Abnormalities of the default-mode network homogeneity and executive dysfunction in people with first-episode, treatment-naive left temporal lobe epilepsy

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Abstract. – OBJECTIVE: Converging evidence has demonstrated that there is aberrant connectivity of the default-mode network (DMN) in left temporal lobe epilepsy (lTLE) yet changes in the network homogeneity (NH) of the DMN in people with first-episode, treatment-naive lTLE remains unclear. In this study, we used an NH method to investigate the NH of the DMN in people with first-episode, treatment-naive, lTLE, at rest.

PATIENTS AND METHODS: We collected resting-state functional magnetic resonance imaging (rs-fMRI), and attention network test (ANT) data from 43 people with lTLE and 42well-matched, healthy control subjects. An NH approach was used to analyze the data.

RESULTS: People with lTLE have decreased NH in the right inferior temporal gyrus (ITG) and the left middle temporal lobe (MTG), and increased NH in the bilateral precuneus (PCu) and right inferior parietal lobe (IPL), as compared with the controls. We also found that people with lTLE had a longer executive control reaction time (RT). No significant correlations were found between abnormal NH values and clinical variables in the subjects.

CONCLUSIONS: These findings suggest that abnormal NH of the DMN exists in lTLE subjects and highlight the significance of the DMN in the pathophysiology of cognitive problems occurring in lTLE.

Key Words:

Temporal lobe epilepsy, Resting-state functional magnetic resonance, Default-mode network, Network homogeneity.

Introduction

Temporal lobe epilepsy (TLE) is a common nervous system disease and is frequently resistant to treatment[1,2]. It is characterized by complex partial seizures and secondary generalization resulting from abnormal electrical activity in the temporal lobe[3,4]. Most people with TLE exhibit some form of cognitive dysfunction involving memory, attention, consciousness, calculation, and behavior after repeated seizures[5-7]. Existing studies have shown that the pathogenesis of epilepsy can be further understood through the study of the properties of the brain network, and interactions between different regions of the brain. The exact mechanism behind the onset of this disorder is, however, still unclear.

New developments in neuroimaging techniques have enabled the detailed observation of alterations in the brain involved in the pathophysiology of TLE. Findings have shown that topo-

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logical patterns of brain structural networks were aberrant in people with TLE[8]. Abnormalities of the uncinate fasciculus correlate with executive dysfunction in people with left TLE (lTLE)[9]. Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful tool to explore brain diseases, and it has opened up new avenues for a survey of the previously neglected field of intrinsic network organization. This technology has been used by a large number of researchers to investigate diverse abnormalities in different brain regions[4,10-17]. Some scholars have proposed that TLE is a disorder involving abnormal epileptogenic networks, rather than having a single focal epileptogenic source[18-20]. Zheng et al[10] have shown that TLE exists in several network disturbances, including the alertness network, the attention network[12], and the default-mode network (DMN)[14,16,21]. Notably, the DMN has received increasing attention because it plays an important role in many neurological illnesses. This network is a suppression of local field potential activity during cognitive task performance as well as during engagement with external sensory stimuli[22]. Researchers have demonstrated that the DMN is closely correlated with episodic memory processing, negative ruminations, and anesthesia[23,24]. Furthermore, the DMN is associated with cognitive functioning, especially executive function[25]. Complementary evidence of dysfunctional DMN activation in people with epilepsy has been detected at rest. However, the results were mixed. For instance, many studies showed that there was increased posterior cingulate cortex (PCC), and decreased medial prefrontal cortex (MPFC) functional connections in TLE[26,27]. Benuzzi et al[28] have found decreased DMN connections in the PCC, anterior frontal gyrus, and parietal regions. These findings consistently showed that DMN plays a crucial role in TLE. However, the pathophysiology of TLE is still ill-defined. In addition, anti-seizure medication and duration of the illness could also contribute to abnormalities in the brain network[29,30]. Therefore, studies with first-episode, treatment-naive subjects may have the advantage of lessening confounders.

In this study, we used the network homogeneity (NH) method to analyze resting-state data in lTLE[31]. This informative approach studies a given network without specifying the location of network abnormalities. It assesses the correlation of a voxel with all other voxels within a specific network of interest. Homogeneity is defined to be the average correlation of the time series of any given voxel with the time series of all other voxels within the network. The NH method is now widely used in investigating neurological and psychiatric disorders[31-38]. When looking at subjects suffering from different types of epilepsy with different discharging areas, the NH method illustrated differences in structural and functional impairments[26], and even in identical brain regions, the left and right sides showed differences[39]. Thus, studies of unilateral TLE may have the advantage of assessing brain function, because it can reduce the confounder effects of differences in discharge areas. Using the NH method, we studied the network homogeneity of the DMN and possible mechanism in people with lTLE.

Patients and Methods

Patients

A total of 43 people with lTLE were recruited from the Epilepsy Clinic of the Department of Neurology at Tianyou Hospital, affiliated with Wuhan University of Science and Technology and Department of Neurosurgery and the Wuhan Clinical Research Center for Diagnosis and Treatment of Severe Traumatic Brain Injury, Wuhan Central Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology. The diagnosis of lTLE was made according to the new diagnostic criteria specified by the International League Against Epilepsy (ILAE)[40]. People who had any of the following symptoms were classified as lTLE subjects: (1) the clinical onset of symptoms suggested the location of epileptogenic focus in the temporal lobe; (2) interictal electroencephalographic (EEG) traces illustrated lesions in the left temporal lobe; and (3) an MRI showed sclerosis or atrophy in the left temporal lobe. A total of 42 age-, gender-, and education- matched healthy controls were recruited from the local community using advertisements.

Exclusion criteria was: being left-handed, history of serious medical diseases, mental disorders or other neurological illnesses, a score of less than 24 in a mini-mental state examination (MMSE).

All participants provided written informed consent before entering the study. The Ethics Committee of the Wuhan Central Hospital, affiliated to the Tongji Medical College, Huazhong University of Science and Technology, approved the study.

Attention Network Test

The executive control reaction times (ECRT) were obtained from the Attention Network Test. The detailed test procedure is described in the **Supplementary Material**.

MRI Scanning and Data Preprocessing

MRI scans were performed with an Achieva 3T MRI scanner (Philips, Ingenia). The imaging data were preprocessed using the Data Processing Assistant for rs-fMRI in MATLAB. Details of data acquisition and preprocessing can be found in the **Supplementary Material**.

DMN Identification

The preprocessed data of all participants were subjected to spatial independent component analysis (ICA). Group ICA was performed to construct the DMN by using the GIFT toolbox (MATLAB)[41]. First, the optimal number of components was set to 20, subject- and group-level principal component analyses (PCAs) were performed to reduce their dimensions. Data from each subject was reduced using PCA according to certain components. The reduced data were separated by ICA using the extended informal algorithm. The group-level PCA was applied to further reduce the temporal dimension of the group fMRI data. The number of independent components (ICs) and time courses for each subject were retroactively reconstructed, and the mean spatial maps for each group were transformed to Z-scores for display. Finally, the independent component that best matched the DMN as previous templates provided by GIFT was selected[42]. The generated DMN was used as a mask for further NH analyses.

NH Analysis

For each subject, the correlation coefficients of each voxel were computed against all other voxels within the DMN mask by using an in-house script developed in Matlab[31]. The mean correlation coefficients were then averaged and transformed to a z-value for each map. The resultant values are used to generate the NH maps. Finally, the NH maps were z-transformed for group comparison.

Statistical Analysis

Demographic information differences (age, gender, years of education, and executive control reaction time) between the lTLE group and the control group were investigated by using either a Chi-square test or a two-sample t-test. The NH maps of two groups were analyzed with a two-sample t-test via voxel-wise cross-subject statistics within the DMN mask. The significance level was set at $p<0.01$ and corrected for multiple comparisons using the Gaussian Random Field (GRF) theory (GRF corrected, voxel significance: $p < 0.001$, cluster significance: $p< 0.01$).

Results

Demographics and Clinical Characteristics of the Subjects

No significant differences were detected between the two groups in terms of gender ratio, age, and years of education. The lTLE group had longer reaction times (RTs) compared to the control group. The demographic information of the recruited subjects is given in Table I and Table II.

The DMN Mask Determined by Group ICA

The DMN mask was selected from all the subjects by using an ICA method. The DMN included the brain regions: bilateral MPFC; PCC/PCu; ventral anterior cingulate cortex; lateral temporal cortex; medial; lateral, and inferior parietal lobes, and cerebellum Crus I and Crus II. As shown in Figure 1, the generated DMN mask was used in further NH analysis.

Table I. Characteristics of the participants.

Demographic data	lTLE (n = 43)	NC (n = 42)	t (or x^2)	p-value
Gender (male/female)	43 (23/20)	42 (22/20)	0.12	0.29[a]
Age (years)	27.91 ± 6.48	26.96 ± 5.31	0.74	0.46[b]
Years of education (years)	13.01 ± 2.67	13.67 ± 1.88	-1.33	0.19[b]
Illness duration (years)	8.49 ± 7.1			
ECRT	91.60 ± 54.85	67.81 ± 48.02	2.13	0.04[b]

[a]The p value for gender distribution was obtained by chi-square test. [b]The p values were obtained by two-sample t-tests. lTLE = left temporal lobe epilepsy, NC = normal control, ECRT = executive control reaction time.

Table II. Characteristics of the participants-

Subjects	Time (hour)	Etiology
Subject 1	18	Symptomatic epilepsy
Subject 2	12	Symptomatic epilepsy
Subject 3	15	Idiopathic epilepsy
Subject 4	14	Hippocampal sclerosis
Subject 5	16	Hippocampal sclerosis
Subject 6	17	Hippocampal sclerosis
Subject 7	18	Hippocampal sclerosis
Subject 8	21	Hippocampal sclerosis
Subject 9	25	Idiopathic epilepsy
Subject 10	14	Symptomatic epilepsy
Subject 11	19	Idiopathic epilepsy
Subject 12	18	Symptomatic epilepsy
Subject 13	15	Idiopathic epilepsy
Subject 14	12	Idiopathic epilepsy
Subject 15	17	Idiopathic epilepsy
Subject 16	16	Idiopathic epilepsy
Subject 17	18	Symptomatic epilepsy
Subject 18	15	Hippocampal sclerosis
Subject 19	15	Hippocampal sclerosis
Subject 20	19	Hippocampal sclerosis
Subject 21	13	Hippocampal sclerosis
Subject 22	25	Symptomatic epilepsy
Subject 23	18	Symptomatic epilepsy
Subject 24	19	Hippocampal sclerosis
Subject 25	15	Hippocampal sclerosis
Subject 26	16	Hippocampal sclerosis
Subject 27	8	Hippocampal sclerosis
Subject 28	13	Hippocampal sclerosis
Subject 29	12	Idiopathic epilepsy
Subject 30	14	Idiopathic epilepsy
Subject 31	16	Idiopathic epilepsy
Subject 32	6	Idiopathic epilepsy
Subject 33	12	Symptomatic epilepsy
Subject 34	13	Hippocampal sclerosis
Subject 35	15	Hippocampal sclerosis
Subject 36	14	Symptomatic epilepsy
Subject 37	15	Symptomatic epilepsy
Subject 38	12	Symptomatic epilepsy
Subject 39	12	Idiopathic epilepsy
Subject 40	8	Hippocampal sclerosis
Subject 41	9	Hippocampal sclerosis
Subject 42	6	Symptomatic epilepsy
Subject 43	17	Idiopathic epilepsy

Time: time between the occurrence of the last seizure and MRI scan.

NH: Group Differences in the DMN

With the two-sample t-tests via voxel-wise cross-subject comparisons, significant differences were observed, within the DMN, and between the NH values of the patient and control groups. Compared to the control, the lTLE patients exhibited a decreased NH in the right inferior temporal gyrus (ITG) and left middle temporal lobe (MTG), but increased NH in the bilateral precuneus (PCu) and right inferior parietal lobe (IPL) (Table III, Figure 2 and Figure 3).

Correlations Between NH and Clinical Variables

The mean NH values were extracted for the five regions (right ITG, left MTG, bilateral PCu, and right IPL) with significant group differences. Pearson's linear correlation analyses were performed between NH and the clinical variables including RT, illness duration, and age at seizure onset in the patient group. Results showed no significant correlation between NH and these clinical variables in the patient group.

Discussion

NH is a novel approach for detecting specific loci of compromised connectivity and for studying within-network coherence. It has been used to study several brain disorders, such as attention deficit/hyperactivity disorder[31], depressive disorder[38,43-45], somatization disorder[35], obsessive-compulsive disorder[46], and schizophrenia[32,47]. We first used this method to estimate the DMN homogeneity in first-episode, treatment-naïve, lTLE subjects at rest. The results showed that lTLE subjects have decreased NH in the right ITG and left MTG but increased NH in the bilateral PCu and right IPL compared with the controls.

Temporal lobes play important roles in the regulation and propagation of epileptic discharges, due to the presentation of epileptic foci, which has been proven to be a common target for both structural and functional studies in TLE. Lee et al demonstrated altered intrinsic functional connectivity in the temporal regions during both the latent and chronic periods of TLE[4]. In numerous studies, neuroimaging repeatedly exposed aberrant regional activation of ITG and/ or MTG. ITG, with the localization of the lateral and inferior surfaces of the temporal neocortex, is thought to be the central region for language formulation, and as a tertiary visual association cortex region[48], relating to cognitive functions such as memory, language, and visual perception[49,50]. Consistent results from neuroimaging studies of people with major depressive disorders demonstrated that this region is involved in emotional processing and social cognition[38,51]. Moreover, the ITG is a key node in the broad network of frontal, temporal, parietal, occipital, and sub-cortical structures. Thus, abnormal activation of this region could significantly impair the function of the temporal lobe. The MTG also plays a critical role in semantic memory and language proces-

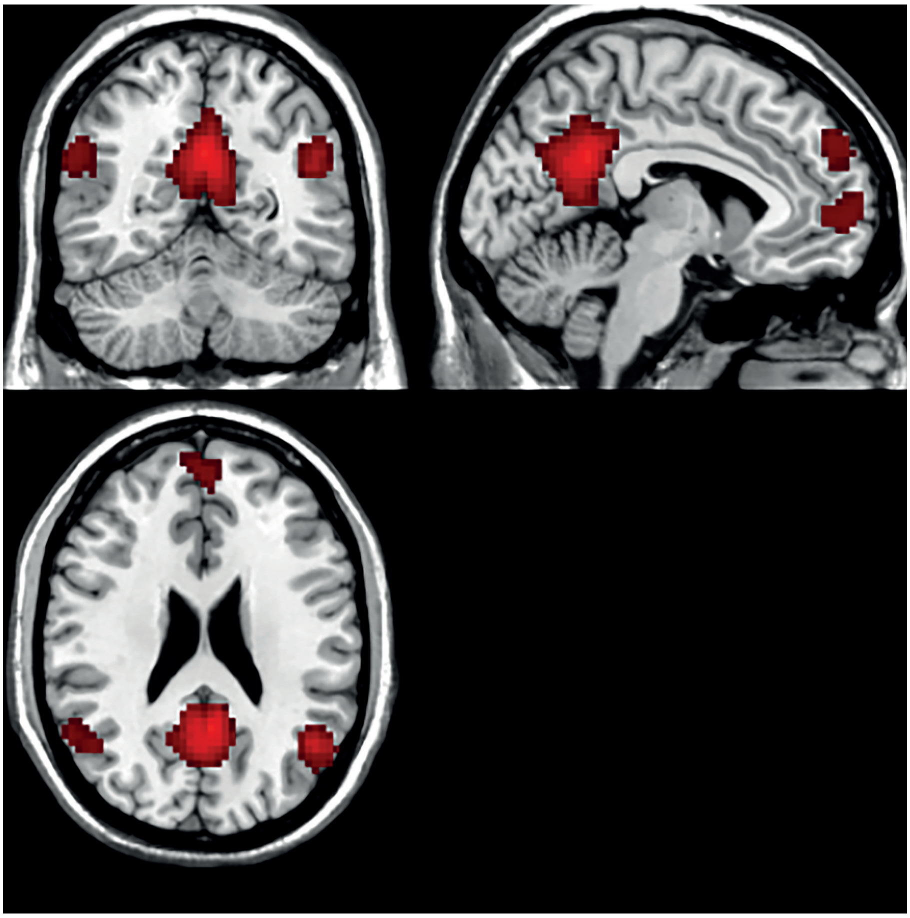

Figure 1. Default Mode Network (based on group-ICA with a threshold of $z \geq 5$).

sing[52]. As a result, abnormal activity in the MTG could also consequently affect the function of the temporal lobe. In this study, we demonstrated decreased NH in the right ITG and MTG. Accordingly, these abnormalities could impair memory and language functions, and result in dysfunction in lTLE subjects.

The PCu, a key region of the DMN, is selectively connected to the intraparietal sulcus, the inferior and superior parietal lobules, and the caudal parietal operculum. These structures work together in the processing of visuospatial information[53-55]. This significant, integrative structure exhibits widespread connectivity with

Table III. Signification differences in NH values between the groups.

	Peak (MNI)					
Cluster location	**X**	**Y**	**Z**	**Number of voxels**	***t*-value**	***p*-value**
Patients < Controls						
RightITG	51	6	-36	135	-4.80	0.00
LeftMTG	-48	-3	30	-70	-4.64	0.00
Patients > Controls						
RightPCu	12	-60	30	45	4.59	0.00
LeftPCu	0	-78	33	50	3.59	0.00
Right IPL	51	-57	48	47	4.16	0.00

MNI= Montreal Neurological Institute. ITG=inferior temporal gyrus, MTG=middle temporal lobe, PCu= Precuneus, IPL=inferior parietal lobe.

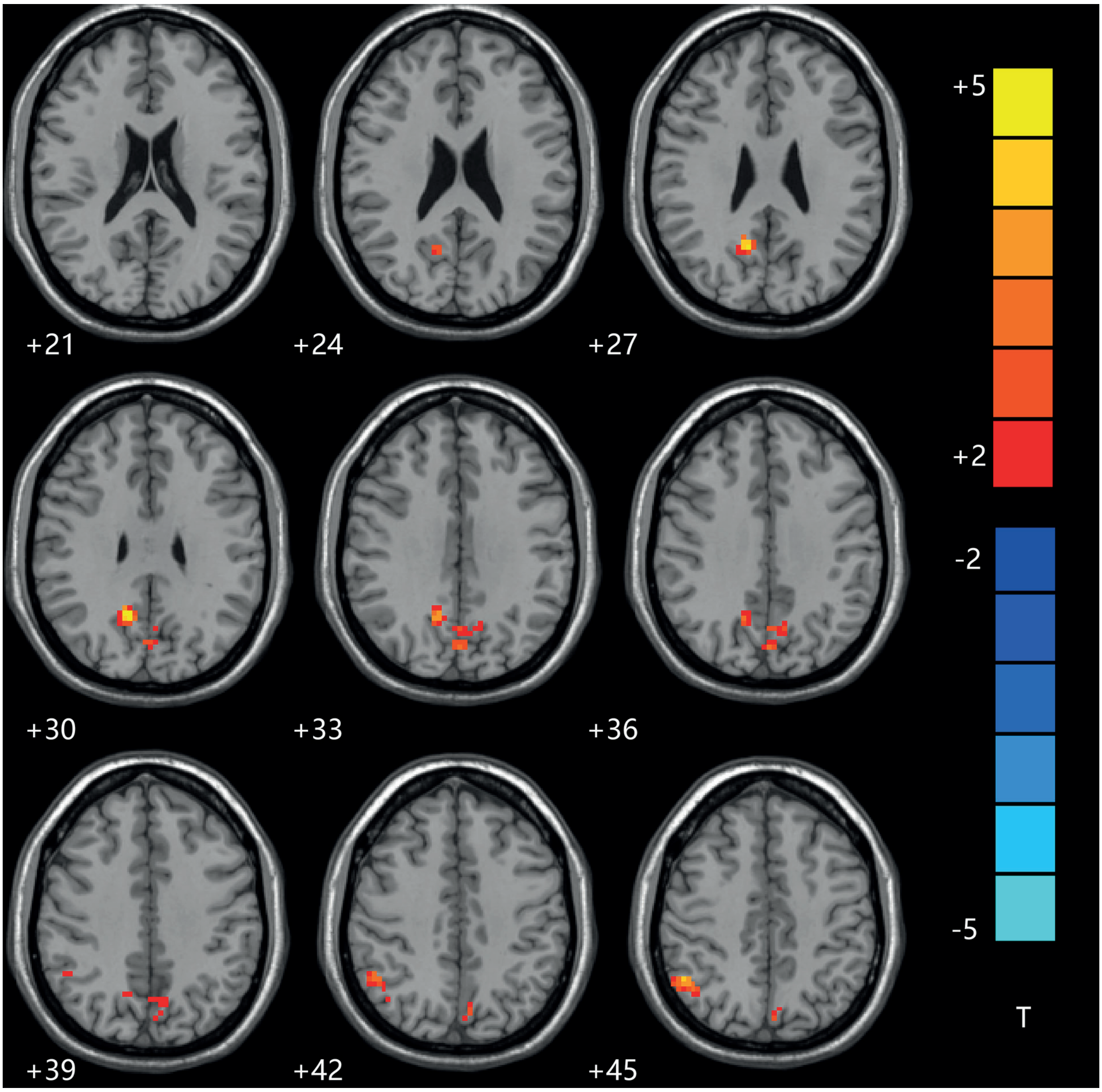

Figure 2. NH differences between people with lTLE and controls. Red denotes higher NH and the color bars represent the T values from a two-sample *t*-test in the group analysis. NH = network homogeneity; lTLE = left temporal lobe epilepsy.

some cortical and sub-cortical regions[56] and performs various essential cognitive and behavioral functions, including episodic memory retrieval, visuospatial imagery, self-processing operations, and consciousness[56,57]. The right IPL is crucial in the DMN and the frontal parietal network, participating in sustaining attention, alertness, and task switching. Studies of lTLE using rest-state fMRI found that the right IPL had lower FC in TLE subjects compared with the control group[12,17], and this might indirectly result in alertness impairment. Because the parietal lobe is connected to the temporal lobe, epileptic discharges from the epileptogenic zone can spread to distant brain regions through the superior longitudinal fasciculus. However, we did not find the same activation pattern in our study. This discrepancy might be because of different epileptic focal positions in the epilepsy subjects recruited in these previous studies. A smaller sample size, and use of different methods, might also influence the results. Another explanation for the inconsistent result may be due to the different analysis methods we

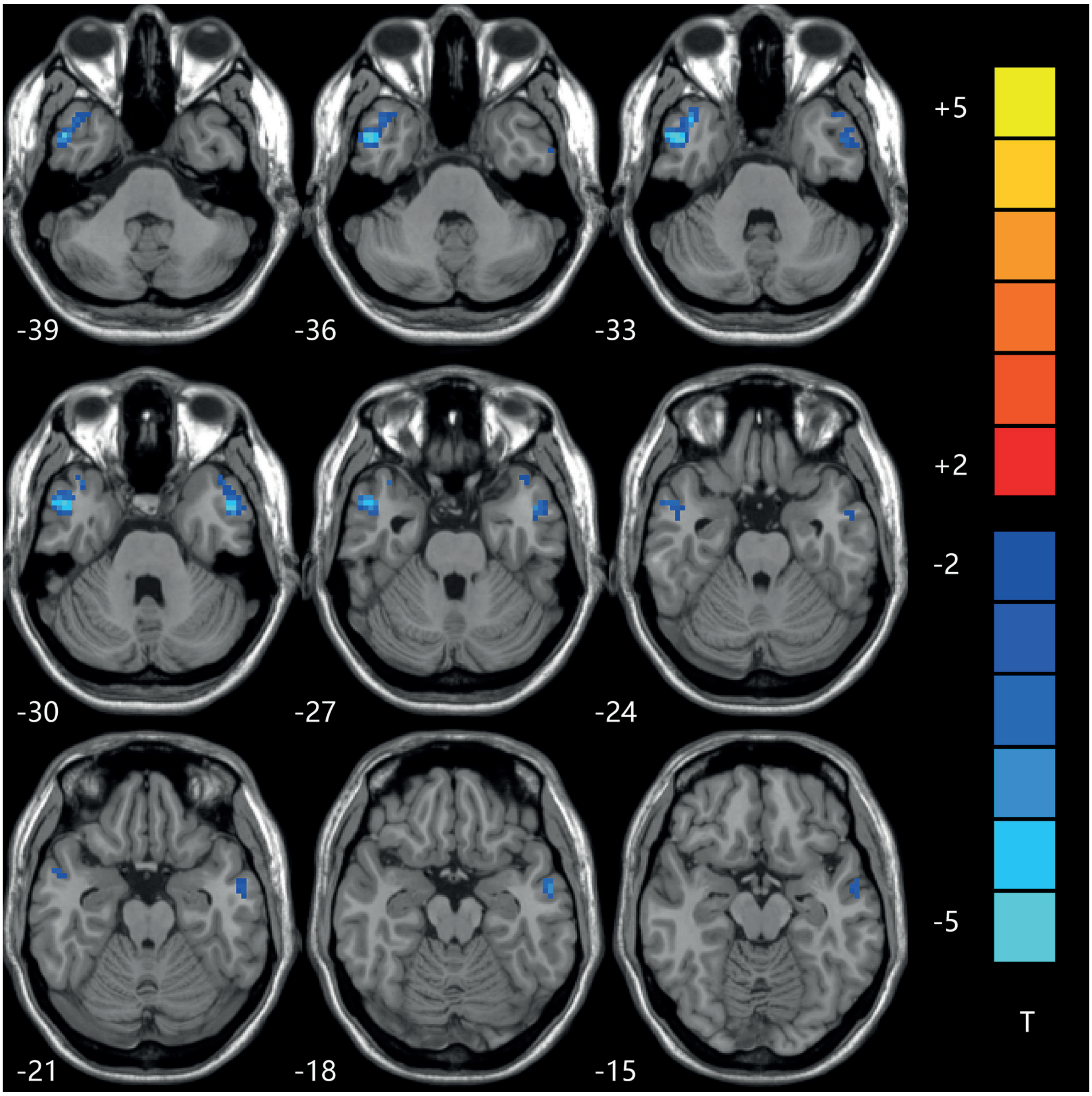

Figure 3. NH differences between people with lTLE and controls. blue denotes lower NH and the color bars represent the T values from a two-sample *t*-test in the group analysis. NH = network homogeneity; lTLE = left temporal lobe epilepsy.

used in our work. Another probable explanation is as follows: according to the roles of the IPL and the PCu in the cognition process, the increased NH in the bilateral PCu and right IPL might be a compensatory function due to the damage in the temporal lobe, with the compensatory function becoming stronger as the severity of the temporal lobe damage increases.

The default mode network refers to a group of brain regions that are functionally consistent, forming a large brain network, and is highly active in the resting state. Activities decreases when the brain is engaged in non-specific attention task execution. The DMN is closely related to the mental activities of advanced cognitive functions such as introspection, scene memory, environmental monitoring, and awareness level[58-62]. A previous study confirmed that the DMN changed, and might be linked to altered cognition and memory, in TLE[21]. Like these studies, we thought that the DMN is associated with dysfunction in the brains of people with TLE, thereby affecting memory and cognition in TLE subjects. Furthermore, our study showed a dissociation pattern of activity in the DMN, which is hypo-activity in anterior regions of the DMN (right ITL and left MTL) and hyperactivity in posterior regions of the DMN (bilateral PCu and right IPL). In other studies, significant differences in the resting-state activity of the DMN were found in TLE, which may explain some of the signs or symptoms exhibited by people with TLE, such as loss of consciousness, impairment to learning and memory, and psychiatric symptoms[63,64]. These consistent results indicated that the DMN is disturbed and these aberrations play an important role in the pathophysiology of TLE.

It is worth noting that people with lTLE had longer RTs, but no significant correlations between abnormal NH values and RTs were found. As studies have demonstrated, lTLE subjects usually suffer from executive function impairment. Since it is universally acknowledged that the DMN plays a crucial role in executive functions, we speculated that the regions that showed abnormal NH in this study, indirectly participate in the executive function. At the same time, no significant correlations between abnormal NH values and RTs, age at seizure onset, and illness duration, were explored. This phenomenon might indicate that abnormal NH values of the DMN might be a trait change in lTLE subjects.

Several limitations need to be highlighted. First, we could not entirely remove the physiological noise at rest, such as cardiac and respiratory rhythm using a 2s repetition time, and that may bias the results. Second, this study focused on DMN. Understanding the neurophysiological abnormalities of the DMN in lTLE would be helpful. However, some meaningful findings from other brain regions besides this network may be excluded. Lastly, previous studies have shown that there are morphological differences between the Chinese population and others[65], which means that our use of the Chinese brain atlas for processing the data in this study, may limit the general applicability of the results.

Despite these limitations, our observations of decreased NH in the right inferior temporal gyrus (ITG) and left middle temporal lobe (MTG) and increased NH in the bilateral precuneus (PCu) and right inferior parietal lobe (IPL) in a large sample of people with first-episode treatment-naive lTLE is of value. These findings further contribute to understanding the pathophysiology of lTLE from a new perspective.

Conclusions

We sought to investigate the NH in the DMN in subjects diagnosed with lTLE, compared with control subjects. We found that lTLE had a longer executive control RT. These findings suggested that abnormal NH of the DMN exists in lTLE subjects and highlighted the significance of the DMN in the pathophysiology of cognitive problems occurring in lTLE. Further research is required to investigate the NH of the DMN in the right TLE subjects in order to clearly understand the pathophysiology of TLE.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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