Published in final edited form as:
Epilepsy Res. 2013 July ; 105(0): 133–139. doi:10.1016/j.eplepsyres.2012.11.008.

A neurodevelopmental basis for BECTS: Evidence from structural MRI

Heath R. Pardoe[a,b], **Anne T. Berg**[c], **John S. Archer**[b], **Robert K. Fulbright**[d], and **Graeme D. Jackson**[a,b,*]

[a]Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

[b]Department of Medicine, University of Melbourne, Australia

[c]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[d]Department of Radiology, Yale School of Medicine, New Haven, CT, USA

Summary

Purpose—BECTS (benign epilepsy with centro-temporal spikes) is one of the most common childhood-onset epilepsy syndromes. We investigated quantitative evidence for brain morphological variation associated with BECTS to provide insights into the neuroanatomical basis of this disorder.

Methods—Three independent BECTS groups were imaged at different stages: (a) near onset (n = 16, mean age 9.3 ± 1.6 years), (b) ~9 years after onset (n = 9, mean age 15.8 ± 2.3 years), and (c) ~15 years after onset (n = 10, mean age 22.7 ± 2.7 years). Age-matched controls were imaged with each group. Whole brain T1-weighted MRI was acquired. Voxel-based morphometry (groups a–c) and cortical thickness analyses (groups b and c) were undertaken within each group and for the groups combined. The relationship between cortical morphology and age was investigated.

*Corresponding author at: Brain Research Institute, Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, 245 Burgundy St, Heidelberg, Victoria 3084, Australia. Tel.: +61 3 9035 7000; fax: +61 3 9035 7307. BRI@brain.org.au (G.D. Jackson).

Contributors

Susan R. Levy, MD (Yale University of Medicine, New Haven, CT), Francine M. Testa MD (Yale University School of Medicine, New Haven, CT), Francis DiMario, MD (Connecticut Children's Medical Center, Hartford, CT), Shlomo Shinnar MD (Albert Einstein College of Medicine, Bronx, NY), David Abbott (Florey Neuroscience Institutes, Australia), Leasha Lillywhite (Austin Health Australia), Richard Masterton (Florey Neuroscience Institutes), Simon Harvey (Royal Children's Hospital, Melbourne), Ingrid Scheffer (University of Melbourne and Florey Neuroscience Institutes), Christina Rios (Yale University School of Medicine, New Haven, CT), Charles Hurst (Yale University School of Medicine, New Haven, CT), and Lyla Johnson (Yale University School of Medicine, New Haven, CT).

Disclosures

Dr. Berg has received travel funding and honoraria from Eisai, the British Pediatric Neurological Association, and the Epilepsy Research Center (Melbourne); travel funding from UCB, the American Epilepsy Society and the International League Against Epilepsy; awards from the American Epilepsy Society and British Pediatric Neurological Association; and consulting fees from Dow Agro Science. She serves on the Editorial Boards of Epileptic Disorders and Epilepsy&Behavior. She is past Chair of the ILAE's Commission on Classification and Terminology, Current Chair of the ILAE's Task Force on Classification-Diagnostic Manual, Member of the ILAE's Pediatric Commission's Task Force on Autism, Member of the AES's Commission on Nonepileptic Seizures, Member ad hoc Task Force of the ILAE Commission on Therapeutic Strategies, member of the AES Suicidality Task Force, Steward for the NINDS Benchmarks in Epilepsy Research.

Dr Archer received a speaking fee from UCB.

Dr. Jackson serves on a scientific advisory board for Neurosciences Victoria and receives royalties from the publication of "Magnetic Resonance in Medicine, 2nd ed." (Elsevier 2005).

The remaining authors have no conflicts 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.

Key findings—The voxel-based morphometry analysis indicated increased bilateral grey matter volume in the superior frontal gyrus, insula and right inferior frontal gyrus regions in BECTS. The magnitude of the increase lessened with age of the cases. Cortical thickness analysis revealed thicker cortex in BECTS along middle and inferior frontal gyri bilaterally, left insula and bilateral supramarginal gyrus in the 9-year-after-onset group, that normalised with age. The rate of cortical thickness changes with age were greater in BECTS cases than in controls.

Significance—Increased cortical gray matter associated with BECTS was found. The decreasing magnitude of the effect with increasing age parallels the natural history of the disorder. The areas affected are consistent with neurocognitive dysfunction in BECTS.

Keywords

Rolandic epilepsy; Developmental disorders; Quantitative MRI; Cortical thickness; Voxel-based morphometry

Introduction

BECTS (benign epilepsy with centro-temporal spikes) is one of the most common electroclinical epilepsy syndromes and accounts for 5–10% of all epilepsy in the pediatric age range (Berg et al., 1999; Callenbach et al., 2010; Jallon et al., 2001). Distinctive features of BECTS include its specific EEG signature (centrotemporal spikes), seizure semiology, and age dependent onset and remission (Wirrell and Nickels, 2010). Children with BECTS are generally of normal intellect, have no antecedent history of a neurological insult or condition that could explain their epilepsy, and have no obvious focal neurological deficits. Clinical neuroimaging including MRI is typically lesion negative. In fact, recent guidelines identify BECTS as one of four pediatric epilepsy syndromes in which clinical imaging can generally be omitted (Gaillard et al., 2011). Virtually all children with BECTS remit by age sixteen (Wirrell and Nickels, 2010; Bouma et al., 1997).

Despite IQ measures that are typically within normal range, neurodevelopmental features of BECTS have been demonstrated in a number of studies. Examples of these features include neurocognitive deficits in language and attention (Danielsson and Petermann, 2009; Giordani et al., 2006; Kavros et al., 2008; Riva et al., 2007; Smith et al., 2012; Staden et al., 1998). Impairments in memory and phonological processing have been reported (Danielsson and Petermann, 2009; Northcott et al., 2005). These features of BECTS are sometimes described as developmental delay and are likely responsible for poorer educational outcomes and behavioural problems (Nicolai et al., 2007; Pinton et al., 2006; Vinayan et al., 2005; Volkl-Kernstock et al., 2009; Yung et al., 2000). It has been previously hypothesised that epileptogenic activity in BECTS may interfere with cognitive development (Metz-Lutz et al., 1999).

Although genetic factors may be important (Rudolf et al., 2009), BECTS is not a simple monogenic epilepsy. A twin study failed to find any of 18 twin pairs (10 monozygous and 8 dizygous) concordant for the classic BECTS phenotype (Vadlamudi et al., 2006). An association between centrotemporal spikes and the ELP4 gene has been reported (Strug et al., 2009), and linkage with locus 11p13 in speech sound disorder (Pal et al., 2010) and loci 1q42 and 7q21 for reading disability in BECTS (Strug et al., 2012). There appears to be a nonspecific increased occurrence of seizures in affected family members of probands with BECTS (Callenbach et al., 1998, 2010; Vears et al., 2012). No genetic association between the full electroclinical syndrome with seizures has been found. These data suggest a general underlying genetic contribution to seizure susceptibility or brain dysfunction in BECTS; however the precise nature of the genetic involvement and the role of other factors that may influence expression of the disorder are not clear at this time.

Advanced neuroimaging methods allow for quantitative, objective assessment of variations in brain morphology associated with neurological disorders, and can be particularly powerful when studying well defined groups of patients. We studied three independent groups of BECTS patients each with controls to determine whether we could find replicable evidence of structural variation associated with BECTS. Because our study groups were scanned over a wide age range, we were also able to examine whether any differences observed might progressively vary as a function of age (maturation) which might be expected given the distinctive age-dependent profile of this disorder.

Methods

Subject recruitment details

Three patient groups were included: (a) from Melbourne, Australia and (b) and (c), two independent groups recruited as part of the Connecticut Study of Epilepsy in Children. Age matched controls were acquired on each of the scanners.

Group A was imaged shortly after onset of BECTS. Subjects were selected from children in teaching hospitals who met clinical criteria for BECTS, attending a normal school and who, at the time they were recruited, also had the characteristic centro-temporal spike EEG finding. Patients were imaged within months of recruitment. Recruitment details of this cohort are described in more detail in Lillywhite et al. (2009).

The BECTS cases in groups B and C were recruited as part of the Connecticut study of epilepsy, a prospective longitudinal study that recruited children from throughout the state of Connecticut at the time they were initially diagnosed with epilepsy during the years 1993–1997. Recruitment, characterization, and follow-up of this cohort have been described in detail elsewhere (Berg et al., 1999, 2009). Group B was imaged during 2002–2006 when case subjects were invited to take part in a comprehensive reassessment which included research MRI scan. Controls were recruited so as to represent the sex and age distribution of all cases being scanned for research purposes. Group C BECTS cases and controls are different from those in group B and participated in a separate assessment protocol, which also included an MRI scan and was conducted during 2007–2011. There is no overlap between the cases or controls in groups A, B or C.

All controls were neurologically normal, without any history of epilepsy, neurologic disorders or other major medical illness. Standard clinical MRI interpretation was normal. Written informed consent of adult subjects or written parental permission and assent of minors were obtained as required by the Institutional Review Board of each site. Ethics approval for the participation of controls and patients were obtained from the relevant authorities.

Image acquisition

Imaging for group A was performed on a 3 T GE LX Horizon MRI scanner. A whole brain coronal T1-weighted SPGR scan was acquired with the following image parameters: echo time, TE = 1.9 ms; repetition time, TR = 9 ms; flip angle, FA = 20°; inversion time, TI = 500 ms; voxel size: 0.48 mm × 0.48 mm × 2 mm. Imaging for group B was performed on a 1.5 T Siemens Sonata MRI scanner. A whole brain coronal T1-weighted MPRAGE scan was acquired with the following image parameters: echo time, TE = 4.38 ms; repetition time, TR = 1730 ms; flip angle, FA = 15°; inversion time, TI = 1100 ms; voxel size: 0.94 mm × 0.94 mm × 1.6 mm. Imaging for group C was performed on a 1.5 T Siemens Sonata MRI scanner. A whole brain coronal T1-weighted MPRAGE scan was acquired with the following image parameters: echo time, TE = 3.05 ms; repetition time, TR = 1730 ms, flip angle, FA = 15°, inversion time, TI = 1100; voxel size: 0.94 mm × 0.94 mm × 1.6 mm.

Image analysis

Voxel-based morphometry—Voxel-based morphometry was carried out using the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm8, Ashburner and Friston, 2000). Images were segmented into gray matter, white matter and CSF using the unified segmentation technique (Ashburner and Friston, 2005). Gray matter segments were normalised to MNI 152 space and modulated to preserve total gray matter volume. 12 mm Gaussian smoothing was applied to the modulated normalised gray matter segments. The smoothing filter of 12 mm was selected to ensure adequate of control of false positive findings when using cluster-level statistical inference, as determined in a previous study (Silver et al., 2011). All modulated normalised gray matter segments were visually assessed to confirm no misregistration or poor quality segmentation had taken place. Voxels containing less than 5% GM were excluded from the analysis.

Voxel-wise comparisons of grey matter volume were undertaken with the output voxel value as the dependent variable and disease status (BECTS/control), age, sex, brain volume and group included as independent variables using a full factorial model specification. Brain volume was calculated using the software package "BET" (brain extraction tool), distributed as part of the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, Smith, 2002). Individual group BECTS-control comparisons were also carried out. These analyses were used to confirm that any regional differences identified using the multi-group comparison also existed in the individual groups.

Significant VBM-based volumetric differences in BECTS were reported using two criteria for statistical significance. The first criterion for statistical significance was based on voxel-wise difference in GM that exceeded a threshold of $p < 0.05$ with an adjusted threshold determined using the family-wise error correction method for multiple comparisons. The second criteria identified significant regions based on the spatial extent of contiguous voxels (clusters). A threshold of $p < 0.001$ has been determined in a previous study to provide adequate control of false positive clusters (Silver et al., 2011). Significant regions were then identified as clusters of supra-threshold voxels with an extent determined to be greater than may be expected by chance. No minimum cluster size was specified.

Cortical thickness mapping—Cortical thickness mapping and across-subject coregistration was carried out using the software package Freesurfer (http://www.surfer.nmr.mgh.harvard.edu/, version 5.0). The image processing steps involved in cortical thickness mapping and coregistration have been described elsewhere (Fischl and Dale, 2000; Fischl et al., 1999). Details of the image processing steps involved in mapping the thickness of the cortex are provided as supplementary material.

Visual inspection of images acquired using the same acquisition as group A in a previous study indicated that the 2 mm slice thickness was unsuitable for modelling of the cortical sheet. Therefore cortical thickness analyses were restricted to MRI scans from groups B and C. Three general linear model analyses were carried out, comprising one combined analysis in which disease status, age, sex and group were included as covariates, and two further individual group analyses of thickness differences between BECTS and controls. Images were processed using the procedure described above, with surface-based smoothing of 10 mm full-width half maximum. Maps of significant differences were corrected for multiple comparisons using the false discovery rate (FDR) method.

Relationship between morphometric differences and age—Given the age dependence of BECTS, further analysis of the VBM and cortical thickness results was undertaken to determine if there is any relationship between age and GM volume/thickness. Statistical analyses were performed using the statistical software package "R".

VBM: Average GM volume over (i) the whole brain and (ii) the regions identified in the previous VBM analysis were used as summary measures. For each summary measure we tested for differences between BECTS cases and controls using a multiple linear regression analysis with disease status, age, sex, brain volume, and group membership (A, B or C) included as explanatory variables. To test whether there was a progressive change in the case-control difference in volume with increasing age, we included an interaction term for case-control status and age at the time of the scan.

Cortical thickness: Average cortical thickness over (i) the whole brain and (ii) the regions identified in the previous cortical thickness analysis were used as summary measures. For each summary measure we tested for differences between BECTS cases and controls using a multiple linear regression analysis with disease status, age, sex, and group membership (groups B or C) included as explanatory variables. To test whether there was a progressive change in the case–control difference in cortical thickness with increasing age, we included an interaction term for case–control status and age at the time of the scan.

A total of four statistical analyses were carried out in this part of the study. A p-value of 0.0125 (= 0.05/4, Bonferroni correction for multiple comparisons) was used as the threshold for significance.

Results

Subject demographic data is supplied in Table 1. All participants had IQ within normal limits (one participant from group B was borderline low IQ). Standard clinical interpretation of the MRI scans was normal. The voxel-based morphometry and cortical thickness analyses both revealed regional increased gray matter in the BECTS subjects. Increased regional gray matter was primarily located in the frontal lobes.

Voxel-based morphometry

VBM analysis of data combined from all three groups revealed significant volume increases bilaterally in the superior frontal gyrus, with additional bilateral volume increases in the insula cortex and right inferior frontal gyrus (Fig. 1A). VBM analysis of volume differences in each site independently indicated similarly located subthreshold GM increases across groups. The spatial extent of the effect was largest in group A, intermediate in group B and smallest in group C imaged at average ages of 9, 16, and 23 years, respectively, (Supplementary material Figure 1). No suprathreshold volume decreases were observed in the VBM analyses.

Cortical thickness mapping

In group B, studied at age 16, the cortical thickness analysis showed similar changes to that seen in the VBM analysis and indicated thickened cortex along the middle and inferior frontal gyrii bilaterally, insular cortex in the left hemisphere and supramarginal gyrus bilaterally (Fig. 1B). More diffuse, scattered regions of thickness increase were located in the parietal lobes. A small spatial extent thickness decrease was observed in the right central sulcus in group B. In group C, which is the oldest cohort studied at age 23, no regions showed significantly increased or decreased cortical thickness.

Relationship between morphometric differences and age

VBM and age—There was a highly significant age related decrease in GM volume with age in BECTS and controls ($p = 2.3 \times 10^{-5}$ in VBM-identified regions, $p = 2.06 \times 10^{-8}$ whole brain, Fig. 1A scatterplot). The expected difference between BECTS and controls was

demonstrated in this analysis ($p = 0.00137$ in VBM-identified regions, $p = 0.037$ whole brain). No significant diagnosis-age interaction was observed in the VBM analyses.

Cortical thickness and age—A highly significant age related decrease in cortical thickness with age in BECTS and controls was observed ($p = 2.7 \times 10^{-6}$ in Freesurfer identified regions, $p = 2.9 \times 10^{-4}$ whole brain, Fig. 1B scatterplot). In addition to the expected increased thickness in BECTS subjects, a significant interaction between diagnosis and age was observed in the thickness analysis ($p = 2.5 \times 10^{-6}$, Freesurfer identified region, $p = 4.9 \times 10^{-3}$ whole brain). BECTS related thickness changes with age are greater than controls.

For BECTS subjects imaged after their late teens by which time the electroclinical syndrome has remitted, cortical thickness and gray matter volume in BECTS more closely resembles controls.

Discussion

BECTS is a well-characterized age dependent electroclinical syndrome with normal clinical imaging, which almost always remits by mid adolescence. In three independent BECTS groups we found regional increased cortical thickness and increased grey matter volume in younger BECTS patients, primarily in frontal and to a lesser extent in insular and parietal regions, that approach normal values after the clinical epilepsy syndrome remits. The regional age-dependent changes in cortex in BECTS patients, primarily in frontal and to a lesser extent in insular and parietal regions, suggests an alteration in the normal development of these cortical regions.

Language utilises a network of cerebral structures (Price, 2010). The anterior and insular structural changes observed in our study are consistent with the reported language deficits (Smith et al., 2012; Nicolai et al., 2007), abnormal fMRI of language in the anterior regions (Lillywhite et al., 2009), and oromotor dyspraxia in BECTS patients (Lundberg et al., 2005). The language deficits are associated with modified functional imaging of language tasks in the inferior frontal gyrus relative to healthy controls (Lillywhite et al., 2009) and could represent a structural correlate of these language performance and functional imaging aspects of abnormal language in BECTS. These anterior structural changes are consistent with other structural studies of BECTS (Kanemura et al., 2011) and language disorder (Clark and Plante, 1998).

Like language networks, fMRI has indicated that attention utilises a distinct network of cerebral structures (Bush and Shin, 2006). The structural differences observed in our study extend into regions associated with attention, in particular in prefrontal cortex and parietal regions. Impairments in attention in BECTS have been reported (Kavros et al., 2008). The cortical regions identified in our study are more extensive than areas that generate centrotemporal spikes (Masterton et al., 2010) and are therefore unlikely to be a direct consequence of epileptiform activity.

The normal brain develops from childhood to young adulthood with a stereotypical pattern of cortical changes (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2006; Sowell et al., 1999), characterised by a progressive regionally specific decrease in cortical gray matter. In our BECTS cohort, the rate of change in cortical thickness is greater than controls and the time to reach normative values is delayed. This raises the possibility that the natural course of BECTS may reflect an altered trajectory in cortical development. Persisting language problems following remission have been reported (Monjauze et al., 2005). These may reflect alterations in language networks due to either developmental abnormality in these areas or

disruption of cortical development during the critical period for language acquisition and consolidation (Penfield and Roberts, 1959).

The cross-sectional data presented in this study suggests a longitudinal hypothesis (changes over time with maturation) that should be further tested in a prospective longitudinal study. Investigating the relationship between structural brain changes and cognitive and behavioural measures that are known to be affected in BECTS would also be an interesting future study. Although images were acquired on different scanners, acquisition of control subjects on each scanner has been demonstrated to be a valid way for adjustment of scanner specific effects in VBM studies (Pardoe et al., 2008) which was done in the current study. Changing scanner technology over time, including software and hardware upgrades in the same scanner, is also an issue for longitudinal studies.

Our findings provide evidence for abnormal cortical morphology in BECTS, including areas associated with language and attention. The findings of this study are consistent with reported developmental delays in BECTS, and the cross-sectional structural changes parallel age-specific features of the clinical disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to gratefully acknowledge Sam Berkovic for helpful comments on the manuscript.

Study funding: National Institutes of Health (NS-R37-31146, PI AT Berg), National Health and Medical Research Council, Australia (project grant 318900), National Health and Medical Research Council Australia (program grant 400121), Victorian Life Sciences Computational Initiative, Australia (VR0056), Victorian Government's Operational Infrastructure Support Program, Australia.

References

Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage. 2000; 11 (6 Pt 1): 805–821. [PubMed: 10860804]

Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005; 26 (3):839–851. [PubMed: 15955494]

Berg AT, Levy SR, et al. Classification of childhood epilepsy syndromes in newly diagnosed epilepsy: interrater agreement and reasons for disagreement. Epilepsia. 1999; 40 (4):439–444. [PubMed: 10219269]

Berg AT, Mathern GW, et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. Brain. 2009; 132 (Pt 10):2785–2797. [PubMed: 19638447]

Bouma PA, Bovenkerk AC, et al. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology. 1997; 48 (2):430–437. [PubMed: 9040734]

Bush G, Shin LM. The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. Nat Protoc. 2006; 1(1):308–313. [PubMed: 17406250]

Callenbach PM, Geerts AT, et al. Familial occurrence of epilepsy in children with newly diagnosed multiple seizures: Dutch Study of Epilepsy in Childhood. Epilepsia. 1998; 39 (3):331–336. [PubMed: 9578054]

Callenbach PM, Bouma PA, et al. Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood. Seizure. 2010; 19 (8):501–506. [PubMed: 20688544]

Clark MM, Plante E. Morphology of the inferior frontal gyrus in developmentally language-disordered adults. Brain Lang. 1998; 61(2):288–303. [PubMed: 9468774]

Danielsson J, Petermann F. Cognitive deficits in children with benign rolandic epilepsy of childhood or rolandic discharges: a study of children between 4 and 7 years of age with and without seizures compared with healthy controls. Epilepsy Behav. 2009; 16 (4):646–651. [PubMed: 19879197]

Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000; 97(20):11050–11055. [PubMed: 10984517]

Fischl B, Sereno MI, et al. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp. 1999; 8(4):272–284. [PubMed: 10619420]

Gaillard WD, Cross JH, et al. Epilepsy imaging study guideline criteria: commentary on diagnostic testing study guidelines and practice parameters. Epilepsia. 2011; 52 (9):1750–1756. [PubMed: 21740417]

Giedd JN, Blumenthal J, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999; 2(10):861–863. [PubMed: 10491603]

Giordani B, Caveney AF, et al. Cognition and behavior in children with benign epilepsy with centrotemporal spikes (BECTS). Epilepsy Res. 2006; 70(1):89–94. [PubMed: 16564678]

Gogtay N, Giedd JN, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A. 2004; 101(21):8174–8179. [PubMed: 15148381]

Jallon P, Loiseau P, Loiseau J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Coordination Active du Reseau Observatoire Longitudinal de l'Epilepsie. Epilepsia. 2001; 42 (4):464–475. [PubMed: 11440341]

Kanemura H, Hata S, et al. Serial changes of prefrontal lobe growth in the patients with benign childhood epilepsy with centrotemporal spikes presenting with cognitive impairments/behavioral problems. Brain Dev. 2011; 33(2):106–113. [PubMed: 20381984]

Kavros PM, Clarke T, et al. Attention impairment in rolandic epilepsy: systematic review. Epilepsia. 2008; 49 (9):1570–1580. [PubMed: 18410358]

Lillywhite LM, Saling MM, et al. Neuropsychological and functional MRI studies provide converging evidence of anterior language dysfunction in BECTS. Epilepsia. 2009; 50 (10):2276–2284. [PubMed: 19292755]

Lundberg S, Frylmark A, Eeg-Olofsson O. Children with rolandic epilepsy have abnormalities of oromotor and dichotic listening performance. Dev Med Child Neurol. 2005; 47(9):603–608. [PubMed: 16138667]

Masterton RA, Harvey AS, et al. Focal epileptiform spikes do not show a canonical BOLD response in patients with benign rolandic epilepsy (BECTS). Neuroimage. 2010; 51 (1):252–260. [PubMed: 20139011]

Metz-Lutz MN, Kleitz C, et al. Cognitive development in benign focal epilepsies of childhood. Dev Neurosci. 1999; 21(3–5):182–190. [PubMed: 10575241]

Monjauze C, Tuller L, et al. Language in benign childhood epilepsy with centro-temporal spikes abbreviated form: rolandic epilepsy and language. Brain Lang. 2005; 92(3):300–308. [PubMed: 15721962]

Nicolai J, van der Linden I, et al. EEG characteristics related to educational impairments in children with benign childhood epilepsy with centrotemporal spikes. Epilepsia. 2007; 48 (11):2093–2100. [PubMed: 17645539]

Northcott E, Connolly AM, et al. The neuropsychological and language profile of children with benign rolandic epilepsy. Epilepsia. 2005; 46 (6):924–930. [PubMed: 15946332]

Pal DK, Li W, et al. Pleiotropic effects of the 11p13 locus on developmental verbal dyspraxia and EEG centrotemporal sharp waves. Genes Brain Behav. 2010; 9(8):1004–1012. [PubMed: 20825490]

Pardoe H, Pell GS, et al. Multi-site voxel-based morphometry: methods and a feasibility demonstration with childhood absence epilepsy. Neuroimage. 2008; 42 (2):611–616. [PubMed: 18585930]

Penfield, W.; Roberts, L. Speech and Brain-Mechanisms. Princeton University Press; Princeton, NJ: 1959.

Pinton F, Ducot B, et al. Cognitive functions in children with benign childhood epilepsy with centrotemporal spikes (BECTS). Epileptic Disord. 2006; 8(1):11–23. [PubMed: 16567321]

Price CJ. The anatomy of language: a review of 100 fMRI studies published in 2009. Ann N Y Acad Sci. 2010; 1191:62–88. [PubMed: 20392276]

Riva D, Vago C, et al. Intellectual and language findings and their relationship to EEG characteristics in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav. 2007; 10(2):278–285. [PubMed: 17267289]

Rudolf G, Valenti MP, et al. From rolandic epilepsy to continuous spike- and-waves during sleep and Landau–Kleffner syndromes: insights into possible genetic factors. Epilepsia. 2009; 50 (Suppl 7): 25–28. [PubMed: 19682046]

Shaw P, Greenstein D, et al. Intellectual ability and cortical development in children and adolescents. Nature. 2006; 440 (7084):676–679. [PubMed: 16572172]

Silver M, Montana G, Nichols TE. False positives in neuroimaging genetics using voxel-based morphometry data. Neuroimage. 2011; 54 (2):992–1000. [PubMed: 20849959]

Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002; 17(3):143–155. [PubMed: 12391568]

Smith AB, Kavros PM, et al. A neurocognitive endophenotype associated with rolandic epilepsy. Epilepsia. 2012; 53 (4):705–711. [PubMed: 22220688]

Sowell ER, Thompson PM, et al. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci. 1999; 2(10):859–861. [PubMed: 10491602]

Staden U, Isaacs E, et al. Language dysfunction in children with Rolandic epilepsy. Neuropediatrics. 1998; 29 (5):242–248. [PubMed: 9810559]

Strug LJ, Clarke T, et al. Centrotemporal sharp wave EEG trait in rolandic epilepsy maps to Elongator Protein Complex 4 (ELP4). Eur J Hum Genet. 2009; 17(9):1171–1181. [PubMed: 19172991]

Strug LJ, Addis L, et al. The genetics of reading disability in an often excluded sample: novel Loci suggested for reading disability in rolandic epilepsy. PLoS One. 2012; 7 (7):e40696. [PubMed: 22815793]

Vadlamudi L, Kjeldsen MJ, et al. Analyzing the etiology of benign rolandic epilepsy: a multicenter twin collaboration. Epilepsia. 2006; 47 (3):550–555. [PubMed: 16529620]

Vears DF, Tsai MH, et al. Clinical genetic studies in benign childhood epilepsy with centrotemporal spikes. Epilepsia. 2012; 53 (2):319–324. [PubMed: 22220564]

Vinayan KP, Biji V, Thomas SV. Educational problems with underlying neuropsychological impairment are common in children with Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS). Seizure. 2005; 14 (3):207–212. [PubMed: 15797356]

Volkl-Kernstock S, Bauch-Prater S, et al. Speech and school performance in children with benign partial epilepsy with centro-temporal spikes (BCECTS). Seizure. 2009; 18 (5):320–326. [PubMed: 19249229]

Wirrell E, Nickels KC. Pediatric epilepsy syndromes. Continuum (Minneap Minn). 2010; 16 (3):57–85. Epilepsy. [PubMed: 22810315]

Yung AW, Park YD, et al. Cognitive and behavioral problems in children with centrotemporal spikes. Pediatr Neurol. 2000; 23(5):391–395. [PubMed: 11118793]

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2012.11.008.

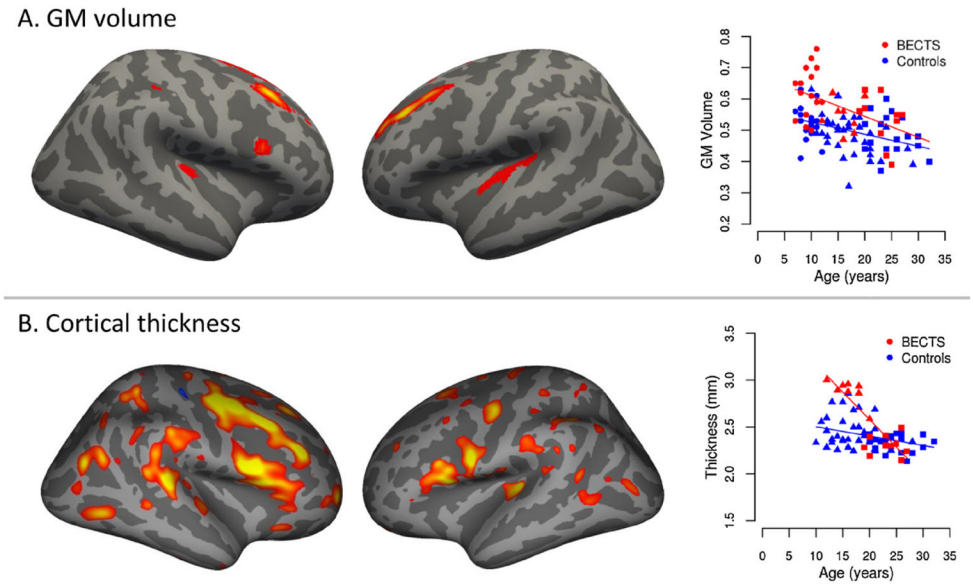

Figure 1.

Regional volume and thickness increases in BECTS. The top row shows volume increases in the BECTS versus control subjects detected using VBM, with MRI data from all three groups combined (relative grey matter volume $p < 0.001$ significant clusters displayed, change with age in graph). The bottom row shows increased cortical thickness in BECTS versus control subjects imaged ~9 years after onset (group B only, $p < 0.05$, false discovery rate corrected). The scatterplots show gray matter volume (A) and thickness (B) changes with age in the respective blobs shown on the inflated brains. The magnitude of gray matter volume and thickness differences in BECTS relative to controls lessened with age.

Table 1

Demographic information for study participants.

Group	Status	Number	Age (years, mean ± SD)	Gender (female)	Handedness (right)	Medication (n)
A	BECTS	16	9.3 ± 1.6	5	16	10
	Controls	20	9.7 ± 1.6	8	18	0
B	BECTS	9	15.8 ± 2.3	6	8	3
	Controls	35	16.9 ± 4.6	18	NA	0
C	BECTS	10	22.7 ± 2.7	7	9	0
	Controls	20	23.7 ± 3.4	12	NA	0