Published in final edited form as:

J Clin Neurophysiol. 2020 January ; 37(1): 79–86. doi:10.1097/WNP.0000000000000615.

Lesion-Constrained Electrical Source Imaging: A novel approach in epilepsy surgery for Tuberous Sclerosis Complex

Jurriaan M. Peters, MD, PhD^{1,2,*‡}, Damon E. Hyde, PhD^{2,*#}, Catherine J. Chu, MD³, Merel Boom, MSc¹, Benoit Scherrer, PhD², Joseph R. Madsen, MD⁴, Scellig S. Stone, MD, PhD⁴, Hakim Ouaalam, MSc², Sanjay P. Prabhu, MBBS², Mustafa Sahin, MD, PhD⁵, Simon K. Warfield, PhD²

¹Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115

²Computational Radiology Laboratory, Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115

³Division of Pediatric Neurology, Massachusetts General Hospital for Children, Boston MA, 02114

⁴Department of Neurosurgery, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115

⁵Translational Neuroscience Center, Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115

Abstract

Introduction: Electrical source imaging may yield ambiguous results in multi-lesional epilepsy. To test the clinical utility of lesion-constrained electrical source imaging (LC-ESI) in epilepsy surgery in children with Tuberous Sclerosis Complex (TSC).

Methods: LC-ESI is a novel method based on a proposed head model in which the source solution is constrained to lesions. Using a goodness of fit analysis, we rank-ordered individual tubers by their ability to approximate interictal and ictal EEG data. We qualitatively determined the overlap with the surgical resection cavity, and placed findings in the context of epilepsy surgical outcome, and compared to the Low Resolution Brain Electromagnetic Tomography (LORETA) solution.

Results: LORETA predicted the surgical cavity in only one patient with good outcome (true positive), and localized to outside of the cavity in two patients with a good outcome (false negative). In one patient with a poor outcome, the interictal LORETA solution overlapped with the cavity (false positive).

[‡]Clinical neurophysiology correspondence: Jurriaan M. Peters, MD, PhD. Division of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, 300 Longwood Ave – Fegan 9, Boston, MA 02115, USA. Tel +1 617 355 5606 Fax +1 617 730 0463 jurriaan.peters@childrens.harvard.edu. [#]Physics and technical correspondence: Damon Hyde, PhD. Computational Radiology Laboratory, Department of Radiology, Boston Children's Hospital, Longwood Center, Boston, MA 02115, USA. Tel +1 857 218 5172 Fax +1 617 730 4644 damon.hyde@childrens.harvard.edu.

*These authors contributed equally

LC-ESI of ictal EEG data identified tubers concordant with the resection zone in three patients with a good surgical outcome (true positive), and appropriately discordant in three other patients with a poor outcome (true negative).

Conclusions: LC-ESI on low-resolution EEG data provides complementary information in the presurgical workup for patients with TSC, although further validation is required. In the appropriate clinical context, the yield of source localization on low-resolution EEG data may be increased by reduction of the solution space.

Keywords

children; tuberous sclerosis complex; electrical source imaging; epilepsy surgery

Introduction

Tuberous Sclerosis Complex (TSC) is a genetic neurocutaneous disorder with a prevalence of 1:6,000. It is characterized by the formation of hamartomas in various organs, which in the brain are referred to as tubers. Neurological symptoms include epilepsy, intellectual disability, behavioral dysregulation, and autism spectrum disorder. Epilepsy has a lifetime prevalence of 80–90%, and is medically refractory in 40–60% of patients. Seizure onset is typically within the first 2 years of life, during a critical time of neurodevelopment [2]. Patients with uncontrolled seizures are at increased risk for poor neurological outcome, and in these patients epilepsy surgery should be explored.

Surgical success hinges on accurate identification of the epileptogenic zone. While there is ongoing debate whether seizures originate in the core of tubers or in the perituber rim [10, 12, 14, 15], resection of an epileptogenic tuber complex results in seizure freedom in 57% of patients with an additional 18% getting more than 90% improvement [8]. Thus, the pre-surgical workup in TSC focuses on identification of the epileptogenic tuber.

The majority of patients display multiple tuber lesions, however, and there is no single non-invasive study modality that reliably detects the epileptogenic tuber. In practice, candidate tubers are proposed after synthesis of data from clinical presentation, seizure semiology, neurophysiology and multiple imaging modalities [25]. While structural, diffusion and nuclear imaging characteristics can provide localizing information at the millimeter level, the resolution of scalp EEG is low.

Electrical source imaging (ESI) can be used to non-invasively localize brain electrical activity from scalp measurements. A forward model, constructed from a description of tissue conductive properties, describes how cortical currents generate surface EEG activity. Solving an inverse problem with this model estimates the cortical currents from the scalp EEG. In routine EEG, there are only 19–25 electrodes and $\sim 10^5$ – 10^6 number of brain regions which could contain a dipole source. Thus, the problem is *ill-posed*; for all voltage patterns on the scalp, the solution is non-unique since the number of candidate dipole sources vastly outnumbers the number of electrodes. This is in part overcome by introducing constraints – e.g. forcing the sources to only be placed in the cortex [1].

While ESI using low-resolution EEG with 19 unregistered electrodes yields clinically meaningful localization in pediatric epilepsy surgery [19], it may have insufficient resolution to detect specific epileptogenic tuber and perituber regions. Higher resolution EEGs have increased fidelity [1] but are not routinely available at all institutions, and are typically used in outpatient settings where ictal data capture is difficult.

We propose a novel method of lesion-constrained ESI (LC-ESI), where the electrical activity in the brain is constrained to originate from any of multiple lesions. In TSC, LC-ESI assumes (peri-)tuber origin of epileptic activity and allows for rank-ordering tuber complexes based on their ability to approximate the measured surface EEG signal. In patients with TSC undergoing epilepsy surgery, we applied LC-ESI to routinely acquired data from the Epilepsy Monitoring Unit (EMU) and determined the spatial overlap with the surgical cavity.

Methods

Patients

All patients were diagnosed with TSC based on clinical or genetic criteria, and followed in the Multidisciplinary Tuberous Sclerosis Program at Boston Children's Hospital [17]. Inclusion criteria were epilepsy surgery before age 18, at least one pre-operative high resolution MRI, and follow-up for at least one year [19]. From our database of 200 patients, 14 were identified who underwent epilepsy surgery from 2011–2015. Excluded were patients with insufficient quality pre-operative MRI (3), single lesions on MRI (2), surgery prior to coming in our care (1), and follow-up less than 1 year (1). The study protocol was IRB-approved.

EEG Collection

EEG was collected during inpatient stay on the EMU, using a 32-channel digital Natus XLTEK system (Neuroworks version 8.5.1.4174), with 23 electrodes as per our inpatient EMU protocol from 2008–2017: 19 standard electrodes according to the International 10–20 System, plus FT9 and FT10, and TP9 and TP10. Impedances were kept below 5 kOhm, and sampling rate was 256 Hz. Reference electrodes were adjacent to Cz. Registration of electrodes to the patient's most recent pre-operative MRI was done using the standard 10–20 electrode positions, not by photogrammetry.

For interictal spikes, an experienced clinical neurophysiologist (JP) determined the dominant focus by (1) concordance with long-term ictal and interictal EEG findings [11]; (2) consistency over time in serial EEGs [9]; (3) amplitude and frequency of occurrence [7]. The mid-slope time-point was used for analysis [13], and a minimal of 30 topologically similar spikes were used [24]. Ictal data was selected after review of all pre-operative EMU data for each patient, and early, stereotyped graphoelements consistent across multiple seizures were marked using the Neuroscan Curry 7.0 software package. Exported data was analyzed on previously published in-house developed software on a Matlab (Natick, MA) platform [5].

MRI Collection and Processing

On a 3T MRI, the clinical epilepsy protocol for patients with TSC in our institution includes a T1-weighted isotropic high-resolution magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence, a T2-weighted turbo spin echo sequence, and a sagittal 3-dimensional isotropic T2 fluid-attenuated inversion recovery (FLAIR) sequence, as detailed previously [18]. These images were used for pre-processing, segmentation of tuber lesions, and generation of a patient-specific head model.

In each patient, all scans were coregistered to the T1w scan and resampled to 1mm isotropic resolution. Residual eddy currents distortion and patient motion in the diffusion scan were compensated for by alignment to the T1 MPRAGE and appropriate reorientation of gradient directions. Intracranial tissues were segmented from the T1 and T2 images using a multi-atlas approach. The scalp surface was identified using Otsu thresholding, and the skull region approximated as a 4mm dilation of the intracranial cavity. The resulting images were combined to construct a five tissue (scalp, skull, cerebrospinal fluid (CSF), grey and white matter) full-head segmentation (Figure 1).

Our laboratory has extensive experience with tuber segmentation [18, 21]. Here, we used ITK-SNAP 2.0 (www.itksnap.org) to manually segment tubers and the resection cavity [26]. Each tuber had a unique identifier. Tubers were expanded in 3 directions to include an 8 mm perituber rim as a potential seizure onset zone.

ESI and LC-ESI

Figure 1 summarizes the LC-ESI approach. For each patient, the head tissue segmentation was used to construct a finite difference bioelectric model at 1mm isotropic resolution [5]. Anisotropic white matter conductivities were incorporated using the method of Tuch [22], and dipole orientation constraints were identified using a model based approach [6]. We have previously demonstrated that this model attains a similar degree of accuracy as the finite element method [4]. This model was used to construct the leadfield matrix, which models the measurement of EEG data as:

$$Y = AX + n \quad (1)$$

Where $A \in \mathbb{R}^{\{N_e \times 3N_v\}}$ is the leadfield matrix relating the measurements $Y \in \mathbb{R}^{N_e \times N_t}$ at N_e electrodes and N_t times to the underlying cortical dipole activations $X \in \mathbb{R}^{3N_v \times N_t}$. In this model, three columns are associated with each of the N_v spatial locations, to account for arbitrary dipole orientations.

Two localization methods were employed for comparison:

First, a conventional distributed source image was computed using a minimum norm approach with a Laplacian regularization function similar that employed in LORETA. Solutions were constrained to cortical tissue, and dipole orientations constrained using a model based approach. This corresponds to solving the minimization problem:

$$\operatorname{argmin}_X \|Y - AC\bar{X}\|_2^2 + \lambda \|LC\bar{X}\|_2^2 \quad (2)$$

Where C is a matrix constraining the dipole orientations to be orthogonal to the cortical surface, and L is a discrete approximation to a Laplacian operator, computed over the cortical volume.

The distributed solution above can reconstruct source activations anywhere in the cortex.

Second, our lesion-constrained approach, as seizures typically arise from one or more epileptogenic tubers. To directly identify such tuber complexes, we propose an epileptogenicity index based on the ability of each individual tuber to approximate the measured data.

Individually for each tuber, we compute this index using the singular value decomposition:

$$A_i = U_i S_i V_i^T \quad (3)$$

Where A_i is the subset of columns of A corresponding to the i th tuber in the segmentation. In this decomposition, $U_i^{(j)}$, the j columns of the matrix U_i , describe the space of observable EEG patterns that can be generated by activity within the i th tuber (Figure 1). A minimum norm estimate of activation in each tuber can be computed as:

$$X_i^{(N)} = \sum_{j=1}^N V_i^{(j)} S_i^{-1} U_i^{(j)T} Y \quad (4)$$

with regularization applied by selecting the value of $N \in [1, N_e]$. Increasing N provides a better fit to the data, but permits spatial high frequencies which may overfit the solution.

For each truncated solution, we compute the associated data fit error as:

$$\delta_i^{(N)} = \|Y - AX_i^{(N)}\|_2^2 \quad (5)$$

We then compute an epileptogenicity score ψ_i for each tuber by averaging across all possible truncations:

$$\psi_i = 1/N_e \sum_{N=1}^{N_e} \delta_i^{(N)} \quad (6)$$

This can be interpreted as an area under the curve measure. With a sufficient number of basis functions, all tubers eventually achieve a good fit. For consistency across patients, we calculated the epileptogenicity score over the first 10 basis functions only (Figure 2). The range of the epileptogenicity score is therefore from 0 – 0.6 for all patients.

Comparison to surgical resection cavity, and clinical outcome

We used this epileptogenicity measure to quantify the ability of individual tubers to describe the measured EEG data. Tubers were rank-ordered and color-coded accordingly. Following the approach from Kargiotis *et al* [11], we qualitatively determined the overlap with the resection cavity as concordant or discordant. When partial overlap was present, the largest volume of the source solution was used to determine concordance (inside resection cavity) or not (outside of resection cavity). Patients were grouped according to good outcome (Engel Class I or II, n=3), and poor outcome (Engel Class III or IV, n=3).

Following the approach from Brodbeck *et al.*, we defined LC-ESI as true positive when the solution and the resection cavity showed either complete overlap or partial near-complete overlap in children with a good surgical outcome (Engel Class I and II) [1]. LC-ESI was true negative when the solution and the resection cavity did not overlap in children with a poor surgical outcome (Engel Class III and IV). False negative LC-ESI was defined as solution outside of the resection cavity in children with a good outcome, and false positive when the solution overlapped with the resection cavity in children with a poor outcome. LC-ESI was assessed with solutions constrained to tubers only, and to tubers including a perituber rim.

Results

Demographics and clinical characteristics of 6 patients included for analysis are shown in Table 1. Cases 1–3 were seizure free (Engle Class IA) after surgery, and Cases 4–6 had a poor surgical outcome (Engel Class II-IV).

Figure 3 shows the pre-operative MRI in 3 directions, with the post-surgical resection cavity superimposed, and ESI solutions. The patients are grouped by outcome, and displays ESI solutions for LORETA (left 2 columns), LC-ESI constrained to tuber only (middle 2 columns), and LC-ESI constrained to tuber and perituber rim (right 2 columns).

LORETA localization of interictal data showed concordance with the surgical cavity in only one patient (Case 1) with good outcome (true positive). Two patients, Cases 5 and 6, showed solutions outside of the resection cavity (true negative). In two patients, Cases 2 and 3, the solution localized outside of the cavity but the patients had a good outcome anyway (false negative). In one patient, Case 4, the solution was concordant with the resection cavity, but the patient had a poor outcome (false positive).

LORETA localization of ictal data yielded the same results as interictal data, with one exception; in Case 4 the ictal localization was more anteriorly and thus outside of the resection cavity (true negative). Overall, the positive predictive value (PPV) was 50% and 100% for interictal and ictal data, respectively. Due to a high number of false negatives (source outside of the cavity in patients with a good outcome), the negative predictive value (NPV) was only 40% and 60% for interictal and ictal data, respectively.

LC-ESI localization of interictal data identified individual tubers within the resection cavity in two children (Cases 1 and 2) out of three with a good outcome (true positive, interictal PPV 66%). Epileptogenic tubers were identified correctly outside of the resection cavity in

two children (Cases 5 and 6) out of three with a poor outcome (true negative, interictal NPV 66%). There was one false negative when the interictal activity localized to a tuber in the temporal lobe rather than in frontal lobe (Case 3), and one false positive where the solution fell within the resection cavity, in a patient with a poor outcome regardless (Case 4).

LC-ESI localization of ictal data showed the best accuracy. The ictal data solution of Case 3 identified tubers in the left inferolateral posterior frontal lobe correctly as the epileptogenic focus. Thus, LC-ESI had true positive solutions for all three patients with a good outcome (ictal PPV 100%). Epileptogenic tubers were identified correctly outside of the resection cavity in Case 4, with a poor outcome. As a result, LC-ESI had true negative solutions for all three patients with a poor outcome (ictal NPV 100%).

There was no difference between LC-ESI solutions constrained to tubers only as compared to those also incorporating a perituber rim.

Discussion

The multilesional nature of TSC poses a surgical planning challenge that is distinct from other epilepsy etiologies. The potential surgical targets, tubers, are readily visible on MRI, and the pre-surgical workup aims to identify which tuber(s) require resection. While EEG is a key aspect of the comprehensive evaluation, the interictal spikes and ictal patterns can involve multiple electrodes (Table 1) and the seizure focus does not necessarily underlie the negative maximum [20].

To directly identify potential epileptogenic tubers among many tubers, we developed a lesion scoring approach. Results in six patients support the potential clinical utility of LC-ESI in the presurgical workup for patients with TSC. In this small series, ictal data was more accurate than interictal data in all models, and LC-ESI outperformed conventional LORETA. Using LC-ESI on ictal EEG data, the epileptogenic tuber identified by LC-ESI was concordant with the resection zone in patients with a good surgical outcome, and appropriately discordant in patients with a poor outcome.

Previous work has demonstrated the clinical utility and a high diagnostic yield of ESI in presurgical evaluations of both children and adults with epilepsy. While solutions based on higher number of EEG electrodes are generally more accurate [1], clinically useful solutions have been shown with as few as 19 channels [19]. For TSC specifically, a study of 13 patients showed partial concordance of low-resolution (31 electrodes) in five out of nine patients with seizure freedom, and in two there was complete concordance [11]. High density EEG data performed better, showing complete concordance in four out of five seizure-free patients. Both low- and high-resolution data, however, was based on interictal data only, using head models with a distributed source solution biophysically constrained to the grey matter.

The results from this methodological paper suggest that for multi-lesional epilepsy, classic distributed inverse solutions like cortically-constrained LORETA could potentially be supplemented by a lesion-scoring approach which further reduces the solution space. In this work, the spatial resolution of the EEG data is still limited, however, and the close range of

tuber scores illustrate that the ill-posed nature of the inverse problem is not overcome by our method (see also Figure 2).

The better performance of LC-ESI as compared to LORETA has multiple explanations. First, the epileptic process in TSC is expected to lie in the tuber or peri-tuber rim [10, 14–16], but activity within these regions may be inaccurately modeled when considering solutions constrained to cortical grey matter only. By employing full tuber volumes rather than cortical tissue alone, the signal generation modeled in LC-ESI may better fit the true intra-tuber epileptic activity. Second, localization from low-density EEG is known to produce larger solution volumes as compared to high density EEG. Spatially constraining activations to lie within the tuber and peri-tuber rim may help overcome this limitation (e.g. Case 3).

LC-ESI performed similarly well with both ictal and interictal data in this study, with ictal data improving predictive value in only one patient (Case 4). Where LORETA gave a false positive result, LC-ESI correctly predicted an alternate surgical site (true negative). The small difference is unsurprising given high concordance between interictal and ictal data in TSC. In a series of 19 patients with TSC, the dominant interictal focus on surface EEG was concordant with the ictal focus in 14 out of 19 patients – although only 6 patients were operated [23]. In another study of 21 patients, the interictal and ictal focus occurred in the region of the epileptogenic tuber in 14 and 16 patients, respectively [12]. However, obtaining interictal localizations that matches those of ictal spikes, however, depends on subjective identification of a dominant interictal spike focus [7, 12].

This study has several limitations. In general, no single modality alone is sufficient for decision making; patients undergo a comprehensive evaluation and surgical planning is based on synthesis of all clinical and auxiliary data. Also, given TSC is a rare disease, the number of patients from our single center is small. Rather than an arbitrary cut-off of 10 basis functions, a technique for optimizing the number of basis functions for each patient would require a larger sample size to study. In addition, as we were developing the technique, we were not blinded to the surgical outcome, potentially introducing a bias for the selection of EEG data for analysis. In a typical clinical setting, however, EEG spikes are selected based on consistency over time, and on data from other tests [9, 3].

Also, this method is based on the assumption that a single epileptogenic tuber is responsible for seizure onset, and further evaluation is necessary to determine whether LC-ESI is applicable in more complicated seizure patterns. Similarly, results of the method further depend on how adjacent tubers are segmented; two contiguous tubers segmented as isolated lesions would likely have a similar LC-ESI rankings, as seen in Case 2. Finally, the number of electrodes used in this retrospective study for presurgical workup is low (23) given its retrospective nature, with only 4 electrodes covering the inferior/basal temporal chain, rather than 6 as recommended in 2017 [20].

Future directions include application with higher resolution neurophysiological techniques including high-density EEG and magnetoencephalography, which will likely improve the accuracy [7]. Observational data collected from multiple centers would be most suitable for

validation, and annotation of EEG elements should be done without the foresight of surgical outcome. After further refinement and validation of the method, we will make the code and instructions available to the scientific community.

Conflicts of Interest and Source of Funding:

COI: JP is receiving honoraria from Philips Neuro, which is unrelated to this work. For the remaining authors none were declared.

Sources of Funding: JP, SC, MS, SW are supported by NIH R01 NS079788 and U01 NS082320 grants. SP is supported by the Department of Defense W81XWH-11-1-0365 and NIH U01 NS082320 grants. MS is additionally supported by an NIH U54 HD090255 grant and the Boston Children's Hospital Translational Research Program. The Developmental Synaptopathies Consortium (U54 NS092090) is part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through collaboration between NCATS, NIMH, NINDS, and NICHD.

References

- [1]. Brodbeck V, Spinelli L, Lascano AM, Wissmeier M, Vargas MI, Vulliemoz S, et al. Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. *Brain* 2011;134(Pt 10):2887–97. [PubMed: 21975586]
- [2]. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;372(9639):657–68. [PubMed: 18722871]
- [3]. Gupta A Epilepsy Surgery in Tuberous Sclerosis Complex: In Pursuit of the Epileptogenic Center(s). *Epilepsy Curr* 2017;17(3):150–2. [PubMed: 28684945]
- [4]. Hyde DE, Dannhauer M, Warfield SK, MacLeod R, Brooks DH. Evaluation of Numerical Techniques for Solving the Current Injection Problem in Biological Tissues. *Proc IEEE Int Symp Biomed Imaging* 2016;2016:876–80. [PubMed: 28479960]
- [5]. Hyde DE, Duffy FH, Warfield SK. Anisotropic partial volume CSF modeling for EEG source localization. *Neuroimage* 2012;62(3):2161–70. [PubMed: 22652021]
- [6]. Hyde DE, Duffy FH, Warfield SK. Voxel-based dipole orientation constraints for distributed current estimation. *IEEE Trans Biomed Eng* 2014;61(7):2028–40. [PubMed: 24951674]
- [7]. Jansen FE, Huiskamp G, van Huffelen AC, Bourez-Swart M, Boere E, Gebbink T, et al. Identification of the epileptogenic tuber in patients with tuberous sclerosis: a comparison of high-resolution EEG and MEG. *Epilepsia* 2006;47(1):108–14. [PubMed: 16417538]
- [8]. Jansen FE, van Huffelen AC, Algra A, van Nieuwenhuizen O. Epilepsy surgery in tuberous sclerosis: a systematic review. *Epilepsia* 2007;48(8):1477–84. [PubMed: 17484753]
- [9]. Jansen FE, van Huffelen AC, Bourez-Swart M, van Nieuwenhuizen O. Consistent localization of interictal epileptiform activity on EEGs of patients with tuberous sclerosis complex. *Epilepsia* 2005;46(3):415–9. [PubMed: 15730539]
- [10]. Kannan L, Vogrin S, Bailey C, Maixner W, Harvey AS. Centre of epileptogenic tubers generate and propagate seizures in tuberous sclerosis. *Brain* 2016;139(Pt 10):2653–67. [PubMed: 27497492]
- [11]. Kargiotis O, Lascano AM, Garibotto V, Spinelli L, Genetti M, Wissmeyer M, et al. Localization of the epileptogenic tuber with electric source imaging in patients with tuberous sclerosis. *Epilepsy Res* 2014;108(2):267–79. [PubMed: 24315017]
- [12]. Koh S, Jayakar P, Dunoyer C, Whiting SE, Resnick TJ, Alvarez LA, et al. Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome. *Epilepsia* 2000;41(9):1206–13. [PubMed: 10999561]
- [13]. Lantz G, Spinelli L, Seeck M, de Peralta Menendez RG, Sottas CC, Michel CM. Propagation of interictal epileptiform activity can lead to erroneous source localizations: a 128-channel EEG mapping study. *J Clin Neurophysiol* 2003;20(5):311–9. [PubMed: 14701992]
- [14]. Ma TS, Elliott RE, Ruppe V, Devinsky O, Kuzniecky R, Weiner HL, et al. Electrographic evidence of perituberal cortex epileptogenicity in tuberous sclerosis complex. *J Neurosurg Pediatr* 2012;10(5):376–82. [PubMed: 22998031]

- [15]. Major P, Rakowski S, Simon MV, Cheng ML, Eskandar E, Baron J, et al. Are cortical tubers epileptogenic? Evidence from electrocorticography. *Epilepsia* 2009;50(1):147–54. [PubMed: 19125835]
- [16]. Mohamed AR, Bailey CA, Freeman JL, Maixner W, Jackson GD, Harvey AS. Intrinsic epileptogenicity of cortical tubers revealed by intracranial EEG monitoring. *Neurology* 2012;79(23):2249–57. [PubMed: 23175730]
- [17]. Northrup H, Krueger DA, Group ITSCC. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr. Neurol* 2013;49(4):243–54. [PubMed: 24053982]
- [18]. Peters JM, Prohl AK, Tomas-Fernandez XK, Taquet M, Scherrer B, Prabhu SP, et al. Tubers are neither static nor discrete: Evidence from serial diffusion tensor imaging. *Neurology* 2015;85(18):1536–45. [PubMed: 26432846]
- [19]. Russo A, Jayakar P, Lallas M, Miller I, Hyslop A, Korman B, et al. The diagnostic utility of 3D electroencephalography source imaging in pediatric epilepsy surgery. *Epilepsia* 2016;57(1):24–31. [PubMed: 26696504]
- [20]. Seeck M, Koessler L, Bast T, Leijten F, Michel C, Baumgartner C, et al. The standardized EEG electrode array of the IFCN. *Clin Neurophysiol* 2017;128(10):2070–7. [PubMed: 28778476]
- [21]. Tomas-Fernandez X, Prabhu S, Peters J, Sahin M, Warfield S. Automatic cortical tuber segmentation based on a combined global-local intensity mixture model MICCAI Challenge Workshop on Segmentation Algorithms, Theory and Applications (SATA). MICCAI 2013 Nagoya, Japan 2013.
- [22]. Tuch DS, Wedeen VJ, Dale AM, George JS, Belliveau JW. Conductivity tensor mapping of the human brain using diffusion tensor MRI. *Proc Natl Acad Sci U S A* 2001;98(20):11697–701. [PubMed: 11573005]
- [23]. van der Heide A, van Huffelen AC, Spetgens WP, Ferrier CH, van Nieuwenhuizen O, Jansen FE. Identification of the epileptogenic zone in patients with tuberous sclerosis: concordance of interictal and ictal epileptiform activity. *Clin Neurophysiol* 2010;121(6):842–7. [PubMed: 20153249]
- [24]. Wennberg R, Cheyne D. EEG source imaging of anterior temporal lobe spikes: validity and reliability. *Clin Neurophysiol* 2014;125(5):886–902. [PubMed: 24210516]
- [25]. Wu JY, Salamon N, Kirsch HE, Mantle MM, Nagarajan SS, Kurelowech L, et al. Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. *Neurology* 2010;74(5):392–8. [PubMed: 20124204]
- [26]. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* 2006;31(3):1116–28. [PubMed: 16545965]

Figure 1. Overview of data processing

(A) Preoperative T1w and T2w MRI were used for automated three tissue segmentation of the brain, and manual segmentation of tubers. (B) Post-operative MRI was co-registered to the preoperative T1w image and the resection cavity segmented. (C) The ESI leadfield was constructed from individual full head segmentations using a finite difference approach. (D) Ictal onset patterns and interictal spikes were marked and averaged from long term inpatient recordings. (E) Distributed localizations of each spike were computed using the LORETA algorithm (left image). For the LC-ESI method, tubers were segmented, and for each tuber an epileptogenicity score was calculated based on each lesion's ability to approximate the measured spike. Next, the tubers were rank-ordered by their epileptogenicity score, with the hottest colors given to the tubers with the highest scores, using the method described in this paper (right image).

Figure 2. Examples of tuber scoring curves

On the X-axis, the number of basis functions added during the fitting process. On the Y-axis, the residual variance, ranging from 1 (100%, no fit at all) to 0 (0%, all basis functions used and thus fit achieved). Each tuber has its own line (black), with tubers overlapping with the future resection cavity indicated in red.

(A) Good outcome example (Case 2): The three lesions that were resected (red curves), are also those curves that have a good fit with a limited number of basis functions; this is evident because of the early steep decline of the red curves. Note that there are 2–3 lesions not resected (black curves overlapping with red curves) which also show a relatively good fit with a limited number of basis functions. Nonetheless, the patient had a good surgical outcome.

(B) Poor outcome example (Case 5): This patient has a higher tuber burden (higher number of curves) than the case above. Three tubers appear distinctly separate from the rest, with a good fit using a limited number of basis functions. Only 2 of these (red curves) were resected. The patient had a poor surgical outcome.

Figure 3. LORETA and Lesion-Constrained Electrical Source Imaging (LC-ESI)

Patients are grouped by outcome and correspond to case numbers from Table 1.

For each patient, axial, sagittal and coronal T1-weighted structural images are shown. In black, the post-surgical resection cavity is superimposed on the pre-operative images, thus representing the “future” resection cavity.

In the left two columns, LORETA solutions are provided for interictal and ictal data. In the middle two columns, a lesion-constrained electrical source imaging (LC-ESI) approach is shown with solutions constrained to only the lesion (tuber). LORETA solutions were thresholded the same across all patients. On the right, two columns show LC-ESI applied to segmented lesions that include the perilesional rim (tuber and perituber rim). The range of the epileptogenicity score is from 0 – 0.6 for all patients, with only the first 10 basis functions used. Each tuber is colored according to this score, as indicated by the color bar (0–0.6). The hottest colors (dark red, then red) indicating tuber lesions with the highest

epileptogenicity scores. The lower the score lesions have, the colder the colors become – ranging from orange to yellow, then green, and ultimately blue and dark blue.

A green checkmark indicates a true positive or true negative; a red X indicates a false positive or false negative localization. See method section for details.

(A) Three patients with a good surgical outcome. In Case 1, all three approaches correctly overlapped with the surgical cavity (true positive). In Case 2, the LORETA solution fell largely outside of the resection cavity, although there was some overlap (most evident in the coronal plane). LC-ESI correctly identified two lesions in the center of the surgical cavity. In Case 3, LORETA solutions were ambiguous, on the border of frontal and temporal lobes, whereas the ictal LC-ESI solution correctly identified a tuber in the infero-lateral frontal lobe.

(B) Three patients with a poor surgical outcome. In Case 4, interictal LORETA and LC-ESI were false positive as resection of the occipital lobe did not result in a good outcome. The ictal LORETA and LC-ESI were true negative, as they localized to an area anterior of the future resection cavity. In Case 5, interictal and ictal LORETA and LC-ESI solutions localized to posterior aspects of the temporal lobe. The resection was more anterior and did not include the posterior extent of the lesion. In Case 6, interictal and ictal LORETA and LC-ESI solutions were largely posterior to the resection cavity, and indeed the patient did not have a good outcome (true negative).

Table 1:

Patient characteristics, ordered by outcome

Sex, age	Seizure history	EEG	Other localizing studies	Surgery	Outcome	Engel Class, binarized
(1) M 22 m.	IS at 3 m. At 18 m., CPS 10–20 s., sudden slump or fall, decreased responsiveness, head and eye deviation to right.	Intermittent right posterior quadrant slowing. Interictal spikes at O2, P4-P8, T8, Pz. 63 seizures with onset at O2, P4, and P8.	MRI with multifocal tuber lesions. PET scan not performed. SISCOM with right posterior parietal increased perfusion.	Single-stage right parietal tuberectomy with intraoperative corticography.	Freedom from targeted seizure type	1A, good
(2) M 24 m.	IS at 5 m. At 9 m., CPS 30–45 s., rhythmic left eye flutter, tonic left arm extension, right arm flexion, truncal flexion. Postictal Todd's paresis left arm.	Intermittent slowing at C4. Interictal spikes at C4-T8, F4, and Cz. 34 electroclinical seizures with onset at F4-C4, P4, Cz.	MRI large contiguous tuber complex and radial migration lines right frontal. PET largest area of decreased uptake right frontal. SISCOM non-localizing. MEG right frontal spikes.	Two-staged surgery with extra-operative intracranial EEG monitoring, and cortical stimulation for motor mapping. Right frontal resection of large tuber conglomerate.	Seizure free, complicated by left hemiparesis	1A, good
(3) F 3.9 y.	Seizure onset with super-refractory status epilepticus at age 16 m. At 21 m., CPS 30 s. - 7 min., staring, decreased responsiveness, right leg flexion and jerking, right arm flexion, obstructive breathing, crooked smile with face pulled to right.	Interictal multifocal spikes at T8-P8, P8, T7-P7, T7-F7, and runs of discharges in the left anterior quadrant, maximum at F7. 26 seizures onset at left anterior quadrant, maximum at F7.	MRI with multifocal tuber lesions. PET with multiple areas of hypometabolism, corresponding to cortical tubers. SISCOM with increased perfusion left posterior temporal lobe and superior right frontal lobe.	Two-staged surgery with extra-operative intracranial EEG monitoring. Interictal spikes lateral and inferior frontal lobe, lateral, basal and posterior temporal lobe. 12 seizures with infero-lateral frontal lobe onset. Partial frontal lobe resection.	Freedom from targeted seizure type.	1A, good
(4) F 6.5 y.	IS at 6 m. At 14 m., CPS 30–60 s., visual aura "spiders", staring, decreased responsiveness, slumping with mild tensing up of extremities	Intermittent left posterior quadrant slowing. Interictal spikes at O1, P3, P7, P8. 26 seizures onset at P3, P7, O1.	MRI with multifocal tuber lesions. PET largest area of decreased uptake left posterior quadrant. SISCOM non-localizing. AMT PET mesial occipital. MEG loosely clustered spikes left posterior temporal and inferior parietal.	Two-staged surgery with extra-operative intracranial EEG monitoring. Hardware removed on post-op day 3 for refractory status epilepticus and lobar edema; occipital lobectomy with intra-operative corticography.	Improvement with reduction of frequency and severity	3A, poor
(5) F 12 m.	IS at 5 m. At 2 m., CPS 15–45 s., eye deviation to left, rapid blinking, audible breathing, facial flushing, left arm flexion	Slowing left posterior quadrant (intermittent irregular), left temporal (semirhythmic, waxing and waning). Interictal multifocal spikes, most at T7, P7, P3, C3, FT9, O1, P3. 33 seizures onset at T7, P7.	MRI with multifocal tuber lesions, large tuber complex left temporal lobe including mesial and posterior aspects. PET largest area of decreased uptake left temporal lobe. Ictal SPECT unable to inject tracer given short duration of seizures.	Single-stage partial lateral temporal lobectomy with intraoperative corticography.	Improvement with reduction of frequency and severity. (Completion of temporal lobectomy 8 m. later resulted in seizure freedom.)	3A, poor
(6) M 4.6 y.	IS at 2 m. At 21 m., CPS 90–120 s., bilateral eye widening and blinking, bilateral hand clenching, left more than right perioral twitching.	Interictal spikes at F3-F7, P3, T8. 10 seizures with 1–2 Hz run of F3 spikes, spread to T7, then switch to T8 1–2 Hz spikes with accelerate.	MRI with atrophy and multifocal tuber lesions. PET multiple areas of hypometabolism corresponding with tubers. Right temporal lobe area of hypometabolism larger than	Two-staged stereoEEG covering left frontotemporal and right temporal regions was recommended.	No significant improvement. (Later, seizure freedom achieved with vigabatrin)	4B, poor

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Sex, age	Seizure history	EEG	Other localizing studies	Surgery	Outcome	Engel Class, binarized
	guttural noise, hypermotor activity both legs.		corresponding MRI. SISCOM scattered increased uptake including right anterior temporal and right posterior parietal regions. AMT-PET with moderately increased uptake in left parietal tuber and right parieto-temporal region.	Patient underwent, however, single stage resection of left frontal lobe tuber complex.		

AMT-PET α-[11C] methyl-l-tryptophan positron emission tomography; CPS Complex Partial Seizures; F Female; IS Infantile Spasms; M male; MEG Magnetoencephalography; m. months; PET Positron Emission Tomography; s. seconds; SISCOM Subtraction Ictal SPECT Co-registered to MRI; SPECT Single-Photon Emission Computed Tomography; y year(s).