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Structural abnormalities in benign childhood epilepsy with centrotemporal spikes (BCECTS)

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ABSTRACT

Purpose: The aim of this study was to investigate cortical thickness and gray matter volume abnormalities in benign childhood epilepsy with centrotemporal spikes (BCECTS). We additionally assessed the effects of comorbid attention-deficit/hyperactivity (ADHD) on these abnormalities.
Methods: Surface and volumetric MR imaging data of children with newly diagnosed BCECTS ($n = 20$, 14 males) and age-matched healthy controls ($n = 20$) were analyzed using FreeSurfer (version 5.3.0, https://surfer.nmr.mgh.harvard.edu). An additional comparison was performed between BCECTS children with and without ADHD (each, $n = 8$). A group comparison was carried out using an analysis of covariance with a value of significance set as $p < 0.01$ or $p < 0.05$.
Results: Children with BCECTS had significantly thicker right superior frontal, superior temporal, middle temporal, and left pars triangularis cortices. Voxel-based morphometric analysis revealed significantly larger cortical gray matter volumes of the right precuneus, left orbitofrontal, pars orbitalis, precentral gyri, and bilateral putamen and the amygdala of children with BCECTS compared to healthy controls. BCECTS patients with ADHD had significantly thicker left caudal anterior and posterior cingulate gyri and a significantly larger left pars opercularis gyral volume compared to BCECTS patients without ADHD.
Conclusion: Children with BCECTS have thicker or larger gray matters in the corticostriatal circuitry at the onset of epilepsy. Comorbid ADHD is also associated with structural aberrations. These findings suggest structural disruptions of the brain network are associated with specific developmental electroclinical syndromes.

1. Introduction

Idiopathic focal epilepsies are often regarded as a developmental disorder, in which the normal developmental trajectory of a focal region in the brain might be disturbed, resulting in seizures and comorbid neuropsychiatric problems [1]. In benign childhood epilepsy with centrotemporal spikes (BCECTS), the marked age-specific onset and remission of electroclinical features, comorbid behavioral and cognitive problems, and genetic predisposition strongly suggest altered brain maturation [1–5]. To further understand developmental disorders of this nature, magnetic resonance imaging (MRI) analysis techniques have been used to identify the microstructural alterations of the brain in children with idiopathic focal epilepsy including BCECTS [6–8]. However, the reported profiles of abnormal structures were inconsistent among these studies, and the exact morphological changes or correct localization of the associated structures in children with idiopathic epilepsy are still unknown. Although several studies have reported widely distributed alterations of brain structure in children with BCECTS at the onset of epilepsy [9–13], the causal relationship between structural variations of the brain, seizures, medication effects, and comorbid neuropsychiatric problems remains unsolved.

We performed our present case-control study to identify the abnormal cortical structures associated with BCECTS using automated measures of cross-sectional brain MRI scans. In addition, we compared the cortical thickness and gray matter volume across

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BCECTS patients with and without attention-deficit/hyperactivity (ADHD) at the time of diagnosis of BCECTS to evaluate potential structural–functional correlations.

2. Materials and methods

2.1. Subjects

Twenty patients (14 males, mean age at diagnosis, 7.5 ± 1.5 years; range, 5.6–10.2) with newly diagnosed BCECTS were enrolled who presented between 2007 and 2013 to Asan Medical Center Children's Hospital. BCECTS was clinically diagnosed by pediatric neurologists according to the International League Against Epilepsy classification (1989). Inclusion criteria were: (1) no epilepsy other than BCECTS; (2) no other neurologic disease; (3) intelligence quotient within normal limits; (4) normal standard clinical brain MRI; (5) not receiving antiepileptic drugs at the time of the MRI study. Twenty healthy controls (14 males, mean age, 7.4 ± 1.5 years; range, 5.0–10.1) were also recruited between 2011 and 2013.

All subjects underwent sleep electroencephalograms (EEGs) before the initiation of antiepileptic drugs. To confirm the laterality of the spike discharges, EEG recordings were prolonged until the stage II sleep were confirmed by the technician. The laterality of interictal centrotemporal spike discharges on sleep EEGs was evaluated by three board-licensed pediatric neurologists (TS Ko, MS Yum, and EH Kim). Considering the known association between handedness and the structural and functional lateralization of brain, handedness was also reviewed. The presence or absence of ADHD at the time of diagnosis of BCECTS was also evaluated. ADHD was clinically diagnosed by a pediatric psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria of ADHD: the diagnosis of ADHD was made when more than six out of nine symptoms of inattention or hyperactivity–impulsivity had persisted for at least 6 months based on the questionnaire of ADHD symptoms for patients. The rating scales for ADHD were not performed in all of them. All eight patients diagnosed with ADHD did not receive the ADHD medication at the time of the brain MRI study. The cortical thickness and gray matter volume were compared between BCECTS patients with (n = 8, 6 males, mean age at diagnosis, 7.4 ± 1.4 years; range, 5.9–9.3) with age-, sex-matched patients without ADHD (n = 8, 6 males, mean age at diagnosis, 7.6 ± 1.8 years; range, 5.7–9.8).

Our study protocol was approved by the Institutional Review Board of Asan Medical Center, Ulsan University College of Medicine, Korea. As all subjects were too young to consent, all informed consents were given by their parents.

2.2. Image acquisition

MRI scans were obtained on a Philips 3T Achieva scanner (Philips Healthcare, Eindhoven, The Netherlands). Three-dimensional whole brain T1 sequence imaging was acquired with the following image parameters: echo time, TE = 4.6 ms; repetition time, TR = 9.8 ms; flip angle, FA = 8.0°; field of view = 224 mm, slice thickness = 1 mm, sagittal images of the entire brain with in-plane resolution 1.0 mm × 1.0 mm. MRI exams were evaluated by a pediatric neuroradiologist (HK Yoon) who was blind to both to the disease status of the subjects and to the study hypothesis.

2.3. Image analysis

FreeSurfer (version 5.3.0, https://surfer.nmr.mgh.harvard.edu) was used for two types of measurement: cortical thickness and partial brain volume (volumes of voxels, global or regional brain volumes). The procedure followed was similar to that described in previous studies [14–17]. After correcting for intensity variations, a normalized intensity image was generated and the skull was removed from the normalized image. A connected components algorithm was then used for the preliminary segmentation, and any interior holes in the components representing white matter were filled. A constructed polygonal surface model was applied to obtain a representation of the gray/white matter boundary and the pial surface after a refinement procedure. Above automatic cortical reconstruction and parcellation technique was used to subdivide each hemisphere into 34 gyral labels [18,19].

2.4. Statistical analysis

Group differences in demographic, clinical, and conventional MRI imaging variables were assessed using the Kruskal–Wallis and the Mann–Whitney U tests for continuous variables and the Fisher exact test for categorical variables (SPSS, version 18.0; SPSS Inc., Chicago, IL). A comparison on the morphology data between the groups was investigated using Freesurfer's build-in GLM tool, Qdec. All Qdec results were corrected for multiple comparisons using the built-in tool for assessment of the cluster size p-value. These multiple-comparisons corrected results were considered significant at a significance threshold of $p < 0.01$. In an additional analysis for differences between BCECTS patients with and without ADHD the significance threshold was set at $p < 0.05$.

3. Results

3.1. Subject characteristics

The mean age at seizure onset in children with BCECTS was 6.9 ± 1.7 years (range, 3.3–9.1), and the mean seizure frequency in the year prior to diagnosis was 3.8 ± 1.3 (range, 1–5) times per year. Centrotemporal spike discharges on EEG at diagnosis were right-sided in four patients, left-sided in eight patients, and bilateral in eight patients. There were no statistical differences in body mass indices or total brain volumes between BCECTS patients and healthy controls. Both groups showed age-related cortical thinning and reduction of gray matter volume across the entire cortex (Fig. 1). Fourteen BCECTS patients were right-handed, two were left-handed, and the handedness of four was unknown; 14 control subjects were right-handed, two were left-handed, two were ambidextrous, and two had unknown handedness.

3.2. Cortical thickness and gray matter volumes of the BCECTS patients and controls

In patients with BCECTS the mean cortical thickness of both hemispheres and the regional gray matter volumes of cortical, subcortical and limbic structures showed a tendency toward greater values compared to the control subjects (Fig. 1). Regional analysis of cortical thicknesses revealed that they were significantly greater on the right superior frontal gyrus (p = 0.005), the right superior and middle temporal gyri (p = 0.001), and the left pars triangularis gyrus (p = 0.004) in BCECTS patients than in the controls (Fig. 2). Compared to control subjects, BCECTS subjects also had larger volumes of cortical gray matter of the right precuneus gyrus ($p < 0.001$), the left orbitofrontal gyrus (p = 0.004), the left pars orbitalis gyrus (p = 0.001), and the left precentral gyrus (p = 0.006) (Fig. 3). Group differences in the regional gray matter volumes of subcortical and limbic structures are displayed in Table S1 and Fig. 4. Patients with BCECTS displayed significantly larger volumes of the bilateral putamen and amygdala (both $p < 0.01$) compared to the healthy controls (Fig. 4).

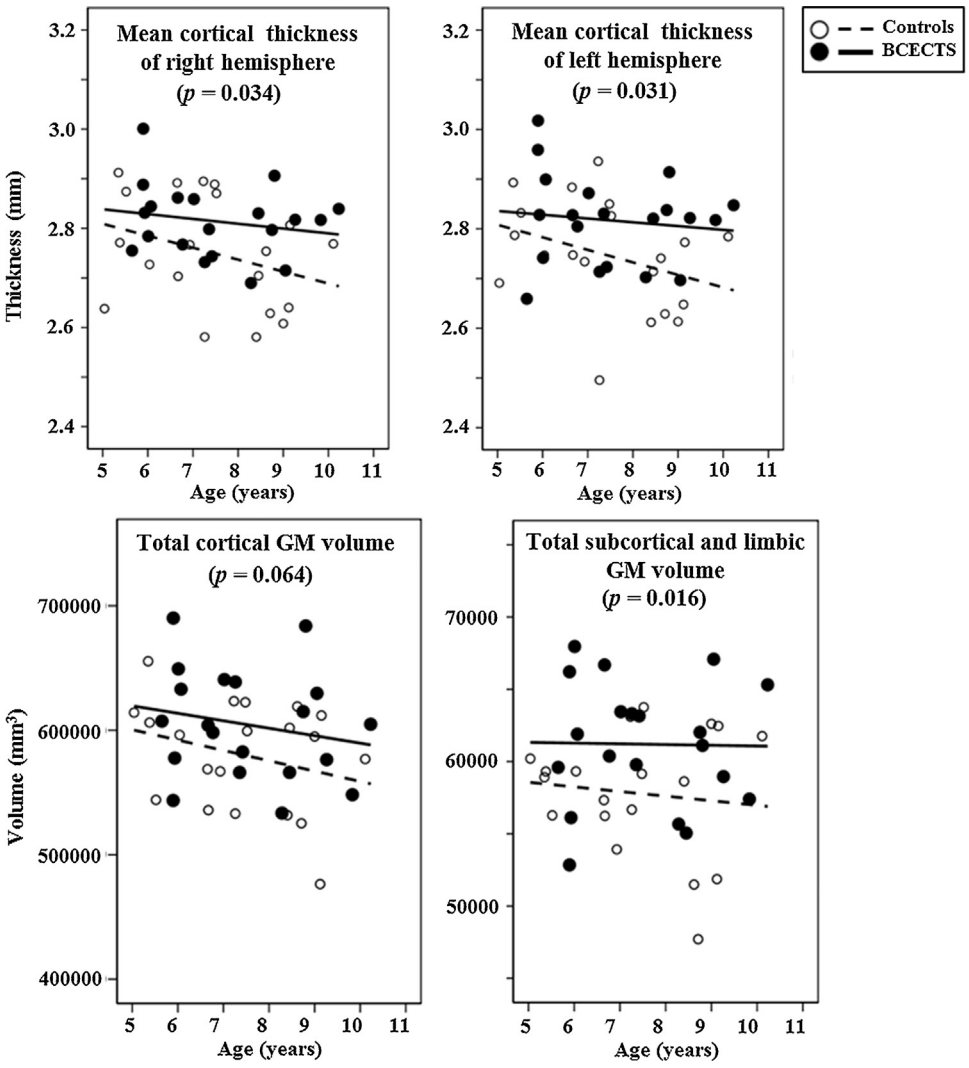

Fig. 1. Scatter plots and trend lines of the mean cortical thickness and gray matter (GM) volume of both cerebral hemispheres according to age at MRI evaluation in BCECTS patients and control subjects. Both groups show age-related cortical thinning and reduction of gray matter volume.

Supplementary Table S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.02.027.

3.3. Subgroup comparison analysis of the BCECTS patients according to their comorbid ADHD

The mean cortical thickness of both hemispheres and the total gray matter volumes of cortical, subcortical and limbic structures showed no significant differences between BCECTS patients with ADHD and those without ADHD (Fig. 5A). After matching for age and gender, BCECTS patients with ADHD ($n = 8$) were shown to possess significantly thicker left caudal anterior ($p = 0.021$) and posterior cingulate gyri ($p = 0.011$) and a significantly larger left pars opercularis gyral volume ($p = 0.034$) compared to BCECTS patients without ADHD (Fig. 5B and C). The regional gray matter volume of subcortical and limic structures between two groups was not significantly different.

4. Discussion

In our current study, we found that BCECTS patients had significantly thicker cortices in the right superior frontal, the right superior and middle temporal, and the left pars triangularis gyrus than control subjects. BCECTS patients also displayed a larger regional gray matter volume in the right precuneus gyrus, the left prefrontal region, the left precentral gyrus and bilateral putamen and amygdala [12]. The involved structures were not only the precentral area among the rolandic area, but also the broad corticostriatal circuits. Recent structural imaging studies of BCECTS have revealed widely distributed morphological abnormalities in cortical and subcortical structures [9–11]. Along with previous studies, the affected regions identified in present study were more extensive than Rolandic areas that generate centro-temporal spikes and were unlikely to be a direct consequence of epileptiform activity. To explain these abnormalities outside the seizure onset zone, it has been previously suggested that the propagation of epileptiform discharges through an underlying network induce the secondary pathology of distal cortical regions as well as white matter [12,13]. These multiple structural alterations of the brain in patients with BCECTS also support the hypothetical relationship between the altered maturation of brain associated with interictal epileptic activity and behavioral and cognitive dysfunction. Discordances between the results of the thickness analysis and those of voxel-based morphometric analysis can be explained by the difference between two- and three-dimensional measures, where the latter is also associated with the network topology [20,21]. Previous research also revealed

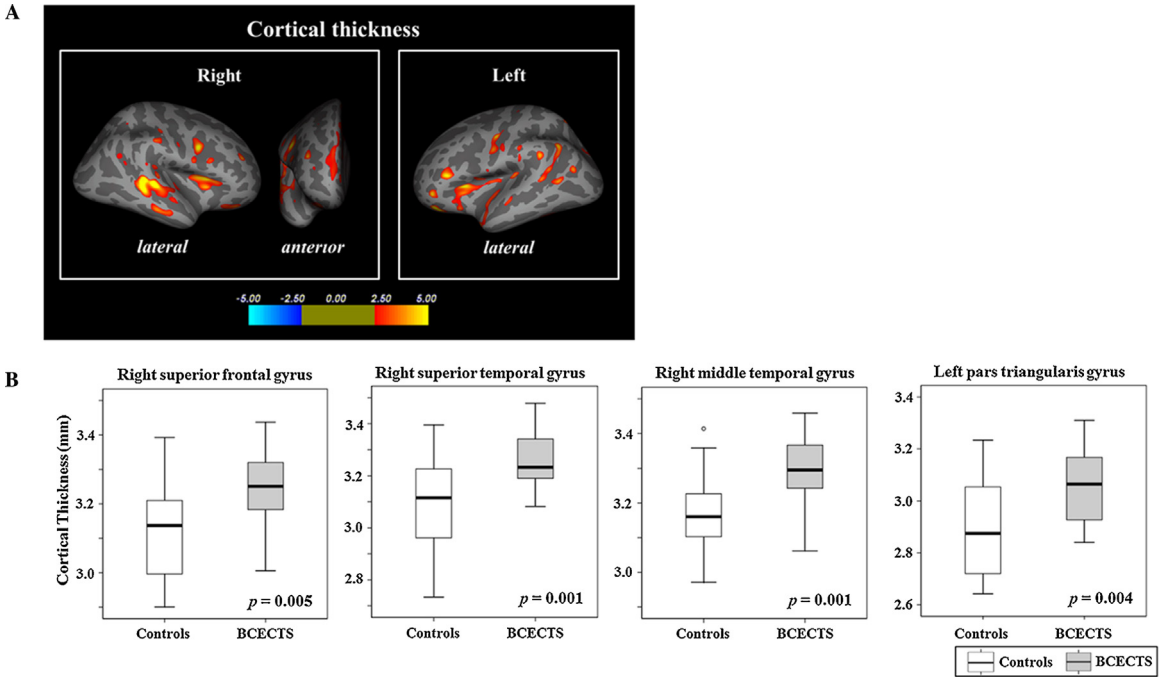

Fig. 2. Regional differences of cortical thickness between patients with BCECTS and healthy control subjects ($p < 0.01$). (A) Representative views are shown with a color-coded depiction of abnormalities. Regions of thicker cortices are shown in red to yellow (color coded according to t value). (B) The right superior frontal, temporal, middle temporal, and left pars triangulate gyri of patients with BCECTS patients are significantly thicker than those of the controls. Comparisons of cortical thicknesses (mm) are presented as boxplots. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

significant hypertrophy and shape deformities of the putamen [9] and increases in the bilateral fronto-temporal surface and volume [11] in children with BCECTS which is consistent with our current findings.

Normal brain development during childhood includes age-related structural changes, resulting from selective elimination of neurons (cortical pruning) and increasing myelination [22]. Longitudinal quantitative MRI investigations of healthy children have also demonstrated age- and region-specific declines in cortical thickness and cerebral gray matter volume along with a concomitant increase in cerebral white matter volume, directly reflecting this neurodevelopmental process [23,24]. Although

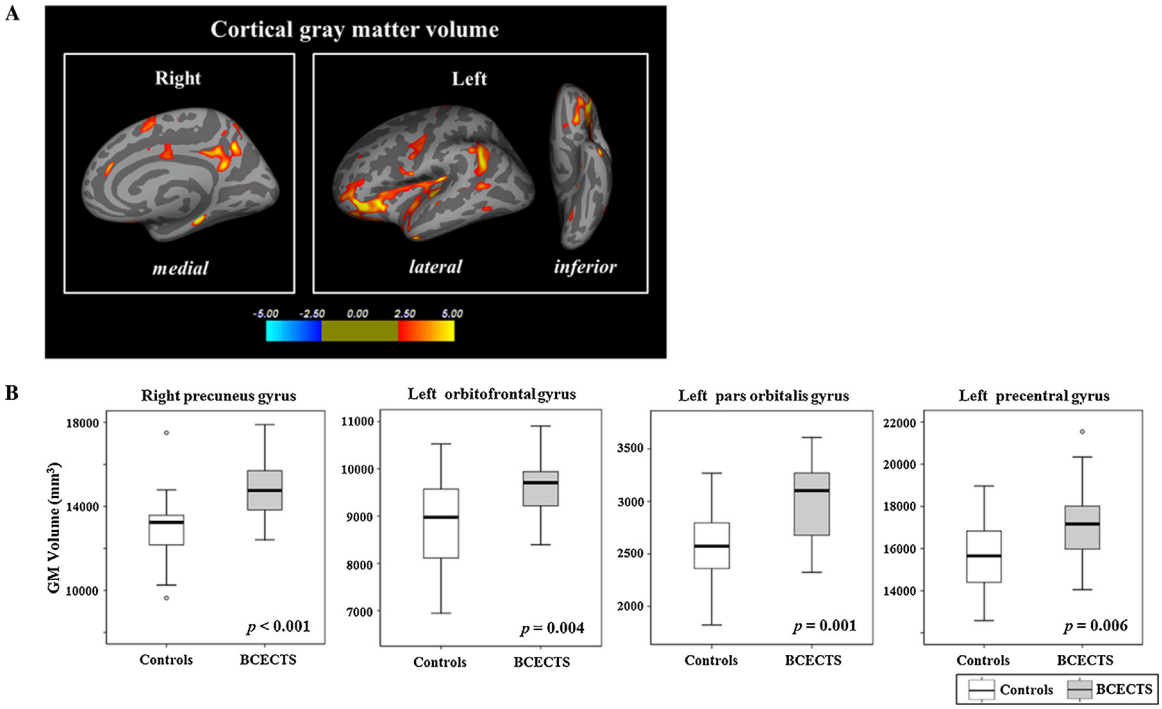

Fig. 3. Illustration of regional differences of cortical gray matter volume between BCECTS patients and healthy control subjects ($p < 0.01$). (A) A color-coded depiction of the abnormalities is shown. Regions of increased cortical gray matter volumes are shown in red to yellow (color coded according to t value) (B) In the BCECTS patients, the left orbitofrontal, pars orbitalis, precentral, and right precuneus gyri displayed a larger volume of cortical gray matter (GM) compared to the controls. Volumes are depicted in mm^3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

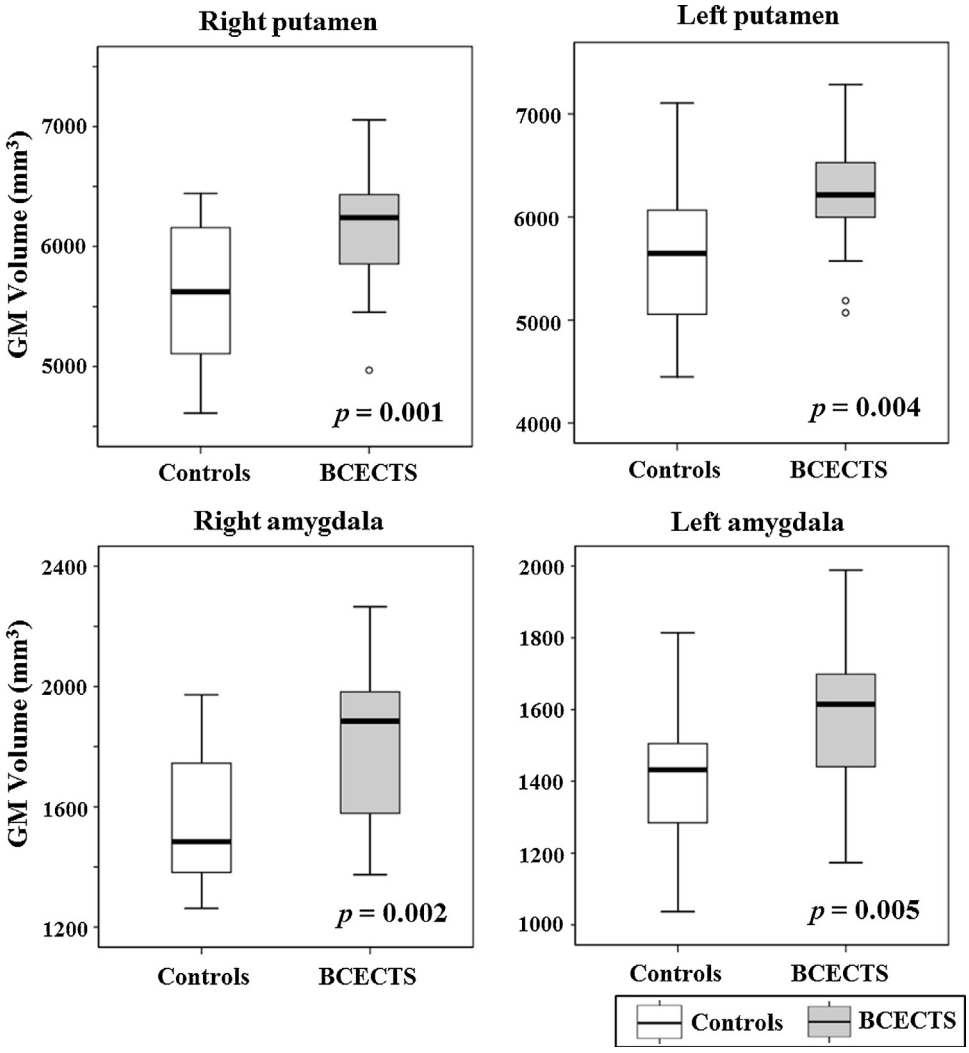

Fig. 4. Regional differences in subcortical and limbic gray matter (GM) volumes in patients with BCECTS compared with healthy control subjects ($p < 0.01$). The bilateral putamen and amygdala of BCECTS patients is larger than those of the controls. The analyzed subcortical GM included the caudate, pallidum, thalamus and limbic structures include the hippocampus and amygdala. Volumes are in mm^3.

these cross-sectional data do not allow any conclusions regarding a relationship between age and development of gray matter, an age dependent decline of gray matter was noticed in both patient and controls in our current investigation. Moreover, the decline of gray matter volume in old age appeared to be delayed in the affected group. The affected areas we here identified are not the same as those described by previous studies, our current results suggest a broad structural abnormality of brain development, which exists at the diagnosis of epilepsy, in BCECTS [11]. However, it remains unclear whether this finding is a result of the delayed subtractive process including synaptic pruning or of the developmental network abnormality including occult or very subtle dysplasia. A recent study, however, suggests delayed developmental processes of patients with BCECTS in which the increased bilateral fronto-temporal surface and volume reverts to normal values at remission [11].

The superior frontal and the pars triangularis gyri are involved in higher cognitive and executive functions [25,26], and the superior and middle temporal gyri have a key role in attentional processing of verbal stimuli and ADHD pathophysiology [27,28]. The precuneus gyrus, bilateral putamen, and amygdala belong to a widespread cortical and subcortical network of executive function, self-processing, and visuospatial imagery [29], and the orbitofrontal and pars orbitalis gyri are important neuroanatomical regions involved in adaptive learning and speech–language production [30]. The higher incidence of learning and behavioral difficulties, language delay, attention deficits, and hyperactive–impulsive symptoms in patients with BCECTS may be associated with this underlying microstructural pathology. However, our present study was limited in its ability to discern this because the incidence of neuropsychiatric diseases was not compared between subjects with BCECTS and controls.

The observed regional pattern of cortical thickness and gray matter volume abnormalities is also influenced by the presence of ADHD. BCECTS patients with ADHD showed cortical thickening in the left caudal anterior and posterior cingulate gyri and increased volume of cortical gray matter in the left pars opercularis compared to BCECTS patients without ADHD. The anterior and posterior cingulate gyri are mainly involved in supporting internally directed cognition, in modulation of emotional responses, and in attentional processing [31,32]. The pars opercularis is critical for speech and language functions [30,33].

A previous MRI study in children with epilepsy and ADHD [34] reported bilateral thinning in the frontal, parietal, and temporal lobes with diminution of subcortical structures similar to the findings of several previous MRI studies in children with ADHD alone [35–37]. Although our current results for ADHD in children with BCECTS identified different abnormalities from a previous

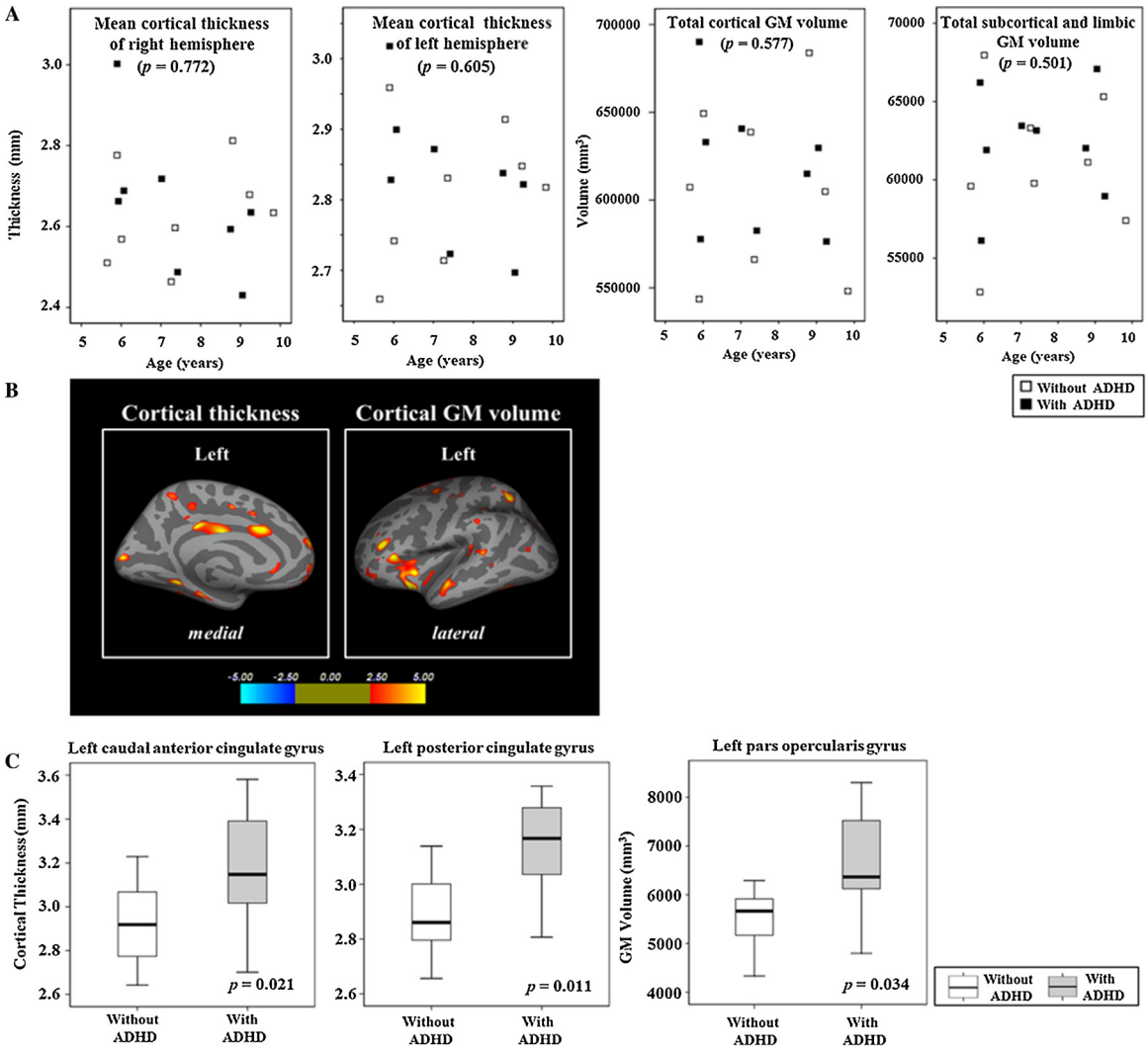

Fig. 5. Subgroup comparisons of cortical thickness and gray matter (GM) volume among patients with BCECTS according to their comorbid ADHD ($p < 0.05$). (A) Scatter plots of the mean cortical thickness and gray matter (GM) volume of both cerebral hemispheres according to age at MRI evaluation in BCECTS patients with ADHD and those without ADHD. (B) Representative views are shown with a color-coded depiction of the abnormalities. Regions of thicker cortices are shown in red to yellow (color coded according to *t* value). (C) The left caudal anterior cingulate, left posterior cingulate, and left pars opercularis gyri of BCECTS patients with ADHD are significantly thicker than those without ADHD. Thickness and volumes are shown in mm and mm^3, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

study of children with epilepsy and ADHD [34], the inclusion of heterogeneous types of epilepsy in that previous study may account for these differences. These structural alterations in ADHD patients disappear during adolescence [38] likewise supporting the paradigm of a delayed neurodevelopmental process leading to ADHD. Longitudinal studies with large and diagnostically homogeneous clinical samples would help to confirm the clinical significance of our study.

This was a cross-sectional study with a number of limitations including small subject numbers and inter-subject variability. The variable time interval between the onset of seizure and the brain MRI study and comorbid psychiatric problems other than ADHD could be possible confounding factors. As we described above, brain volume is critically affected by the age and the volumetric analysis should be based on the age-matched samples. Small sample size including patients with various age limited the critical evaluation of handedness and laterality of centrotemporal spikes on the brain volumes. Another limitation is the lack of comprehensive neuropsychological examination in diagnosis of ADHD. Although abnormal gray matter volume or cortical thickness in BCECTS represents an altered trajectory in cortical development, these cross-sectional findings cannot demonstrate the causality. Longitudinal studies at multiple time points with neurocognitive measurements would further advance the understanding of the abnormal trajectories of BCECTS and their relationship with cognitive and behavioral functions.

5. Conclusion

Children with BCECTS demonstrate thicker cortices and a larger cortico-striatal gray matter. Moreover, among children with BCECTS, children with ADHD possess a thicker left cingulate cortex and a larger left pars opercularis volume. This altered trajectory in cortical development in children with BCECTS suggests a structural–functional correlation of idiopathic focal epilepsies and indicates a need for a prospective and longitudinal controlled study using brain MRI analysis in these cases.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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