Altered functional and effective connectivity in anticorrelated intrinsic networks in children with benign childhood epilepsy with centrottemporal spikes

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Abstract

There are 2 intrinsic networks in the human brain: the task positive network (TPN) and task negative network (alternately termed the default mode network, DMN) in which inverse correlations have been observed during resting state and event-related functional magnetic resonance imaging (fMRI). The antagonism between the 2 networks might indicate a dynamic interaction in the brain that is associated with development.

To evaluate the alterations in the relations of the 2 networks in children with benign childhood epilepsy with centrottemporal spikes (BECTS), resting state fMRI was performed in 17 patients with BECTS and 17 healthy controls. The functional and effective connectivities of 29 nodes in the TPN and DMN were analyzed. Positive functional connectivity (FC) within the networks and negative FC between the 2 networks were observed in both groups.

The patients exhibited increased FC within both networks, particularly in the frontoparietal nodes such as the left superior frontal cortex, and enhanced antagonism between the 2 networks, suggesting abnormal functional integration of the nodes of the 2 networks in the patients. Granger causality analysis revealed a significant difference in the degree of outflow to inflow in the left superior frontal cortex and the left ventral occipital lobe.

The alterations observed in the combined functional and effective connectivity analyses might indicate an association of an abnormal ability to integrate information between the DMN and TPN and the epileptic neuropathology of BECTS and provide preliminary evidence supporting the occurrence of abnormal development in children with BECTS.

Abbreviations: BECTS = Benign childhood epilepsy with centro-temporal spikes, BOLD = blood oxygenation level-dependent, DLPFC = Dorsolateral prefrontal cortex, DMN = default mode network, EEG = Electroencephalography, FC = functional connectivity, FEF = frontal eyefield, fMRI = functional magnetic resonance imaging, FSIQ = full scale intelligence quotient, HC = healthy control, IPS = intraparietal sulcus, IQ = intelligence quotient, PCC = posterior cingulate cortex, PIQ = performance intelligence quotient, ROI = regions of interest, SD = standard deviation, SFC = superior frontal cortex, SMA = Supplementary motor area, TPN = task positive network, VIPS = ventral intraparietal sulcus, VIQ = Verbal Intelligence Quotient.

Keywords: antagonism, benign childhood epilepsy, default mode, effective connectivity, functional connectivity, functional magnetic resonance imaging
1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS) is the most common type of idiopathic epilepsy in children. The onset of this disorder ranges from 1 to 14 years old. Electroencephalography (EEG) has revealed that epileptiform discharges are localized to the centrotemporal region (Rolando's region). This syndrome remits spontaneously after adolescence and does not result in structural brain damage or cognitive deficits. However, recent studies have shown that children with BECTS exhibit the following symptoms that strongly influence their daily lives: an increased frequency of partial motor seizures during sleep, the daytime appearance of atypical absence seizures, negative myoclonus, and loss of tension. Additionally, BECTS is thought to be associated with abnormal development, psychiatric disorders associated with reduced IQ, dyscalculia, dyslexia, spatial perception and orientation problems, and visuomotor impairments. Selective language deficits have been observed during the active phase of the syndrome. These behavioral abnormalities may be associated with disturbed cerebral organization in children with BECTS.

Spontaneous low-frequency blood oxygenation level-dependent (BOLD) signals can reflect the synchronization of remote brain regions in the resting state, and are suggestive of many inherent networks in the human brain. Research has shown that the BOLD signals are synchronized between brain regions that are connected anatomically or functionally. Human brain is intrinsically organized into dynamic, anticorrelated systems that include the task negative network and the task positive network (TPN). The TPN, which is mainly responsible for the processing of external stimuli, including the transfer of information and spatial attention, consists of the bilateral frontal eye fields, the dorsolateral prefrontal cortex, the inferior parietal lobule, the intraparietal sulcus, the supplementary motor area, and the insula. The task negative network, also known as the default mode network (DMN), includes the posterior cingulate cortex (PCC), ventral mesial prefrontal cortex, lateral parietal cortex, bilateral superior frontal cortex, and superior temporal gyrus, and deactivation is often observed in this network during the performance of specific tasks.

In resting state functional magnetic resonance imaging (fMRI), the 2 functional networks exhibit significant negative correlations, that is, antagonism, in which the nodes were positively (13 typical nodes in DMN) or negatively (16 typical nodes in TPN) correlated with the special region PCC. This antagonism might indicate dynamic competition between the 2 networks when multiple types of information are simultaneously processed. One hypothesis is that the reciprocal relationship might reflect a low-frequency toggling between the extrastate and the self-referential introspective states (task independent). The extrastate and introspective states represent a preparedness to ensure that an individual is attentive to novel or unexpected environmental events. The potential degree of antagonism between the 2 systems might be associated with the binding mechanism that the brain utilizes to process multiple threads while simultaneously performing psychophysiological functions. Some researchers have suggested that this antagonism may be of more scientific interest than the default mode activity. In addition, the resting state functional connectivity (FC) between and among the 2 networks is also influenced by the prior brain states.

Recently, many studies have reported altered anticorrelations between the 2 networks in patients with autism, schizophrenia, and attention deficit hyperactivity disorder based on resting state fMRI. A proper neural machinery is important for maintaining normal neurocognitive and neuropsychological states, and the lack of a proper neural machinery has been considered to be associated with altered antagonism in these patients. Furthermore, research has found that children with BECTS exhibit less activation in the DMN compared with control children during resting states and less deactivation in the DMN compared with control children when the subjects are asked to perform language tasks. Thus, the dynamic interactions within and between the DMN and TPN might provide some evidence that will aid the understanding of the behavioral abnormalities in patients with BECTS. Granger causal analysis is often used to assess effective connectivity in the human brain based on resting state fMRI data. These analyses may help to predict neuronal activity levels and FC dynamics in the human brain. The dynamic features of the DMN have been evaluated in healthy controls and patients with Alzheimer disease. Therefore, the alterations in the functional and effective connectivities between the TPN and DMN in patients with BECTS might be associated with disturbed neurocognitive function and abnormal development.

The purpose of this study was to test the functional and effective connectivities between and within the 2 antagonistic networks in patients with BECTS. First, using FC analysis between regions of interest (ROI) within the network, we reconstructed the functional connections within and between the ROIs in the TPN and DMN in the patient and control groups. We then assessed the effective connectivities using conditional Granger causality analysis. The effective and functional connections between each pair of ROIs were compared between 2 patients and healthy controls.

2. Materials and Methods

2.1. Subjects

Twenty-one BECTS patients (all right handed, 13 girls, age range: 6–11.5 years, 4 cases with right discharges, 7 cases with left discharges, and 10 cases with bilateral discharges) participated in the current study. These patients were recruited at the Affiliated Hospital of the North Sichuan Medical College. All of the patients underwent a comprehensive clinical evaluation for the diagnoses of BECTS according to the epilepsy classification of the International League Against Epilepsy. The exclusion criteria were as follows: brain lesions on routine brain MRI scans, developmental disabilities, and other accompanying neurologic disorders. Twelve patients were newly diagnosed with epilepsy and did not receive antiepileptic drugs, and 9 patients received monotherapy with valproic acid or levetiracetam. Twenty healthy volunteers (all right handed, 10 girls, age range: 6–12) were recruited as the healthy control group. The controls had no neurological or psychiatric disorders. There was no difference in the ages or genders between the 2 groups (2-sample t test of age P > 0.05 and Pearson Chi-square test of gender P > 0.05). The demographic information of the subjects is shown in Table 1. This research was approved by the Ethics Committee of the affiliated hospital of North Sichuan Medical College. All subjects and parents provided the written informed consent before any study procedure was initiated. All subjects were also included in our previous study.

2.2. Neuropsychological assessment

The verbal intelligence quotient (IQ), performance IQ, and full-scale IQ based on the Chinese version of the Wechsler Intelligence Scale for Children (WISC-III) were assessed in both BECTS and control participants. The verbal IQ includes common sense,
Thirteen ROIs in DMN
Sixteen ROIs in TPN

Brain regions and abbreviations
Brodmann area
DMN

TPN

The 29 ROIs in DMN and TPN.

Table 1
Demographic, clinical characteristics of patients with BECTS and HC.

|               | BECTS    | HC       | P      |
|---------------|----------|----------|--------|
| Sex (M/F)     | 21 (13/8)| 20 (10/10)| 0.443  |
| Age, y        | 9.12±1.51| 9.26±1.96| 0.614  |
| Age at onset, y | 8.02±1.64|          |        |
| Duration, mo  | 13.41±12.96|        |        |

WISC

|               |    |        |        |
|---------------|----|--------|--------|
| VIQ           | 81.06±11.88| 101.5±6.37| <0.001 |
| PIQ           | 80.12±11.23| 115.93±6.21| <0.001 |
| FSIQ          | 78.0±12.24| 108.93±6.40| <0.001 |

BECTS = benign focal epilepsy of childhood with centrotemporal spikes, FSIQ = full-scale intelligence quotient, HC = healthy control, PIQ = performance intelligence quotient, VIQ = verbal intelligence quotient.

Table 2
The 29 ROIs in DMN and TPN.

| Brain regions and abbreviations | Brodmann area | MNI coordinates |
|---------------------------------|---------------|-----------------|-----------------|
|                                 | X  | Y   | Z   |
| Sixteen ROIs in TPN             |    |     |     |
| 1. Left intraparietal sulcus (LIPS) | 7  | –23 | –70 | 46  |
| 2. Right intraparietal sulcus (RIPS) | 7  | 25  | –62 | 53  |
| 3. Left inferior parietal lobule (LPL) | 7  | –42 | –48 | 51  |
| 4. Right inferior parietal lobule (RPL) | 40 | 48  | –41 | 54  |
| 5. Left ventral intraparietal sulcus (LviPS) | 19 | –26 | –84 | 24  |
| 6. Right ventral intraparietal sulcus (RviPS) | 19 | 35  | –85 | 27  |
| 7. Left frontal eye field (LEF) | 6  | –24 | –15 | 66  |
| 8. Right frontal eye field (RFEF) | 6  | 28  | –10 | 58  |
| 9. Inferior precentral sulcus (IPCS) | 6  | –55 | –2  | 38  |
| 10. Supplementary motor area (SMA) | 2  | –2  | –2  | 55  |
| 11. Left dorsolateral prefrontal cortex (LDLFC) | 46 | –40 | 39  | 30  |
| 12. Right dorsolateral prefrontal cortex (RDLFC) | 46 | 38  | 41  | 26  |
| 13. Left ventral occipital lobe (LOO) | 19 | –47 | –71 | –8  |
| 14. Right ventral occipital lobe (ROO) | 37 | 55  | –64 | –13 |
| 15. Left anterior insula (Lins) | 19 | –45 | 5   | 9   |
| 16. Right anterior insula (Rins) | 19 | 45  | 3   | 15  |

| Thirteen ROIs in DMN |    |     |     |
|----------------------|----|-----|-----|
| 17. Medial prefrontal cortex (VPC) | 11 | –4  | 43  | –11 |
| 18. Medial prefrontal cortex (DPC) | 10 | 0   | 61  | 13  |
| 19. Posterior cingulate cortex (PCC) | 23 | –4  | –33 | 40  |
| 20. Left lateral parietal cortex (LLPC) | 39 | –53 | –66 | 41  |
| 21. Right lateral parietal cortex (RLPC) | 39 | 55  | –66 | 43  |
| 22. Left superior frontal cortex (LSFC) | 9  | –17 | 47  | 49  |
| 23. Right superior frontal cortex (RSFC) | 9  | 17  | 37  | 49  |
| 24. Left inferior temporal cortex (LITC) | 20 | –67 | –35 | –19 |
| 25. Right inferior temporal cortex (RITC) | 21 | 69  | –18 | –18 |
| 26. Left parahippocampal gyrus (LPHG) | 35 | –25 | –28 | –17 |
| 27. Right parahippocampal gyrus (RPHG) | 35 | 26  | –28 | –17 |
| 28. Cerebellar tonsils (CT) | —  | 7   | –58 | –48 |
| 29. Retrosplenial (RET) | 30 | 2   | –52 | 10  |

DMN = Default Mode Network, MNI = Montreal Neurological Institute, ROI = Regions of Interest, TPN = Task Positive Network.
standard Montreal Neurological Institute space and resampled to $3 \times 3 \times 3$ mm$^3$. Finally, spatial smoothing was applied with a Gaussian kernel of 6 mm at full width at half-maximum.

### 2.5. Functional connectivity of the DMN and TPN

First, based on previous study, the number of ROIs in 2 networks was set as 29, including 13 ROIs in the DMN and 16 ROIs in the TPN. Then, the PCC ($-1, -33, 40$) was selected as a seed to identify the DMN (positivity connection map) and TPN in both groups. The peak voxel with the most significant connection to PCC in each of 29 regions was extracted as the center of ROI. Detailed information about the ROIs is listed in Table 2. The mean time series of each ROI was obtained by averaging the time series of all voxels in the spheres with a 6-mm radius around the central coordinates (Table 2). The time series were further temporally hand-pass filtered (0.01–0.1 Hz), and the 6 motion parameters obtained by rigid body correction, the white matter and the whole brain signals were regressed out. The residuals of these regressions were processed by the linear detrending. For each subject, a temporal correlation test was used to identify the directed causal connection as a causal flow for each group. The causal connectivity amplitudes were required to differ from the null distribution. The bootstrap methodology (the randomly sampled number of surrogate time series was 1000) was used to construct the null distribution of causal connectivity amplitudes. Lastly, the outflow degrees which represents the amount of the number of outflows of a given nodes, and inflow degrees which sums all the inflows were calculated for each node and each subject. The difference between the inflow- and outflow degrees was defined as the out–in degrees, which were tested to quantify the differences between the 2 groups.

### 3. Results

#### 3.1. Demographic characteristics and neuropsychological tests

Four patients and three controls were excluded due to excessive motion (translation greater than 2 mm in three patients and 2 controls; head rotation greater than 1.5° in 1 patient and 1 control). Seventeen patients with BECTS and 17 controls were included in the FC analysis. Table 1 illustrates the demographic characteristics and the results of the neuropsychological tests.

#### 3.2. Functional Connectivity analysis

There were 406 ($C_{29}^{2}$) pairs of potential functional connections between the 29 nodes. The average functional correlation coefficients are illustrated in Fig. 1. Consistent with previous studies, both groups of subjects exhibited positive relationships within the TPN and DMN and negative relationships between the 2 networks. However, more obvious functional connections within and between networks were observed in the patients than in the healthy controls: the control group revealed 33 significantly positive functional connections and 35 marked negative

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**Figure 1.** The functional connectivity in patients BECTS (right) and healthy controls (left). The significant connections with $P < 0.001$ (FDR corrected for the multiple comparisons) are illustrated. The nodes in TPN are colored in red, and the nodes in DMN are colored in blue. The red lines delineate the positive functional connections (within network), and the blue lines represent the negative functional connections (between 2 networks).
functional connections; the patients with BECTS exhibited 53 positive functional connections and 61 negative functional connections. The significance level was set at \( P < 0.001 \) in 1 sample \( t \) test for each group (FDR corrected for the multiple comparisons).

Regarding the positive functional connections within the networks, the patients with BECTS exhibited 1 pair of increased functional connections within the DMN and 3 pairs of increased functional connections within the TPN relative to the healthy controls (Table 2), but no decreased functional connections were observed in the 2 networks. Regarding the negative functional connections between the networks, there were 2 pairs of functional connections with significantly decreased anticorrelations between the networks in the patients with BECTS compared with the healthy controls (Table 3). No increased functional connections were observed. In other words, the antagonism between the 2 networks was enhanced in the patients with BECTS.

Additionally, the patients with BECTS also exhibited stronger connectivity between the SMA and rDLPFC; this connectivity was significantly positively correlated with the duration of epilepsy \( (r = 0.687, P = 0.002) \) after controlling for the effects of gender and age. There were no significant correlations between FC and IQ scores.

### 3.3. Granger causality analysis

The average values of the Granger causal flows in the patients and healthy controls are shown in the Supplementary Material (S_Table 1 http://links.lww.com/MD/B28 for the patients and S_Table 2 http://links.lww.com/MD/B28 for the healthy controls). The significant Granger causal flows were delineated with arrowed line in Fig. 3. The within-group level out–in degree is illustrated in Fig. 4. The pattern in the healthy controls was clearly distinct from that in the patients. Compared with the healthy controls, the patients exhibited decreased out–in degrees in the left ventral occipital lobe and the left superior frontal cortex. The main inflow and outflow connections of 2 nodes were showed in the Supplementary Material (S_Figure 1, http://links.lww.com/MD/B28).

### 4. Discussion

Using functional and effective connectivity analyses on the resting state fMRI data, the current study primarily investigated the
intrinsic connectivity between the nodes in the DMNs and TPNs of patients with BECTS and healthy controls. Positive FC within the networks and negative connectivity between the 2 networks were observed in both groups. Compared with the healthy controls, 2 main findings were observed in the patients. First, the patients exhibited more marked increases in FC within both networks, particularly in the frontoparietal nodes, including the left superior frontal cortex, and enhanced antagonism between the 2 intrinsic networks, which suggested abnormal functional integration among the nodes of the 2 networks in the patients. Second, the effective connectivity analysis revealed a significant difference in the degree of outflow relative to inflow in the left superior frontal cortex and left ventral occipital lobe in which the main forward causal interaction (output) in the healthy controls was changed into a backward causal flow (left ventral occipital lobe) or no significant out-in flow (left superior frontal cortex). These findings indicated an altered effective connection pattern in the patients with BECTS that might be related to the some frontoparietal nodes which located the epileptogenic zones in previous studies.[30,31] In general, the alterations of the functional and effective connectivities might reflect not only the association between the abnormal information integration ability and epileptic neuropathology in BECTS but also the abnormal development of the patients with cognitive impairments. In previous studies, decreased FC has often been reported in patients with different types of epilepsy,[26,32,33] suggesting that the epileptiform activity interrupts the functional interactions of the brain. Interestingly, more obvious FC was observed in the patients with BECTS than in the healthy controls. There are 2 possibilities that might help to interpret this unusual phenomenon. On the one hand, the potential epileptogenic zones of BECTS are thought to be in the frontoparietal lobe, that is, in the postcentral gyrus,[30] which is associated with the TPN. In addition, the seizure focus and propagation were investigated by the resting state function connectivity analysis[34] and effective connectivity analysis.[35] Thus, the functional integration between nodes of the network might be enhanced because of the long-term epileptiform activity in these regions associated with epileptogenic zones. On the other hand, the essential clinical feature of BECTS, that is, the remission of seizures spontaneously after adolescence,[36] might contribute to the differences in the findings related to BECTS and other types of epilepsy with poor prognoses. Future studies are needed to confirm these speculations.

In general, the slowing or regression of development in children with epilepsy is primarily due to seizures, abnormal interictal
cortical and subcortical epileptic activity, or both.\cite{37,38,39} BECTS is a common type of childhood epilepsy. We presumed that the epileptic activity would contribute to the cognitive behavioral defects and abnormal neuroimaging findings in children with BECTS. The DMN, which is sensitive to development,\cite{40,41} and its anticorrelated network, the TPN, were investigated in this study. In previous studies, the functional integration of the DMN has been found to change from sparse to cohesive during childhood.\cite{42} Here, the patients with BECTS exhibited not only altered FC between the nodes in the DMN but also anticorrelated activity between the nodes of the DMN and TPN. The abnormal FC related to the DMN might indicate that the developmental trajectory of the default mode of the brain was interrupted in these children patients. Additionally, the patients recruited for this study also exhibited decreased IQ scores relative to the healthy controls of the same age. Because the BECTS was considered as a benign epilepsy syndrome without or with slight cognitive impairments,\cite{43,44} our BECTS group would represent a cohort of specific patients with BECTS syndrome. These cognitive impairments might be related with the interrupted development in children patients. The regressions in cognitive development are typically observed in childhood and adolescence with reductions in IQ, language impairments, and neurobehavioral disturbances.\cite{37,45} However, the use of a longitudinal design rather than the cross-sectional analysis used in this study would provide a preferable avenue to study development. Therefore, our findings reflect the abnormal development of BECTS children with cognitive impairments to some extent. The DMN and its associated regions (including the anticorrelated regions) might provide a potential window to investigate the abnormalities of development in children with epilepsy.

Findings from studies with simultaneous EEG and fMRI have shown significant negative activations in regions of the DMN and positive activations in regions of the TPN in response to both general and local epileptic discharges.\cite{46} These regions are considered to be associated with the origination and/or propagation of the epileptic activity. The pre- and postcentral gyri have been observed to exhibit significant activation related to the local epileptiform spikes of BECTS in simultaneous EEG and fMRI.\cite{39} In scalp EEGs, the centrotemporal region (i.e., the frontotemporal lobe) is commonly observed to exhibit epileptiform discharges in patients with BECTS.\cite{31} Significantly increased functional connections between the frontal (SFC, DLPFC, and FEF) and parietal nodes (IPS and vIPs) were observed in this study. The increased FC exhibited in these nodes in the frontotemporal lobe might reflect the abnormal features of the connections of these regions and their tight associations with long-term epileptic activity. Moreover, the increased FC between the DLPFC and SMA was positively correlated with the duration of epilepsy. Moreover, consistent with the increased FC with the SFC, the effective connectivity analysis also demonstrated obvious alterations and abnormal causal flow directions and magnitudes in the left SFCs of the patients compared with the healthy controls. This causality may represent physiological inhibitory and excitatory effects and elucidates the pathophysiology of severe disorders.\cite{37,41} According to the out–in degree (Fig. 4), the patients exhibited a predominant driving (outflow) effect from the left SFC to the other nodes in which feedback (inflow) was observed in the healthy controls. Altogether, our findings derived from combined functional and efficient connectivity analyses provided further evidence that interruptions in the frontotemporal nodes of the DMN and TPN may be associated with epileptiform activity in BECTS.

With regard to the limitations of this study, it could be argued that the antiepileptic drugs might cause the altered brain connectivity. Nine in 21 patients received the antiepileptic drugs in this study. The effects of the drugs might confound our observation. Second, the side of spikes in unilateral BECTS might influence the findings showed in the current study. More patients with BECTS would be recruited in future to investigate the lateral spikes’ effect on the functional and effective connectivity among the nodes in DMN and TPN. Then, the BECTS syndrome is in general not associated with significant cognitive abnormalities. Our patients’ group showed decreased IQ compared with the healthy controls, thus, the findings would represent only one aspect of typical BECTS syndrome. Finally, the patients with BECTS were just performed the clinical routine EEG in this study. It is difficult to evaluate the precise source of spikes and the relation with the findings of functional and effective connectivity showed here. The high density EEG would be recorded to noninvasively localize the epileptic focus in future.

5. Conclusion

In this study, the intrinsic functional organization of the brain was investigated with functional and effective connectivity analyses of synchronized low-frequency fluctuations of the BOLD signals in the TPN and DMN in BECTS. We found that the patients with BECTS exhibited significantly altered functional connectivities within the networks and antagonism between the networks. Additionally, the nodes in the frontotemporal lobe with altered FC exhibited abnormal effective connectivities. These findings derived from combined functional and effective connectivity analyses might indicate an abnormal information integration ability of the DMN–TPN with the epileptic neuropathology of BECTS. These findings provide preliminary evidence supporting the occurrence of abnormal development in BECTS children with cognitive impairments.

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