



Comparison of topological properties of functional brain networks with graph theory in temporal lobe epilepsy with different duration of disease

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Background: Our study was performed to measure the alterations in topological properties of the functional brain network of temporal lobe epilepsy (TLE) at different durations, exploring the potential progression and neuropathophysiological mechanisms of TLE.

Methods: Fifty-eight subjects, including 17 TLE patients with a disease duration of ≤ 5 years (TLE-SD), 20 TLE patients with a disease duration of > 5 years (TLE-LD), and 21 healthy controls firstly underwent the Attention Network Test (ANT) to assess the alertness function and received the resting-state functional magnetic resonance imaging (rs-fMRI). Next, a functional brain network was set up, and then the related graph of theoretical network analysis was conducted. Finally, the correlation between network property and the neuropsychological score was analyzed.

Results: The global and local efficiencies of functional brain networks in TLE-SD patients significantly decreased and tended toward random alterations. Also, the degree centrality (DC) and nodal efficiency (Ne) in right medial pre-frontal thalamus (mPFtha) and right rostral temporal thalamus (rTtha) of TLE-SD patients significantly reduced. Further analysis showed that alertness was positively associated with the characteristic path length but negatively related to the global and local efficiencies in TLE-SD patients; alertness was negatively related to the Ne of mPFtha in TLE-LD patients.

Conclusions: Our study showed that the functional brain network of TLE patients might undergo compensatory reorganization as the disease progresses, which provides useful insights into the progression and mechanism of TLE.

Keywords: Alertness function; duration of disease; graph theory; resting-state functional magnetic resonance imaging (rs-fMRI); temporal lobe epilepsy (TLE)

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Introduction

Temporal lobe epilepsy (TLE) is a focal disease, and its prevalence is 0.1% (1). However, a previous study showed that TLE could be considered as a neurological network disorder and is closely related to brain functions from the perspective of the occurrence of epilepsy and the

spread of seizures (2). Recently, TLE-related cognition dysfunction has attracted widespread concerns and could cause equivalent or more significant harm than those caused by the epileptic seizures themselves (3,4). Previous studies showed that cognitive impairments in TLE patients ranged from inadequate attention, language, and

memory to globally decreased cognition (5), and of which attention decline was most common (3,6). Alertness refers to maintaining a sensitive state to receive information network information, and the alertness network is one of the most critical attention networks, which was proved to be an essential factor for studying attention and cognitive psychology (7,8). The abnormality of the alertness network of TLE patients has attracted people's attention (9,10); however, how the alertness of TLE patients changes and its underlying neural mechanism remains to be elucidated.

Epilepsy is a chronic disease. Many earlier studies have found that the imaging characteristics of epilepsy are associated with the duration of disease. Specifically, Cheung *et al.* (11) found that the speech and visual memory of TLE patients were negatively associated with the duration of disease. Further, Li *et al.* (12) confirmed that the functional connectivity (FC) in the hippocampus of TLE with hippocampal sclerosis was positively correlated with the duration of the disease. Haneef *et al.* (13) found that a longer epilepsy duration was associated with a lower betweenness centrality (BC). Haneef *et al.* (14) found that TLE showed reduced connectivity diversity as epilepsy progression. However, the characteristics of the TLE network have rarely explicitly been studied. In the well-known SANAD trial (15), the average duration of epilepsy tracked for newly diagnosed patients was five years. Rathouz *et al.* (16) found that childhood epilepsy was characterized by early (nearly onset and diagnosis) cognitive abnormalities that follow with overtime (up to 6 years), which persisted in a mostly unchanged manner with no signs of progress or recovery and could serve as a model for adult epilepsy. However, it is unknown whether the topological properties of the TLE network progress or recover with the increase of the duration of epilepsy, and the time of this change needs to be further studied.

Resting-state fMRI has been proved to can non-invasively measure the intrinsic or spontaneous activity of the human brain (17,18), and is widely applied on studying interregional functional connection patterns that connect healthy individuals with diseased people (19,20). Previous rs-fMRI reports showed lots of important topological properties of functional brain networks, including small-worldness characteristics for balancing functional separation and integration, important modular structures, and densely connected hubs using graph theory methods (21-23). A previous study showed that the graph-based network methods were not only beneficial for the architecture of the whole-brain network but also were valuable for

further exploring the underlying mechanisms of various cognitive deficits (24). Recent studies also characterized the topological properties of brain networks under health and disease conditions using this method (25,26). Therefore, studies on rs-fMRI functional networks based on the graph theory are of great significance for exploring the topological mechanism of large-scale brain networks under health and disease conditions.

We hypothesized that TLE patients showed the brain network alterations of the topological properties with the extension of the duration of disease, and the time for these alterations might be 5 years. The brain network alterations might be the potential neural mechanisms of cognitive dysfunction. To further verify this hypothesis, the patterns of alterations in the functional brain network of TLE patients under the different duration of disease were systematically studied and compared with healthy participants and exploring the potential neural mechanisms of cognitive dysfunction in TLE patients.

We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-6823>).

Methods

Participants

From January 1, 20¹19, to October 1, 2019, 58 right-handed participants including 37 TLE patients (17 TLE patients with short duration of disease (≤ 5 years; TLE-SD) and 20 TLE patients with long duration of disease (> 5 years; TLE-LD) and 21 healthy controls (HCs, matched with age, sex and education level) were included in this trial. All participants were recruited from the First Affiliated Hospital of Guangxi Medical University and the local community. We performed the diagnosis for TLE following the guidelines of the International Anti-Epilepsy Alliance (27,28). All participants received a comprehensive standard clinical assessment, including detailed medical history investigation, neurological examination, neuropsychological assessment, electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) scanning. We listed detailed demographics and clinical characteristics of all subjects in *Table 1*.

The inclusion criteria for participants were: (I) the symptoms of clinical seizures were shown as the origin of the temporal lobe; (II) EEG showed that epilepsy originated from the origin of the unilateral temporal lobe; (III) participants had no epileptic seizures within the last

Table 1 Demographics, clinical characteristics, and neuropsychological tests of all subjects

Variables	TLE-SD (n=17)	TLE-LD (n=20)	HCs (n=21)	P
Age (years)	32.06±10.03	32.75±9.08	28.24±7.27	0.103 ^c
Sex M/F	3/14	8/12	8/12	0.328 ^a
Education (years)	12.41±3.20	12.25±3.52	13.90±2.43	0.358 ^c
Age of onset (years)	27.88±9.39	21.45±10.01	–	0.053 ^e
Seizure frequency (per month)	4.68±10.88	4.54±7.67	–	0.577 ^d
Monotherapy/polytherapy	9/8	9/11	–	0.746 ^a
Alertness (ms)	43.45±19.67	58.78±29.87	49.32±19.34	0.144 ^b
RT _{no-cue} (ms)	669.05±95.38	704.94±119.53	598.67±64.72	0.003 ^{bΔ}
RT _{double-cue} (ms)	625.59±94.24	646.88±126.83	547.97±55.95	0.002 ^{b*Δ}

Data were represented as the mean ± SD. ^a, P was calculated using the chi-square test; ^b, P was calculated using ANOVA; ^c, P was calculated using the Kruskal-Wallis test; ^d, P was calculated using the Mann-Whitney test; ^e, P was calculated using two independent sample *t*-test; *, post hoc comparison results showed a significant difference between TLE-SD patients and HCs, no difference between TLE-SD and TLE-LD patients; ^Δ, post hoc comparison results showed a significant difference between TLE-LD patients and HCs, no difference between TLE-SD and TLE-LD patients. TLE-SD, temporal lobe epilepsy short duration; TLE-LD, temporal lobe epilepsy long duration; HCs, healthy controls; M, male; F, female; RT, response time.

three months (IV) there was no identifiable lesion in the brain MRI; (V) the duration of the disease > one year; (VI) all participants have been regularly taking anti-epileptic drugs (AEDs).

The exclusion criteria for subjects were: (I) mental illness, alcohol or drug abuse histories; (II) combination with the cognitive-affected diseases including craniocerebral trauma, brain tumors, stroke, intracranial infection, multiple sclerosis, and Alzheimer's diseases; (III) MRI scanning showed abnormalities in other structures except for hippocampal sclerosis; (IV) mini-mental state examination score ≤24; (V) left-handed; (VI) examination could not cooperate; (VII) Patients taking or taking topiramate or barbiturates.

The Ethics Committee of the First Affiliated Hospital of Guangxi Medical University approved this experimental protocol (No. 2020-KY-040). Each participant signed formal written consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Neuropsychological examination of alertness

Attention Network Test (ANT) was used to assess the alertness of each participant, as previously reported (29). This test requires the subject to sit in front of a computer and respond to different visual stimuli composed of cues

and targets via pressing the right buttons. Meanwhile, this test also requires the subject to measure whether the center target arrow is left or right and react fast and accurately via pushing the left or right arrow buttons. Also, there can be a warning showed by an asterisk or no warning before the center target arrow appears. Based on the presence or absence and the position of the asterisk, four kinds of prompt conditions are: (I) no cue (NC), no asterisk appears before the target appears, and only one cross representing the fixed point that exists on the screen; (II) double cues (DC), the asterisk appears above and below the fixed cross; (III) center cue (CC), the asterisk appears in the center of the screen replacing the fixed cross and does not provide any information about the target location; (IV) space cue (SC), an asterisk appears above or below the cross to show where the arrow is about to appear. This test comprised 24 exercises and three sets of trails, each comprising 96 tests, and the entire test time was about 25 minutes. The correct rate and response time (RT) of each subject were recorded using computers. According to Fan's ANT design principle (30), alertness was measured: alertness = RT no cue-RT double cues, and the more significant the difference, the higher the efficiency.

MRI data collection

The 3.0-T scanner (Philips, The Netherlands) was used

to perform MRI, and Rs-fMRI and high-resolution T1-weighted anatomic imaging data were collected from each participant. The rs-fMRI scanning prolonged for 450 seconds, and 225 brain volumes were retrieved. During the scanning, headphones and cushions were used to diminish noise interferences and avoid head movements. The subjects needed to close their eyes, stay awake and relaxed, avoid thinking about anything special, and avoid head movement. And we used a magnetization-prepared rapid gradient echo sequence to collect the high-resolution T1-weighted images in sagittal orientation. Then, we used an axial T2 fluid-attenuated inversion recovery sequence to remove the clinically silent brain lesions. The rs-fMRI parameters were: TR/TE =2,000/30 ms, flip angle =90°, field of view (FOV) =220 mm × 220 mm, image matrix =64×62, slice thickness =3.5 mm, slice gap =0.5 mm, voxel size =3.44 mm × 3.44 mm × 4 mm, 41 slices. The parameters of T1-weighted structural images are: TR/TE = 7.8/3.46 ms, flip angle =9°, FOV =256 mm × 256 mm, image matrix =256×256, slice thickness =2 mm, voxel size =1.0 mm × 1.0 mm × 1.0 mm, 176 slices.

MRI data preprocessing

As previously described (31), we used GRETNA (<http://www.nitrc.org/projects/gretna>) software, which was based on MATLAB R 2013b(The Math Works, Natick, Massachusetts, USA) platform and SPM12(<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) software, to preprocess the retrieved fMRI images, and the steps were: (I) removing the first 10 volumes of rest data to ensure magnetization equilibration; (II) correcting slice time; (III) realigning the remaining images to the mean volume for the correction of head movements; (IV) spatially normalizing the images to the Montreal Neurological Institute (MNI) template via the diffeomorphic anatomical registration using the exponentiated Lie algebra (DARTAL) technique (32); (V) to resample the images at a voxel size of 3×3×3 mm; (VI) spatially smoothing the normalized functional data with full width at half maxima (FWHM) Gaussian kernels of 4 mm; (VII) excluding linear and quadratic trends; (VIII) performing nuisance variable regression through regressing out mean signals for white matter, cerebrospinal fluid and Friston-24 head motion parameters; (IX) Finally, minimizing the influences of low-frequency drift and high-frequency physiological noises by using a band-pass (0.01–0.10 Hz) filter (33). All participants were included with our defined head motion threshold (the translation parameter <2 mm,

the rotational motion parameter <2°).

Establishment of brain networks

GRETNA toolbox was used to set up the functional brain networks comprising nodes and edges. Each node stood for the brain region, and each edge stood for the connection between 2 nodes. The nodes and edges were defined according to the Brainnetome atlas (34). The Brainnetome Atlas is a fine-grained, cross-validated atlas that associates the anatomy of the brain with psychological functions and contains 210 cortical regions and 36 subcortical regions. For graph analysis, ROI was the node in the functional brain network. Then we averaged the fMRI time courses of all voxels in each ROI, and calculated the mean time series.

As previously described, functional parcellation could improve the reliability of the test-retest network (35). In this study, Pearson correlation coefficients between the regional time series of all pairs of brain regions were measured to assess the FC between regions, and then a correlation matrix (246×246) for every participant was derived. The Pearson correlation was not based on local correlation but had a higher retest network reliability (9). Next, each correlation matrix (Pearson correlation coefficient value) was set as a threshold into an undirected binarization matrix with a fixed sparsity (the sparsity threshold: 0.05–0.4; interval = 0.01) (36,37). A set of 246×246 binarization matrices were retrieved from each object using this threshold.

Graph theory analysis

According to the topology method, we used GRETNA software to calculate global and regional network metrics of the brain network. Global network metrics contained the small-world parameters (clustering coefficient, C_p ; characteristic path length, L_p ; normalized clustering coefficient γ , normalized characteristic path length λ , and small-worldness σ) and global network efficiency parameters (global efficiency, E_g , local efficiency, and E_{loc}) (38). The detailed descriptions of the above parameters were: (I) the C_p refers to the possibility of interconnection between neighbors of a node, and its value ranges from 0 to 1. It is a measurement for local network connectivity, and the denser connection, the high C_p ; (II) the L_p is the least number of edges connecting two nodes in network. It is a measurement for global network connectivity, and the shorter distance, the lower L_p ; (III) the γ quantifies the proportion of the C_p in the real network and the random network. The C_p

and the normalized C_p quantify the brain networks; (IV) the λ quantifies the proportion of the L_p between the real network and the random network. The L_p and the normalized L_p represent the functional integration of the brain networks; (V) the σ quantifies the proportion of γ and λ , and it reflects the balance between functional segregation and integration; (VI) the E_g is the reciprocal of L_p , which reflects the average efficiency of the global network and represents the functional integration of the network; (VII) the E_{loc} refers to the information transfer efficiency of a local network formed by a node and all its neighbors, it is the reciprocal of the characteristic path length of the node, which reflects the average efficiency of the local network.

Nodal network metrics comprised BC, degree centrality (DC), and nodal efficiency (N_e). BC is the number of the shortest paths through a node divided by the number of all possible shortest paths through that node. It reflects the contribution of each node to the shortest path between all other point pairs. DC refers to the number of edges directly connected to a node, which reflects the number of neighbors of the node in the network. N_e refers to the inverse of the average of the shortest path length between a node and all other nodes. Reflects the ability of a node to spread information to other nodes in the network. The above 3 nodal parameters were together used to test the centrality of individual nodes in the network (12).

Finally, each network metric was used to calculate the area under the curve (AUC) over the sparsity. The AUC data have a summary scalar value for the topology characteristics of the brain network, regardless of the single threshold for each network. This method can explore the difference between groups of relative network organizations. The difference was sensitive to the changes of topological properties in brain disorders (39,40).

Statistical analysis

We used SPSS 18.0 to analyze the demographic, clinical, and neuropsychological data. For the data with a normal distribution and homogeneity of variance, we used ANOVA or independent samples *t*-test to analyze the difference between groups. If there was a significant difference, then the post hoc analysis was conducted. For the data without a normal distribution or variance, Kruskal-Wallis and Mann-Whitney tests were used. For the qualitative variables, the chi-square test was used. The statistical significance level was set at 0.05.

For network topology metrics, we employed univariate

analysis of covariance (ANCOVA) to compare differences between the three groups, with age, sex, and education level as covariates ($P < 0.05$, corrected with FDR). Paired post hoc *t*-tests were conducted on the metrics that detected the significant differences in ANCOVA. Then, a partial correlation analysis was conducted between the network metrics with differences between groups and alertness. We used GRETNA software for statistical analysis of all network parameters.

Validation analysis

For the graph-based network analysis, the node definition was proved to be an important factor (36,39,41). We further assessed whether the primary findings would be affected by distinct types of network establishment strategies. Segmenting brain regions according to functions could promote the functional homogeneity of voxels within a node and described regional brain activities more accurately (41). These type of templates were more suitable for measuring between-group differences in topological properties of brain functional network (42). Therefore, we use three functional templates, including the Dosenbach template of 160 ROIs (Dosenbach-160) (43), the Craddock template of 200 ROIs (Craddock-200) (44), and the Power template of 264 ROIs (Power-264) (45) to construct the network validating the results. We also used these three templates to calculate the global metrics, and then the statistical analysis was performed. Notably, we did not quantify the nodal metrics since it was challenging to match these nodes across different parcellation schemes because of their different spatial locations and network sizes.

Results

Demographic, clinical, and neuropsychological data

As shown in *Table 1*, the demographic, clinical, and alertness information were summarized and analyzed. The results showed that no differences were found among three groups in age, sex, and education level. Also, no differences in age of onset, seizure frequency, and the Monotherapy/Polytherapy of AEDs between TLE-SD and TLE-LD groups were observed. However, there were significant differences in the RTs of NC and DC among these three groups. Post hoc test showed that no difference between TLE-SD and TLE-LD patients were found, while there were significant differences between TLE-SD or TLE-LD

Table 2 Differences in global properties among TLE-SD and TLE-LD patients and HCs

Network metric	Participants			Group ANOVA P value	Post hoc <i>t</i> -test		
	TLE-SD (n=17)	TLE-LD (n=20)	HCs (n=21)		TLE-SD vs. TLE-LD	TLE-SD vs. HCs	TLE-LD vs. HCs
Gamma (γ)	0.547±0.117	0.625±0.109	0.677±0.072	0.004	n.s.	TLE-SD < HCs	n.s.
Lambda (λ)	0.386±0.016	0.378±0.010	0.377±0.007	0.033	n.s.	n.s.	n.s.
Sigma (σ)	0.494±0.119	0.571±0.105	0.619±0.070	0.004	n.s.	TLE-SD < HCs	n.s.
Cp	0.206±0.010	0.203±0.009	0.204±0.009	0.598	–	–	–
Lp	0.714±0.081	0.671±0.045	0.656±0.021	0.011	n.s.	TLE-SD > HCs	n.s.
Eg	0.185±0.014	0.193±0.007	0.195±0.004	0.006	n.s.	TLE-SD < HCs	n.s.
Eloc	0.263±0.007	0.267±0.004	0.270±0.005	0.006	n.s.	TLE-SD < HCs	n.s.

TLE-SD, temporal lobe epilepsy short duration; TLE-LD, temporal lobe epilepsy long duration; HCs, healthy controls; ANOVA, analysis of variance; n.s., no significance was found.

patients and HCs. Also, the RTs in the TLE group were longer than those in the HCs group.

Global properties of the functional brain networks

It was found that all three groups had small-worldness attributes ($\gamma > 1$, $\lambda \approx 1$, $\sigma > 1$) based on the previous report (46). The ANCOVA test results were shown in *Table 2* and showed that marked differences in Lp, γ , λ , and σ were observed. Also, marked differences in Eg and Eloc were found. The post hoc comparisons showed that the γ , σ , Eg and Eloc were lower, but the Lp was higher in TLE-SD patients than those in HCs (all $P < 0.05$, corrected with FWER). However, there was no difference between the remaining two groups. More detailed data about the global network properties of the TLE-SD and TLE-LD patients and HCs were presented in *Figure 1* and *Table 2*.

The global metric data were expressed as mean \pm SD. ANOVA was conducted to compare the differences, and then post hoc two independent sample *t*-test between 2 groups was performed (using FWE correction), with age, sex, and education level as covariates.

Nodal properties of functional brain networks

ANCOVAs showed that there were marked differences in the right medial pre-frontal thalamus (mPFtha) and the right rostral temporal thalamus (rTtha) between DC and Ne groups (all $P < 0.05$, FDR corrected) (*Figure 2*). Post hoc analysis showed that compared to HCs, the TLE-SD patients showed decreased Ne in the mPFtha and rTtha.

However, no marked differences between the rest of the two pairs were observed, as showed by the post hoc analysis. Also, ANCOVAs did not reveal marked differences in BC.

Correlation between network metrics and alertness

The results (*Table 3* and *Figure 3*) showed a positive correlation between the Lp and alertness in TLE-SD patients. And the Eg and alertness in TLE-SD patients and the Eloc and alertness in TLE-SD patients were negatively correlated.

Besides, Pearson correlation analysis was also performed between the nodal network parameters with significant differences and alertness. The result showed only a negative correlation between alertness and low Ne values for the mPFtha in the TLE-LD group (*Figure 4*).

Validation results

We use three functional templates to construct the network and calculated the global metrics, respectively. When using Dosenbach-160 atlas to construct the network, ANCOVA showed marked differences in Lp, γ , σ , and Eg (all $P < 0.05$; *Table S1*). Post hoc analysis showed that, compared with HCs, TLE-SD patients had lower γ and σ (all $P < 0.05$, corrected with FWER). When using Power-264 atlas to construct the network, we retrieved comparable results (*Table S2*). When using Craddock-200 to construct the network, we retrieved comparable results to the Brainnetome atlas. However, post hoc analysis revealed that apart from the differences between TLE-SD patients and

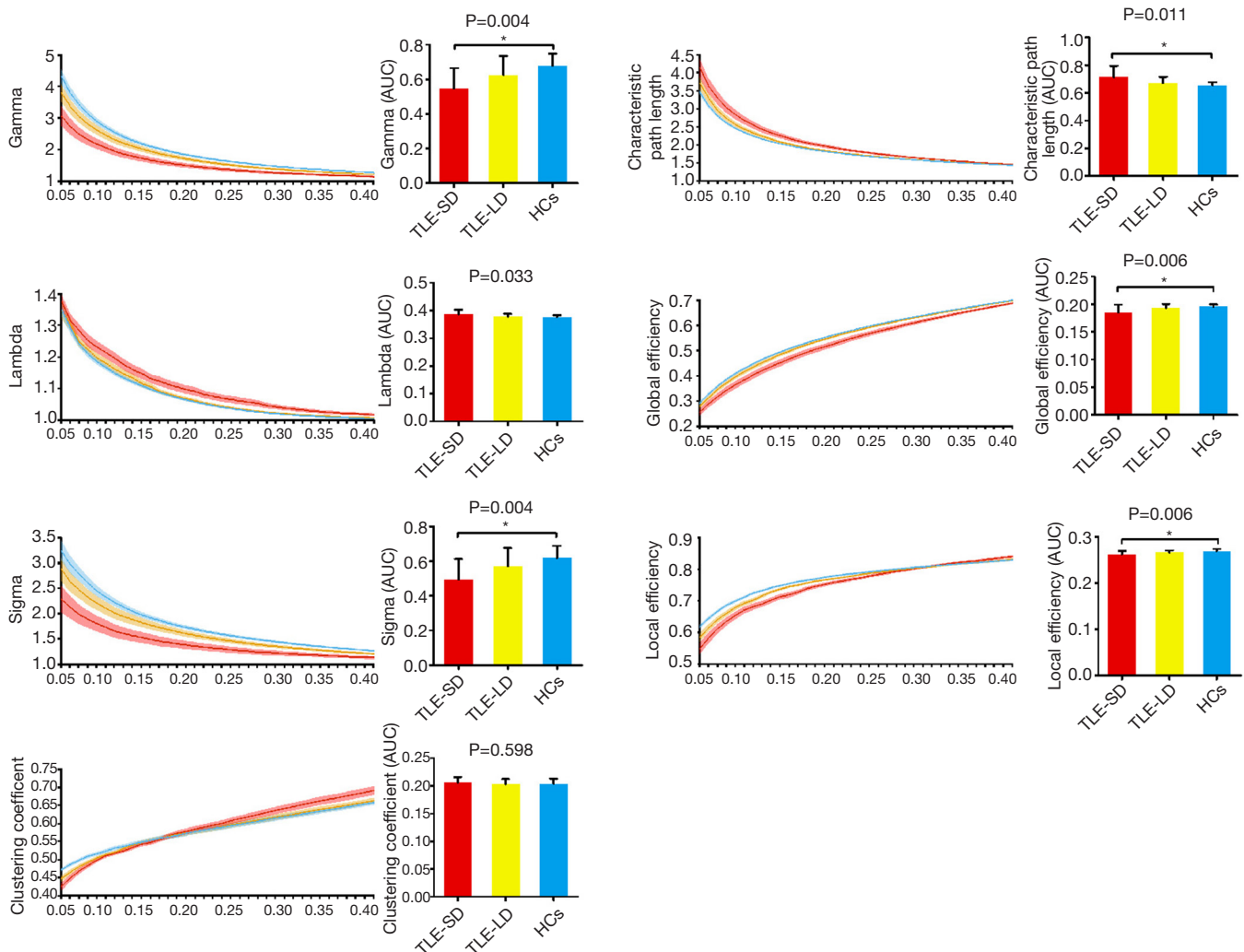


Figure 1 Functional networks in all three groups. Functional brain networks of HCs (blue), TLE-SD (red), and TLE-LD patients (yellow). The left column stood for the sparsity range (0.05–0.4). Straight lines show the average, and the corresponding transparent areas stood for the standard error. The right column is the AUC. *, post hoc *t*-test showed $P < 0.05$, multiple comparisons correction. HCs, healthy controls; TLE-SD, temporal lobe epilepsy short duration; TLE-LD, temporal lobe epilepsy long duration; AUC, area under the curve.

HCs, significant differences between TLE-SD and TLE-LD patients (TLE-SD patients had lower Eloc than TLE-LD patients) (Table S3).

Discussion

In current study, we investigated the topological alterations of functional brain networks in TLE patients with different durations of disease by using graph theory. The results were: (I) small-world characteristics were observed in both TLE patients and HCs; (II) the global-level finding was that the Eg and Eloc of brain functional networks in TLE-

SD patients significantly decreased and tended toward random alterations; (III) the nodal-level finding was that TLE-SD patients had significantly reduced DC and Ne in the mPFtha and the rTtha; (IV) correction analysis showed that alertness was positively related to the Lp but negatively related to the Eg and Eloc in TLE-SD patients; and alertness was negatively correlated with the Ne of mPFtha in TLE-LD patients.

It was also found that the functional brain networks in 3 groups were all characteristic of small-world properties (47). Park *et al.* (48) reported that the duration of epilepsy was negatively correlated with the Eg in focal epilepsy patients.

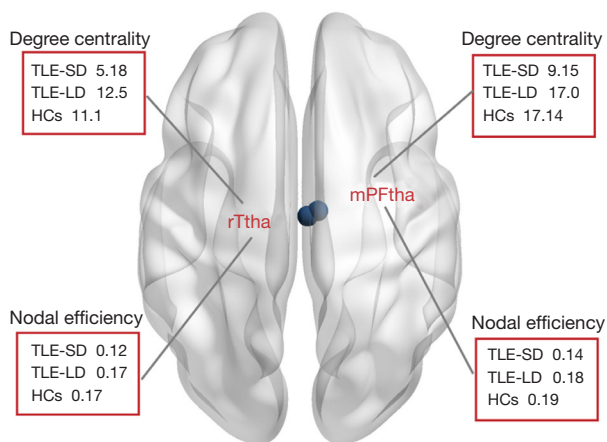


Figure 2 Nodal properties and alertness analysis. The region distribution with differences in DC and Ne, mapped by the BrainNet Viewer toolbox. DC, degree centrality.

Paldino *et al.* (49) found that modularity and, to a lesser extent, path length and Eg were independently related to epilepsy duration in children with focal epilepsy. Our study found that the global topological properties with significant differences among the three groups included Gamma, Lambda, Sigma, Lp, Eg, and Eloc. In previous studies on TLE (50,51), it was found that the topological properties of whole brain functional networks in TLE patients was disrupted, such as the small-worldness, global efficiency and other parameters decreased, and our results were similar. However, post hoc analysis showed a significant difference only between TLE-SD and HCs, while there was no difference between TLE-LD and HCs, which means the functional network of TLE patients has a shorter duration rather than longer duration and is shifting to “randomization”. And the network “randomization” reflects that the local specialization and global integration are reducing. Our previous 2-year longitudinal study on TLE patients (52) found that TLE patients at follow-up showed decreased FC but enhanced amplitude of low-frequency fluctuation (ALFF) compared to HCs at baseline, which suggests that a compensatory reorganization mechanism may exist. Brain compensation represents the ability of the brain to enhance fMRI activity in task-specific networks and to recruit other cortical regions to be beneficial for behavioral performance (53). Many functional neuroimaging reports showed that many patients with neurodegenerative disorders, including Huntington’s disease (54,55), exhibited enhanced fMRI activity and recruited other brain regions to maintain a comparable level of behavioral performance with

HCs. Our results showed that no marked differences in sex, age, education level, onset time, frequency of onset and single/multidrug treatment between TLE-SD and TLE-LD patients were observed, as showed by the demographic and clinical data. Therefore, we hypothesize that as the course of the disease prolongs, the brain will develop a modern compensation mechanism to restore Eg and information processing speed. This process is gradual since the course may be 5 years or more because of individual differences. In addition, for the study on the graph-based brain networks, the definition and selection of nodes are important to construct the functional brain networks. In our research, we use 3 different functional network templates to establish the network and calculate the global topological properties, and the results were consistent with our major results, which further validates the reliability of our results.

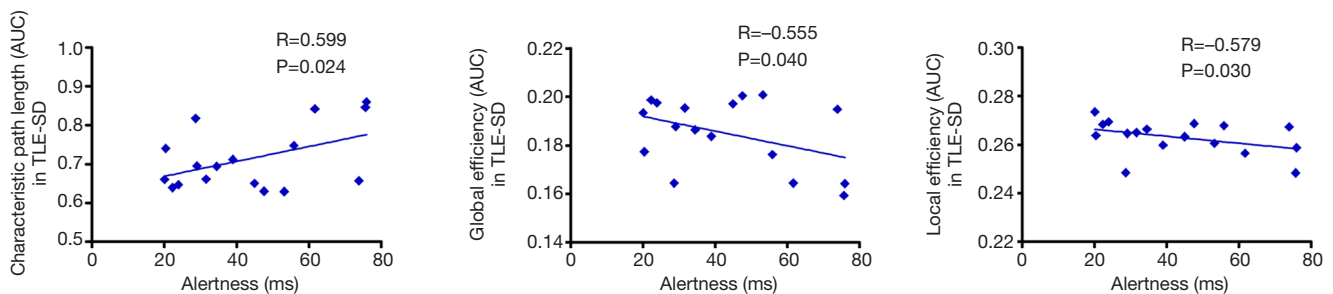
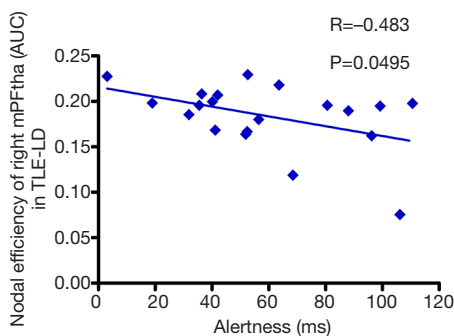
Our study showed that the significantly decreased nodes in DC and Ne were distributed in the right thalamus (mPFtha and rTtha). Kim *et al.* (56) found that the duration of disease and the strength of bilateral pre-frontal cortical thalamus function in patients with idiopathic generalized epilepsy were negatively correlated. Lee *et al.* (57) found thalamic nuclear atrophy in the TLE patients with HS. Morgan *et al.* (58) found that it was susceptible to TLE seizures for the anterior nucleus and pulvinar of the thalamus as subregions. Also, González *et al.* (59) found that patients with TLE showed impaired connectivity in thalamic arousal networks, and these disturbances could partially recover following successful epilepsy surgery. Our findings were like the earlier studies showing that the thalamus and its related networks played a crucial role in TLE progression.

Although our behavioral analysis showed that no significant differences in alertness between TLE-LD or TLE-SD patients and HCs were observed, and the RTs of NC and DC of patients were longer than those of HCs, suggesting that there was a potential impairment in the alertness of TLE patients, and which might be more severe in the TLE-LD patients. After analyzing the correlation between the different functional network characteristics and the alertness of TLE, we observed that in the TLE patients with short duration (<5 years), there was a positive correlation between alertness and the Lp, and a negative correlation between alertness and the Eg and Eloc; and there was a negative correlation between alertness and the Ne of mPFtha in the TLE patients with long duration (>5 years). It appears to be a counterintuitive finding. Dinkelacker *et al.* (60) found a negative correlation between

Table 3 Correlation analysis between global network parameters and alertness

Network metrics	TLE-SD		TLE-LD	
	r	P	r	P
Gamma (γ)	-0.240	0.408	-0.212	0.413
Lambda (λ)	0.510	0.063	0.374	0.140
Sigma (σ)	-0.268	0.355	-0.234	0.367
Lp	0.599	0.023*	0.350	0.168
Eg	-0.555	0.040*	-0.364	0.150
Eloc	-0.579	0.030*	-0.136	0.604

*, represented a significant correlation. Correlation analysis showed a positive correlation between the Lp and alertness in TLE-SD patients, but a negative correlation between the Eloc or EG and alertness in TLE-SD patients. TLE-SD, temporal lobe epilepsy short duration; TLE-LD, temporal lobe epilepsy long duration.

**Figure 3** Significant correlation between global network parameters and alertness. TLE-SD, temporal lobe epilepsy short duration.**Figure 4** Correlation analysis showed a negative correlation between Ne and alertness of left and right medial pre-frontal thalamus in TLE-LD patients. TLE-LD, temporal lobe epilepsy long duration.

the number of hippocampal-thalamus fiber connections in TLE patients and their performance in some executive tasks. Ellmore *et al.* (61) reported that the total number of

fibers in the hippocampus of TLE patients decreased, but the fractional anisotropy increased. Bonilha *et al.* (62) found the limbic circuitry in TLE patients paradoxically increased, as showed by a higher Cp and a more substantial nodal degree of the ipsilateral hippocampus thalamus. Therefore, the reorganization of the limbic system might cause neuropsychological abnormalities in TLE. As for the results of the correlation analysis in our research, it is speculated that as the disease progresses, the global network has been reconstructed, and the alertness might be a function that multiple brain regions concurrently process information, rather than as a single group of neurons or a single neuronal circuit. And thalamus might be a critical region for the alertness networks.

There were some limitations in our study. Our study design limited the ability to show how the brain's functional network dynamically reorganizes as the disease progresses. We also divided the disease into subgroups for five years, which is not strictly in line with reality because the functional reorganization of the brain is a gradual

process and may change at other time points. And further longitudinal studies were needed. Because of the small sample size, TLE patients (such as lateralization of epilepsy areas) were not considered in subgroup analysis.

Further research enrolled more participants were needed to increase the reliability of results and to verify the current results. Many clinical factors, including the dose and type of anti-epileptic drugs, also had the potential influences on our findings. However, it is challenging to remove these factors because drug therapy must be taken to prevent the disease from worsening.

In conclusion, the rs-fMRI and graph theory analysis showed that the functional brain network efficiency of TLE patients decreased and was randomized. And as the disease progressed, compensatory reorganization might occur. Thalamus and its related networks might play a key role in TLE progression. A negative relationship between the alertness (neuropsychological testing) and the disruption of the topological properties of the functional network in TLE patients was observed. Our findings might be beneficial for a better understanding of the potential disease progression neuropathophysiological mechanisms of TLE.

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Footnote

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appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). All protocols were allowed by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (No. 2020-KY-040). Formal written consent was retrieved from every subject.

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