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Interhemispheric functional and structural alterations and their relationships with alertness in unilateral temporal lobe epilepsy

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Abstract. – OBJECTIVE: Many neuroimaging studies have shown that temporal lobe epilepsy (TLE) is associated with functional and structural abnormalities at specific brain areas. Unfortunately, relatively limited information has been presented about the alterations of interhemispheric functional and anatomic connectivity in patients with unilateral TLE. In the present study, we investigated interhemispheric functional connectivity using a voxel-mirrored homotopic connectivity (VMHC) method. We further revealed fractional anisotropy (FA) changes in the areas with abnormal VMHC values in TLE patients by diffusion tensor imaging (DTI). Moreover, their relationships with alertness in patients with drug-naïve unilateral TLE were also investigated.

PATIENTS AND METHODS: Forty-three patients with unilateral TLE (21 left TLE and 22 right TLE) and 20 normal controls (NC) were recruited for case-control study. All of the subjects underwent acquisition of resting-state functional magnetic resonance images, Mini-Mental State Examination (MMSE) and the attention network test. DTI images were collected in 26 patients with unilateral TLE (10 left TLE and 16 right TLE) and 20 NCs. Functional connectivity between bilateral homotopic voxels was calculated. Homotopic regions showing abnormal functional connectivity in patients were adopted as regions of interest for the analysis of DTI. The FA values, MMSE scores, and alertness were compared between groups. Correlation analyses were employed to examine the relationships between each radiographic parameter (VMHC and FA) and each clinical and neuropsychological parameter in patients with drug-naïve unilateral TLE.

RESULTS: Compared with NC, patients with left TLE exhibited significantly higher VMHC values in the bilateral angular gyrus, inferior occipital gyrus and superior parietal gyrus and lower VMHC values in the bilateral supplementary motor area, inferior parietal lobule, middle temporal gyrus, and medial superior frontal gyrus. In patients with right TLE, higher VMHC values were found in the bilateral inferior occipital gyrus, parahippocampal gyrus and cerebellum; lower VMHC values were observed in the bilateral middle temporal gyrus and precentral gyrus/inferior frontal gyrus. FA values of the commissural fiber bundles connecting the bilateral parahippocampal gyrus were smaller in the right TLE than those in the NC group. Meanwhile, the alerting effect of patients was determined to be impaired and positively correlated with FA values of the commissural fiber bundles connecting the bilateral parahippocampal gyrus in right TLE patients.

CONCLUSIONS: Our findings indicate that the bilateral parahippocampal gyrus may be important to the pathophysiology of patients with drug-naïve unilateral TLE. The significant correlation between the FA values and alertness indicates that structural changes are involved in the alterations in the alertness network in unilateral right TLE patients.

Key Words:
Temporal lobe epilepsy, Functional magnetic resonance imaging, Voxel-mirrored homotopic connectivity, Diffusion tensor imaging, Fractional anisotropy, Attention Network Test, Alerting affect.

Introduction

Many neuroimaging studies have shown that temporal lobe epilepsy (TLE) is associated with structural and functional abnormalities in specific brain areas[1]. The homotopic connections may reflect the importance of interhemispheric communication in the integration of brain function[2] and have been considered important in depicting the

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physiologic and pathologic features of the brain. Functional magnetic resonance imaging (fMRI) studies have shown asymmetric connections between hemispheres[3-5] and decreased connectivity between bilateral hippocampi in mesial TLE6. To explore the interhemispheric resting state functional connectivity in patients with TLE, we used a sensitive approach, voxel-mirrored homotopic connectivity (VMHC), which examines the functional connectivity between each voxel and its mirrored counterpart in hemispheres[7] Subsequently, we used diffusion tensor imaging (DTI) method to evaluated the structural connectivity between the interhemispheric mirrored regions that possess abnormal VMHC values in unilateral TLE patients.

Central to many behavioral functions, attention is one of the most pivotal issues in neurosciences[8]. The alertness network is involved in the ability to increase and maintain response readiness in preparation for an impending stimulus[9], and it is a prerequisite for continuous information processing and attention. Impairment of attention is considered to be one of the cognitive domains predominantly affected in TLE patients[10-12]. Our previous task-based fMRI studies showed that the alertness network is deficient in TLE patients despite normal performance on neuropsychological tests[13,14]. Chen et al research[15] showed the neuropsychological impairment encompassing the intrinsic and phasic alertness domains in right TLE. Considering the importance of functional interhemispheric synchronicity, we formed the hypothesis that the impairment in alertness in unilateral temporal lobe epilepsy might be connected to alterations of interhemispheric functional connectivity. In this study, we combined VMHC with the DTI technique to investigate whether there is any alteration in interhemispheric resting state functional connectivity and whether the functional changes are associated with corresponding alterations of anatomic connectivity.

Patients and Methods

Patients

The present study was approved by local Ethics Committee of First Affiliated Hospital of Guangxi Medical University. All of the subjects were informed in detail about the experiment. Written informed consent was obtained from each subject.

Patients with unilateral TLE were recruited from the Epilepsy Clinic of the First Affiliated Hospital of Guangxi Medical University. A diagnosis of TLE was made in compliance with the diagnostic criteria of International League Against Epilepsy (ILAE) classification. All the patients with unilateral TLE (left TLE, LTLE or right TLE, RTLE) were included if satisfied at least two of the following inclusion criteria[16]: (1) typical semiology of seizures, suggesting that the epileptogenic focus was located in the temporal lobe; (2) only unilateral lesions, including hippocampal atrophy, sclerosis within the right or left temporal lobes as shown by MRI; (3) ictal/interictal scalp electroencephalogram indicating that the epileptic.

Twenty-four right-handed healthy subjects were recruited as the normal control (NC) from the staff of the First Affiliated Hospital of Guangxi Medical University.

Exclusion criteria for all subjects included the following: left handed, history of serious medical diseases or other neurological illness, any history of addictions, any lifetime psychiatric disorder, younger than 18 years or older than 60 years, structural MR images showing identifiable focal abnormalities other than hippocampal sclerosis or atrophy.

Data Acquisition

MRI data were acquired using a 3.0T MRI scanner (Philips, Amsterdam, The Netherlands) with a 12-channel head coil. Foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. Subjects were required to keep eyes closed, not think of anything, and not fall asleep during the entire session. 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; (2) resting-state fMRI scan: gradient-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 (FOV) = 220 mm, flip angle = 90°, voxel size = 3.44 mm × 3.44 mm × 6.00 mm with 31 slices and 180 dynamic. The anatomic connectivity analysis was based on the diffusion data of these subjects. The diffusion sensitizing gradients were applied along 30 non-linear directions (b =1000 s/mm^2) together with an acquisition without diffusion weighting (b = 0 s/mm^2).

Each volume consisted of 45 contiguous axial sections with a slice thickness of 3 mm and no gap, TR = 6100 ms, TE = 93 ms, number of signals acquired = 4; flip angle = 90°; FOV = 240 × 240 mm^2; data matrix size = 256 × 256; voxel size = 0.94 × 0.94 × 3 mm^3.

Data Preprocessing

Functional Images

Image preprocessing was analyzed using the DPARSF software (http://resting-fmri.sourceforge.net), which is based on statistical parametric mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each functional time series were discarded to ensure steady state conditions. Preprocessing of the fMRI data sets included standard slice timing, realignment, spatial normalization (normalized to a conventional EPI template in the Montreal Neurological Institute space with voxel size resampling of 3 mm × 3 mm × 3 mm) and smoothing (full-width half maximum (FWHM) = 4 mm). Participants with head motion greater than 2 mm or 2 degrees in any of the 6 parameters (x, y, z, pitch, roll, yaw) were excluded. Linear trend removal and a temporal band-pass filter (0.01 Hz < f < 0.08 Hz) were applied to reduce the effects of high-frequency noise and low-frequency drift.

VMHC Processing

VMHC analysis was performed using the RSET toolkit (http://resting-fmri.net). Each subject's normalized gray matter images were averaged to create a mean normalized gray matter template. This image with its left-right mirrored version was averaged to produce a group-specific symmetrical template. Next, the normalized gray matter images were registered to this symmetrical template. Nonlinear registration to this symmetrical template was performed, and the resultant transformation was applied to each subject's preprocessed functional images. Lastly, we spatially smoothed the images with a 6-mm FWHM isotropic Gaussian kernel. Individual VMHC maps were generated by computing the Pearson correlation (Fisher z-transformed) between a given voxel and a corresponding voxel in the opposite hemisphere. The resulting correlations for each paired voxel constituted a VMHC map. This map was used for subsequent group-level analyses. The regions showing abnormal VMHC values were extracted as regions of interest (ROIs) for further DTI analysis.

DTI Data Processing

Data for DTI analysis were preprocessed in Matlab using Pipeline for Analyzing Brain Diffusion Images (PANDA (http://www.nitrc.org/projects/panda[17]), FSL (http://www.fsl.fmrib.ox.ac.uk/fsl/) and the Diffusion Toolkit[18]. (1) Imaging data were corrected for head motion and eddy current. (2) DTI were geometrically corrected by an unweighted B0 image (b = 0 sec/mm^2) and a filed map. Through affine transformations, diffusion-tensor images were coregistered to the B0 image to minimize head movements. Diffusion-tensor models were evaluated by employing the linear least-squares fitting method at each voxel using the diffusion toolkit. (3) Whole-brain fiber tracking was processed in the native diffusion space for each subject through fiber assignment with the continuous tracking algorithm, which was embedded in the Diffusion Toolkit. Fiber tracking termination conditions were FA values less than 0.15 or angular variation greater than 35n[19]. Fibers less than 10 mm were discarded.

The ANT for Neuropsychological Assessment

Alertness was evaluated using the Attention Network Test (ANT)[20], which combining multiple warning cues and target flankers (Figure 1). In each trial, the participant was instructed to focus on a fixation cross, which was presented at the center of a computer screen throughout the test. When the target appeared, the participant was required to press the button that matched to the direction of the target as quickly and accurately as possible. After performing a practice block of 24 trials, the formal test consisting of 3 blocks with 96 trials in each block was performed. The correct/incorrect reactions and reaction times (RTs) were recorded. The correct trials were singled out to calculate the efficiency of alertness, which was calculated by subtracting the mean RT in the double cue condition from the mean RT in the no cue condition, regardless of the type of flanker stimuli.

Statistical Analysis

Distributions of age, years of education, MMSE scores, and alertness among the LTLE, RTLE and NC groups were analyzed with one-way analysis of variance (ANOVA). Chi-square test was used to compare gender distributions.

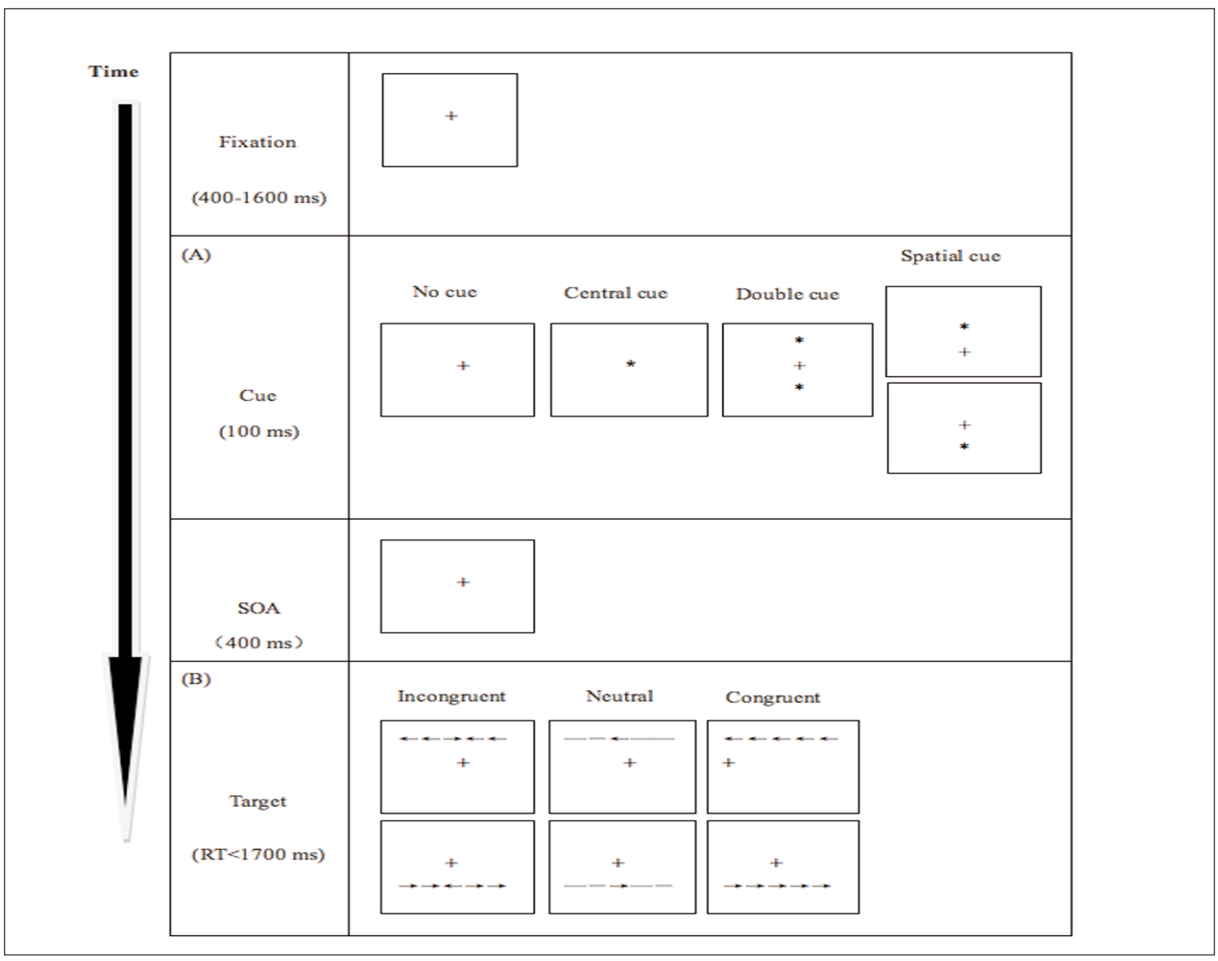

Figure 1. Design and procedure of the attention network test (ANT). The sequence of events in one trial is conveyed in the left column, and all possible stimuli associated with each event are presented in the right column. ***A,*** The four warning cue conditions. ***B,*** The three flanker conditions. The participants' task was to determine whether the *central arrow* in the flanker display was pointing to the left or right. All four cue types are equally probable in the task, as are all three flanker conditions. The target display was presented equally above (as shown here) or below central fixation (+). The following subtractions were used to calculate the alertness effect: Trimmed mean reaction time (RT) for no cue-trimmed mean RT for double cues. SOA: stimulus onset asynchrony.

The significant differences in VMHC between groups, and differences in FA values of the commissural tracts connecting the bilateral ROIs between groups were analyzed using a two-sample *t*-test. Pearson's correlation analysis was performed between the VMHC values or FA values and each clinical or neuropsychological parameter. These analyzed clinical and neuropsychological variables included illness duration, age of onset, and alertness (including $RT_{no\ cue}$, $RT_{double\ cue}$ and alerting effect).

All tests were two-tailed, and $p < 0.05$ was considered statistically significant. All analyses were conducted using SPSS16.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics, Clinical Characteristics And Neuropsychological Parameters of the Participants

Five patients and 4 controls were excluded due to mania, coma or refusing MRI scanning. Twenty normal controls, 21 LTLE patients and 22 RTLE patients remained to proceed the study. The demographic, clinical and neuropsychological details of the included subjects are shown in Table I. There differences of RT for the no cue condition ($RT_{no\text{-}cue}$) ($F = 33.264$, $p < 0.001$), RT for the double cue condition ($RT_{double\text{-}cue}$) ($F = 66.068$, $p < 0.001$) and alertness effect ($F =$

Table I. Demographic, clinical and neuropsychological information of study subjects.

	NC (n = 20)	LTLE (n = 21)	RTLE (n = 22)	F (or t or χ^2)	p
Gender (M/F)	11/9	12/9	14/8	0.355	0.837
Age (years)	26.35 ± 8.09	27.48 ± 7.94	25.55 ± 6.11	0.368	0.694
Handedness (right/left)	20/0	21/0	22/0	–	–
Duration (years)	–	1.22 ± 0.61	1.27 ± 0.84	-0.240	0.812
Age of onset (years)	–	26.26 ± 7.79	24.27 ± 6.16	0.929	0.358
Education (years)	11.15 ± 1.76	12.33 ± 1.91	11.32 ± 2.17	2.229	0.116
MMSE	26.00 ± 1.08	26.38 ± 1.36	26.23 ± 1.23	0.496	0.611
RTno-cue (ms)	552.99 ± 26.35	610.64 ± 25.52[a]	609.90 ± 25.98[a]	33.264	< 0.001
RTdouble-cue (ms)	509.64 ± 22.41	582.14 ± 24.71[a]	587.18 ± 25.18[a]	66.068	< 0.001
Alertness effect (ms)	43.34 ± 11.88	28.50 ± 7.28[a]	23.67 ± 6.84[a]	27.569	< 0.001

LTLE: left temporal lobe epilepsy. RTLE: right temporal lobe epilepsy. NC: normal controls. MMSE: Mini-Mental State Examination. RT: reaction time; $RT_{no\text{-}cue}$: RT for the no cue condition; $RT_{double\text{-}cue}$: RT for the double cue condition.ms: millisecond. a Significant compared to NC.

27.569, $p < 0.001$) among the three groups were significant. Compared with NC group, both the LTLE and RTLE group had longer $RT_{no\text{-}cue}$ ($p < 0.001$), longer $RT_{double\text{-}cue}$ ($p < 0.001$) and lower alertness effect ($p < 0.001$). No significant differences of RTs ($RT_{no\text{-}cue}$ and $RT_{double\text{-}cue}$) and the alertness effect were found between LTLE and RTLE groups (Table I).

We had planned to acquire DTI for each subject included in the study. However, this imager is used mainly for clinical examinations. This limited the MRI scans available to all participants of our research. Consequently, only 26 patients (10 LTLE patients and 16 RTLE patients) and 20 controls underwent an fMRI brain scans for DTI. The demographic, clinical and neuropsychological parameters for these 46 subjects are shown in Table II.

VMHC

Using the one-sample *t*-test, within-group comparisons showed that each group, including the LTLE, RTLE and NC group, had robust homotopic functional connectivity with regional differences in strength (Figure 2).

Group comparisons of VMHC values between the LTLE and NC groups indicated that patients with LTLE exhibited lower VMHC in the bilateral supplementary motor area, middle temporal gyri, and medial superior frontal gyri and inferior parietal lobule, as well as higher VMHC in bilateral angular gyri, inferior occipital gyris and superior parietal gyri (Figure 3).

Compared with the NCs, the RTLE patients exhibited significantly decreased VMHC in the bilateral temporal poles and bilateral precentral

Table II. Demographic, clinical and neuropsychological information of some subjects who underwent a DTI scan.

	NC (n = 20)	LTLE (n = 10)	RTLE (n = 16)	F (or *t* or χ^2)	p
Gender (M/F)	11/9	6/4	9/7	0.069	0.966
Age (years)	26.35 ± 8.09	29.10 ±8.48	25.81 ± 6.33	0.625	0.540
Handedness (right/left)	20/0	10/0	16/0	–	–
Duration (years)	–	1.25 ± 0.80	1.28 ± 0.83	-0.095	0.925
Age of onset (years)	–	27.85 ± 8.19	24.53 ± 6.20	1.173	0.252
Education (years)	11.15 ±1.76	11.70 ± 1.64	10.56 ± 1.41	1.569	0.220
MMSE	26.00 ± 1.08	26.50 ± 1.58	26.06 ± 1.06	0.623	0.541
RTno-cue (ms)	552.99 ± 26.35	610.87 ± 24.85[a]	604.53 ± 27.15[a]	23.937	< 0.001
RTdouble-cu (ms)	509.64 ± 22.41	580.63 ± 23.60[a]	582.55 ± 26.21[a]	50.932	< 0.001
Alertness effect (ms)	43.34 ± 11.88	30.23 ± 5.90[a]	22.67 ± 6.89[a]	22.728	< 0.001

LTLE: left temporal lobe epilepsy. RTLE: right temporal lobe epilepsy. NC: normal controls. MMSE: Mini-Mental State Examination. RT: reaction time; $RT_{no\text{-}cue}$: RT for the no cue condition; $RT_{double\text{-}cue}$: RT for the double cue condition. ms: millisecond. a Significant compared to NC

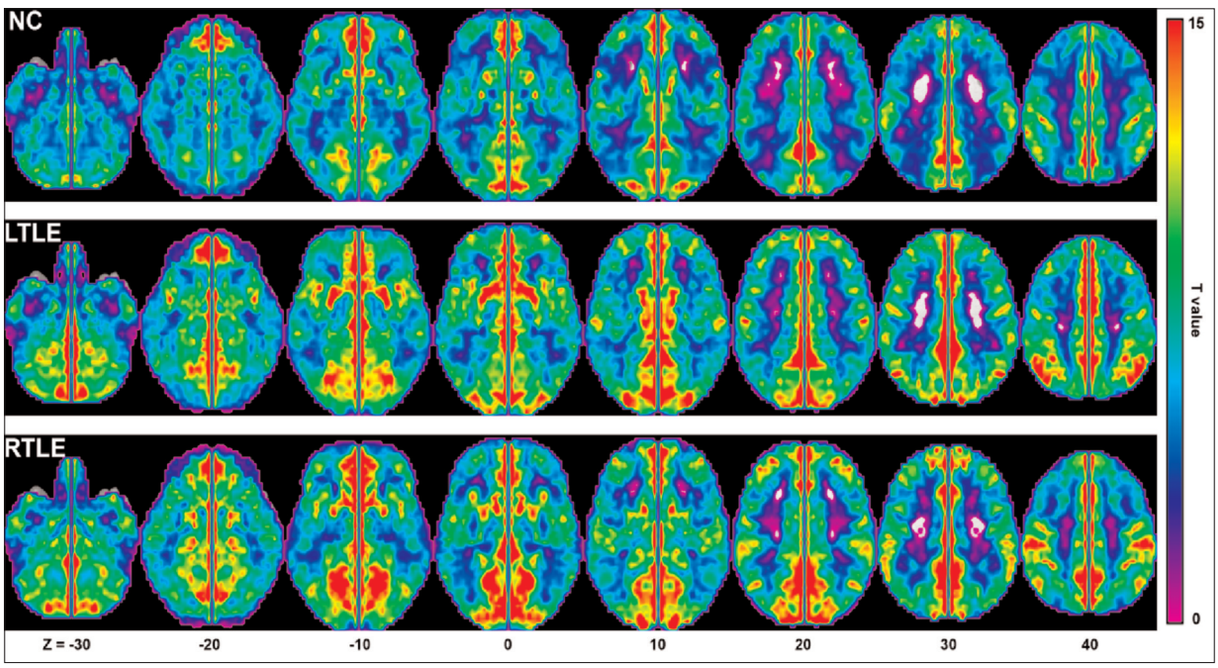

Figure 2. Axial MR images show interhemispheric functional connectivity within groups. Regions show significant interhemispheric functional connectivity in NC, LTL and RTLE patients, respectively. ($p < 0.05$, AlphaSim corrected). NC: normal controls, LTLE: left temporal lobe epilepsy, RTLE: right temporal lobe epilepsy.

gyri/inferior frontal gyri. The bilateral inferior occipital gyri, parahippocampal gyri and cerebellum showed greater VMHC in the RTLE group (Figure 3).

The correlation analysis revealed no significant correlation between the VMHC values of the above-mentioned brain regions and clinical variables between the VMHC and alertness values in patients.

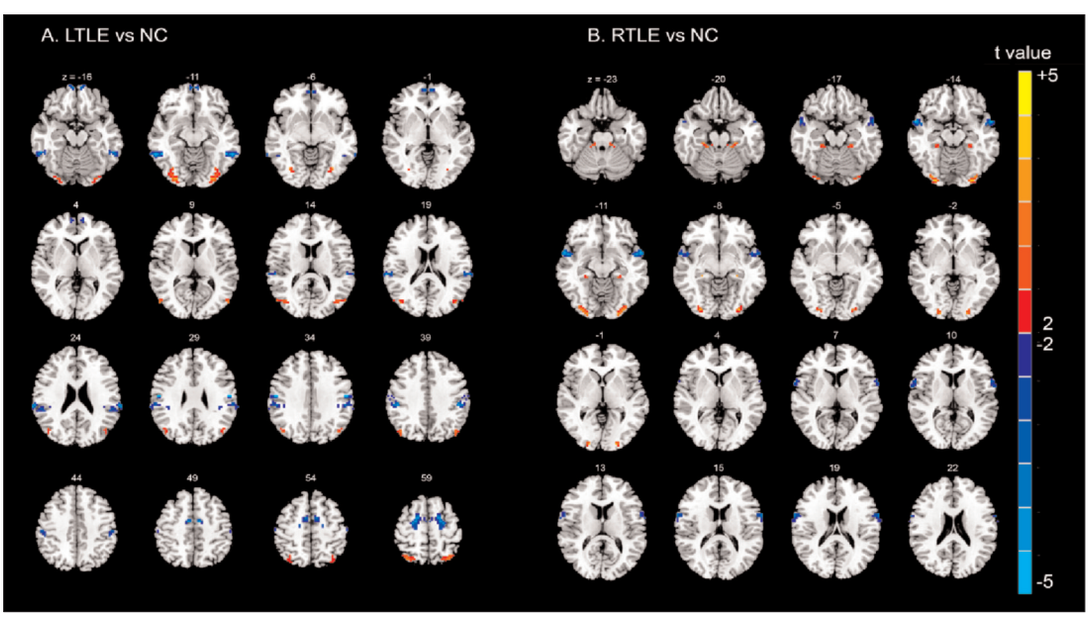

Figure 3. Statistical maps showing interhemispheric functional connectivity differences between groups. Homotopic regions show increased (*warm colors*) or decreased (*cool colors*) functional connectivity in the patient group ($p < 0.05$, AlphaSim corrected). NC: normal controls, LTLE: left temporal lobe epilepsy, RTLE: right temporal lobe epilepsy.

Table III. Regions showing significant differences in VMHC between groups.

Brain regions	Peak MNI coordinates			Cluster size	Peak T-value
	x	y	z		
LTLE *vs*. NC					
Angular gyrus	± 54	-78	12	73	3.03
Inferior occipital gyrus	± 33	-72	-9	66	4.25
Superior parietal gyrus	± 27	-69	63	48	3.62
Supplementary motor area	± 21	-6	60	166	-3.35
Inferior parietal lobule	± 57	-15	30	157	-3.66
Middle temporal gyrus	± 60	-48	-12	54	-3.50
Medial superior frontal gyrus	± 3	57	-3	46	-3.20
RTLE *vs*. NC					
Inferior occipital gyrus	± 30	-90	-9	53	3.22
Parahippocampal gyrus	± 15	-30	-30	50	3.32
Cerebellum	± 24	-30	-45	48	3.50
Middle temporal gyrus	± 60	6	-12	57	-4.26
Precentral gyrus/inferior frontal gyrus	± 66	3	18	50	-3.29

VMHC: voxel-mirrored homotopic connectivity. MNI: Montreal Neurological Institute. LTLE: left temporal lobe epilepsy. RTLE: right temporal lobe epilepsy. NC: normal controls. x, y, z, coordinates of primary peak locations in the MNI space.

Diffusion-Tensor Imaging

Only one commissural tract that connected the bilateral parahippocampus was found in RTLE patients. No commissural tracts connecting bilateral ROIs were detected in LTLE patients.

The inter-group comparison showed that the FA values of commissural tracts connecting the bilateral parahippocampus in RTLE patients were less than those of NC. There was a significant negative correlation between FA values and the alertness effect in the RTLE group. While no significant correlation was found between FA and the alertness effect In the NC group.

Discussion

In present study, combining fMRI and DTI techniques, we investigated interhemospheric functional and anatomic connectivity in patients with unilateral TLE, as well as the relationship between interhemospheric connectivity with alertness. Patients with LTLE exhibited lower VMHC

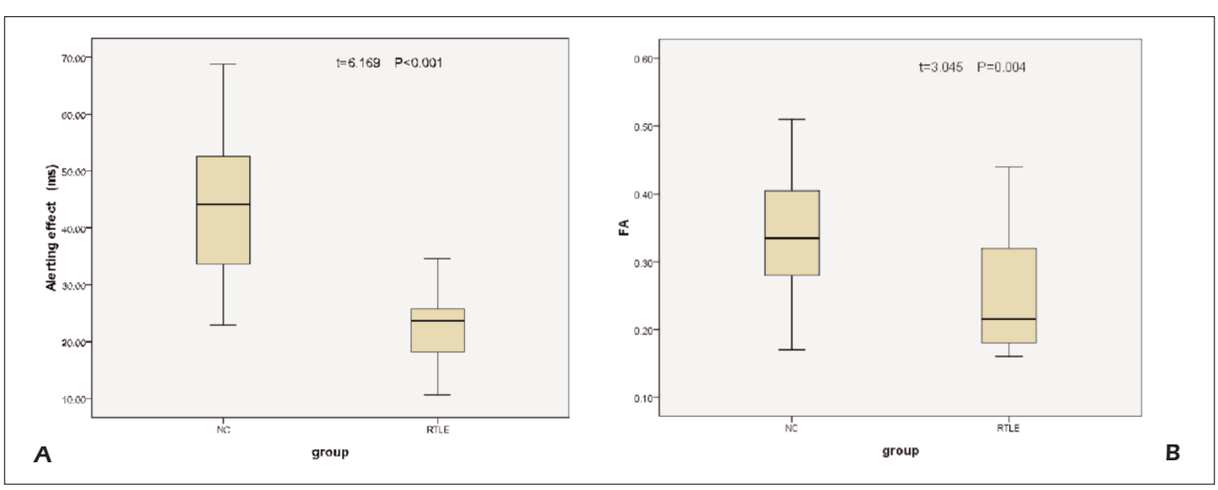

Figure 4. The difference of the alertness effect and FA between the RTLE and NC groups. ***A,*** The difference in the alertness effect; ***B,*** The difference in FA. FA: fraction anisotropy; RTLE: right temporal lobe epilepsy; NC: normal controls. The *p*-values were obtained by two-sample *t*-tests.

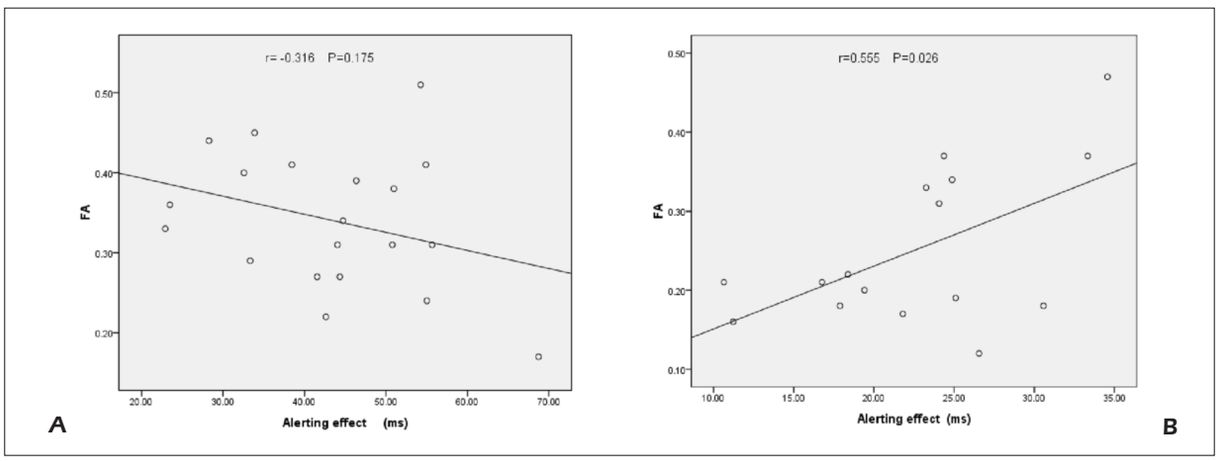

Figure 5. Correlation between the alertness effect and FA values of tracts connecting bilateral parahippocampal gyri in ***A,*** NC group, ***B,*** RTLE group, respectively. FA: fraction anisotropy; RTLE: right temporal lobe epilepsy; NC: normal controls. The p-values were obtained by Pearson's correlation.

in the bilateral supplementary motor area, inferior parietal lobule, bilateral middle temporal gyri and bilateral medial superior frontal gyri; higher VMHC at bilateral angular gyri, inferior occipital gyri and superior parietal gyri. In RTLE, we found decreased VMHC at bilateral middle temporal gyri and bilateral precentral gyrus/inferior frontal gyri; and higher VMHC at bilateral parahippocampal gyri, bilateral inferior occipital gyri and bilateral cerebellum. The specific alterations of VMHC demonstrate that the effects of TLE to the brain are asymmetric.

Disturbances of visual perception are a characteristic feature of TLE[21]. In our study, increased functional connectivity between the inferior occipital gyri was observed in both TLE groups. The increased VMHC between the bilateral visual cortex of the occipital lobe in patients during the interictal state may be correlated with the visual aura experienced by a substantial number of patients with TLE[22]. This increase in interhemicerebral connectivity is likely driven by the sub-threshold excitatory state before or after seizures[23].

In the RTLE and LTLE groups, we found decreased connectivity between the bilateral middle temporal gyri. The middle temporal gyrus has been suggested to be involved in several cognitive processes[24], including linguistics and semantic memory processing[24,25]. This reduced connectivity may be associated with the functional deficits in these cognitive domains, such as language, memory, which are experienced by a great deal of TLE patients. Decreased interhemispheric connectivity was also found in the supplementary motor area (SMA) in the LTLE group. This decline was also shown in the precentral gyrus in the RTLE group. It is generally believed that the precentral gyrus, also known as the motor strip or the primary motor cortex, is a critical part of the brain's neocortex responsible for executing voluntary movements. SMA plays a pivotal role in the development of the action intention through its mediation between medial limbic cortex and primary motor cortex[26]. The decreased VMHC in the interhemispheric motion-related cortex is associated with the motion abnormality that characterizes patients with TLE.

Our results also showed that the RTLE patients exhibited an increase in VMHC in the bilateral cerebella. Studies have suggested that the cerebellum exerts surprisingly potent effects on normal hippocampal information processing[27], and interventions targeting the cerebellum could be considered to be a potential therapy for epilepsy[28,29]. The increased interhemispheric connectivity in the cerebellum observed in the present study may be implicated in the strong modulation of the cerebellum. Relative to the left TLE, significantly more heterotopic neurons have been observed in right TLE patients[30], and more frequent propagations of ictal discharges to the contralateral hemisphere in the right mesial TLE were reported in a previous study[31]. In the present study, the altered VMHC in the cerebellum observed only in RTLE may be related to differences in the histologic or pathogenetic changes between the left and right TLE.

In the LTLE group, robust changes of functional synchronization were observed in the bilateral superior parietal gyri, angular gyri, medial superior frontal gyri and inferior parietal lobule. These regions are mainly included in the default mode network (DMN), which is associated with conscious and resting state cognition. Using ROI-based connectivity of the posterior and anterior parts of the DMN, the reduced posterior DMN connectivity in right TLE and increased connectivity of the posterior and anterior DMN in left TLE were observed[27-29]. The differences of DMN connectivity between the left TLE and right TLE demonstrated the DMN disruption may be more likely in right TLE[29]. However, areas of altered homotopic connectivity were observed only in LTLE in our study, which is different from the above-mentioned reports. We speculate that this phenomenon may be due to the inclusion of different ages and subtypes of TLE patients in our study.

We revealed that the parahippocampal gyrus (PHG) showed decreased homotopic connectivity in RTLE, accompanied by decreased FA values, which represented neuronal fibrous lesions in commissural tracts connecting bilateral PHG. TLE patients often display extensive gray matter atrophy and widespread abnormalities of white matter tracts within and beyond the ipsilateral temporal lobe[32], involving dysfunction and structural changes in a network that includes the parahippocampal gyrus[33]. Anatomical studies have established that PHG has many reciprocal connections with extensive cortex involvement[34-37]. As a result, parahippocampal structures are critically implicated in the generation, propagation and modulation of seizures in TLE[38-42]. Furthermore, it has been indicated that the PHG, implicated in TLE, is a crucial node of the DMN. PHG mediates the communication between the hippocampal formation and neocortex, such as the posterior cingulate cortex, the posterior cortical hub of the DMN[43]. PHG might participate in the alertness network through the regulation of this communication. In this study, the presence of both functional and anatomic changes further demonstrated the abnormality of PHG and PHG pathways in the RTLE group. And the positive correlation observed between the alertness effect and the FA values of fibers connecting the bilateral PHG in RTLE further confirmed this view. However, considering that there was no difference in MMSE scores and alertness values, there was no evidence to indicate that the RTLE patients had more serious cognitive impairment compared with LTLE in the present study. Some authors have suggested that these apparent differences between the behavioral and neurological data suggest that fMRI measures might be more sensitive to attentional deficits than ANT under some circumstances[15,44]. We explained this unconformity as follows: there may be an early functional disruption of the brain network in TLE prior to clinical evidence of cognitive impairment. In our study, lower alertness effect in the pool of patients was observed. Considering the algorithm for network effect of alertness, the lower efficiency of the alertness network exhibited in TLE patients indicates a smaller RT difference between trials with and without warning cues, and may be regarded as the impairment of the ability to use the warning cue (double cue) to speed up response time (that is, a longer RT in the double cue condition), or the impairment of the ability to maintain alertness without a cue (a shorter RT in the no cue condition). We speculate that TLE patients' capacity to take full advantage of the additional information of the cue to shorten their reaction time in the cued trials has declined.

There are several limitations to this study: (1) This study only observed interhemispheric homotopic connectivity, while the intra- and interhemispheric communication were correlated. Future measures of both intra- and interhemispheric communication might be conducive to a further understanding of the pathophysiology underlying TLE. (2) A longitudinal and comprehensive study design is also required to explore the dynamic changes of alertness performance or cognitive function, as well as the exact relationship between the interhemispheric homotopic connectivity changes during the resting state and alterations of alertness.

Conclusions

We found altered functional synchronization in multiple brain regions in unilateral TLE. The reduced VMHC and FA values found in bilateral PHG in RTLE patients demonstrated that the bilateral PHG may be important in the pathophysiology of the right TLE. The FA values of fibers connecting the bilateral parahippocampal gyri are negatively related to the alertness effect, which provided further evidence that structural changes are involved in the alertness network alterations in right TLE.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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