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A quantitative analysis of
thalamocortical white matter
development in benign childhood
epilepsy with centro-temporal spikes (BECTS)

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Thesis

**A QUANTITATIVE ANALYSIS OF THALAMOCORTICAL WHITE MATTER
DEVELOPMENT IN BENIGN CHILDHOOD EPILEPSY WITH CENTRO-
TEMPORAL SPIKES (BECTS)**

by

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B.A., Western Washington University, 2010

Submitted in partial fulfillment of the
requirements for the degree of
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ABSTRACT

Background: A number of epilepsy syndromes are characterized by sleep-activated epileptiform discharges, however drivers of this process are not well understood. Previous research has found that thalamic injury in early life may increase the odds of sleep-activated spikes. Benign childhood epilepsy with centrotemporal spikes (BECTS) is among the most common pediatric-onset epilepsy syndromes, characterized by sleep-potentiated spike activity, a focal sensorimotor seizure semiology, and deficits in language, attention, and behavioral functioning. Though ictal and interictal electro-clinical activity resolves during mid-adolescence, adverse psychosocial outcomes may persist. Previous findings from monozygotic twin and neuroimaging studies suggest a multifactorial pattern of disease and raise suspicion for structural changes in thalamocortical connectivity focal to the seizure onset zone, though this has not been explored.

Objective: This research aims to (1) assess white matter differences in focal thalamocortical connectivity between BECTS cases and healthy controls using validated probabilistic tractography methods, (2) assess the association between spike burden and white matter connectivity focal to the seizure onset zone, and (3) evaluate longitudinal changes in thalamocortical connectivity across four cases.

Methods: 42 subjects ages 6-15 years were recruited between November 2015 and February 2018, including 23 BECTS cases and 19 healthy controls. Subjects underwent 3 Tesla structural and diffusion-weighted magnetic resonance imaging (2mm x 2mm x 2mm) with 64 gradient directions (b-value=2000) and 72 electrode sleep-deprived electroencephalographic (EEG) recordings. Seed and target regions of interest (ROIs) were created within each hemisphere using the *Desikan-Killiany* atlas, with the thalamus set as a seed ROI, and SOZ cortex and non-SOZ (NSOZ) cortex as target ROIs. Probabilistic tractography was executed using *PROBTRACKX2* with 500 streamlines per seed voxel, 0.5 millimeter steps, and a curvature threshold of 0.2. All streamlines reaching the target ROI were summed and normalized by seed voxel count. Results for BECTS and healthy controls were plotted by age. The slope of thalamocortical connectivity versus age was computed for each group and compared between groups using nonparametric bootstrap analysis. Additionally, the association between SOZ connectivity and spike burden was assessed in a subgroup analysis using a linear regression model, controlling for age.

Results: A significant difference in the developmental trajectory of thalamocortical connectivity to the SOZ in BECTS cases compared to healthy controls was found ($p=0.014$), where the increase in connectivity with age observed in healthy controls was not present in BECTS children. These results did not extend to NSOZ thalamocortical connections ($p=0.192$). Longitudinal results support these observations, where all BECTS cases who underwent repeat imaging ($N=4$) showed a decrease in thalamocortical

connectivity to the SOZ over the follow-up period. No relationship was found between thalamocortical connectivity and spike burden ($p=0.840$).

Conclusions: These findings suggest that children with BECTS show subtle alterations in thalamocortical white matter development focal to the seizure onset zone.

Thalamocortical connectivity to the SOZ does not appear to directly mediate non-REM sleep spike potentiation in BECTS. Limitations of this study include the potential for selection bias and limited power to detect sample differences. Additional research is needed to further characterize thalamocortical network changes and electrographic and neuropsychological correlates.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS	iv
ABSTRACT.....	vi
TABLE OF CONTENTS.....	ix
LIST OF TABLES	xi
LIST OF FIGURES	xii
LIST OF ABBREVIATIONS.....	xiii
INTRODUCTION	1
A clinical overview of BECTS	1
Epilepsy and the thalamus	5
Neuroanatomical features of development and BECTS	8
SPECIFIC AIMS	11
METHODS	13
RESULTS	21
DISCUSSION.....	27

REFERENCES 31

VITA 38

LIST OF TABLES

Table 1. Descriptive characteristics of the study sample.....	21
Table 2. Sample characteristics of cases with EEG activity.....	22

LIST OF FIGURES

Figure	Title	Page
1	Spatial mapping of the primary sensorimotor cortex	2
2	Schematic of EEG electrode coordinates	14
3	Example <i>Desikan-Killiany</i> atlas exclusion label	16
4	Probabilistic tractography processing pipeline	20
5	Relationship between thalamo-SOZ CI and age	23
6	Relationship between thalamo-SOZ CI and spike rate	24
7	Relationship between thalamo-SOZ CI and age among longitudinal subjects	25

LIST OF ABBREVIATIONS

ASM.....	Anti-Seizure Medication
BECTS	Benign Childhood Epilepsy with Centro-Temporal Spikes
CI.....	Connectivity Index
CSWS.....	Continuous Spike-Wave of Sleep
EDL.....	Early Life Developmental Lesion
EEG.....	Electroencephalography
EKG	Electrocardiography
EOG	Electrooculography
FA	Fractional Anisotropy
FSL.....	FMRIB Software Library
MEG.....	Magnetoencephalography
MRI.....	Magnetic Resonance Imaging
NREM.....	Non-Rapid Eye Movement
TE.....	Echo Time
TR	Repetition Time

INTRODUCTION

A clinical overview of BECTS

Benign childhood epilepsy with centrotemporal spikes (BECTS) is among the most common pediatric epilepsies, accounting for between 8-20% of focal syndromes.^{1,2} BECTS is named for its highly stereotyped electrographic pattern, characterized by sleep-potentiated spike activity localizing to the centrotemporal electrodes on electroencephalography (EEG), which overlay the pre- and post-central cortical gyri.^{1,2} Spikes may present bilaterally, lateralized, or show a shifting predominance.² Children demonstrate a stereotyped focal seizure semiology and age-specific period of seizure onset and epilepsy remission.¹⁻³ The classical seizure presentation begins with lateralized, distal upper extremity clonus that progresses to ipsilateral mouth or facial twitching, which may be accompanied by hypersalivation and expressive aphasia.²⁻⁵ Spatial mapping indicates that the inferior portion of the pre- and post-central gyri are associated with upper body motor and somatosensory activation, consistent with the previously described semiology (Figure 1b). Given the concordance between electrographic and semiological features, BECTS seizures are also eponymously described as the *Rolandic march*, named for the nineteenth-century anatomist who first described the division of the cortex into pre- and post-central gyri by the central sulcus, or *fissure of Rolando* (Figure 1).⁷

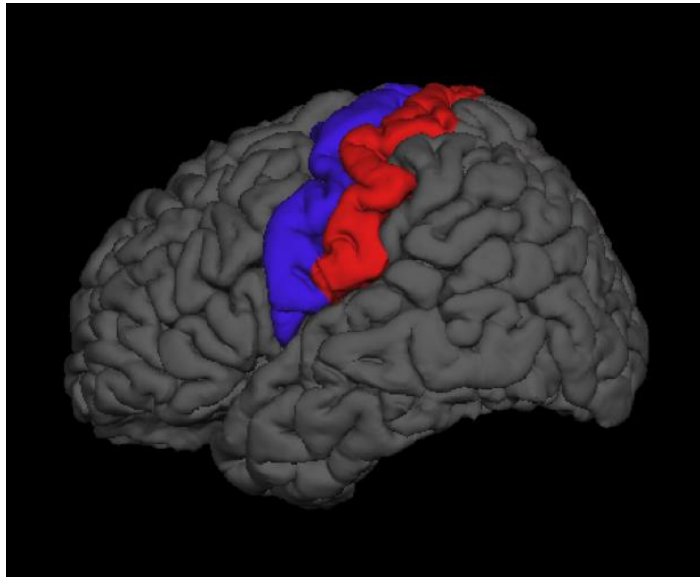


Figure 1. Spatial mapping of the primary sensorimotor cortex. Top: Labeling of pre-central (blue) and post-central (red) cortex separated by the central sulcus. Bottom: Visualization of the sensorimotor homunculus, corresponding to the spatial mapping of primary motor and somatosensory cortex.⁸

BECTS cases are diagnosed primarily through a combination of clinical presentation and EEG-confirmed biphasic spike activity localizing to the centrotemporal scalp electrodes.⁹ Ictal and interictal spike activity occur predominately during the non-

rapid eye movement (NREM) stages of sleep and may thus go unrecognized and underdiagnosed.^{5,9}

BECTS reaches peak incidence by ages 7-10 years and remission is typically confirmed by age 16 years.^{2,5,10} Disease duration and severity are difficult to estimate, due to a variable seizure presentation. Remission is often defined clinically as seizure freedom of at least one year sustained following medication taper.¹⁰ BECTS is 1.5 times more common in males than females.⁶ The disorder is also commonly accompanied by language, cognitive, and behavioral difficulties.^{1,11-13}

Poor performance specific to language and verbal memory cognitive domains are reported.^{11,12} Language appears to be significantly impacted early in disease progression and may predate diagnosis.¹¹ Deficits in attention have also been reported, and the presence of *Rolandic* epileptiform activity on EEG is estimated to occur in 3.5 to 5.6 percent of children with a diagnosis of Attention Deficit Hyperactivity Disorder.^{14,15} More recently, disturbances in declarative memory have been found in children with BECTS.¹⁶ The sleep disturbances associated with active disease raise the possibility that memory consolidation is impaired by disruptions in NREM rhythms, however neuropsychological correlates to spike burden remain unconfirmed.

Historically, BECTS has been presumed to share a genetic etiology similar to other pediatric epilepsies. This understanding has been challenged by a retrospective analysis of BECTS in a multicenter, prospective study, which included population-based cohorts in Denmark, Virginia, Norway, and Australia.¹⁷ Among the combined 1,952 twin pairs, BECTS was identified in 18 individuals, and found to be discordant in all 10

monozygotic and eight dizygotic twin pairs.¹⁷ Other first-degree relatives were likewise found to be unaffected, with five experiencing febrile seizures and one experiencing symptomatic epilepsy.¹⁷ The considerable potential for a multifactorial, environment-mediated process in BECTS merits investigation of neuroanatomical biomarkers of disease, in addition to further exploration of genetic susceptibility.^{17,18}

There remains a paucity of evidence-based guidance for the clinical management of BECTS. During the stage of active disease, EEG studies display some preponderance of epileptiform activity during NREM sleep, however the frequency and duration of these electrographic abnormalities as well as the frequency and type of seizures experienced may vary considerably both within and between individuals.¹⁹ Furthermore, variation in neuropsychological measures of cognition, language, and executive functioning contribute to a complicated and unpredictable disease course.²⁰ Children with BECTS have been shown to experience poorer psychosocial outcomes that extend beyond disease remission, in addition to suffering from the typical risks associated with uncontrolled epilepsy.^{11,21,22} In one study, 23% required speech therapy, while 35% were found to repeat a year in school, rates much higher than their non-BECTS peers.²³ Given this complex clinical picture, the ILAE formally recommended the reclassification of ‘benign’ as ‘self-limited’ in a 2010 special report published in *Epilepsia*.²⁴

There is disagreement in the literature concerning the seizure control effectiveness of available pharmacologic therapies. A review of randomized controlled trials found no short-term effectiveness in a six-month follow up among FDA-approved medications, and insufficient evidence on medium or long-term effectiveness.²⁵ Medication may

further modulate seizure patterns and contribute adversely to neuropsychological function, limiting the study and identification of phenotypical predictors of disease outcomes. Previous research has suggested cognitive deficits were more likely in the presence of EEG discharges, multiple seizures, and medication.²⁶ In a review of 96 articles, it was found that nearly one third of authors did not recommend treating BECTS with anti-seizure medications (ASMs).²⁷ Clinicians thus possess little evidence-based guidance to counsel individual families on individual risk of seizure recurrence or expected neuropsychological trajectory following a BECTS diagnosis. Further understanding of disease etiology and seizure prediction are urgently needed to provide information regarding potential therapeutic targets and to minimize the potential for iatrogenic harm.

Epilepsy and the thalamus

The thalamus is a centralized brain structure made up of two symmetric, almond-shaped nuclei bundles, located superior to the mesencephalon with extensive cortical connections.³⁰ Additionally, it serves as the primary relay center for sensorimotor information traveling between the cortex and brain stem and is intimately involved in the regulation of sleep physiology.^{30,31} It has also been demonstrated convincingly in experimental animal models to possess intrinsic self-oscillatory properties, and thus capable of hyperexcitability.^{30,31} Experimental observations also suggest a temporal relationship between thalamic firing and pertinent scalp EEG spike correlates.³¹ These intrinsic thalamic oscillations are furthermore tonically inhibited during wake and REM

sleep.^{30,31} Their activation during NREM sleep thus temporally co-occurs with the preponderance of electrographic abnormalities present in several epilepsy syndromes.

The cause of this phenomenon is not well understood. Previous work has found that early thalamic injury may predispose patients to sleep-potentiated spikes, but an underlying mechanism has not been identified.^{32,33} Continuous spike-wave of sleep (CSWS), a childhood-associated epileptic syndrome, is characterized by regressive aphasia and continuous epileptiform activity during NREM sleep.³³ Recent neuroimaging and neurophysiological studies have found associations between CSWS and early-life thalamic lesions.³²⁻³⁴ In a case-control study which stratified CSWS subjects according to sleep-potentiated epileptiform spike rate during NREM sleep, increases in spike burden were associated with increased odds of early developmental lesions visible on 1.5 Tesla Magnetic Resonance Imaging (MRI), and substantially greater odds of early-life thalamic lesions (14.0% vs. 2.1%).³² In a case series of nine children with CSWS and thalamic lesions on MRI, probabilistic tractography revealed white matter volume loss specific to thalamocortical radiations in four cases.³³ In a prospective cohort of 14 subjects with early-life thalamic hemorrhage due to neonatal thrombosis, three were later observed to develop sleep-potentiated epileptiform activity on EEG or focal epilepsy without apparent NREM spike correlate, while five individuals were diagnosed with CSWS.³⁴ Notably, thalamic nuclei have demonstrated vulnerability to perinatal hypoxic-ischemic induced apoptosis in animal models and human cases.³⁵

Studies of other common pediatric epilepsies further raise the possibility of links to the thalamocortical network. Childhood Absence Epilepsy (CAE) has been linked to

genetic mutations in thalamocortical calcium channels.³⁶ Differences in thalamocortical network white matter cytoarchitecture have likewise been described in temporal lobe epilepsies incident during childhood.³⁷

Today, more careful assessment of thalamocortical networks is possible using modern neuroimaging to infer white matter tracts non-invasively from diffusion MRI.

White matter tractography

Diffusion MRI enables noninvasive mapping of the fiber architecture of the white matter tracts in the brain using diffusion tensor imaging (DTI) and related models.³⁸ DTI leverages the proton-rich water diffusion properties of different tissue to map differences in proton movement using unique MRI pulse sequences.^{38,39} This is based on the assumption that water in free space diffuses in all directions equally, and when constricted by large hydrophobic white matter fiber bundles of the brain, flows primarily along the length of the fibers.^{38,39} In DTI modeling, a tensor composed of the principal diffusion eigenvector and corresponding eigenvalue, as well as principal orthogonal eigenvectors and eigenvalues, are fit to each voxel.^{38,39} Fractional anisotropy (FA), representing a scaled measure of variance between eigenvalues, is used as a measure of white matter strength.^{38,39} In white matter tractography, these or similar measurements are evaluated using advanced computer algorithms to infer spatial characteristics of fiber architecture.^{39,40}

Diffusion-based white matter tractography may be used to estimate clinical features of neurological disorders and white matter pathologies across development.⁴⁰

Neuroanatomical features of development and BECTS

The complex, likely multifactorial, etiological picture underlying BECTS, along with its transient occurrence in the setting of dramatic brain development, raises suspicion for the existence of structural alterations in brain connectivity. Recent advances in the resolution and integration of neuroimaging technology, including multimodal high-density EEG and magnetoencephalography (MEG), 3T magnetic resonance imaging (MRI), post-acquisition algorithmic signal distortion correction, and probabilistic tractography models, have ushered in an era of research with new information regarding network-associated changes in neuroanatomy throughout normal development and disease.⁴⁰⁻⁴² These tools have resulted in a robust characterization of neurotypical development related to grey and white matter maturation.⁴⁰⁻⁴² Advances have also contributed to understanding of neuroanatomical abnormalities in a wide range of epilepsy syndromes.⁴³ Fewer studies exist which have attempted to characterize pediatric epilepsies, in particular development-associated network changes in BECTS.

Neurotypical development

It is now understood that the human brain undergoes neuronal maturation and remodeling throughout childhood and adolescence, extending into young adulthood.⁴⁴ Animal models and human studies demonstrate that migration and maturation of subcortical thalamic radiations to the developing cortex extends into the post-natal period.^{45,46} Significant increases in myelination follow this process. In human cross-sectional and longitudinal analysis, increases in white matter connectivity, a measure of fiber density and degree of myelination, are observed to continue between ages 4 and 20

years.⁴⁷ Differences in the lateralization of white matter changes are unknown, though there is some suggestion that it is more prominent in the left-dominant hemisphere.⁴⁸ White matter maturation has also been associated with increases in cognitive functions, language, and semantic memory.⁴⁹⁻⁵¹

Early grey matter development-associated changes include thickening of the cortex as the cortical sub-plate is replaced by differentiation of cortical layers, as well as selective synaptic pruning, the latter of which has been implicated in a number of neuropsychiatric disorders.^{45,50} In longitudinal analysis, regionally-specific changes in cortical grey matter volume have been observed, including frontal and parietal increases until age 12, temporal increases until age 16, and occipital increases through age 20.⁴⁷

Potential sex dimorphisms in white matter development during childhood and adolescence remain poorly characterized.^{52, 53}

Microstructural white matter differences in BECTS

Diffusion-weighted imaging techniques have been used to assess microstructural differences in white matter within pediatric epilepsies.⁵⁴ Decreases in fractional anisotropy (FA) has been observed in children with BECTS.⁵⁵⁻⁵⁷ A cross-sectional DTI analysis of white matter maturation in 25 BECTS children compared to 25 age-matched healthy controls found decreased FA and increased diffusivity measures, particularly in left primary sensorimotor cortex, and ipsilateral to the EEG focus.⁵⁶ Interestingly, FA was also found to correlate inversely with epilepsy duration.⁵⁶ A second cross-sectional DTI study of microstructural differences involving 28 children with BECTS and 19 healthy controls similarly found greater regional loss of FA in the hemisphere ipsilateral

to spike activity, as well as bilaterally in the cingulate gyrus.⁵⁷ The FA in these regions were also found to be inversely associated with seizure frequency.⁵⁷ It remains unconfirmed whether this finding relates to specific white matter tracts.

A review of the existing literature yielded no known investigation of development-associated differences in thalamocortical connectivity focal to the seizure onset zone in children with BECTS.

SPECIFIC AIMS

There is a demonstrable need to identify biomarkers of disease to aid in clinical decision-making and therapeutic targets in BECTS. Recent advances in multimodal high density electrography and neuroimaging provide a noninvasive opportunity to investigate neuroanatomical and neurophysiological biomarkers of disease that until recently may have been undetectable in traditional clinical settings.

This research aims to (1) compare development-associated changes in thalamocortical connectivity to the seizure onset zone (SOZ) and non-SOZ (NSOZ) in BECTS cases relative to healthy controls through the collection of 3 Tesla structural and diffusion-weighted MRI and validated probabilistic white matter pathway estimation techniques; (2) assess the association between thalamo-SOZ connectivity and NREM spike burden through the collection of electrographic data from high-density EEG; and (3) assess intrasubject changes in thalamocortical connectivity over development through the collection and analysis of longitudinal data in 4 BECTS subjects.

We hypothesize that BECTS cases will demonstrate focal differences in the trajectory of thalamocortical connectivity over development in the SOZ, relative to healthy controls. We also hypothesize that NREM spike burden will be a positive, independent predictor of connectivity focal to the seizure onset zone.

High resolution MRI, high-density multimodal MEG and EEG, and sophisticated pathway reconstruction techniques have the potential to reveal new information regarding microstructural white matter differences. Modeling network abnormalities in BECTS, a disease with stereotyped electrographic, semiological, and age-dependent patterns, has

the potential to identify biomarkers that may aid in the identification of therapeutic targets, effective treatments, and patient counseling. Results of this study may also have broad implications in the study and treatment of other forms of epilepsy.

METHODS

Study population

This research utilized data from an ongoing single-center, case-control study which recruited subject at a major academic medical center in Boston, Massachusetts between December 2015 and February 2018. Children ages 6-15 years were recruited using systematic chart review to identify cases and public advertising to recruit healthy controls. Case subjects were required to have a clinical and EEG-confirmed BECTS diagnosis, while control subjects were required to have no history of neurocognitive disease. Individuals who completed a baseline visit, which included multimodal MEG and EEG data acquisition, followed by MRI data acquisition, were invited to complete an optional repeat visit one year following the baseline visit.

Data acquisition

Electrographic data

EEG data was collected by trained researchers using a 70 electrode cap, with two temporal electrodes, as well as ground, reference, EOG, and EKG. Cap sizes included two centimeter head circumference intervals between 50 and 60 centimeters. All data was collected during a morning timeslot and subjects were requested to sleep fewer hours the evening prior to the visit. In preparation for monitoring, any electrodes which could not achieve below the targeted impedance value of 5 mV were documented. EEG electrodes were spatially encoded using a digitizing stylus. Rest data was collected in four minute intervals over 10-12 trials.

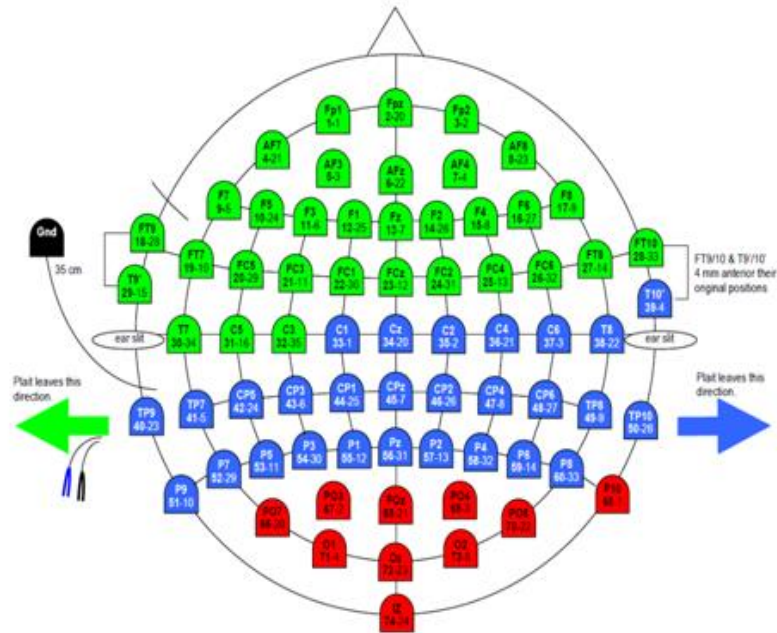


Figure 2. Schematic of EEG electrode coordinates. Spatial coordinates of the 70 electrode EEG cap.

All EEGs were manually reviewed by a board-certified pediatric neurophysiologist in bipolar, common average, and nasion-physical reference. Centrottemporal epileptiform spikes were manually marked and spike rate quantified per hemisphere per subject (.e.g. spikes per minute).

Neuroimaging data

Structural and diffusion imaging data for each subject was collected with a Prisma 3 Tesla MRI scanner. Structural imaging data was collected according to the following parameters: root mean square average of four echo times (TE) = TE 2.69 milliseconds (ms), TE 3.55 ms, TE 5.41 ms , and TE 7.27 ms; repetition time (TR)=2530 ms; voxel size=1x1x1; slice thickness=1 mm; slices per slab=176; reconstruction matrix=256x256. Diffusion-weighted imaging was collected according to the following parameters: TE=64

ms, TR=5300 ms, voxel size=2x2x2; slice thickness=2 mm; 64 gradient directions with $b=2000$ s/mm²; reconstruction matrix=128x128. Spatial encoding was anterior to posterior. B₀ imaging included TE=56 ms and spatial encoding posterior to anterior.

Data processing

The principal investigator of this study, a trained neurophysiologist and epilepsy specialist, independently reviewed all raw EEG data to classify sleep state. Spike rate per second during NREM Stage 2 (N2) sleep was calculated by hemisphere in active subjects with spike activity captured on EEG during the study. Sample characteristics of this subset are summarized in Table 2.

MRI data underwent reconstruction, white matter segmentation, and cortical parcellation using Freesurfer v5.3 and FSL.⁵⁸ This process also included correction for gradient nonlinearity during spatial encoding. Subsequently, data underwent signal distortion correction for motion, eddy currents, and field inhomogeneities. A trained radiologist was consulted to confirm the quality of corrected data.

A method of *simple partial volume* modeling with Markov Chain Monte Carlo (MCMC) sampling, using FMRIB's Bayesian Estimation of Diffusion Parameters Obtained Using Sampling Techniques (BEDPOSTX), was then executed to construct voxel-wise probability density functions (PDF) of model parameters. A detailed explanation of this technique can be found in Behrens et al. (2007).⁵⁹ To summarize, BEDPOSTX is a method of representing the uncertainty in the principal direction of diffusion at each voxel by estimating the joint posterior distribution of polar coordinate parameters, θ and ϕ . Diffusion-weighted voxels are segmented and associated parameters

evaluated by MCMC across gradient directions to estimate the marginal probability density functions (PDFs) of θ and ϕ . The joint marginal posterior PDF, $(p(\theta, \phi))$ is later used in tractography.

Region of interest (ROI) creation

Diffusion seed and target ROI masks were created using labels from FMRIB's *Desikan-Killiany* atlas fit to the diffusion imaging of each subject. Seed masks included left and right hemisphere thalamus labels, shown in Figure 4b. Target masks included left and right hemisphere seizure onset zone (SOZ) and non-seizure onset zone (NSOZ) cortical labels, shown in Figure 4b. Additionally, exclusion masks were created to encompass the hemisphere contralateral to seed and target ROIs, enabling separate evaluation of the hemispheres (Figure 3). All masks were independently visually inspected to confirm appropriate fitting.

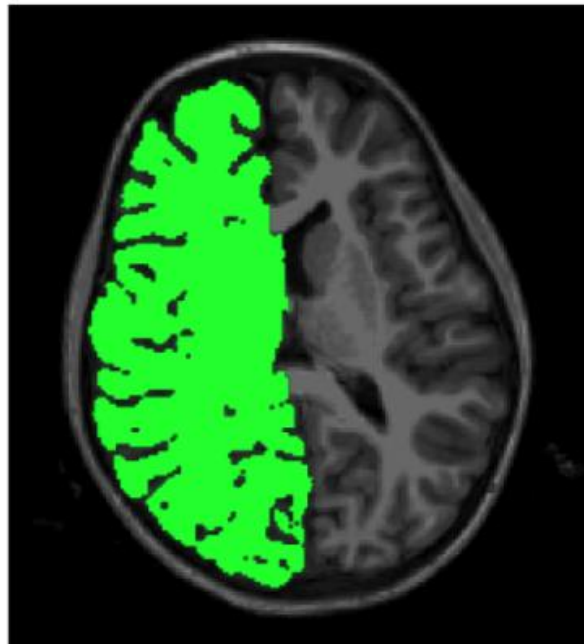


Figure 3. Example *Desikan-Killiany* atlas exclusion label. Example right hemisphere exclusion mask.

Probabilistic tractography

Probabilistic tractography was executed using *PROBTRACKX2*, a component of FMRIB, with specification of appropriate ROI masks and local joint posterior PDFs. At each seed voxel, the principal direction of diffusion parameter was sampled from the local posterior PDF, and a .5mm step along this path was taken. The process was then repeated until termination of the streamline in the target mask or at 2000 steps. 500 streamlines were executed per seed voxel to construct a spatial PDF of connectivity between the seed and target ROIs. Additionally, the contralateral hemisphere of each trial was set as an exclusion mask and pathway steps were restricted to a curvature threshold of .2. This process was repeated for each target ROI by hemisphere. In contrast to deterministic methods, this process enables continuation along paths that are not the most highly connected pathway, as well as paths which have focal areas of reduced connectivity. Notably, this methodology was validated using ROI-based thalamus seed and cortical targets.⁵⁹ An overview of the tractography pipeline is shown in Figure 4.

Data analysis

Resulting tractography matrices for SOZ and NSOZ connectivity were used to extract the number of streamlines that successfully terminated in the target ROI and were normalized by the total number of streamlines sent per hemisphere:

$$\begin{array}{l}
LH_{SOZ} \\
= \frac{n \text{ streamlines reaching target}}{n \text{ total seed streamlines}} \\
RH_{SOZ} \\
= \frac{n \text{ streamlines reaching target}}{n \text{ total seed streamlines}}
\end{array}
\qquad
\begin{array}{l}
LH_{NSOZ} \\
= \frac{n \text{ streamlines reaching target}}{n \text{ total seed streamlines}} \\
RH_{NSOZ} \\
= \frac{n \text{ streamlines reaching target}}{n \text{ total seed streamlines}}
\end{array}$$

Hemispheres were then averaged to yield three measures of connectivity:

$$CI_{SOZ} = \frac{LH_{SOZ} + RH_{SOZ}}{2}$$

$$CI_{NSOZ} = \frac{LH_{NSOZ} + RH_{NSOZ}}{2}$$

All statistical tests were performed for both SOZ and NSOZ connectivity indices (CI). A nonparametric bootstrap test was used to assess differences in connectivity slope by group, given that this approach requires fewer assumptions and is based exclusively on sample characteristics. Two groups of equal size to case (N=23) and control (N=19) groups were sampled from the union of both groups (N=42) and used to calculate a mean slope difference. This process was iterated over 10,000 trials to ensure convergence. The resulting observed confidence interval of slope differences was evaluated against the empirical slope difference between groups at an $\alpha=.05$ level. Finally, linear regression adjusting for age was used to assess spike burden as a predictor of connectivity in BECTS cases with spike activity captured on EEG.

(C) Probabilistic Tractography

(B) Pre-processing

(A) Image Acquisition

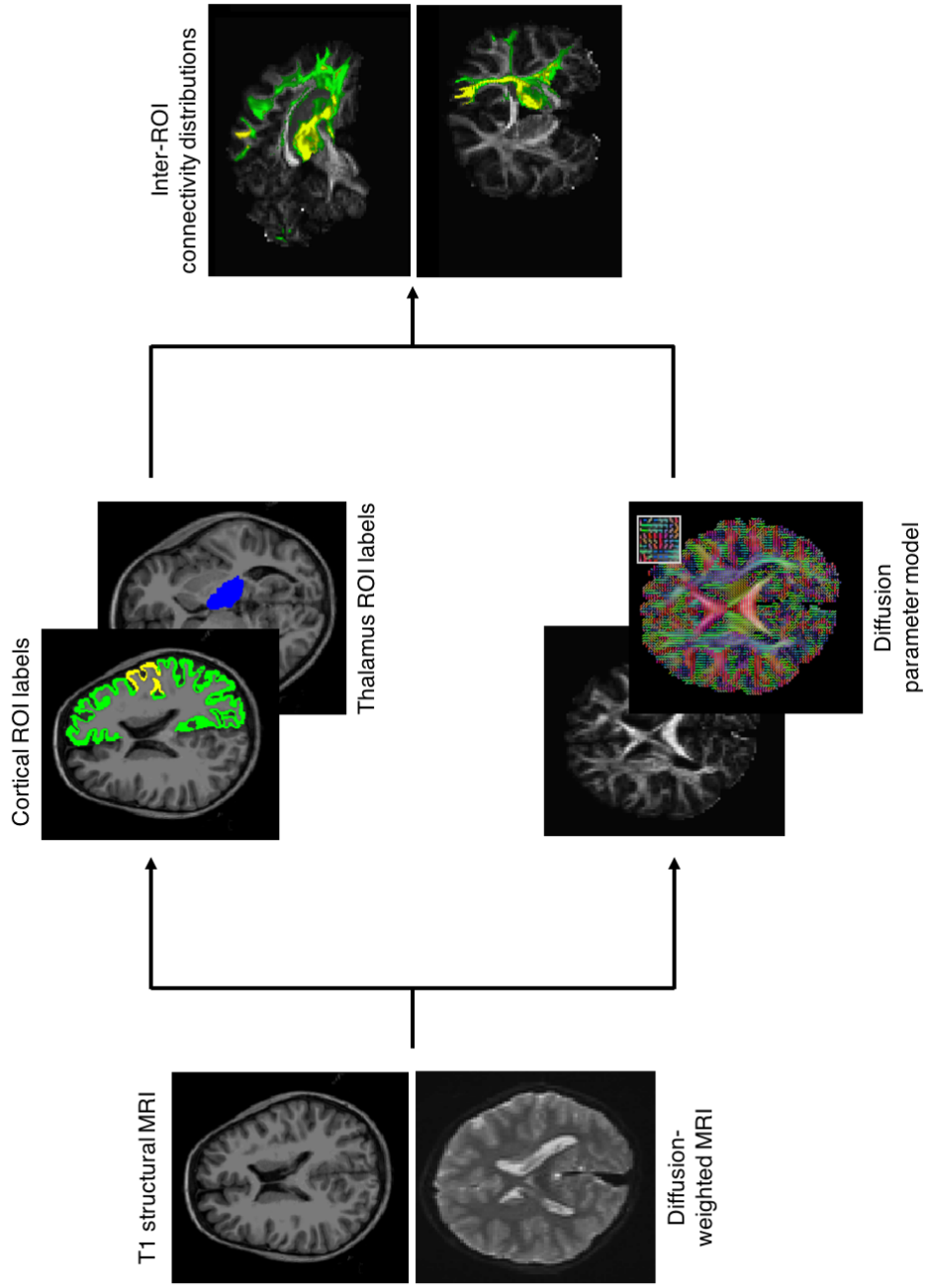


Figure 4. Thalamocortical tractography processing pipeline. A) High resolution structural and diffusion MRIs are acquired. B) Structural MRIs are used to generate cortical and thalamic labels (top). Diffusion MRIs are used to extract diffusion parameters per voxel from 64 gradient directions (example principal directions of diffusion for 25 voxels shown in inset). C) Distribution of diffusion parameters is repeatedly sampled to infer the probability of white matter tracts between ROIs.

RESULTS

A total of 48 subjects were enrolled in the study. Three cases who did not tolerate diffusion imaging and one case with excessive motion artifact were excluded from analysis, yielding a final sample of 23 BECTS cases and 19 healthy controls. Sample characteristics can be found in Table 1.

11 BECTS cases demonstrated spike activity on EEG and were included in the subset analysis of the association between connectivity and spike burden. Subset sample characteristics are summarized in Table 2.

Additionally, 4 subjects repeated all study activities an average of 1.30 years (SD: .32) following the baseline visit. Changes in the connectivity indices over the follow-up period are summarized in Figure 8.

Table 1. Descriptive characteristics of the study sample, N=42.

	Cases N=23	Controls N=19	p^1
Mean age (SD)	11.3 (2.3)	11.0 (2.1)	.09
Male count (%)	18 (78.3)	9 (47.4)	.04*
Disease status count (%)			
<i>Active</i> †	15 (65.2)	-	-
<i>Seizure free</i> ‡	2 (8.7)	-	-
<i>Remission</i> §	6 (26.1)	-	-

†History of seizures in the previous 12 months ‡no history of seizures in the previous 12 months and ASM use, §no history of seizures in the previous 12 months and no ASM use, ¹ $\alpha=.05$

Table 2. Sample characteristics of active cases with spike activity captured on EEG.

	Male [†]	Age [‡]	Bilateral spikes [†]
Subset (N=11)	7 (63.6)	10.6 (9.1-14.7)	6 (54.5)

[†]Count (%) [‡]Median (range)

Thalamocortical connectivity and disease

Sex was found to be a statistically significant covariate predictive of group ($p=.04$), while age was not (Table 1).

Visual analysis revealed an increase in thalamocortical connectivity to the SOZ in healthy control subjects that was not apparent in BECTS subjects (Figure 5A, B). This pattern was not observed in the NSOZ.

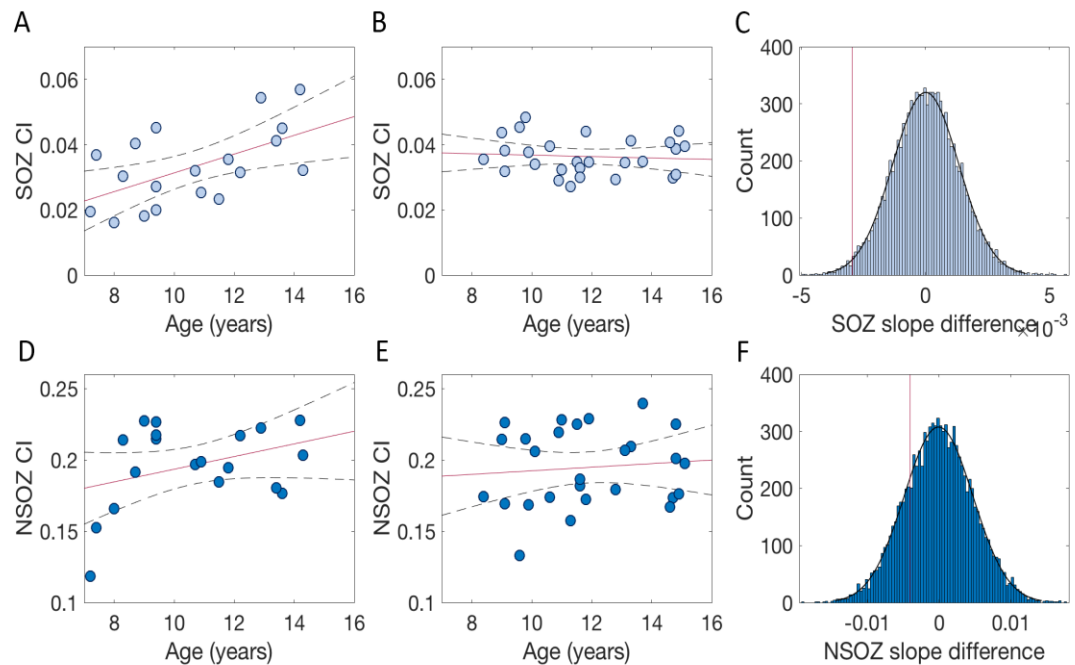


Figure 5. Relationship between thalamo-SOZ connectivity index and age. A) Visual analysis reveals a relationship between age and CI to the SOZ among healthy controls. Solid line indicates linear regression model fit, dashed lines indicate 95% confidence intervals. B) Visual analysis reveals no relationship between age and CI to the SOZ among BECTS subjects. C) Bootstrap analysis reveals a significant difference between the slopes of the healthy controls and BECTS subjects ($p=0.0123$). D) Visual analysis reveals a no relationship between age and CI to the NSOZ among healthy controls or E) BECTS. Solid line indicates linear regression model fit, dashed lines indicate 95% confidence intervals. F) Bootstrap analysis reveals no difference between the slopes of NSOZ CI between the healthy controls and BECTS subjects ($p=0.19$).

Nonparametric bootstrap analysis showed a difference in the slope of thalamocortical CI to the SOZ across age between BECTS cases and healthy controls compared to the observed null slope difference frequency distribution ($p=0.0123$, Figure 5A-C). There was no difference in the thalamocortical CI developmental trajectory to the NSOZ between BECTS and healthy controls ($p=0.19$, Figure 5D-F). Multiple logistic

regression analyses adjusting for sex did not find significant differences in group across CI predictors ($p>0.05$).

Thalamocortical connectivity and spike rate during N2 sleep

In a simple linear analysis of BECTS cases with spike activity captured on EEG, spike burden was not found to significantly predict SOZ CI measures ($p=0.11$). Age and sex were not found to be significant covariates.

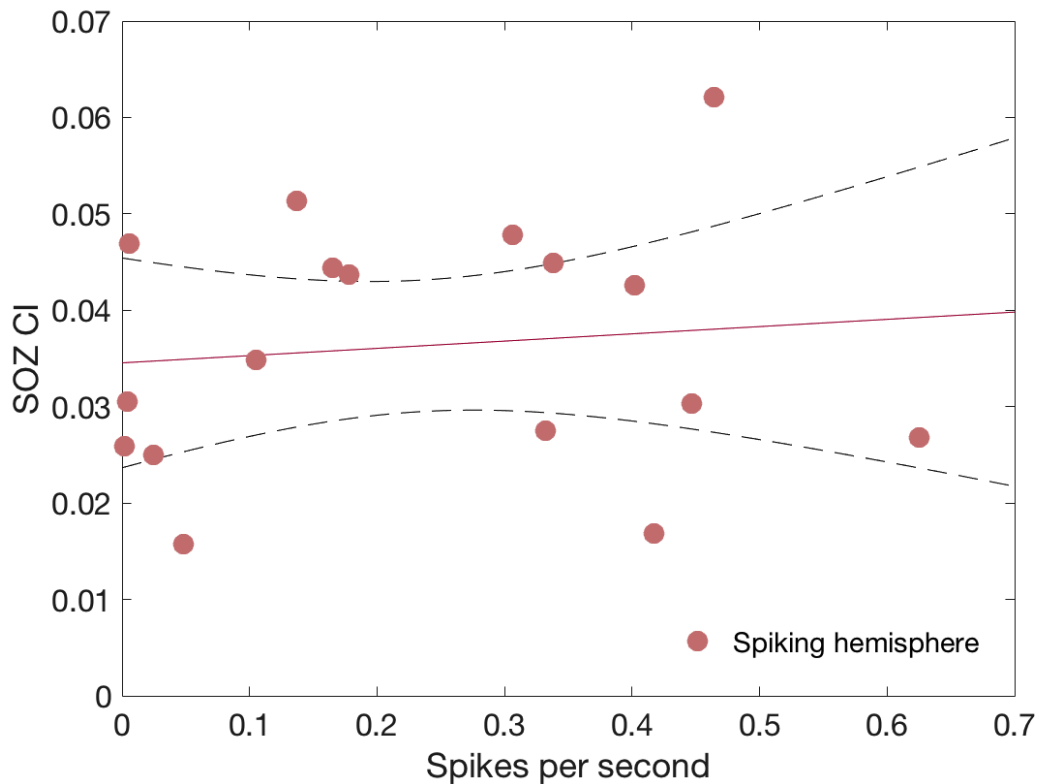


Figure 6. Relationship between thalamo-SOZ CI and spike rate. Among BECTS subjects, there is no relationship between CI and spike rate ($p=0.11$). Solid line indicates linear regression model fit, dashed lines indicate 95% confidence intervals.

Case study of longitudinal changes in thalamocortical connectivity

Four subjects returned for repeat MRI and EEG data collection sessions approximately one year after their initial evaluation (mean 1.3 years, range 1.1-1.8). To confirm the deviation from increased thalamocortical connectivity to the SOZ present in normal development that was observed in the cross-sectional datasets above, the change in thalamocortical CI to the SOZ in these four longitudinal BECTS subjects over development was evaluated. Consistent with the cross-sectional data, a decrease in thalamocortical CI to the SOZ in each of the longitudinal subjects with age was found (Figure 7).

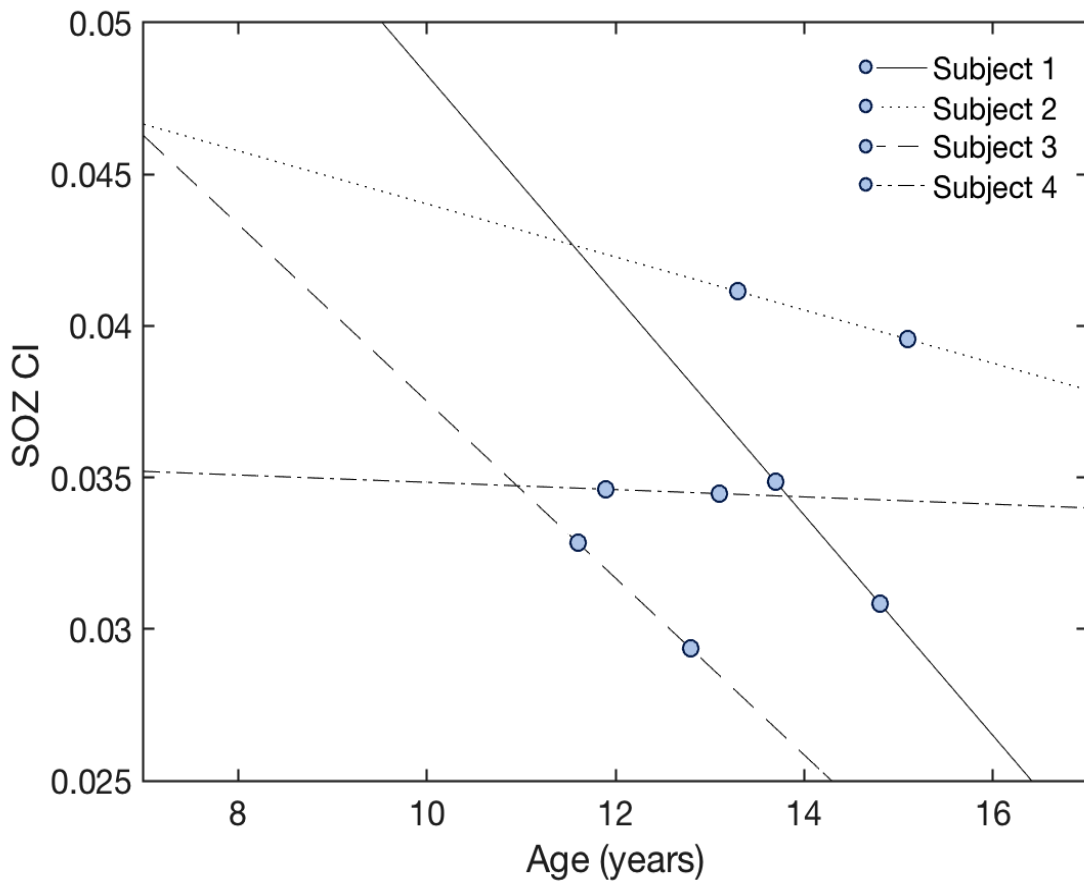


Figure 7. Relationship between thalamo-SOZ CI and age among longitudinal subjects. Consistent with the cross-sectional data, connectivity decreases with age in BECTS subjects.

DISCUSSION

In this study, healthy controls showed a positive developmental trajectory in global thalamocortical connectivity to the sensorimotor cortex with age. This finding is consistent with the well-established literature on white matter maturation during childhood and adolescence.^{47-49,51-53} This maturation is associated with the neuroanatomical features of increases in myelination, axon diameter, and density of white matter fiber tracts.^{47,51}

In contrast, no overall differences in thalamocortical connectivity indices were observed in BECTS cases compared to healthy controls. Notably, BECTS cases showed this aberrant developmental change with age specific to the seizure onset zone (i.e. primary sensorimotor cortex). NSOZ thalamocortical connectivity remained similar between groups across age. These findings support previous research demonstrating a lower fractional anisotropy in white matter focal to the seizure onset zone.⁵⁵⁻⁵⁷ Longitudinal analysis of 4 BECTS cases each showed a reduction in SOZ connectivity, further supporting this finding.

The development-associated difference in the trajectory of thalamic connectivity focal to the seizure onset zone is of particular interest in the context of disease progression. In this study, abnormal development-associated changes appear to occur as the natural history of disease advances toward remission. Findings corroborate the existing literature that reduced FA correlates with increases in the duration of epilepsy.⁵⁵ It is unclear whether this abnormality results from a primary disease process that occurs in parallel with other network drivers of disease resolution, or whether these changes

occur as a response to disease features. One possible explanation could be that the connectivity is qualitatively abnormal and could undergo remodeling or an increase in myelination to offset deficits, resulting in relatively undetectable macroscopic changes in connectivity over time. Given the previous observations that aberrant cortical thinning occurs between ages 8-14 in BECTS, a potential mechanism for white matter loss could be cortical pruning of thalamocortical projections to layer IV of the cortex, resulting in gradual distal regression toward subcortical nuclei according to neurological processes described in the literature.⁶⁰ Apoptosis of reciprocal corticothalamic nuclei in cortical layer VI would likewise account for these observations.

Decreases of FA focal to the pre- and post-central gyrus have been previously associated with increases in spike burden.⁵⁵⁻⁵⁷ Our findings that spike burden was not predictive of SOZ connectivity raises questions about the disease-modifying potential of epileptiform spikes, which merits further exploration.

There are a number of limitations to this study. It should be noted, foremost, that we cannot rule out the potential that tractography analyses non-specifically captured projections originating in the cortex (i.e. corticothalamic pathways), though the seed specification of our model excluding the corticospinal tract pathway worked to limit this. Regardless, these processes are intimately linked during development, and further research is required to quantify the unique structural features of these pathways as well as the temporal directionality of changes in connectivity.

Additional limitations include power to detect sample differences and potential confounding. The confounding of covariates such as sex cannot be ruled out, given the

discordant literature on development-associated sex dimorphisms in focal white matter pathways.^{52,53}

A limited sample size likewise precluded further subset analysis of spike rate by lateralization of spike activity. It is possible that spike burden could vary between bilateral, and left or right lateralizing phenotypes. The case-control design of this study also potentially limits its generalizability to the BECTS and healthy control populations. Recruitment of cases from a single outpatient center and controls willing to undergo imaging cannot fully eliminate the potential for selection bias.

An important direction for future research is the contemporaneous assessment of peri-thalamic and peri-cortical measures of white matter connectivity over time. Further case-specific longitudinal analysis over the active and remission periods of disease would likewise help to validate group findings. Future studies exploring other measures of disease stage, including time from last seizure, with respect to connectivity, could help to assess the reliability of spike burden correlates.

One area not examined in this study, but which merits further investigation, is the relationship between thalamocortical connectivity and measures of cognition, language, and behavior. A structural basis for neurocognitive features of BECTS has not been delineated. The aberrant thalamocortical trajectory specific to the seizure onset zone observed in this study, taken together with the constellation of impairments that characterizes disease pathology, suggests multiple spatially- and temporally-dependent structural and physiological network aberrations. Further study of neuropsychological

correlates and changes in connectivity across the thalamocortical network could further identify microstructural biomarkers of BECTS onset and progression.

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