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Abnormal default-mode network homogeneity in patients with temporal lobe epilepsy

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Abstract

Default-mode network (DMN) plays a key role in a broad-scale cognitive problem, which occurs in temporal lobe epilepsy (TLE). However, little is known about the alterations of the network homogeneity (NH) of DMN in TLE. In the present study, we employed NH method to investigate the NH of DMN in TLE at rest.

A total of 47 patients with TLE (right TLE [rTLE] 29, and left TLE [lTLE] 18) and 35 healthy controls who underwent resting-state functional magnetic resonance imaging were enrolled. NH approach was used to analyze the data.

rTLE exhibited decreased NH in the right middle temporal pole gyrus and increased NH in the bilateral posterior cingulate cortex compared to the control group. In lTLE, decreased NH was observed in left inferior temporal gyrus and left hippocampus. Meanwhile, we found that lTLE had a longer performance reaction time. No significant correlation was found between abnormal NH values and clinical variables in the patients.

These findings suggested that abnormal NH of the DMN exists in rTLE and lTLE, and highlighted the significance of DMN in the pathophysiology of cognitive problems occurring in TLE and also found the existence of abnormality of executive function in lTLE.

Abbreviations: AAL = anatomical automatic labeling, AEDs = antiepileptic drugs, ANT = attentional network test, DMN = default-mode network, EPI = echo planar imaging, FOV = field of view, GRF = Gaussian random field, HIC = hippocampus, ICA = independent component analysis, ITG = inferior temporal gyrus, lTLE = left TLE, MMSE = mini-mental state examination, MNI = Montreal Neurological Institute, MPFC = medial prefrontal cortex, MTPG = middle temporal pole gyrus, NH = network homogeneity, PCC = posterior cingulate cortex, rTLE = right TLE , ROI = region of interest, rs-fMRI = resting-state functional magnetic resonance imaging, RT = reaction time, TLE = temporal lobe epilepsy.

Keywords: default-mode network, network homogeneity, resting-state functional magnetic resonance, temporal lobe epilepsy

1. Introduction

Epilepsy is a prevalent neurologic disorder characterized by abnormal and excessive discharge of brain neurons, covering about more than 50 million people worldwide.[1] Temporal lobe epilepsy (TLE) is the one of the most common types of partial epilepsy referred for surgery, and is often refractory to antiepileptic drugs (AEDs).[2] Of all the types of epilepsy, the incidence of TLE accounted for about 1/3 to 1/2 the number of refractory epilepsies.[3] Patients with TLE usually suffer from cognitive impairments, such as memory, and ability to think clearly.[4,5] Increasing efforts have been made to elucidate its neural correlates by advanced imaging technique, such as resting-state functional magnetic resonance imaging studies (rs-fMRI).

Default-mode network (DMN) plays a significant role in consistently exhibiting coherent intrinsic activity and in the neurobiology of TLE,[6] which includes the medial prefrontal cortex (MPFC), lateral posterior cortices, and posterior cingulate cortex (PCC).[7] In recent years, DMN connectivity has been extended to include the lateral temporal gyrus[8] and the cerebellar Crus 1 and Crus 2.[9] The DMN activity is usually higher at rest, but lower during task-related cognitive processes.[7,10] This in turn demonstrated the correlation of DMN with episodic memory processing, negative ruminations, complex self-referential stimuli,[11] and at some special mind states, such as anesthesia and sleep.[12]

Increasing evidences showed a connectivity of abnormal resting state within the DMN in patients with epilepsy, but the results were mixed. For example, many studies found that there are decreased MPFC and increased PCC functional connectivities in TLE.[13,14] However, some researchers have found decreased DMN connectivities in PCC, anterior frontal, and parietal regions.[15,16] There are at least 2 reasons that account for the discrepancy of DMN findings in patients with epilepsy. First, most of the previous studies recruited patients with different epileptic focal position, and second, smaller sample size and application of different methods might also affect the results. In addition to these, AEDs and illness duration could also contribute to the abnormality of DMN.[17] Also patients with different discharging places and different epileptic types illustrated differences in the structure and functional impairments,[13] and even the identical brain regions, the left and right sides showed differences.[18] Hence, studies on unilateral TLE belonging to complex partial seizures may have the advantage for assessing brain function, and in turn can lessen the confounder effects of differences in discharging places.

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Seed-based region of interest (ROI) and independent component analysis (ICA) have been frequently and mainly used to assess the resting brain networks in fMRI. Seed-based ROI methods are used to test temporal coherence between the time series of the predefined seeds or a given ROI and the time series of all other voxels in the global brain.[19] This method has its own disadvantages of differential placement of seeds which may lead to varied results for the same network. Compared to seed-based ROI, ICA is a model-free measure with the power to investigate even the largely overlapping spatial processes. Nevertheless, it is unclear as how best we can compare the components across patients and/or between groups.[20] Therefore, a novel and unbiased approach to analyze imaging data is urgently required.

Here, we used a network homogeneity (NH) method designed by Uddin et al[21] to analyze the resting state data in TLE. This method studies a given network without specifying the requirement of location of network abnormalities, assesses the homogeneity of the whole network, and acts as an aspect of intrinsic network organization that has long been overlooked in an unbiased manner. NH is a voxel-wise measure that correlates with all the other voxels within a given network of interest. The mean correlation of a given voxel is defined as the NH value of this voxel. Homogeneity is defined as the similarity of the time series at a given voxel to those of the other voxels of the specific network. To date, NH method has been widely used in attention-deficit/hyperactivity disorder, somatization, depression, schizophrenia, and their unaffected siblings.[21–28]

The DMN is associated with cognitive functioning, especially executive function. When the brain is performing tasks, the DMN is negatively activated.[29] The reaction time (RT) measures obtained from the attentional network test (ANT)[30] can be used to assess the executive function. Moreover, age of seizure onset and illness duration impacted the DMN on frontal cortex (FC).[31,32] Therefore, in the present study, we hypothesized that patients with TLE show abnormal DMN homogeneity, which would be correlated with clinical variables such as illness duration, age of seizure onset, and RT.

2. Materials and methods

2.1. Patients

The study comprised 47 patients with TLE (29 rTLE and 18 lTLE) and 35 healthy controls. All were recruited from the Epilepsy Clinic of Department of Neurology of the First Affiliated Hospital of Guangxi Medical University. TLE diagnosis was made in compliance with the diagnostic criteria of International League Against Epilepsy.[33] Epileptic patients who met any of the 2 following symptoms were classified as TLE patients: the clinical onset of symptoms suggested the location of epileptogenic focus in the temporal lobe; the MRI showed sclerosis or atrophy in the right/left temporal lobe; and interictal electroencephalographic traces suggested lesions in the temporal lobe. Exclusion criteria were as follows: left-handed, history of serious medical diseases, mental diseases, or other neurologic illnesses, a score <24 in a mini-mental state examination (MMSE). The MMSE, developed by Folstein et al in 1975, is one of the most influential tools for the examination of standardized mental status as a cognitive impairment test. It can be used to screen patients with intellectual disabilities.

All the patients gave written informed consent before entering the study. The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University.

2.2. Scan acquisition

Scanning was conducted on Achieva 3T MRI scanner (Philips, Amsterdam, the Netherlands). Participants were instructed to lie down with their eyes closed and remain awake. A prototype quadrature birdcage head coil fitted with foam padding was applied to minimize the head movement. The parameters used for functional imaging included: repetition time/echo time = 2000/30 milliseconds, slice thickness = 5 mm, pitch = 1 mm, field of view = 220 mm × 220 mm, and flip angle = 90°.

2.3. Data preprocessing

Imaging data of rs-fMRI were preprocessed by using DPARSF software[34] in MATLAB. The first 5 time points were removed. Slice time and head motion were corrected. No participants had more than 2 mm of maximal displacement in x, y, or z axis and more than 2° of maximal rotation. The structure of each patient was registered to its functional image. The structure of each patient was divided, and a template was created to normalize the structures of the patients after they were defined according to the Montreal Neurological Institute (MNI) standard template, the standardization process of the spatial deformation of the modulation and the structure of the voxel size using $1 \times 1 \times 1$ mm. Finally, the use of the structure of each patient to the function of the conversion matrix was also standardized to the MNI space. During the process of functional image normalization, head motion parameters, white matter signal, and cerebrospinal fluid signal were used as removal covariates (Nuisance regression), and voxel size of $3 \times 3 \times 3$ mm was used as functional covariate. The obtained images were subsequently smoothed with an 8 mm full width at half-maximum Gaussian kernel, band pass filtered (0.01–0.1 Hz), and linearly detrended to lessen the effect of low-frequency drifts and physiologic high-frequency noise. Several spurious covariates were removed, including signal from a region centered in the white matter, 6 head motion parameters obtained by rigid body correction, and signal from a ventricular ROI. The global signal removal may introduce artifacts into the data and distort resting-state connectivity patterns. Furthermore, the regression of the global signal may significantly distort results when studying clinical populations. Therefore, the global signal was preserved.[35,36]

2.4. DMN identification

The ICA was performed using the group ICA method to pick out DMN components according to the templates provided by GIFT.[8] The ICA analysis included 3 steps in using the toolbox GIFT (http://mialab.mrn.org/software/#gica): data reduction, independent component separation, and back reconstruction. For each component, a statistical map was created and thresholded by voxel-wise 1-sample t tests ($P < .01$ for multiple comparisons corrected via Gaussian random field [GRF] theory; voxel significance: $P < .01$; cluster significance: $P < .01$). Masks were generated for the DMN components. Finally, the masks were combined to generate a DMN mask used in the following NH analysis.

2.5. NH analysis

An NH analysis was calculated by using an in-house script in Matlab (Mathworks, Massachusetts). For each patient, the correlation coefficients were obtained in a given voxel with all other voxels within the DMN mask. The mean correlation coefficient was defined as the homogeneity of the given voxel, and

Table 1

Characteristics of the participants.

Demographic data	rTLE (n = 29)	lTLE (n = 18)	NC (n = 35)	F (ort, x^2)	*P*
Gender (male/female)	29 (13/16)	18 (7/11)	35 (15/20)	0.161	0.923*
Age, y	28.74 ± 7.32	28.42 ± 7.7	27.42 ± 5.7	0.327	0.722†
Years of education (y)	14.07 ± 1.89	12.78 ± 2.26	13.97 ± 1.91	2.745	0.07†
MMSE	27.8 ± 0.9	27.6 ± 1.4	27.4 ± 0.4	1.478	0.234†
Illness duration (y)	8.49 ± 7.1	7.05 ± 7.13		0.667	0.51‡
Age of seizure onset (y)	20.26 ± 10.2	21.37 ± 8.6		0.403	0.69‡
RT	106.87 ± 35.48	114.59 ± 38.05	88.88 ± 37.05	3.67	0.03†

MMSE = mini-mental state examination, NC = normal control, RT = reaction time, rTLE = right temporal lobe epilepsy, lTLE = left temporal lobe epilepsy.

* T*P*-value for gender distribution was obtained by Chi-squared test.

† *P*-value was obtained by analysis of variance.

‡ *P*-value was obtained by 2-sample *t* tests.

subsequently changed into z-value by using z-transformation to improve the normal distribution as described. The resultant values generated the NH maps. Finally, the NH maps were z-transformed for group comparison.

2.6. Statistical analyses

Demographic information, including age, sex, educational level, and imaging data were calculated between the rTLE/lTLE and the control groups. Categorical data were compared using Chi-squared test and continuous variables were compared by using 2-sample *t* test. To test for regional group differences in NH, individual-level NH maps entered into 1 group-level voxel-wise *t* test analysis using 2-sample *t* test. Then, the NH maps were analyzed with analysis of covariance via voxel-wise cross-patient statistics within the DMN mask. The significance level was set at $P < .01$ and corrected for multiple comparisons using GRF theory (GRF corrected, voxel significance: $P < .001$, cluster significance: $P < .01$).

3. Results

3.1. Demographics and clinical characteristics of the patients

The demographic information of the study participants were presented in Table 1. No significant differences were observed among the 3 groups in terms of gender, age, years of education, and MMSE. The lTLE group had longer RT and no significant differences of RT were found between rTLE group and the controls, and between rTLE group and lTLE group.

3.2. DMN maps determined by group ICA

By employing ICA method, the DMN mask was picked out from the control group. The DMN included bilateral MPFC, PCC/PCu, ventral anterior cingulate cortex, lateral temporal cortex, medial, lateral, inferior parietal lobes, and cerebellum Crus 1 and Crus 2. Hence, we used the DMN mask in the following NH analysis.

3.3. NH: group differences in the DMN

Two-sample *t* tests showed significant group differences of NH values between the patients (rTLE/lTLE) and the controls within the DMN mask. Compared to the control, patients with rTLE had lower NH in the left middle temporal pole gyrus (MTPG), and significantly higher NH values in the bilateral posterior cingulated cortex (PCC). Patients with lTLE had lower NH in the left inferior temporal gyrus (ITG) and hippocampus (HIC).

3.4. Correlations between NH and clinical variables

The mean NH values were extracted in the 4 regions (right MTPG, bilateral PCC, left ITG, and HIC) with significant group differences. Pearson linear correlation analyses were performed between NH and RT, illness duration, age of seizure onset clinical variables in the patient group. Results showed no significant correlation between NH and these clinical variables in the patient group (Tables 1 and 2, Figs. 1–4).

4. Discussion

In the present study, NH method was employed to survey the DMN in patients with TLE. The patients with rTLE showed

Table 2

Signification differences in FC values between the groups.

Cluster location	Peak (MNI)			Number of voxels	*T*-value	*P*-value
	x	y	z			
rTLE > Controls						
Bilateral PCC	6	−45	5	88	3.6853	.01
rTLE < Controls						
Right MTPG	48	3	−3	41	−0.0226	.01
lTLE < Controls						
Left ITG	−45	6	−33	36	4.7472	.01
Left HIC	−27	−30	−9	29	−0.8827	.01

HIC = hippocampus, ITG = inferior temporal gyrus, lTLE = left temporal lobe epilepsy, MNI = Montreal Neurological Institute, MTPG = middle temporal pole gyrus, PCC = posterior cingulate cortex, rTLE = right temporal lobe epilepsy.

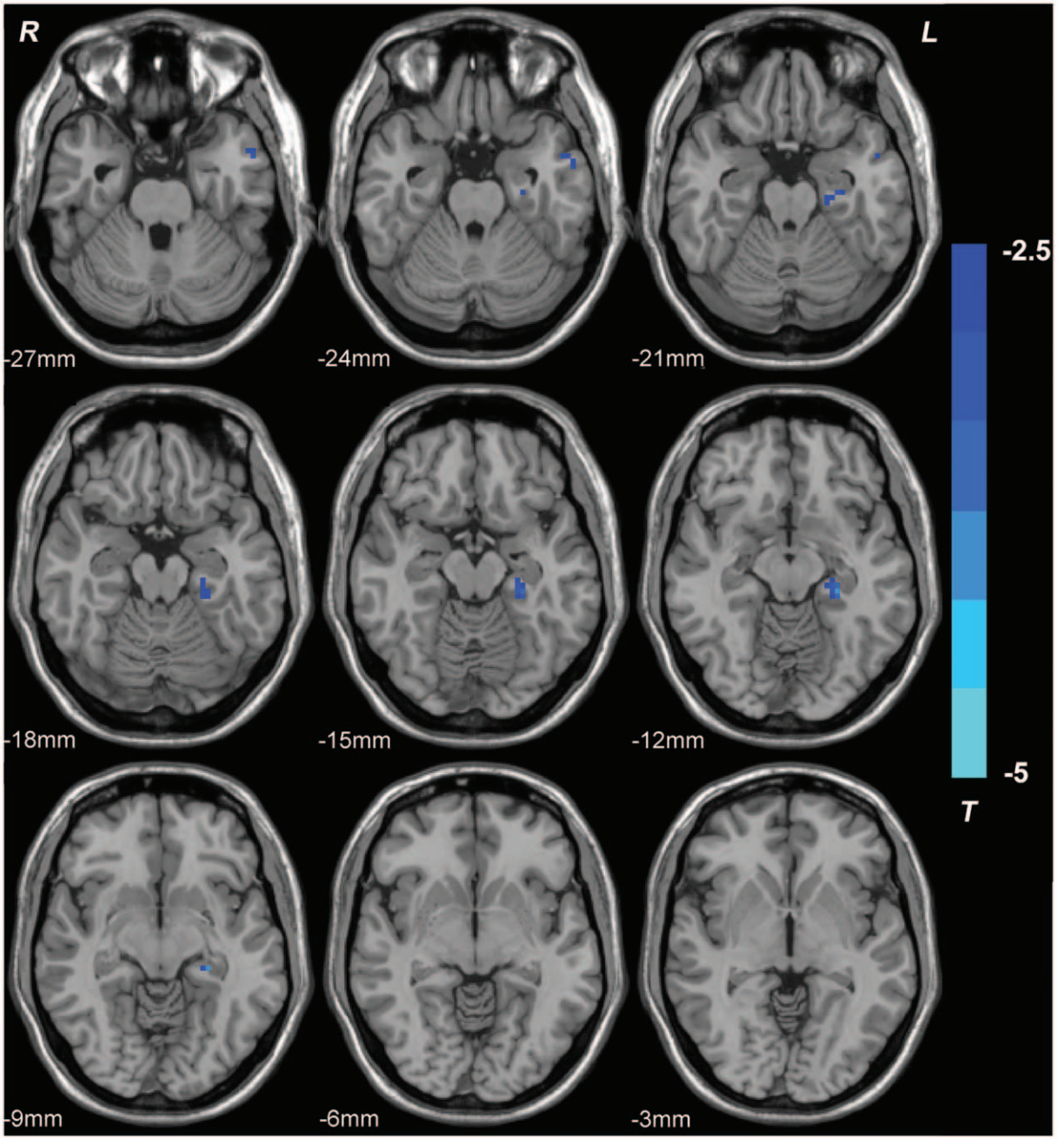

Figure 1. Statistical maps showing network homogeneity (NH) differences in the left hippocampus between left temporal lobe epilepsy group and control. Blue denotes lower NH and the color bar indicates the *T* values from 2-sample *t* tests.

significantly lower NH in the right MTPG and higher NH in the bilateral PCC compared to the controls. In patients with lTLE, decreased NH was observed in left ITG and left HIC. Although there were no significant correlations observed between abnormal NH values of the 5 above-mentioned brain regions and illness duration, performance RT in the lTLE differed between the patient group and the controls.

The epileptic discharge could lead to the decreased functional connectivity, abnormal activity, and white matter lesions.[37] Moreover, for language and memory, left regions were easily impaired in patients with TLE.[38,39] Consistent with our findings, there are only abnormalities of NH values in patients with lTLE. Nonetheless, several studies have demonstrated abnormal activation and functional connectivity in the contralateral regions of unilateral epilepsy,[40,41] and also observed contralateral white matter lesions using animal models of chronic TLE.[42] But the impairments were smaller than the ipsilateral regions.[18] Furthermore, Akman et al confirmed that epileptic discharge impacted bilateral brain glucose metabolism in TLE.[43] However, a recent study demonstrated a decrease in the effective connectivity, involving MTG interactions within the lesional hemisphere, while an enhancement in the effective connectivity parameters in the contralesional hemisphere.[44] Furthermore, Dresler et al found that training reorganized the functional network organization of the brain.[45] These studies revealed that the compensatory mechanism and cognition training activated

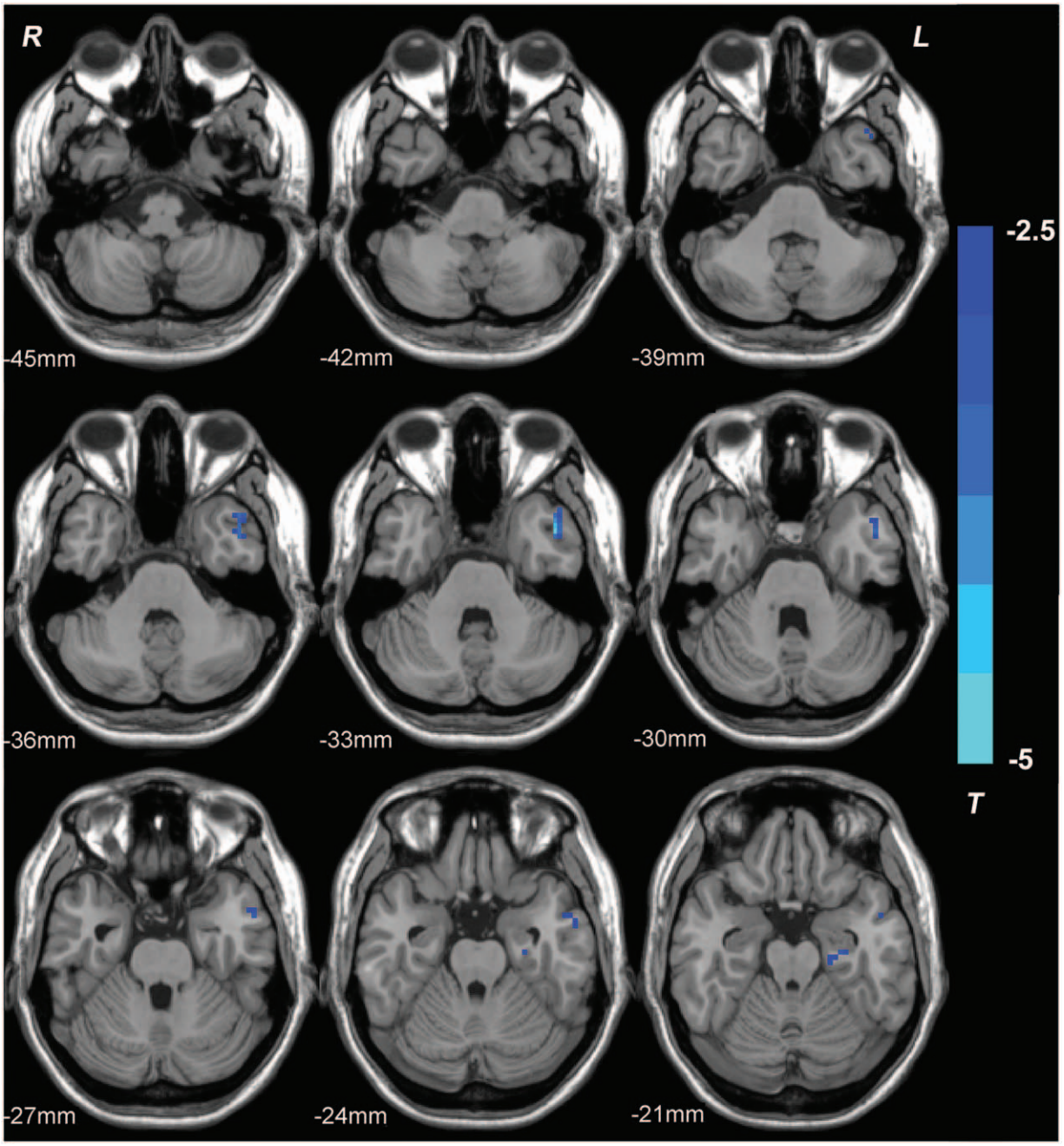

Figure 2. Statistical maps showing network homogeneity (NH) differences in the left inferior temporal gyrus between left temporal lobe epilepsy group and control. Blue denotes lower NH and the color bar indicates the *T* values from 2-sample *t* tests.

the compensation mechanism to keep the structural and functional normality in the contralesional hemisphere. Therefore, our findings demonstrated no abnormal NH values in the contralateral regions in patients with rTLE/lTLE.

The temporal lobe including HIC, parahippocampal gyrus, amygdaloid nucleus, and entorhinal cortex was the common target for both functional and structural studying in patients with TLE. The MTG and HIC play a key role in language processing and semantic memory.[46,47] Zhang et al reported decreased functional connectivity within MTG in patients with TLE.[37] Therefore, lower NH values in left ITG and HIC are related to cognitive deficits as seen in the lTLE, although memory testing was not evaluated in the present study.

As a "core hub" in the DMN, PCC serves a variety of cognitive functions, especially those linked with long-term memory and working memory.[48,49] Patients with TLE exhibited decreased amplitude of low-frequency fluctuations in the PCC.[40] However, increased activation and connectivity in PCC have been exploited in patients with epilepsy.[14] One possible interpretation for the paradox was that there might be a compensatory mechanism that occurs in the resting state results. Similar findings were found in patients with depression.[50] Consistent with these findings of hyperactivity in PCC, our results demonstrated increased NH in the bilateral PCC and were speculated as a compensatory mechanism in rTLE at rest.

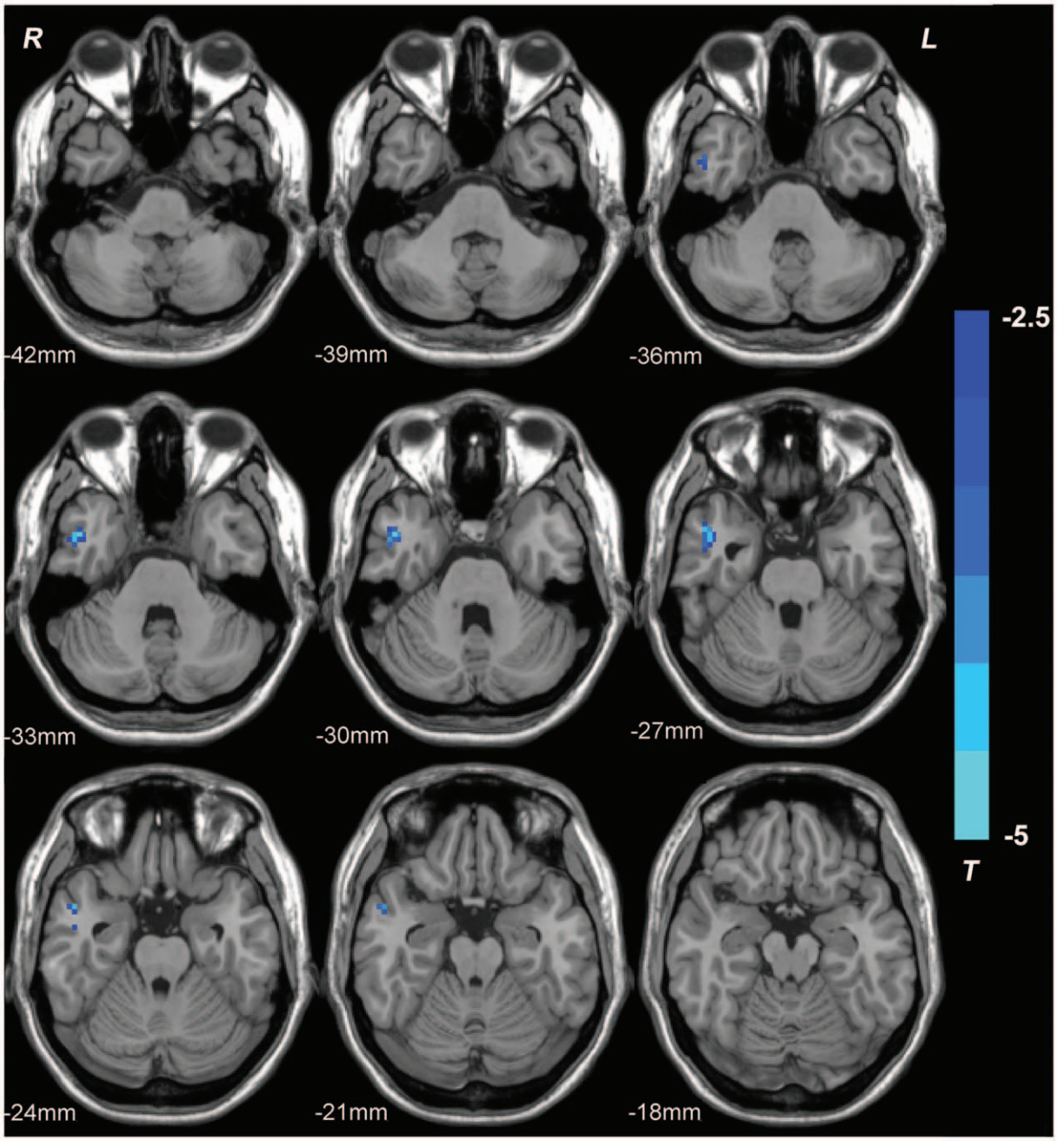

Figure 3. Statistical maps showing network homogeneity (NH) differences in the right middle temporal pole gyrus between right temporal lobe epilepsy group and control. Blue denotes lower NH and the color bar indicates the *T* values from 2-sample *t* tests.

It is universally acknowledged that there are impairments in the prefrontal lobe in patients with TLE, and this in turn plays a crucial role in executive functions.[51] Furthermore, the lesions of the prefrontal lobe contribute to the abnormality of executive function.[52] Therefore, the patients with TLE are usually accompanied with executive functional impairment. The explicit reason for this might be due to the epileptic discharge that caused parietal impairment through circuit of limbic system,[53] which mainly included the HIC, amygdala, cingulate gyrus, temporal lobe, and prefrontal cortex. Interestingly, these regions with abnormal NH were found in all parts of the limbic system. Therefore, we speculate that these regions indirectly participate in the executive function. Furthermore, we found that there are abnormal executive functions due to longer RT in patients with lTLE. One possible reason was that these regions with abnormal NH had correlation with executive function. Based on these speculations, we found that there were significant correlations between abnormal NH values and RT, as well as age of seizure onset and illness duration. Therefore, no correlation between these factors was somewhat unexpected. There are 2 possible reasons accounting for the phenomenon: first, the abnormal NH values of the DMN might be a trait change in patients who were independent of these factors. Second, our sample size was too small and all participants concentrated on the younger (from 19 to 35) population.

The present study has several limitations. First, we did not test the memory, and thus, we could not correlate between abnormal

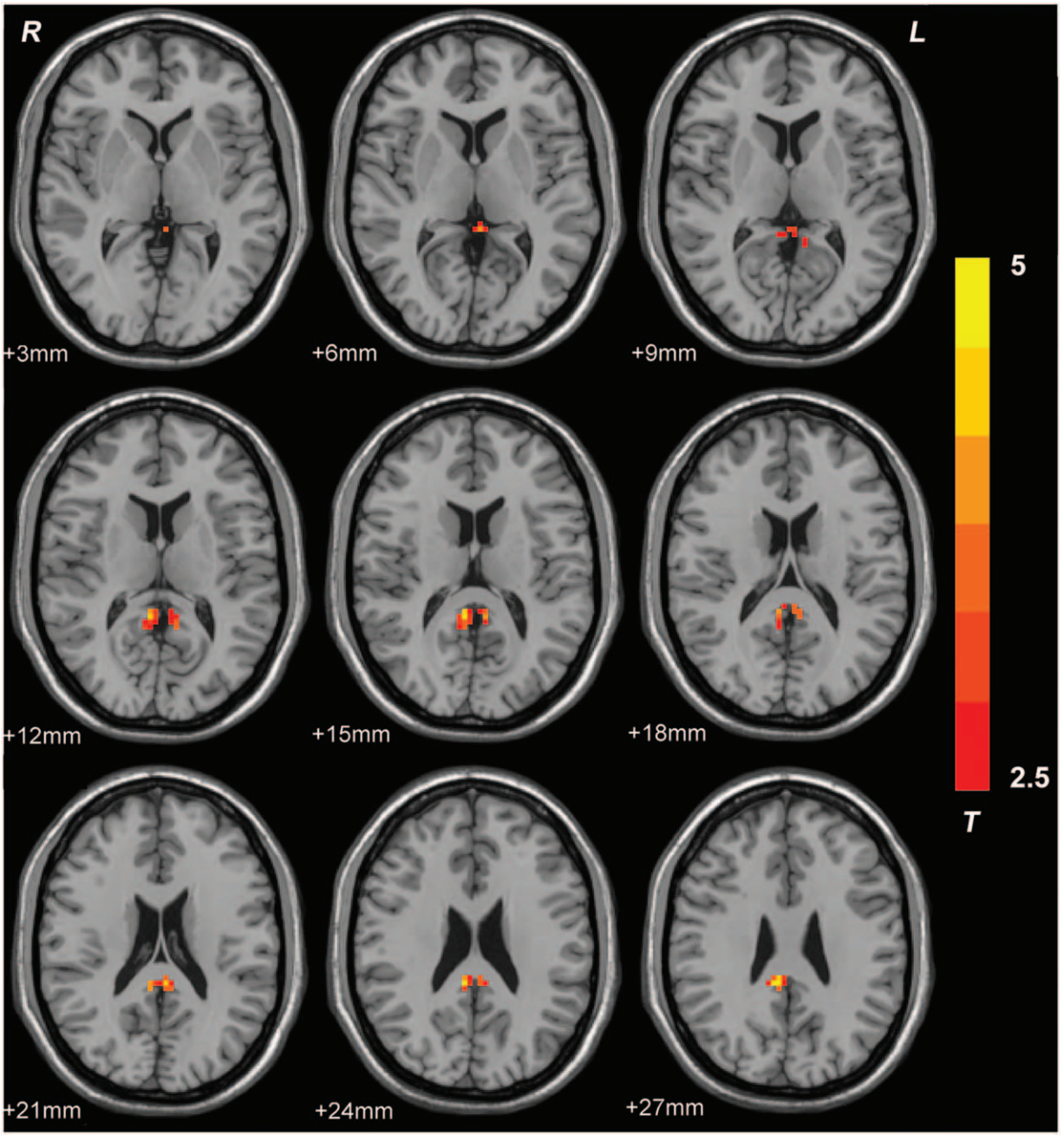

Figure 4. Statistical maps showing network homogeneity (NH) differences in the bilateral posterior cingulate cortex between right temporal lobe epilepsy group and control. Red denotes higher NH and the color bar indicates the *T* values from 2-sample *t* tests.

NH and memory. Second, although the patients with TLE were classified into left/right groups and our patients are medically stable, we did not dispose the confounding factor of AEDs, such as what AEDs were used by patients, and how many AEDs are used? Finally, our study focused only on the alterations in DMN, although it remained helpful to illustrate the pathophysiologic contribution of DMN, some significant information in other brain regions could be neglected.

Despite these limitations, our study results still suggested that abnormal NH of DMN existed in patients with TLE. Also a significantly new way of exploring NH in patients to improve the understanding of the nature of TLE has put forwarded. Hence, the present study highlights the importance of DMN in the pathophysiology of TLE.

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