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Disrupted functional network in patients with temporal lobe epilepsy with impaired alertness

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ABSTRACT

Cognitive impairment is common in patients with temporal lobe epilepsy (TLE). Alertness is an important subfunction of cognition, but it is poorly understood in TLE. We hypothesized that disruptions to underlying brain networks may affect alertness in patients with TLE. Patients with unilateral TLE were grouped into low-alertness and high-alertness groups, and they were matched with healthy controls (HCs) (n = 20 each). Functional magnetic resonance imaging (fMRI) was used to construct functional brain networks, and graph theory was used to identify topological parameters of the networks. At the global level, patients with low alertness had networks with less small-worldness and less normalized clustering than HCs. At the nodal level, patients with low alertness exhibited decreased centrality of the bilateral parahippocampal gyrus compared with HCs and increased centrality of the right postcentral gyrus compared with patients with high alertness. This study reveals a decreased separation, tending toward randomization, of the functional network in patients with TLE with impaired alertness. Our results also suggest that the parahippocampal gyrus may contribute to impaired alertness and the right postcentral gyrus plays an important role in the modulation of alertness in patients with TLE.

1. Introduction

The cognitive impairment that is concomitant with temporal lobe epilepsy (TLE)—the most common type of focal epilepsy in adults [1]—is considered to cause equivalent or greater harm than the epileptic seizures themselves [2,3]. Forms of cognitive impairment in patients with TLE range from deficits in attention, language, and memory to global cognitive deterioration [4], but a reduction in attention is particularly common [2,5].

Efficient attentional processes are important for cognitive processing [6]. Alertness is responsible for producing and maintaining phasic and tonic states of processing readiness for impending nonspecific inputs [7,8], and it is an important factor in the study of attention and cognitive psychology [9,10]. Moreover, improving alertness is considered key to all forms of cognitive rehabilitation following brain injury [9,10]. However, alertness in patients with TLE remains poorly understood.

Previous studies have shown that the alertness system in healthy individuals involves fronto/parietal cortical networks, the thalamus, and the brainstem, and it is regulated by the norepinephrine system [6,7,11]. Hence, the concept of a brain network for alertness has been proposed [11]. Although disrupted brain networks in patients with TLE and related cognitive impairments such as impaired attention have been observed [2,5,12], changes in the alertness network have rarely been specifically studied.

In our previous work [13,14], we observed abnormal alertness networks in patients with TLE. However, we included only patients with right-hemisphere TLE (rTLE) in these studies. Although patients with rTLE potentially serve as a good model of impaired alertness because of the presumed right lateralization of alertness [7,9], other possibilities should be seriously considered [6,8]. Indeed, structural magnetic resonance imaging (MRI) of a large sample of healthy individuals suggests that alertness may actually be lateralized to the left hemisphere [6]. Moreover, the alertness efficiency of patients with rTLE was not significantly different from healthy controls (HCs) in our previous studies. Similarly, it has been reported that long-term cognitive function and attention are not considerably different between patients with TLE and healthy individuals [3]. It is also possible that the changes we observed in the brain network in patients with rTLE could be due to the disease and be unrelated to impaired alertness. Therefore, further investigation of these prior results is merited.

Other findings of our previous studies also warrant careful consideration. There was significantly greater variability in alertness in the patient group than in the HC group. Because of the heterogeneity among patients with TLE, their deficits in cognition and alertness may vary widely [15]. Ignoring the variability of alertness and combining patients with different levels of alertness into a single group for analysis may obscure the changes in alertness in a subset of patients with significantly

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impaired alertness. We therefore hypothesized that abnormalities in the functional brain network of this subset of patients correlate with the impaired alertness.

The graph theory has recently been widely used to study the human brain network in healthy individuals [16,17] and those with diseases [18–20]. In healthy individuals, the brain operates as a small-world network and balances the separation and integration functions [16]. In patients, the balance is always disrupted, and the small-world networks tend to be random networks or regular networks [12,18–20]. Specially, Vlooswijk et al. [12] reported the reduced separation of functional networks in patients with impaired cognition with TLE.

In the present study, patients with unilateral (left or right) TLE were divided into a low-alertness (LA-TLE) group and a high-alertness (HA-TLE) group. We used functional magnetic resonance imaging (fMRI) to construct functional brain networks and graph theory to identify differences in the topological parameters of these networks among the groups. Finally, we assessed the relationship between topological parameters of the functional network and alertness performance in patients with TLE with impaired alertness.

2. Materials and methods

2.1. Participants

Consecutive patients with TLE were recruited from July 2016 to January 2018 at the Epilepsy Clinic of the First Affiliated Hospital of Guangxi Medical University. Temporal lobe epilepsy was diagnosed according to guidelines of the International League Against Epilepsy (ILAE) [21,22].

Inclusion criteria were as follows: (1) all patients had unilateral TLE, which was diagnosed from structural MRI images, video-electroencephalogram (EEG) evaluation during ictal and interictal phases, and analysis of clinical manifestations; (2) all patients had been taking antiepileptic drugs (AEDs) regularly; (3) all patients had no seizures during the last six months [23]; and (4) all patients were right handed.

Exclusion criteria were as follows: (1) patients with comorbidities affecting cognition, including traumatic brain injury, intracranial tumor, stroke, infection, multiple sclerosis, and Alzheimer's disease; (2) patients with a score of <24 on the Mini-Mental State Examination (MMSE); (3) patients who had taken or were taking topiramate or barbiturates [23]; and (4) patients who exhibited abnormalities in structural MRI images, excluding hippocampal sclerosis.

Overall, 80 patients with TLE were initially recruited to this study. Alertness scores were assessed with the attention network test (ANT) (see details below), which has been widely used to assess alertness in healthy individuals [6,7,9,11,24,25] and in patients with other diseases [26,27]. Patients ranking in the top and bottom quartiles for alertness scores were defined as the high-alertness and low-alertness groups, respectively. This grouping method has been widely used in other fields [28,29]. Thus, there were 20 patients in each of the high-alertness (HA-TLE) and low-alertness (LA-TLE) groups. The HC group consisted of 20 healthy volunteers matched to the patient groups in terms of age, gender, and years of education. We did not split HC individuals to subgroups according to their alertness because the variation of alertness was not significant in the HC individuals. Further, the purpose of the current study was to observe the functional brain network of patients with TLE with impaired alertness. All control participants had no history of mental or neurological disorders. All procedures were approved by the Medical Research Ethics Committee of the hospital. All participants provided signed informed consent prior to participating in the study.

The details of demographic, clinic characteristics, and MMSE scores are summarized in Table 1.

2.2. Neuropsychological test of alertness

The alertness of each participant was assessed with ANT (the version of AttentionExp1.1B5) downloaded from Dr. Jin Fan's web page (https://www.sacklerinstitute.org/cornell/assays_and_tools/ant/jin.fan/). The current version contains three blocks of 96 trials each. The 96 trials of each block were comprised of different cues and targets pseudorandomly. Twenty-five percent of the trials had no warning (= no cue) before the presentation of targets, and the other 75% of trials featured the target presentation preceded by one of three possible warning cues: the central cue, the double cue, or the spatial cue (the details are shown in Fig. 1A). The participants had to show the direction (left/right) of each target arrow disregarding the flankers by pressing the corresponding button. The four flankers on either side of the target arrow represent three types of conditions: the neutral condition, congruent condition, and incongruent condition (the details are shown in Fig. 1B). The procedure of one trial is depicted in Fig. 1C.

The efficiency of the alertness network is reflected by changes in reaction time (RT) in different warning conditions. E-prime software (Psychology Software Tools, Pittsburgh, PA) was used to control the experimental procedure and collect RT and accuracy data for every condition. In several previous studies [8,9,11,25], the authors subtracted the mean RT in the double-cue condition from the mean RT in the no-cue condition, and the efficiency of the alertness network was calculated. This calculation is based on Posner's theory that the no-cue condition indicates tonic alertness and the double-cue condition indicates phasic alertness to the upcoming target [9]. However, this calculation has

Table 1
Patient and control group demographics, MMSE, and alertness.

	Patients with LA-TLE (n = 20)	Patients with HA-TLE (n = 20)	Controls (n = 20)	*P* value
Age (mean ± SD)	31.7 ± 9.0	31.2 ± 8.4	30.6 ± 7.2	0.950 (ANOVA)
Gender (% female)	65	55	60	0.812 (χ^2)
Education years, median (range)	12 (6–19)	12 (7–16)	12 (9–16)	0.946 (Kruskal–Wallis)
Side (right)	16	11	NA	0.091(χ^2)
Epilepsy duration years, median (range)	6.5 (0.04–23)	6 (1.5–38)	NA	0.578 (Kruskal–Wallis)
Age at onset (mean ± SD)	23.548 ± 10.076	23.375 ± 10.409	NA	0.958 (t-test)
Seizure frequency, monthly median (range)	3 (0.042–12)	3 (0.08–30)	NA	0.765 (Kruskal–Wallis)
Number of AED median (range)	1.50 (0–3)	2 (1–3)	NA	0.545 (Kruskal–Wallis)
Dosage of AED mg/day, median (range)				
OXC	600 (600–600)	750 (300–1200)	NA	0.210 (Kruskal–Wallis)
LTG	200 (150–250)	200 (150–300)	NA	0.596 (Kruskal–Wallis)
VPA	800 (500–1000)	800 (500–1250)	NA	0.399 (Kruskal–Wallis)
LEV	1000 (1000–1000)	1000 (1000–1000)	NA	1.000 (Kruskal–Wallis)
CBZ	600 (200–600)	600 (200–600)	NA	0.430 (Kruskal–Wallis)
MMSE (mean ± SD)	26.95 ± 1.05	27.60 ± 1.10	27.65 ± 1.04	0.076 (ANOVA)
Alertness, median (range)	0.033 (0.003–0.049)	0.102 (0.079–0.246)	0.093 (0.026–0.156)	0.000 (Kruskal–Wallis)

MMSE, Mini-Mental State Examination; AEDs, antiepileptic drugs; OXC, oxcarbazepine; LTG, lamotrigine; VPA, valproic acid; LEV, levetiracetam; CBZ, carbamazepine.

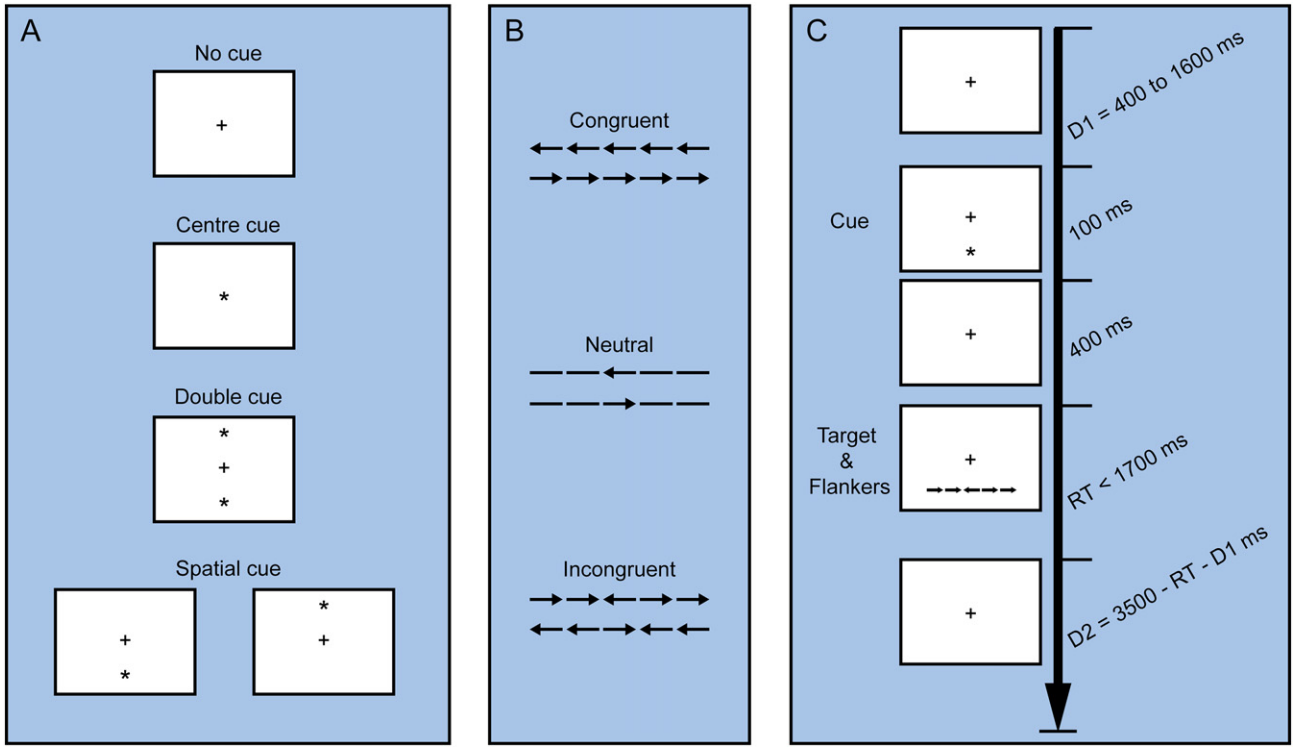

Fig. 1. Design and procedure of the attention network test (ANT). (A) The four types of warning cue. (B) The six stimuli (target and flankers) used in the test. (C) The procedure in one trail. First, there was a fixation period for a variable duration (D1): 400 to 1600 ms. Then, a warning cue was presented for 100 ms. After the warning cue, there was a short fixation period for 400 ms. Then, the target and flankers appeared simultaneously and were presented until the participant responded, but for no longer than 1700 ms. After participants responded, the target and flankers disappeared, and there was the second variable duration (D2) of a fixation period. The second variable duration was based on the duration of the first fixation and RT (3500 ms minus duration of the first fixation minus RT). Then, the next trial began. Each trial lasted for 4000 ms. The fixation cross appeared at the center of the screen during the whole trial.

yielded results with limited reliability [25] because of bias caused by a general increase in RT associated with aging and disease. To eliminate this bias, we instead calculated ratio effect scores to assess alertness:

$$\text{Alertness} = (\text{RT}_{\text{no cue}} - \text{RT}_{\text{double cue}})/\text{RT}_{\text{double cue}}$$

Ratio effect scores exhibit increased sensitivity and have been widely used in recent studies [6,24]. Since incongruent trials reflect executive control as well as attention, we excluded incongruent trials from the calculation of alertness [9]. None of the participants had any prior experience with the ANT.

2.3. Imaging

Functional magnetic resonance imaging was performed with a 3T Achieva MRI scanner (Philips, The Netherlands). Imaging of subjects and scanning parameters were as follows: resting-state fMRI (repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle = 90°, field of view (FOV) = 220 mm × 220 mm, matrix = 64 × 64, 31 axial slices, slice thickness = 5 mm/1 mm gap, and voxel size = 3.44 × 3.44 × 6.00 mm^3), with 180 volumes acquired during each 6-min scan. A cushion was used to limit head motion. All participants wore headphones to reduce the noise of the scan. All participants were instructed to lie still, keep their eyes closed, stay awake, and avoid thinking about anything in particular. At the conclusion of the scanning session, some simple questions were asked to assess whether the participant fell asleep during the scan. Attention network test and MRI data were obtained during a single visit. We performed the ANT first and then immediately started the MRI scanning during 5 pm to 8 pm. Two patients had the second MRI scanning after ANT in 24 h because of the unqualified image data.

No participants were excluded because of missing MRI data. The sample size of each group remained unchanged.

2.4. Image preprocessing

The fMRI images were preprocessed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), MATLAB R 2013b (The Math Works, Natick, Massachusetts, USA) and the GRETNA software (http://www.nitrc.org/projects/gretna) [30]. Preprocessing steps comprised removal of the first 10 images, slice timing correction, realignment, spatial normalization to the Montreal Neurological Institute (MNI) template using the Echo Planar Imaging (EPI) template, and resampling with a resolution of 3 mm × 3 mm × 3 mm. Subsequently, Friston-24 head motion parameters, the averaged white matter signal, and the cerebrospinal fluid signal were regressed out as confounding variables. Finally, the normalized fMRI time series were bandpass filtered in a frequency range of 0.01 to 0.08 Hz [31]. All participants' fMRI images were within the defined head motion thresholds (i.e., the translational parameter was less than 2 mm and the rotational motion parameter was less than 2°).

2.5. Functional network construction

The functional brain network for each individual was constructed in the GRETNA software, and each network consisted of nodes and edges. For nodes, an automated anatomical labeling (AAL) template [32] was used to segment the whole brain (left and right) into 90 regions, including cortical and subcortical regions. These 90 regions served as nodes for the functional network. For each participant, the mean time series of each node was obtained by averaging the time series over all voxels within the region. For edges, Pearson correlation coefficients between the regional mean time series of all paired nodes were calculated.

Thus, a 90 × 90 correlation functional connectivity matrix for each participant was constructed [16]. Then, the functional connectivity matrix was thresholded (the sparsity threshold was from 0.1 to 0.34 with an interval of 0.01) [18,33] to produce a binary matrix. Finally, the topological parameters of the functional connectivity network were calculated by graph theoretic analyses via the GRETNA toolbox.

2.6. Network analysis

Global and nodal network measurements were calculated at each sparsity threshold. The global level measurements consisted of five small-world property measurements and two network efficiency measurements [34]. The five small-world property measurements are as follows: (1) the clustering coefficient quantifies functional segregation of the brain network, (2) the characteristic path length quantifies the functional integration of the brain network, (3) the normalized clustering coefficient represents the ratio of the clustering coefficients in real and random networks. The clustering coefficient and normalized clustering coefficient quantify functional segregation [34] of the brain network, (4) the normalized characteristic path length represents the ratio of the characteristic path length between real and random networks. The characteristic path length and normalized characteristic path length quantify the functional integration of the network [34], and (5) small-worldness (small-worldness = normalized clustering coefficient / normalized characteristic path length) represents the balance of segregation and integration in a network [34]. The network efficiency measurements are as follows: (1) global efficiency is the reciprocal of the characteristic path length and also represents the integration of the brain network and (2) local efficiency represents the segregation and the fault tolerance of the network.

The nodal level measures consisted of three metrics: (1) degree, (2) efficiency, and (3) betweenness. These three nodal measurements assess the centrality of individual nodes in the network. Nodes with high centrality play an important role in network resilience to damage because they can interact with many other nodes in the network [34]. The area under the curve (AUC) for each topological property was calculated to improve sensitivity and avoid multiple comparisons across multiple thresholds [33,35]. The illustrations of graph theoretical terms were summarized in Table 2.

Because the lateralization of the epileptic zone is considered a factor in cognitive impairment in patients with TLE [3], and because alertness is right lateralized in some studies [7,9], we further divided the patients with TLE into left and right subgroups according to epileptic zone lateralization. Then, we analyzed the functional networks of the patients with rTLE with different levels of alertness (16 patients in the group with LA-rTLE and 11 patients in the group with HA-rTLE). Because of the small sample of patients with left TLE (four patients) in the group with LA-TLE, a similar analysis was not performed for these patients.

Table 2
The description of graph theoretical terms.

Term	Description
Global level measurements	
Clustering coefficient	Segregation function of the network
Normalized clustering coefficient	Segregation function of the network
Characteristic path length	Integration function of the brain network
Normalized characteristic path length	Integration function of the brain network
Small-worldness	The balance of segregation and integration in a network
Global efficiency	Integration function of the brain network
Local efficiency	Segregation and the fault tolerance of the network
Nodal level measurements	
Degree	The centrality of individual nodes in the network
Efficiency	
Betweenness	

2.7. Statistical analysis

The statistical analyses of the MMSE results, demographics, and clinical characteristics were performed with one-way analysis of variance (ANOVA) (Tukey's significant difference test was used for post hoc analysis) and chi-square tests. The rank sum test was used to compare characteristics that were not normally distributed (Kolmogorov–Smirnov test). These tests were conducted in SPSS software (version 18). To determine the differences in topological properties among the three groups, we conducted an analysis of covariance (ANCOVA) ($P < 0.05$, False discovery rate method (FDR) corrected) in the GRETNA software. We regressed the age, gender, and years of education of participants as nuisance covariates in the ANCOVA. In the analyses between paired groups, we first performed two sample t-test in the GRETNA software ($P < 0.05$, FDR corrected) and then performed Bonferroni significant difference test ($P < 0.05$) as the second correction for multiple comparisons. Analyses of the relationships between topological properties and alertness or clinical variables were conducted in SPSS ($P < 0.05$, Bonferroni corrected). All statistical analyses were two-tailed, with a significance level of 0.05. The same statistical analysis methods were applied to the groups with LA-rTLE, HA-rTLE, and HC.

2.8. Network visualization

We used Brainnet Viewer to display the results of the group functional network analysis at the nodal level [36].

3. Results

3.1. Demographics, clinical characteristics, and MMSE

The groups with LA-TLE, HA-TLE, and HC were well matched in age, gender, and years of education. No significant differences were observed between the groups with LA-TLE and HA-TLE in age at onset, duration of epilepsy, seizure frequency, or the current number of AEDs. No significant differences in MMSE scores were observed among the three groups. The details are summarized in Table 1. Similar results were obtained in the analysis of the groups with LA-rTLE, HA-rTLE, and HC. Additionally, considering the sedation of AEDs, we compared the dosage of AEDs of the two patient groups, and no significant differences were observed. We exhibited the details of AEDs in Table 1.

3.2. Reduced alertness in patients in the low-alertness group

None of the participants had any RTs of >1500 ms or <200 ms [6], and all participants had ≥80% accuracy. As mentioned before, patients ranking in the top and bottom quartiles for alertness scores from ANT were defined as the high-alertness (LA-TLE) group and the low-alertness (HA-TLE) group, respectively. The group with LA-TLE showed lower alertness ($P < 0.001$, Kruskal–Wallis) than the HC groups (Table 1 and Fig. 2A). Similar results were observed in the comparison between the groups with LA-rTLE, HA-rTLE, HC (Fig. 2B).

3.3. Reduced small-worldness and clustering in patients with TLE with low alertness

To assess the difference in functional segregation and integration of the brain network among the two patient groups and the HC group, we compared the global network measurements. As described in the methods, small-worldness represents simultaneous reconcilement of functional segregation and integration of a network. The normalized clustering coefficient quantifies the functional segregation of the

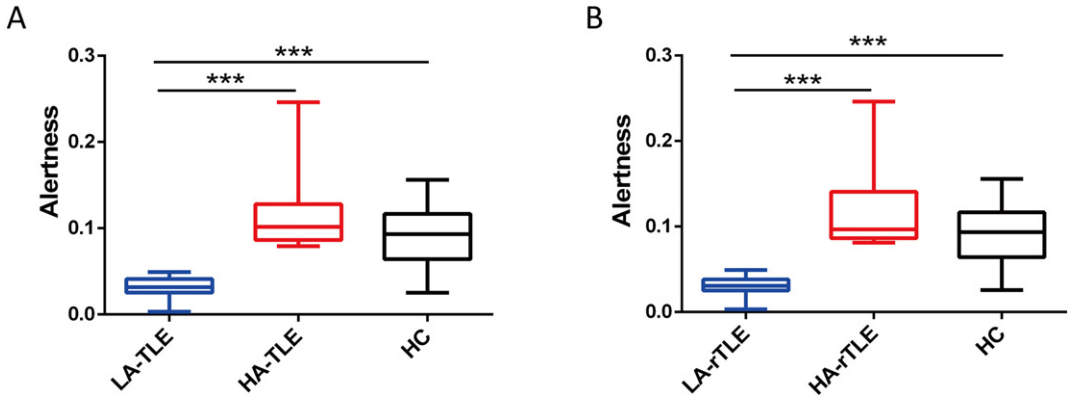

Fig. 2. Alertness is diminished in the low-alertness group. (A) Alertness in the two patient groups (low-alertness group, LA-TLE; high-alertness group; HA-TLE) and in healthy controls (HC), assessed using attention network test (ANT). n = 20, each. (B) As for A, but for patients with right TLE (LA-rTLE: n = 16; HA-rTLE: n = 11). ***$P < 0.001$, multiple independent samples nonparametric tests.

network, and the normalized characteristic path length quantifies the functional integration of the network [34]. The functional networks exhibited typical small-worldness (small-worldness >1) in all three groups. We observed that the small-worldness and normalized clustering coefficient decreased from the HC group to the group with HA-TLE and were lowest in the group with LA-TLE (Fig. 3A, B). The group with LA-TLE exhibited significantly lower small-worldness and normalized clustering coefficient than the HC group (both $P = 0.005$; Fig. 3A, B). There were no significant differences in normalized characteristic path length among the three groups ($P > 0.05$). We also observed a significant intergroup difference in global efficiency ($P = 0.048$) with a decreasing trend from the HC group to the group with HA-TLE and finally to the group with LA-TLE. However, no significant differences were found in the post hoc analysis (Fig. 3C). No significant differences were observed in local efficiency among the three groups ($P > 0.05$). In the secondary analysis of patients with rTLE and HC, we observed similar trends of global network measurements among the three groups (Fig. 3D, E). At the global level, the patients with low alertness exhibited significantly reduced functional segregation of the brain network.

3.4. Parahippocampal gyrus and right postcentral gyrus involvement in TLE alertness deficits

We also compared three nodal measurements to assess the centrality of individual nodes in the networks among the two patient groups and the HC group. We observed reduced nodal degree in the bilateral

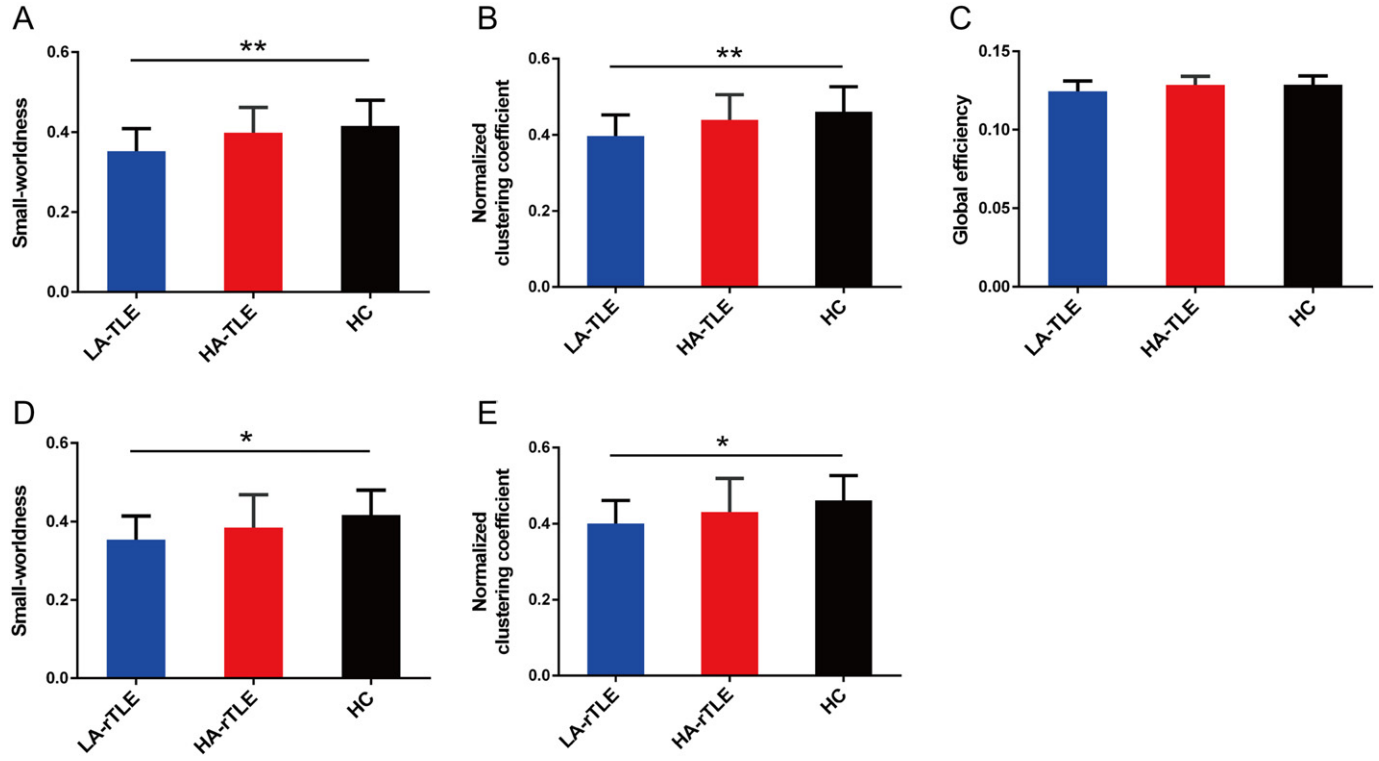

Fig. 3. Global network measurements are diminished in patients with low alertness. (A) Small-worldness in the two patient groups (low-alertness group, LA-TLE; high-alertness group; HA-TLE) and in healthy controls (HC). n = 20, each. (B) and (C) As for A, but for the normalized clustering coefficient and global efficiency. For C, ANCOVA $P = .056$. (D) and (E) Small-worldness and normalized clustering coefficient in the two patient groups with right TLE (LA-rTLE: n = 16; HA-rTLE: n = 11) and in healthy controls (HC: n = 20). **$P < 0.01$, *$P < 0.05$, paired t-test with Bonferroni–Holm correction for multiple comparisons.

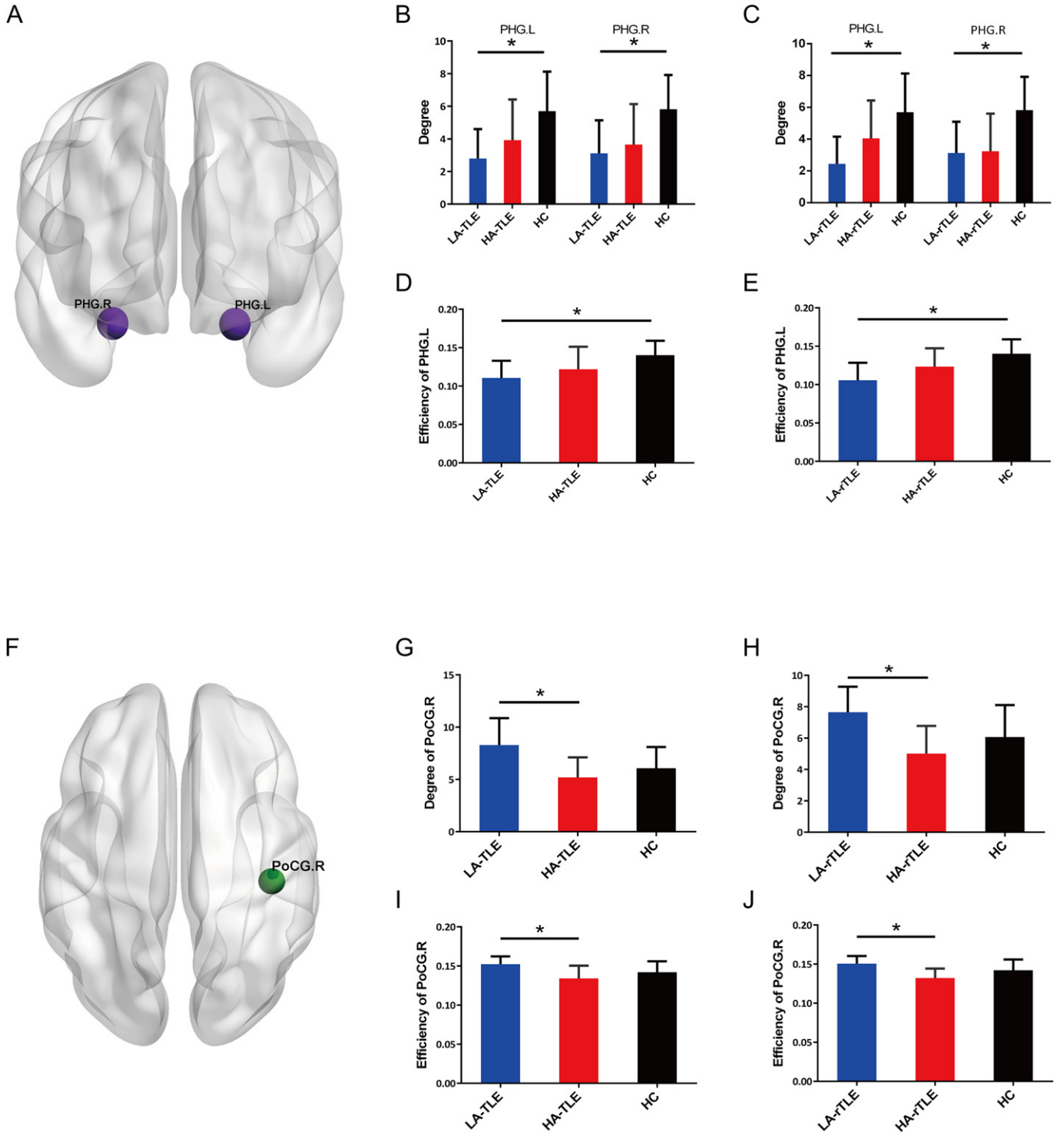

Fig. 4. Altered centrality of the bilateral parahippocampal gyrus (PHG) and the right postcentral gyrus (PoCG) in patients with low alertness. (A) Location of the PHG. (B) Nodal degree of bilateral PHG in the two patient groups (low-alertness group, LA-TLE; high-alertness group; HA-TLE) and in healthy controls (HC). n = 20, each. (C) As for B, but for patients with right TLE (LA-rTLE: n = 16; HA-rTLE: n = 11). (D) Nodal efficiency of left PHG in the group with LA-TLE, the group with HA-TLE, and the HC group. (E) As for D, but for patients with right TLE. (F) Location of the right PoCG. (G) Nodal degrees of right PoCG in the group with LA-TLE, the group with HA-TLE, and the HC group. (H) As for G, but for patients with right TLE. (I) Nodal efficiency of right PoCG in the group with LA-TLE, the group with HA-TLE, and the HC group. (J) As for I, but for patients with right TLE. PHG, parahippocampal gyrus; PHG.L, left parahippocampal gyrus; PHG.R, right parahippocampal gyrus; PoCG, postcentral gyrus; PoCG.R, right postcentral gyrus. *$P < 0.05$, paired t-test with first FDR correction ($P < 0.05$) and then with Bonferroni significant difference test ($P < 0.05$) as the second correction for multiple comparisons.

parahippocampal gyrus and nodal efficiency in the left parahippocampal gyrus decreased from the HC group to the group with HA-TLE and were lowest in the group with LA-TLE (Fig. 4B, D). The group with LA-TLE had a significantly lower nodal degree in the bilateral parahippocampal gyrus and significantly lower nodal efficiency in the left parahippocampal gyrus than the HC group (Fig. 4B, D). The degree and efficiency in the right postcentral gyrus decreased from the group with LA-TLE to the HC group and finally to the group

with HA-TLE (Fig. 4G, I). The group with LA-TLE had a significantly higher degree and efficiency in the right postcentral gyrus than the group with HA-TLE (Fig. 4G, I). No significant differences in nodal betweenness were observed among the three groups. The statistical analysis of the subgroups with rTLE exhibited similar results (Fig. 4C, E, H, J). At the nodal level, the patients with low alertness exhibited decreased centrality in the bilateral parahippocampal gyrus and increased centrality in the right postcentral gyrus.

3.5. Left parahippocampal gyrus nodal efficiency may be correlated with alertness in patients with TLE with low alertness

To examine potential relationships between topological properties and alertness in patients with epilepsy, we next performed partial correlation analyses of all altered topological properties and alertness in which we controlled for the effects of age, gender, and years of education. In the group with LA-TLE, the nodal efficiency of the left parahippocampal gyrus suggested a positive correlation with alertness ($r = 0.488$, $P = 0.047$, uncorrected; Fig. 5). However, the result was not statistically significant after the multiple comparison correction. No other correlations were observed between topological properties and alertness in the groups with LA-TLE, HA-TLE, LA-rTLE, or HA-rTLE. No correlations were observed between any topological properties and alertness in the HC groups.

Further, considering the effect on alertness, we also performed partial correlation analyses of clinical variables, including epilepsy duration, age at onset, seizure frequency, and number of AEDs [3,37], and topological properties in the group with LA-TLE. However, we did not find correlation between clinical variables and topological properties in the group with LA-TLE. These may be related to the small sample size of this group.

4. Discussion

In the present study, we constructed functional brain networks of patients with TLE with different levels of alertness and observed different patterns of functional networks between them. In patients with impaired alertness, the functional network is disrupted and tends toward randomization. The bilateral parahippocampal gyrus and right postcentral gyrus may contribute to impaired alertness in patients with TLE.

4.1. The bilateral parahippocampal gyrus and right postcentral gyrus contribute to the impairment and modulation of alertness in patients with TLE

Cognition depends on the integrity of the whole brain network [12]; disruption to crucial regions disturbs the brain network and impairs cognitive functions [38,39]. The parahippocampal cortex belongs to the medial temporal lobe subsystem of the default mode network [40], which has been shown to correlate with attention and alertness [41]. Reduced thickness of the parahippocampal cortex is common in TLE [42], and the correlation between parahippocampal cortex abnormalities and cognitive deficits in patients with TLE has been reported in previous studies [43–45]. However, no previous study has demonstrated atypical nodal centrality in patients with TLE with impaired alertness. In the present study, decreased centrality of bilateral parahippocampal cortex together with a possible positive correlation between the left parahippocampal cortex centrality and alertness indicate that the parahippocampal cortex may be involved in impaired alertness in the patients with TLE. A similar result has been reported for Alzheimer's disease, with reduced parahippocampal cortex centrality deemed to play an underlying role in patients' cognitive deficits [38]. Even the basis for parahippocampal cortex involvement remains unclear, and studies in rodents and healthy human individuals have

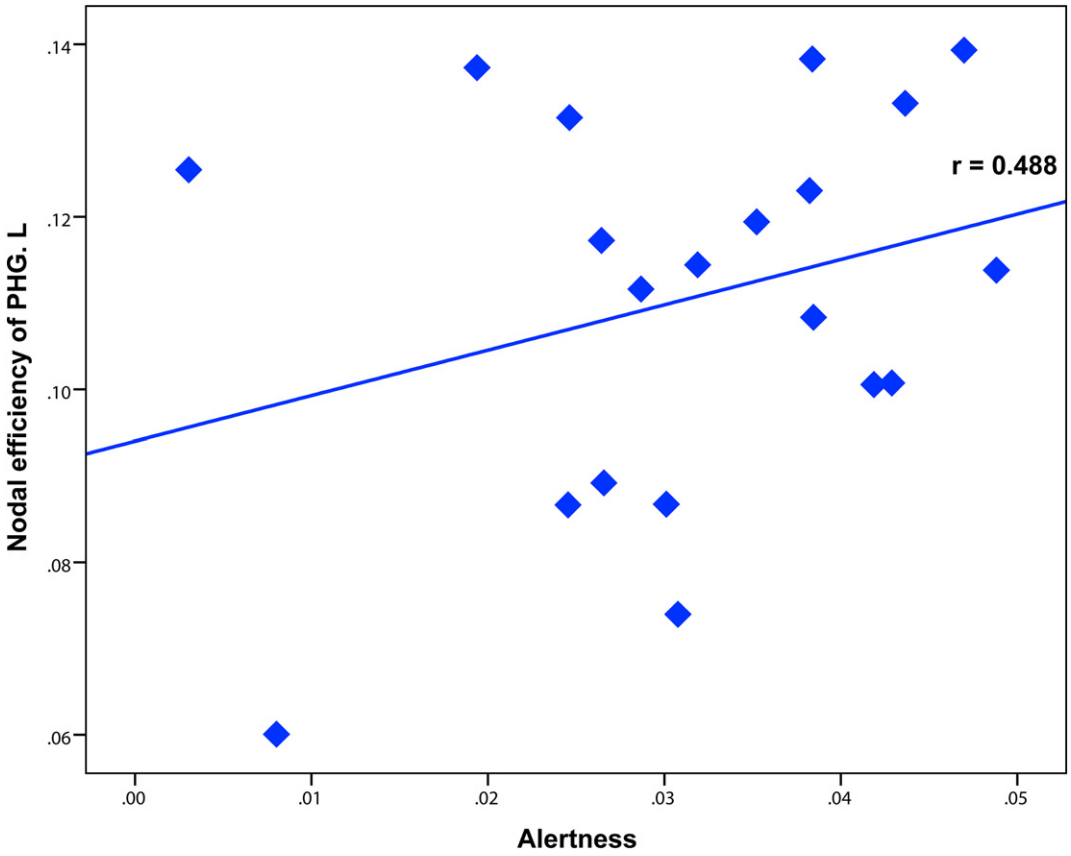

Fig. 5. Efficiency of left parahippocampal gyrus (PHG.L) is positively correlated ($P = 0.047$, uncorrected) with alertness in patients with low alertness. PHG.L, the left parahippocampal gyrus.

provided some insight. The parahippocampal cortex receives inputs from the sensory and association cortex and projects to the hippocampus [46]. These projections play a central role in visuospatial analysis [47] and visual attention [48] (and, as described above, the ANT used in the present study was based on visual stimulation [9]). The reduced thickness of the parahippocampal cortex secondary to recurrent seizure may be related to the decreased connectivity. We speculate that decreased connectivity between the parahippocampal cortex and other crucial regions plays a role in the impaired alertness of patients with TLE. Reduced connectivity between the parahippocampal cortex and the posterior cingulate cortex is thought to play a key role in cognitive and attention deficits in posttraumatic amnesia [49]. The reduced functional connectivity between the left parahippocampal cortex and the hippocampus in patients with TLE with memory deficits also supports our speculation [50].

The right postcentral gyrus is known to be involved in the deficits in attention alertness and primary information processing in epilepsy [51]. Additionally, the right postcentral gyrus is involved in alertness in healthy people [11] and patients with TLE [13]. The concordance of this may help validate the reliability of our results. Interestingly, in the present study, the centrality of the right postcentral gyrus was significantly increased in the group with LA-TLE compared with the group with HA-TLE. This is consistent with our previous study that found increased functional connectivity in the right parietal lobes in patients with rTLE [13]. The postcentral gyrus is the location of the primary somatosensory cortex. Outputs from the postcentral gyrus project to the parahippocampal cortex and to the hippocampus for further processing [46]. Moreover, abnormal connectivity between the hippocampus and the postcentral gyrus has been observed in patients with TLE [52]. We speculate that the increased connectivity from the right postcentral gyrus to other crucial brain regions reflects an attempt to compensate for the decreased alertness. The right postcentral gyrus may act to regulate inputs to the alertness system in patients with TLE. The trend toward reduced right postcentral gyrus centrality in patients with HA-TLE supports this speculation (Fig. 4G–J).

In our present study, we did not observe nodal differences in the frontal cortex, thalamus, and brainstem, which are considered the key regions of the alertness network. We speculate that this may be due to the stronger compensation and robustness of these key brain regions in patients with epilepsy. The absence of these key regions may be consistent with findings of previous studies that thought the cognition of patients with TLE may be robust [3]. The concordance of the parietal lobe may help validate the reliability of our results.

4.2. Reduced separation of functional networks in patients with TLE with impaired alertness

The human brain operates as a small-world network. Small-world networks can optimize efficiency by implementing high local clustering of the rule network and short path lengths of the random network [16]. In the present study, the low small-worldness value in the group with LA-TLE may indicate that the network tends toward randomization in these patients. Reduced local connections and increased long-distance connections can both lead to network randomization [18]. The low normalized clustering coefficient in the group with LA-TLE but unchanged normalized characteristic path length supports the former possibility. The reduced normalized clustering coefficient indicates that network separation has declined in patients with impaired alertness. Although studies relating cognitive impairment in patients with TLE to topological parameters are sparse, the results of the present study are consistent with those that have been reported [12,53]. Vlooswijk et al. [12] reported a decreased clustering coefficient in the functional brain network of patients with TLE with significant cognitive impairment. Reduced clustering and greater path length are strongly associated with cognitive impairment in patients with chronic epilepsy [53]. Furthermore, reduced clustering was observed in a study of attentional decline with aging in healthy individuals [54].

A reduced global efficiency value indicates declining integration of the network and is strongly related to cognitive impairment [55]. Even though reduced global efficiency in patients with TLE has been widely reported [12,14,31], the relationship between reduced global efficiency and impaired cognition in patients with TLE has rarely been studied. In the current study, no significant differences in global efficiency were identified in the post hoc analysis, but the main effect of the ANCOVA was significant. Moreover, a post hoc comparison between the groups with LA-TLE and HCs yielded a nearly significant P value of 0.056. This suggests that reduced alertness was accompanied by a slight decrease in the integration of the brain network.

4.3. Patients with left TLE should be included in studies of alertness

No additional evidence in previous studies was found to support the viewpoint that patients with rTLE exhibit more severe impairment of alertness. Investigations of the alertness of patients with left TLE are rare. However, studies on cognitive and attention deficits have provided additional information about disruption of the hippocampus and related brain networks in patients with left TLE, supporting the hypothesis that more serious cognitive impairment is found with left TLE [50,56]. Our secondary analysis of patients with rTLE alone did not show any additional significant differences in network measurements over those found in the initial study of patients with right or left unilateral TLE. Furthermore, no significant differences in global efficiency were observed between the groups with rTLE and HC, and there were no correlations between nodal centrality and alertness in the groups with rTLE. These results may be due to the small sample size; however, it is clear that impaired alertness and brain network disruption in patients with left TLE cannot be ignored and that more studies on this topic are needed.

4.4. Limitations

The present study has some limitations. First, the optimal analytic strategy for graph theory is still controversial [57]. We used 90 brain regions as nodes to build the network, and future work should use different partition schemes to test the reproducibility of our results. Second, a new method for computing attention network scores has been proposed [58,59]. The alertness score obtained with the new method should be considered in the future to test the reproducibility of our results. Third, we captured alertness at one point during the day and therefore, do not capture the fluctuation in alertness that likely occurs within one individual during the day. Fourth, alertness and brain network metrics in patients with left TLE alone were not analyzed because of the small sample size. Larger samples of patients with left TLE will be necessary to directly compare alertness and brain networks in patients with left versus right TLE. Fifth, similar to most studies to date in epilepsy and cognition, some results of functional and structural brain networks may be confounded by the effects of AEDs [5]. Additionally, the sedation of AEDs and its effect to alertness should be considered in the current study. Last, because of the cross-sectional design of the present study, a causal relationship between the network measurements and alertness could not be determined.

5. Conclusions

Our study demonstrates that the functional brain network tends toward randomization in the patients with TLE with impaired alertness. The bilateral parahippocampal gyrus and the right postcentral gyrus may contribute to the alertness deficit in patients with TLE. Appropriate alertness is important for cognitive processing, and establishing improved alertness is crucial to all forms of cognitive rehabilitation following brain injury [9,10]. The present study demonstrates that patients with TLE with different levels of alertness have different functional

networks, which may direct different cognitive rehabilitation strategies for clinical treatment. In future rehabilitation of alertness and cognition, it may be necessary to group patients with TLE with different levels for different treatment strategies.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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