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Abnormal ventral attention network homogeneity in patients with right temporal lobe epilepsy

D.-B. LI[1,2], R.-S. LIU[3], X. WANG[4], P.-A. XIONG[5], H.-W. REN[6], Y.-F. WEI[2], L.-M. ZHANG[1], Y.-J. GAO[7]

[1]Department of Neurology, The First Affiliated Hospital of Harbin Medical University, Harbin, China
[2]First Department of Neurology and Neuroscience Center, Heilongjiang Provincial Hospital, Harbin, China
[3]Department of Neurology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China
[4]Department of Mental Health, Taihe Hospital, Hubei University of Medicine, Shiyan, China
[5]Department of Taihe Hospital Reproductive Medicine Center Affiliated to Hubei University of Medicine, Shiyan, China
[6]Department of Medical Imaging, Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, China
[7]Department of Psychiatry, Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, China

Dongbin Li and Ruoshi Liu contributed equally to this work

Abstract. – OBJECTIVE: The attention network is the structural basis of cognitive function. As one of the two known attention networks, the ventral attention network (VAN) has a significant impact on the cognitive impairment of patients with epilepsy. Nevertheless, changes in network homogeneity (NH) are rarely reported in the VAN of right temporal lobe epilepsy (rTLE) patients. Therefore, we explored the NH of the VAN in rTLE patients in this study.

PATIENTS AND METHODS: Seventy rTLE patients and 69 healthy controls were recruited. All participants underwent resting-state functional magnetic resonance imaging (fMRI), which was the primary method of evaluation. The executive control reaction time (ECRT) was examined via the attentional network test. The Data Processing Assistant for Resting-State fMRI (DPARSF) was used to analyze NH. The independent component analysis (ICA) and correlation analysis were used in data analysis.

RESULTS: Compared to the control group, patients with right temporal lobe epilepsy showed a lower NH in the right superior temporal gyrus, and a longer ECRT. However, abnormal NH values had no significant association with the clinical measurements.

CONCLUSIONS: Patients with right temporal lobe epilepsy have abnormal NH values in the VAN, and the executive functions in rTLE patients are also altered. The altered NH values in VAN may help provide new insights into the pathophysiology of cognitive impairment in rTLE.

Key Words:
Right temporal lobe epilepsy, Ventral attention network, Network homogeneity, Resting-state functional magnetic resonance imaging.

Introduction

Epilepsy is a severe brain condition, characterized by the recurrence of seizures, and results in a massive burden on the healthcare infrastructure and economy[1]. As one of the most common forms of focal epilepsy, temporal lobe epilepsy (TLE) is characterized by cognitive dysfunctions and refractoriness[2]. With the advent of new and widely applied imaging techniques, structural abnormalities in several brain regions of patients with epilepsy have been identified. TLE was confirmed as a condition associated with network-level destruction[3]. Increasing evidence, provided by resting-state functional magnetic resonance imaging studies (fMRI), has also confirmed the presence of neural connections, which were thought to be the most direct approach to functional connectivity among separated regions of the brain at

Corresponding Authors: Liming Zhang, MD; e-mail: zfx001@yahoo.com
Yujun Gao, e-mail: gaoyujun19820214@163.com

rest. Thus, fMRI analysis is the primary method for research into brain networks.

The ventral attention network (VAN) is a resting-state network and an array of brain regions in the right cerebral hemisphere are centered on the temporo-parietal junction (TPJ) and the ventrolateral prefrontal cortex[4]. As one of the two well-known attention networks in the human brain, the VAN modulates bottom-up "exogenous" attention, which directs attention to an unexpected stimulus. When an unexpected event occurs, the VAN activates and generates an "interrupt signal" to break the current focus of attention and reallocate attention to a new spatial location[5]. The VAN has been reported to correlate with cognition, information processing speed, emotion regulation, depression, and anxiety[6-8]. Because of its location, structure, and function, the VAN has been reported to be highly associated with many neuropsychiatric disorders, including Alzheimer's, schizophrenia, and autism spectrum disorder[9-11]. Recent works have found that cognitive impairment and attention deficit are prominent in epileptic patients[12,13], and, as the basis of advanced nervous function, attention function plays an essential role in cognitive processing. Considering the importance of the VAN, which is associated with attention functioning, especially visual-spatial attention[14,15], studies on the action of the VAN in epileptic patients would be important. As a survey method, network homogeneity (NH) was thought to be an ideal parameter with which to assess the connectivity of brain networks in many neuropsychiatric diseases, such as attention-deficit/hyperactivity disorder, schizophrenia, and somatization[16-24]. As a voxel-wise survey, NH correlates with other voxels within a given network, and can be utilized to assess the connectivity of a voxel with the other brain voxels of a predefined network. NH is defined as the average connectivity of any specific time series of a voxel with the time series of every other voxel in the network. With this approach, compromised network homogeneity in brain regions of a specific disease can be identified[17]. As NH combines the advantages of the region-of-interest, seed-based functional connectivity method and the independent component analysis method, it offers an unbiased, hypothesis-driven measure of a given brain network. Thus, group differences can be identified without the need for *a priori* knowledge of where in the network abnormalities might be[16]. However, the VAN homogeneity in patients with rTLE has not been reported. Therefore, we measured the differences in the NH values of the VAN between the rTLE patients and healthy controls and investigated the potential mechanism of impaired attention function of rTLE.

Patients and Methods

Patients

Seventy patients with rTLE were recruited from the Department of Psychiatry, Tianyou Hospital Affiliated to Wuhan University of Science and Technology. Sixty-nine healthy people were recruited from those who underwent a standard physical examination at the medical examination center of the Tianyou Hospital Affiliated to Wuhan University of Science and Technology. Seventy rTLE patients were diagnosed according to the International League Against Epilepsy[25]. The inclusion criteria for the rTLE were as follows (epilepsy patients who met any two of the following symptoms): (1) the clinical onset of symptoms suggested epileptic foci in the temporal lobe, such as psychiatric symptoms, abnormal emotional experiences, automatisms, epigastric rising, or dystonic posturing of the limbs; (2) the interictal electroencephalographic traces suggested abnormality in the right temporal lobe; and (3) the imaging results showed atrophy or sclerosis in the right hippocampus. The exclusion criteria for all subjects were as follows: (1) structural MRI finding identifiable focal abnormalities other than hippocampal sclerosis atrophy; (2) left-handed; (3) any lifetime psychiatric disorder; (4) history of serious medical diseases or other neurological illness; and (5) Mini-Mental State Examination scores ≤ 24. All subjects gave written, informed consent before participating in the study. Our study was performed according to the Declaration of Helsinki and approved by the Medical Ethics Committee of the Tianyou Hospital Affiliated to Wuhan University of Science and Technology.

Behavioral Paradigm

The executive function was assessed by the attentional network test (ANT)[26] "In the center of the testing screen, four cue signals indicating forthcoming target signals consisted of a double asterisk, a central asterisk, an asterisk above or below, and no asterisk. Arrows could appear in one of the following: one target arrow in the center and another four arrows for interference. Two different directions randomly appeared between the central and interfering arrows in congruent or incongruent directions. Participants were required to quickly and correctly determine the target orientation. Reaction time (RT) was then recorded by the ANT software, and by subtracting the consistent arrow direction RT from the inconsistent arrow direction RT, the executive control reaction time (ECRT) was calculated.

The detailed steps which are quoted in this paragraph were excerpted from our previous study[27]. A longer ECRT indicates lower executive function.

Scan Acquisition

An Achieva 3T MRI scanner (Philips, Amsterdam, the Netherlands) was used for the resting-state functional magnetic resonance imaging. "Participants were instructed to lie down with their eyes closed and remain awake. A prototype quadrature birdcage head coil filled with foam padding was used to limit head motion" (excerpted from a previous study[27]). The scanning parameters were as follows: DTI scan: repetition time/echo time (TR/TE) = 2,000/30 ms; 5 mm slice thickness; 1 mm pitch; 24 cm field of view (FOV); and 90◦ flip angles. For the structural scan (T1-weighted), the following parameters were used: spin-echo sequence, TR = 20 ms; TE = 3.5 ms; 1 mm slice thickness; and 24 cm FOV.

Data Preprocessing

The data processing assistant for resting-state fMRI (DPARSF) software[28] in MATLAB (Mathworks) was applied to the imaging data. After signal stabilization, head motion and slice-timing correction were conducted[29,30]. The subjects had a maximal translation ≤ 2 mm in the x, y, or z direction and an angular rotation ≤ 2° on each axis. The functional images were normalized to the standard template in the Montreal Neurological Institute (MNI) template and spatially resampled to a voxel size of 3 mm × 3 mm × 3 mm. The head motion parameters obtained by rigid body correction, the white matter signal, and the cerebrospinal fluid signal were removed from the images by linear regression. The signal was bandpass-filtered (0.01-0.1 Hz) and linearly detrended to reduce high-frequency physiological noise and low-frequency drift. The global signal removal can introduce artifacts into the data and distort resting-state connectivity patterns. In addition, the regression of the global signal may significantly distort results when studying clinical populations. Therefore, the global signal was preserved[31,32] (excerpted from our previous study[27]).

Ventral Attention Network Identification

The GIFT toolbox[32] was used to select VAN as a mask from all participants through the group ICA method. We used three steps from the GIFT toolbox as follows: data reduction; independent component separation; and back reconstruction. When every component was considered, a statistical map was generated and threshold by a voxel-wise, one-sample *t*-test ($p<0.01$ for multiple comparisons corrected via Gaussian random field (GRF) theory; voxel significance: $p<0.01$; and cluster significance: $p<0.01$). Masks were created for the VAN components. Finally, the masks were combined to generate a VAN mask that could be used in the subsequent NH analysis (excerpted from our previous study[27]).

Network Homogeneity Analysis

MATLAB was used for NH analysis[16,17]. "Individual homogeneity maps were generated by calculating the KCC concordance of each time series to those of its 26 nearest neighbors for each voxel. To eliminate any effect of individual differences, the homogeneity of each voxel was converted into a z-score by subtracting the average homogeneity value and dividing the value thus obtained by the standard deviation of the whole-brain homogeneity map, yielding a standard homogeneity value. Finally, the NH maps within the VAN mask were applied for group comparison." The detailed steps that are quoted in this paragraph were excerpted from our previous study[27].

Statistical Analysis

Demographic information, including sex, age, education degree, and imaging data were calculated between the patient and control groups. Continuous variables were analyzed with a two-sample *t*-test, and categorical data were analyzed with a chi-square test by using the IBM SPSS Statistics 22.0 software (IBM, Armonk, NY, USA). To test for regional group differences in NH, voxel-wise two-sample *t*-tests were used, and NH maps were analyzed with an analysis of covariance through voxel-wise, cross-subject statistics in the VAN mask. The significance level was set at the corrected $p<0.01$ for multiple comparisons using the Gaussian Random Field (GRF) theory (GRF corrected, voxel significance: $p<0.001$, cluster significance: $p<0.01$). Pearson correlation tests were performed between NH and clinical variables in the patient group through the IBM SPSS Statistics 22.0 software (IBM, Armonk, NY, USA).

Table I. Characteristics of the participants.

Characteristics	Patients (n = 70)	NC (n = 69)	*p*-value
Gender (male/female)	70 (36/34)	69 (38/31)	0.667[a]
Age, years	27.71 ± 5.78	26.69 ± 5.40	0.281[b]
Years of education, years	12.89 ± 2.62	12.74 ± 2.14	0.718[b]
ECRT	117.11 ± 51.21	67.13 ± 36.81	0.00[b]

[a]The *p*-value for gender distribution was obtained by the chi-square test. [b]The p-values were obtained by two sample *t*-tests. *Abbreviations:* NC, normal control; ECRT, executive control reaction time.

Results

In total, 70 rTLE patients and 69 healthy controls were recruited for the study. The demographic and clinical characteristics of the study subjects are provided in Table I. No significant differences were observed between the two groups regarding age, sex, and years of education. The patient group showed longer ECRT.

VAN Maps as Ascertained by Group ICA

In this study, we selected the VAN masks from the control group via the ICA method. The area involved in the VAN was the right superior temporal gyrus (Figure 1). The VAN was used as a mask in the following NH analysis.

Group Differences of NH in the VAN

The NH values within the VAN masks of patients and controls were compared using the two-sample *t*-test. Compared to the controls, rTLE patients showed lower NH in the right superior temporal gyrus (Figure 2).

Correlation Analyses

To examine the correlations between abnormal NH values and clinical variables, Pearson linear correlation analysis was used in this study. No significant correlations were observed between NH and these clinical variables.

Discussion

In this paper, the NH method was used to survey the VAN in rTLE patients. Compared to the controls, patients with rTLE showed significantly lower NH in the right superior temporal gyrus. The temporal lobe plays an important role in the regulation and transmission of epileptic discharge and was found to be the core area of structure and function in TLE using the brain functional connectivity analysis method. A previous study indicated that internal functional connectivity in the temporal lobe had already changed during the latent and chronic periods of epilepsy[33]. Meanwhile, many functions, including social cognition, language ability, emotion processing, and memory performance, have been proved to be strongly linked to the superior temporal gyrus[34-37]. Furthermore, there is evidence that the impaired superior temporal gyrus affects many brain disorders, including the autism spectrum disorder[38], major depression disorders[39], and obsessive-compulsive disorder[40]. And the superior temporal gyrus was an optimal location for the temporal lobe epilepsy surgical treatment known as the trans-superior temporal gyrus keyhole approach[41].

Attention is a neurocognitive function that selects currently relevant information and ignores

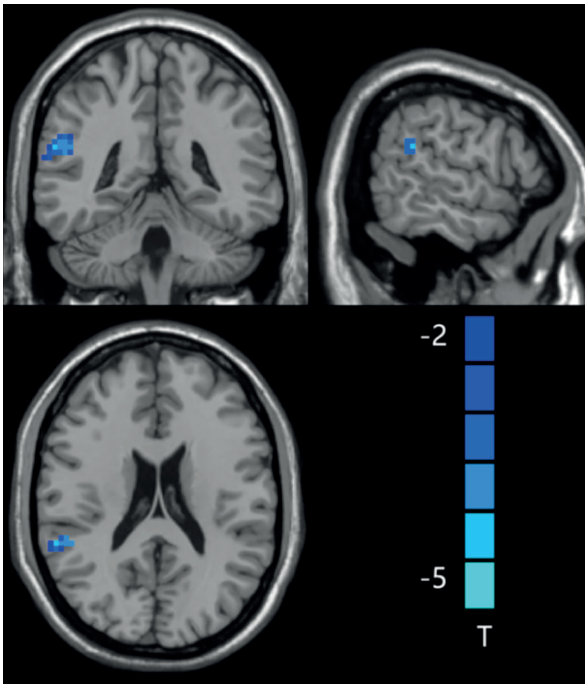

Figure 1. Ventral attention network (based on group-ICA with threshold at z ≥ 5).

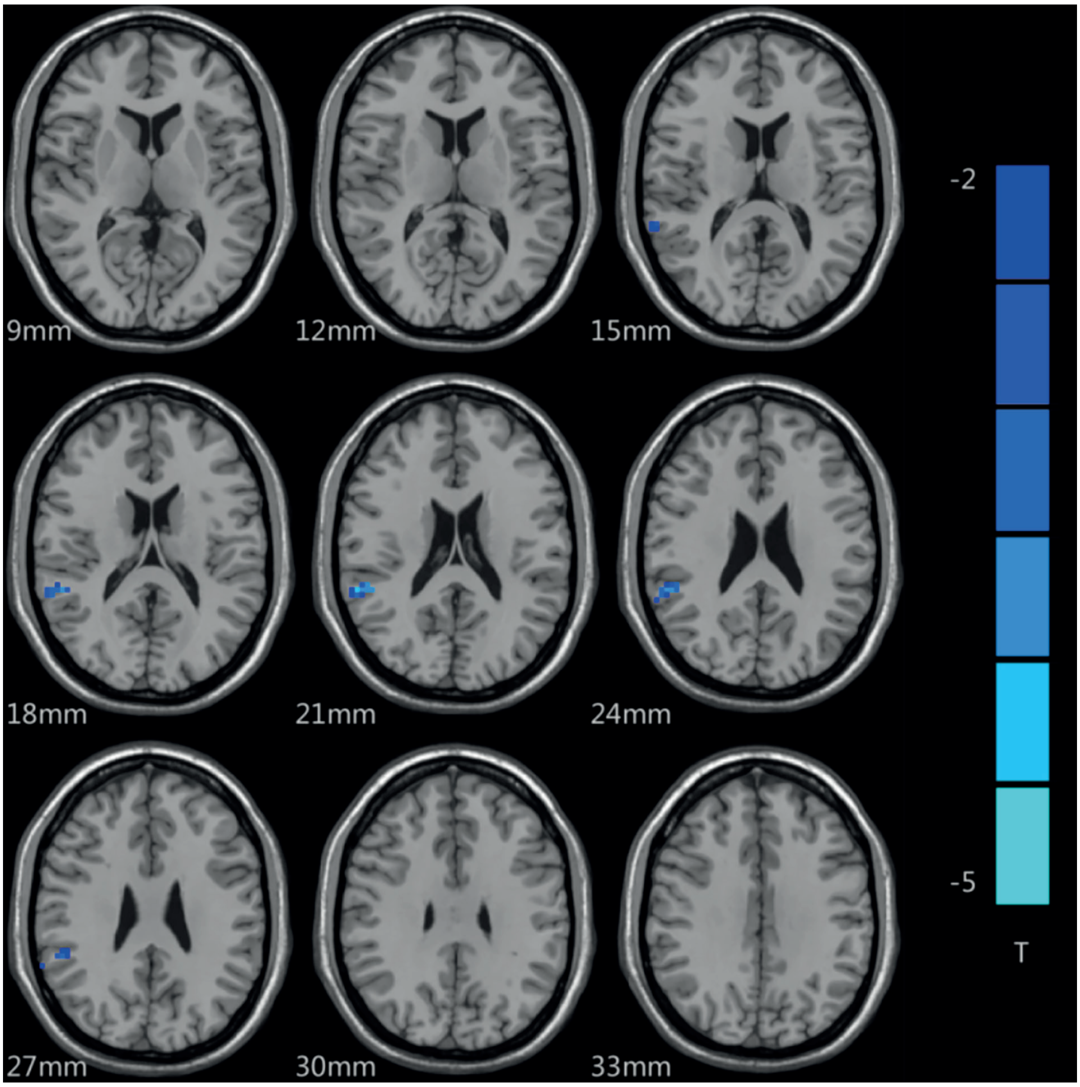

Figure 2. Statistical maps showing NH differences in the right superior temporal gyrus between groups (blue indicates a lower NH and the color bar indicates the T-values from a two-sample *t*-test).

irrelevant information. Two partially segregated attention networks that subserve attention orienting were demonstrated by resting-state fMRI functional connectivity analyses: the ventral attention network (VAN) and the dorsal attention network (DAN)[14]. The DAN was also known as a "visual spatial attention network," comprising the frontal cortex and intraparietal sulcus, and thought to modulate spatial attention and visual movement; more specifically, the DAN modulates voluntary, goal-driven, top-down endogenous signals. The VAN comprises the right TPJ and the right ventrolateral prefrontal cortex, is thought to modulate bottom-up exogenous signals. However, much of the research in attention networks have focused on the dorsal rather than the ventral attention network in the past. Ptak et al[42] observed that the DAN mediates orientation toward behaviorally relevant stimuli in spatial neglect. Cao et al[43] found that the long-range connections within the DAN become more dominant until around the age of ~30 years. Esposito et al[44] found that disruptions to the DAN are associated with mild cognitive impairment. However, recent studies have shown that the VAN plays a special, valuable, and irreplaceable role in the attention network[6,8,45].

The NH is a novel method that combines the advantages of independent component analysis and the region-of-interest, seed-based functional connectivity. Thus, it offers an unbiased, hypothesis-driven measure for a given brain network that is associated with a pathophysiologic process or a specific disorder. A higher NH value means stronger resting-state functional connectivity, and *vice versa*, the functional connectivity decreases. Previously, we examined the NH of a default-mode network in patients with rTLE, and found decreased NH in the right middle temporal gyrus and increased NH in the bilateral posterior cingulate cortex[27]. However, only a small fraction of the VAN, the right superior temporal gyrus, showed abnormal NH values in the present study. We hypothesize that the decreased NH in the superior temporal gyrus is caused by its unique anatomic position. As part of the VAN, the TPJ becomes included more and more in cognitive neuroscience studies; however, the TPJ does not, in fact, map accurately onto any specific anatomical features[46]. It is well known that the superior temporal gyrus, which is located at the junction of the temporal and parietal gyrus, and adjacent to the frontal lobe, should be the core of the VAN. And the inner side of the temporal lobe is the hippocampus, the most widely studied brain structure in epilepsy. Hence, the decreased NH of the superior temporal gyrus best represents the alterations of the VAN in patients with rTLE. To our knowledge, this is the first report of abnormal NH in the VAN with right temporal lobe epilepsy, which could enhance the understanding of the pathophysiology of rTLE.

Previous research had found that the VAN is a right-lateralized ventral cortical network and is associated with attention functions[14]. By altering the bottom-up, stimulus-driven attentional controls, the VAN participates in information processing[8]. In addition, during the target task, the VAN plays a pivotal role in maintaining sustained attention[41]. Attention is a central theme in advanced cognitive functions, which comprise memory, language, and executive functions[47,48]. Epilepsy patients usually display cognitional impairment and longer executive control reaction time[27,48]. The parameter ECRT is based on the ANT test[26], which has been also utilized in other research, such as obsessive-compulsive disorder and movement disorder[49,50]. Since the execution functions are reported to be associated with the activated VAN in the right superior temporal gyrus and the parameter ECRT indicates the efficiency of the prompt executive control network[51], we supposed that there were correlations between abnormal NH values and clinical variables (i.e., illness severity and ECRT). Although longer ECRTs were observed in the rTLE patients compared to healthy controls, it was unexpected that no correlations were found between these factors in our study. The possible explanation for this phenomenon is that abnormal NH is a trait alteration for rTLE independently of seizure severity. In the present study, all rTLE patients had received 1-2 weeks of normal anti-epileptic drug therapy before resting-state fMRI, and all the patients have not recurred anymore. Thus, despite the fact that antiepileptic drugs may have effects on functional networks, the drug impact is minimal.

There are several limitations to the study: (1) physiological noise could not be removed thoroughly; (2) the sample size was relatively small; and (3) we focused only on abnormalities of the VAN in rTLE, and, although illuminating the pathophysiological contribution of the VAN is instrumental, other significant brain networks may be neglected.

Conclusions

Our study is the first to examine the network homogeneity of the VAN in patients with rTLE. The results suggested that decreased homogeneity in the VAN may be involved in the pathophysiology of rTLE, and thus, highlight the attention network contribution to the pathophysiology of rTLE.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

Informed consent was obtained from all individual participants included in the study.

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