REPORT

Volumetric Changes in Hippocampal Subregions and Memory Performance in Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Received: 12 April 2017 / Accepted: 3 July 2017 / Published online: 1 November 2017
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Abstract In the present study we explored the different patterns of volumetric atrophy in hippocampal subregions of patients with left and right mesial temporal lobe epilepsy with hippocampal sclerosis (TLE-HS). Meanwhile, the memory impairment patterns in Chinese-speaking TLE-HS patients and potential influencing factors were also determined. TLE-HS patients (21 left and 17 right) and 21 healthy controls were recruited to complete T2-weighted imaging and verbal/nonverbal memory assessment. The results showed that both left and right TLE-HS patients had overall reduced hippocampal subregion volumes on the sclerotic side, and cornu ammonis sectors (CA1) exhibited maximum atrophy. The verbal memory of left TLE-HS patients was significantly impaired ($P < 0.001$) and was not associated with the volumes of the left hippocampal subregions. Verbal or nonverbal memory impairment was not found in the patients with right TLE-HS. These results suggested that the atrophy of hippocampal subregion volumes cannot account for the verbal memory impairment, which might be related to the functional network.

Electronic supplementary material The online version of this article (doi:10.1007/s12264-017-0186-2) contains supplementary material, which is available to authorized users.

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Introduction

Temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) is a common epilepsy syndrome, which is commonly resistant to antiepileptic medications [1] and is associated with a prominent memory deficit [2, 3]. Patients with left and right TLE-HS show different types of memory deficits [4]. In those with left TLE-HS, the verbal memory deficit is prominent, while nonverbal memory is preserved [5, 6]. A previous study suggested nonverbal memory deficit is prominent in right TLE-HS [7]; however, other studies did not find a similar association [8].

Histologically, the hippocampus contains different subregions: cornu ammonis sectors (CA) 1–4, dentate gyrus (DG), and subiculum (Sub) [9]. The entorhinal cortex (EC) is adjacent to the hippocampus and serves as a gatekeeper of signals between the hippocampus and temporal neocortex [10]. Patients with TLE-HS frequently show a volumetric decrease in all hippocampal subregions [11, 12], most severe in CA1 [12, 13]. Several studies exploring the correlation between the hippocampal subregion volumes and memory function displayed different results [14–16]. Using specimens from TLE patients who underwent epilepsy surgery, Witt *et al.* [14] found that the overall pathological status of the left hippocampus, rather than a specific subregion, was predictive for verbal memory. However, Coras *et al.* [15] found granular cell loss in the DG was more correlated with verbal memory than CA1 cell loss. Compared to histopathological analysis of the hippocampus, manual segmentation of the hippocampus in MRI scans containing the whole hippocampal body and a part of the hippocampal head and tail is more appropriate. However, few studies have used MRI to explore the relationship between hippocampal subregions and memory function in TLE-HS. Mueller *et al.* used manual

segmentation of the hippocampal subregions with MRI and found that CA3 and the DG were linked to immediate verbal memory [3]. However, their method only segmented five slices to obtain the volume of each subregion, which might be inaccurate.

In addition, studies on classified verbal and nonverbal memory in Chinese-speaking TLE-HS patients have been carried out on small sample and are limited [4]. However, Chinese is considered to be a hieroglyphic language, which differs from alphabetic systems such as English [17]. Readers of Chinese must encode and remember more visual shapes than those reading English. Thus, we hypothesized that the memory deficit pattern in Chinese TLE-HS patients might be different.

Here, using the CLW protocol (abbreviated by the initials of the authors/contributors, Carr, LaRocque, and Wagner) for the segmentation of hippocampal subregions, as described previously [18–20], we segmented the hippocampus with > 20 slices to obtain the hippocampal subregions, and investigated the volumetric atrophy patterns in TLE-HS patients who were native Chinese speakers; their memory performance was also assessed. Furthermore, we examined the potential correlation between the impaired memory performance and the volume of hippocampal subregions, as well as clinical parameters.

Materials and Methods

Study Population

This study was approved by the Ethics Committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China (certification number: Y 2014-151). Written informed consent was given by all participants. A total of 38 TLE-HS patients and 21 healthy volunteers, who were native Chinese speakers, were recruited from February 2014 to August 2016. The diagnosis was based on the detailed history, neurological examination, video-EEG recordings, and imaging findings. Some patients who required surgery were diagnosed with TLE-HS after stereo-EEG evaluation as their scalp EEG recordings did not provide adequate localization or lateralization information. Patients (24 females, 31.4 ± 9.8 years of age) who fulfilled the following criteria were included: (1) unilateral HS without other major lesions such as tumors, vascular malformations, or malformations of cortical development, and (2) electroclinical features suggesting ipsilateral TLE. Patients with (1) a history of brain trauma or surgery, (2) evidence of an infectious origin, (3) a severe psychiatric disorder, or (4) bilateral TLE were excluded. The control group consisted of 21

healthy volunteers (10 females, 35.0 ± 9.3 years of age) without any prior history of neurological or psychiatric disorders.

Neuropsychological Testing

All patients and healthy controls were subjected to neuropsychological evaluation, which included the Edinburgh Handedness Inventory, Mini-Mental State Examination (MMSE), and the Verbal Paired Associates and Logical Memory of the Wechsler Memory Scale-Revised, Chinese version (WMS-RC), in order to investigate the verbal memory, and the Recognition and Visual Reproduction of the WMS-RC to investigate nonverbal memory. The immediate recall raw score was used as the performance measure. All the MMSE scores of patients and controls were >23.

MRI Acquisition

The MRI scans were obtained at the Department of Radiology using a 3.0 Tesla Discovery MR750 (GE Healthcare, USA) MRI scanner, which was equipped with an 8-channel head coil. The following sequences were acquired: (1) For the measurement of hippocampal subregions, a high-resolution T2-weighted structural MRI perpendicular to the long axis of the hippocampus was scanned with a repetition time (TR) = 5514 ms, echo time (TE) = 176 ms, flip angle (FA) = 110° , matrix size = 512×512 , voxel size = $0.39 \times 0.39 \times 2 \text{ mm}^3$, slice thickness = 2 mm (no gap), 30 slices, acquisition time = 5 min 20 s. (2) For shape analysis and measurement of intracranial volume (ICV), a three-dimensional brain volume imaging (3D-BRAVO) sequence was scanned; the parameters were as follows: TR = 8.208 ms, TE = 3.220 ms, inversion time = 450 ms, FA = 12° , matrix size = 256×256 , voxel size = $0.47 \times 0.47 \times 1 \text{ mm}^3$, 206 slices, acquisition time = 9 min 18 s. (3) The 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 = $3.75 \times 3.75 \times 4 \text{ mm}^3$, slice thickness = 4 mm (no gap), 38 slices, acquisition time = 6 min 50 s. A total of 205 volumes were acquired for each participant.

Manual Segmentation of Hippocampal Subregions

Hippocampal segmentation was based on the T2-weighted sequence using the CLW protocol as described previously [18–20]. Briefly, the segmentation was completed only within the middle section, where the dark bands separating the hippocampal layers were clear. We segmented CA1, CA23+DG, Sub, and EC. We combined CA23 and DG

because these regions cannot be reliably distinguished. The combined subregions (without subregion segmentation) were used to define the remaining hippocampal head and tail (Fig. 1). The segmentation was guided by the standard anatomical guidelines [9]. Manual segmentation of the hippocampal subregions was performed using the ITK-SNAP program (version 2.2, University of Pennsylvania, Philadelphia, PA, www.itksnap.org) [21] by a single rater (CHJ). The intra-rater reliability for the volumes of hippocampal subregions was assessed by retracing the images from 5 participants (10 hippocampi) at an interval of 1 week later. The interclass correlation coefficient (ICC) for the hippocampal subregion segmentation was 0.895 for CA1, 0.980 for DG, 0.930 for Sub, and 0.951 for EC.

Shape Analysis

We used Brain Extraction Tool (BET) [22] in FSL v5.0.9 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) to delete non-brain tissue from the 3D-BRAVO image. Then, the FMRIB's Integrated Registration and Segmentation Tool (FIRST) was used for hippocampal shape analysis [23]. The left and right hippocampi were automatically segmented. The image obtained from each participant was registered to the Montreal Neurological Institute (MNI) standard brain to optimize the subcortical structures. The quality of segmentation and registration was verified visually. We performed vertex analysis between the left/right TLE-HS and control groups with gender and age as covariates. The vertex-wise *F* statistics were calculated along the hippocampal surface, which was reconstructed in the MNI152 space. The family-wise error rate-corrected $P < 0.05$ was used for cluster-based multiple comparison corrections.

Statistical Analysis

Analyses were performed using IBM SPSS, version 20.0 (SPSS, Chicago, IL). ICC was calculated based on a one-way fixed-effects design. The volume of each hippocampal subregion was normalized by the following method: $\text{normalized volume}_{\text{subject}} = \text{raw volume}_{\text{subject}} \times 1000/\text{ICV}_{\text{subject}}$. The Kolmogorov–Smirnov test was used to investigate the distribution of each variable. The categorical variables such as sex between groups were compared by the χ^2 test. The quantitative variables between groups were compared using the independent *t*-test or Mann–Whitney test according to the distribution of the samples. Group differences in the hippocampal subregion volumes were compared using MANCOVA; sex and age served as the covariates. To compare the severity of volume losses, we calculated the *z*-score using the

following formula: $\text{volume } z\text{-score} = (\text{normalized volume}_{\text{subject}} - \text{mean volume}_{\text{controls}}) / \text{standard deviation volume}_{\text{controls}}$. *Z*-scores were compared within the ipsilateral hippocampal subregions using the analysis of variance (ANOVA) or Kruskal–Wallis test according to the distribution of *z*-scores. Based on the memory impairment results, the correlations between the impaired memory and volumetric data and the clinical parameters were evaluated by Pearson or Spearman correlation. Educational level was log-transformed for analysis. A *P*-value < 0.05 was considered as a statistically significant difference.

Results

Demographic and Clinical Features

A total of 21 left TLE-HS and 17 right TLE-HS patients, and 21 healthy volunteers were included in the study (Table 1). There was no difference in age ($P = 0.230$), gender ($P = 0.455$), or education ($P = 0.615$) between the groups. The right TLE-HS group had a higher seizure frequency than the left group ($P = 0.044$). There was no difference between the two groups with respect to epilepsy duration ($P = 0.217$) or number of antiepileptic medications ($P = 0.352$).

Hippocampal Subregion Volumes and Surface Shape Analysis

Both left and right TLE-HS patients had reduced volumes in all hippocampal subregions on the sclerotic side compared with the control group (Fig. 2A). The right TLE-HS group also showed an increased volume in the left Sub ($P = 0.047$). In order to identify the degree of atrophy in each subregion in the left and right TLE-HS patients, the *z*-scores were compared. Significant effects for subregions were found on the sclerotic side of both the left ($P < 0.001$) and right ($P < 0.001$) TLE-HS groups (Fig. 2B). *Post-hoc* analyses showed that the mean CA1 *z*-scores of the sclerotic side were significantly lower than any other ipsilateral hippocampal subregions in both left and right TLE-HS patients.

The results of hippocampal surface shape analysis are presented in Fig. 2C (see Supplementary Materials for tabulated results). Both left and right TLE-HS groups had significant inward surface deflation (atrophy) of the ipsilateral hippocampus primarily in the lateral aspect; the contralateral hippocampus showed no surface deflation. No regional shape expansion was found in patients compared to controls.

Fig. 1 Slices from T2-weighted images for segmentation of hippocampal subregions of one representative healthy control (A–H). Demarcation varied across the long axis. **A** First slice with the limen insulae, connecting the frontal lobe to the temporal lobe, starting segmentation of the EC. **B** First slice of the anterior hippocampus, starting segmentation of the head. **D** First slice where hippocampal subregions are differentiated. Dark bands separating hippocampal layers are clear. The superior boundary of CA1 was drawn by bisecting the most lateral undulation of the hippocampus. **E** Moving posteriorly, the CA1 was drawn 3/4 of the way up the lateral bend of the hippocampus and its medial extension bisected the CA23+DG regions. **H** The most posterior slice of the body; the medial extension of CA1 was drawn in line with the medial extent of CA23+DG. CA23+DG, CA2, CA3 and dentate gyrus; EC, entorhinal cortex; Head, hippocampal head; Sub, subiculum

Memory Scores

The verbal memory of patients with left TLE-HS was lower than in controls ($P < 0.001$) (Fig. 3). There was no

decrease in verbal memory in the right TLE-HS group. No impairment in nonverbal memory was found in patients with either left ($P = 0.309$) or right ($P = 0.594$) TLE-HS. The verbal memory in the left TLE-HS was negatively

Table 1 Summary of demographic and clinical data

Demographic	Control	Left TLE-HS	Right TLE-HS	<i>P</i> value
Sample size	21	21	17	
Age (years, mean $\pm$ SD)	35.0 $\pm$ 9.3	30.0 $\pm$ 9.1	33.1 $\pm$ 10.6	0.230 ^a
Gender (male/female)	11/10	7/14	7/10	0.455 ^b
Education (years, mean $\pm$ SD)	11.4 $\pm$ 4.1	11.6 $\pm$ 3.1	10.5 $\pm$ 2.8	0.615 ^c
Epilepsy duration (years, mean $\pm$ SD)	N/A	15.4 $\pm$ 11.0	19.7 $\pm$ 10.0	0.217 ^d
Seizure frequency (mean $\pm$ SD, per year)	N/A	17.0 $\pm$ 12.8	27.5 $\pm$ 18.2	0.044 ^d
Number of antiepileptic medications (mean $\pm$ SD)	N/A	2.1 $\pm$ 0.8	2.3 $\pm$ 0.8	0.352 ^e

^aKruskal-Wallis analysis; ^b χ^2 test (two-tailed); ^cKruskal-Wallis analysis (log-transformed data); ^dindependent-sample *t* test (two-tailed); ^eMann-Whitney test

correlated with the seizure frequency ($\beta = -0.487$, $P =$

Fig. 2 Volumetric changes of hippocampal subregions and hippocampal surface shape analysis. **A** Volumes of subregions in left (red) and right (blue) TLE-HS patients and in controls (black). **B** Z-scores for the severity of volume loss in each hippocampal subregion. **C** Hippocampal surface shape analysis of left/right TLE-HS and

controls. Yellow, 3D template mesh of the hippocampus; red, areas of significant shape difference between groups. (*) $P < 0.05$ compared to control. L, left; R, right; Sub, subiculum; EC, entorhinal cortex; hippo, hippocampus; CA23, CA2 and CA3

0.025) and positively with the level of education ($\beta = 0.661$, $P = 0.001$). However, it was not associated with the other clinical parameters or any hippocampal subregion volumes on the left side. And the verbal memory in both the right ($\beta = 0.572$, $P = 0.016$) and the whole ($\beta = 0.503$, $P = 0.001$) TLE-HS groups were correlated with the educational level; however, neither was correlated with any other clinical parameters.

Discussion

The present study was based on Chinese TLE-HS patients whose native language was hieroglyphic and found the following: (1) Both left and right TLE-HS patients had reduced hippocampal subregion volumes on the sclerotic side, including CA1-4, DG, Sub, and EC; CA1 exhibited the most dramatic atrophy. (2) Verbal memory deficit was

Fig. 3 Memory scores in patients with left and right TLE-HS (* $P < 0.05$ compared to control)

found in the patients with left TLE-HS, while nonverbal memory was not significantly impaired in both the left and the right TLE-HS groups. (3) The impaired verbal memory was associated with seizure frequency and educational level; however, it was not related to any left hippocampal subregion volume.

In our study, the volume reduction of the overall ipsilateral hippocampal subregions in unilateral TLE-HS patients is in agreement with other studies [11, 12]. Furthermore, the CA1 sector on the sclerotic side displayed more dramatic atrophy than any other subregions in both left and right TLE-HS patients, also in agreement with the published meta-analysis [12]. However, these studies did not compare the CA1 volume with DG, Sub, or EC, but only among CA1, CA2, CA3, and CA4. Another similar study found that ipsilateral CA1 and CA3+DG exhibited a more striking volume loss than CA2, Sub, and EC, as assessed by the manual marking technique [24]. However, only five slices of the hippocampal body were segmented, which might have led to the random errors. HS can be divided into several types according to the pathology, and the most common is classical HS with neuronal loss primarily involving the CA1 and CA4 subregions [25]. This phenomenon is also consistent with our results. Another longitudinal study showed a progressive atrophy in the CA1 sector in TLE patients with or without HS [10]. The relatively high expression of N-methyl-D-aspartate receptors in CA1 might explain its vulnerability to excitotoxicity in the context of hypoxia associated with seizures [26]. Hence, our findings indicate that the CA1 sector is more vulnerable than other hippocampal subregions.

In our study, the right TLE-HS group had preserved nonverbal memory that could be for several reasons. First,

a previous study in healthy Japanese individuals found that learning Chinese characters might improve nonverbal memory [27]. Second, Smith and Milner reported that a nonverbal memory deficit could not be detected in patients with right temporal-lobe excisions when recalled immediately following the presentation; impaired recall was detected only after a 4-min delay [28]. Incisa *et al.* reported similar results [29]. In the current study, we only detected immediate recall, which might be preserved better than delayed recall. A delayed recall in nonverbal memory necessitates further study. Lastly, fMRI has shown a diffuse and bilateral representation of nonverbal memory in the brain [30]. The network of nonverbal memory may be more complicated and bilateral than verbal memory. In addition, we found verbal memory impairment in the left TLE-HS patients, consistent with a majority of the results in the English-speaking population [5, 31, 32]. Therefore, our results suggest that dysfunction of the left temporal lobe has a strong relationship with the impairment of verbal memory, while dysfunction of the right temporal lobe shows a less consistent relationship with nonverbal memory in Chinese TLE-HS patients.

Verbal memory was negatively correlated with seizure frequency and educational level in the left TLE-HS group, with no relation to the duration of epilepsy or any hippocampal subregion volume. A large number of previous studies have found that seizure frequency is associated with verbal memory [33, 34]. A study based on 1156 patients with TLE suggested that seizure activity causes developmental hindrance so that the patients reach poor memory performance levels much earlier than controls [31]. Our findings suggest that more seizures result in greater cerebral damage and the likelihood of memory deficits. Helmstaedter *et al.* also found no acceleration in the decline in verbal memory with a longer duration of epilepsy [31], which is consistent with our result. Another study demonstrated that the duration of epilepsy is a less potent predictor of cognitive impairment [33], and explained that the duration of epilepsy represents a heterogeneous combination of circumstances (including impact of seizures and anti-epileptic drugs), the impact of which on memory development is difficult to disentangle [33]. However, we did not find any correlation between verbal memory and hippocampal subregion volumes in the left TLE-HS group, suggesting that memory function is more dependent on the functional network than hippocampal volumes according to our previous results [35]. With resting-state fMRI data, it was shown that intra-hemispheric functional connectivity between the left anterior hippocampus and EC is positively correlated with verbal memory in patients with left TLE-HS [35].

Nevertheless, the present study had several limitations. First, we only evaluated the immediate recall verbal and

nonverbal memory, while delayed recall memory might be necessary and may lead to a different result. Further completion of these memory evaluations is essential. Another limitation was that our sample was relatively small, and the result necessitates confirmation in a larger population.

By segmenting the hippocampal subregions manually, we found that CA1 was the most vulnerable region in both left and right TLE-HS. And we suggested that the memory impairment pattern in Chinese TLE-HS was different, with left TLE-HS patients having verbal memory impairment and right TLE-HS patients having no verbal or nonverbal memory deficit. Furthermore, the atrophy of hippocampal subregion volumes could not explain the verbal memory impairment, which might be correlated with the functional network.

Acknowledgements This work was supported by the National Natural Science Foundation of China (81271435 and 81671282). We thank Dr. Han Liu at the Second Affiliated Hospital, School of Medicine, Zhejiang University, for help with psychological evaluation. Dr. Peiyu Huang is acknowledged for assistance with imaging analysis.

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