Abnormal Basal Ganglia Functional Connectivity in Idiopathic Generalized Epilepsy

Cheng Luo, Yang Xia, Zhi-Wei Guo, and Dong Zhou

***Abstract*—The basal ganglia have been implicated in a modulation role in idiopathic generalized epilepsy (IGE) by an invasive electrophysiolgic means. This paper investigates the basal ganglia functional connectivity by using the region-wise functional connection analysis in resting-state functional magnetic resonance imaging (fMRI) in IGE. The increased functional connectivity within basal ganglia, and between the basal ganglia and the thalamus, and decreased functional connectivity between basal ganglia and motor cortex are found in IGE compared with the controls. These findings not only implicate dysfunctional integration in the motor loop in IGE and the enhanced interaction in the modulated loop, but also suggest that the basal ganglia modulate the generalized epileptic discharges with the influence over thalamus in the corticothalamus network.**

***Index Terms*—Basal ganglia, functional magnetic resonance imaging, functional connectivity, idiopathic generalized epilepsy.**

1. Introduction

The idiopathic generalized epilepsy (IGE) is an epileptic syndrome that occurs in otherwise neurologically normal individuals and is characterized by the bilateral synchronous epileptic discharge, such as spike and wave discharge (SWD), in electroencephalography (EEG). The abnormal oscillations in the corticothalamic networks may contribute to the generation and propagation of generalized SWD. The electrophysiolgic studies have revealed that the basal ganglia may modulate the occurrence of SWD through their feedback circuits to the thalamus and the cerebral cortex, specially, an intact substantia nigra (a neural nucleus in the basal ganglia) may be necessary for the propagation of seizure activity[1]–[3]. In magnetic resonance imaging (MRI) study in IGE, Seeck and his colleagues found the reduced volume in the basal ganglia (included putamen and caudate nucleus)[4], and we also reported the diffusion and volume abnormality in basal ganglia in absence epilepsy[5]. In the functional neuroimaging studies, the regional cerebral blood flow change in the basal ganglia was examined using single photon emission computed tomography during the ictal and post-ictal periods in patients with dystonic posturing[6] and with secondary generalized tonic-clonic seizures[7]. In our previous simultaneous EEG and functional magnetic resonance imaging (fMRI) studies in IGE, the decreased blood oxygenation level-dependent (BOLD) signals associated with the inter-ictal SWD have been demonstrated in the basal ganglia[8]. Besides, using the independent component analysis (ICA), we found the basal ganglia network modulated the generalized epileptic discharge in IGE[9]. These accumulated evidences indicate that the generalized epileptic discharges are remarkably related to the basal ganglia function.

Conventionally, the basal ganglia have been implicated in a variety of motor-related functions, including the motor selection, preparation, and execution[10]. In addition, the basal ganglia dysfunction has been associated with disturbances in movement. Some evidence suggests that the nuclei of the basal ganglia are involved in the pathophysiology of movement disorders such as the Parkinson's disease, the Huntington's chorea, and the Tourette's syndrome. Patients with IGE are found to have various abnormal brain functions, such as abnormity in cognition, behavior, executive function, and controlled motor[11], [12]. It has been suggested that abnormal activity in the subcortical structures including the basal ganglia may be crucial for the motor manifestations in epilepsy[7], [9]. Thus, the functional connectivity related to the basal ganglia may be altered in IGE.

Recently, the resting-state fMRI has been widely used to investigate the functional connectivity in brain. In our previous studies, we found some altered functional connectivity in epilepsy, such as the altered default model network in absence epilepsy[13] and temporal lobe epilepsy[13], [14]. Specially, we found that the integration of the basal ganglia network prominently enhanced accompanies with the increased number of epileptic discharges in IGE[9]. In current study, we presumed that the

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C. Luo, Y. Xia, and Z.-W. Guo are with the Key Laboratory for NeuroInformation of Ministry of Education, the School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China.(e-mail: hl7roch@yahoo.com.cn, xiayang@ uestc.edu.cn, and guoyinwei87@163.com).

D. Zhou is with the Department of Neurology, West China Hospital of Sichuan University, Chengdu 610041, China. (e-mail: zhoudong66@ yahoo.de)

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functional connectivity among the variable regions in the basal ganglia network should be also increased in IGE to response the modulation role for the generalized epileptic discharges, moreover, the functional connectivity between the basal ganglia and the corticothalamic network should be altered in IGE. A functional connectivity analysis based on region of interesting (ROI) was used to test the hypothesis in resting-state fMRI. In order to avoid the transient effects of the epileptic discharges, the simultaneous EEG was used to monitor the electrophysiolgic activity during acquisition of resing-state fMRI data.

2. Subjects and Methods

2.1 Participants

A total of 29 patients with IGE were recruited from epilepsy clinics for the EEG-fMRI study at the Neurology Department in the West China Hospital, Sichuan University. All patients underwent clinical brain structural MRI and 24-hour video EEG. No patient exhibited any radiological abnormalities. Diagnosis was established according to the diagnostic scheme published by the international league against epilepsy in 2001[15]. A total of 25 right-handed, age- and sex-matched healthy participants were selected for the control group. Informed consent was obtained from each participant or parents (for children).

2.2 Data Acquisition

BOLD-sensitive MRI data were acquired by using gradient-echo echo-planar imaging (EPI) sequences in a 3T MRI scanner (EXCITE, GE Milwaukee, USA) with an eight-channel-phased array head coil. The imaging parameters were as follows: thickness=5 mm (no gap), TR =2000 ms, TE=30 ms, FOV=24 cm×24 cm, flip angle=90°, matrix=64×64. Two hundred and five volumes (30 slices per volume) were acquired during 410 seconds of an fMRI session. To ensure steady-state longitudinal magnetization, the first five volumes were discarded. We performed between two and five fMRI sessions, depending on patient endurance. During data acquisition, participants were required to relax with eyes closed, without falling asleep. Anatomical T1-weighted images were acquired by using a three-dimensional (3D)-spoiled gradient recalled (SPGR) sequence, generating 156 axial slices (thickness=1 mm (no gap), TR=8.5 ms, TE=3.4 ms, FOV=24 cm×24 cm, flip angle=12°, matrix=512×512).

During acquisition of fMRI data for IGE patients, EEG data were continuously recorded using a 10/20 system with 32 Ag/AgCl electrodes attached to the scalp with conductive cream. Two ECG channels were simultaneously recorded. The amplifier was a Mizar 40 (EBNeuro, Florence, Italy), with 32 channels applied for MR. Data were sampled at 4096 Hz. The EEG dynamic range was ±65.5 mV to prevent MRI artifact waveforms that could saturate the EEG/ECG. Since the electrodes would result in the pressure or uncomfortableness, once the patient complained the next session would be terminated. The MR artifact was filtered online[16] using the software BE-MRI Toolbox (Galileo New Technology, Florence, Italy). Inter-ictal SWD timing and duration were marked independently by two skilled electroencephalographers. If the SWD was detected during a particular session, the fMRI data were excluded in the next processing steps. Simultaneous EEG was not recorded in healthy participants.

2.3 Data Preprocess Analysis and ROI Definition

Pre-processing of fMRI data was conducted by using the SPM2 software package (statistical parametric mapping http://www.fil.ion.ucl.ac.uk/spm). The slice time correction, 3D motion detection and correction, spatial normalization to the montreal neurological institute (MNI) template, and spatial smoothing using an isotropic gaussian kernel (8 mm full width at half maximum) were included. Only participants with head motion of less than 1 mm and 1° during EEG-fMRI acquisition were included.

Based on the anatomical information, the basal ganglia were divided into six ROIs (bilateral caudate nuclei, putamen and pallidum). The thalamus, anterior cingulated cortex (ACC), and posterior cingulated cortex (PCC) were important for the occurrence and propagation of SWD, and the altered functional connectivity between them was shown in absence epilepsy[13], [17], so they were selected as ROIs. Besides, the primary sensorimotor cortex (precentral gyrus and postcentrol gyrus) and supplementary motor area (SMA) were also selected, as the anatomical connection between them and basal ganglia implicated the motor functional loops. So a total of 18 ROIs were defined. The anatomical ROIs were labeled by using the automated anatomical labeling and extracted by the MarsBaR toolbox (http://marsbar.sourceforge.net). Finally, the quality of the ROIs' extraction was manually checked and confirmed for each subject.

2.4 ROI-Wises Functional Connectivity

The averaged fMRI time course was obtained across all voxels in a ROI. Several procedures were used to remove the possible variances from the time course of each ROI. 1) Temporal band-pass filtering (pass band 0.01 Hz to 0.1 Hz) was conducted through a phase-insensitive filter, which reduced the effects of the low-frequency drift and the high-frequency noise. 2) Through linear regression, the time course was further corrected to eliminate the effect of six head motion parameters obtained in the realigning step and the effect of the signals from a cerebrospinal fluid region, a white matter region. The residuals of the regressions were linearly detrended, and then used for the

next functional connectivity analysis. The correlation coefficient was calculated between the resulting time course of each pairs of ROIs for each subject, and then an $N \times N$ (N=18) correlation matrix was obtained. A Fisher's r-to-z transformation was applied to normalize the correlation coefficient. For each group, a z-score matrix was averaged across all subjects. To compare the connectivity between two groups, the two-sample two-tailed t-tests were performed on all the 153, (C_{18}^2), possible connections represented in the 18×18 correlation matrices between the patients and the controls.

3. Results

Through reviewing the EEG data by experts, eighteen of 29 patients were selected because no epileptic discharge was found and the head motion criteria were fulfilled (translation<1 mm, or rotation<1°) in these sessions. Nine of 18 patients were diagnosed as generalized tonic-clonic seizure only (GTCS), 8 patients were diagnosed as childhood absence epilepsy (AS), and one patient was diagnosed as juvenile myoclonic epilepsy (MS). Eight patients were receiving antiepileptic medication, including valproic acid (VPA), lamotrigine (LTG), and clonazepam (CZP). The clinic details were shown in Table 1. The healthy controls included 23 participants.

The averaged functional connectivity matrix of each group was calculated and displayed in Fig. 1 and Fig. 2. The strong functional connectivity (large correlation coefficient) was found between the basal ganglia and the thalamus, among the basal ganglia and among cortex related to the sensorimotor function (bilateral SMA, precentral gyrus and postcentral gyrus). The negative correlation coefficient was found between the putamen, the pallidum, the cortex related to sensorimotor function (bilateral SMA, precentral gyrus, and postcentral gyrus) and the PCC. The anticorrelation ship (negative correlation) was consistent with the previous study.

Compared with the controls, 7 significantly decreased functional connections were found (p<0.05, FDR corrected) in patients (Table 2). These connections, which were positive correlation in controls (Table 2), occurred among the cortex related to sensorimotor function or between them and the basal ganglia. Seventeen functional connections increased in patients compared with controls (p<0.05, FDR corrected) (Table 3). Five of 17 increased functional connections displayed between thalamus and basal ganglia or among basal ganglia. The remained 12 functional connections were associated with the PCC, and they showed negative correlation coefficient in controls. In other words, the result demonstrated that the anticorrelation ship decreased in patients (closer to zero).

Table 1: Basic information of 18 patients

NO.	Sex	Age	Age of onset	Seizure type	Antiepileptic drugs
1	M	24	10	AS	VPA
2	M	8	7	GTCS	VPA/CPZ/LTG
3	M	18	9	GTCS	None
4	M	5	4	AS	None
5	F	9	7	AS	None
6	F	9	4	AS	VPA/CPZ/LTG
7	M	19	9	MS	None
8	M	12	2	GTCS	None
9	F	20	10	GTCS	VPA
10	F	5	4	AS	None
11	M	17	4	GTCS	VPA
12	M	21	13	GTCS	VPA
13	M	14	9	AS	None
14	M	18	5	AS	None
15	M	10	5	AS	None
16	F	12	11	GTCS	None
17	M	16	13	GTCS	VPA
18	M	19	16	GTCS	VPA

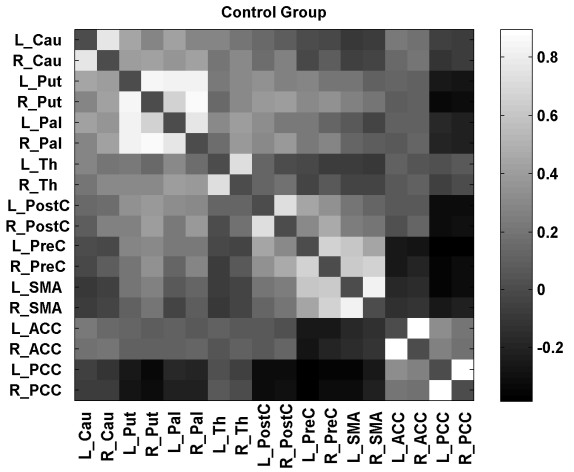

Fig. 1. Mean correlation coefficient matrix in the control group. The abbreviation: R: right, L: left, Cau: caudate, Put: putamen, Pal: pallidum, Th: thalamus, PostC: postcentral gyrus, PreC: precentral gyrus, SMA: supplementary motor area, ACC: anterior cingulated cortex, and PCC: posterior cingulated cortex.

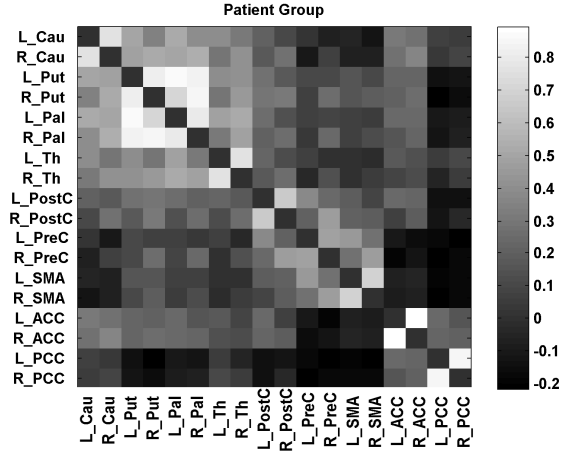

Fig. 2. Mean correlation coefficient matrix in the patient group. The abbreviations were the same as the representation in Fig. 1.

Table 2: Decreased functional connect ions in the patients compared with the controls

ROI 1	ROI 2	*p*-value	*T*-value	Mean in patients	Mean in controls
L_PreC	R_Put	0.000*	3.98	0.074	0.310
L_PreC	R_Pal	0.001*	3.53	0.026	0.216
L_PreC	L_Put	0.005	3.01	0.110	0.277
L_PreC	L_Pal	0.005	2.97	0.077	0.232
R_PreC	L_SMA	0.000*	4.83	0.284	0.630
R_PreC	R_SMA	0.006	2.92	0.474	0.655
L_SMA	R_SMA	0.002*	3.24	0.688	0.833

Note: '*' denotes significance $p<0.01$(FDR corrected)
The abbreviations were the same as the representation in Fig. 1.

Table 3: Increased functional connections in the patients compared with the controls

ROI 1	ROI 2	*p*-value	*T*-value	Mean in patients	Mean in controls
L_PCC	L_PreC	0.000*	4.139	–0.170	–0.390
L_PCC	L_Put	0.008	2.792	–0.150	–0.260
L_PCC	L_SMA	0.008	2.794	–0.180	–0.360
L_PCC	R_PostC	0.002*	3.381	–0.120	–0.320
L_PCC	L_PostC	0.004	3.037	–0.140	–0.320
R_PCC	R_Put	0.003*	3.231	–0.160	–0.320
R_PCC	L_PostC	0.006	2.924	–0.130	–0.310
R_PCC	R_PostC	0.000*	4.153	–0.040	–0.290
R_PCC	L_Put	0.002*	3.318	–0.130	–0.280
R_PCC	L_Pal	0.003*	3.148	–0.090	–0.230
R_PCC	R_Pal	0.009	2.722	–0.080	–0.210
R_PCC	L_PreC	0.008	2.810	–0.220	–0.370
R_Put	L_Th	0.005	2.967	0.293	0.136
R_Pal	L_Th	0.003*	3.213	0.320	0.159
L_Put	L_Th	0.002*	3.293	0.395	0.225
L_Pal	L_Th	0.006	2.915	0.486	0.312
R_Cau	L_Pal	0.009	2.771	0.503	0.354

Note: '*' denotes significance $p<0.01$(FDR corrected)
The abbreviations were the same as the representation in Fig. 1.

4. Discussions

By using the invasive electrophysiolgic means, it has been proposed that the basal ganglia could regulate the occurrence of SWD. In the current study, the resting-state fMRI functional connectivity result, the increased connectivity among the basal ganglia during the inter-ictal period without any epileptic discharge, might reflect the enhanced interaction between the modulated role and the generated or propagated role in IGE. Besides, the decreased functional connectivity between the basal ganglia and the sensorimotor functional cortex was found in IGE. These findings were consistent with our previous study. The second finding showed significantly enhanced functional connectivity between the basal ganglia and the thalamus in IGE. It expanded the regulated interpretation, and suggested that the basal ganglia modulated the generalized epileptic discharges with influence over thalamus in the corti-cothalamus network. The third finding demonstrated the significantly increased negative relationship between the PCC and motor cortex in IGE. The alteration might be related to the intrinsic functional organization of brain (anticorrelation ship) in IGE.

4.1 Functional Connection Region Related to Basal Ganglia

According to the structural connection evidence, the basal ganglia received projection originated from three parts of cortex, including associative cortex, sensorimotor cortes and limbic regions, and indirectly via the thalamus target cortical or limbic regions from which the basal ganglia input originated[18]. At function level, the basal ganglia have been implicated in a variety of motor-related functions. Here the sensorimotor cortex and SMA whose activations correlated with the motor function were selected as ROIs and the relationship with the basal ganglia was investigated. The relationship reflected the motor loop at both structure level and function level. In previous EEG-fMRI studies in IGE[8], [19], the deactivation in default model network including ACC and PCC was often found, and the activation was found in thalamus. These regions were significantly responded to the generalized epileptic discharges in IGE. In current study, we selected these regions that correlated with the motor function or with the generalized epileptic discharges. So the network could implicate the altered motor function in IGE and the modulation function of epileptic discharges.

4.2 Motor Functional Abnormality in IGE

The decreased functional connectivity in this study occurred between the basal ganglia and primary motor cortex (precentral gyrus) or among the sensorimotor cortex. All of these connections were related to the motor function. The abnormal behavior and executive function have been wildly mentioned in the studies about the IGE[11], [12]. In the movement disorders, such as the Parkinsonism, the varying forms of abnormally patterned activity throughout the motor loop of the basal ganglia were identified. Our finding may reflect the dysfunctional integration in motor function in IGE.

4.3 Modulation Function for Generalized Epileptic Discharges

The basal ganglia mainly receive afferents from the cerebral cortex. Subsequently, the input signal is relayed via direct and indirect routes and transmitted to the principal output nuclei. The output nuclei project directly to the thalamus, midbrain and medulla, and indirectly to target cortical and limbic regions through thalamus. Although, functional neuroimaging does not reflect the pathway between neurons, these underlying pathways may result in the functional network connectivity. Here, we

showed the increased functional connectivity between the basal ganglia and thalamus in IGE contrast to the controls. According to the electrophysiolgic evidence in the IGE, bilaterally synchronous epileptic discharge reflected abnormal oscillations in corticothalamic network and the connection between substania nigra pars reticulate (basal ganglia output nuclei) and ventromedial thalamic nucleus might modulate the generalized epileptic discharges[1]. The pharmacological study in rat model of absence epilepsy shows that the application of GABA agonists within the substania nigra pars reticulate suppresses the seizures, but an aggravation of cortical paroxysms occurs after the application of GABA antagonists[20]. The deep brain stimulation study in epilepsy[21] also confirmed that the interference in basal ganglia has an application to modulate epileptic discharge and seizure. In current study, the findings were obtained during the period without any epileptic discharge. It implicated that the enhanced interaction between the basal ganglia and the thalamus should be a stable change in IGE. In short, our findings, the increased functional connectivity between the basal ganglia and thalamus, provided convincing neuroimaging evidence to support the basal ganglia modulation roles in IGE, moreover, the basal ganglia might achieve the modulation by influence over thalamus in the corticothalamus network.

4.4 Abnormal Antagonism in IGE

The brain activity was organized through both correlated spontaneous fluctuations within a network and anticorrelation between the networks (the task-positive network and the task-negative network) in the resting state[22], [23]. The apparent antagonism reflected a dynamic, ongoing, and underlying intrinsic functional organization of the brain[24]. Fransson has also proposed that the antagonism of the two networks may reflect a binding mechanism between an introspective and extrospective attention orientation[25]. For the ROIs selected in the current study, the PCC was a node in the task-negative network; and the SMA, precentral and postcentral gyrus were included in the task-positive network. The negative correlation coefficient was found between the PCC and the SMA; precentral or postcentral gyrus in controls was consistent with the finding in the previous study. These connections were significantly altered (closer to zero) in IGE compared with that in controls. It means that the normal antagonism was disturbed in IGE. In truth, the decreased antagonism was also found in the autism[26] and attention deficit/ hyperactivity disorder[27], and the finding was interpreted by an imbalance in the switching between the two networks, driven by a deficit of mental function, such as paucity of introspective thought in autism and attention lapses in attention deficit/hyperactivity. The attention impairment was found in IGE in the behavior or fMRI studies. It may lead to the disturbed antagonism in the two networks. On the other hand, the disrupted antagonism might mean the decreased desynchronicity between the two networks, and probably related to the epileptic discharge synchronicity in the entire brain in IGE.

4.5 Methodological Consideration and Limitation

The major consideration was concerned with global signal removal. The global correction could introduce the negative correlations and reduce the positive correlation. Still now, the removal of the global signal by regression remains a problem. It was omitted in this work, because the BOLD signal of the thalamus highly correlates with this signal. However, the further studies should investigate the underlying mechanisms of the globe signal.

Because of the anatomic connection between the basal ganglia and the widespread cortex, the selection of partial cortical ROIs in this work was not optimal to discuss the relationship between the basal ganglia and the entire cortex. However, we only focused on the altered functional connectivity related to basal ganglia in the IGE, including the motor function and the modulation role for the IGE. In fact, it is probable that the functional connection between the other cortex region and the basal ganglia was abnormal in IGE, and the altered connection may implicate the various functional abnormalities in IGE.

Besides, the influence of the antiepileptic drugs should be considered. The antiepileptic drugs may modulate the BOLD signal to affect the functional connectivity. The further studies are needed to clear the mechanism of the antiepileptic drugs with regard to the basal ganglia functional connectivity.

5. Conclusions

In the current study, we used the resting-state fMRI to investigate the functional connectivity related to the basal ganglia. The increased functional connectivity among the basal ganglia and decreased functional connectivity between the basal ganglia and the motor cortex were found in IGE compared with the controls. These findings were consistent with our previous studies[9]. It is meaningful that the increased functional connectivity was found between the basal ganglia and the thalamus, and it implicated that the basal ganglia modulated the generalized epileptic discharges with influence over the thalamus in the cortico-thalamus network. Besides, the significantly increased negative relationship between the PCC and motor cortex was found. It might reflect the decreased desynchronicity between the two various networks, and probably relates to the epileptic discharge synchronicity in the entire brain in IGE.

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Cheng Luo was born in Sichuan Province, China, in 1976. He received the B.S. degree from the North Sichuan Medical College, Nanchong, in 1999 and the M.S. degree from the University of Electronic Science and Technology of China (UESTC), Chengdu, in 2006. He is currently pursuing the Ph.D. degree with the School of Life Science & Technology, UESTC. His research interests include functional magnetic resonance imaging in neurologic disorders.

Yang Xia received her M.S degree from the West China Center of Medical Science, Sichuan University, Chengdu, in 1997. She is currently an associate professor with the School of Life Science and Technology, UESTC. Her research interests include neurobiology and neuroelectrophysiology

Zhi-Wei Guo was born in Henan Province China, in 1988. He received the B.E. degree in biomedical engineering from Changchun University of Science and Technology, Changchun, in 2010. He is currently pursuing the M.E. degree with the School of Life Science & Technology, UESTC. His research interests include functional magnetic resonance imaging.

Dong Zhou received M.S. degree from the West China Center of Medical Science, Sichuan University, Chengdu, in 1989, and the M.D. degree from University of Erlangen, Erlangen, Germany. He has been a professor since 1999, and the Director of Department of Neurology, West China Hospital of Sichuan University.