Resting-state fMRI study of treatment-naïve temporal lobe epilepsy patients with depressive symptoms

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Abstract

Background: Patients with temporal lobe epilepsy are at high risk for comorbid depression, and it is hypothesized that these two diseases are share common pathogenic pathways. We aimed to characterize regional brain activation in treatment-naïve temporal lobe epilepsy patients with depressive symptoms and compare the results to epilepsy patients without depressive symptoms and to healthy controls.

Subjects and methods: We recruited 23 treatment-naïve patients (including anti-epilepsy drugs (AEDs) and antidepressants) and 17 matched healthy controls for this study. The patients were further divided into two groups: patients with depressive symptoms and patients without; the patients then used a self-rating depression scale (SDS) to assess their depression. All participants underwent resting functional magnetic resonance imaging (fMRI) scans using the Trio Tim magnetic resonance (MR) image system (3.0 T). The data were processed and analyzed using REST and SPSS11.5 software.

Results: The patients with depressive symptoms showed significantly higher activity in the bilateral thalamus, insula and caudate and right anterior cingulate compared with the two other groups (p<0.05, corrected). Brain network connectivity analysis revealed that connectivity decreased in the prefrontal-limbic system and increased within the limbic system and angular gyrus in patients with depressive symptoms (p<0.05, corrected).

Conclusion: The epilepsy patients with depressive symptoms showed regional brain activity alterations and disruption of the mood regulation network at the onset of seizures. The present study offers further insight into the underlying neuropathophysiology of epilepsy with depressive symptoms.

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Introduction

Up to 20 to 55% of patients with temporal lobe epilepsy (TLE) have psychological depressive symptoms (Kanner, 2008; Tellex-Zenteno et al., 2007). This prevalence is significantly higher than in patients with other chronic diseases, such as diabetes and asthma (Ettinger et al., 2004), and the symptoms lead to a decreased quality of life and a higher risk of suicide (Christensen et al., 2007). Furthermore, when major depression precedes the first epileptic attack, it is associated with a 1.7-fold increased risk of developing seizures (Hesdorffer et al., 2006). Contrary to traditional beliefs, which proposed that depressive symptoms result from a secondary reaction to the epileptic episodes, Kanner (2004)suggested that depressive symptoms may share common pathogenic pathways with epilepsy and that these common pathways may facilitate the development of one condition in the presence of the other. Moreover, depressive disorders may be a predictor of treatment-resistant epilepsy (Kanner, 2008).

To date, animal models and human neuroimaging studies have been used to study the bidirectional relationship between the two conditions (Gilliam et al., 2007; Hasler et al., 2007; Mazarati et al., 2007; Savic et al., 2004). A rat animal model demonstrated that depressive behavior developed due to neuronal plasticity that was associated with repeated electrical kindling (Mazari et al., 2007). A positron emission tomography (PET) study found significantly decreased serotonin (5HT1A) binding potentials (BP) in the epileptogenic hippocampus and amygdala and a negative correlation between depressive symptoms and the BPs in the anterior cingulate (ACC) (Savic et al., 2004). Using 1H-MRS to detect the creatine/N-acetylaspartate (Cr/NAA) ratio, Gilliam et al. (2007) found abnormalities in
the hippocampus that correlated with depressive symptoms in patients with TLE (Gilliam et al., 2007). These findings highlight the involvement of the prefrontal-limbic system and paralimbic structures in these conditions. However, previous neuroimaging experiments were conducted on patients receiving anti-epilepsy drugs (AEDs) and antidepressants; thus, the potential impact of AEDs and antidepressants on brain activity could not be ruled out. To the best of our knowledge, no experiments on treatment-naïve patients with epilepsy (PWES) have been carried out, and these studies may be critical to elucidate the underlying mechanisms.

Resting state functional magnetic resonance imaging (fMRI) employs the amplitude of low-frequency (0.01–0.08 Hz) fluctuations (ALFF) of the blood-oxygen-level dependent (BOLD) signal to detect regional activity alterations and is widely used to study neuropsychological illnesses. Resting state fMRI can provide information not only on synchronous regional cerebral activity using the ALFF intensity (Goncalves et al., 2006; Shmuel and Leopold, 2008), but it also avoids performance confounds in task-design fMRI research (Callicott et al., 2003). Moreover, resting state fMRI allows the integrity of brain networks to be examined using connectivity analysis.

The present investigation is the first to use resting state fMRI to examine both regional ALFF intensity and brain network connectivity in treatment-naïve TLE patients with and without depressive symptoms compared with a cohort of normal controls. We hypothesized the following: 1. TLE patients with depressive symptoms show ALFF alterations in the prefrontal-lobelimbic systems; and 2. connectivity analysis in the patients with depression symptoms (PDSs) group reveals disruption of the mood regulation network compared with the two other groups, while the patients without depression symptoms (nPDSs) group would show epileptic network alteration.

**Materials and methods**

**Participants**

A total of 23 treatment naïve (including AEDs and antidepressants) TLE patients (all right handed, male/female: 13/10, average age: 35.0±8.8) and 17 healthy controls (all right handed, male/female: 10/7, average age: 34.9±6.9) were recruited from the outpatient department in the West China Hospital of Sichuan University, China, from July, 2009, to August, 2010. This study was approved by the local ethics committee, and all participants signed informed consent forms. Patients had clinical interviews and physical examinations that were conducted by board-certified neurologists. Patients evaluated their existing depressive symptoms using the self-rating depression scale (SDS) (Zung, 1965). The inclusion criteria included the following: 1. seizure types and epileptic syndromes as diagnosed according to the classification of the International League Against Epilepsy (Anon., 1981, 1989); and 2. TLE diagnosis when continuous ictal scalp video electroencephalography showed complex partial seizures of temporal origin. The exclusion criteria were as follows: 1. patients with structural lesions other than medial temporal sclerosis; 2. patients with a history of psychological diseases, or use of anti-depressive drugs, or other chronic diseases, such as diabetes and asthma; 3. pregnant and nursing women; and 4. patients who experienced seizures within 15 days prior to fMRI scanning. All controls were also screened using the SCID (non-patient version) to confirm the lifetime absence of psychiatric illness.

**Data acquisition**

MR images detecting BOLD signal were obtained using a Trio Tim (3 T) magnetic resonance (MR) imaging system (Siemens; Erlangen) with a gradient-echo echo-planar imaging sequence: repetition time/echo time (TR/TE), 2000/30 ms; voxel size, 3.75×3.75×5 mm³; flip angle, 90°; slice thickness, 5 mm (no gap); matrix, 64×64; and FOV, 240×240 mm². Each brain volume comprised 30 axial slices, and each functional run contained 200 volumes following 5 dummy volumes, with a total scan time of 416 s. All participants were instructed to keep their eyes closed and not to think of anything in particular during the resting-state MR scan.

**Data processing**

Functional image preprocessing was carried out using DPARSF (State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University; http://resting-fmri.sourceforge.net/) software following these steps: conversion of the DICOM data to NIFTI images; removal of the first 10 time points from each patient’s data; slice timing correction; realignment to the middle image; spatial normalization to the Montreal Neurological Institute (MNI) template; and resampling of each voxel to 3×3×3 mm³ without spatial filtering. ALFF maps were calculated using REST (State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University; http://resting-fmri.sourceforge.net). Following band pass filtering (0.01–0.08 Hz) and linear-trend removal, the time series was transformed to the frequency domain using a fast Fourier transform (FFT). The power spectrum obtained by FFT was square root-transformed and averaged across the frequency of 0.01–0.08 Hz. The averaged square root of activity comprised the ALFF. Functional connectivity (FC) was examined by analyzing a seed area provided by REST. Five areas were selected as seed regions based on ALFF findings and former neuroimaging findings (Hermann et al., 2008) and included the right ACC, bilateral insula and thalamus.

**Statistical analysis**

ALFF maps from the patient and control groups were compared on a voxel-wise basis with an ANCOVA in REST, covarying for disease duration and number of seizures (when comparing with normal controls we didn’t use disease duration and number of seizures as covarying factors). Whole-brain analysis was conducted with statistical threshold of P<0.05 (FDR corrected). The FC map was compared across the three groups using a statistical threshold of P<0.05 (Alpha sim corrected).

**Results**

We acquired resting fMRI data from 23 patients (male/female: 13/10, average age: 35.0±8.8) and 17 normal controls (male/female: 10/7, average age: 34.9±6.9) on a 3.0 T MR system (Siemens, Trio Tim, Erlangen). The 23 PWE were divided into two groups based on their SDS score. The patients who scored over 50 were included in the PDS group (male/female: 4/3, average age: 37.2±11.1) and the remaining patients were placed into the nPDS group (male/female: 9/7, average age: 34.0±7.8). The disease duration, localization of epileptic discharge and the number of seizures did not differ between these two groups (P>0.05). Age, gender and years of education did not differ between the three groups (Table 1).

We used the DPARSF (State Key Laboratory of Cognitive Neuroscience and Learning in Beijing Normal University; http://resting-fmri.sourceforge.net) software to explore alterations in regional ALFF (0.01–0.08 Hz) signals. By comparing the whole brain ALFF map between the three groups, using ANCOVA, we found that PDSs, compared with nPDSs, showed a significantly elevated ALFF value in the right ACC, bilateral thalamus and insula and decreased ALFF in the left amygdala and left medial prefrontal cortex (mPFC). When the PDS group was compared with healthy controls, the ALFF showed increased values in the right ACC, bilateral caudate and insula. There were no significantly decreased areas in the PDS group. The nPDS group showed increased regional activity in the right ACC and left anterior insula compared with the healthy control group and decreased
ALFF in the bilateral thalamus and right posterior insula (P<0.05, FDR corrected, Table 2, Figs. 1.1–6).

Functional connectivity analysis was employed to explore alterations in the brain network. The selection of seed regions was based on findings from the whole brain analysis. Connectivity maps were compared across the three groups using an ANCOVA. We found a decreased brain network between the limbic system and angular gyrus when comparing the PDS group with the nPDS group. When comparing the PDS group with the healthy control group, we found increased connectivity among the limbic system and angular gyrus when comparing the PDS and nPDS groups. When comparing the PDS group with the healthy control, we found decreased connectivity among the precentral gyrus, superior temporal gyrus and limbic system (P<0.05, alpha sim corrected, Table 3).

Discussion

We are the first to demonstrate that treatment naïve patients show altered regional brain activity in the prefrontal-limbic system and a disruption in the mood regulation network. We found significantly increased ALFF values in the bilateral thalamus, insula and right ACC and decreased ALFF values in the left amygdala and left mPFC for the PDS group compared with the nPDS group. Using connectivity analysis, we found a decreased brain network between the limbic system, temporal lobe and inferior prefrontal lobe, and increased connectivity between the limbic system and the angular gyrus when comparing the PDS and nPDS groups. When comparing the PDS group with the healthy control, we found decreased connectivity between the limbic system and prefrontal lobe (Brodmann area 10) and increased connectivity between the limbic system, angular gyrus and prefrontal lobe (Brodmann area 8).

The pathogenic mechanism underlying depression in epilepsy patients has received much attention in the last decade. Kanner (2004) suggested that epilepsy and psychiatric disorders may share common pathogenetic pathways. This proposal was supported by previous experiments on a kindling-induced animal model of depression and 5-HT1A receptor research in PWE with depressive symptoms (Mazarati et al., 2007; Savic et al., 2004). However, previous neuroimaging experiments have focused on PDSs receiving AED treatment (Hasler et al., 2007). Our work demonstrates regional brain activity and connectivity alterations in treatment-naïve patients with short seizure duration, thus ruled out this potential confounding factor.

The altered ALFF value may represent the abnormal regional activity of the prefrontal-limbic system in the PDS group and nPDS group. The prefrontal-limbic system, including the amygdala, striatum, insula, ACC and thalamus, is implicated in mood regulation and the pathogenic pathways of epilepsy. The amygdala is a classic component of mood regulation and also of TLE seizures. Epileptic mice with the Bassoon gene mutation demonstrate pathological forms of plasticity and an imbalance in brain-derived neurotrophic factor (BDNF) distribution in fast-spiking (FS) interneurons and medium spiny (MS) neurons in the striatum with concomitant behavioral alterations (Ghilieri et al., 2010). The mPFC has been suggested to regulate the limbic system, especially the amygdala (Folland et al., 2008). Post-mortem analysis has revealed reduced Really Interesting New Gene (RING) Finger 41 (Rnf41) expression in the prefrontal lobe that has proven critical in depressive anxiety-like behavior and beta-carboline-induced seizures in animal models (Kim et al., 2009).

In cross-sectional and longitudinal MR imaging research on cortical thickness, the cingulate cortex has been found to be thinner in TLE patients, and atrophy of the insula has been associated with residual seizures in post-operation patients (Bernhardt et al., 2010). Our results, which demonstrate increased regional activity in the mood regulation system, support our first hypothesis. Considering the short duration of our patients’ epilepsy, this alteration may not be due to the recurrent chronic stress. Our results suggest a common etiology between these two conditions (epilepsy and depression).

The epileptiform discharges affected the ALFF values and the connectivity (Bettus et al., 2011). Our patients’ EEGs showed that the interictal discharge localizations were matched between these two patient groups. Thus, the lateral interictal discharges didn’t introduce a bias in the functional connectivity comparisons (Bettus et al., 2009).

In the PDS group, we found decreased connectivity between the limbic system, temporal lobe and prefrontal lobe (inferior frontal components and the prefrontal lobe (Brodmann area 10) and increased connectivity among the limbic system, angular gyrus and prefrontal lobe (Brodmann area 8). When comparing the nPDS group with the HC group, we found increased connectivity among the precentral gyrus, superior temporal gyrus and limbic system (P<0.05, alpha sim corrected, Table 3).
gyrus and Brodmann area 10) compared with the nPDS group. These data are consistent with the classical top-down mood regulation network that implicates the pre-frontal lobe and limbic system (Foland et al., 2008). Kushnir noted activation of the angular gyrus in acute abstinent nicotine-dependent individuals when facing cigarettes cues (Kushnir et al., 2010). The angular gyrus is part of the visuospatial attention circuit. Our result, showing increased connectivity between the limbic system and angular gyrus, may indicate the heightened sensitivity of the PDS group to their surrounding environment (Kushnir et al., 2010). A recent review noted the damaged brain

Fig. 1. The ALFF value alterations between each group. 1.1: The PDS group showed higher ALFF values in the right anterior cingulate (ACC), bilateral thalamus and insula compared with the nPDS group; (P<0.05). 1.2: The nPDS group showed higher ALFF values in the left amygdala and left medial prefrontal cortex (nPCl) compared with the PDS group; (P<0.05). 1.3: The PDS group showed higher ALFF values in the right ACC, bilateral caudate and insula compared with the healthy controls; (P<0.05). 1.4–5: The nPDS group showed increased regional activity in the right ACC and left anterior insula compared with healthy controls; (P<0.05). 1.6: The healthy control group showed higher ALFF values in the bilateral thalamus and right posterior insula compared with the nPDS group; (P<0.05).

Table 3
The alteration of brain network in PDS/nPDS groups.

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<thead>
<tr>
<th>Groups</th>
<th>Seeds</th>
<th>Connectivity network</th>
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<tr>
<td>PDS vs nPDS</td>
<td>R-ACC</td>
<td>R-Tha L-Tha R-Cau L-Cau</td>
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<td>PDS vs HC</td>
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<td>nPDS vs HC</td>
<td>R-ACC</td>
<td>R-Tha L-Tha R-Cau L-Cau</td>
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Red dot represents increased functional connectivity.

Blue dot for the decreased functional connectivity (P<0.05 Alpha sim corrected).

L: left; R: right; Ins: Insula; PCC: posterior cingulate; Para: Parahippocampus gyrus; Amy: Amygdala; Tha: Thalamus; Cau: Caudate; ACC: anterior cingulate; Ang: Angular gyrus; Fron: Frontal lobe, 1, 4, 6, 8 stand for inferior frontal and brodmann area 10 (B10); 9, 10, 11 for B8; 13, 15, 17, 18, 20 for precentral gyrus; Tem: Temporal lobe, 2, 3, 5, 7 for medial temporal gyrus; 12, 14, 16, 19, 21 for superior temporal gyrus; §: for increased connectivity among superior frontal gyrus (brodmann area 8) and decreased connectivity among B10.
network present in TLE patients [Vlooswijk et al., 2010]. We found decreased connectivity within the limbic system and medial temporal gyrus that might reflect disruption in the network due to the pathological epileptic condition, as reported in previous research on epilepsy (Auer et al., 2008; Liao et al., 2010).

When comparing the PDS group with HC s, the network may reflect both epileptic and depressive characteristics. We found increased connectivity within the superior frontal gyrus (Brodmann area 8–B8) and decreased connectivity within Brodmann area 10 (B10). B10 is involved in strategic processing for memory retrieval and executive functioning. The impairment in the connectivity in B10 may lead to cognitive impairment, which is common in epilepsy patients and patients with depressive symptoms (Monkul et al., 2011; Shelton et al., 2011). The B8 area is involved in management of uncertainty, which is critical in depressive conditions.

We also found increased connectivity between the limbic system and the precentral gyrus in the nPDS group that may reflect the ongoing epileptic condition in the nPDS group. Research has shown motor system hyperconnectivity in juvenile myoclonic epilepsy, and the effect is more robust in patients with ongoing epilepsy compared with healthy controls (Vollmar et al., 2011). We also observed increased connectivity between the limbic system and superior temporal gyrus. Similarly, Liao et al. (2010) reported increased connectivity between the temporal lobe and other areas in TLE patients. These latter data suggest elevated synchronization between the temporal lobe and the default-mode network that may indicate a heightened monitoring of internal thoughts and feelings (Mason et al., 2007).

Our finding of increased connectivity between the ACC and limbic system in epilepsy patients has not previously been reported, although one publication noted increased connectivity in the PCC (Zhang et al., 2010). Our finding may be due to compensatory action in the ACC due to the disruption in the prefrontal lobe-limbic system connection (Holmes and Pizzagalli, 2008). However, it may also be due to the limited number of subjects. Taken together, the findings on connectivity alterations reported here may indicate an excitatory–inhibitory imbalance in brain activity and an epileptic network alteration in epilepsy patients (Waites et al., 2006).

There were two issues that should be considered when interpreting our results: first, the relatively small number of participants may limit the statistical power, and an enlargement of the database may provide a more complete picture of the problem; second, the experiment cannot per se provide longitudinal alteration data on the participants because our study was cross sectional. We cannot determine whether the characteristic alteration in the PDS group predicts the poor treatment outcomes that were the concern of Kanner (2008), although a retrospective analysis in patients who received surgical operations revealed that the Beck depression index predicted postoperative seizure frequency and seizure freedom (Metternich et al., 2009). In the future, longitudinal research may answer these questions and provide evidence on the natural history of these two conditions (Herrmann et al., 2008).

Conclusion

Taken together, the current results demonstrate that treatment-naïve TLE patients show hyperactivity in the prefrontal-limbic and striatal brain areas and in the ACC with decreased functional connectivity within the prefrontal-limbic system in the PDS group. Longitudinal studies of these patients may illustrate whether the alteration in the PDS group predicts treatment outcomes, and these studies may help understand the lifetime disease course in PDS patients (Herrmann et al., 2008).

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