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ORIGINAL RESEARCH

Abnormal dynamics of functional connectivity density in children with benign epilepsy with centrotemporal spikes

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Abstract

Converging evidence has shown the link between benign epilepsy with centrotemporal spikes (BECTS) and abnormal functional connectivity among distant brain regions. However, prior research in BECTS has not examined the dynamic changes in functional connectivity as networks form. We combined functional connectivity density (FCD) mapping and sliding windows correlation analyses, to fully capture the functional dynamics in patients with respect to the presence of interictal epileptic discharges (IEDs). Resting-state fMRI was performed in 43 BECTS patients and 28 healthy controls (HC). Patients were further classified into two subgroups, namely, IED ($n = 20$) and non-IED ($n = 23$) depending on the simultaneous EEG–fMRI recordings. The global dynamic FCD (dFCD) was measured using sliding window correlation. Then we quantified dFCD variability using their standard deviation. Compared with HC, patients with and without IEDs both showed invariable dFCD (decreased) among the orbital fontal cortex, anterior cingulate cortex and striatum, as well as variable dFCD (increased) in the posterior default mode network ($P < 0.05$, AlphaSim corrected). Correlation analysis indicated that the variable dFCD in precuneus was related to seizure onset age ($P < 0.05$, uncorrected). BECTS with IEDs showed variable dFCD in regions related to the typical seizure semiology. The abnormal patterns of fluctuating FCD in BECTS suggest that both active and chronic epileptic state may contribute to altered dynamics of functional connectivity associated with cognitive disturbances and developmental alterations. These findings highlight the importance of considering fluctuating dynamic neural communication among brain systems to deepen our understanding of epilepsy diseases.

Keywords BECTS · Dynamic functional connectivity density · IEDs · Resting-state fMRI · Variability

Introduction

Benign epilepsy with centrotemporal spikes (BECTS) is the most common childhood epilepsy syndrome characterized by nocturnal epileptiform spikes originating in the rolandic or sensorimotor cortex. Children with BECTS usually develop symptoms before 11 years old, and seizures tend to resolve at adolescence, regardless of treatment (Hughes 2010). Although considered benign, BECTS is often associated with cognitive disturbances that reflect the interference between the epileptic focus and developmental brain alterations. There is accumulating evidence that BECTS have abnormal cognitive and behavior maturation, with impaired attention, language and executive function (Kavros et al. 2008; Overvliet et al. 2011). These findings suggest that epileptogenic processes may include stable alterations in functional neural circuit organization and cognitive impairments in BECTS patients.

Resting-state functional connectivity, which is measured by functional magnetic resonance imaging (fMRI), can be used to investigate the integration of functional brain network at rest. To date, resting-state functional connectivity has been widely used in neuroimaging studies to study functional alterations in

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various types of epilepsy (Haneef et al. 2014; Li et al. 2016). Aberrant functional connectivity has also been identified in BECTS, particularly in the default mode network (DMN), striato-cortical circuit, and between motor and language areas (Besseling et al. 2013b; Li et al. 2017). The abovementioned studies indicated that the abnormal functional integration among brain regions may underlie the pathological mechanism of BECTS regardless of the active or chronic epileptic state. However, most previous studies used a seed-based analysis or independent component analysis (ICA), which may be biased because of the use of preselected seeds and incomplete description of brain functional architecture. Therefore, neither seed-based analysis nor the ICA approach can fully characterize the brain functional connectome (Joel et al. 2011).

Graph theoretical analysis is an unbiased approach that could provide a powerful framework to characterize the functional connectivity within the whole-brain network (Bullmore and Sporns 2009). In particular, functional connectivity density (FCD) mapping (D. Tomasi and Volkow 2010) is a novel voxel-wise graph theory approach that was used to identify hubs in the human brain. Thus, FCD is a feasible measure that allows us to characterize the functional alterations associated with epileptiform activity in BECTS. However, human brain connectivity is dynamic and associated with ongoing rhythmic activity, rather than stationary activity, over time (Calhoun et al. 2014). An emerging area of study is dynamic functional connectivity (Hutchison et al. 2013a), which can be investigated by measuring variability in strength. Although much remains unknown about the neurocognitive significance of dynamic functional connectivity, a previous work suggests that changes in functional connectivity can be associated with changes in psychological states (Hutchison et al. 2013b). Disruption of this intrinsic functional connectivity through pathological processes, such as active or chronic epileptic discharges, may be a significant mechanism underlying brain dysfunction and cognitive impairments in epilepsy patients. Therefore, the investigation of functional dynamics may provide new insights into abnormal brain communication in BECTS.

We combined FCD approach and sliding windows correlation analysis to explore the dynamic FCD (dFCD) changes in BETCS patients with interictal epileptiform discharges (IEDs) and without IEDs. Based on the previous findings (Li et al. 2017, 2018; Oser et al. 2014), we hypothesized that the patients with and without IEDs would have significantly altered dFCD in certain brain regions, especially in the regions of the DMN and those that are broadly involved in higher cognitive functions. In addition, patients with IEDs would show specific dFCD differences in regions associated with seizure origination or behavioral semiology.

Methods

Subjects

Study participants included 45 children who were diagnosed with BECTS from the Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. These clinical data were derived from our previously reported studies (Zhu et al. 2015; Li et al. 2017). All human procedures were approved by the Local Medical Ethics Committee of the Center for Cognition and Brain Disorders of Hangzhou Normal University, and written informed consents were obtained from the parents of these children. All the datasets were collected between June 2013 and April 2015. The inclusion for patients included the following: (1) diagnosed with BECTS in accordance with the International League Against Epilepsy classification (Berg et al. 2010), (2) aged 6–13 years and attending regular schools, (3) with no other developmental disability, (4) full-scale intelligence quotient (IQ) above 70, and (5) no history of addiction or disease other than epilepsy. The criteria for diagnosing BECTS were (1) presence of simple partial, often facial, and motor or tonic–clonic seizures during sleep and (2) spike waves in the centrotemporal regions visible on EEG. Exclusion criteria were (1) conspicuous MRI lesions and (2) falling asleep during scanning, which was assessed by self-report and the loss of alpha wave on simultaneously recorded EEG data. Finally, 43 patients with BECTS were included in this study, including 27 patients treated with antiepileptic drugs. The antiepileptic drug information for patients under treatment is provided in Table S1.

Healthy controls matched for sex, age and education were randomly recruited through local primary schools. These subjects had no history of neurological disorders or psychiatric illnesses and had no gross abnormalities on brain structural MR images.

Simultaneous EEG data acquisition

All patients underwent one or two simultaneous EEG and fMRI scans to record IEDs within 1 week after recording sleep EEG. EEG data were continuously recorded with an MR-compatible EEG recording system (Brain Products, Germany) during fMRI acquisition. A total of 32 Ag/AgCl electrodes were attached to the scalp and connected to a BrainAmp amplifier. EEG data sets were processed offline to remove MR and ballistocardiographic artifacts (Brain Vision Analyzer 2.0; Brain Products, Munich, Germany). The IEDs were recorded independently by two experienced electroencephalographers according to both spatial distribution and morphology. Accordingly, we placed BECTS patients into subgroups, namely, IED ($n = 20$) and non-IED ($n = 23$) based on the detection of IEDs during scanning. All patients with IEDs presented centrotemporal spikes on their

EEGs during the time of EEG–fMRI recording. In the IED group, the frequency of IEDs was in the ranged 2–293 (mean number of spikes = 91.05 ± 88.16).

fMRI data acquisition

The fMRI data were obtained on a 3.0 Tesla MRI scanner (GE Discovery 750, Milwaukee) at the Center for Cognition and Brain Disorders, in Hangzhou Normal University. For the fMRI scans, subjects were instructed to simply rest with their eyes closed. The acquisition parameters for functional imaging were as follows: repetition time/echo time = 2000 ms/30 ms, flip angle = 90°, field of view = 220 × 220 mm^2, matrix = 64 × 64, 43 transverse slices with slice thickness = 3.2 mm, and no interslice gap. For each subject, 240 volumes were acquired, resulting in a total scan time of 480 s. High-resolution 3D T1-weighted anatomical images were also acquired in the sagittal orientation using a magnetization-prepared rapid acquisition gradient-echo sequence (repetition time/echo time = 8.06 ms/3.136 ms, flip angle = 8°, field of view = 220 × 220 mm^2, matrix = 256 × 256, slice thickness = 1 mm, no interslice gap, and 176 slices).

Neuropsychological assessment

General intelligence (IQ), including verbal IQ, performance IQ and full-scale IQ, was assessed using the Chinese version of the Wechsler Intelligence Scale for Children (WISCIII). All scores were standardized for age and sex.

Data preprocessing

Functional data preprocessing was performed using Data Processing Assistant for Resting-State fMRI software (DPARSF, Advanced Edition, V3.2) (http://www.restfmri.net/forum/). The initial 10 functional images of each subject were discarded to ensure a steady-state longitudinal magnetization. Subsequently, we performed slice timing and alignment correction for the remaining 230 frames. We required that the transient movement during the scanning was no more than 3 mm of translation and 3° of rotation. Individual 3D T1-weighted anatomical images were coregistered with functional images. The 3D T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF), and normalized to the Montreal Neurologic Institute (MNI) space. These transformation parameters were then applied to functional images. The normalized images were resliced at a resolution of 3 × 3× 3 mm^3. The images were not smoothed to avoid introducing artificial local spatial correlations (Wang et al. 2009). The resulting data were further linear detrended and band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drifts and high-frequency physiological noise. Finally, several sources of nuisance signals (i.e., 24 head motion parameters, averaged signals from CSF, white matter and global signal) were regressed out using multiple linear regression analysis. A recent study evaluated the impact of global signal regression (GSR) on dFC and revealed that GSR possibly changed the functional connectivity variability in specific regions (Xu et al. 2018). Thus, the global signal was also regressed out in the current study. Functional connectivity analysis is sensitive to gross head motion effects (Power et al. 2012); thus, the mean frame-wise displacement (FD) was calculated to further determine the comparability of head movement across groups. The largest FD obtained from the subjects was less than 0.3 mm.

Dynamic functional connectivity density analysis

To identify the dynamic functional maps for each subject, we used a sliding window dFCD approach in the DynamicBC toolbox (Liao et al. 2014). In the sliding window-based dynamic analysis, window length is an open area of research and an important parameter. A "rule of thumb" is that the minimum window length should be no less than $1/f_{min}$, because short time segments would introduce spurious fluctuations. In this relation, f_{min} was the minimum frequency of the correlating time courses (Leonardi and Van De Ville 2015). Here, sliding window length of 50 TR was selected to optimize the balance between capturing a rapidly shifting dynamic relationships (with shorter windows) and achieving reliable estimates of the correlations between regions (with longer windows). The entire resting-state fMRI scan for each subject was segmented into sliding windows of 50 TR (100 s) and shifted with a step size of 10 TR, resulting in 19 windows in total. We also tried other window lengths (10 TR to 90 TR) and shifting step (1 TR and 5 TR) to further examine their possible effects on the dFCD results.

In each sliding window, we computed the Pearson's correlations between the truncated time series of pairs of brain voxels to obtain a whole-brain functional connectivity map at voxel level. This procedure was limited within a gray matter mask, which was generated based on the automated anatomical labeling (AAL) atlas without cerebellum. The number of functional connections k_i was defined using a given threshold r_0. Here, the correlation coefficient threshold was set at 0.2 to eliminate the weak correlations possibly arising from noise, according to significance level of $P < 0.001$. For a given voxel i, the global FCD was defined as the global number of functional connections k_i, between i and all other N-1 = 47,635 voxels in the brain. Two voxels were considered functionally connected if the correlation coefficient was larger than r_0. The calculation was repeated for all the voxels in the brain and involved the computation of a N^2 correlation matrix. Consequently, a set of sliding window FCD correlation maps were created for each participant. The temporal variability was then estimated by calculating the standard deviation of FCD

across sliding windows voxel by voxel. Finally, spatial smoothing (FWHM = 6 mm) was applied to the dFCD maps to reduce the brain functional anatomy differences among participants (Tomasi and Volkow 2010, 2011). For each subject, dFCD variability distributions were further normalized by the average strength in the whole brain to reduce the individual overall differences in the strength of dFCD variability.

Statistical analysis

One-way analysis of variance (ANOVA) was performed on the dFCD variance at each voxel to examine the difference of dFCD variability patterns among three groups. The resulting statistical map was AlphaSim corrected for multiple comparisons to a significant level of $P < 0.05$ by combining an individual voxel $P < 0.05$ and a minimum cluster size of 203 voxels. The brain regions showing significant differences based on the results of one-way ANOVA were subsequently defined as regions of interests (ROIs) for further post hoc analysis using the Bonferroni correction. The Bonferroni-corrected significance level was $P < 0.05$ divided by the number of ROIs and the total number of comparisons.

Clinical correlation analysis

The potential relationships among the brain regions with significant dFCD differences and clinical variables (disease duration, age at onset, and number of IEDs), and with the neuropsychological parameters (verbal IQ, performance IQ and full-scale IQ) in BECTS patients were determined using Pearson's correlation analysis. The threshold of $P < 0.05$ was considered statistically significant.

Verification analyses

To validate the current findings, the significant group differences of dFCD variability were reanalyzed with different conditions (window length, shifting step, medication and seizure lateralization) to confirm the reproducibility (see detailed information in Supplementary Materials).

Results

Demographics and neuropsychological characteristics

The demographic and clinical data of all participants are listed in Table 1. The three groups did not differ significantly in terms of sex, age, IQ, and mean FD. The age of symptom onset, disease duration, seizure frequency, and medication use of the patients with IEDs were similar to those of patients without IEDs (all $P > 0.05$, Table 1).

dFCD variability results

The average distribution maps of dFCD variability for each group are shown in Fig. 1. The average dFCD variability was highly localized in the visual cortex, the sensorimotor cortex, and the prefrontal cortex. The patterns of average dFCD variability had a similar distribution in patients and in the HC group. Figure 2 illustrates the dynamic dFCD variability differences among three groups. (one-way ANOVA, corrected for multiple comparisons using AlphaSim with $P < 0.05$). The statistical analysis revealed significant differences in the clusters of orbital portions of frontal gyrus, supramarginal

Table 1 Demographic and clinical information of subjects

Characteristics	IED(n = 20)	non-IED ($n = 23$)	HCs ($n = 28$)	P value
Age (years)	9.00 ± 1.95	10.22 ± 2.13	10.00 ± 2.31	0.63[a]
Sex (female: male)	13:7	11:12	13:15	0.40[b]
Onset age (years)	6.95 ± 1.85	7.48 ± 2.43	–	0.43[c]
Duration (months)	23.28 ± 31.90	34.27 ± 35.92	–	0.32[d]
Side of EEG (L:R:Bil)	6:13:1	10:11:2	–	0.52[e]
Number of seizures (/year)	2.27 ± 2.13	6.12 ± 11.75	–	0.42[d]
Treatment: Naive	10:10	6:17	–	0.11[e]
Medication (LEV:VAL:LTG:OXC)	2:2:2:5	6:4:4:3	–	0.45[e]
IQ				
Full-scale IQs	111.80 ± 11.52	107.40 ± 14.85	113.80 ± 14.59	0.31[a]
Verbal IQ	107.50 ± 14.05	105.00 ± 16.54	114.50 ± 15.84	0.13[a]
Performance IQ	113.90 ± 13.38	108.70 ± 16.51	109.50 ± 14.36	0.52[a]
mean FD (mm)	0.08 ± 0.06	0.06 ± 0.03	0.09 ± 0.06	0.15[a]

All values are mean ± standard deviation. L = left; R = right; Bil = bilateral; LEV = levetiracetam; VAL = sodium valproate; LTG = lamotrigine; OXC = oxcarbazepine; FD = frame-wise displacement. [a] One-way analysis of variance (ANOVA); [b] Kruskal-Wallis ANOVA; [c] two-sample t test; [d] Mann Whitney U-test; [e] Chi-square test

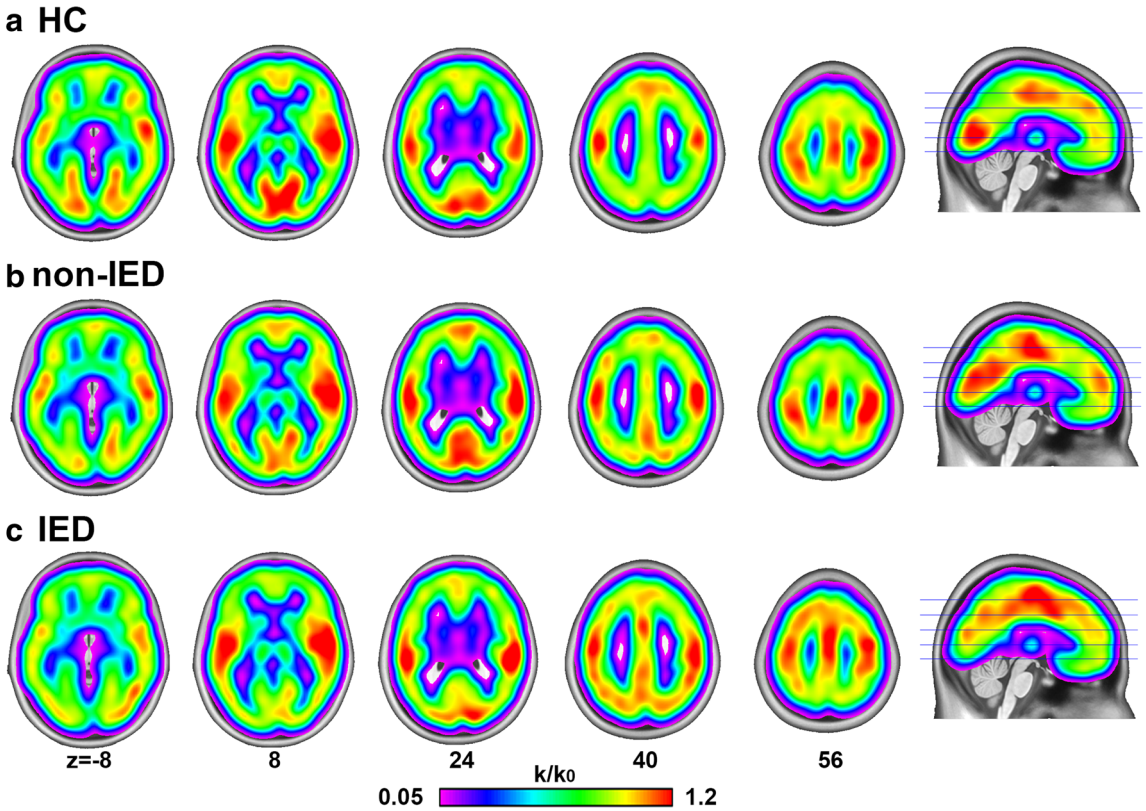

Fig. 1 The average distribution maps of dynamic fucntional connectibity density (dFCD) variability for each group. **a** The HC goup. **b** The non-IED patients group. **c** The IED patients group. The dFCD variability of each voxel was normalized by dividing the individual mean value. L, left; R, right

gyrus and precuneus (Fig. 2a). More detailed information about these significant clusters is shown in Table 2. Post hoc analyses were performed for the ROIs encompassing each region (Fig. 2b; $P < 0.05$, Bonferroni correction.). Compared with the HC group, the patients with and without IEDs exhibited significantly decreased dFCD variability in the orbital portions of inferior frontal gyrus and increased dFCD variability in the precuneus. The IED group showed higher dFCD variability in the cluster of supramarginal gyrus compared with the non-IED and the HC groups.

Correlation between dFCD variability and clinical variables

Secondary correlation analyses showed that the excessive dFCD variability of precuneus was negatively correlated with the onset age of seizure in non-IED group (Fig. 3, $r = -0.61$, $P = 0.0055$), whereas no significant correlation relationship was found between the excessive dFCD variability of precuneus and onset age in the IED group ($r = 0.19$, $P = 0.9122$). No significant correlations was found between the dFCD variability of other ROIs and disease duration or IQ scores in either the IED group or non-IED patient group.

Verification analyses

In the verification analyses, the group differences of dFCD variability with different conditions remained similar to the main findings. Detailed information is presented in the Supplementary Materials. In the window length and shifting step analyses, the group differences in dFCD variability remained similar to the main results obtained using window length of 50 TR and shifting step of 10 TR (Figs. S1 and S2). In addition, the decreased dFCD variability in the orbital frontal cortex and increased dFCD variability in the DMN persisted in the drug-naïve condition. The IED group also showed higher dFCD variability in the cluster of centrotemporal areas compared with the non-IED group and HC (Fig. S3). In addition, seizure lateralization did not have a significant effect on the group differences except for the region of orbital frontal cortex (Fig. S4).

Discussion

In this study, the dynamics of FCD associated with IEDs in children with BECTS was investigated for the first time. Previous studies have linked BECTS with disrupted static functional connectivity, especially among regions of the default

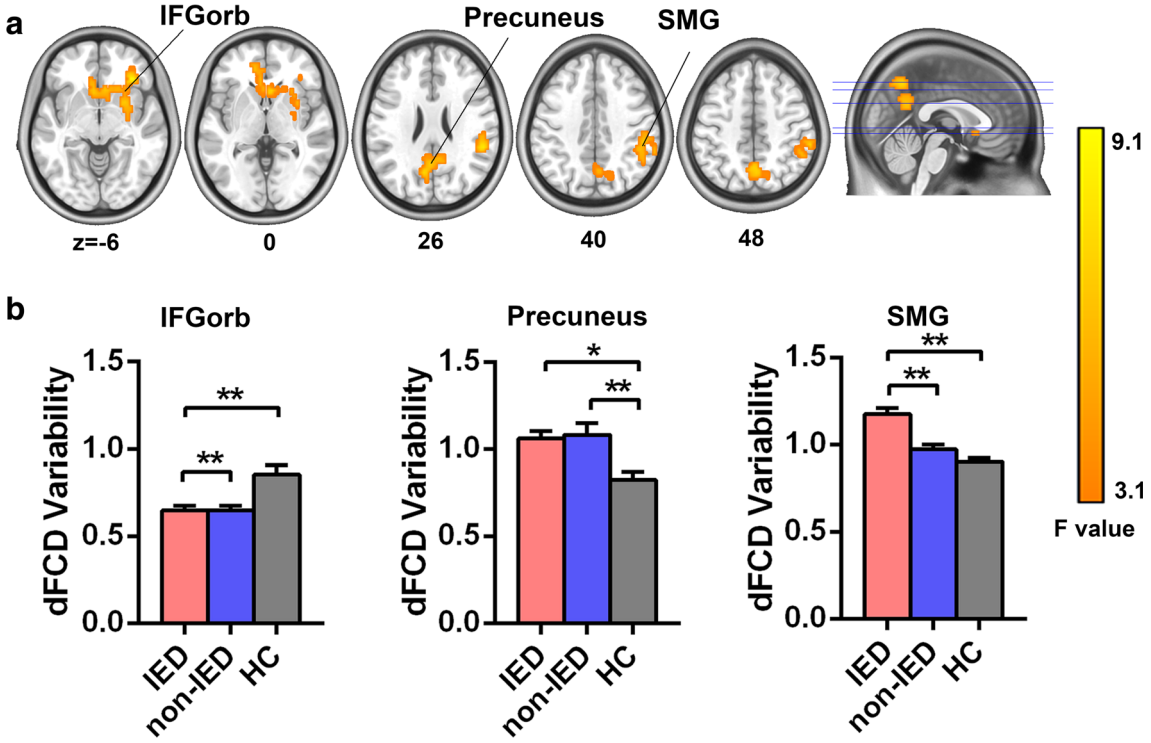

Fig. 2 The dynamic fucntional connectibity density (dFCD) variability differences among three groups. **a** Brain regions with significant group differences in dFCD variability revealed by one-way analysis of variance (ANOVA). The results were corrected for multiple comparisons using AlphaSim with $P < 0.05$ (combined an individual voxel $P < 0.05$ and a minimum cluster size of 203 voxels). Significant differences were observed in the orbital part of inferior frontal gyrus (IFGorb), precuneus, and supramarginal gyrus (SMG). L, left; R, right. **b** Bar graph showing the ROI-wise post hoc analysis results. *$P < 0.05$, uncorrected; **$P < 0.05$, Bonferroni correction

network, frontal regions, and between motor and language areas (Besseling et al. 2013b; Li et al. 2017). The present results complemented the results obtained by previous works by showing that BECTS is characterized by abnormal patterns of fluctuating FCD in overlapping regions. Patients with IEDs and without IEDs both exhibited decreased dFCD in the orbital portions of frontal cortex and increased dFCD in the posterior of the DMN. Specifically, BECTS with IEDs showed variable dFCD in the centrotemporal areas relative to the non-IED group and control subjects. This finding has important implications methodologically and enhances our understanding of the functional dynamics underlying the epileptic processes of BECTS.

Table 2 Brain regions that showed significant differences in dFCD variability among three groups

				MNI coordinates			
	Brain region	BA	Cluster size	X	Y	Z	F value
Cluster 1	Right inferior frontal gyrus, orbital part	47	253	36	33	−9	9.10
	Bilateral anterior cingulate cortex	11					
	Bilateral caudate	25					
	Right putamen	48					
Cluster 2	Right supramarginal gyrus	40	244	51	−39	30	8.78
	Right inferior parietal lobule	40					
	Right superior temporal gyrus	42					
	Right postcentral gyrus	43					
Cluster 3	Right precuneus	23/7	223	3	−63	45	7.82
	Bilateral posterior cingulate cortex	23					

Statistical significance level is corrected for multiple comparisons using AlphaSim with $P < 0.05$ (combined an individual voxel $P < 0.05$ and a minimum cluster size of 203 voxels). The peak coordinate is defined in the MNI space. dFCD, dynamic functional connectivity density; BA, Brodmann area

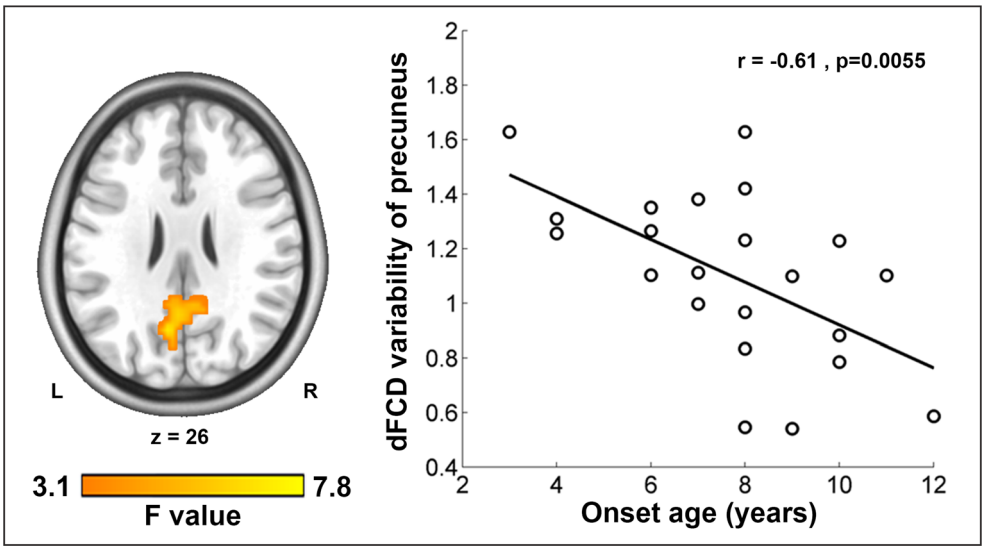

Fig. 3 Correlation between dynamic functional connectivity density (dFCD) variability in the precuneus and the onset age of seizures in the non-IED group. Left panel displays the axial view of the precuneus with significant group differences (AlphaSim corrected, combined height threshold $P < 0.05$ and a minimum cluster size of 203 voxels). L, left; R, right. Right panel shows the scatter plot of the negative correlation between the mean dFCD variability in the precunues/ posterior cingulate cortex and age at onset in the non-IED group

One of the important findings of the current study is that BECTS showed decreased dFCD variability in the cluster of orbital frontal cortex, anterior cingulate cortex (ACC) and striatum compared with the controls. Previous research suggests the regions involved in higher functions usually show higher dynamic functional connectivity, which is a pattern that may be related to functional flexible coupling of regulatory systems with other brain networks (Gonzalez-Castillo et al. 2014). The inferior frontal gyrus, ACC and striatum play a critical role in executive control and cognitive functions, such as language, response inhibition and motor processing (MacDonald et al. 2000). Based on the results, we speculate that the invariable functional connections of inferior frontal gyrus and ACC in BECTS may signify weaknesses in functional communication in brain circuits responsible for cognitive control, and could be related to the behavioral difficulties and language delays that are usually reported in BECTS (Sarco et al. 2011; Monjauze et al. 2005). Our findings are consistent with and significantly extended the results of recent reports using seed-based connectivity approaches. By investigating connectivity of sensorimotor seeds (Besseling et al. 2013a, b), Besseling and colleagues demonstrated that patients with rolandic epilepsy showed decreased connectivity between the sensorimotor area and the inferior frontal gyrus, which linked epileptiform activity/seizures originating from the sensorimotor cortex to language impairment in patients. For the seed at putamen, Luo et al. reported that BECTS patients show decreased functional connections with right anterior cingulate and frontal areas (Luo et al. 2015). It is interesting that the decreased dFCD variability of orbital part of frontal cortex, ACC and striatum was found in patients with and without IEDs, regardless of the active or chronic epileptic state. Previous studies suggested that the chronic epileptogenic processes may include stable alterations in altered regional activity patterns and aberrant functional synchrony (Laufs et al. 2014), which may contribute to lasting behavioral and cognitive disturbance. Hence, the present result of invariable dFCD in the inferior frontal gyrus, ACC, and striatum may be an indication of chronic dysfunction associated with repeated epileptogenic processes.

The variable dFCD in the cluster of precuneus and posterior cingulate cortex (PCC) in BECTS was another important finding. As suggested by previous studies (Buckner et al. 2009), these regions are possibly the functional hubs of the human brain. Meanwhile, the precuneus/ PCC is an interconnected core component of the DMN (Fransson and Marrelec 2008), which are more active at rest than during cognitive task performances (Fox et al. 2005). The DMN constitutes a favorable baseline neurometabolic environment for self-related processes, which is implicated in the consciousness impairment in epilepsy patients (Danielson et al. 2011). A previous task-related fMRI study has reported the decreased functional connectivity in the precuneus/PCC in BECTS patients (Oser et al. 2014). Recent EEG-fMRI studies also demonstrated reduced DMN activity in the presence of epileptiform discharges (Siniatchkin et al. 2010) and abnormal pattern of anticorrelation between the rolandic areas and the DMN in rolandic epilepsy (Xiao et al. 2016). Our finding of excessive dFCD variability in DMN in BECTS patients may imply that chronic and transient epileptic activities interfere with the globally brain functional interactions of DMN, thereby may contribute to unstable dynamic functional integration. Moreover, the increased dFCD variability of the precunues/PCC was negatively correlated with the age of epilepsy onset. According to the traditional view of normal DMN development, the functional connectivity of nodes of the DMN weakens during the process of aging (Damoiseaux et al. 2008). Given that BECT is thought to be part of a spectrum of neurodevelopmental disorders (Gobbi et al. 2006), the significant negative

correlation between the dFCD variability of DMN and the onset age may imply that epileptic processes can influence the functional development of BECTS, and this effect could be more dominant with an early age of onset. This finding provides further evidence for the delayed brain functional development of BECTS patients.

In addition to the consistent FCD variability alterations identified in both patient groups, we also found specific dFCD changes in spike-related brain areas only in patients with IEDs. Higher dFCD variability in the centrotemporal clusters including the supramarginal gyrus, inferior parietal lobule, superior temporal gyrus and postcentral gyrus was found in the IED group. Transient epileptic events such as IEDs are associated with altered brain activation and connections in syndrome-specific circuits. Previous studies have reported spike-related activation and altered functional connections in syndrome-specific regions such as motor areas and somatosensory association cortex (Zhu et al. 2015; Li et al. 2017; Archer et al. 2003). Consistent with these findings, the current increased dFCD variability in regions around the rolandic fissure suggest that there may exist specific dynamic patterns associated with active epileptogenic state that can characterize the functional abnormalities in BECTS.

This study has several limitations. First, although dynamic FC is widely used in previous clinical studies (Kaiser et al. 2016; Liu et al. 2017), much is unknown about what dynamic FC represents in terms of neurocognitive functioning. Second, the antiepileptic medications administered to some patients may have confounded the resting-state imaging and neurocognitive test results. Although we assessed for the treatment effect on dFCD variability in a relatively limited number of drug-naïve patients, these findings required replication in a larger homogeneous, prospective investigation. Third, previous studies (Adebimpe et al. 2015) have suggested that the laterality of spikes in BECTS may have significant effect on the functional connectivity. However, in the current analysis, we did not observe too much lateralization effects on the dFCD results. It is possible that the original spike foci may sometimes shift from one hemisphere to the homologous region of the other hemisphere in rolanidc epilepsy (Kellaway 2000). Further longitudinal studies are required to assess the side of the spike focus on lateralized functional dynamics. In addition, children with BECTS are usually associated with several cognitive comorbidities, particularly language dysfunction (Datta et al. 2013). IQ may not be the most sensitive measure of cognition. Thus, multidimensional cognitive tests are needed to assess cognitive functions of BECTS patients. Lastly, dFCD was calculated as the average of all the connections across the whole-brain in spite of short- and long-range connections. It would be interesting to calculate FCD with short- and long-range connections separately in a future study.

Conclusion

In summary, a combination of voxel-based FCD mapping and sliding windows correlation analysis demonstrated abnormal functional dynamics in BECTS. Decreased dFCD variability among orbital frontal cortex, ACC and striatum in patients may be related to interruptions to cognitive control and language function. Increased dFCD variability among areas of DMN may be associated with delayed brain functional development. In addition, patients with IEDs showed increased dFCD variability in regions related to the typical seizure semiology and the location of the seizure origination zone. Our results support the dynamic functional alterations associated with chronic and transient epileptic activity in patients with BECTS. These findings highlight the importance of considering fluctuating dynamic neural communication among brain systems to deepen our understanding of epilepsy diseases.

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Compliance with ethical standards

Conflict of interest Rong Li, Liangcheng Wang, Heng Chen, Xiaonan Guo, Wei Liao, Ye-Lei Tang, and Huafu Chen declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethnical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinksi Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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