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Changes in Functional Organization and Functional Connectivity during Story Listening in Children with Benign Childhood Epilepsy with Centro-Temporal Spikes

Jennifer Vannest, Ph.D.¹, Thomas C. Maloney¹, Jeffrey R. Tenney, M.D., Ph.D.¹, Jerzy P. Szaflarski, M.D. Ph.D.², Diego Morita, M.D.¹, Anna W. Byars, Ph.D.¹, Mekibib Altaye, Ph.D.¹, Scott K. Holland, Ph.D.¹, and Tracy A. Glauser, M.D.¹

¹Cincinnati Children's Hospital Medical Center

²University of Alabama at Birmingham

Abstract

Children with Benign Epilepsy with Centrotemporal Spikes (BECTS), despite high likelihood for seizure remission, are reported to have subtle difficulties in language and other cognitive skills. We used functional MRI and a story listening task to examine the effect of BECTS on patterns of activation and connectivity. Language and cognitive skills were assessed using standardized measures. Twenty-four children with recently diagnosed BECTS and 40 typically-developing children participated. In a functionally-defined region of interest in right inferior frontal gyrus, BECTS patients showed a lower level of activation. Across both groups combined, increased activation in superior/middle temporal regions of interest was associated with better language scores. Connectivity in the story processing network was similar between groups, but connectivity within left inferior frontal gyrus was decreased in children with BECTS. These results suggest that language networks are largely maintained in new-onset BECTS, but some subtle changes in activation and connectivity can be observed.

Keywords

Benign Epilepsy with Centrotemporal Spikes; story processing; functional MRI; functional connectivity; receptive language; electroencephalography

Corresponding Author: Jennifer Vannest, Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue - ML 5033, Cincinnati, OH 45229-3039, Phone: 513-636-6959, Fax: 513-636-3754, Jennifer.Vannest@cchmc.org.

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1. INTRODUCTION

1.1. Benign Childhood Epilepsy with Centro-Temporal Spikes (BECTS)

Children with BECTS, one of the most common pediatric epilepsy syndromes, have relatively infrequent brief, focal seizures with no impairment of consciousness. The seizures may generalize and are often related to sleep (Camfield & Camfield, 2002, 1989; Wirrell, 1998). BECTS is characterized by a typical interictal pattern on EEG: very frequent high-voltage centro-temporal spikes (CTS) typically activated by sleep. The prognosis for seizure outcome in BECTS is excellent; most patients have less than 10 seizures, and seizure activity is expected to cease by adulthood (Blom & Heijbel, 1982; Camfield & Camfield, 2002; Dalla Bernardina, Sgro, & Fejerman, 1995; Loiseau, Duche, Cordova, Dartigues, & Cohadon, 1988; Panayiotopoulos, 1999). However, a growing body of literature has documented subtle cognitive and/or behavioral problems in children with BECTS, particularly affecting language function (Baglietto et al., 2001; Danielsson & Petermann, 2009; Ebus, Overvliet, Arends, & Aldenkamp, 2011; Goldberg-Stern et al., 2010; Jurkeviciene et al., 2012; Northcott et al., 2005; Overvliet, Aldenkamp, Klinkenberg, Nicolai, et al., 2011; Overvliet, Besseling, van der Kruijs, et al., 2013; Overvliet, Besseling, et al., 2011; Samaitiene, Norkuniene, Jurkeviciene, & Grikinine, 2012; Samaitiene, Norkuniene, Tumiene, & Grikinine, 2013; Verrotti, Filippini, Matricardi, Agostinelli, & Gobbi, 2014; Volkl-Kernstock, Bauch-Prater, Ponocny-Seliger, & Feucht, 2009).

1.2. Language and Cognitive Problems in BECTS

Typically, children with BECTS have normal general intellectual function (full-scale IQ) compared to their peers (Piccinelli et al., 2008; Pinton et al., 2006; Riva et al., 2007; Tedrus, Fonseca, Melo, & Ximenes, 2009). However, children with BECTS perform poorly when compared to controls on tests of expressive language (including naming and verbal fluency), receptive language, and verbal memory skills (Danielsson & Petermann, 2009; Garcia-Ramos et al., 2015; Goldberg-Stern et al., 2010; Overvliet, Besseling, van der Kruijs, et al., 2013; Piccinelli et al., 2008; Volkl-Kernstock et al., 2009). Earlier age of onset has been suggested to be associated with lower language scores (Jurkeviciene et al., 2012; Ma, Chen, Wang, & Xu, 2015) and, in fact, delayed language skills may appear as a precursor to the diagnosis of BECTS (Overvliet, Aldenkamp, Klinkenberg, Vles, & Hendriksen, 2011). These authors noted that 23% of 48 children with BECTS had a history of speech therapy and 35% repeated a year in primary school, both higher than the general population. A recent meta-analysis of studies of language and literacy in BECTS found that standardized language scores in BECTS were typically lower than healthy controls, with moderate to large effect sizes, but these differences were larger in older children and children with lower IQ (A. B. Smith, Bajomo, & Pal, 2015).

While language skills have been the most frequently studied in children with BECTS, non-verbal skills also appear to be affected, including non-verbal memory, attention, and inhibition (Baglietto et al., 2001; Danielsson & Petermann, 2009; Ebus et al., 2012; Garcia-Ramos et al., 2015; Kim, Yum, Kim, & Ko, 2014; Northcott et al., 2005; Piccinelli et al., 2008; Verrotti et al., 2013; Volkl-Kernstock et al., 2009). Difficulties in reading and other areas of academic achievement have also been reported (Ebus et al., 2011; Overvliet,

Aldenkamp, Klinkenberg, Vles, et al., 2011; Piccinelli et al., 2008; Tedrus et al., 2009). Across domains, in the majority of studies cited above children with BECTS score in the normal range (i.e. not greater than 1.5 standard deviations below the population mean). However, these children consistently show performance significantly lower than their healthy peers, suggesting a subtle impact of BECTS on language and cognition.

1.3. Neuroimaging abnormalities observed in BECTS

The impact of BECTS on brain structure and function has also been observed. One diffusion tensor imaging (DTI) study in children with BECTS showed decreased white matter integrity when compared to controls. Specifically, these changes were observed in the pre and post-central gyrus ipsilateral to the patient's centro-temporal spikes and the assumed origin of seizures with these findings being more prominent in patients with a duration of epilepsy of at least 1 year (Ciumas et al., 2014). Another study found reduced cortical thickness in 24 children with BECTS (ages 8–14, mean duration of epilepsy 2.4 years) in left perisylvian regions relative to healthy controls (Overvliet, Besseling, Jansen, et al., 2013). Among children with BECTS, cortical thinning was increased with age but language scores did not directly correlate with the degree of cortical thinning. Another recent structural imaging study revealed thinning, compared to controls, in areas of frontal, temporal, and occipital cortex in 13 children with BECTS of less than one year duration (Garcia-Ramos et al., 2015). Two years later, children with BECTS showed minimal regions of cortical thinning in isthmus cingulate and frontal cortex, in contrast to control participants, who showed extensive cortical thinning in both hemispheres, consistent with other studies of typical development (Lenroot & Giedd, 2006). These studies support a pattern of structural abnormalities that emerge during brain development in children with BECTS.

Brain structural abnormalities associated with BECTS are likely related to functional reorganization. Several studies have identified functional changes in language networks when comparing children with BECTS to controls. Aberrations in left-lateralization of language function in the inferior frontal gyrus have been found in BECTS patients (Datta et al., 2013; Lillywhite et al., 2009; Vannest et al., 2013), using a variety of functional MRI tasks. Also, we previously observed a more posterior shift of language-related activation in children with BECTS within the left-hemisphere during a story listening task (Vannest et al., 2013). Another group used both a word generation fMRI task and resting state functional MRI to examine connectivity between language and sensorimotor (Rolandic) networks in 23 children with BECTS ages 8–14 and found a reduction in connectivity in children with BECTS relative to controls between Rolandic regions and the left inferior frontal gyrus activated during the word generation task (Besseling, Jansen, et al., 2013). In a similar study, where the sensorimotor network was defined by a finger-tapping task, connectivity between the right inferior frontal gyrus (again identified from a word generation task) and left sensorimotor regions was reduced in children with BECTS relative to controls (Besseling, Overvliet, et al., 2013). However, in these studies, the mean duration of epilepsy was over 2 years, and their EEG findings were not described in detail, so the mechanism underlying the connectivity changes is difficult to infer.

These results suggest that children with BECTS have structural and functional alterations in the brain networks, including atypical organization of language networks, and reduced connectivity between language networks and other brain regions that possibly underlie their language difficulties. While abnormalities have been observed in peri-Rolandic regions, where centro-temporal spikes and seizures originate, the effect of BECTS on brain development is likely more widespread. The presence or absence of such abnormalities can be further explored with an fMRI probe that engages bilateral language networks e.g., story listening (Schmithorst, Holland, & Plante, 2006, 2007; Szaflarski et al., 2012).

In this study we used fMRI during a passive story listening task to examine receptive language function in children with recent-onset BECTS. Listening to a story involves multiple levels of language processing: speech perception, word recognition, analysis of syntax and discourse, and narrative comprehension. Consistent with this engagement of multiple language skills, the task activates bilateral, but left-lateralized superior/middle temporal regions and inferior frontal gyri in children as young as 3 months, and may also activate left angular gyrus and anterior cingulate/superior frontal gyrus (Ahmad, Balsamo, Sachs, Xu, & Gaillard, 2003; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Horowitz-Kraus, Vannest, & Holland, 2013; Karunanayaka et al., 2007; Papathanassiou et al., 2000; Schmithorst et al., 2006, 2007; Sroka et al., 2015; Vannest, Karunanayaka, Altaye, et al., 2009). We hypothesized that changes in functional organization related to BECTS would be revealed using this task. We also examined the relationship between language performance (on standardized testing) and fMRI activation and connectivity, to understand to what extent variability in these patterns underlies variability in language skill in BECTS.

2. METHODS

All study procedures were approved by Cincinnati Children's Hospital Medical Center Institutional Review Board.

2.1 Participants

Twenty-nine patients with clinical presentation and an EEG pattern consistent with BECTS (ages 5–12; 13 females) were recruited from Neurology Clinics at Cincinnati Children's Hospital Medical Center. Five children with BECTS did not complete the MRI portion of the study because they were unable to tolerate the MRI environment; they were excluded from further analysis. All children in the BECTS group were less than one year from their BECTS diagnosis as determined by a board-certified epilepsy specialist, had a history of 1–9 seizures at time of participation, and were not taking anti-epileptic medications (AEDs), except for one patient that began levetiracetam less than one week prior to study participation. Median time since first seizure was two months (see Table 1); one patient had a first recognized seizure 34 months before study enrollment, but this patient's EEG was read as normal at that time. A second recognized seizure occurred less than one month before study enrollment, at which time clinical EEG confirmed the typical pattern for BECTS.

Forty typically-developing children (ages 5–12; 20 females) also participated in the study. All patients and controls were native speakers of English with no history of

neuropsychological or learning disorders (based on parent report). Two children with BECTS were left-handed; all other participants were right-handed (per parent report). Informed consent was obtained from a parent/guardian for all participants, including written assent from participants age 11 and up.

2.2 Neuropsychological Evaluation

To measure general intelligence, participants were administered the Wechsler Abbreviated Scale of Intelligence – First Edition (Wechsler, 1999). Five-year olds (4 BECTS, 6 controls) were administered the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Third Edition (Wechsler, 2002). These tests yield verbal and performance composites, and full-scale IQ scores. Language skill was assessed using the core subtests of the Clinical Evaluation of Language Fundamentals – Fourth Edition (Semel, Wiig, & Secord., 2003). Non-language testing was included to assess visuo-spatial skill and general speed of processing: the Developmental Test of Visuomotor Integration – Sixth Edition (Beery & Buktenica, 1997), and Symbol Search and Coding subtests from the WPPSI-III and the Wechsler Intelligence Scale for Children – Version IV (Wechsler, 2002, 2003). Not all participants completed all testing; the numbers of patients and controls for whom scores were obtained are included in Table 2.

2.3 fMRI Methods

2.3.1 Story Processing Task (Schmithorst et al., 2006; Szaflarski et al., 2012; Vannest, Karunanayaka, Altaye, et al., 2009)—This task used a 30-second alternating block design in which a different story, read by an adult female speaker, was presented during each active period. Each story, designed by a speech-language pathologist to be appropriate for children 5 and up, contained 10 sentences with a variety of syntactic constructions. The baseline condition included a non-speech, broadband noise sweep with center frequency from 200–400Hz and durations of 0.5–2.0 seconds. Five blocks of control stimuli and four blocks of active were presented for a total scan time of 4 minutes 30 seconds.

2.3.2 Imaging Parameters—Participants were scanned on a 3T Philips Achieva MRI scanner using a 32-channel head coil. (functional MRI parameters: TR/TE = 2000/38 ms, FOV 24 X 24 cm, matrix 64 X 64, slice thickness = 4 mm, resulting in a voxel size of 3.75x3.75x4 mm, 37 axial slices). In addition, a 3D, T1-weighted 1mm isotropic anatomical image was acquired for use in coregistration and alignment of the participants.

2.4 Data Analysis

2.4.1 Neuropsychological Scores—Group comparisons of neuropsychological scores were conducted via t-test, corrected for multiple comparisons using a false discovery rate (FDR) method (Benjamini & Hochberg, 1995). Scores from WASI, WPPSI, and WISC subtests were analyzed separately.

2.4.2. EEG analysis in Children with BECTS—A board-certified pediatric epileptologist reviewed one hour of awake EEG and two hours of sleep EEG for all children with BECTS (recorded within two weeks before or after the neuroimaging session). Spike

rates (per minute) in each child, in each hemisphere, during wakefulness and sleep, were calculated based on this sample of EEG. Because of our limited sample size, and an imbalance in our patient group for right- versus left-predominant centrotemporal spikes, we did not categorically separate children with BECTS based on the predominant side of their spikes. Spike rates during wakefulness and sleep in each hemisphere were examined as continuous variables using Pearson correlation in analyses described below.

2.4.3 First-level fMRI analysis—First-level fMRI data processing was carried out using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and AFNI (Analysis of Functional Neuroimages, <http://afni.nimh.nih.gov>). Standard pre-processing steps, such as reorientation, slice timing correction and brain extraction, were carried out using FSL's *fslreorient2std*, *slicetimer* and *BET* (S. M. Smith, 2002), respectively. Outlying functional volumes were detected using FSL's *fsl_motion_outliers* (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers>). Motion correction of the BOLD time-series was carried out using *MCFLIRT* (Jenkinson, Bannister, Brady, & Smith, 2002). The functional file was interpolated to 2x2x2 mm voxel size and aligned to the Montreal Neurological Institute (MNI) template by first co-registering it with the participant's T1 image using FSL's *FLIRT* (Jenkinson et al., 2002; Jenkinson & Smith, 2001; S. M. Smith, 2002). The motion related artifacts were then regressed from the data by setting up a general linear model design using 24 motion parameters (6 motion parameters, the 6 motion parameters squared, a first order autoregressive model of the 6 motion parameters and a first order autoregressive model of the 6 motion parameters squared) plus an additional parameter as a marker for motion outliers (Friston, Williams, Howard, Frackowiak, & Turner, 1996). The residuals from the GLM were bandpass filtered from .01 to .1 Hz and smoothed with a 6mm Gaussian filter using AFNI's 3dBandpass. A second general linear model was then applied to contrast the BOLD activation during the stories compared to noise at the single-subject level.

2.4.4 Group composites and comparisons—A general linear model was used to identify brain regions associated with story processing (stories>noise) in each group and regions that differed between children with BECTS and controls. For display purposes, the group composite maps were thresholded with an initial $z > 3.71$ and corrected for multiple comparisons using FSL's cluster based inference to $p < 0.05$.

Finally, in order to examine potential group differences in more detail, we extracted z-scores for each participant from four regions of interest (ROIs) based on bilateral regions of activation during the story processing task in the group composite map in healthy controls. We focused on regions known to participate in the story processing network across studies: superior/middle temporal gyrus, and inferior frontal gyrus (for comparison see Figure 1A in Szaflarski et al., 2012). Group comparisons of mean z-scores were conducted via t-test, corrected for multiple comparisons using a false discovery rate (FDR) method (Benjamini & Hochberg, 1995). Using Pearson correlation, we examined the relationship between BOLD activation (stories>noise) in these regions and CELF composite scores. In children with BECTS, we also examined the relationship between BOLD activation in these regions and spike rates in each hemisphere during sleep and wakefulness; in this analysis, we used FDR

correction for multiple testing over the four spike rates examined (left sleep/wakefulness, right sleep/wakefulness).

2.4.5 Functional Connectivity Analysis—These analyses were performed using the CONN toolbox in SPM12 [v15, <http://www.nitrc.org/projects/conn>](Whitfield-Gabrieli & Nieto-Castanon, 2012)]. Two functional connectivity analyses were performed. In the first analysis, we began with the four ROIs described above from the bilateral regions that are typically activated during the story processing task; found in the composite map of the group of 40 healthy children. For connectivity analysis, these ROIs were narrowed to 5mm radius spheres centered at the center-of-mass for each cluster of activation (see Table 3 and Figure 1A). Bivariate regression coefficients were estimated to represent the total linear temporal association between the ROIs. Bivariate correlation (i.e., connectivity) during the story-listening condition for each participant was calculated. Group differences between the connections (children with BECTS versus controls), were examined at a threshold of $p < 0.05$ FDR-corrected (Benjamini & Hochberg, 1995). We then used Pearson correlation to examine whether connectivity between these pairs of regions, adjusted for age, was related to CELF composite scores or spike rates (in children with BECTS) in each hemisphere during sleep or wakefulness. FDR correction was used as in the ROI analysis above.

In the second analysis, we used a seed-to-voxel approach and used as seeds the four previously defined 5mm radius sphere ROIs (see above). In this analysis, the connectivity between each seed and all other voxels in the brain was examined. Using each seed ROI, we looked for those clusters of voxels where there were significant group differences in connectivity with the seed (BECTS versus controls, FDR-corrected at $p < 0.05$). This analysis revealed one region of group difference in connectivity (see section 3.5 below). We then used Pearson correlation to examine whether the connectivity between the seed ROI and this region was related to CELF composite scores, or spike rates (in children with BECTS) in each hemisphere during sleep or wakefulness.

3. RESULTS

3.1 Demographics and Clinical Data

The 24 children with BECTS (13 female) that were included in the imaging analysis did not differ from the control group in age (Table 1), estimated household income (parent report) or mother's education level. The frequency of centro-temporal spikes on EEG during an hour of wakefulness ranged from 0–19.45 per minute, and during two hours of sleep ranged from 0.20–77.57 per minute. Six patients had predominately left-sided centro-temporal spikes (>70% left), five had bilateral independent spikes, and thirteen had predominately right-sided centro-temporal spikes (>70% right).

3.2. Neuropsychological Testing

Not all participants were able to complete all testing – numbers of participants and mean scores are included in Table 2. Neuropsychological scores in children with BECTS and controls did not differ (see Table 2).

3.3. Imaging Results – Group Composites

Regions of significant group activation during story processing relative to noise in healthy controls included bilateral auditory cortex and superior/middle temporal gyri, as well as bilateral inferior frontal gyri. Smaller clusters of activation were also present in right thalamus, right precentral/postcentral gyrus, right occipital cortex, and left superior/middle frontal gyri (Figure 1A). In the children with BECTS, only one significant cluster of activation appeared in the left superior/middle temporal gyrus (Figure 1B). The location of centroids and size of activation clusters are listed in Table 3. Although Figures 1A and 1B suggest that there may be different patterns of activation for children with BECTS and controls, there is no statistically significant difference between them. In order to understand the pattern of activation in more detail, we extracted mean z-scores from the ROIs defined by the active regions ($z > 3.71$, $p < 0.05$ corrected) in healthy controls in the superior/middle temporal and inferior frontal gyri bilaterally. This revealed a high level of variability in activation in these regions in both children with BECTS and controls (Figure 2). Children with BECTS had a lower level of activation in the right inferior frontal gyrus [$t(62) = 2.61$, $p = 0.044$ corrected]. There was also a non-significant trend suggesting a lower level of activation in the right superior/middle temporal ROI ($p = 0.07$, uncorrected). None of the four regions in children with BECTS showed a relationship between rate of centro-temporal spikes during wakefulness or sleep in either hemisphere (all $p > 0.2$).

There was a significant positive correlation, across patients and controls combined, between CELF composite scores and activation (mean z-score) in the right superior/middle temporal ROI and [$r = 0.33$; $p = 0.011$, 0.044 corrected], and a similar trend, after FDR correction, in the left superior/middle temporal ROI [$r = 0.27$; $p = 0.034$, 0.068 corrected], see Figure 3.

3.4. Imaging Results – ROI-to-ROI connectivity

Pairwise connectivity between the four 5mm radius spherical ROIs, selected based on the control group activation and shown in Figure 1A, did not differ between children with BECTS and controls (all $p > 0.60$). There were also no significant relationships between pairwise connectivity and CELF scores (all $p > 0.20$) or spike rates in BECTS patients (all $p > 0.15$).

3.5 Imaging Results – Seed-to-Voxel connectivity

Using each of the four spherical ROIs as seeds, there was one significant region of higher connectivity in controls relative to children with BECTS. From the 5mm radius spherical seed in the left inferior frontal gyrus, controls had significantly higher connectivity in a proximal area of the left inferior frontal gyrus extending into orbitofrontal cortex (Figure 4 and Table 3). Connectivity between this pair of regions showed no significant relationship with CELF scores ($p > 0.60$), and, in children with BECTS, it was not related to the rate of centro-temporal spikes in either hemisphere during wakefulness or sleep (all $p > 0.17$).

4. DISCUSSION

Our results show evidence of functional reorganization and changes in functional connectivity during language processing in BECTS. Interestingly, unlike in previous studies,

our children with BECTS showed scores comparable to controls on standardized tests of language and cognitive skill. This may be due to the children with BECTS being relatively early in the course of their epilepsy, though previous studies have identified poorer performance in participants with new-onset BECTS (Garcia-Ramos et al., 2015). . Smith et al note that across studies of language skill in BECTS, differences from controls tend to be larger in older children – our mean age for BECTS and control participants (8.13 and 7.9 years, respectively) and the age range (5–12) was lower than in many studies included in the Smith et al meta-analysis (A. B. Smith et al., 2015). They also note that language problems in BECTS are more likely to be detected in children with lower IQ. Our participants had generally high IQ (WASI FSIQ was 109.74 in controls and 107.65 in BECTS, a few 5-year olds completed WPPSI, see Table 2 for mean scores). These factors may contribute to the lack of differences in CELF scores observed in our study.

The similarity in language skills (CELF and Verbal IQ) in children with BECTS compared to controls allows us to examine possible *compensatory* changes in functional organization and connectivity in BECTS; these patients may use an atypical network to support a similar level of language skill, at least at the initial stage of active BECTS. We note, however, that we did not directly assess performance on the in-scanner receptive language task, and did not include a specific assessment of narrative comprehension in our battery, so it is possible that the groups differed in their skills in this specific domain.

As mentioned above, the story listening task been shown to engage bilateral, but left-lateralized activation in the superior/middle temporal and inferior frontal gyri as well as left postcentral/angular gyrus and anterior cingulate/superior frontal gyrus in children across development (Horowitz-Kraus et al., 2013; Karunanayaka et al., 2007; Schmithorst et al., 2006, 2007; Sroka et al., 2015; Vannest, Karunanayaka, Altaye, et al., 2009). Our results in healthy controls were consistent with these previous studies, but revealed a pattern of decreased activation in children with BECTS in the region of right inferior frontal gyrus active during the task (the right temporal ROI showed a similar, but non-significant trend toward reduced activation in BECTS).

However, we did not find a direct correlation between the rate of centro-temporal spikes recorded and decreased activation. There was a significant positive correlation, across patients and controls combined, between CELF composite scores and activation activation in bilateral superior/middle temporal regions (significantly on the right, and a trend, when corrected, on the left). Verbal skills may be stronger in children who are able to more actively engage these regions, which support primary auditory processing of speech as well as, phonological and semantic processing (see(Price, 2012; Vannest, Karunanayaka, Schmithorst, Szaflarski, & Holland, 2009; Weiss-Croft & Baldeweg, 2015)for discussion of the functional neuroanatomy of these regions).

ROI-to-ROI functional connectivity between regions of the language network (left inferior frontal gyrus, left superior temporal gyrus, and right hemisphere homologues) did not differ between children with BECTS and controls. This suggests that the network is established in children with BECTS, even if they are not activating it to the same degree as their healthy peers. A difference in connectivity did emerge, however, within the left inferior frontal

gyrus, where there was decreased connectivity for BECTS compared to the control group. Unlike previous fMRI studies that report decreased activation or decreased left-lateralization specific to inferior frontal regions in BECTS (Datta et al., 2013; Lillywhite et al., 2009; Vannest et al., 2013), we found similar levels of left inferior frontal activation, but differences in regional connectivity. Interestingly, this decreased connectivity within the left inferior frontal gyrus did not correspond to poorer performance in BECTS, as language scores were similar to healthy controls (Datta et al. 2013 also found significant differences in language activation patterns for children with BECTS compared to controls, with no difference in performance). It is possible that children with BECTS may rely on alternative circuitry to achieve language skills comparable to controls. However, within the sensitivity of the methods used in our study, we did not find any regions where, as a group, children with BECTS consistently showed increased connectivity compared to controls. We speculate that the alternative compensatory circuitry may vary among patients depending on the location/lateralization of the focus of their seizures and centro-temporal spikes. With the imbalance of left, right and bilateral CTS we were unable to sub-divide patients into groups by localization.

We note that one drawback to the story listening task is that the children do not actively provide responses to the language stimuli. However, in children as young as 5, this is not always feasible, and may increase the likelihood of head motion corrupting the imaging data. Importantly, in one study, we compared an active-response version of the task, with interleaved comprehension questions, with the passive listening version, in a group of 11–13 year olds (Vannest, Karunanayaka, Altaye, et al., 2009). The two versions of the task showed similar patterns of activation and lateralization, though the active task demonstrated slightly more extensive activation in frontal regions. We concluded that language lateralization, and inferior frontal and superior temporal involvement, could be assessed using the passive story listening task, especially in a younger population who might not be able to participate in an active task. In addition, our group has found that the pattern of activation associated with this task when children are expecting to answer post-scan comprehension questions (Schmithorst et al., 2006, 2007; Szaflarski et al., 2012), is quite similar to when they are simply asked to listen, as in the present study (Hutton, Horowitz-Kraus, Mendelsohn, DeWitt, & Holland, 2015; Schmithorst et al., 2015; Sroka et al., 2015), though we have not contrasted these two conditions directly. Further evidence that the passive listening task engages multiple levels of language processing is shown in independent component analysis (Karunanayaka et al., 2007; Schmithorst et al., 2006), where phonological and semantic processing networks emerge. However, without associated performance data, we cannot have complete confidence that younger children, or children with BECTS, are fully attending to or comprehending the narrative stimuli.

As an exploratory measure, some participants (n=18 BECTS patients and n=28 controls) completed the Test of Variables of Attention, Version 8 (Leark, Greenberg, Kindschi, Dupuy, & Hughes, 2008). Children BECTS and controls did not differ on any of the standard scores derived from the TOVA (ADHD score, Errors, Response Time, and Response Time Variability, all $p>0.25$). While not all participants completed this assessment, this pattern suggests that attention in children with new-onset BECTS is not different from healthy controls.

Another limitation of our study was that data were collected only at a single time point relatively early after BECTS diagnosis. Longitudinal data examining neuropsychological outcomes in BECTS, and how they relate to changes in functional connectivity and EEG profiles, would help to clarify the factors that may lead to poorer outcomes in some children with BECTS, as have been reported in the literature. The present results represent a demonstration of the potential for plasticity in BECTS and the resilience of the language network, which is largely maintained even in patients with nocturnal epileptiform discharges as frequent as 70/minute. Ultimately, a better understanding of the interaction between these centro-temporal spikes, changes in functional organization and connectivity, and neuropsychological outcome in BECTS will allow for earlier identification of those patients who may have a more severe impact of BECTS on language and cognition, compared to those who will remain resilient.

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Highlights

- Existing literature suggests children with BECTS show subtle cognitive difficulties
- We used functional MRI and a story listening task in BECTS and controls
- Right inferior frontal activation for story processing was reduced in BECTS patients
- Connectivity in the story processing network was similar between groups
- Connectivity within left inferior frontal gyrus was decreased in BECTS

Figure 1.

Group composite activation maps for story listening>noise for (A) 40 healthy controls and (B) 24 children with BECTS. Both composite maps are thresholded at initial $z > 3.71$, corrected to $p < .05$. Spherical ROIs (5mm radius) used as seeds in connectivity analysis are indicated by green circles.

Figure 2.
Mean z-scores for each group in functionally-defined ROIs based on regions of activation in Figure 1A.

Figure 3. Mean activation (z-scores) for each participant in the BECTS and Control Groups in Regions of Interest (ROI) significantly correlated with CELF scores. (A) shows the left superior temporal gyrus ROI, and (B) shows the right superior temporal gyrus ROI.

Figure 4. Region of significantly increased connectivity for healthy controls > children with BECTS (initial $p < .001$, corrected to $p < .05$), from the seed in the left inferior frontal gyrus (seed indicated by blue circles).

Table 1

Demographic and Clinical Characteristics of BECTS patients and controls who completed fMRI and neuropsychological testing.

		BECTS n=24	Controls n=40
Age	<i>mean</i>	8.13	7.9
	<i>SD</i>	<i>2.07</i>	<i>2.15</i>
Gender		13 F	20 F
Maternal Education (approximate years)	<i>mean</i>	15.67	16.66
	<i>SD</i>	<i>2.03</i>	<i>1.86</i>
Age Onset (years)	<i>mean</i>	8.15	N/A
	<i>SD</i>	<i>1.97</i>	
Months Since First Seizure	<i>mean</i>	4.88[*]	
	<i>SD</i>	<i>7.46</i>	
Number of Seizures	<i>mean</i>	2.5	
	<i>SD</i>	<i>1.87</i>	
AED use		1 patient,	
		LEV for	
		<1 week	

^{*} One patient had a first recognized seizure 34 months before study enrollment, but this patient's EEG was read normal at that time. A second recognized seizure occurred less than one month before study enrollment, at which time clinical EEG confirmed the typical pattern for BECTS.

Table 2

Neuropsychological Outcomes

			BECTS	Controls
CELF	Core	mean	98.57	102.14
		SD	12.74	14.97
		n	23	37
WASI (age >5)	Full scale IQ	mean	107.65	109.74
		SD	12.71	13.24
		n	20	31
	Verbal Composite	mean	108.10	111.81
		SD	11.97	13.54
		n	20	31
	Performance Composite	mean	105.30	105.23
		SD	13.64	13.42
		n	20	31
WISC Processing Speed Index (age >5)		mean	95.75	101.93
		SD	12.61	10.50
		n	20	30
WPPSI (age 5)	Full scale IQ	mean	88.67	103.67
		SD	3.22	10.03
		n	3	6
	Verbal Composite	mean	88.67	104.00
		SD	9.02	10.79
		n	3	6
	Performance Composite	mean	92.33	101.17
		SD	7.767	7.885
		n	3	6
WPPSI Processing Speed Index (age 5)		mean	97.67	106.17
		SD	18.90	8.38
		n	3	6
Beery VMI		mean	95.67	97.22
		SD	12.01	11.39
		n	24	37

Table 3

Size and location of clusters of activation in A) stories>noise in healthy controls ($z>3.71$, $p<0.05$ corrected); B) stories>noise in children with BECTS ($z>3.71$, $p<0.05$ corrected); C) Region of decreased connectivity in BECTS patients compared to controls from the 5mm radius spherical seed in left inferior frontal gyrus.

Extent in Voxels	X (mm)	Y (mm)	Z (mm)	
A. Regions of activation for stories>noise in healthy controls				
3522	-53.8	-24.7	0.6	Left Superior/Middle Temporal Gyrus
2546	56.4	-14.8	-9.6	Right Superior/Middle Temporal Gyrus
270	-46.6	23.2	15.9	Left Inferior Frontal Gyrus
270	18.7	-21.6	-3.13	Right Thalamus
228	-20.7	-6.96	64.7	Left Superior Frontal Gyrus
200	25	-8.71	57.8	Right Precentral Gyrus
191	47.2	-75.7	-12.1	Right Lateral Occipital Cortex
126	-44.7	3.93	52.4	Left Middle Frontal Gyrus
89	53.2	27.4	15.7	Right Inferior Frontal Gyrus
85	32.8	-26.1	48.1	Right Precentral/Postcentral Gyrus
43	62.4	-54.1	15.2	Right Angular Gyrus
28	40.5	6.29	59.8	Right Middle Frontal Gyrus
26	12.5	-13.8	-13.5	Right Amygdala
22	-16.8	-29.4	-4.47	Left Thalamus
22	-33.8	-93	-14.1	Left Occipital Pole
B. Regions of activation for stories>noise in children with BECTS				
780	-58	-18.4	2.25	Left Superior/Middle Temporal Gyrus
C. Region of decreased connectivity in BECTS patients from the LIFG seed				
900	-32.8	39.9	-5.62	