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Altered language network in benign childhood epilepsy patients with spikes from non-dominant side: A resting-state fMRI study

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ABSTRACT

Benign childhood epilepsy with centrotemporal spikes (BECTS) is one of the most common childhood epilepsy syndromes, and language deficits associated with BECTS have become a hot topic. This study investigated alterations of the language network in BECTS children with spikes from the non-dominant side in comparison with healthy controls. Twenty-three children with BECTS and 20 age-matched healthy controls were enrolled. Region of interest − based whole brain functional connectivity analysis was used to identify the potential differences in the functional connectivity of the Broca's area between the two groups. Increased positive functional connectivity within the Broca's region was detected mainly at the left superior frontal gyrus (Brodmann area 8), bilateral insula, and anterior and posterior cingulate in the BECTS group. No regions showed significantly decreased connection in the BECTS patients compared to the controls. This study suggested alterations in the language network that was related with the Broca's area in children with BECTS from the non-dominant side. Further studies with longitudinal assessments from the perceptive of functional neuroimaging are needed to illustrate the dynamic course of language development and corresponding neuroimaging evidence.

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS) is one of the most common childhood epileptic syndromes and represents about 20% of epilepsies in children under age 15 (Panayiotopoulos et al., 2008). The prognosis is favorable because seizures and spike foci are self-limited and age-dependent; thus, it is considered "benign epilepsy". However, various language impairments in children with BECTS, including impairments in phonological production, verbal fluency and syntactic comprehension and cognition, were reported in the last two decades (Pesantez-Rios et al., 2016), which made BECTS not entirely benign. These language impairments may be of greater clinical concern than the seizures because they may persist after spontaneous remission of the latter. However, the underlying mechanism of the relationship between BECTS and language deficits remains to be investigated.

Currently, many studies have tried to address this relationship with methods such as neuroimaging, genetics experiments, and so on. Imaging methods have revealed that structure alterations exist, in BECTS patients, in the inferior frontal gyrus, posterior superior temporal gyrus, temporal lobe, and other regions that constitute the language network, and the alterations have been correlated with language test scores (Overvliet et al., 2013). In addition, fMRI studies have found reorganization of the language network and alterations in the default mode network during language task performances (Lillywhite et al., 2009; Oser et al., 2014). Furthermore, genetic research found a novel mutation in *foxp2* (p.M406T) in BECTS patients that might impair the regulation of *srpx2*'s promoter activity by FOXP2, which might lead to speech-related disorders (Roll et al., 2010).

At the same time, analysis of brain networks has provided new insight into the mechanism of pathological alterations in brain. For example, functional communication between brain regions plays a key role in complex cognitive processes, and resting-state functional connectivity (FC) has been widely used to demonstrate the communication. Resting state FC measures the temporal correlations in low frequency (< 0.1 Hz) spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals among brain regions without behavioral task confounds (van de Ven et al., 2004). In recent years, a growing body of studies applied this approach to investigating alterations in the default mode network in different clinical populations, such as individuals with Alzheimer's disease (Wang et al., 2006), schizophrenia (Liang et al., 2006), and partial epilepsy (Morgan et al., 2010), as well as to the study

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of the language and reading network (Lillywhite et al., 2009; Veroude et al., 2010).

In addition, a few neuroimaging studies revealed the impact of interictal epileptic discharge spikes (IEDs) on brain functions. For example, Zhu et al. demonstrated that thalamic dysfunction contributed to IEDs emergence while BECTS patients without IEDs exhibited intrinsic activity abnormalities in the middle frontal gyrus and superior parietal gyrus (Zhu et al., 2015). Ji. et al. showed that decreased global and regional efficiency could be readily identified with resting-state functional MRI and that it was prominent functional deficits in both BECTS patients with IEDs and those without (Ji et al., 2017). Meanwhile, another study showed IED patients to have decreased FC within the default mode network (DMN) compared with non-IED patients and increased positive correlations between the auditory network (AN) and the somato-motor network (SMN) (Li et al., 2017).

Despite the previous studies, FC analysis has not been carried out in BECTS from the non-dominant side. Some reports denoted that differences existed in the language network of BECTS patients with spikes from different sides, and the pathological spikes might contribute to white matter reorganization, which might influence focal connectivity (Boscariol et al., 2015; Xiao et al., 2016). Therefore, it is intriguing to investigate alterations in the language network in right-sided BECTS patients to determine how the spikes influence the network.

The Broca's area is a well-established speech production area. Functional MRI studies have also associated activation patterns in the Broca's area with various language tasks (Horwitz et al., 2003). Thus, we chose the Broca's area as the region of interest (ROI) to analyze its FC with other brain regions in BECTS patients and healthy controls. We were aimed to find out whether the FC between the Broca's area and other brain regions would differ between BECTS patients and healthy children during rest.

2. Methods and materials

2.1. Participants

A total of 23 newly diagnosed BECTS children with right-sided spike discharges (male/female: 12/11, average age: 8.8 ± 2.6years) were recruited from Epilepsy Clinic of the Department of Neurology, West China Hospital of Sichuan University from 1 June 2009 to 30 June 2014. The diagnosis of BECTS was made according to the classification criteria of International League Against Epilepsy (ILAE) (Engel 2006). This study was performed according to the standards set by the Declaration of Helsinki and approved by the Ethics Committee of the West China Hospital. The parents or guardians of all the children were informed of all research procedures and provided their consent before the experiment. All the patients received standard clinical assessments before the fMRI scanning, including age at onset of seizures, detailed seizure history, brain structural magnetic resonance imaging, history of febrile convulsions, family history and neurological examination. Additionally, patients were required to finish a 24 h video electroencephalogram (EEG) monitoring.

The inclusion criteria included the following: (1) right-handed BECTS children and no family history of left handedness; (2) centrotemporal spikes on EEG and concordant seizure semiology representing anarthria, hemiclonia involving the face and/or unilateral extremities, or secondarily generalized seizures; (3) uneventful pregnancy and delivery, normal neonatal status, early psychomotor development, enrollment in a standard school, and no academic underachievement reported; (4) no other neurologic, psychiatric, or somatic disorders or aphasia reported; and (5) no evidence of structural brain damage based on cranial structural MRI. The exclusion criteria were as follows: (1) atypical forms of BECTS (Tovia et al., 2011), Landau-Kleffner syndrome (LKS), or LKS-like cases; and (2) bilateral epileptic discharges or spikes shifting sides during 24 h Video-EEG monitoring.

Of the 23 patients, 3 were born by caesarean sections, 1 had a history of head trauma and 2 had a history of febrile convulsions. All the patients were right-handed (Edinburgh Handedness Inventory), native Chinese speaking, and enrolled in age-appropriate grades at school. The 24 h video EEG monitoring showed that only 16 cases had strictly right-sided epileptic discharges while 3 had left-sided discharges, and 4, bilateral IEDs. Ultimately, the 16 children with strictly right-sided BECTS were included for subsequent resting-state fMRI scanning. Twenty age-matched, right-handed healthy controls were also recruited. None of the controls had a history of neurological, psychiatric, or medical conditions as evaluated by an interviewer.

2.2. Neuropsychological testing

All the subjects were administered the Wechsler Intelligence Scale for Children —Revised for China, and all had a full-scale IQ above 75. Language abilities were examined using phonological awareness test, morphological awareness test, and Boston naming test. Well-trained doctors blinded to the experimental conditions administered the tests to all the subjects.

2.3. Data acquisition

During the MRI scanning, the subjects were instructed to relax with their eyes closed, remain motionless as much as possible, empty their minds, and be awake during the scanning (confirmed by the investigator immediately after the test). Foam pads and ear defenders were used to minimize motion and improve patients' comfort during the scan. BOLD-sensitive MRI data were acquired using gradient-echo echo-planar imaging sequences in a 3T MRI scanner (SIEMENS, Erlangen, Germany). The imaging parameters were as follows: 30 axial slices, thickness = 5 mm with no gap, TR/TE = 2000/30 ms, FA = 90°, in-plane resolution = 64 × 64, FOV = 240 mm × 240 mm. Exactly 205 vol. (30 slices per volume) were acquired during 410 s of an fMRI run. To ensure steady-state longitudinal magnetization, the first 5 vol. were discarded.

2.4. Data pre-process analysis

Functional image preprocessing was carried out by using SPM8 software package (statistical parametric mapping at http://www.fil.ion.ucl.ac.uk/spm). The slice time correction, 3D motion detection and correction, and spatial normalization to the MNI template supplied by SPM were included. To prepare the data for the main analyses, images were sampled to 3 × 3 × 3 mm3 cubes and smoothed with an 8 mm full-width at half maximum of an isotropic Gaussian filter. Two patients were excluded in the next analysis as they had had head motion of more than 1 mm or 1° during the fMRI acquisition. To extract the time series for cerebrospinal fluid (CSF) and white matter (WM), CSF and WM seeds were created. First, each spherical region (radius 5 mm) was selected as the seed, which was visually positioned in a relative area ([−18, −30, 21] and [−30, −21, 33]). Next, each mean signal intensity time course was extracted from the seed, and then CSF and WM time series were generated, respectively.

2.5. Resting state functional connectivity analysis with seed in the Broca's area

A single spherical region (radius 5 mm) positioned in the Broca's area (Brodmann area 44) [−53, 12, 19] (Papoutsi et al., 2009) was selected as the seed. The mean BOLD signal intensity time course was extracted from the seed. Two procedures were used to remove possible variances from the seed averaging time series. (1) Temporal band-pass filtering (0.01–0.1 Hz) was conducted through a phase-insensitive filter, which reduced the effects of low-frequency drift and high-frequency noise. (2) Through linear regression, the time series was further corrected to eliminate the effect of six parameters of head motion obtained during realigning and the effect of the signals from the CSF region, WM region, and global brain signal. After the same procedures were applied to the time series extracted from each brain voxel, cross-correlation functional connectivity analysis was performed by computing the temporal correlation between the seed and all brain voxels. Correlation coefficients of each voxel were normalized to Z-scores with Fisher's r-to-z transformation. Therefore, an entire brain Z-score map was created for each subject.

2.6. Statistical analysis

SPM8 was used to assess the voxel-wise statistical significance of functional correlations at the group level, as well as differences between controls and right-sided BECTS patients. First, an individual Z-score map was used in the random effect one-sample t-test. A statistical map of significant and positive functional connectivity with Broca's area was created for each group. The significance level was set at $p < 0.05$ and was corrected for multiple comparisons using the FDR criterion (Genovese et al., 2002), with cluster size > 540 mm3 (20 adjacent voxels). Next, to determine the differences between controls and BECTS patients in FC, the Z-scores maps were also processed in a random effect two-sample t-test with SPM8. To ensure that results could be further accounted for the discrepancies in the positive FC network between controls and patients, a union of positive T-maps that were defined in the proposed one-sample t-test was created and further used as a mask for SPM8. The significance level was set to $p < 0.05$ (FDR-corrected) and cluster size > 540 mm3 (20 adjacent voxels).

3. Results

3.1. Baseline information of the patients

Two patients (subjects number 3 and 7) were excluded due to head motions that exceeded 1 mm or rotations larger than 1° during the scanning. In the end, we acquired resting fMRI data from 14 patients (male/female: 8/6; mean age: 8.7 ± 2.6 years) and 20 healthy controls on a 3.0 T MR system. The clinical characteristics of the patients are listed in Table 1. Among the patients, 3 were drug naïve, and 11 received antiepileptic medication regularly (Valproate in 6 cases, Levetiracetam in 4 and Oxcarbazepine in 1). All the patients had been seizure-free for at least one week prior to fMRI scanning. None of the children suffered from epileptic status, 7 patients suffered from partial seizures, 4, generalized seizures, and 3, both types.

3.2. Broca region connectivity: within-group analyses

One-sample t-tests were performed for each of the two groups of patients and controls. The connectivity maps to the Broca's area seed in each group are shown in Fig. 1 (P < 0.05, FDR-corrected). In the control group, the connectivity analysis revealed positive FC to regions adjacent and homologous to the Broca's area and those extending bilaterally from the superior and middle temporal gyrus. Negative FC is mostly apparent in the posterior cingulate cortex. The BECTS group showed substantially similar positive FC patterns to the controls, but no negative FC was seen in this group in any brain area. The results are shown in Fig. 1.

3.3. Broca region connectivity: between-group analysis

Between-group analysis was performed at two levels using the SPM8 two sample t-test (P < 0.05, FDR-corrected, 20 adjacent voxels). First, the FC maps of the controls and the patients were compared throughout the brain in search for differences in FC between the groups. The analysis showed that the patients had increased FC in the precuneus, frontal lobe, anterior and mid cingulate cortex, and insula. Second, since there were negative FC in the controls but not in the patients (Fig. 1), if one region showed negative FC in the controls while positive in the patients, the difference in this region between the two groups would most likely be a false positive. Therefore, we combined all the areas only with positive connectivity in either group and compared FC in these areas between the groups. We found significantly increased connectivity from the Broca's area to the left superior frontal gyrus (Brodmann area 8), bilateral insula, and anterior and posterior cingulate in the BECTS group (Fig. 2 and Table 2). In contrast, no regions showed significantly decreased connectivity to the seed in the BECTS patients compared to controls at the level of whole-brain comparison or of the areas with positive FC. The results revealed that FC within the Broca's area was changed in the BECTS patients.

4. Discussion

To the best of our knowledge, this is the first report of connectivity comparison between the Broca's areas in BECTS patients with spikes from the non-dominant side and healthy volunteers. This study found patterns of Broca's area's connectivity network in regions such as the bilateral superior temporal gyrus (Wernicke's area BA22) and temporoparietal junction, and these regions have been shown to promote language processing in children and adults (Nunez et al., 2011). The second-level comparison found increased connectivity located in regions of the bilateral insula, anterior and posterior cingulate cortex, and left superior frontal gyrus (BA8) in BECTS patients.

Identification of connections to the Broca's area has been considered a cornerstone in the understanding of language processing. Connection studies in monkeys showed reciprocal connections between the inferior

Table 1
Baseline information of the BECTS patients.

Patient no.	Sex	Age	Age at seizure onset	Seizure type	Frequency	AEDs
1	Male	12	8	Partial	Once per few months	VPA
2	Male	9	9	partial	A total of 4 times	LEV
4	Male	12	11	Partial	A total of twice	/
5	Female	12	9	Partial	Once per month	LEV
6	Male	10	9	Partial, Generalized	A total of 3 times	/
8	Female	7	6	Generalized	Several times per month	VPA
9	Female	6	5	Partial, Generalized	A total of 4 times	LEV
10	Female	8	7	Partial	Once per few months	/
11	Male	6	1	Generalized	Once per month	VPA
12	Male	11	10	Partial, Generalized	A total of 7 times	VPA
13	Male	7	4	Generalized	A total of 4 times	VPA
14	Female	5	3	Partial	Once per few months	LEV
15	Male	6	6	Partial	A total of twice	OXC
16	Female	11	11	Generalized	A total of 3 times	VPA

Subjects 3 and 7 were excluded because of excessive head motions; VPA: Valproate Acid; LEV: Levetiracetam; OXC: Oxcarbazepine.

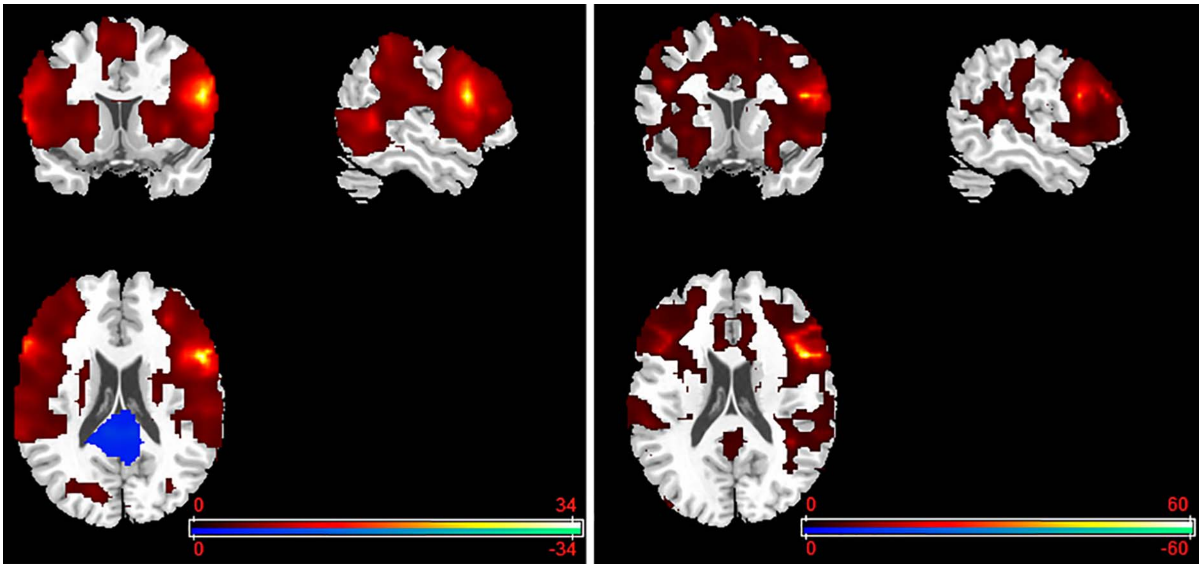

Fig 1. Results of one-sample *t*-tests of the functional connectivity (FC) to the Broca area (seed in MNI = [-53, 12, 19], Left IFG) in BECTS (right, k = 20, T = 4.52) and controls (left, k = 20, T = 3.69). The warm and cold colors indicate the brain regions with positive and negative FC to the Broca area, respectively ($P < 0.05$, FDR-corrected, 20 adjacent voxels). The left side of the image corresponds to the left side of the brain.

temporal area and the Broca's area (BA45) via the uncinate fasciculus, which supports the significance of this circuit in semantic processing (Webster et al., 1994). Connection between the Broca's area and the supramarginal gyrus was also found to play an important role in phonological processing (Zatorre et al., 1996).

The increased connectivity map in regions of the bilateral insula, anterior and posterior cingulate cortex and left superior frontal gyrus, found in this study, may also enrich our understanding of language processing. The insula is important in integrating afferent and efferent connections to a wide range of cortical and limbic areas. It has strong

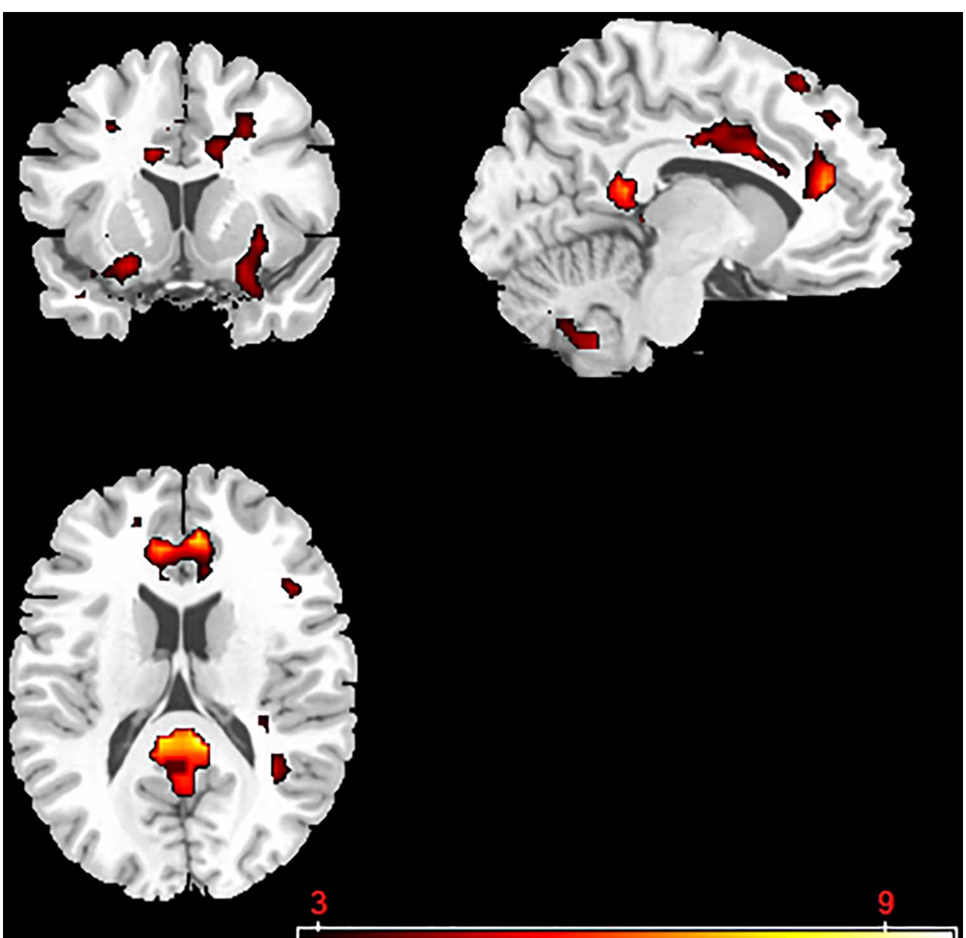

Fig. 2. Results of two-sample *t*-tests of the FC with the Broca area between BECTS and controls ($P < 0.05$, corrected by FDR, k = 20, T = 2.86). The warm color indicates the brain regions with significantly increased functional connectivity in BECTS compared to controls. The left side of the image corresponds to the left side of the brain.

Table 2
ROI-based analysis of FC between two groups within the language network.

Location	Talairach			Voxel size	Peak t	P value
	x	y	z			
ACC	−6	38	13	136	7.59	< 0.05
Mid cingulum	−4	−11	38	275	6.41	< 0.05
PCC	−6	−40	16	289	7.72	< 0.05
Left-insula	−24	8	−20	66	4.60	< 0.05
Right-insula	39	17	−26	115	5.25	< 0.05
Left frontal lobe (BA8)	−15	23	46	93	4.49	< 0.05

Data were FDR corrected. Abbreviations: ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; BA: Brodmann area.

connectivity with the orbitofrontal and the ventrolateral prefrontal cortex, which has been interpreted as evidence for its involvement in language acquisition (Chee et al., 2004). More recently, Baldo et al. declared the insula as "region for coordinating speech articulation", based upon cliniconeuroimaging studies (Baldo et al., 2011). The cingulate cortex, described as the center of emotion, sensation, and action processing, also plays a key role in cognitive processing. Kaneda noted the activation of the anterior cingulate cortex (ACC) in verbal working memory, whereas the posterior cingulate cortex (PCC) was linked to memory, including memory recollection (Kaneda and Osaka, 2008). A study recently demonstrated that decreased connectivity of the ACC with other brain areas might underlie a broad range of language deficits, such as impairment in perception, comprehension, retrieval, and production (Bush et al., 2000). The prefrontal region (traditionally comprised of BA 8, 9, 10, 11, 44, 45 and 47) has been associated with language and memory processing since Petersen et al. provided the first line of functional neuroimaging evidence that implicated the region in the semantic analysis of words (Price 2010).

All the data from the previous studies and our findings point to engagement of altered networks in the neural systems for language processing in BECTS patients. We, therefore, hypothesize on the following three possible mechanisms underlying the altered FC in BECTS.

4.1. Brain activity background alteration

An EEG study on BECTS patients found that Rolandic spikes increased Low Resolution Elec- tromagnetic Tomography activity in the BECTS group, as compared to the controls, in the left and right temporal lobes and in the angular gyri in the parietal lobes (Petersen et al., 1989). The altered background activity might influence the language network located mainly in the temporal lobe. This view was also supported by a genetic study, which illustrated that focal epilepsy focus might influence brain functions globally, especially the language function (Roll et al., 2010).

4.2. Compensatory mechanism

It has been shown that reorganization of the language network was frequent in epileptic patients, especially those with temporal lobe epilepsies with neural plasticity-dependent changes. Piccirilli et al. concluded that epileptiform activity in BECTS could modify the hemispheric lateralization of language (Piccirilli et al., 1988). Another study, by combining fMRI and voxel-based morphometry, also showed that frequent IEDs might induce reorganization of functions originally localized in areas that IEDs originated in or propagated to (Labudda et al., 2012). Lillywhite et al. conducted an fMRI study on language lateralization of BECTS patients and concluded that language-related activation was less lateralized to the left hemisphere in the anterior brain in BECTS patients with left-sided discharge (Lillywhite et al., 2009). It is possible that altered connectivity within the language network in BECTS children may be due to compensatory action related with epileptic discharges and disruption in the physiological language processing. This hypothesis was supported by Bates and his colleagues (Bates et al., 2001), whose study indicated no difference in language production between children with left-side versus right-side brain damages. They demonstrated that a complete neural and behavioral plasticity could follow early brain damages. We propose that the alterations may solicit new functional pathways compensating for the impaired language network.

4.3. Delay in brain development

BECTS manifests during a critical phase of brain maturation. Developmental studies have revealed functional connectivity in typically developing children to have age-dependent patterns of cortical maturation. Using connectivity analysis, investigators have described the differences in the resting state networks of children, adolescents, and adults. Resting state networks are present in infancy, develop during childhood, and mature after adolescence (van de Ven et al., 2004). Children with BECTS are experiencing fast physical development, including maturation of language networks. It is thus possible that BECTS patients exhibit developmental delays in the maturation of their neural circuitry. The altered FC within the Broca's area in BECTS patients might be correlated with the delay in neural development. In fact, a longitudinal group study on BECTS claimed that temporal neuropsychological impairments were often observed in BECTS patients, whereas the more long-lasting and more specific neuropsychological deficits were observed in Landau-Kleffner syndrome (Metz-Lutz and Filippini, 2006). From this point of view, developmental studies with regular longitudinal assessments are needed to confirm the reconstruction of normal language network after remission of BECTS.

4.4. Limitations

Several limitations should be noted here. First, our sample size was modest, which might have led to reduced sensitivity to the effects of interest including group activation and connectivity differences. Second, some patients in the present study were treated with Valproate or Levetiracetam, and we cannot eliminate the effects of antiepileptic drugs on the brain network. Furthermore, the influence of interictal discharges during the scans was not accounted for. Future studies, therefore, should rely on simultaneous EEG to monitor the interictal discharges, which will minimize confounding factors of interictal discharges.

5. Conclusions

In conclusion, the investigation on resting-state functional connectivity in BECTS patients using fMRI provides novel insights into the language network alterations in BECTS. We detected several increased Broca's area-related connectivity networks. This study partly supports the proposition that the normal language network is disrupted in BETCS children. However, the underlying mechanism is still not completely revealed. Multimodal longitudinal designs are necessary to fully characterize changes in the language network that occur over the lifespan of these children, especially the period from disease onset, through the active epilepsy phase, to remission.

Disclosure

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