Left hippocampal volume reduction is strongly coupled with structural and functional connectivity in patients with left mesial temporal lobe epilepsy

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Introduction

The hippocampal sclerosis (HS) is the general abnormality observed in patients with mesial temporal lobe epilepsy (MTLE). Our previous study has demonstrated the strong positive correlation between the integrity of the inferior cingulum bundle (CB) and the volume of hippocampal gray matter in left MTLE [1]. Inferior CB is a bundle of axons projecting from posterior cingulate cortex (PCC) to the ventral side of hippocampus (HP). We have confirmed the altered structural connectivity related to HS or hippocampal atrophy in left MTLE, however, the functional connectivity between these two regions is still unclear. In this study, we applied the general linear model (GLM) with PCC seed to examine the strength of functional connectivity in HP on SPM platform [2]. We hypothesized that there were relationships existed between structural and functional connectivity caused by HS.

Methods

The subjects consisted of 8 adults with clinical diagnosis of MTLE with left HS and 8 age-, sex- and handedness-matched healthy adult controls. All images were performed on a 3T MRI system (TIM Trio, Siemens). DSI was acquired using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, FOV 200 mm, image matrix size 80 x 80, and s 2.5 mm slice thick. A total of 102 diffusion encoding gradients with the maximum diffusion sensitivity bmax = 4000 s/mm^2 were sampled on the grid points in the 3D q-space with $|q| \leq 3.6$ units [3]. Functional images in the resting state were acquired using the following parameters: TR/TE = 2000/24 ms, flip angle = 90 deg, 34 slices, 3 mm thick with no gap interleaved, FOV 256 mm, matrix size 64 x 64, and 180 volumes per run with additional 2 volumes of dummy scans in advance. We discarded the first 3 volumes and used the remaining 177 volumes. T1-weighted image with 1 mm isotropic voxels was acquired in the coronal plane by 3-D MPRAGE with following parameters: TR/TE = 2000/2.98 ms, flip angle = 9 deg, FOV 256 mm. To reconstruct white matter tracts of bilateral inferior CB, we placed regions of interest (ROI) at bilateral PCC and HP by from automated anatomical labeling [4] in WFU pickatlas [5]. The ROIs were transformed from Montreal Neurological Institute (MNI) space through the DSI template performed by large deformation diffeomoffic metric mapping [6] to the individual brains. The mean generalized fractional anisotropy (mGFA), an index representing the white matter integrity, was measured by calculating the weighted sum of the GFA sampled along each tract bundle. We used SPM8 and in-house MATLAB codes to analyze functional data. Individual data were preprocessed with the slice timing, realignment and spatial normalization to MNI space, low-pass filtered at 0.08Hz, and spatially smoothened with FWHM 6 mm. The spherical seed ROI (radius = 6 mm, volume = 903 mm^3) was created and centered at PCC with Talairach coordinate ([-2, -51, 27]) from the previous study [7]. The regressors of GLM at the first level statistic included realignment parameters and the averaged time series extracted from PCC seed, white matter and cerebrospinal fluid. The resultant contrast images with T-value were then transformed into images with Z-score using Fisher Z-transformation. We then applied bilateral HP masks to extract the averaged Z-scores from the contrast images as the strength of functional connectivity in each group. We also did the second level group comparison using analysis of covariance (ANCOVA) model performed by SPM8. The volume measurement of bilateral HP using T1 image was conducted by FreeSurfer [8]. Mann-Whitney U test was used to compare the averaged Z-score of each HP between two groups. To evaluate the relationship among GFA of bilateral inferior CB, the averaged Z-scores and the volume of HP, these three indices were used to compute the correlation coefficients using Spearman correlation.

Results

Patients showed the volume of left HP was positively correlated to mGFA of left inferior CB ($r = 0.905$, $p = 0.002$), and negatively correlated to bilateral HP's averaged Z-scores (left HP: $r = -0.905$, $p = 0.002$; right HP: $r = -0.881$, $p = 0.004$). For the relationship between structural and functional connectivity, patients showed strong negative correlation between mGFA of left inferior CB and left HP's averaged Z-score ($r = -0.857$, $p = 0.007$); mGFA of right inferior CB was positively correlated to both sides of HP's averaged Z-scores (left: $r = 0.810$, $p = 0.015$; right: $r = 0.738$, $p = 0.037$) (Table 1). These relationships were absent in controls. In addition, both groups showed the positive correlation between left and right HP's averaged Z-scores (patients: $r = 0.786$, $p = 0.021$; controls: $r = 0.714$, $p = 0.047$). For group comparison, there was no significant difference in the averaged Z scores of bilateral HP between groups. However, for the second level group comparison using ANCOVA, patients showed decreased functional connectivity in bilateral superior and middle temporal gyrus compared to healthy controls (Figure 1).

Conclusion

The present study reveals the relationships among the integrity of the inferior CB, the volume of hippocampal gray matter and the strength of functional connectivity in the lesion side of patients with HS. It indicates that the reduced HP volume and the impaired integrity of the inferior CB are quite related to the enhanced functional connectivity between HP and PCC. We also demonstrated that patients with left MTLE declined functionally in the superior and middle temporal gyrus. These findings are consistent with previous functional studies [9]. We speculate that the enhanced functional connectivity in HP compensates hippocampal deficits and the connection between PCC and temporal regions in patients with HS to maintain their memory functions. Furthermore, patients showed slightly higher correlation in the averaged Z score between left and right HP comparing with controls. Previous study has reported that this cross hippocampal connectivity is also the compensatory effect in MTLE [10]. A future study will investigate the correlation between functional connectivity and neuropsychological scores about memory functions in patients with MTLE.

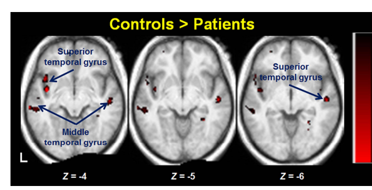

Figure 1: The group comparison result using SPM 8 (N=8 for each group, p < 0.05). The blue arrows indicate the peak activations in bilateral superior and middle temporal gyrus. L: left hemisphere.

Table 1. The correlation coefficients among HP volume, GFA of inferior CB, and averaged Z score in HP

	HP volume (L) (mm^3)	HP volume (R) (mm^3)	mGFA in CB (L)	mGFA in CB (R)	Averaged Z score in HP (L)	Averaged Z score in HP (R)
HP volume (L) (mm^3)		r = -0.190 p = 0.651	r = 0.905** p = 0.002	r = -0.762* p = 0.028	r = -0.905** p = 0.002	r = -0.881** p = 0.004
HP volume (R) (mm^3)	r = 0.595 p = 0.120		r = -0.071 p = 0.867	r = -0.095 p = 0.823	r = 0.048 p = 0.911	r = 0.405 p = 0.320
mGFA in CB (L)	r = 0.143 p = 0.736	r = -0.667 p = 0.071		r = -0.619 p = 0.102	r = -0.857** p = 0.007	r = -0.643 p = 0.086
mGFA in CB (R)	r = 0.452 p = 0.260	r = 0.000 p = 1.000	r = 0.333 p = 0.420		r = 0.810* p = 0.015	r = 0.738* p = 0.037
Averaged Z score in HP (L)	r = -0.333 p =0.420	r = 0.095 p = 0.823	r = -0.500 p = 0.207	r = -0.619 p = 0.102		r = 0.786* p = 0.021
Averaged Z score in HP (R)	r = -0.595 p = 0.120	r = -0.143 p = 0.736	r = -0.381 p = 0.352	r = -0.667 p = 0.071	r = 0.714* p = 0.047	

Note. N = 8 for each group. HP: hippocampus. L: left; R: right. *: p < 0.05. **: p < 0.01. The correlation coefficients marked with red color indicates patients with left MTLE; blue color indicates healthy controls.

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