Impaired self-referential processing in mesial temporal lobe epilepsy: A functional MRI study

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HIGHLIGHTS
- Impaired self-referential processing in mesial temporal lobe epilepsy is proposed.
- Patients and healthy controls underwent self-reference task-fMRI scans.
- Patients showed decreased activation in the mesial prefrontal cortex.
- fMRI activation was negative correlated with behavioral and clinical data.
- fMRI results indicate impairment of self-referential processing in patients.

ARTICLE INFO
Article history:
Received 16 May 2013
Received in revised form 13 August 2013
Accepted 23 September 2013

Keywords:
Self-reference
Mesial temporal lobe epilepsy
fMRI

ABSTRACT
Mesial temporal lobe epilepsy (mTLE) presents typical symptoms of cognitive impairments and mental disorders, which is presumed to be related to impairment of self-referential processing. This study aims to investigate the alterations of self-reference in mTLE using functional magnetic resonance imaging (fMRI). Fifty patients with unilateral mTLE (26 left- and 24 right-sided mTLE) were recruited in the present study. Traditional task paradigm of internally-cued condition vs. externally-cued condition was employed to induce self-referential activation. fMRI activation in each group of patients was compared with that of 30 healthy controls. Moreover, fMRI responses in the dorsal mesial prefrontal cortex were specifically addressed by correlating with behavioral data of reaction times and clinical data of epilepsy duration, respectively. Compared with the healthy controls, both two groups of patients showed decreased behavioral performance (reaction times) and decreased fMRI activation of self-reference in the anterior and posterior cortical midline structures. Moreover, fMRI activation was found to be negatively correlated with behavioral performance and epilepsy duration. The present findings implicate functional impairment of self-reference caused by epilepsy in mTLE. This study provided imaging evidence for functional impairments of self-referential processing and brain default-mode function in mTLE.

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1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common type of intractable epilepsy. Chronic seizures often lead to extensively cognitive impairments, including memory, language, attention and perceptive deficits [7,25] in patients. Imaging studies have demonstrated structural and functional abnormalities corresponding to the cognitive deficits [28,32,34]. The prefrontal cortex is one of the most reported regions showing imaging abnormality, and have been considered to be associated with high-order cognitive deficits in mTLE [11,23,31]. Especially, this region has been correlated with change of the default-mode network (DMN) in mTLE [18,23,30,33]. The DMN alteration in the prefrontal cortex has also been suspected to be underlain by self-referential impairments in mTLE [18,33]. However, there still lacks direct imaging evidence to support this presumption.
Self-reference is a mental activity relevant to self, and plays critical roles in higher-order cognitive processes including self-awareness and personality [10, 15, 26]. Impairment of self-reference has been investigated in several mental disorders, such as major depression [19], autism [17] and schizophrenia [27]. MTLE typically presents symptoms of high-level social cognitive impairments and mental disorders [7, 13], which also motivates us to assume that there may be impairments of self-reference in MTLE. Thus in the present study, we aimed to explore the possible alteration of self-referential process in patients with MTLE using fMRI.

2. Methods

2.1. Subjects

Fifty right-handed patients with unilateral MTLE (26 left-sided and 24 right sided) were recruited (demographic and clinical information were detailed in Table 1). Diagnosis of MTLE was performed according to ILAE 2001 classification through a comprehensive evaluation, including seizure history and semiology, neurological examination, diagnostic MRI, and EEG records in all patients. Further inclusive criteria were provided in the Supplementary material 1. Moreover, 30 healthy subjects were recruited as controls from the staff of our Hospital. They did not suffer from neurological or psychiatric disorders at the time of this study. There were no differences of ages and genders between the controls and patients (Table 1).

This study was approved by the Medical Ethics Committee in Jinling Hospital, Nanjing University School of Medicine. Written informed consent was obtained from all the participants.

2.2. Experimental design

In line with the previous studies [8, 15], we adopted a traditional task paradigm to induce self-referential activation. Three types of tasks, i.e., externally-cued condition (ECC), internally-cued condition (ICC) and a control condition were blocked designed. Each task condition repeated 5 times pseudorandomly, and totally 15 blocks were included in one session. Each block consisted of 5 trials. In each trial, subjects were instructed to respond to the questions displayed on screen by pressing a two-button key. For the ECC, participants were instructed to judge correct or error for a short sentence describing common sense in daily life. E.g., ‘北京是中国的首都’ (Beijing is the capital of China). If it was correct, press left button, otherwise press the right one. For the ICC, participants were asked to judge yes or no for the short sentence describing themselves. E.g., ‘我很容易生气’ (I get angry easily). These sentences were abstracted from Eysenck Personality Questionnaire for adults, revised version in Chinese. If yes, press left button, otherwise press the right one. The numbers of characters displayed in sentences of two tasks were counter-balanced across all blocks. All the stimuli in the ECC and ICC tasks were simple sentences, and were easy to be understood for all the participants. In the control task condition, participants were instructed to judge between circle and cross (the cross is much larger than the fixation cross) (if it was a circle, press the left button, otherwise press the right one). Each stimulus was displayed for 4000 ms at most. If the RT is less than 4000 ms, the screen will become blank until the fixation cross is present. Each intervened crosshair displayed also in the center of the screen and lasted for 1000 ms always. Reaction time (RT) of all tasks and ratio of error in the ECC were recorded. The task required in total 375 s. The experiment paradigm was illustrated using a schematic figure in Supplementary material (Fig. S2).

2.3. Data acquisition

Imaging data were acquired on a Siemens 3T MAGNETOM Trio scanner. Functional MR images were axially gathered with a single shot gradient recalled echo echo-planar imaging sequence based on BOLD effect (TR/TE = 2000 ms/30 ms, FA = 90°, resolution in plane = 3.75 mm × 3.75 mm, matrix: 64 × 64, slice thickness/gap = 4.0/0.4 mm, 30 slices covering the whole brain, 188 volumes). Information of structural images was provided in the Supplementary material 3.

Stimuli of task were presented by E-prime software program running on a computer and projected onto a screen positioned at the head end of the MRI scanner bore by a set of MR-compatible projector. Subjects viewed the screen through a mirror mounted on the head coil and responded by pushing the two-button box. The behavioral data, including the RTs and ratio of error were recorded through E-prime. All participants were asked not to move intentionally and were limited by foam padding around their heads.

2.4. Data analysis

2.4.1. Behavioral data

The RT scores of three groups were analyzed for each task condition using a one-way analysis of variance (ANOVA). In addition, the ratio of error scores of the control task and the ECC were compared between two patient groups and healthy subjects using ANOVA.

2.4.2. fMRI data

fMRI data preprocessing was performed using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB (Mathworks Inc., Sherborn, MA). Image volumes were corrected for slice-time, realignment, and
normalized into Montreal Neurological Institute (MNI) template, and then smoothed with a 6 mm FWHM Gaussian kernel. Head translation and rotation of all subjects did not exceed 1.0 mm or 1°. In each subject, the task conditions were convolved with the canonical hemodynamic response function (HRF), and modeled as regressors in general linear model. In each subject, the BOLD activation was estimated using a first-level ANOVA with task condition as main factor: ICC vs. control task, ECC task vs. control task, and ICC vs. ECC. We considered that the ICC vs. ECC contrast induced self-referential activity \[8\].

For the second-level analyses, one sample t-tests on each activation model were conducted in each group at statistical threshold of \(P<0.01\), FDR correction. Subsequently, a two-way 3 (ICC, ECC, and ICC vs. ECC) × 3 (left- and right-sided mTLE patients and healthy controls) ANOVA was conducted to investigate the differences of activation among task conditions and groups. The results were masked by the activation and deactivation regions of one-sample t-tests of all subjects. AFNI AlphaSim program (http://afni.niddk.nih.gov/afni/docpdf/AlphaSim.pdf) was used for multiple correction at \(P<0.05\).

Subsequently, a post hoc ROI-based analysis was performed. We made a spherical ROI centered at the peak activation of self-reference (i.e., ICC vs. ECC) in the one-sample t-test result of all subjects (locating at the mesial prefrontal cortex: \(-2, 54, 8\) ), the radius of this ROI was 10 mm. The statistical parameters of BOLD response of each condition within the ROI were extracted, and were compared among the three groups using ANOVA.

Furthermore, the imaging result was correlated with behavioral data (RT scores of ICC) and clinical variables (epilepsy duration). Voxel-based correlations were performed between the self-referential activation and epilepsy duration and the RT scores, respectively (\(P<0.05\), AlphaSim correction). Considering that the self-reference activation located at midline structures, we combined two groups of patients for correlation analyses. Moreover, years of education were regarded as covariate for two-sample t-test and correlation analyses in the second level analyses.

3. Results

3.1. Behavioral results

One patient was excluded due to failure of behavioral data acquisition. For the control task, there was no significant difference in mean RTs among three groups \([F(2, 76)=0.678, P=0.510]\). However, for the ECC and ICC tasks, the mean RTs of the left and right mTLE patients were both significantly longer than healthy controls \([F(2, 76)=8.550, P<0.001\] and \(F(2, 76)=15.303, P<0.001\), respectively\). Similarly, there was no group difference of error rate during the control task \((P=0.196, \text{obtained by Pearson } \chi^2 \text{ two-tailed test})\). The patients presented higher error rate than the controls for responding to the ECC \((P<0.001, \text{obtained by Pearson } \chi^2 \text{ two-tailed test})\) (Table 1).

3.2. fMRI results

One sample t-tests revealed typical patterns of activation responding to the ICC, ECC and self-reference (i.e., ICC vs. ECC) in three groups of subjects (Fig. 1A). Voxel-wise two-way 3 × 3 ANOVA revealed group differences of activation responding to ECC, ICC and self-reference (SR). For the comparisons of ECC and ICC results, the patients showed decreased activation in the dorsal ACC. For the self-reference condition, both the left and right mTLE patients showed decreased activation in the DMPFC (BA10/9) and posterior cingulate cortex (PCC). Moreover, the left mTLE patients showed decreased activation in the left hippocampus and inferior frontal gyrus (BA47/38) (Fig. 1B).

ROI based ANOVA further explicitly demonstrated group difference of activation responding to different task conditions. Both the left- and right-sided mTLE patients showed significantly lower BOLD changes responding to the SR (ICC vs. ECC) than the healthy controls \((P<0.05)\). However, there was no difference of ICC or ECC-induced activation among three groups (Fig. 2).
Voxel-based correlation analysis revealed that the strengths of self-reference-related activation in the MPFC were negatively correlated $(−4, 42, 8)$ ($r = −0.502$, $p < 0.001$) with RTs (Fig. 3A). Moreover, self-reference-related activation in the dACC ($r = −0.354$, $p < 0.05$) were negatively correlated with epilepsy duration (Fig. 3B).

4. Discussion

The present study using specific task-induced fMRI demonstrated alteration of BOLD activation responding to self-reference in the patients with mTLE. As our hypothesis, the medial prefrontal cortex (MPFC) showed decreased activation in the patients.
Moreover, the self-referential activation in the MPFC was negatively correlated with behavioral presentation of RTs; while self-referential activation in the dACC was found to be negatively correlated with epilepsy duration. This study for the first time implicates the impairments of self-referential processing in the patients with mTLE.

Self-referential activity can be induced by various self-related contents, such as sense of one's abilities, traits and attitudes [10,15,26]. ICC vs. ECC design is the most traditional experimental protocols in neuroimaging studies of self-reference [8,15]. Commonly, the ECC task can induce brain activation in the pre-somatomotor cortex and SMA, dorsal attention cortex and visual cortex, associated with attention, decision-making, motor and language processes [15]. And the ICC task induces activation in the same regions besides the dorsal MPFC. By subtracted ECC from ICC, the results remove the mutually activated regions, and directly show brain regions associated with self-reference [5,8]. A number of recent neuroimaging studies employing self-referential tasks in the healthy persons have robustly reported activation in the MPFC and ACC [10,15,26]. Imaging abnormalities have been also reported in a few brain disorders associated with self-reference impairment [14,19,27]. In line with the previous studies [8,10,12,22,26,27,29], we found typical activation responding to self-reference in the MPFC, ACC, ICC, and some fronto-temporal cortex related with self-reference.

The patients presented poorer performances for both the tasks of ECC and ICC, but not the control task. Moreover, less fMRI activation responding to the ECC and ICC in the patients confirmed the behavioral results. We reasoned that the tasks of ECC and ICC both need employment of semantic processing, and might be vulnerable to be impaired in mTLE [1]. Decreased activation responding to the condition of ICC vs. ECC might suggest functional deficit of self-reference in this epilepsy. MTLE, especially with complex partial epilepsy can be viewed as a syndrome from the borderland of psychiatric and neurological disorder [13]. We speculated that impairment of self-referential processing may contribute to the psychopathological mechanism of mTLE.

We specifically addressed the self-reference associated activation in the dMPFC, and found decreased BOLD response in the patients with mTLE. Firstly, the region of dMPFC played prominent role in the processing of self-reference. For the functions on reappraisal of self-related stimuli [21], re-representation of affective and cognitive states, and directly or explicitly describing and reasoning about internal states [22,29]. Aberrant activation in the dMPFC has been reported in the brain disorders with self-referential impairment [17,19,27]. In the present study, the patients with mTLE showed decreased BOLD activation in the dMPFC, and BOLD activation was negatively correlated with behavioral presentation of self-referential operations, suggesting functional deficits of self-reference may be mainly underlay by abnormal dMPFC brain activity.

Secondly, MPFC is one of the most damaged regions, and plays critical role in the pathological processing of mTLE. PET/SPECT studies have shown metabolic and perfusion abnormalities in mTLE [3,4], suggesting functional impairments due to epileptic activity propagated from mesial temporal lobes [20]. Functional damage of the MPFC has been associated with many high-order cognitive deficits in mTLE [11,16]. In the present study, for the ECC and ICC, neither the left- nor right-sided mTLE patients showed significantly different BOLD response relative to the healthy controls. However, in the ICC vs. ECC, there was significant decrease in BOLD response in both patient groups relative to the controls (Fig 2). These findings suggested that the internal mentation, i.e., self-referential processing is specifically impaired. In addition, negative correlation between BOLD activation of self-reference and epilepsy durations further supported functional impairment of self-reference caused by epilepsy (Fig 3).

In addition, the patients with mTLE showed decreased BOLD activation in the PCC and hippocampus. Together with the MPFC, these regions are considered as important nodes constituting the brain default-mode network [24]. The DMN is proposed to play key roles in self-reference, awareness keeping, alertness and episodic memory [2,9]. Functional impairments of the DMN in mTLE have been studied using resting-state fMRI in the previous works of ours [33] and others [30]. Moreover, epileptic discharges-induced deactivation in the default-mode regions has also been reported [17]. This study specifically pointed out the self-reference deficits in the impairment of the DMN in mTLE.

However, there exist a few of limitations in this work. Firstly, we did not address the possible effect of anti-epileptic drug on cognitive processing in the patients [6]. Secondly, specific scales for self-reference measurement were not used. Thirdly, future study combining task-induced fMRI and resting-state fMRI would be more informative for understanding to the brain mechanism of self-referential processing. Finally, despite years of education had been taken as covariate in the second level analyses, which might influence the fMRI results.

5. Conclusion

In this work, we used specific self-related task based fMRI to investigate alteration of self-referential activation in the patients with mTLE. Decreased BOLD activation and behavioral performance in the patients suggest functional deficits of SR in mTLE. The prominent alteration of BOLD response in the dMPFC and negative correlation with epilepsy duration implicate self-referential impairment caused by epilepsy. This study provided imaging evidence for the insight into the mechanisms of functional impairments for the self-referential and DMN processing in mTLE.

Acknowledgments

This research was supported by the Natural Science Foundation of China (Grant nos. 81271553, 81301198, 81201155, 81201178, and 8102018022), Grants for Young Scholar of Jinling Hospital (Grant nos. 2011060 and 2011045).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.09.054.

References
