

Altered Structural and Functional Feature of Striato-Cortical Circuit in Benign Epilepsy with Centrottemporal Spikes

Cheng Luo^{*,§}, Yaodan Zhang[†], Weifang Cao^{*}, Yue Huang[‡], Fei Yang[†],
Jianjun Wang[‡], Shipeng Tu^{*}, Xiaoming Wang^{†,¶} and Dezhong Yao^{*,||}

**Key Laboratory for NeuroInformation of Ministry of Education
Center for Information in BioMedicine
High-Field Magnetic Resonance Brain Imaging
Key Laboratory of Sichuan Province
University of Electronic Science and Technology of China
Chengdu 610054, China*

*†Neurology Department
Affiliated Hospital of North Sichuan Medical College
North Sichuan Medical College
NanChong 637007, China*

*‡Pediatric Department
Affiliated Hospital of North Sichuan Medical College
North Sichuan Medical College
NanChong 637007, China*

§chengluo@uestc.edu.cn

¶wangxm238@163.com

||dyao@uestc.edu.cn

Accepted 7 May 2015

Published Online 29 June 2015

Benign epilepsy with centrottemporal spikes (BECT) is the most common form of childhood idiopathic focal epilepsy syndrome. We investigated quantitative evidence regarding brain morphology and functional connectivity features to provide insight into the neuroanatomical foundation of this disorder, using high resolution T1-weighted magnetic resonance imaging (MRI) and resting state functional MRI in 21 patients with BECT and in 20 healthy children. The functional connectivity analysis, seeded at the regions with altered gray-matter (GM) volume in voxel-based morphometry (VBM) analysis, was further performed. Then, the observed structural and functional alteration were investigated for their association with the clinical and behavior manifestations. The increased GM volume in the striatum and fronto-temporo-parietal cortex (striato-cortical circuit) was observed in BECT. The decreased connections were found among the motor network and frontostriatal loop, and between the default mode network (DMN) and language regions. Additionally, the GM of striatum was negatively correlated with age at epilepsy onset. The current observations may contribute to the understanding of the altered structural and functional feature of striato-cortical circuit in patients with BECT. The findings also implied alterations of the motor network and DMN, which were associated with the epileptic activity in patients with BECT. This further suggested that the onset of BECT might have enduring structural and functional effects on brain maturation.

Keywords: Benign epilepsy with centrottemporal spikes; striato-cortical circuit; functional connectivity; voxel based morphometry; resting state functional MRI.

Cheng Luo and Yaodan Zhang contributed equally to this work.

1. Introduction

Benign epilepsy with centrotemporal spikes (BECT) is the most common form of childhood idiopathic focal epilepsy syndrome (15–20% of all childhood epilepsy cases, with a male predominance), and the most frequent age of onset is 7–10 years of age.^{1,2} The spontaneous remission occurs in almost 90% of patients with BECT before the age of 16 years.^{1,3} The distinctive clinical manifestations include short-lasting focal motor or sensory seizures that occur during sleep,^{1,3} specific biphasic sharp wave discharges arising from the centrotemporal regions (rolandic spikes).² Ciumas and colleagues illustrated diffusion tensor imaging (DTI) evidence of white matter (WM) abnormalities in patients with BECT, suggesting that the abnormal developmental trajectory of the brain is influenced by epileptic activity.⁴ BECT is therefore considered a development disease.

The epileptogenic zone of rolandic spikes involves neuronal networks inside the rolandic cortex surrounding the central fissure.⁵ However, rolandic spikes resulted from abnormal cortical excitability,^{6,7} can commonly lead to disturbances within a hemisphere including the opercularis of the frontal and parietallobes. Although BECT is considered as a type of “benign” epilepsy due to the good prognosis and remission of seizures before adulthood, neuropsychological abnormalities involving memory, language and executive function are often found in patients with BECT.^{8,9} Neuroimaging evidence has shown disturbed activation responses to language tasks^{10,11} and altered structural and functional connections between the motor and language networks.¹² The gray matter (GM) features, including volume and thickness,^{13,14} and WM parameters, including diffusion and fiber tracking,^{4,15} were also observed in the cortical (the rolandic region, perisylvian regions and pre- and postcentral gyri) and subcortical regions (the putamen and caudate nuclei) in patients with BECT. Together, these studies suggest that the cortical and subcortical disturbances in BECT may be associated with the various neuropsychological deficits.

Voxel-based morphometry (VBM), an automated tool to assess the regional anatomical differences in gray or WM between groups *in vivo*, which is based on high resolution magnetic resonance imaging (MRI), has been widely applied to explore the alterations of brain structures in patients

with neuropsychiatric disorders.^{16–18} GM volume is a useful parameter that reflects the amount of regional GM. The chronic effects of epileptic discharges may increase the extracellular space and cause structural reorganization, which may induce microstructural changes. VBM studies have illustrated structural abnormalities in patients with different types of epilepsy.^{19,20} Functional connectivity analysis based on resting state fMRI signals may allow a better understanding of characteristics of brain organization.^{21–23} This type of analysis has been used in several types of epilepsy to delineate functional abnormalities.^{24–29} In patients with BECT, Besseling *et al.* showed abnormal intrinsic functional connectivity between sensorimotor and language regions.³⁰ The functional connectivity to the regions with structural alteration may reflect the functional abnormality associated with the structural abnormality. The approach combined VBM and functional connectivity analysis would provide more meaning findings to the neuroanatomical foundation, and is adopted in neuropsychiatric disorders.^{16,31,32} However, to our knowledge, there is almost no study that combines VBM and functional connectivity analysis for the investigation of functional disturbances of the brain in BECT patients.

In general, the structural alteration of brain accompanies with the functional abnormality. Contrary to previous connectivity studies, in which seeds were defined based on *a priori*, the present study employed structural alteration (VBM results) as a seed to analyze the functional connectivity. We hypothesize that the regions with significant changes in GM volume may be involved in functional connectivity abnormalities. Our approach combining VBM and functional connectivity analysis will contribute to the understanding of the potential pathophysiological mechanisms of BECT.

2. Methods

2.1. Participants

Twenty-one patients with BECT, aged 6–11.5 years, were recruited over a two-year period (from June 2012 to May 2014) from among pediatric epilepsy outpatients and the inpatient department of the Affiliated Hospital of North Sichuan Medical College (demographic and clinical information are detailed in Table 1). Our selection criteria included (i) the

Table 1. Demographic, clinical and neuropsychological features of the subjects.

	BECT	HC	P value
Gender (male/female)	21 (13/8)	20 (10/10)	0.443 ^a
Age (year)	9.12 ± 1.51 (6–11.5 years)	9.26 ± 1.96 (6–12 years)	0.614 ^b
Age at onset (year)	8.02 ± 1.64	—	—
Epilepsy duration (month)	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 ± 12.24	108.93 ± 6.40	<0.001

Notation: ^aChi-square test, ^btwo-sample *t*-test.

Abbreviations: BECT: benign focal epilepsy of childhood with centrottemporal spikes; HC: healthy control; WISC: Wechsler intelligence scale for children; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; FSIQ: full scale intelligence quotient.

diagnosis of BECT was established according to the criteria of the International League Against Epilepsy (ILAE)³³ by pediatric epileptologists (X.W., J.W. and Y.H.) and was based on clinical and electroencephalogram characteristics; (ii) no other accompanying neurologic psychological disorders (e.g., ADHD) were present; (iii) normal routine brain MRI scans and (iv) no developmental disabilities were present. All patients underwent routine clinical EEG recordings. Left-sided spikes were observed in seven patients, right-sided spikes were observed in four patients and bilateral spikes were observed in ten patients including eight patients with left-side predominance. Nine patients received monotherapy with valproic acid or levetiracetam, and 12 patients were newly diagnosed with epilepsy and did not receive antiepileptic drugs (AEDs). Twenty healthy subjects, aged 6–12 years, were recruited as a control group. All of the controls were interviewed to confirm that they had no history of neurological and/or psychiatric disorders. There were no differences in the ages and genders between the two groups (Table 1). All subjects were right-handed native Chinese speakers. Subjects and his/her parents were gave informed consent for the study. This research was reviewed and approved by the Ethical Committee of the Affiliated Hospital of North Sichuan Medical College. All

patients could perform cognitive assessments independently.

2.2. Neuropsychological tests

Both BECT and control participants completed a battery of neuropsychological tests using the Chinese version of the Wechsler intelligence scale for children (WISC-III), which provided composite scores for full scale intelligence quotient (IQ), verbal conceptual reasoning (verbal IQ), and nonverbal reasoning (performance IQ).

2.3. Image acquisition

Brain MRI scans were acquired on a 3T MRI scanner (GE DISCOVERY MR750) using an eight-channel standard whole head coil. High-resolution T1-weighted images were acquired using a three-dimensional fast spoiled gradient echo (T1-3D FSPGR) sequence (TR = 6.008 msec, TE = 1.984 msec, FA = 90°, matrix = 256 × 256, FOV = 25.6 × 25.6 cm², slice thickness (no gap) = 1 mm) to generate 152 slices. Resting state functional MRI data were acquired using gradient-echo EPI sequences (TR = 2000 ms, TE = 30 ms, FA = 90°, matrix = 64 × 64, FOV = 24 × 24 cm², slice thickness = 4 mm (no gap), 32 slices per volume). All subjects underwent a 410s resting state scan yielding 205 volumes. To ensure stabilization of the major magnetic field (B₀), the first five volumes were discarded. During data scanning, subjects were instructed to close their eyes without falling asleep.

2.4. Voxel-based morphometry analysis

All T1 images were reviewed by a radiologist (C. L.). One patient was excluded due to motion artifacts in T1 images. VBM was performed using a statistical parametric mapping package (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). First, all T1 images were manually coregistered with the standard T1 template provided by SPM8. The coregistered images were then segmented into GM, WM and cerebrospinal fluid (CSF) using the unified segmentation procedure.¹⁷ A diffeomorphic nonlinear registration algorithm (DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra), which provides improved registration accuracy compared with conventional VBM,³⁴ was used to warp

the GM partitions into a new customized references space representing an average of all the subjects. The resulting images of average size were further spatially normalized to MNI space using an affine spatial normalization. Second, to preserve the volume of a particular tissue (GM or WM) within a voxel, a further modulation step was included. This step involved multiplying the spatially normalized GM by its relative volume before and after spatial normalization.¹⁷ When using modulated images for performing subsequent group comparisons, the inference was made on measures of volume rather than tissue concentration (density). Finally, the segmented modulated images for GM were smoothed with an isotropic Gaussian kernel (8 mm full width at half maximum).

Voxel-based comparisons of gray-matter volume were performed between the two groups using two-sample *t* tests in SPM8. The age, gender and whole brain volume were corrected by including them as confounding covariates. The level of significance for group differences was set at $p < 0.05$ (FDR-corrected).

The ROIs were defined based on the results of the VBM comparison. The averaged GM volumes of each ROI were correlated with clinical factors (age at onset and epilepsy duration) and neuropsychological scores (verbal IQ, performance IQ and full-scale IQ) using partial correlation analysis, controlling for the effects of age, gender and AED. The study included 12 newly diagnosed patients who did not receive AEDs. We used the values of one or zero to represent patients who did or did not receive AEDs, respectively, and the resulting sequence was used as a covariate in the partial correlation analysis. Thus, the information regarding AEDs only represented whether a given patient received AEDs, rather than the category and dose of the drugs.

2.5. Functional connectivity analysis

Imaging data were preprocessed using the SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm/>). The functional data of each subject were corrected for slice timing and motion. Subjects with head motion more than two mm (translation) and 1.5° (rotation) during scanning were excluded. Next, the functional data were spatially normalized to standard Montreal Neurological Institute (MNI)

space and resampled to $3 \times 3 \times 3 \text{ mm}^3$. Then, spatial smoothing was applied with a 6-mm full-width at half maximum (FWHM) Gaussian kernel. Finally, the six head motion parameters, CSF and WM and globe signals were regressed out in the general linear model for each subject.³⁵ After excluding four patients and three control subjects due to excessive head motion, the remaining 34 subjects, including 17 patients and 17 controls, were analyzed in the following functional connectivity analysis.

Functional connectivity analysis was performed using REST software (<http://www.restfmri.net>).³⁶ The seed was defined with a radius of 6 mm and a center voxel at the peak of the difference compared to the VBM. For a given seed, the Pearson's correlation was calculated between the time courses from seed and each voxel in whole brain. Then, correlation coefficients were converted to a normal distribution by Fisher's *z* transform. For each group, individual *z*-value maps were analyzed with a random effect one-sample *t*-test to identify voxels that showed a significant correlation with the seed. Finally, a two-sample *t* test was used to compare the differences between groups. The group comparison was restricted to the clusters with significant functional connectivity maps in both groups by using an explicit mask from the union set of the one-sample *t*-test results.

3. Results

3.1. Demographic characteristics and neuropsychological tests

Demographic characteristics and IQ scores are presented in Table 1. The group mean age was 9.12 years (SD = 1.51) in patients and 9.26 years (SD = 1.96) in healthy controls, and no difference was found between groups ($p = 0.614$). The IQ scores, including verbal IQ, performance IQ and full scale IQ, are illustrated in Table 1. The IQ scores of patients were significantly lower than the healthy controls ($p < 0.001$).

3.2. Voxel-based morphometric analysis

Table 2 presents eight clusters with significant differences in GM volume between groups ($p < 0.05$, FDR-corrected). Compared with the controls, patients with BECT showed significantly increased GM volume in the bilateral putamen, paracentral

Table 2. The cluster with increased GM volumes in patients with BECT compared with controls.

Abbreviation	Region	t value	Cluster size (voxel)	Brodmann area	MNI coordinate		
					X	Y	Z
R_ITG	Inferior temporal gyrus	5.45	83	BA 20	57	-52	-14
R_SMA	supplementary motor area	5.38	159	BA 6	4.5	-18	55.5
R_PCL	Paracentral lobule	5.17	214	BA 7	13.5	-42	55.5
R_Ins/FOpe	Anterior insula/frontal operculum	4.56	181	BA 47	48	24	-4.5
L_CB	Cerebellum	4.03	115	—	-18	-72	-47
R_Put.	Putamen	4.02	202	—	18	12	-9
L_PCL	Paracentral lobule	4.01	192	BA 7	-7.5	-42	60
L_Put.	Putamen	3.61	59	—	-22	3	-7.5

lobule (PCL), right anterior insula/frontal operculum, right supplementary motor area (SMA), right inferior temporal gyrus and left cerebellum (Fig. 1). The results were visualized using the xjView toolbox (<http://www.alivelearn.net/xjview>).

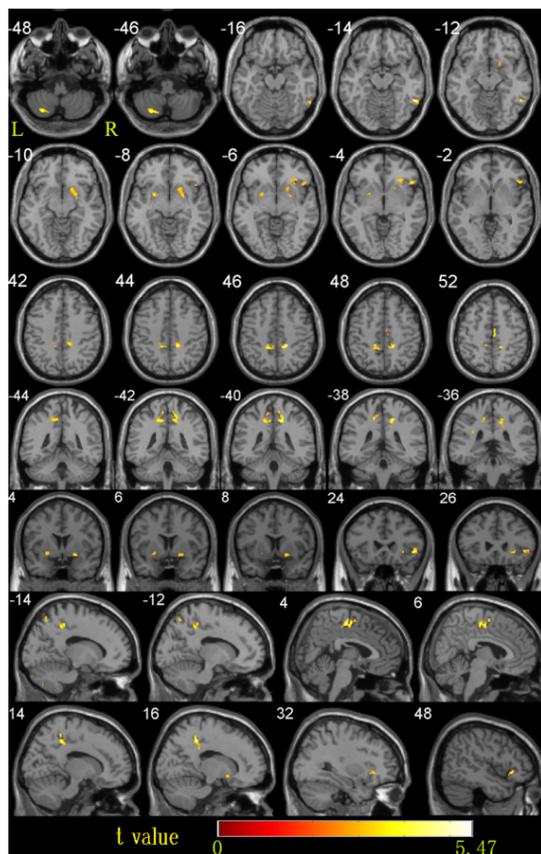


Fig. 1. The difference of GM volume between groups. The increased volume in patients contrast to healthy controls is shown in hot color. No decrease GM volume was observed in patients.

For eight ROIs with significantly increased GM volume (peak voxels shown in Table 2), we found a significant negative correlation between the GM volume of the bilateral putamen and age of epilepsy onset after controlling for the effects of age, gender and AEDs (Fig. 2; $r = 0.586$, $p = 0.017$ for the left putamen; $r = 0.520$, $p = 0.039$ for the right putamen). We observed a significant positive correlation of the volume of the right anterior insula/frontal operculum with the verbal IQ ($r = 0.644$, $p = 0.007$) and full scale IQ ($r = 0.708$, $p = 0.002$). These findings are demonstrated in Fig. 3. We did not find a significant association with clinical factors for the remaining ROIs.

3.3. Functional connectivity analysis

We chose eight ROIs based on the differences of GM volumes between groups, including bilateral putamen, PCL, right anterior insula/frontal operculum, right SMA, right inferior temporal gyrus and left cerebellum. The peak of these ROIs is shown in Table 2. To assess the effect of structural alterations in patients with BECT on intrinsic functional connectivity, we further explored changes in the spontaneous functional networks of the eight ROIs.

Resting state functional connectivity analysis revealed the alteration of functional connection in four ROIs ($p < 0.05$, FDR corrected; Table 3 and Fig. 4), but no significant difference between groups was found in the remaining four ROIs, which included the left putamen, left cerebellum, right PCL and right temporal lobe. For the seed at the right putamen, patients showed the decreased functional connections with right anterior cingulate

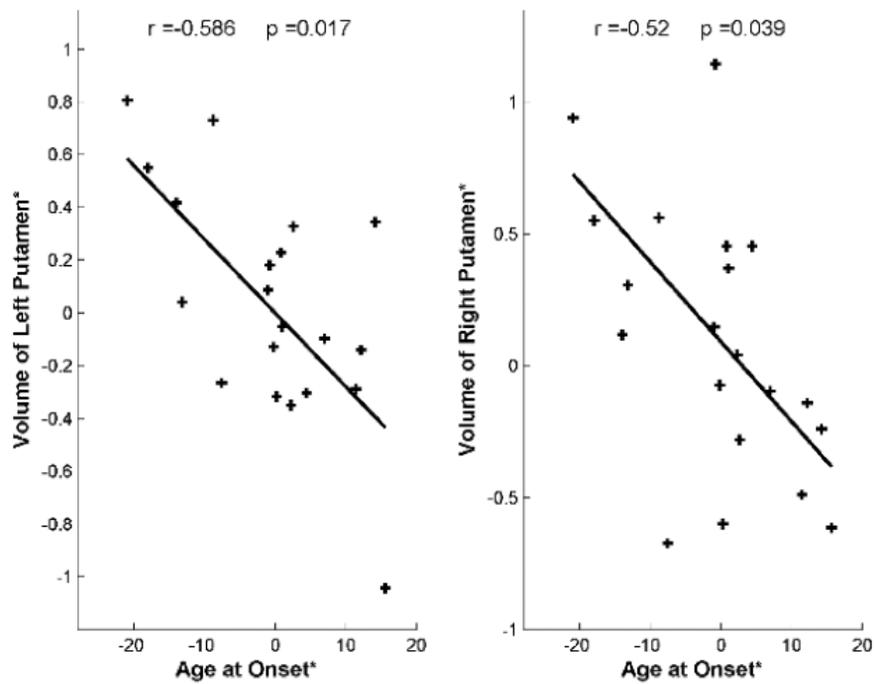


Fig. 2. The negative correlation between age at onset and the GM volume in bilateral putamen in patients. * represents the adjusted values controlling for the influence of the gender, age and AEDs (linear regression with covariates including gender, age and AEDs).

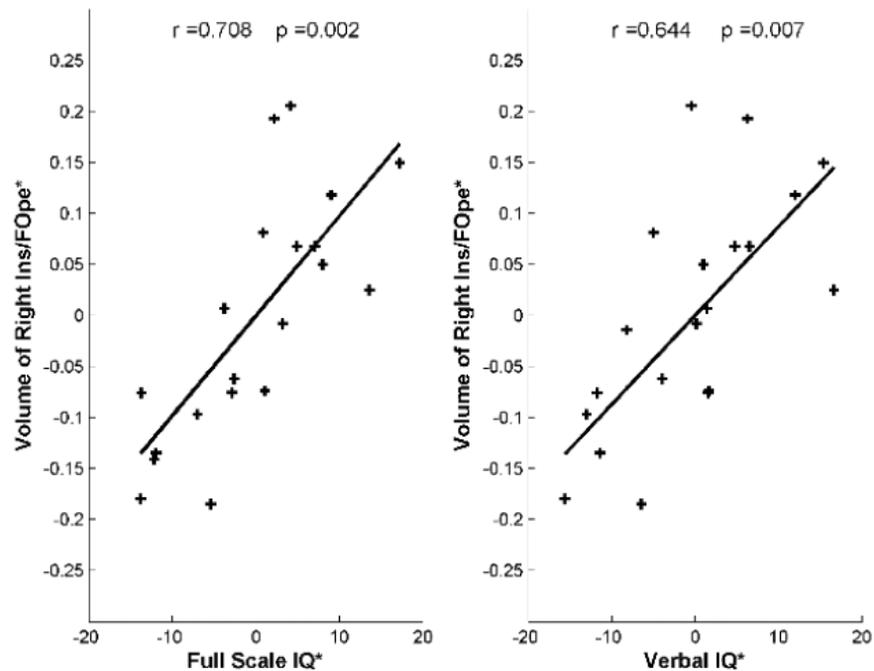


Fig. 3. The positive correlation between the GM volume in right anterior insula/frontal operculum and full scale IQ (left) and verbal IQ (right) in patients. * represents the adjusted values controlling for the influence of the gender, age and AEDs (linear regression with covariates including gender, age and AEDs).

Table 3. Altered intrinsic functional connectivity seeded at regions with increased GM volume in patients with BECT compared with controls.

ROIs	Region	t value	Cluster size (voxel)	Brodmann area	MNI coordinate		
					X	Y	Z
R_Put.	Right medial frontal gyrus	-6.03	132	BA 10	21	44	-8
	Right anterior cingulate	-5.67		BA 32	6	35	-8
R_Ins/Ope.	Left superior frontal gyrus	-5.82	100	BA 11	-18	44	-11
	Left caudate	-4.02		—	-15	23	-2
	Left anterior cingulate	-4.80	49	BA 24	-3	26	25
	Right thalamus	-4.57	43	—	9	-7	1
	Right middle frontal gyrus	-3.92	55	BA 9	27	29	25
R_SMA	Left precentral gyrus	-5.57	81	BA 6	-39	-7	58
	Left precentral gyrus	-5.16	93	BA 44	-54	8	13
L_PCL.	Right angular gyrus	-5.03	101	BA 40	57	-58	37
	Right middle temporal gyrus	-4.84	77	BA 21	69	-25	-11
	Left middle temporal gyrus	-4.31	81	BA 21	-54	-22	-14
	Left precuneus	-4.29	100	BA 7	-3	-70	40
	Left superior frontal gyrus	-3.89	84	BA 8	-3	38	49
	Right medial frontal gyrus	-3.84		BA 8	3	41	43

cortex (ACC, BA 32) and right medial frontal gyrus (BA 10).

For the right anterior insula/frontal operculum, patients also showed the decreased functional connections with the bilateral ACC (BA 24), left superior frontal gyrus (BA 11), left caudate head, right middle frontal gyrus (BA 9) and right thalamus. For the right SMA, patients showed the decreased functional connections with the left precentral gyrus (BA 6, 44). Decreased functional connections to the left PCL were also found in the right angular gyrus (BA40), bilateral precuneus (BA7), bilateral medial superior frontal gyri (BA 8) and bilateral middle temporal gyri (BA 21) in BECT. These differences are visualized in Fig. 4 using the xjView toolbox. For each ROI, no significantly increased functional connection was observed in patients compared with healthy controls. For the four ROIs with differences in functional connections between groups, no significant correlation with the clinical factors was observed.

4. Discussion

To the best of our knowledge, the current cross-sectional study is the first to utilize a combination of

results from neuroanatomical feature and functional connectivity analysis in patients with BECT. There are three major findings of this study: first, the increased GM volume of the bilateral putamen was negatively correlated with the age at epilepsy onset and disturbed functional connectivity in the frontostriatum loop; second, patients showed the increased volume in language-related cortical areas (the right inferior temporal gyrus and right anterior insula/frontal operculum) and the decreased functional connection between these regions and ACC, frontal cortex and thalamus; and third, patients showed the increased GM volume in motor-related areas (the bilateral PCL and right SMA) and the decreased functional connection within these regions and connection between these regions and default mode network (DMN). These findings indicated the altered structural and functional feature of the striato-cortical circuit in BECT which included the fronto-temporo-parietal cortex. Moreover, the onset of BECT is associated with neurodevelopmental abnormalities of the striatum. These findings also implied alterations in motor networks and the DMN, which are associated with the epileptic activity in patients with BECT. The current observations may contribute to the understanding of the mechanisms

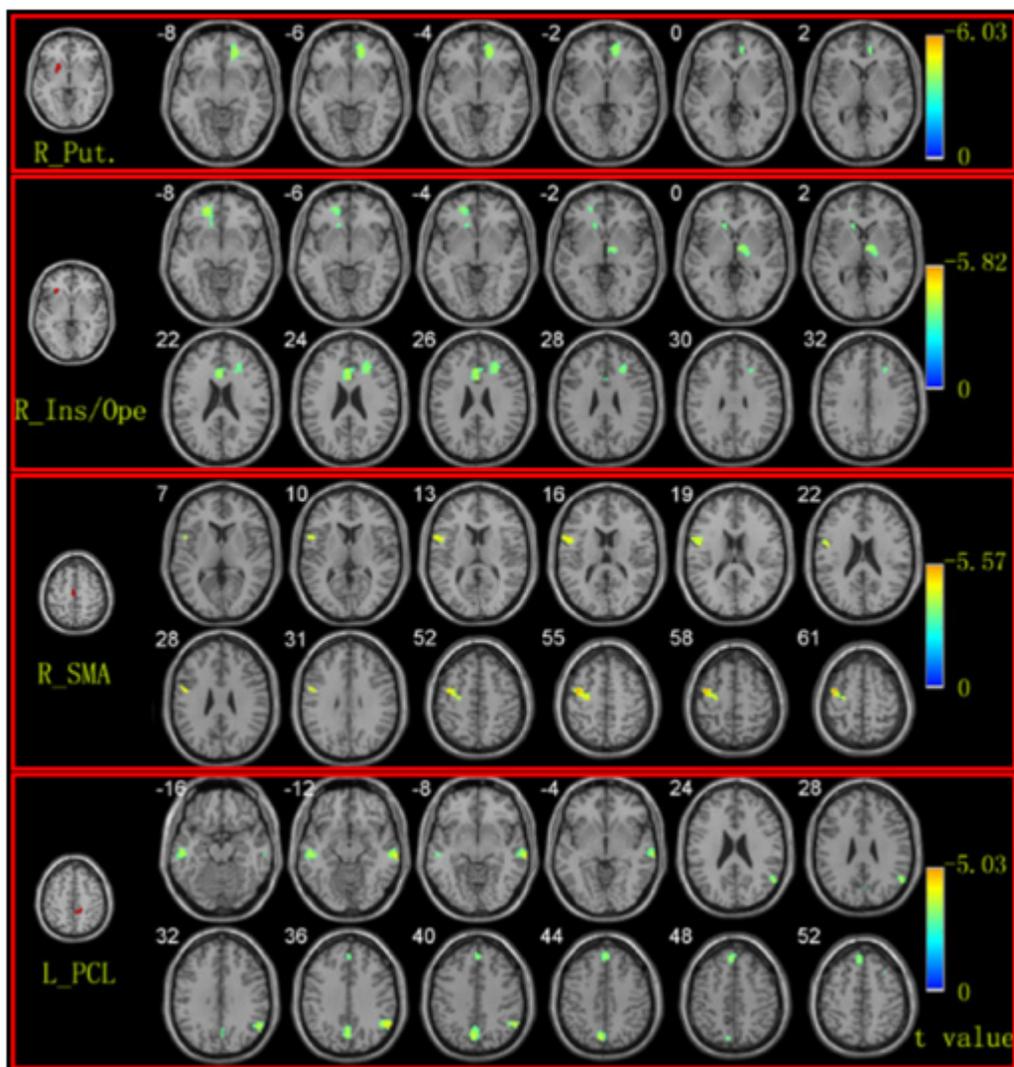


Fig. 4. The functional connection difference between groups. The first row exhibits the decreased functional connections with right putamen; the second and third rows show the decreased functional connections with right anterior insula/frontal operculum; the fourth and fifth rows show the decreased functional connections with right SMA; the sixth and seventh rows show the decreased functional connections with left PCL. No increased functional connection was observed in patients compared with healthy controls for each ROIs.

of psychosocial functional impairments in patients with BECT.

The original goal of the current study was to investigate neuroanatomic alterations in patients with BECT. Recently, studies have revealed extensive structural alterations in subcortical or cortical regions in patients with BECT. For example, Lin and colleagues demonstrated a hypertrophied putamen in new-onset patients with BECT,³⁷ and Pardoe *et al.* observed the increased cortical GM volumes in the frontal lobe and insula.¹⁴ Consistent

with these studies, patients with BECT also showed the increased GM volumes in these regions in the current study. As opposed to previous studies, we observed disturbed functional connectivity of these regions with altered GM volume. Functional connectivity investigation has shown that resting state brain activity is spatially organized in sets of specific coherent patterns that putatively correspond to a specific brain function.³⁸ In epilepsy, the spikes illustrated in EEG can directly reflect the abnormality of electrical activity in the specific brain

regions, which included lots of information to detect the seizures.^{39–42} Additionally, the high correlation exists between spiking activity and the metabolic information such as fMRI BOLD changes.⁴³ For example, a linear relationship between spiking activity and negative BOLD responses was observed in anesthetized monkeys.⁴⁴ Here, the complementary results of combined functional and anatomical MRI analysis help to assess differences in the crosstalk among brain regions, reflecting abnormal metabolic activations in response to altered GM volume in patients.

The putamen, which mainly receives projections from the motor and motor association cortices, is thought to play a key role in motor processing and executive function. In our previous studies, patients with absence seizures presented with altered anatomy and function of the striatum.^{26,45} These findings suggested that the striatum was closely associated with epileptic activity.^{46,47} A hypertrophied putamen was found in patients with BECT in a previous study,³⁷ suggesting an association with aberrant cognitive control and executive function and development abnormalities in patients with BECT. Consistent with the findings of Lin *et al.*, we found the increased volume in the bilateral putamen in patients with BECT. Moreover, the magnitude of the increase lessened with age at epilepsy onset in the cases. According to the traditional view of normal striatal development, in which the volume of striatum declines linearly with the age of subjects,⁴⁸ our findings might imply that epileptic activity could influence the striatal developmental trajectory, and the effect could be more dominant with an early age of onset. In addition, the GABAergic neurons of basal ganglia have direct suppressed effects for the epileptic discharges.^{49–51} Based on the tight coupling between the metabolic and electrophysiologic activity,⁵² the BOLD signals would be altered by the epileptic discharges. In this study, we also assessed the functional connectivity of the putamen and found the decreased connections of the right putamen with the right medial prefrontal cortex and ACC. This might reflect the disturbed frontostriatal network in patients with BECT. Investigators have argued that the frontostriatal circuit is implicated in emotion processing,⁵³ the filtering and focusing of cortical input, and selecting among potential cognitive and behavioral representations.⁵⁴ Moreover, the patients

with BECT also showed a significantly reduced performance IQ in the current study. Therefore, the attenuated functional connectivity in the frontostriatal circuit might contribute to the understanding of the cognitive deficits and abnormalities of executive function in patients with BECT.

We also observed the increased volume in the right inferior temporal gyrus and anterior insula/frontal operculum. Previous studies have indicated that the frontal operculum and right inferior temporal gyrus support different functions during language processing and that left-hemisphere language dominance is observed in normal right-handed subjects.⁵⁵ Recently, studies have reported language deficits and altered hemispheric lateralization in patients with BECT.^{11,56} The patients recruited in this study also exhibited the decreased verbal IQ. In addition, a larger volume of the right anterior insula/frontal operculum was linked to better performance on the verbal intelligence test in patients. We therefore speculated that the increased volume in the right language related regions, rather than in the left hemisphere with language dominance, implied a contralateral compensation for the language deficit in patients with BECT. The altered asymmetry in the language association cortex was also observed in other children with language abnormalities caused by disturbed language development,⁵⁷ such as autism.⁵⁸ In addition, Beseling *et al.* showed aberrant structural and functional connectivity between the motor and language networks in patients with BECT.^{15,30} Although an alteration in connectivity between motor regions and language areas was not found in this study, our findings might explain the decreased language performance in BECT patients to some extent.

Patients with BECT revealed altered GM volume in the bilateral PCL, right SMA and left cerebellum, as well as reduced functional connections between the right SMA and left primary motor cortex in this study. These regions are involved in motor function and are thought to play a key role in interictal epileptiform discharges in BECT patients.^{3,4,59} A recent diffusion study demonstrated abnormal diffusion parameters in the pre- and postcentral gyri and the rolandic region, and stated the probability that chronic epileptic activity leads to microstructural alteration of these regions.⁴ In a previous study using EEG-fMRI, Masterton and colleague

illustrated BOLD responses related to interictal epileptic discharges in the rolandic regions.⁶⁰ Therefore, our findings combining structural and functional analysis might delineate the alterations in motor networks related to the epileptic activity in patients with BECT. In addition, the decreased functional connections between the left PCL and regions in the DMN also might reflect abnormalities associated with epileptic activity because the DMN, which linked to the fundamental level of brain function during the resting state, showed remarkable deactivation in response to epileptic spikes and abnormal functional connectivity in patients with epilepsy.

This study is a cross-sectional study with several associated limitations. First, we suggested a developmental hypothesis that should be further tested in prospective longitudinal studies which further investigate the association between cerebral abnormalities and development. Second, the AEDs used by some patients might confound our findings, although half of the patients did not receive drugs. The type and dose of drugs should be detailed in the future studies. Finally, we did not observe clinical seizures by visual monitoring of all patients during fMRI scans. The data from fMRI, however, may be affected by interictal epileptic discharges because simultaneous EEG was not performed during fMRI scans. In conclusion, the findings of this study demonstrated regional GM volume abnormalities and their disrupted functional connections involving the striato-cortical circuit in patients with BECT. Moreover, larger GM volume in the striatum was linked to younger age at epilepsy onset, and the right insula/frontal operculum to better performance on verbal IQ tests by patients. These findings support the structural and functional alterations associated with chronic epileptic activity in the motor network and deficits in language and executive function in patients with BECT. The findings further suggest that BECT may link with the structural and functional effects on brain maturation. Future studies employing longitudinal designs may be helpful to further investigate cerebral abnormalities and their association with cognitive impairment and development.

Conflict of Interest

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. None of the authors has any conflict of interest to disclose.

Note Added

This study is our original unpublished work and the manuscript or any variation of it has not been submitted to another publication previously.

Acknowledgments

This project was funded by grants from the 973 Project (2011CB707803), the National Nature Science Foundation of China (81271547, 91232725, 813-71636, 81471638), the PCSIRT project (IRT0910), and The "111" project (B12027). We thank eight anonymous reviewers for their nice comments. We thank Dr. Shan Gao and Dr. John Adamson for their English language assistance.

References

1. G. B. Cavazzuti, Epidemiology of different types of epilepsy in school age children of Modena, Italy, *Epilepsia* **21** (1980) 57–62.
2. P. M. Callenbach, P. A. Bouma, A. T. Geerts, W. F. Arts, H. Stroink, E. A. Peeters, C. A. van Donselaar, A. C. Peters and O. F. Brouwer, Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood, *Seizure* **19** (1980) 501–506.
3. C. P. Panayiotopoulos, M. Michael, S. Sanders, T. Valeta and M. Koutroumanidis, Benign childhood focal epilepsies: Assessment of established and newly recognized syndromes, *Brain* **131** (2008) 2264–2286.
4. C. Ciumas, M. Saignavongs, F. Iliski, V. Herbillon, A. Laurent, A. Lothe, R. A. Heckemann, J. de Bellescize, E. Panagiotakaki, S. Hannoun, D. S. Marinier, A. Montavont, K. Ostrowsky-Coste, N. Bedoin and P. Ryvlin, White matter development in children with benign childhood epilepsy with centro-temporal spikes, *Brain* **137** (2014) 1095–1106.
5. P. A. Bouma, A. C. Bovenkerk, R. G. Westendorp and O. F. Brouwer, The course of benign partial epilepsy of childhood with centrotemporal spikes: A meta-analysis, *Neurology* **48** (1997) 430–437.
6. P. R. Bauer, S. Kalitzin, M. Zijlmans, J. W. Sander and G. H. Visser, Cortical excitability as a potential clinical marker of epilepsy: A review of the clinical application of transcranial magnetic stimulation, *Int. J. Neural. Syst.* **24** (2014) 1430001.
7. R. A. Badawy, G. D. Jackson, S. F. Berkovic and R. A. Macdonell, Cortical excitability and refractory epilepsy: A three-year longitudinal transcranial

- magnetic stimulation study, *Int. J. Neural. Syst.* **23** (2013) 1250030.
8. F. Pinton, B. Ducot, J. Motte, A. S. Arbues, C. Barondiot, M. A. Barthez, Y. Chaix, R. Cheminal, M. O. Livet, M. J. Penniello, S. Peudener, A. de Saint-Martin and C. Billard, Cognitive functions in children with benign childhood epilepsy with centrotemporal spikes (BECTS), *Epileptic Disord.* **8** (2006) 11–23.
 9. A. Verrotti, M. Filippini, S. Matricardi, M. F. Agostinelli and G. Gobbi, Memory impairment and Benign Epilepsy with centrotemporal spike (BECTS): A growing suspicion, *Brain Cogn.* **84** (2014) 123–131.
 10. A. N. Datta, N. Oser, F. Bauder, O. Maier, F. Martin, G. P. Ramelli, M. Steinlin, P. Weber and I. K. Penner, Cognitive impairment and cortical reorganization in children with benign epilepsy with centrotemporal spikes, *Epilepsia* **54** (2013) 487–494.
 11. C. Monjauze, H. Broadbent, S. G. Boyd, B. G. Neville and T. Baldeweg, Language deficits and altered hemispheric lateralization in young people in remission from BECTS, *Epilepsia* **52** (2011) e79–83.
 12. R. M. Besseling, G. M. Overvliet, J. F. Jansen, S. J. van der Kruijs, J. S. Vles, S. C. Ebus, P. A. Hofman, A. J. de Louw, A. P. Aldenkamp and W. H. Backes, Aberrant functional connectivity between motor and language networks in rolandic epilepsy, *Epilepsy Res.* **107** (2013) 253–262.
 13. G. M. Overvliet, R. M. Besseling, J. F. Jansen, S. J. van der Kruijs, J. S. Vles, P. A. Hofman, S. C. Ebus, A. de Louw, A. P. Aldenkamp and W. H. Backes, Early onset of cortical thinning in children with rolandic epilepsy, *Neuroimage Clin.* **2** (2013) 434–439.
 14. H. R. Pardoe, A. T. Berg, J. S. Archer, R. K. Fulbright and G. D. Jackson, A neurodevelopmental basis for BECTS: Evidence from structural MRI, *Epilepsy Res.* **105** (2013) 133–139.
 15. R. M. Besseling, J. F. Jansen, G. M. Overvliet, S. J. van der Kruijs, S. C. Ebus, A. de Louw, P. A. Hofman, J. S. Vles, A. P. Aldenkamp and W. H. Backes, Reduced structural connectivity between sensorimotor and language areas in rolandic epilepsy, *PLoS One* **8** (2013) e83568.
 16. W. Liao, Q. Xu, D. Mantini, J. Ding, J. P. Machado-Sousa, J. E. Hallak, C. Trzesniak, C. Qiu, L. Zeng, W. Zhang, J. A. Crippa, Q. Gong and H. Chen, Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder, *Brain Res.* **1388** (2011) 167–177.
 17. J. Ashburner and K. J. Friston, Voxel-based morphometry — The methods, *Neuroimage* **11** (2000) 805–821.
 18. L. D. Olson and M. S. Perry, Localization of epileptic foci using multimodality neuroimaging, *Int. J. Neural. Syst.* **23** (2013) 1230001.
 19. A. Labate, A. Cerasa, A. Gambardella, U. Aguglia and A. Quattrone, Hippocampal and thalamic atrophy in mild temporal lobe epilepsy: A VBM study, *Neurology* **71** (2008) 1094–1101.
 20. H. Pardoe, G. S. Pell, D. F. Abbott, A. T. Berg and G. D. Jackson, Multi-site voxel-based morphometry: Methods and a feasibility demonstration with childhood absence epilepsy, *Neuroimage* **42** (2008) 611–616.
 21. P. Piaggi, D. Menicucci, C. Gentili, G. Handjaras, A. Gemignani and A. Landi, Singular spectrum analysis and adaptive filtering enhance the functional connectivity analysis of resting state fMRI data, *Int. J. Neural. Syst.* **24** (2014) 1450010.
 22. D. Rangaprakash, X. Hu and G. Deshpande, Phase synchronization in brain networks derived from correlation between probabilities of recurrences in functional MRI data, *Int. J. Neural. Syst.* **23** (2013) 1350003.
 23. M. Ahmadlou and H. Adeli, Functional community analysis of brain: A new approach for EEG-based investigation of the brain pathology, *Neuroimage* **58** (2011) 401–408.
 24. W. Liao, Z. Zhang, Z. Pan, D. Mantini, J. Ding, X. Duan, C. Luo, Z. Wang, Q. Tan, G. Lu and H. Chen, Default mode network abnormalities in mesial temporal lobe epilepsy: A study combining fMRI and DTI, *Hum. Brain Mapp.* **32** (2011) 883–895.
 25. C. Luo, D. An, D. Yao and J. Gotman, Patient-specific connectivity pattern of epileptic network in frontal lobe epilepsy, *Neuroimage Clin.* **4** (2014) 668–675.
 26. C. Luo, Q. Li, Y. Xia, X. Lei, K. Xue, Z. Yao, Y. Lai, E. Martinez-Montes, W. Liao, D. Zhou, P. A. Valdes-Sosa, Q. Gong and D. Yao, Resting state basal ganglia network in idiopathic generalized epilepsy, *Hum. Brain Mapp.* **33** (2012) 1279–1294.
 27. Z. Zhang, W. Liao, H. Chen, D. Mantini, J. R. Ding, Q. Xu, Z. Wang, Yuan C., G. Chen, Q. Jiao and G. Lu, Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy, *Brain* **134** (2011) 2912–2928.
 28. C. Luo, C. Qiu, Z. Guo, J. Fang, Q. Li, X. Lei, Y. Xia, Y. Lai, Q. Gong, D. Zhou and D. Yao, Disrupted functional brain connectivity in partial epilepsy: A resting-state fMRI study, *PLoS One* **7** (2011) e28196.
 29. C. Luo, T. Yang, S. Tu, J. Deng, D. Liu, Q. Li, L. Dong, I. Goldberg, Q. Gong, D. Zhang, D. An, D. Zhou and D. Yao, Altered intrinsic functional connectivity of the salience network in childhood absence epilepsy, *J. Neurol. Sci.* **339** (2014) 189–195.
 30. R. M. Besseling, J. F. Jansen, G. M. Overvliet, S. J. van der Kruijs, J. S. Vles, S. C. Ebus, P. A. Hofman, A. Louw, A. P. Aldenkamp and W. H. Backes, Reduced functional integration of the sensorimotor and language network in rolandic epilepsy, *Neuroimage Clin.* **2** (2013) 239–246.

31. T. Gili, M. Cercignani, L. Serra, R. Perri, F. Giove, B. Maraviglia, C. Caltagirone and M. Bozzali, Regional brain atrophy and functional disconnection across Alzheimer's disease evolution, *J. Neurol. Neurosurg. Psychiatry*. **82** (2011) 58–66.
32. W. Pu, L. Li, H. Zhang, X. Ouyang, H. Liu, J. Zhao, Z. Xue, K. Xu, H. Tang, B. Shan, Z. Liu and F. Wang, Morphological and functional abnormalities of salience network in the early-stage of paranoid schizophrenia, *Schizophr. Res.* **141** (2012) 15–21.
33. J. Engel, Jr., A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology, *Epilepsia* **42** (2001) 796–803.
34. J. Ashburner, A fast diffeomorphic image registration algorithm, *Neuroimage* **38** (2007) 95–113.
35. J. D. Power, A. Mitra, T. O. Laumann, A. Z. Snyder, B. L. Schlaggar and S. E. Petersen, Methods to detect, characterize, and remove motion artifact in resting state fMRI, *Neuroimage* **84** (2014) 320–341.
36. X. W. Song, Z. Y. Dong, X. Y. Long, S. F. Li, X. N. Zuo, C. Z. Zhu, Y. He, C. G. Yan and Y. F. Zang, REST: A toolkit for resting-state functional magnetic resonance imaging data processing, *PLoS One* **6** (2011) e25031.
37. J. J. Lin, J. D. Riley, D. A. Hsu, C. E. Stafstrom, K. Dabbs, T. Becker, M. Seidenberg and B. P. Hermann, Striatal hypertrophy and its cognitive effects in new-onset benign epilepsy with centrotemporal spikes, *Epilepsia* **53** (2012) 677–685.
38. D. M. Cole, S. M. Smith and C. F. Beckmann, Advances and pitfalls in the analysis and interpretation of resting-state fMRI data, *Front Syst. Neurosci.* **4** (2010) 8.
39. P. Sharma, Y. U. Khan, O. Farooq, M. Tripathi and H. Adeli, A wavelet-statistical features approach for nonconvulsive seizure detection, *Clin. EEG Neurosci.* **45** (2014) 274–284.
40. S. Ghosh-Dastidar and H. Adeli, A new supervised learning algorithm for multiple spiking neural networks with application in epilepsy and seizure detection, *Neural Netw.* **22** (2009) 1419–1431.
41. H. Adeli, Z. Zhou and N. Dadmehr, Analysis of EEG records in an epileptic patient using wavelet transform, *J. Neurosci. Meth.* **123** (2003) 69–87.
42. S. Ghosh-Dastidar, H. Adeli and N. Dadmehr, Mixed-band wavelet-chaos-neural network methodology for epilepsy and epileptic seizure detection, *IEEE Trans. Biomed. Eng.* **54** (2007) 1545–1551.
43. R. Mukamel, H. Gelbard, A. Arieli, U. Hasson, I. Fried and R. Malach, Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex, *Science* **309** (2005) 951–954.
44. A. Shmuel, M. Augath, A. Oeltermann and N. K. Logothetis, Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1, *Nat. Neurosci.* **9** (2006) 569–577.
45. C. Luo, Y. Xia, Q. Li, K. Xue, Y. Lai, Q. Gong, D. Zhou and D. Yao, Diffusion and volumetry abnormalities in subcortical nuclei of patients with absence seizures, *Epilepsia* **52** (2011) 1092–1099.
46. H. Adeli, S. Ghosh-Dastidar and N. Dadmehr, A wavelet-chaos methodology for analysis of EEGs and EEG subbands to detect seizure and epilepsy, *IEEE Trans. Biomed. Eng.* **54** (2007) 205–211.
47. S. Ghosh-Dastidar and H. Adeli, Improved spiking neural networks for EEG classification and epilepsy and seizure detection, *Integr. Comput.-Aided Eng.* **14** (2007) 187–212.
48. J. N. Giedd, J. W. Snell, N. Lange, J. C. Rajapakse, B. J. Casey, P. L. Kozuch, A. C. Vaituzis, Y. C. Vauss, S. D. Hamburger, D. Kaysen and J. L. Rapoport, Quantitative magnetic resonance imaging of human brain development: Ages 4–18, *Cereb. Cortex*. **6** (1996) 551–560.
49. R. A. Badawy, A. Lai, S. J. Vogrin and M. J. Cook, Subcortical epilepsy? *Neurology* **80** (2013) 1901–1907.
50. H. Adeli and S. Ghosh-Dastidar, *Automated EEG-based Diagnosis of Neurological Disorders: Inventing the Future of Neurology* (CRC Press, Boca Raton) (2010).
51. I. Rektor, R. Kuba and M. Brazdil, Interictal and ictal EEG activity in the basal ganglia: An SEEG study in patients with temporal lobe epilepsy, *Epilepsia* **43** (2002) 253–262.
52. Y. Nir, L. Fisch, R. Mukamel, H. Gelbard-Sagiv, A. Arieli, I. Fried and R. Malach, Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to interneuronal correlations, *Curr. Biol.* **17** (2007) 1275–1285.
53. S. H. Kim and S. Hamann, Neural correlates of positive and negative emotion regulation, *J. Cogn. Neurosci.* **19** (2007) 776–798.
54. S. Grillner, J. Hellgren, A. Menard, K. Saitoh and M. A. Wikstrom, Mechanisms for selection of basic motor programs — Roles for the striatum and pallidum, *Trends Neurosci.* **28** (2005) 364–370.
55. A. D. Friederici, Pathways to language: Fiber tracts in the human brain, *Trends Cogn. Sci.* **13** (2009) 175–181.
56. J. Vannest, J. P. Szaflarski, K. P. Eaton, D. M. Henkel, D. Morita, T. A. Glauser, A. W. Byars, K. Patel and S. K. Holland, Functional magnetic resonance imaging reveals changes in language localization in children with benign childhood epilepsy with centrotemporal spikes, *J. Child Neurol.* **28** (2013) 435–445.
57. D. V. Bishop, Cerebral asymmetry and language development: Cause, correlate, or consequence? *Science* **340** (2013) 1230531.

58. M. R. Herbert, D. A. Ziegler, C. K. Deutsch, L. M. O'Brien, D. N. Kennedy, P. A. Filipek, A. I. Bakardjiev, J. Hodgson, M. Takeoka, N. Makris and V. S. Caviness, Jr., Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis, *Brain* **128** (2005) 213–226.
59. S. Ghosh-Dastidar, H. Adeli and N. Dadmehr, Principal component analysis-enhanced cosine radial basis function neural network for robust epilepsy and seizure detection, *IEEE Trans. Biomed. Eng.* **55** (2008) 512–518.
60. R. A. Masterton, A. S. Harvey, J. S. Archer, L. M. Lillywhite, D. F. Abbott, I. E. Scheffer and G. D. Jackson, Focal epileptiform spikes do not show a canonical BOLD response in patients with benign rolandic epilepsy (BECTS), *Neuroimage* **51** (2010) 252–260.