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Temporal lobe epilepsy: Decreased thalamic resting-state functional connectivity and their relationships with alertness performance

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ABSTRACT

Objectives: Studies have provided evidence regarding the pathology of the thalamus in patients with temporal lobe epilepsy (TLE). The thalamus, particularly the right thalamus, is one of the subcortical structures that are most uniformly accepted as being significantly involved in alertness. Moreover, alertness impairment in epilepsy has been reported. This study aimed to investigate alterations in thalamic resting-state functional connectivity (FC) and their relationships with alertness performance in patients with TLE; an issue that has not yet been addressed.

Methods: A total of 15 patients with right TLE (rTLE) and 16 healthy controls were recruited for the present study. All of the participants underwent a resting-state functional magnetic resonance imaging (fMRI) scan and the attention network test (ANT). Whole-brain voxel-wise FC analyses were applied to extract the thalamic resting-state functional networks in the patients with rTLE and healthy controls, and the differences between the two groups were evaluated. Correlation analyses were employed to examine the relationships between alterations in thalamic FC and alertness performance in patients with rTLE.

Results: Compared to the healthy controls, the FC within and between the bilateral thalamus was decreased in the patients with rTLE. Moreover, in the patient group, the bilateral anterior cingulate cortex (ACC) and subcortical regions, including the bilateral brainstem, cerebellum, putamen, right caudate nucleus, and amygdala, exhibited decreased FC with the ipsilateral thalamus ($p < 0.05$, AlphaSim corrected, cluster size > 44) but not with the contralateral thalamus ($p < 0.05$, AlphaSim corrected, cluster size > 43). The intrinsic and phasic alertness performances of the patients were impaired ($p = 0.001$ and $p < 0.001$, respectively) but not correlated with decreased thalamic FC. Meanwhile, the alertness performance was not altered in right TLE but was negatively correlated with decreased thalamic FC with ACC ($p < 0.05$).

Conclusions: Our findings highlight the functional importance of the thalamus in TLE pathology and suggest that damage to the thalamic resting-state functional networks, particularly ipsilateral to the epileptogenic focus, is present in patients with TLE.

1. Introduction

Temporal lobe epilepsy (TLE) is the most prevalent type of focal epilepsy. There is evidence that brain abnormalities in TLE are not confined to the epileptogenic focus but rather extend throughout the whole brain. The thalamus, which is a core relay that possesses reciprocal connections to cortical and subcortical structures, plays an important role in modulating seizure activity and propagating extratemporal structures in TLE. A stereoelectroencephalography study of patients with TLE suggested that the thalamus functions as an amplifier and synchronizer of seizure activity [1]. Metabolic abnormalities of the thalamus in patients with TLE have been found by positron emission tomography studies [2]. Additionally, a cortical thickness study demonstrated ipsilateral thalamic atrophy in TLE [3]. Strengthening these observations, a voxel-based morphometry meta-analysis of mesial TLE showed that consistent structural changes are only present in the bilateral thalamus and the epileptogenic hippocampus. Subsequently, the authors determined that the ipsilateral thalamus and hippocampus are functionally coactivated and participate in the same network [4]. Moreover, a diffusion tensor imaging (DTI) study showed that the diffusion properties of the bilateral thalamus are altered in TLE and that the existence of hippocampal sclerosis reinforces these ipsilateral changes [5]. Moreover, quantitative magnetic resonance imaging (MRI) studies have revealed that reduced thalamic volume is significantly correlated with cognitive impairment in TLE [6,7]. In summary, damage to the bilateral thalamus is observed

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in TLE, and this damage is more severe in the thalamus ipsilateral to the epileptogenic focus. However, limited information has been presented regarding the functional interaction between the thalamus and whole-brain regions during the resting state.

Interactions between brain regions can be evaluated with functional connectivity (FC) analysis, which is a commonly used method for the analysis of resting-state functional magnetic resonance imaging (fMRI) data that involves calculating the correlations of intrinsic low-frequency fluctuations in spontaneous blood oxygen level-dependent (BOLD) signals between different brain regions [8]. Since this technique was first reported in 1995, resting-state fMRI has been the focus of neuroimaging studies. Resting-state fMRI avoids several limitations of task-based fMRI and is a useful tool for investigations of natural brain functions [9]. Resting-state fMRI studies have reported that altered thalamic FC is related to cognitive dysfunctions in mild traumatic brain injury [10], Alzheimer's disease [11], and multiple sclerosis [12]. However, few researchers have studied TLE.

Cognitive impairment is common in TLE [13,14]. Attention is central to many cognitive functions [15]. In 1990, Posner and Petersen proposed that the attention system can be further divided into three networks, i.e., the alertness, orientation, and execution networks [16]. Alertness is a condition in which an alert state is achieved and maintained. Alertness comprises two domains [17]: (1) intrinsic alertness, which is considered to be related to the internal control of arousal or wakefulness in the absence of an external cue, and (2) phasic alertness, which represents the short-lived ability to enhance response readiness after an external cue stimulus is detected. Both of these domains can be assessed by measuring reaction times (RTs) to the appearance of a target with or without a preceding warning cue. Alertness is considered to be the fundamental form of attention [15] and represents the attention intensity aspect that probably is a prerequisite for the more complex and capacity-demanding component of attention selectivity [18]. Attentional deficits have previously been observed in patients with TLE [19,20], but limited information has been presented regarding alertness. Given that many cognitive functions rely on the basal aspect of attention, alertness is an important issue for research. Additionally, in a systemic review of rolandic epilepsy, researchers found that the alertness network is impaired in patients with active centrotemporal spikes [21]. Behavioral data also suggest that tonic alertness and phasic alertness are impaired in childhood absence epilepsy [22]. In brief, these reviewed studies revealed the increasing attention that has been given to alertness dysfunctions in epilepsy. Temporal lobe epilepsy is a common form of epilepsy. Furthermore, the decreased activation of the alertness network in TLE has been reported by us previously in a task-based fMRI study [23]. The alertness network comprises cortical and subcortical structures, such as the frontal, parietal, and temporal cortices, and brainstem and thalamic structures [17,24,25]. The views regarding the exact brain regions that are related to alertness are inconclusive; however, the thalamus, particularly the right thalamus [17,25,26], is one of the subcortical structures that are most uniformly accepted as being significantly and consistently involved in alertness [19,24].

Brain structural and functional damage may play a role in cognitive dysfunction. In the present study, we aimed to investigate alterations in thalamic resting-state FC and their relationships with alertness performance in patients with TLE. These issues have not previously been addressed but should be explored to fill gaps in our knowledge in these domains and aid our understanding of the neuromechanisms that underlie brain dysfunction and cognitive impairment in TLE. To investigate these issues, we initially performed resting-state fMRI scans of a patient group with right TLE (rTLE) and a healthy control group and performed whole-brain voxel-wise FC analyses. We then subjected all of the participants to the attention network test (ANT) to assess their alertness performances. The correlation between altered thalamic FC and alertness performance in the patient group was determined.

2. Materials and methods

2.1. Participants

Sixteen patients with rTLE [mean age ± standard deviation (SD) = 27.53 ± 6.63 years, mean years of education ± SD = 11.47 ± 3.27 years, eight males] were recruited from the Epilepsy Clinic of the First Affiliated Hospital of Guangxi Medical University. Epilepsy was diagnosed in accordance with the diagnostic criteria proposed by the International League Against Epilepsy (ILAE). All of the patients with rTLE satisfied at least two of the following inclusion criteria [27]: (1) typical semiology of seizures suggesting that the epileptogenic focus was located in the temporal lobe including epigastric rising, abnormal emotional experiences and psychiatric symptoms, automatisms, and dystonic posturing of the limbs; (2) MRI showing right hippocampus atrophy, sclerosis, or other abnormal signals only in the right temporal lobe; and (3) ictal or interictal electroencephalogram revealing epileptic discharges in the right temporal lobe. All of the patients regularly took antiepileptic drugs in accordance with the ILAE treatment guidelines [28]. Additionally, Mini-Mental State Examination scores were >24. Patients with TLE were excluded if they simultaneously suffered from serious diseases in other systems or psychiatric or neurological diseases. Table 1 shows the characteristics of each patient.

Sixteen healthy controls (mean age ± SD = 27.19 ± 3.82 years, mean years of education ± SD = 12.31 ± 2.89 years, eight males) were included, and the controls were matched in terms of sex, age, and degree of education. All of the subjects were right-handed. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. All of the participants were informed in detail about the experiment and provided written informed consent.

2.2. fMRI data acquisition

The MRI scans were acquired on an Achieva 3T MRI scanner (Philips, the Netherlands) with a 12-channel head coil. The subjects were instructed to lie still, close their eyes, and avoid thinking as much as possible. Headphones and padding were used to reduce noise and prevent head motion. All of the subjects were also instructed not to fall asleep during the entire scan. The scanning parameters were as follows: (1) structural scan (T1-weighted): spin-echo sequence, repetition time (TR) = 3000 ms, echo time (TE) = 10 ms, slice thickness = 5 mm, and slice gap = 1 mm; and (2) resting-state fMRI scan: gradient-echo echo planar imaging (EPI) sequence, TR = 2000 ms, TE = 30 ms, slice thickness = 5 mm, slice gap = 1 mm, acquisition matrix = 64 × 64, field of view = 220 mm, flip angle = 90°, and voxel size = 3.44 mm × 3.44 mm × 6.00 mm with 31 slices and 180 dynamics.

2.3. fMRI data processing and statistical analyses

2.3.1. fMRI data preprocessing

The resting-state fMRI data were analyzed using DPARSF (http://resting-fmri.sourceforge.net) software, which is based on statistical parametric mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). The first 10 dynamics were removed to allow for magnetization equilibrium. The slice-timing correction was based on the middle slice. The functional data were realigned to the first dynamic by rigid body correction, and six parameters of the head movements were then generated. Participants who exhibited head motion of more than 2 mm of translation or 2° of rotation were excluded. One patient was excluded based on these criteria. Moreover, only 15 patients with rTLE and 16 healthy controls were subjected to the subsequent analysis. The data were then normalized to a conventional EPI template in the Montreal Neurological Institute (MNI) space with voxel size resampling of 3 mm × 3 mm × 3 mm. Subsequently, a 4-mm full-width half-maximum Gaussian kernel