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Cortical Thickness in Childhood Left Focal Epilepsy: Thinning Beyond the Seizure Focus

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Abstract

Objective —Structural brain differences are found in adults and children with epilepsy, yet pediatric samples have been heterogeneous regarding seizure type, MRI findings, and hemisphere of seizure focus. This study examines whether cortical thickness and surface area differ between children with left hemisphere focal epilepsy (LHE) and age-matched typically developing (TD) peers. We examined whether age differentially moderated cortical thickness between groups and if cortical thickness was associated with duration of epilepsy, seizure frequency, or neuropsychological functioning.

Methods —35 LHE and 35 TD children completed neuropsychological testing and 3T MR imaging. Neuropsychological measures included general intelligence and executive functioning. All MRIs were normal. Surface-based morphometric processing and analyses were conducted using FreeSurfer 6.0. Regression analyses compared age by cortical thickness differences between groups. Correlational analyses examined associations between cortical thickness in these areas with neuropsychological functioning or epilepsy characteristics.

Results —LHE displayed decreased cortical thickness bilaterally compared to TD controls across 6 brain regions but no differences in surface area. Moderation analyses revealed quadratic

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relationships between age and cortical thickness for left frontoparietal-cingulate and right superior frontal regions. Higher PIQ and VIQ and fewer parent reported executive function problems were associated with greater cortical thickness in TD children.

Significance —LHE children displayed thinner cortex extending beyond the hemisphere of seizure focus. The nonlinear pattern of cortical thickness across age occurring in TD children is not evident in the same manner in LHE children. These differences in cortical thickness patterns were greatest in children 8-12 years old. Greater cortical thickness was associated with higher IQ and fewer executive control problems in daily activities in TD. Thus, differences in cortical thickness in the absence of differences in surface area, suggest cortical thickness may be a sensitive proxy of subtle neuroanatomical changes that are related to neuropsychological functioning.

Keywords

Pediatric; Brain Development; FreeSurfer; Neuropsychology; Executive Functioning

1. Introduction

Children with epilepsy are at risk for cognitive difficulties including executive functioning deficits, which are skills essential to regulating thoughts, actions, and emotions in a goal directed manner [1–9]. Epilepsy is associated with neuroanatomical changes and the use of neuroimaging to find biomarkers of cognitive dysfunction is a common pursuit. Previous studies have used surface-based magnetic resonance imaging (MRI) to explore widespread structural abnormalities in both children and adults with epilepsy, including alterations to volume, surface area, and cortical thickness in the absence of MRI abnormalities [10–18]. Cortical volume is composed of two determinants, surface area and cortical thickness, and has been used to measure anatomical change in children with epilepsy [10,11]. Surface area and cortical thickness differentially contribute to cortical volume as a function of sex and developmental stage [19]. Surface area is a marker of cortical folding and gyrification, particularly sensitive to sex differences [19]. Cortical thickness is a marker of neuroanatomical maturation, neural pruning and sculpting, and is sensitive to developmental change in typically developing and clinical populations [19–21]. In typical development (TD), the rate of change in cortical thickness is associated with neuropsychological performance, particularly intellectual abilities and executive functioning [22–32]. The purpose of the current study was to compare cortical thickness and surface area in children with left hemisphere focal epilepsy (LHE) to children with TD and determine whether cortical thickness or surface area differences are associated with neuropsychological performance.

Previous studies have explored cortical morphology in pediatric epilepsy populations. Despite relatively small samples and inclusion of heterogeneous seizure types and location of seizure focus, a consistent finding across studies is the occurrence of abnormally thinner cortex [10–17]. This thinner cortex extends beyond the epileptic focus in focal epilepsy populations [13,14] and is evident in patients with new-onset seizures [17,18]. However, only two studies have addressed how cortical thinning is related to functioning in childhood epilepsies [14,15]. One study comparing children with rolandic epilepsy to controls focused

on language functioning but found no associations with cortical thickness differences [14]. The other study examined psychosocial functioning in children with recent onset epilepsy of both focal and generalized epilepsy. Better social skills were associated with increased cortical thickness and worse behavior problems, particularly internalizing symptoms (withdrawal/depression, inattention, thought problems) were associated with decreased cortical thickness, however, the study did not include a control group for comparison [15]. Given the wide range of neuropsychological difficulties in pediatric epilepsy, there remains a lack of investigation into other cognitive domains. This is a gap in our knowledge considering cortical integrity is a sensitive measure of disease progression and cognitive changes in adults and children [33,34]. Executive function is a ubiquitous domain of impairment in pediatric epilepsy, evident on direct neuropsychological testing and parent-reported measures [1–9] yet has not been investigated in relation to cortical thickness differences.

In TD populations, cortical developmental trajectories are not linear as they show an initial period of childhood increase in thickness followed by a decline in adolescence and then stabilization in younger adulthood [19–21]. The rate of cortical development is related to intellectual abilities. A thinner cortex in early childhood followed by a rapid and extended period of cortical thickness increase into adolescence is associated with higher intelligence and better executive functioning [22–24,26,30–32]. In late adolescence, a decrease in cortical thickness is associated with higher intelligence, hypothesized to reflect selective synapse elimination and reorganization of neural networks leading to greater brain efficiency [14,28,29,35,36]. The present study examined whether cortical thickness differs between children with LHE and age-matched TD peers and explored whether cortical thickness has utility as biomarker for risk of neuropsychological dysfunction. For whole brain analysis, we hypothesized cortical thickness would be thinner in LHE compared to TD, with no differences in surface area. Then, for brain areas where cortical thickness differences between TD and LHE were found, we examined whether age differentially moderated cortical thickness trajectories between groups. Given the nonlinear trajectory of normal development, we hypothesized age would moderate cortical thickness differences between groups. Next, we tested our hypothesis that decreased cortical thickness was associated with neuropsychological functioning. We hypothesized that decreased cortical thickness would be associated with worse performance in verbal/nonverbal intellectual functioning and executive functioning. For the patients, we examined if duration of epilepsy and seizure frequency was associated with cortical thickness. Because a previous study of children with new onset epilepsy found no relationship with cortical thickness and epilepsy [17], we hypothesized there would be no relationships in our sample with a relatively short duration of epilepsy.

2. Material and methods

2.1 Participants

Participants included 35 children with left hemisphere epilepsy (LHE; 15 girls) and 35 age-matched typically developing controls (TD; 16 girls). Age matching was by year and successfully yielded similar means and ranges. The mean age of the patients was 10.5 years

[standard deviation (SD) 3.0 years; range 5.2 – 15.7 years]. The mean age of the TD controls was 10.5 years (SD 3.0 years; range 5.2 – 15.9 years). Participants were recruited through multiple clinical research protocols that included common measures but had different aims but the majority were related to examining language reorganization. Thus, patients were included if they had focal epilepsy in the left hemisphere and globally normal MRI. The exclusion criteria for the original protocols limited the sample to right handers with Wechsler IQ ≥ 80 , without any contra-indications for MRI, or any prior history of an acquired neurological injury or central nervous system disease, except seizures for patients. All subjects were recruited from Children's National Health System's neurology clinics and the Washington, D.C. metropolitan community via flyers and pamphlets. The study was approved by, and performed according to, the policies of the Children's National Institutional Review Board. Parent informed consent and child assent were obtained prior to the evaluation.

Patients had left hemisphere epilepsy confirmed by a child neurologist and/or clinical neurophysiologist as determined by seizure characteristics, EEG and/or video EEG. No children with Rolandic epilepsy were included. Seven (20%) of the children with epilepsy had the following comorbidities: four patients had ADHD; one had depression; one had anxiety; and one had ADHD, anxiety, and depression. To ensure that our results were not influenced by this subset of children with comorbidities, we performed cortical thickness and statistical analyses with and without these seven patients. Whole brain cortical thickness findings were highly similar. Thus, we included the full sample for our primary analysis of examining cortical thickness. For neuropsychological data, when the seven patients were excluded, the patients no longer were statistically different on neuropsychological functioning. Therefore, we also conducted analyses with neuropsychological variables for both the whole sample without these patients as well as for patients and TD children separately. Detailed information about seizure onset, duration, frequency, focus, and antiepileptic medications are provided in Table 1. A majority had seizures arising from the frontal and/or temporal lobes (66%), were on one medication (62%), and had at least one seizure in the last six months (57%).

2.2 Measures

Participants underwent neuropsychological testing and a neuroimaging session across two separate visits. Parents completed questionnaires to characterize their child's neurodevelopmental and behavioral history. All study participants (5–15 years) received an age-appropriate measure within the domain, as highlighted below.

2.2.1 Intellectual Functioning —The Wechsler Abbreviated Scale of Intelligence (WASI) [37] was administered to assess intellectual ability. The WASI contains two verbal (Vocabulary and Similarities) and two nonverbal (Matrix Reasoning and Block Design) subtests. The WASI provided a Full-Scale IQ (FSIQ) score used to determine study eligibility. Verbal (VIQ) and nonverbal (PIQ) composite scores were used in bivariate correlational analysis. The lower limit of the WASI age range is six; therefore, the five-year-old study participants received the Differential Ability Scales (DAS) [38] to assess intellectual ability. The DAS General Conceptual Ability score was used similarly to WASI

for study eligibility (General Conceptual Ability for FSIQ, Verbal Ability for VIQ, Nonverbal Ability for PIQ). Both measures use Standard Scores with a mean of 100 and standard deviation of 15.

2.2.2 Executive Functioning —The Behavior Rating Inventory of Executive Function (BRIEF) [39] was used to assess everyday executive functioning skills via parent rating. The BRIEF is an 86-item questionnaire consisting of eight subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory (WM), Plan/Organize (P/O), Organization of Materials, and Monitor. Each of the eight BRIEF subscales contributes to one of two indices, the Behavioral Regulation Index (BRI) and the Metacognition Index (MI) which were used in bivariate correlational analysis. The BRIEF-Preschool was used for five-year-old study participants with the BRIEF Inhibitory Self-Control index used for BRI and the BRIEF Emerging Cognition index used for MI. The BRIEF also provides validity scales; no ratings were in the unacceptable range.

2.3 MRI Procedures

2.3.1 MRI Acquisition —Sagittal T1-weighted MPRAGE structural MRI scans were performed on all participants using a 3.0T Siemens Magnetom Trio equipped with a standard CP head coil. Scan parameters: slice thickness 1 mm; repetition time (TR) = 2530 ms; echo time (TE) = 3.5 ms; flip angle = 7°; field of view = 256 mm; voxel = 1 mm × 1 mm × 1 mm. Foam padding was placed around the head to limit motion during the scan. Participants were given headphones and earplugs to minimize noise while inside the scanner. Children were also often watching a video of their choice to assist in minimizing motion in the scanner.

2.3.2 MRI Processing —Images were processed with the FreeSurfer 6.0 image analysis suite. FreeSurfer is a freely available online software (<http://surfer.nmr.mgh.harvard.edu/>), commonly used for the study of cortical and subcortical anatomy. The technical details of FreeSurfer's procedures for morphometric analysis are detailed in prior publications [40–43]. The reported data were produced using the FreeSurfer default processing stream (recon-all), which includes transformation to Talairach space, intensity normalization for correction of magnetic field inhomogeneities, and removal of non-brain tissues (i.e., skull-stripping). We visually inspected the resulting surface models for motion artifact, and manually edited the surfaces in cases where there was overinclusion of skull, pial matter, or white matter. During visual inspection, 21 scans (13 TD; 8 LHE) were thrown out for motion or poor quality prior to age matching. FreeSurfer calculates cortical thickness as the distance (in mm) from the grey matter-white matter boundary to the pial surface at each vertex of the tessellated surface [42]. FreeSurfer calculates surface area as the average area of tessellated triangles touching at each vertex on the gray matter surface. After visual inspection and manual interventions, we obtained vertex-level cortical thickness and surface area. The vertex-level cortical thickness values were mapped onto a normalized cortical surface and smoothed with a 15 mm full width at half maximum kernel. The surface area volumes were mapped onto a normalized cortical surface and smoothed with a 5 mm full width at half maximum kernel.

2.4 Data Analyses

We investigated the differences in cortical thickness and surface area across the whole brain between LHE and TD using FreeSurfer's statistical tool, Qdec. To correct for multiple comparisons, we implemented a Monte-Carlo simulation with 10,000 iterations, with a cluster-forming threshold set to $p < 0.05$. After we identified clusters of differences between groups, we exported individual cortical thickness measurements to Statistical Package for the Social Sciences (SPSS; IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY, U.S.A.) for regression and correlational analysis. We further tested if age moderated the relationship between group and cortical thickness using regression analyses. Previous research has characterized cortical growth patterns in typical development as cubic, linear and quadratic trajectories [19,21]. Therefore, we used Aiken and West [44] centering to produce linear and quadratic interaction terms for age by group relationships and examined each cortical thickness cluster separately. Independent samples *t*-tests were conducted to determine group differences in neuropsychological functioning. Using Pearson correlation coefficients, we examined the relationship between cortical thickness and general intelligence (PIQ and VIQ), and executive functioning (parent BRIEF BRI and MI). For patients, we also examined duration of epilepsy and seizure frequency as correlates of interest.

3. Results

3.1 Cortical Thickness Analyses

Cortical thickness was decreased for children with LHE compared to TD children across six clusters bilaterally (2 Left; 4 Right; Figure 1, Table 2). Left clusters included the frontoparietal-cingulate cortex ($p < 0.001$) and parieto-occipital junction ($p = 0.002$) and together the two clusters on the left were comparable in overall size to the four smaller right-hemisphere clusters. Right clusters included supramarginal ($p = 0.02$), paracentral ($p = 0.02$), and superior frontal gyri ($p = 0.04$), as well as the parieto-occipital junction ($p = 0.01$). Moderation analysis revealed a relationship between quadratic age change and cortical thickness by group for left frontoparietal-cingulate (Figure 2a; $p = 0.03$) and right superior frontal (Figure 2b; $p = 0.01$) thickness. Quadratic age change accounted for 52% of the variance between groups in left frontoparietal-cingulate ($F[5,64] = 13.902$, $p < 0.001$) and 26% of the variance in the right superior frontal cluster ($F[5,64] = 4.486$, $p = 0.001$). Cortical thickness differences were greatest between groups from ages 8 - 9.5 in the left frontoparietal-cingulate region (average difference = 0.23 mm^2) and ages 10.5 - 11.5 in the right superior frontal region (average difference = 0.34 mm^2). Additionally, there was trend for a quadratic age change and group for right supramarginal gyrus cluster ($p = 0.07$). No linear or quadratic age relationships were found for the other three clusters (left and right parieto-occipital junction or right paracentral).

3.2 Surface Area Analyses

There were no group differences in surface area for either hemisphere. Thus, no further analyses were conducted relating to neuropsychological functioning or epilepsy characteristics.

3.3 Cortical Thickness and Neuropsychological Functioning

Children with LHE had lower intellectual skills (VIQ $t[68] = 2.91$, $p = 0.005$; PIQ $t[68] = 2.37$, $p = 0.02$) and more executive function problems (BRIEF MI $t[68] = -2.53$, $p = 0.01$) than TD controls. Despite this statistical difference, both groups performed in the average range for intellectual skills and overall were not clinically elevated for executive functioning measures (Table 3). Moreover, when we removed the seven patients with comorbid diagnoses, the intellectual and executive functioning differences were no longer significant. In consideration of these neuropsychological differences, we performed analyses for patients and TD controls as a single combined group as well as for each group separately. For the combined sample analyses, we removed the seven patients with comorbidities to have more power to detect relationships between cortical thickness and functioning and because without these seven patients, there were no longer significant differences in neuropsychological functioning. Then, for individual groups, we analyzed TD controls separately and patients both with and without the subgroup with comorbidities.

3.3.1 Combined Sample Analysis —Examining only the six brain areas where cortical thickness was different between groups, we found six significant relationships between cortical thickness and neuropsychological functioning with small to medium effect sizes. Specifically, greater PIQ was associated with greater cortical thickness in three regions: left frontoparietal-cingulate region (Figure 3a; $r = 0.383$, $p < 0.01$), left parieto-occipital junction (Figure 3b; left $r = 0.301$, $p = 0.02$), and right supramarginal gyrus (Figure 3c; $r = 0.291$, $p = 0.02$). Greater VIQ was also associated with greater cortical thickness in the right parieto-occipital junction (Figure 3d; $r = 0.321$, $p = 0.01$). More parent-reported executive function problems were associated with decreased cortical thickness in the left frontoparietal-cingulate region (Figure 3e; BRIEF MI $r = -0.286$, $p = 0.02$) and the right supramarginal region (Figure 3f; BRIEF MI $r = -0.290$, $p = 0.02$).

3.3.2 Individual Group Analysis —Given the group differences in neuropsychological functioning, we examined if the relationship between cortical thickness and neuropsychological functioning differed by group. Three of the six findings in the whole sample were no longer significant for either group, indicating that with the smaller sample size, the small to moderate relationships were no longer detected. There was also one new finding for the TD control group.

LHE: We found no significant correlations between cortical thickness and neuropsychological measures for the LHE group alone. Similarly, when the seven patients with comorbidities were removed, there also were no significant correlations. Regarding seizure characteristics, seizure frequency and duration of epilepsy were not significantly correlated with any of the areas of cortical thickness difference.

TD Controls: Four correlations were found for TD children. As with the whole sample results, greater PIQ remained associated with greater cortical thickness in the left parieto-occipital junction (Figure 3b; $r = 0.414$, $p = 0.01$) and right supramarginal gyrus (Figure 3c; $r = 0.362$, $p = 0.03$) and greater VIQ remained associated with greater cortical thickness in the right parieto-occipital junction (Figure 3d; $r = 0.371$, $p = 0.03$). One new association was

found for executive function, the left parieto-occipital junction was positively correlated with BRIEF BRI score (Figure 3g; $r = 0.353$, $p = 0.04$).

4. Discussion

In a cross-sectional analysis of age-matched children 5 to 15 years old, we found decreased cortical thickness in LHE compared to TD controls, ipsilateral and contralateral to the hemisphere of seizure focus, but no differences in surface area. We also found that these areas of cortical thickness difference correlated with higher IQ and better executive control for TD but not LHE. Overall, our study supports cortical thickness as a possible biomarker of developmental differences between children with epilepsy and TD children.

Similar to previous studies of pediatric focal and generalized epilepsy populations, regardless of seizure types and employing different methods, we found bilateral decreased cortical thickness [13–15]. We hypothesize that cortical thickness abnormalities in the contralateral hemisphere may be related to the propagation of epileptiform activity through underlying functional networks. Of the pediatric studies with samples most similar to our study (e.g., focal epilepsy) there was overlap in frontal, parietal, occipital, and cingulate regions [13,14]. The areas commonly found in pediatric studies are less widespread, but overlap with adult studies [12,45–47]. It is possible that the differences found in childhood persist into adulthood and increase over time to become more widespread and include areas such as the temporal lobe, reflecting how neural networks develop. Age is an important factor in understanding cortical thickness differences in epilepsy.

Unlike most previous epilepsy studies, we carefully examined the effect of age and found that these cortical thickness differences are moderated, in part, by age, which has been demonstrated by only one study to date [14]. Differential age-related trajectories between LHE and TD controls were revealed. Even in this relatively small cross-sectional study of TD controls, the expected developmental pattern [19–21] of increasing cortical thickness at younger ages and a decline in cortical thickness in adolescence emerged. In contrast, for the epilepsy group, the association between age and cortical thickness appears to be more muted. Maximal group differences occurred in the age range of 8–12 years old. Thus, it appears that the cortical thickness differences found across age in TD children are not occurring to the same extent as they are for children with epilepsy. In typical development, cortical changes are conceptualized as a proxy for neuronal maturation and optimization-driven pruning [14]. However, in LHE children this process appears mitigated, suggesting that important pruning may not be occurring in the same manner.

These age-dependent structural differences were associated with neuropsychological functioning. Specifically, we found an association between cortical thickness and metacognitive functioning, which is often an area of difficulty for children with pediatric epilepsy [9]. When examining each group separately, we confirm prior findings for TD children in this age range showing that better neuropsychological functioning is associated with increased cortical thickness [22–32]. In contrast, for LHE children alone, there were no significant associations between cortical thickness and neuropsychological functioning. Only two other studies have examined the relationship between functioning and cortical

thickness in children with epilepsy, and our study is the first to examine intellectual and executive functioning. One study examined social-emotional and behavioral functioning in children with focal and generalized epilepsy using a widely used parent questionnaire (Child Behavior CheckList) but did not include a control group for comparison. They found that increased cortical thickness was associated with fewer attention problems and better total social-emotional competence for epilepsy patients [15]. The other study examined cortical thickness and language skills in a rolandic epilepsy group compared to controls. In contrast to the extant literature, *thinner* cortex (in the left inferior occipital lobe, near lingual gyrus) was associated with better language performance in epilepsy patients only [14]. We extend prior work by showing that the nonlinear changes in cortical thickness that occur in TD children are occurring in a different pattern for children with LHE. Since that process of thickening is related to better neuropsychological functioning in TD children, we propose that change in cortical thickness is important to the development of neuropsychological skills, especially those that are developing in this time period, namely executive functioning. The areas found in our study overlap with several regions that tap into central networks as shown by functional connectivity studies [48] (i.e. Default Mode Network, Central Executive Network). Development of cortex in these regions is critical for cognitive and behavioral functioning. Thus, differences in structural brain maturation may underlie worse neuropsychological functioning found in children with LHE.

Abnormal development of cortical thickness may be a useful biomarker for neuropsychological dysfunction, even in epilepsy patients with no obvious MRI abnormalities. It remains unclear whether the structural abnormalities seen in pediatric epilepsy are a result of interictal or ictal activity, or whether they precede seizure activity and are a potential risk factor for neurological abnormality. While epilepsy duration was not associated with cortical thickness in the current study—possibly due to the relatively young cohort and thus short duration—studies in adults with epilepsy show that duration of epilepsy is related to cortical differences [45,49].

4.1 Limitations

The cross-sectional design cannot capture dynamic longitudinal cortical changes. This is an important next step to pursue in order to truly determine the atypicality of the neuroanatomical trajectories of children with epilepsy and how they might predict functional outcomes. Additionally, we only examined patients with left hemisphere focal epilepsy, and did not include a right hemisphere group (or other epilepsy types) for comparison. We excluded participants with FSIQ < 80 and those with MRI abnormalities, which resulted in a more homogeneous sample, but smaller group. Even still, patients were significantly different from patients on neuropsychological measures, which were driven by the seven patients with identified comorbidities. Future studies with larger samples or different recruitment criteria could examine the impact of epilepsy with and without comorbidities. There are several factors that need to be explored which might underlie the observed cortical differences, including epilepsy etiology, propagation of epileptiform activity through underlying networks, maturational differences, and neurotoxic effects of antiepileptic medications [12,13]. We were unable to explore the impact of antiepileptic medications due to limited statistical power but this may be a factor as sodium valproate, which was reported

across four patients, has been associated with reduced cortical thickness and brain volume [50]. Ideally, future studies would perform neuroimaging in children prior to beginning medication and follow them longitudinally to determine the degree of cortical trajectory divergence from normative age expectations and its impact on neuropsychological performance, accounting for different medications and their possible influences.

5. Conclusions

Our study found differences in cortical thickness in the absence of differences in surface area; both of these measures determine brain volume. Our results suggest that cortical thickness may be a sensitive proxy of subtle neuroanatomical changes that might be responsible for previously reported findings of cortical volume differences in pediatric epilepsy. We found that children with LHE displayed widespread regions of thinner cortex, extending beyond the location and hemisphere of seizure focus. These differences were moderated by age in a nonlinear fashion with maximum group differences at ages 8-12. Greater cortical thickness in controls was associated with higher IQ and fewer everyday executive control challenges. These cortical differences might be a consequence of differential maturational processes, which in turn, drive differences in neuropsychological functioning in pediatric epilepsy. Future studies should utilize longitudinal designs capable of elucidating whether potentially abated normative cortical thinning in pediatric epilepsy precedes neuropsychological dysfunction.

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Disclosure of Conflicts of Interest

Dr. Berl reports grants from NINDS. During the conduct of the study, Dr. Gaillard reports receiving grant support from NIH, National Science Foundation (NSF), Patient-Centered Outcomes Research Institute (PCORI), American Epilepsy Society, Epilepsy Foundation, Citizens United for Research in Epilepsy (CURE), and Infantile Epilepsy Research Foundation (funded by Lundbeck). Dr. Gaillard sits on the editorial board of *Epilepsia* and holds stock with spouse from Pfizer (>\$10,000), Siemens (>\$10,000), and General Electric (>\$10,000), and receives funds related to patient care of patients with epilepsy. The remaining authors have no conflicts of interest to report. 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.

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Highlights

- Children with LHE displayed widespread cortical thinning compared to TD.
- Cortical thinning extended beyond seizure focus into the contralateral hemisphere.
- Cortical thickness differences were age-dependent, and maximal between ages 8-12.
- Thicker cortex in TD was associated with higher IQ & better executive functioning.
- Cortical thinning may be a biomarker for risk of neuropsychological dysfunction.

Figure 1. Left and Right Hemisphere Cortical Thickness Differences –
Visualization of the cortical thickness differences between LHE and TD using FreeSurfer's Qdec. Clusters indicate areas where LHE was thinner than TD after Monte-Carlo correction.

Figure 2. Cortical Thickness by Age Between Groups – Scatterplots showing the significantly different cortical thickness by age relationships between LHE and TD groups in the **A.** left frontoparietal-cingulate region and **B.** right superior frontal region.

Figure 3. Cortical Thickness and Neuropsychological Performance – Scatterplots showing significant and non-significant linear relationships between cortical thickness and neuropsychological measures for Combined Sample and Individual Group analyses. Greater PIQ was associated with greater cortical thickness in the **a.** left frontoparietal-cingulate region (Combined Sample: $p < 0.01$), **b.** left parieto-occipital junction (Combined Sample: $p = 0.02$; TD: $p = 0.01$), **c.** right supramarginal gyrus (Combined Sample: $p = 0.02$; TD: $p = 0.03$). Greater VIQ was associated with greater cortical thickness in the **d.** right parieto-occipital junction (Combined Sample: $p = 0.01$; TD: $p = 0.03$). More parent

reported problems of executive function were associated with decreased cortical thickness in the **e.** left frontoparietal-cingulate region (Combined Sample: BRIEF MI $p=0.02$), **f.** right supramarginal region (Combined Sample: BRIEF MI $p=0.02$). For the TD group only, fewer parent reported problems of executive function were associated with increased cortical thickness in the **g.** left parieto-occipital junction (TD: BRIEF BRI $p=0.04$).

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Table 1.

Patient Seizure Characteristics

	N (%)	Mean (SD; Range)
Epilepsy Variables		
Age at seizure onset (years)	35	6.59 (3.13; 1-15)
Epilepsy duration (years)	35	3.87 (3.80; 0.4-12.4)
Seizure frequency		
Daily	5 (14%)	
Weekly	2 (6%)	
Monthly	8 (23%)	
1-5 Times	5 (14%)	
Has not had a seizure in the past 6 months	15 (43%)	
Seizure lobe focus		
	Left Hemisphere	
Frontal	8 (23%)	
Temporal	7 (20%)	
Frontotemporal	8 (23%)	
Parietal	2 (5%)	
Occipital	1 (3%)	
Multifocal (excluding frontotemporal)	2 (6%)	
Undetermined Lobe	7 (20%)	
AEDs		
Number of AEDs at time of study (%)		
1	21 (62%)	
2	8 (24%)	
3	4 (12%)	
4	1 (3%)	
Total participants on AEDs	34 (97%)	

Table 2.

Cluster corrected regions differing in cortical thickness between LHE and TD

Region	Size (mm ²)	X	Y	Z	Clusterwise P-Value	Number of Vertices
Left Frontoparietal-Cingulate	2923	-13.3	-10.1	38.8	0.0001	6822
Left Parieto-Occipital	1161	-17.0	-89.2	20.1	0.002	1605
Right Parieto-Occipital	908	31.8	-79.8	16.7	0.013	1410
Right Paracentral	862	3.3	-29.6	61.5	0.018	1922
Right Supramarginal	880	35.3	-32.0	36.4	0.016	2396
Right Superior Frontal	723	20.9	-1.0	54.7	0.044	1411

Table 3

a. Neuropsychological Performance by Group – Including LHE with Comorbidities					
Measure	Group	N	Mean	Std. Deviation	P-value
WASI VIQ	TD	35	116.49	14.52	0.005**
	LHE	35	103.83	21.20	
WASI PIQ	TD	35	109.60	12.55	0.021*
	LHE	35	101.40	16.20	
BRIEF BRI	TD	35	46.37	9.67	0.080
	LHE	35	51.17	12.75	
BRIEF MI	TD	35	48.66	11.96	0.014*
	LHE	35	56.29	13.22	
b. Neuropsychological Performance by Group – Excluding LHE with Comorbidities					
Measure	Group	N	Mean	Std. Deviation	P-value
WASI VIQ	TD	35	116.49	14.52	0.07 (NS)
	LHE	28	108.14	20.72	
WASI PIQ	TD	35	109.60	12.55	0.13 (NS)
	LHE	28	104.00	16.03	
BRIEF BRI	TD	35	46.37	9.67	0.44 (NS)
	LHE	28	48.43	11.21	
BRIEF MI	TD	35	48.66	11.96	0.07 (NS)
	LHE	28	54.29	11.79	

*
P < 0.05

**
P < 0.01

NS P > 0.05; Not Significant