



Regional and remote connectivity patterns in focal extratemporal lobe epilepsy

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Background: Focal epilepsy accounts for most epilepsy cases, and frontal lobe epilepsy (FLE) accounts for the largest proportion of cases of extratemporal epilepsy syndrome. The epileptogenic zone is usually not easy to locate, contributing to a lack of imaging studies. The objective of this study was to evaluate functional connectivity patterns to explore the underlying pathological mechanisms of this disorder.

Methods: Forty-three patients with focal extratemporal epilepsy [mean age \pm standard deviation (SD): 29.51 \pm 8.04 years, 19 males] and the same number of healthy controls (mean age \pm SD: 29.56 \pm 8.02 years, 19 males) were recruited to undergo functional magnetic resonance imaging. Mean regional homogeneity (ReHo) was measured, and regions showing significant alterations in ReHo in patients were identified to examine functional connectivity (FC). In particular, FC within the default mode network (DMN) in patients was analyzed.

Results: Patients with extratemporal lobe epilepsy showed significantly higher ReHo in the bilateral precentral gyrus, and lower ReHo in frontal-cerebellum regions than healthy controls [$P < 0.05$, Gaussian random field (GRF)-corrected]. FC analysis based on regions of interest showed significantly higher connectivity in the frontoparietal-insula region and lowered FC in the frontal-cerebellum regions ($P < 0.05$, GRF-corrected). Altered FC within DMN was also demonstrated ($P < 0.05$, GRF-corrected).

Conclusions: Analyses of ReHo and FC based on regions of interest suggest epilepsy-related neural networks are located mainly in frontal regions in extratemporal lobe epilepsy. These findings reveal disruptions of interactions and connectivity of large-scale neural networks and frontotemporal-cerebellar regions, suggesting connectivity-based pathophysiology.

Keywords: Extratemporal lobe epilepsy; focal cortical dysplasia (FCD); regional homogeneity; functional connectivity; default mode network (DMN)

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Introduction

Epilepsy is a common disorder marked by seizures stemming from abnormal electrical activity due to genetic or acquired causes. Focal epilepsy is a major type of epilepsy that is more common than generalized epilepsy and may lead to drug resistant epilepsy (1,2). Although focal epilepsy was originally thought to arise in local regions, the disorder has been shown to involve widespread network alterations (3). Recent studies suggest that epileptogenesis in focal epilepsy results from alteration of the functional network rather than a specific region (4). Therefore, further evaluations of intrinsic neural activity and epileptic networks are increasingly important to understand the neuropathological mechanisms underlying focal epilepsy.

The development and propagation of epileptic seizures can alter structural integrity and disturb connections between structures, resulting in large-scale network instability (5,6). Functional magnetic resonance imaging (fMRI) is a non-invasive, convenient approach to assess neural activity and epileptic networks in epilepsy patients (7). Alterations of connections related to the epileptogenic zone and remote functional networks have been implicated (8,9). While the association between connectivity and clinical features, including epilepsy duration and seizure frequency, suggests progressive reorganization of connectivity over time, this remains poorly explored in focal extratemporal lobe epilepsy because neuroimaging studies of focal epilepsy have focused on abnormal connectivity in temporal lobe epilepsy (TLE) (10,11).

Although epilepsy is considered a disorder of neural networks, focal epilepsy is a much more widespread brain disease. Frontal lobe epilepsy (FLE) is a representative syndrome of extratemporal lobe epilepsy (12), which usually manifests as brief seizures. It is not easy to diagnose and accurately localize the epileptic region based only on clinical symptoms and an electroencephalogram (EEG) since imaging results are often negative for these patients. An EEG-fMRI study detected activation or deactivation of multiple brain regions during heterogeneous inter-ictal epileptiform discharges in FLE (13). Focal cortical dysplasia (FCD) is a frequent hidden cause of MRI-negative epilepsy (14,15), particularly among patients with extratemporal lobe epilepsy or FLE (16). Fewer imaging studies have been carried out on patients with FLE than on patients with TLE, and system-wide analyses of FLE are lacking. By characterizing the brain as a complex and interconnected system, we can holistically map the network-level

dysfunction underlying extratemporal lobe epilepsy (17).

Regional homogeneity (ReHo) is a metric widely employed to assess synchronization during time series, reflecting local similarity between neuronal regions. Altered values of ReHo suggest aberrant connectivity. The intrinsic activity and altered assemblies of neuronal regions may contribute to epileptogenesis in focal epilepsy. The properties of local spontaneous activity and remote functional connectivity in extratemporal lobe epilepsy have not been adequately investigated, hindering the elucidation of hubs in epilepsy-related neural networks. This is particularly important for understanding focal epilepsy, where increasing evidence suggests aberrant connections within hubs of the default mode network (DMN). Therefore, a comprehensive characterization of the functional connectivity patterns is needed to explore the underlying pathological mechanism of this disorder. Here we employed fMRI to study the ReHo and region of interest (ROI)-based functional connectivity (FC) of epilepsy patients.

We present the following article in accordance with the MDAR reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-1374>).

Methods

Subjects and clinical assessment

This study included 43 patients with extratemporal lobe epilepsy (19 males) who attended the Comprehensive Epilepsy Center of West China Hospital, Sichuan University (Chengdu, Sichuan province) for presurgical evaluation during Jul. 2017 and Nov. 2019. In addition, 43 age- and sex-matched healthy subjects (19 males) were enrolled.

Patients with extratemporal epilepsy were diagnosed based on the 1989 International League against Epilepsy (ILAE) classification of epileptic syndromes (18). Refractory epilepsy was defined as ongoing seizures (failure of sustained seizure freedom) after using two kinds of appropriate and tolerated antiepileptic drugs, either as monotherapies or in combination (19). Frequencies of seizure attacks were classified as yearly (1–10/year), monthly (1–10/month), or daily (1–10/day). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consent was signed by each subject. The study protocol was approved by the Ethics Committee of West China Hospital (No. 2019: 372).

Inclusion criteria: The manifestation of MRI is FCD

or negative; epilepsy patients; the semiology, video-EEG, and positron emission tomography (PET) suggest the extratemporal lobe as the focal origin. Exclusion criteria: Structural alteration additional to FCD including other malformations of cortical development, ganglioglioma, hippocampal sclerosis, tumor and brain injury, and pregnant women.

MRI data acquisition

Functional and structural MRI datasets were obtained at West China Hospital using a 3.0 T Siemens (Tim Trio) MRI. The resting state fMRI sensitized to alterations in BOLD signal were obtained by echo-planar imaging (EPI) sequence using the following parameters: TR 2,000 ms, echo time 30 ms, flip angle 90°, slice with no slice gap and thickness of 5 mm, the field of view 240×240 mm², voxel size 3.75×3.75×5 mm³, with 30 axial slices and 200 volumes. Additionally, high-resolution brain structural images were acquired using a three-dimensional T1-weighted rapid gradient echo in axial orientation, and the parameters were TR 1,900 ms, TE 2.26 ms, FOV 256×256 mm², flip angle 90°, matrix 512×512, slice thickness 1mm, number of slices 176, and acquisition time 6.4 min. Each subject was instructed to relax their mind and body during data collection, close their eyes, and not think anything in particular. Head motion was minimized by foam padding, and scanning noise was reduced by earplugs.

Data reconstruction and processing

Preprocessing

Functional image preprocessing was carried out using SPM12 software (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12>) and DPRSFA V4.4 (<http://rfmri.org/DPARSF>). The following steps were performed: (I) removal of the first 10 time points; (II) slice timing correction; (III) head motion correction, which saw datasets with head motion exceeding 3 mm in translation and 3° in rotation excluded; (IV) spatial normalization. The individual T1 image was co-registered to the mean functional image, and the co-registered T1 image was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using a unified segmentation algorithm. The co-registered functional images were then normalized into Montreal Neurologic Institute (MNI) space and resampled to 3×3×3 mm³ resolution; (V) detrend; (VI) covariates regressed including the Friston-24 head motion parameters,

WM signal, and CSF signal, and adding the mean of the time series back; (VII) band-pass filter (0.01–0.08 Hz) was applied; (VIII) all post-processing images were smoothed with a Gaussian kernel of 4 mm FWHM.

ReHo calculation

ReHo was calculated for each voxel based on Kendall's coefficient of concordance (KCC) between that voxel and the 27 nearest neighbor voxels. ReHo for each voxel was normalized by dividing by the mean across all voxels in the entire brain. Band-pass filtering was not performed in preprocessing.

Functional connectivity (FC) analysis

The left medial Superior Frontal Gyrus (mSFG) was defined in the Montreal Neurological Institute (MNI) space and used as a seed in the FC analysis. We computed the mean time course of the seed as a reference to establish a correlation with the time courses of all voxels of the brain. A Fisher z-transformation was applied to all correlation maps to improve normality.

Functional connectivity (FC) within DMN calculation

To evaluate functional connectivity within DMN, 11 DMN nodes were defined as follows: a1 (−6, 52, −2), a2 (−8, −56, 26), a3 (0, 52, 26), a4 (−54, −54, 28), a5 (−60, −24, −18), a6 (−50, 14, −40), a7 (0, 26, −18), a8 (−44, −74, 32), a9 (−14, −52, 8), a10 (−28, −40, −12), and a11 (−22, −20, −26). Pearson's correlation was then applied between the time series of each voxel and all voxels in whole brain, then Pearson's correlation coefficients were converted to z scores using Fisher's r-to-z transformation to obtain zFC. Finally, szFC maps were obtained by smoothing with a Gaussian kernel of 4 mm FWHM.

Statistical analysis

Two sample *t*-tests were performed to compare the group differences between HCs and patients in szFC by using DPABI V4.0 software (<http://www.rfmri.org/dpabi>). In the case of ReHo, the statistical threshold of multiple comparisons was set at $P < 0.001$ at voxel level and $P < 0.05$ at the cluster level, where cluster size > 18 voxels and *P* values were two-tailed and Gaussian random field theory (GRF)-corrected. FC differences between healthy controls and patients were assessed using DPABI software and the two-sample *t*-test. The significance threshold was defined as $P < 0.001$ at the voxel level and $P < 0.05$ at the cluster level,

Table 1 Clinical features of extratemporal lobe epilepsy patients and HCs

Clinical features	Patients (n=43)	HCs (n=43)	P value
Age (years)	29.51±8.04	29.56±8.02	0.9786
Sex (male/female)	19/24	19/24	1.0000
Education years	10.28±3.20	11.28±2.61	0.1153
MMSE scores	27.67±0.87	27.95±0.78	0.1211
Onset age (years)	17.21±9.19	–	–
Duration (years)	12.29±6.53	–	–
Frequency (daily/monthly/yearly)	3/27/13	–	–
Seizure type (focal-only/sGTCS)	27/16	–	–
Medication (mono/duo/poly-therapy)	14/26/3	–	–
Semiology (frontal/frontal-parietal/occipital)	37/5/1	–	–
FCD lesion on MRI	11	–	–
FCD location (frontal/parietal)	10/1	–	–

HCs, healthy controls; sGTCS, secondarily generalized tonic-clonic seizures; MMSE, mini-mental state examination; FCD, focal cortical dysplasia; MRI, magnetic resonance imaging.

where P values were GRF-corrected. The threshold of resultant T-maps of szFC were defined as $P < 0.05$ at the voxel level and $P < 0.05$ at the cluster level (GRF-corrected).

Results

Subject characteristics

A total of 43 extratemporal epilepsy subjects were enrolled in this study (19 males, mean \pm SD, 29.51±8.04 years), with a mean age at seizure onset of 17.21±9.19 years. All included patients were defined as drug-resistant epilepsy based on the definition listed above. Most patients (30/43) had at least monthly seizures despite receiving two kinds of antiepileptic strategies (Table 1).

In this extratemporal epilepsy cohort, 11 patients showed specific imaging characteristics of FCD; with 10 in the frontal lobe and one in the parietal lobe. While most remaining patients were MRI-negative, we speculate they had subtle lesions because semiology, video-EEG, and PET suggested a focal origin in the frontal lobe (37 patients) or frontal-parietal lobe (6 patients).

Disrupted intrinsic activity

The patient group showed higher ReHo in the bilateral precentral gyrus and lower ReHo in frontal-cerebellum

regions (Table 2 and Figure 1).

ROI-based functional connectivity analysis

None of the regions where ReHo was significantly altered correlated with clinical features such as epilepsy duration or seizure frequency. We used the left medial Superior Frontal Gyrus (mSFG) as a seed for more detailed analysis. This region was the largest to show altered ReHo and is a critical hub in the DMN and in extratemporal lobe epilepsy. Patients showed significantly higher FC in frontoparietal-insula regions but significantly lower FC in frontal-cerebellum regions (Figure 2, Table 3).

FC within DMN

FC within the DMN differed significantly between groups of patients and healthy controls (Figure 3).

Discussion

The present study provides evidence of the presence of specific functional alterations in extratemporal epilepsy. We applied one of the most used MRI metrics, ReHo, to assess synchronicity of local intrinsic activity and detected higher ReHo in the bilateral precentral gyrus but lower ReHo in the mSFG and MFG of patients compared to

Table 2 Regions showing abnormal ReHo in extratemporal lobe epilepsy patients compared with HCs

Brain regions	Peak MNI coordinates			Voxel size	T
	X	Y	Z		
Regions with higher ReHo in patients relative to HCS					
Precentral_R	33	-15	60	84	5.19
Precentral_L	-33	-15	60	18	5.19
Regions with lower ReHo in patients relative to HCS					
Frontal_Sup_Medial_L	-6	54	12	87	-4.59
Cerebellum_Crus2_L	-21	-78	-33	83	-5.01
Frontal_Mid_R	45	48	18	23	-4.76
Fusiform_L	-30	-63	-9	18	-4.22

ReHo, regional homogeneity; MNI, montreal neurological institute; HCs, healthy controls; Precentral_R, right Precentral gyrus; Precentral_L, left Precentral gyrus; Frontal_Sup_Medial_L, left medial Superior frontal gyrus; Frontal_Mid_R, right Middle frontal gyrus; Fusiform_L, left Fusiform gyrus; Cerebellum_Crus2_L, left Inferior Cerebellum.

controls. When ROIs were defined based on the mSFG, we observed higher remote FC in the frontoparietal-insula regions but lower remote FC in the frontal-cerebellum region of patients. These results demonstrate that patients with extratemporal lobe epilepsy have remote functional alterations that may potentially affect the entire brain and further demonstrate that BOLD metrics may be useful for characterizing these alterations.

Epilepsy is a complicated disorder of altered neural networks. Different epilepsy syndromes are related to widespread disruption of neural networks, which has been linked to focal epileptic discharges. Further, diverse changes in neural network connectivity have also been described in response to various treatments in focal epilepsy. Studies have identified regions showing altered connectivity between patients with well-controlled epilepsy and those with treatment-resistant epilepsy (20,21). In this study, all included patients were medically refractory.

Even though focal epilepsy was originally thought to originate in specific locations within one hemisphere, the disease is increasingly considered to involve widely distributed epileptic networks (22). Consistent with this concept, studies have observed complex associations among intrinsic activity, structural pathology, and network-level or whole-brain connectivity in focal epilepsy (23). For example, fMRI has revealed aberrant connections between frontal regions and wider brain zones (parietal-temporal-cerebellum regions) in FLE (24), and abnormal functional connectivity in FLE appears to be widespread within the

frontal regions (25).

ReHo has been widely recognized as a metric for measuring an intrinsic neural activity and detecting similarities in activity between different regions that may form part of an epileptogenic zone. The abnormal ReHo in the precentral gyrus is also in line with clinical hyper motor features. Our findings support the idea that seizures in FLE originate in sensorimotor regions extending across the cerebellum and frontal lobe regions. FLE patients were previously reported to exhibit impaired structural and effective connectivity involving the frontal and cerebellum regions (26). Another FLE study (27) using a novel metric of FOCA to measure the spatiotemporal consistency of adjacent local activity demonstrated higher FOCA in the left precentral gyrus yet lower FOCA in the cerebellum and precuneus. The FOCA findings are consistent with our results here to a large extent, but some differences may reflect that ReHo focuses on regional functional synchronization. At the same time, FOCA is more sensitive to local spatiotemporal consistency and the stability of activity states. Many studies have implicated altered synchronization and stability of intrinsic activity in extratemporal lobe epilepsy.

We observed significantly higher FC in the frontal-insula regions of the patient group but lowered FC in the cerebellum. Most of our patients were considered to have FLE based on evaluating their epileptic features, ictal EEG, and metabolic examinations. Previous research has linked alterations in frontoparietal-insula regions, and

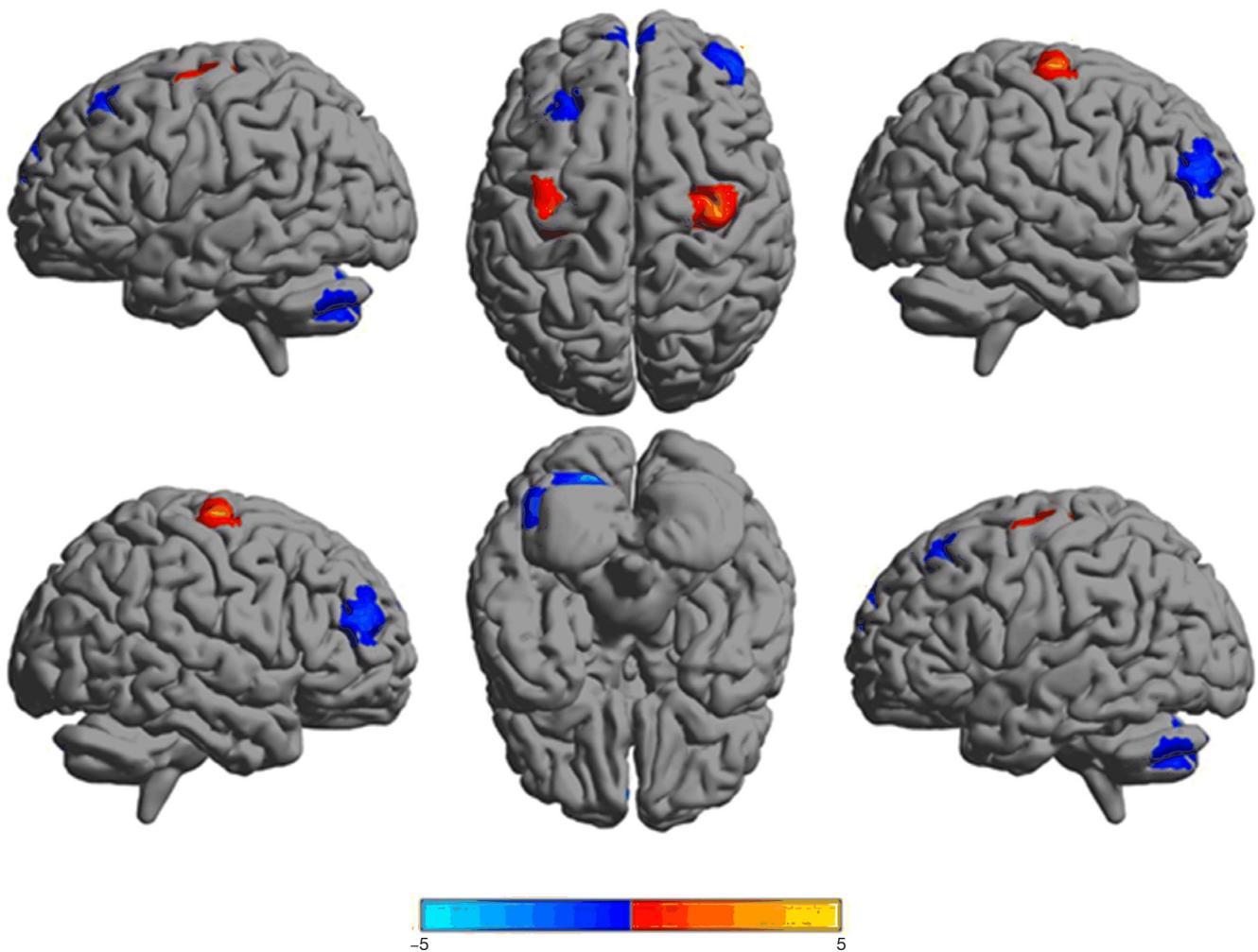


Figure 1 Brain regions showing significant differences in regional homogeneity (ReHo) between patients with extratemporal lobe epilepsy and healthy controls. The patient group showed higher ReHo in the bilateral precentral gyrus, but lower ReHo in frontal-cerebellum regions. Color bars indicate T values, where red indicates higher connectivity and blue indicates lower connectivity. ReHo was compared between brain regions using two-sample *t*-test, and differences associated with $P < 0.05$ (Gaussian random field-corrected) were considered significant.

the cerebellum to the altered FC in epilepsy, and patients with nocturnal FLE were reported to have higher uptake in frontal regions based on PET (28,29). A dynamic FC study of FLE patients revealed significantly disturbed communication of the frontoparietal system (30), and frontoparietal circuits are also involved in the cortical motor system (31). Our observation of abnormal interregional FC suggests the remote neural network is altered in extratemporal lobe epilepsy. The involvement of these brain regions is consistent with the semiology of hyper motor activity and dystonic posture during seizures, which

may also be related to epileptic discharges and impaired cognition.

FLE usually manifests as a bilateral asymmetric tonic or hyper motor activity, as observed in our patients, and this may reflect impairment in both the cerebellum and frontal lobe (26). The DMN is a well-characterized epilepsy-related network (32), and abnormal FC within the DMN is an indicator of impaired network integrity associated with treatment resistance and cognitive decline. A study of patients with idiopathic generalized epilepsy (IGE) showed reduced DMN connectivity, and drug-resistant

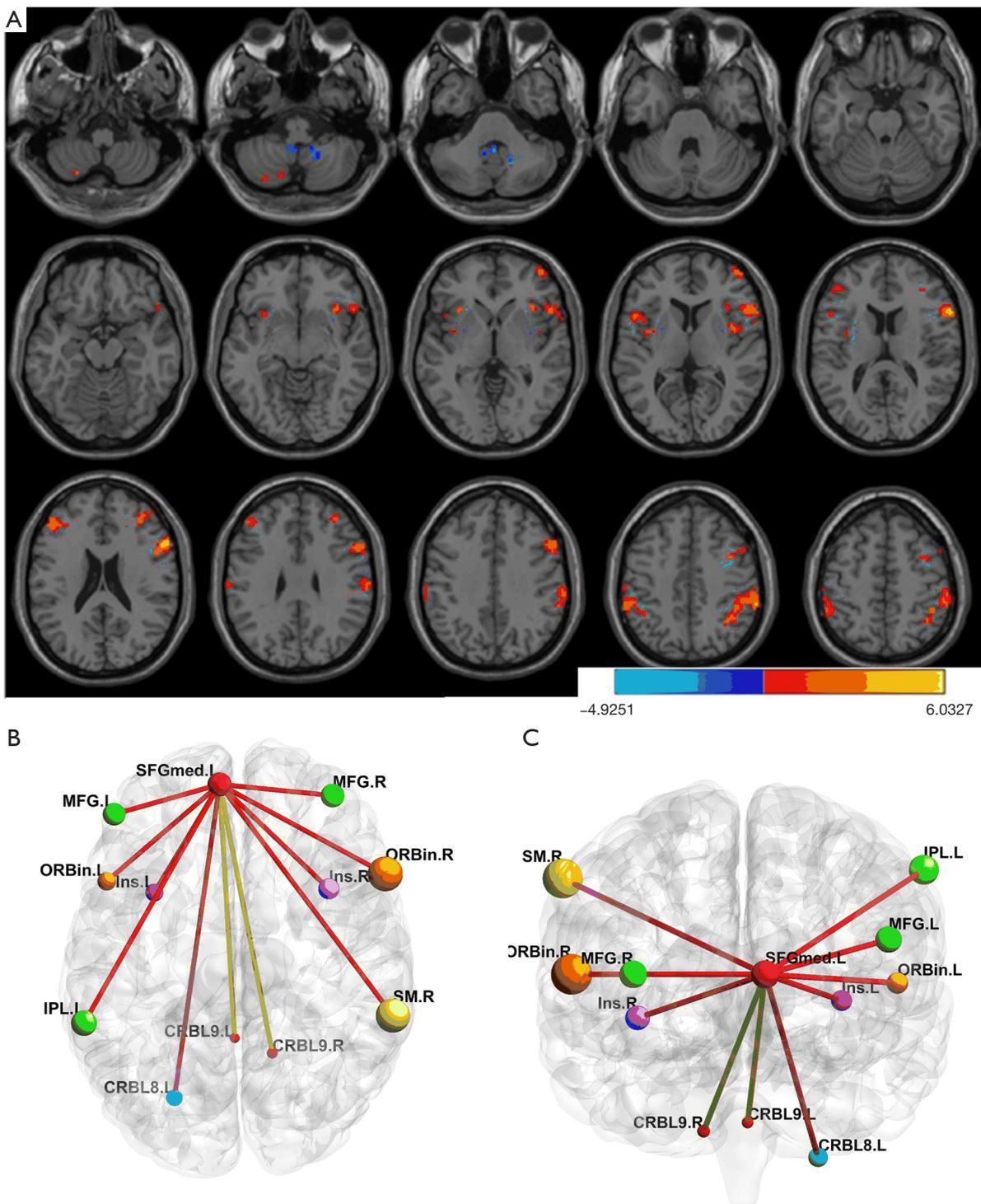


Figure 2 Altered FC involving the mSFG between patients with extratemporal lobe epilepsy and healthy controls. Patients showed significantly higher FC in frontoparietal-insula regions but significantly lower FC in the frontal-cerebellum regions. (A) Axial imaging of FC alterations. Color bars reflect T values. (B,C) Three-dimensional reconstruction of FC alterations. Red indicates higher connectivity and yellow indicates lower connectivity. Two-sample t -test (GRF-corrected) has been performed and $P < 0.05$ was considered statistically significant. mSFG, medial superior frontal gyrus; FC, functional connectivity; GRF, Gaussian random field.

Table 3 Regions showing abnormal interregional FC in the patient group compared with HCs

Seed	Connected area	Peak MNI coordinates			Voxel size	T
		X	Y	Z		
Regions with higher FC in patients relative to HCS						
Frontal_Sup_Medial_L	Frontal_Inf_Oper_R	60	18	12	288	6.03
	SupraMarginal_R	63	-39	45	263	5.11
	Parietal_Inf_L	-60	-42	48	103	4.85
	Frontal_Mid_L	-48	42	24	73	4.39
	Frontal_Mid_R	36	42	21	48	4.56
	Frontal_Inf_Oper_L	-51	15	9	46	5.09
	Cerebelum_8_L	-24	-72	-51	38	4.59
	Insula_R	36	21	-9	34	4.43
	Frontal_Mid_R	42	57	3	34	4.63
Regions with lower FCS in patients relative to HCS						
Frontal_Sup_Medial_L	Cerebelum_9_R	15	-54	-42	20	-4.93
	Cerebelum_9_L	0	-48	-39	18	4.31

FC, functional connectivity; HCs, healthy controls; MNI, Montreal Neurological Institute; L, left; R, right; Frontal_Sup_Medial_L, left medial Superior frontal gyrus; Frontal_Inf_Oper_R, right inferior frontal gyrus, opercular part; SupraMarginal_R, right Supramarginal gyrus; Parietal_Inf_L, left Inferior parietal gyrus; Frontal_Mid_L, left Middle frontal gyrus; Frontal_Mid_R, right Middle frontal gyrus; Frontal_Inf_Oper_L, left Inferior frontal gyrus, opercular part; Insula_R, right Insula; Frontal_Mid_R, right Middle frontal gyrus; Cerebelum_8_L, left Inferior Cerebellum; Cerebelum_9_R, right Inferior Cerebellum; Cerebelum_9_L, left Inferior Cerebellum.

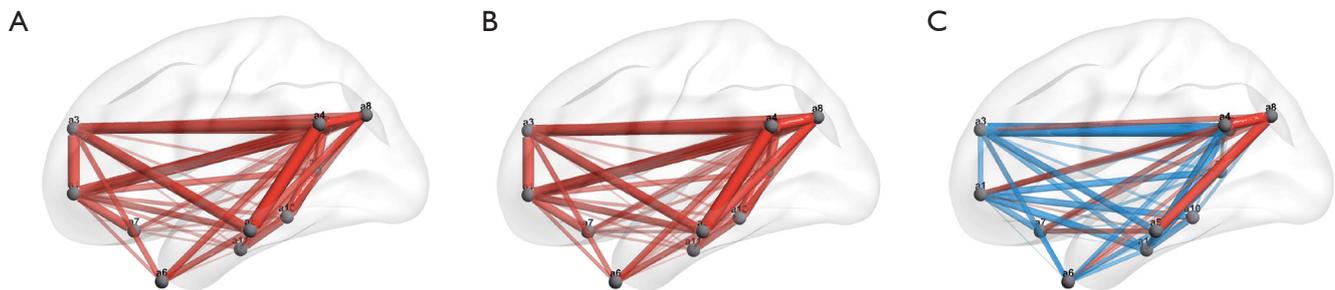


Figure 3 Alterations in functional connectivity in regions of interest (ROIs) (a1-a11) within the default mode network (DMN). (A) Connectivity within the DMN in patients. (B) Connectivity within the DMN in healthy controls. (C) Differences in connectivity between patients and healthy controls. Red indicates higher connectivity in patients and blue indicates lower connectivity. *ROI descriptions*: L: Left; a1. Frontal_Med_Orb_L (Superior frontal gyrus, medial orbital), a2. Precuneus_L (Precentral gyrus), a3. Frontal_Sup_Medial_L (Superior frontal gyrus, medial), a4. Angular_L (Angular gyrus), a5. Temporal_Inf_L (Inferior temporal gyrus), a6. Temporal_Pole_Mid_L (Temporal pole: middle temporal gyrus), a7. Rectus_L (Gyrus rectus), a8. Occipital_Mid_L (Middle occipital gyrus), a9. Calcarine_L (Calcarine fissure and surrounding cortex), a10. Fusiform_L (Fusiform gyrus), a11. ParaHippocampal_L (Parahippocampal gyrus).

patients showed even lower DMN connectivity than drug-responsive ones (33). Lower connectivity within the DMN was also reported in TLE (34). In the absence of seizure

patients, the DMN can show altered integration related to awareness and cognition, even in the absence of interictal epileptic activity or seizures (35). Another FLE study

revealed an association between abnormality in frontal-DMN zones and cognitive deficit (27). Decreased DMN connectivity is thought to reflect impaired consciousness, which is a common symptom in patients with extratemporal lobe epilepsy.

There are several limitations to this study. Firstly, the sample size was relatively small, and few patients underwent surgery. The heterogeneity among patients with extratemporal lobe epilepsy cannot be neglected, even though we included subjects that appeared to have FLE. Secondly, hidden, lesion-like, subtle FCD cannot be detected by 3-T MRI, and such FCD can influence FC and network patterns in extratemporal lobe epilepsy. This is one reason why relatively few studies have examined FC in this disorder. Thirdly, the use of antiepileptic drugs may have confounded our FC analysis. Future research should verify and extend our findings to elucidate FC patterns comprehensively in this disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consent was signed by each subject. The study protocol was approved by the Ethics Committee of West China Hospital (No. 2019: 372).

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