immediate areas surrounding the intracranial electrode contacts, which is a limitation of EEG methods. Thus, many studies used other noninvasive methods to identify neural activities during the brain resting state without performing an explicit task in mTLE patients (Holmes et al., 2014; Morgan et al., 2010; Pereira et al., 2010; Pittau et al., 2012). Previous studies mostly involved the FC of the entire structure of the hippocampus and associated it with relatively static and chronic indices, such as the disease duration and hippocampal volume, which were found to not be powerful indicators of outcome. Moreover, the abnormal effect of functional or anatomical hippocampus network always results in complex cognitive and behavioral conditions. Furthermore, the mechanisms underlying brain plasticity in mTLE remain largely unknown (Berg, 2008; Pittau et al., 2012). Thus, we investigated how impairment in mTLE-HS will affect the healthy HP network, i.e., contralateral to the

side of mTLE-HS because this is more meaningful when compared to normal healthy controls.

The objectives of the present study was to use rs-fcMRI to (1) identify alterations in FC patterns of the hippocampus in two groups of patients, those with left and right mTLE-HS; (2) characterize the intra hippocampal functional connectivity between different unilateral mesial temporal lobe epilepsy patients by examining associations between altered FC and clinical index, i.e., episodes of epilepsy. We hope that our results will complement previous studies and further extend our understanding of mTLE hippocampus networks. Moreover, we will evaluate the different roles that the hippocampus plays between left and right mTLE patients. We firmly believe that a more refined delineation of the pathology and function of the hippocampal structure will help to optimize surgical procedure, improve prognosis and reduce the risk of disability in patients (Bonilha et al., 2012).

2. Methods and materials

2.1. Subjects

This is a prospective study that was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from all participants in this study. There were a total of 35 right-handed (Oldfield, 1971) participants enrolled in this study; 22 patients and 13 age-matched healthy volunteers. The patients were recruited from those who visited clinics of the Neurology Department and Neurosurgery Department, Wuhan Union Hospital, China from 2007 to 2009. The 22 patients (6 females) with an age ranging from 16 to 43 years (mean age of 24.5 \pm 9.3) were diagnosed with mesial Temporal Lobe Epilepsy (mTLE) and unilateral Hippocampal Sclerosis (HS). They were further divided into two sub-groups, those

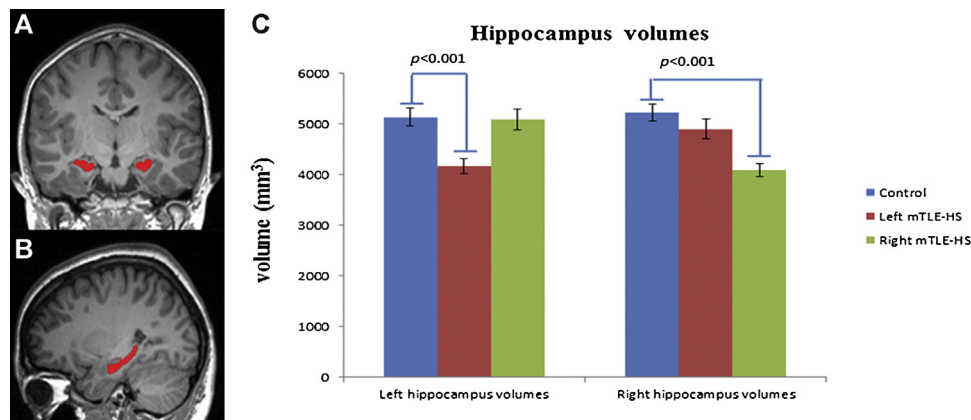


Fig. 1. Hippocampal manual volumetric analyses. (A) Bilateral hippocampi were manually drawn on a coronal structural image from a representative subject; (B) hippocampus on a sagittal structure image; and (C) manual volumetric analyses showed significant atrophy of the ipsilateral hippocampus in each group of patients compared to controls ($p < 0.001$ for left mTLE-HS and $p < 0.001$ for right mTLE-HS) by the Dunnett *t*-test, but no signs of atrophy on the contralateral side. Below are the sample images of the manual drawing.

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