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Altered basal ganglia-cortical functional connections in frontal lobe epilepsy: A resting-state fMRI study

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ABSTRACT

Objectives: The purpose of this study was to investigate alterations of basal ganglia-cortical functional connections in patients with frontal lobe epilepsy (FLE).
Method: Resting-state functional magnetic resonance imaging (fMRI) data were gathered from 19 FLE patients and 19 age- and gender-matched healthy controls. Functional connectivity (FC) analysis was used to assess the functional connections between basal ganglia and cerebral cortex. Regions of interest, including the left/right caudate, putamen, pallidum and thalamus, were selected as the seeds. Two sample *t*-test was used to determine the difference between patients and controls, while controlling the age, gender and head motions.
Results: Compared with controls, FLE patients demonstrated increased FCs between basal ganglia and regions including the right fusiform gyrus, the bilateral cingulate gyrus, the precuneus and anterior cingulate gyrus. Reduced FCs were mainly located in a range of brain regions including the bilateral middle occipital gyrus, the ventral frontal lobe, the right putamen, the left fusiform gyrus and right rolandic operculum. In addition, the relationships between basal ganglia-cingulate connections and durations of epilepsy were also found.
Conclusion: The alterations of functional integrity within the basal ganglia, as well as its connections to limbic and ventral frontal areas, indicate the important roles of the basal ganglia-cortical functional connections in FLE, and provide new insights in the pathophysiological mechanism of FLE.

1. Introduction

Frontal lobe epilepsy (FLE) is a second most common type of localization-related epilepsies, which accounts for 20–30% of all partial epilepsies (Manford et al., 1992). So far, there are various epileptogenic zones in frontal lobe epilepsy: perirolandic, supplementary sensorimotor area, dorsolateral, orbitofrontal, anterior frontopolar, opercular and cingulate types (Bagla and Skidmore, 2011). Furthermore, frontal lobe seizures are varied, including complex partial seizure (CPS), simple partial seizure (SPS) and secondary generalized tonic-clonic seizure (SGTCS). Because epileptic seizures reflect abnormal neuronal synchronization (Jiruska et al., 2013), the frontal lobe seizures may have effects on the brain activity in FLE patients without distinct anatomical abnormalities. It has been suggested that seizures will impact on a broad range of cognitive domains in FLE patients, ranging from impairment of executive functions to the problem of the more complex behaviors such as social functioning (Braakman et al., 2012, 2011; Exner et al., 2002). The epileptic discharges in frontal lobe would play a role in cognitive impairment. However, the potential mechanism of FLE is not as well understood.

The basal ganglia mainly consist of the striatum, the pallidum, the subthalamic nucleus and the substantia nigra. Parallel, segregated and closed-loop projections are suggested for the connectional architecture between the basal ganglia and functionally disparate regions of cerebral cortex (McHaffie et al., 2005; Selemon and Goldman-Rakic, 1985). The basal ganglia have been suggested to implicate in a variety of motor-related function, including motor selection, preparation, and execution (Gerardin et al., 2004), and be involved in the pathophysiology of movement disorders such as Huntington's chorea, Parkinson's disease and Tourette's syndrome. In epilepsy, the basal ganglia has been widely suggested to

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play important roles in the regulation and propagation of epileptic discharges (Norden and Blumenfeld, 2002). Many of functional (Li et al., 2009; Luo et al., 2012; Moeller et al., 2008) and structural (Luo et al., 2015; Seeck et al., 2005) evidences indicated the basal ganglia may be crucial for the modulation of epileptic activity. These evidences implied that the basal ganglia may be involved in the pathophysiological mechanism of epilepsy sub-types such as FLE.

Resting-state functional connectivity (FC) of functional magnetic resonance imaging (fMRI) has been widely used as a powerful tool for studying spontaneous neuronal synchronization and brain functions (Biswal et al., 1995; Fox and Raichle, 2007). Many valuable findings of resting-state fMRI were observed in various types of epilepsy such as partial epilepsy (Zhang et al., 2015), absence epilepsy (Luo et al., 2014b; Yang et al., 2013), and juvenile myoclonic epilepsy (Jiang et al., 2016). Using fMRI, altered functional connectivities within the frontal lobe, as well as connectivities between the frontal lobe and a range of brain regions (containing the parietal lobe, temporal lobe, cerebellum and basal ganglia), have been found in FLE patients (Braakman et al., 2013). It implied that FCs of frontal lobe may be associated with cognitive impairment in pediatric FLE. However, while previous resting-state functional connectivity studies of FLE focused on the connectivity pattern of epileptic network (Luo et al., 2014a), single functional network such as motor network (Woodward et al., 2014), or relationships between resting-state networks (Cao et al., 2014; Widjaja et al., 2013), the functional connectivity between the basal ganglia and cerebral cortex in FLE is not fully understood. Investigation of basal ganglia-cortical functional connectivity in FLE patients may provide further information that will help to better understand the mechanisms of FLE.

The purpose of the current study was to investigate the potential alterations of basal ganglia-cortical functional connections in FLE patients using resting-state fMRI. Functional connectivity of basal ganglia was conducted on resting-state fMRI data of each group, and then compared between groups of FLE patients and controls using two sample *t*-test. In addition, the relationships between FC alterations and clinical factors in FLE were also investigated.

2. Material and methods

2.1. Subjects

Nineteen FLE patients (9 females; age range = 13–51 years; mean age = 24.2 years; standard deviation = 9.5 years) were recruited from the Center for Information in Medicine of University of Electronic Science and Technology of China (UESTC). All patients were diagnosed (by neurologists, P.W., S.T. and C.Z.) based on clinical history, 24-h video-EEG recording, ictal semiology, routine imaging (CT and/or MRI) and the International League Against Epilepsy (ILAE) guidelines (Engel and International League Against, 2001). No anatomical abnormalities in FLE patients were found using routine examinations of CT and MRI scanning. All patients underwent 24-h (overnight including the sleep period) scalp video-EEG recordings (EEG–9100 K, Nihon Kohden, Tokyo, Japan). For EEG, 16 electrodes were distributed according to 10–20 international standard system, and the sampling rate was set at 256 Hz. Using 24-h EEG recording, 3/19 FLE patients showed burst of sharp waves; 10/19 patients showed sparse sharp waves; 4/19 patients showed sparse sharp-slow waves; and 2/19 patients showed burst of sharp-slow waves. And, 10/19 patients demonstrated interictal discharges in the frontal regions; 6/19 patients demonstrated interictal discharges in the frontotemporal areas; and 3/19 patients demonstrated discharges in the frontcentral regions. All patients received antiepileptic drug (AED) treatments with regular outpatient follow-up. The detailed demographic information and the clinical characteristics of FLE patients can be seen in Table 1. A total of 19 age- and gender-matched, healthy subjects were also recruited as controls (5 females; age range = 11–41 years; mean age = 20.9 years; standard deviation = 8.9 years). Written consent forms of all FLE patients and controls were obtained. The study protocol was approved by the Ethics Committee of UESTC.

2.2. MRI acquisition

MRI data were collected by a 3 T MRI scanner (Discovery MR750, GE, USA) in the Center for Information in Medicine of UESTC. T1-weighted anatomical images were gathered using a 3-dimensional fast spoiled gradient echo (3D FSPGR) sequence, and the scan parameters were as follows: TR/TE = 6.008 ms/1.984 ms; flip angle = 9°; field of view = 25.6 × 25.6 cm^2; matrix size = 256 × 256; slices = 152 and slice thickness = 1 mm (no gap). The functional images were gathered using a gradient-echo echo-planar imaging (EPI) sequence. The scan parameters were as follows: TR/TE = 2000 ms/30 ms; flip angle = 90°; field of view = 24 × 24 cm^2; matrix size = 64 × 64; slices = 35 and thickness = 4 mm. A total of 255 vol were obtained over a 510 s period. All FLE patients and controls were explicitly instructed to relax and close their eyes without falling asleep during scanning.

2.3. Data preprocessing

For resting-state fMRI data of each subject, the first 5 vol were discarded to remove the T1 saturation effects. Then, resting-state fMRI preprocessing comprised slice time correction, realignment, spatial normalization ($3 \times 3 \times 3\ mm^3$) and smoothing [6-mm full-width at half maximum (FWHM)]. The analysis of preprocessing was conducted using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). To remove possible nuisance noises, two procedures were used (Fox et al., 2005, 2009). (1) Several nuisance signals, including linear trend, 6 head motion parameters, global signal, individual mean WM and CSF signals, were removed from fMRI data using a multiple linear regression analysis. (2) Temporal band-pass filtering (pass band 0.01–0.08 Hz) was conducted on fMRI data. In addition, the head motion of each subject was calculated using the following formula:

$$headmotion = \frac{1}{M-1}\sum_{i=2}^{M}\sqrt{|\Delta d_{x_i^1}|^2 + |\Delta d_{y_i^1}|^2 + |\Delta d_{z_i^1}|^2 + |\Delta d_{x_i^2}|^2 + |\Delta d_{y_i^2}|^2 + |\Delta d_{z_i^2}|^2} \quad (1)$$

where M is the number of the fMRI time points; x_i^1/x_i^2, y_i^1/y_i^2 and z_i^1/z_i^2 are translations/rotations at the *i*th time point in the *x*, *y* and *z* directions, respectively; $\Delta d_{x_i^1} = x_i^1 - x_{i-1}^1$, and similar for others. All patients and controls were translation < 1 mm and rotation < 1°.

2.4. Functional connectivity analysis

Regions of interest (ROIs) including the left/right caudate (Caudate_L/R), putamen (Putamen_L/R), pallidum (Pallidum_L/R) and thalamus (Thalamus_L/R), which were extracted according to the Automated Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002), were selected as seeds. All ROIs were coregistered to normalized MNI space, and mean signals for these ROIs were extracted. Then, FC analysis was performed by calculating temporal Pearson's correlation between the seeds and all brain voxels. An entire brain Z-score map of each subject was created after transforming correlation coefficients of each voxel (Fisher's r-to-z transformation).

Table 1
Demographic and clinical information of FLE patients.

No.	Sex	Age	Age of epilepsy onset	Interictal EEG	Seizure type	Medication	Family history of epilepsy
1	M	24	16	Right; Burst of theta sharp waves; FP2, F4, F8	SGTCS	CBZ/PIR	Brother
2	F	22	12	Bilateral; Sparse sharp-slow waves; FP1, FP2, F3, F4, F8	SPS	TPM	Sister
3	M	42	38	Left; Sparse sharp waves; F7, T3	SPS	TPM/OXC/TCM	–
4	F	23	16	Bilateral; Burst of sharp-slow waves; FP2, C3, F3, F4, F8,	CPS	LTG	–
5	F	15	11	Bilateral; Burst of sharp waves; C3, F7, F4, F8	SPS	*	Brother
6	M	27	10	Right; Sparse sharp waves; F4, F8	CPS	VPM/PIR	–
7	F	14	3	Bilateral; Sparse sharp waves; FP2, F7, T3	CPS	CBZ/GAS	Sister
8	M	18	7	Bilateral; Sparse sharp waves; FP2, F7, F8, T3	SPS	TPM/OXC	–
9	F	32	18	Bilateral; Sparse sharp waves; FP1, F7,T3, F8	CPS	VPA	–
10	F	13	10	Right; Sparse sharp and sharp-slow waves; FP2, F4, C4	SPS	OXC/PIR	Brother
11	M	23	13	Bilateral; Sparse sharp waves; FP2, F4, F7, F3	SGTCS	VPM/PIR	–
12	F	16	7	Right; Sparse sharp waves; F4, F8	CPS	LEV	–
13	M	25	8	Right; Burst of sharp waves; F4, F8, T4	SPS	CBZ	–
14	M	21	12	Left; Sparse sharp-slow waves; FP1, F3	SPS	CBZ/TCM	–
15	F	28	18	Bilateral; Burst of sharp-slow waves; FP1, FP2, F3, F4, F8	SGTCS	VPM/OXC	–
16	M	14	11	Left; Sparse sharp-slow waves; FP1, F3	CPS	OXC/TCM	–
17	F	31	3	Right; Sparse sharp waves; FP2, F4	CPS	VPA/TPM	Sister
18	M	51	51	Left; Sparse sharp waves; F3, F7, T3	SGTCS	**	–
19	M	20	10	Bilateral; Sparse sharp waves; FP1, FP2, F4, F7	CPS	VPA	Sister

VPA: valproic acid; VPM: valpromide; LTG: lamotrigine; CBZ: carbamazepine; TPM: topiramate; PIR: piracetam; OXC: oxcarbazepine; LEV: levetiracetam; GAS: gastrodin; TCM: traditional Chinese medicine; CPS: complex partial seizure; SPS: simple partial seizure; SGTCS: secondary generalized tonic-clonic seizure; *: has no medication for about 2 months; **: drug-naive; M: male; F: female.

To assess voxel-wise statistical significance of functional connectivity at the group level for each ROI, one sample *t*-test was first conducted on Z-score maps. The significance was set at $P < 0.05$ [false discovery rate (FDR) corrected] and cluster size >23 adjacent voxels (621 mm^3). Two sample *t*-test was also conducted to determine the difference between patients and controls, while controlling the age, gender and head motions ($P < 0.001$, cluster size > 23 voxels).

2.5. Relationships between duration of epilepsy and FC

To detect the underlying relationships between FCs (Z-scores) and duration of epilepsy, partial correlation analysis was performed in FLE patients, while controlling for the age, gender and head motion. The Z-scores were extracted from the brain regions of significant differences between patients and controls.

3. Results

As illustrated in Fig. 1, one sample *t*-test was conducted on each group to demonstrate the significant brain regions for all ROIs ($P < 0.05$, FDR corrected, cluster size > 23 voxels). For Caudate_L, positive correlation maps were mainly found in the bilateral caudate, the putamen, the pallidum, the anterior thalamus, the anterior cingulate [Brodmann Area (BA) 32], the ventral frontal lobe (BA11) and left superior frontal lobe (BA9) for both groups. The maps of negative correlation were primarily found in the bilateral lingual gyrus (BA18), the fusiform gyrus (BA20), the temporal lobe (BA37), the supra-marginal gyrus (BA48) and parietal lobe (BA40/7) for both groups. FLE patients additionally showed positive connectivity in the bilateral cerebellum, while controls additionally showed negative connectivity in the bilateral middle cingulate gyrus (BA23). For Caudate_R, correlation maps were similar to the results of Caudate_L, but additionally showed positive correlations in the bilateral superior frontal lobe (BA32) for both groups. For Putamen_L/R, similar positive correlations were found in the bilateral caudate, the putamen, the pallidum, the thalamus, the insula (BA48), the supra-marginal gyrus, the anterior cingulate (BA32), the middle frontal lobe (BA9), the precentral gyrus (BA6) and supplementary motor area (BA6) for both groups. Negative correlations were primarily found in DMN regions including the bilateral precuneus (BA7), the angular gyrus (BA39) and medial frontal lobe (BA9) for both groups. FLE patients additionally showed negative connectivity in the bilateral occipital lobe (BA18/19). For Pallidum_L/R, similar positive correlations were located in the bilateral cerebellum, the caudate, the putamen, the pallidum, the thalamus, the insula (BA48), the anterior cingulate (BA32), the precentral gyrus (BA6) and supplementary motor area (BA6) for both groups. FLE patients additionally showed positive connectivity in the left middle frontal lobe (BA46). Negative correlations were primarily located in the bilateral precuneus (BA7) and angular gyrus (BA39). For Thalamus_L/R, similar positive correlations were found in the bilateral cerebellum, the caudate, the putamen, the pallidum, the thalamus, the anterior cingulate (BA32) and supplementary motor area (BA6) for both groups. Negative correlations were primarily found in the bilateral fusiform gyrus and occipital lobe (BA19).

Significant differences between Z-score maps of FLE patients and controls were illustrated in Table 2, Figs. 2 and 3 ($P < 0.001$, uncorrected, cluster size > 23 voxels), while controlling for the age, gender and head motion. For Caudate_L, compared with controls, increased FCs in FLE patients were found in the right fusiform gyrus (BA20). For Putamen_L, compared with controls, increased FCs in FLE patients were found in the bilateral cingulate gyrus (BA23) and precuneus (BA7). Decreased FCs in FLE patients were also found in the bilateral middle occipital gyrus (BA19). For Putamen_R, increased FCs in FLE patients were located in the left cingulate gyrus and right cingulate gyrus. Decreased FCs in FLE patients were located in the right inferior frontal gyrus (BA47), the left medial frontal gyrus (BA10) and middle occipital gyrus (BA19). For Pallidum_L, increased FCs in FLE patients were found in the right cingulate gyrus (BA23), while decreased FCs in the right putamen. For Pallidum_R, increased FCs in FLE patients were found in the bilateral cingulate gyrus (BA24). Decreased FCs in FLE patients were located in the left fusiform gyrus (BA19), right rolandic operculum (BA48) and putamen. In addition, there were no significant differences between FLE patients and controls for ROIs of Caudate_R and Thalamus_L/R.

The Z-scores of FCs in the brain regions of significant differences were partially correlated with the duration of epilepsy in FLE patients, while controlling for the age, gender and head motions. Significant partial correlations were found in the FCs between the right putamen and left cingulate gyrus ($r = 0.52$, $P = 0.041$), FCs

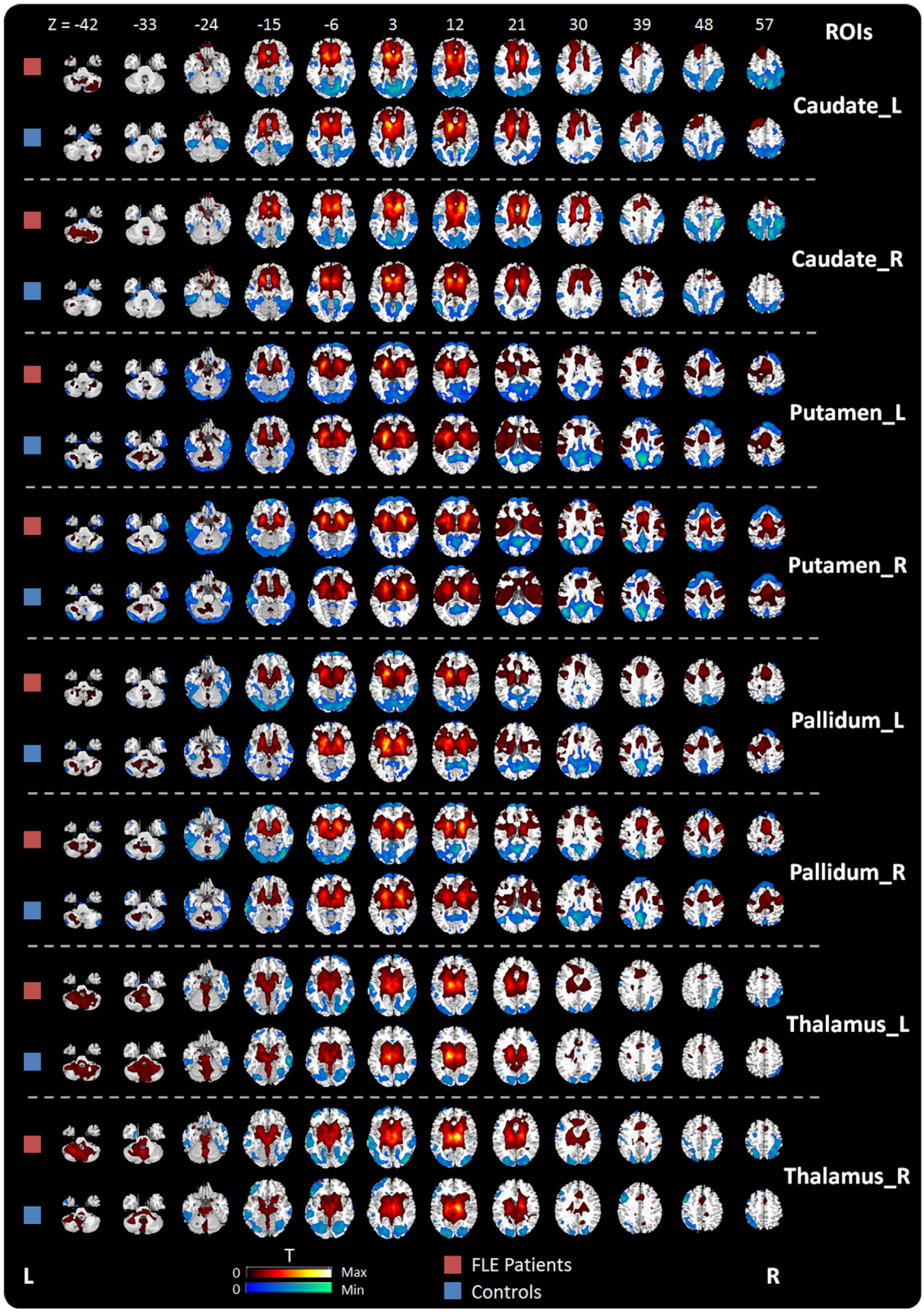

Fig 1. T-maps of functional connectivity in FLE patients and controls (one sample *t*-test, P < 0.05, FDR corrected, cluster size > 23 voxels). The names of ROIs are showed on the right side. L: left; R: right; T: *T*-value.

between right putamen and cingulate gyrus (r = −0.53, P = 0.036), as well as the FCs between the right pallidum and cingulate gyrus (r = −0.51, P = 0.042) (Fig. 4).

4. Discussion

In the current study, we used resting-state fMRI to investigate alterations of the basal ganglia-cortical functional connections in FLE patients. The main findings were as follows: 1) compared with

Table 2
The results of two sample *t*-test between FC maps of FLE patients and controls, while controlling for the age, gender and head motion.

ROIs	MNI coordinates			L/R	Lobe	Brodmann Area	*T*-value	Voxels
	x	y	z					
Caudate_L	30	−27	−30	R	Fusiform Gyrus	BA20	5.24	42
Putamen_L	6	−27	33	R	Cingulate Gyrus	BA23	4.39	97
	9	−48	39	R	Precuneus	BA7	4.38	73
	−6	−48	36	L	Precuneus	BA31/7	3.76	
	−45	−87	3	L	Middle Occipital Gyrus	BA19	−5.1	39
	45	−84	−6	R	Middle Occipital Gyrus	BA19	−4.87	29
Putamen_R	−6	−24	42	L	Cingulate Gyrus	BA24	4.18	48
	6	−27	36	R	Cingulate Gyrus	BA31	3.82	
	15	36	−12	R	Inferior Frontal Gyrus	BA47	−4.84	67
	−45	−87	0	L	Middle Occipital Gyrus	BA19	−4.77	38
	−15	39	−12	L	Medial Frontal Gyrus	BA10	−4.34	38
Pallidum_L	6	−24	33	R	Cingulate Gyrus	BA23	4.16	59
	33	−9	3	R	Putamen		−3.95	26
Pallidum_R	3	−15	39	R	Cingulate Gyrus	BA24	4.43	63
	−3	−24	42	L	Cingulate Gyrus	BA24	4.28	
	−39	−66	−18	L	Fusiform Gyrus	BA19	−4.51	23
	57	3	15	R	Rolandic Operculum	BA48	−4.43	25
	33	−3	0	R	Putamen		−4.04	23

P < 0.001, uncorrected, cluster size > 23 voxels. The positive *T*-values represent increased FCs in FLE patients, while negative *T*-values represent decreased FCs in patients.

controls, FLE patients showed significant increased FCs between basal ganglia and regions including the right fusiform gyrus, the bilateral cingulate gyrus, the precuneus and anterior cingulate gyrus; and 2) reduced FCs in FLE patients were located in a range of brain regions including the bilateral middle occipital gyrus, the ventral frontal gyrus, the right putamen, the left fusiform gyrus and right rolandic operculum. In addition, significant relationships between FCs and durations of epilepsy were also found in the cingulate gyrus.

The basal ganglia has been suggested to project to a wide range of cerebral cortical regions, and based on the tripartite model, basal ganglia-cortical connections have acted as parallel, segregated and closed-loop projections (McHaffie et al., 2005; Selemon and Goldman-Rakic, 1985). The brain regions connected to the basal ganglia are also suggested to be divided into sensorimotor, associative and limbic cortices. In our results, both FLE patients and controls showed that cortical areas including supplementary motor area, limbic cortex, insula and cerebellum are connected to the basal ganglia. These results are consistent with the prediction of the sensorimotor and limbic loops (Selemon and Goldman-Rakic, 1985), as well as expanded connections to insula and cerebellum (Luo et al., 2012; Postuma and Dagher, 2006).

In epilepsy, it is widely suggested that the basal ganglia play important roles in the regulation and propagation of epileptic discharges (Norden and Blumenfeld, 2002). Many functional (Li et al., 2015, 2009; Moeller et al., 2008) and structural (Luo et al., 2015; Seeck et al., 2005) evidences also indicated the involvement of the basal ganglia in epileptic activity. Further evidences for the involvement of the basal ganglia in the modulation of epileptic activity have been suggested in several studies of computational evidence in absence seizures (Chen et al., 2014), neuropharmacology (Danober et al., 1998; Deransart et al., 1998) and deep brain stimulation in epilepsy (Loddenkemper et al., 2001). In this study, decreased FCs between pallidum and putamen in FLE patients were observed. The inhibitory phasic GABAergic projection between pallidum and striatum has been suggested in epileptic animal models (Deransart et al., 1998). The decreased interaction between them may reflect the reduced inhibitory of striatum to pallidum, suggesting facilitation of seizures. Thus, our findings may also imply the important roles of the basal ganglia in the modulation and propagation of epileptic activity in FLE. Furthermore, changes of connections between basal ganglia and limbic and frontal areas, including the bilateral cingulate gyrus, the anterior cingulate gyrus, the ventral frontal gyrus and right rolandic operculum, were found in FLE patients in our results. In FLE, a wide range of cognitive dysfunctions and behavioral disturbances have been found in patients, ranging from impairment of executive to the problem of social withdrawal (Braakman et al., 2012, 2011; Exner et al., 2002). Because of important roles of the frontal lobes in several functional domains including elemental functions (e.g. motor functions), volitional eye movements, speech and language abilities, motivational behaviors, executive functions and social competency (Cummings and Miller, 2007), structural and/or functional abnormalities related to epilepsy in the frontal lobes may account for the cognitive dysfunctions in FLE patients (Braakman et al., 2011; Exner et al., 2002). Braakman et al., found altered functional connections in pediatric FLE patients within frontal lobe, as well as connections between the frontal lobe and a wide range of brain regions including the parietal lobe, temporal lobe, cerebellum and basal ganglia (Braakman et al., 2013). And these altered functional connections may be associated with cognitive impairment in pediatric FLE. Further evidences for altered functional connections of the frontal lobe in FLE patients have also been reported in studies of resting-state fMRI (Cao et al., 2014; Luo et al., 2014a). Together with our findings of altered functional connections within the basal ganglia, as well as connections between basal ganglia and limbic and frontal cortex, it may imply an important role of the basal ganglia-cortical functional connections in the propagation of epileptic activity, and may account for the cognitive impairment in FLE patients. Of interest, significant relationships between basal ganglia-cortical FCs and durations of epilepsy were also found in FLE patients. This finding further supported the crucial roles of the basal ganglia-cortical functional connections in FLE.

Another remarkable finding in our study is the increased FCs between the left putamen and bilateral precuneus in FLE patients. The precuneus and posterior cingulate cortex have been suggested as crucial nodes of the default model network (DMN) which reflects the baseline state in the human brain (Buckner et al., 2008; Raichle et al., 2001). Meanwhile, a number of studies have found that the widespread deactivation in the DMN regions (especially in the precuneus/posterior cingulate cortex) exists in epilepsy patients using simultaneous EEG-fMRI (Aghakhani et al., 2004; Archer et al., 2003; Gotman et al., 2005; Hamandi et al., 2006; Li et al., 2009). These findings suggested that epileptic activity may interrupt the resting state and cause the deactivation and suspension of the DMN. Therefore, we speculated that increased FCs in the precuneus of

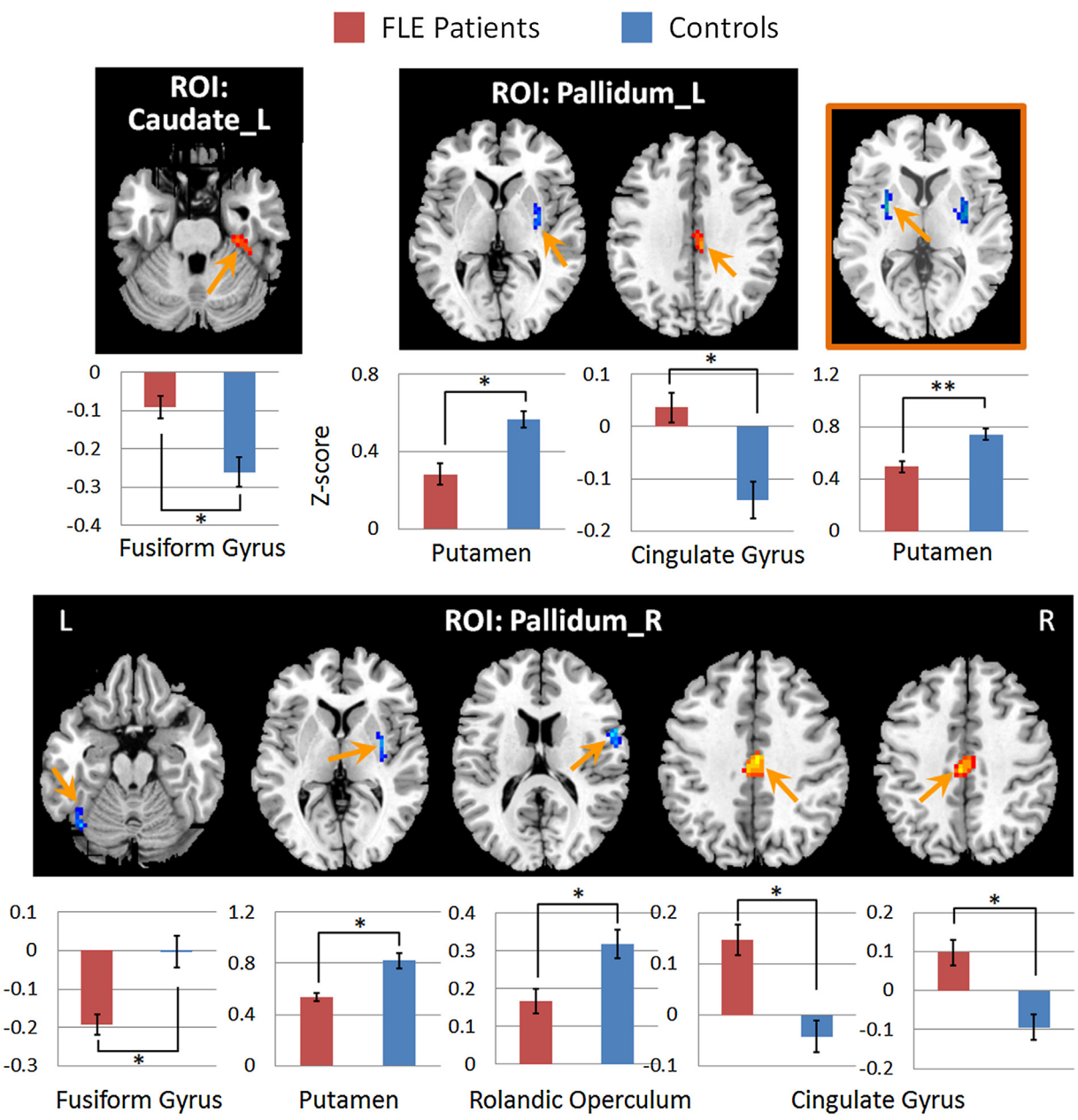

Fig. 2. The significant differences of FC maps (ROIs: Caudate_L and Pallidum_L/R) between FLE patients and controls, while controlling for the age, gender and head motion (two sample *t*-test, P < 0.001, uncorrected, cluster size > 23 voxels). *T*-values overlaid on the structural template were shown with hot color for positive values (patients > controls) and cool colors for negative values (patients < controls). For ROI Pallidum_L, decreased FCs in the left putamen (lower threshold, P < 0.005) are showed in the right brown box. Histograms of mean fisher z-scores (with standard error) in the regions of differences were also shown. L: left; R: right; *: P < 0.001; **: P < 0.005.

FLE patients may be associated with epileptic activity, which may eventually cause DMN functional impairments. In addition, significant impairments of visual-spatial functions have been found in children with FLE (Braakman et al., 2012, 2011). Hence, the results of decreased FCs between the basal ganglia and visual regions (the middle occipital gyrus and fusiform) may be associated with the potential impairments of visual-spatial functions in FLE patients.

Several limitations should be noted in this study. First, the possibility of interictal epileptic discharges may influence the basal ganglia-cortical FCs in FLE patients. Using simultaneous EEG-fMRI, Ibrahim et al., found that interictal epileptiform discharges had effects on the functional connectivity networks in children with focal epilepsy (Ibrahim et al., 2014). Furthermore, as all FLE patients have withdrawn the antiepileptic drugs for 24 h, more frequent interictal discharges may have effects on FCs of basal ganglia. Because of non-recording of EEG during fMRI scanning, it is hard to rule out the potential effects of interictal epileptic discharges on the basal ganglia-cortical FCs. The simultaneous EEG-fMRI recording will be conducted to clarify the relationship between FCs and the interictal epileptic discharges in FLE patients in the future. Second, the sample size (only 19 FLE patients) of the current study is modest. More FLE patients should be recruited to determine the results of the study in the future. Third, despite the fact that FLE patients had discontinued medication for about 24 h, the medication may have potential impacts on our results. In the previous fMRI studies, AEDs have been reported to have effects on functional networks in epilepsy patients during task (Szaflarski and Allendorfer, 2012; Tang et al., 2016; Wandschneider et al., 2014; Yasuda et al., 2013). Therefore, interactions among AEDs, interictal epileptic discharges and resting-state basal ganglia-cortical FCs should be explored, and

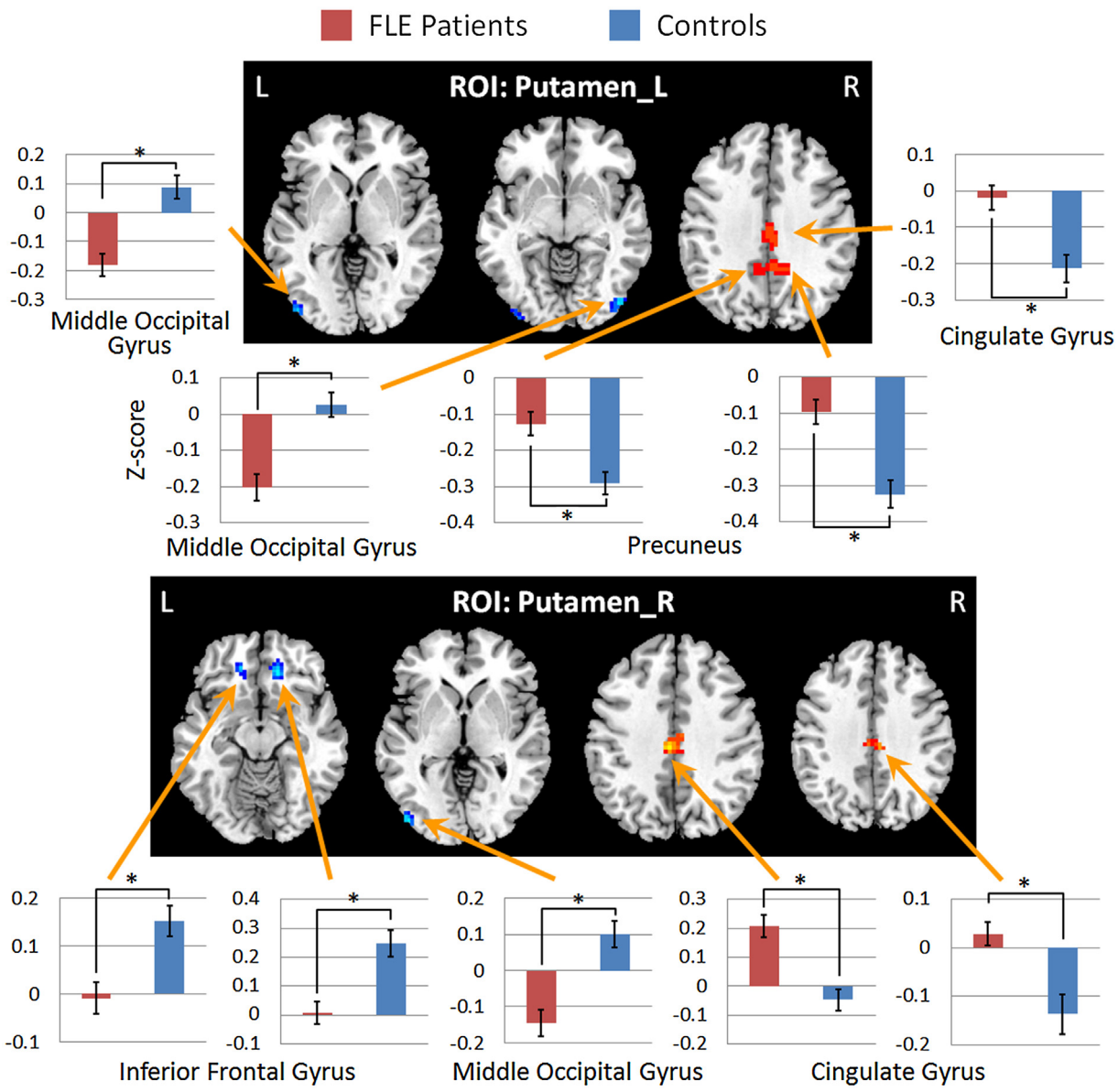

Fig. 3. The significant differences of FC maps (ROIs: Putamen_L/R) between FLE patients and controls, while controlling for the age, gender and head motion (two sample *t*-test, P < 0.001, uncorrected, cluster size > 23 voxels). *T*-values overlaid on the structural template were shown with hot color for positive values (patients > controls) and cool colors for negative values (patients < controls). Histograms of mean fisher z-scores (with standard error) in the regions of differences were also shown. L: left; R: right; *: P < 0.001.

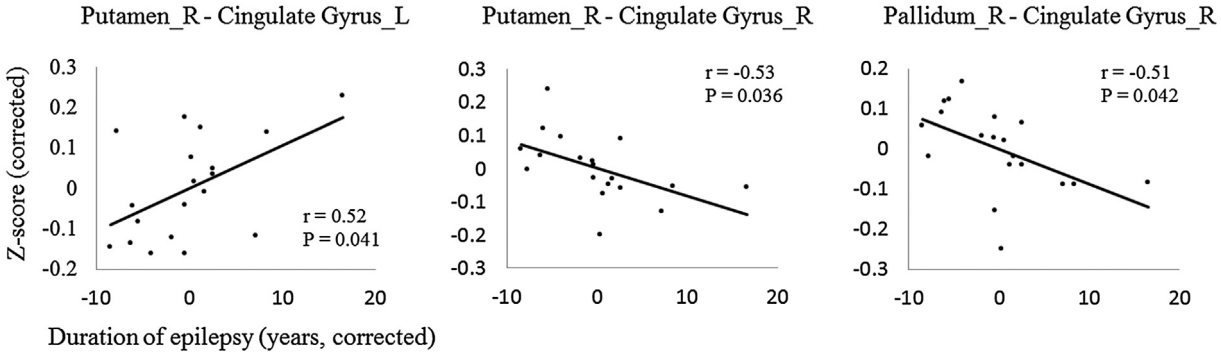

Fig. 4. Partial correlations between FC values (fisher z-scores) and the duration of epilepsy (years) in FLE patients while controlling for the age, gender and head motion. Z-scores and duration values were corrected by regressing out the age, gender and head motion. r: partial correlation coefficient; P: P-value.

a long-term effort is expected to continue this work in the future. Finally, neuropsychological evaluations in FLE patients were not conducted for correlation analysis of behavior with resting-state functional connectivity.

5. Conclusions

In conclusion, using resting-state functional connectivity analysis, basal ganglia-cortical connections in FLE patients were investigated in the current study. FLE patients demonstrated alterations of FCs within the basal ganglia, as well as connections to distant brain regions including the limbic, frontal, parietal and occipital areas. In addition, the relationships between basal ganglia-cingulate connections and durations of epilepsy were also found in FLE patients. The importance of the alterations of functional integrity within the basal ganglia, as well as its connections to limbic and frontal areas implies the important roles of the basal ganglia-cortical functional connections in FLE, and provides new insights in the pathophysiological mechanism of FLE.

Conflicts of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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