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3D-EEG Source Imaging Moving Dipole Methodology Reduces Surgical Failure in Pediatric Patients with Tuberous Sclerosis Complex

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1. Abstract

1.1. Objective: To investigate the localizing ability and surgical outcome using 3D-EEG Source Imaging (3D-ESI) Moving Dipole (MD) methodology in children with Tuberous Sclerosis Complex (TSC).

1.2. Methods: We retrospectively studied a cohort of pediatric patients with TSC and multiple tubers undergoing excisional surgery for drug resistant epilepsy. Patients were under age 18 years at time of surgery and had at least one year of outcome data. Rotating Dipole (RD) and MD models were constructed for individual interictal spike or sharp wave discharges and each inverse algorithm was compared to the surgical resection cavity (SRC). MD findings were considered "single touch" if the solution included only one tuber, and "multi-touch" when the solution included more than one tuber. We also compared 3D-ESI findings and surgical outcome to the ictal SPECT (iSPECT).

1.3. Results: RD analyses were highly correlated with SRC location (85% at year 1, 84.6% at year 2), the highest correlation being achieved in patients undergoing temporal lobe resection (100.0% at years 1 and 2) compared to extra-temporal (84.6% at year 1, 88.9% at year 2) or multilobar resection (75% at year 1, 66.7% at year 2). Outcome was uniformly favorable when the RD solution was inside the SRC and the MD was one-touch. When the RD solution was inside the SRC and the MD multi-touch zone the outcome was favorable if surgery comported with a multi-touch MD solution. 3D-ESI showed equivalent sensitivity and superior specificity compared to iSPECT at 1 and 2 years post-operatively. Sensitivity was improved when surgery was performed when the RD finding was associated with the MD solution.

1.4. Significance: 3D-ESI showed equivalent sensitivity and superior specificity compared to iSPECT at 1 and 2 years post-operatively, and greater sensitivity when the RD and MD solutions were analyzed together. Analyzing a composite RD-MD solution could improve our understanding of the epileptogenic networks underlying TSC.

2. Introduction

Tuberous sclerosis complex is a multi-organ genetic disorder with variable effects on the central nervous system characterized by

aberrant neuronal differentiation and proliferation, and multiple central nervous system hamartomas [1,2]. Epilepsy occurs in more than 80% of TSC patients with nearly two-thirds being medically refractory and potential surgical candidates [3,4]. Although multiple tubers are common, seizures often arise from a single tuber [5,15]. However, precise identification of the epileptogenic tuber presents unique challenges [16-25].

Ictal SPECT is currently one of the most definitive procedure for selecting the epileptogenic tuber but is often not feasible for seizures that are infrequent or unpredictable [26-34]. When SPECT findings are inconclusive, definitive localization typically requires invasive EEG studies [35,36].

Given the inherent challenges of performing a diagnostic ictal SPECT study, and the cost and risks of invasive monitoring, we analyzed the utility of 3D-ESI in pediatric patients with TSC. Our study assessed the localizing ability and surgical outcome for 3D-ESI in TSC patients harboring multiple tubers.

3. Methods

3.1. Patient Population

We retrospectively analyzed scalp EEG data from pediatric patients with TSC, multiple tubers and drug-resistant epilepsy being evaluated for excisional surgery at our institution between 2008 and 2016. Inclusion criteria were (1) age 18 years or younger at surgery, (2) at least one pre-surgical volumetric brain MRI, (3) at least one year of follow up. Exclusion criteria included prior excisional surgery and epileptic encephalopathy with multifocal interictal discharges without a clearly prevalent interictal focus and/or disorganized background activity. Our analyses focused on single or multi-tuber excisional procedures. Analysis was conducted in accordance with an institutionally approved human subjects' protection protocol.

3.2. EEG and MRI Acquisition

Scalp EEG data was recorded using a 32-channel digital XLTEK system (Neuroworks Ver.7.1.1) at a sampling frequency of 512 Hz. After 2007 we added 4-10 electrodes to the standard 10-20 system. This created a locally dense EEG matrix (LD-EEG) covering the region of interest in order to boost signal and avoid noise from unrelated regions. The LD-EEG configuration was based on known seizure semiology, imaging findings and previously identified interictal discharges. In cases lacking a clear semiology, imaging, or electrophysiology data, sub-temporal electrodes were utilized to overcome poor sampling from the temporal base. Volumetric T1 sequences were obtained on a Signal Horizon LX 3 Tesla MRI scanner.

3.3. 3D-ESI Analysis

Pre-operative EEG and individual volumetric MRI were imported into CURRY V.7.0 software from NeuroScan for 3D-ESI analysis. MRI images were used to construct a realistic subject-dependent Boundary Element Model (BEM) which was utilized for each dipole analysis. CURRY software determined electrode positions by idealized label-matching.

Two experienced epileptologists reviewed standard bipolar and referential montages to select three interictal spikes or sharp waves for each patient. Concordance with ictal discharges was not taken in account. Discharges were selected as typical for each patient without any pre-processing and not utilizing the added channels from the LD-EEG.

3D-ESI findings were calculated from the onset of the discharge to the peak of the negative phase.27 The bandwidth for analysis was 1-30 Hz. An RD model was constructed for each discharge to maximize Signal-to-Noise Ratio (SNR). The RD model maintains a single position for the dipole with orientation and strength allowed to change through the spike. MD modeling and Independent Component Analysis (ICA) evaluated propagation effects and validity of the single dipole model. The MD model allows the position, orientation and strength of the dipole to vary independently for each analyzed time point resulting in a trace of dipoles. Single RD and MD models were selected for each interictal epoch.

3.4. Comparison of 3-D ESI to Surgical Resection

Two experienced epileptologists reviewed the position of the RD dipole model and compared it to the Surgical Resection Cavity (SRC) for all three analyzed discharges per subject. RD to SRC locations were considered localizing if the results were concordant for at least two of the three analyzed discharges. The MD finding was considered invalid if the RD solution was non-concordant with the SRC.

When the RD solution co-localized with the SRC, the MD findings were designated single touch for MD solutions localized to one tuber (Figure 1) or multi-touch for MD solutions localized to multiple tubers (Figure 2).

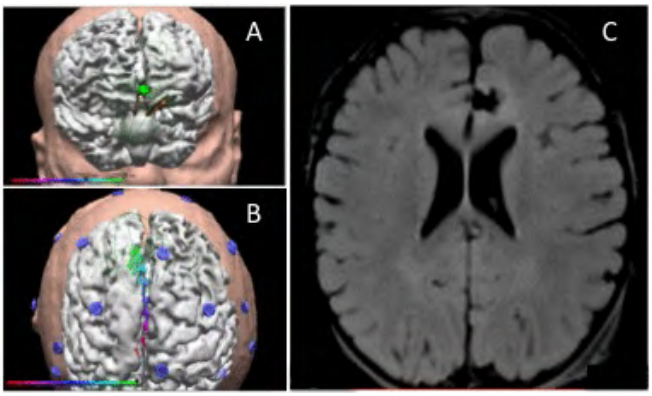

Figure 1: Electroencephalography source imaging. 3D-ESI of single spikes (A) using a Rotating Dipole (B) Moving Dipole (C) models reveals one possible source in the right frontal region. Comparison of 3-D ESI to Surgical Resection. 3D-ESI sources using the Rotating Dipole (A) and Moving Dipole (B) models were both localized within the surgical resection cavity (C).

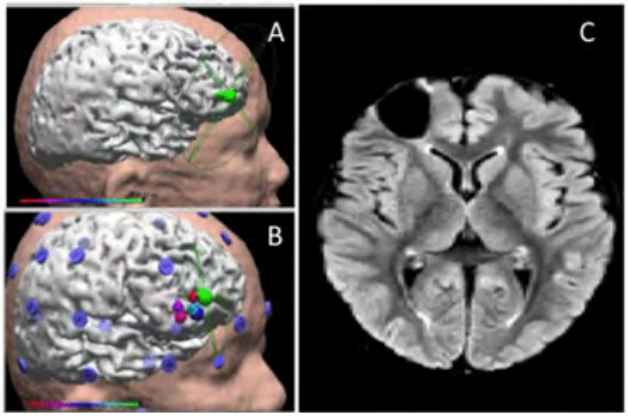

Figure 2: Electroencephalography source imaging. 3D-ESI of single spikes (A) using a Rotating Dipole (B) Moving Dipole (C) models reveals one possible source in the parasagittal left frontal region. Comparison of 3-D ESI to Surgical Resection. 3D-ESI sources using the Rotating Dipole (A) and Moving Dipole (B) models. Moving dipole findings extends beyond the source indicated by the Rotating dipole

If the primary reviewers' assessments were divergent, a third reviewer assessed the images and the final determination was based on consensus.

3.5. Ictal SPECT Data

Ictal SPECT imaging was performed by administering 14.2 mCi of 99mTc-HMPAO within 30 seconds of electrographic seizure onset. iSPECT images were acquired within four hours of radiotracer injection [28]. iSPECT scans were interpreted by Neuroradiologists blinded to the clinical histories. Subtraction of ictal SPECT co-registered to MRI (SISCOM) data was not utilized in our analysis as it is unavailable at our institution.

3.6. Comparison of ictal SPECT Imaging to Surgical Resection

All iSPECT images were independently re-evaluated by two epileptologists and classified as localizing only if the perfusion abnormalities were resected completely. We classified iSPECT scans with abnormalities outside the SRC or with multifocal functional abnormalities as non-localizing. Subtraction of ictal SPECT co-registered to MRI (SISCOM) data was not utilized in our analysis, as it was performed infrequently.

3.7. Surgical Procedure and Outcome

Surgical resections were guided by MR imaging and EEG data while 3D-ESI and iSPECT served as adjunctive procedures. We typically employ 3D-ESI to assist in lobar and sub-lobar localization rather than delineate between various possible tubers to resect. Surgical resections were categorized as temporal, extra-temporal or multilobar. Multilobar cases were characterized as continuous areas spanning more than one lobe, not separated by discrete epileptogenic foci.

Engel Classification of surgical outcome data was obtained via direct clinical assessment or telephone interview at one and two years post resection.

We defined true positives as cases with a localizing RD and Engel Class I or II outcomes, and true negatives as cases with a non-localizing RD and Engel Class III or IV outcomes. We defined sensitivity as the percentage of true positives among all patients with Class I and II outcomes, and specificity as the percentage of true negatives among all patients with unfavorable Class III and IV outcomes.

4. Results

4.1. Patients

Twenty patients met inclusion criteria. Mean age at surgery was 6 years (range 1–18 years). All patients underwent video-EEG monitoring and brain MRI. Thirteen patients had ictal SPECT. There were three temporal (15%), thirteen extra-temporal (65%) and four multilobar (20%) resections.

4.2. 3D-ESI and iSPECT Findings in Relation to the Surgical Resection

Table 1 summarize the RD findings of 3D-ESI analyses and iSPECT findings.

RD analyses were highly correlated with the SRC (85% at year 1, 84.6% at year 2), with the highest correlation found in patients undergoing temporal lobe resection (100% at years 1 and 2) compared to either extra-temporal (84.6% at year 1, 88.9% at year 2) or multilobar resection (75% at year 1, 66.7% at year 2).

Thirteen patients (65%) underwent at least one iSPECT. The RD method was more localizing than iSPECT in extra-temporal (62.5% at years 1 and 2) and multilobar resections (33.3% at year 1, 0% at year 2), but there were no differences in outcome for temporal resections (100% at years 1 and 2).

Table 1: Localizing value of 3D-ESI and iSPECT for Surgical Resection.

Year 1	n (%)	Temporal	Extratemporal	Multilobar
3D-ESI	20	3	13	4
RD Localizing	17 (85)	3 (100)	11 (84.6)	3 (75)
iSPECT	13	2	8	3
Localizing	8 (61.5)	2 (100)	5 (62.5)	1 (33.3)
Year 2	n (%)	Temporal	Extratemporal	Multilobar
3D-ESI	13	1	9	3
RD Localizing	11 (84.6)	1 (100)	8 (88.9)	2 (66.7)
iSPECT	11	1	8	2
Localizing	6 (54.5)	1 (100)	5 (62.5)	0 (0)

Legend: 3D-ESI: 3D-EEG source imaging; RD: rotating dipole; RD: Rotating Dipole; iSPECT: ictal single-photon emission-computed tomography; n: number of patients.

4.3. 3D-ESI and Surgical Outcome

Table 2 summarizes the relationship between 3D-ESI, resection area and surgical outcome at one and two years. All patients with a RD outside the SRC had an unfavorable surgical outcome.

In contrast, the outcome was uniformly favorable in all patients (100%) when the RD solution was inside the SRC and the MD was one-touch (50%).

When the RD solution was inside the SRC but the MD was multi-touch (35%) the outcome was unfavorable for surgeries limited to one tuber, but favorable if surgery comported with a multi-touch MD solution.

4.4. Comparative Sensitivity and Specificity of Different Localizing Tests

Table 3 presents the respective sensitivity and specificity of 3D-ESI and iSPECT for surgical outcome. 3D-ESI showed equivalent sensitivity and superior specificity compared to iSPECT at both 1 and 2 years post-operatively.

In addition, table 2 shows an improvement in sensitivity if surgery followed the RD finding in association with the MD solution (blue color).

Table 2: Relationship of 3D-ESI to surgical outcome.

Type of surgery	Concordance RD-SRC	Moving Trajectory	Multi-touch Surgery	YEAR 1	YEAR 2
Extratemporal	YES	Multi-touch	No	III	III
Temporal	YES	One touch		I	I
Multilobar	YES	Multi-touch	Yes	I	I
Extratemporal	YES	Multi-touch	No	III	*
Extratemporal	YES	One touch		II	II
Multilobar	NO	*		III	III
Extratremporal	YES	One touch		I	I
Extratremporal	YES	Multi-touch	No	III	III
Extratremporal	YES	One touch		II	II
Multilobar	YES	Multi-touch	Yes	I	I
Extratemporal	YES	Multi-touch	No	III	III
Temporal	YES	One touch		I	*
Temporal	YES	One touch		I	*
Extratremporal	NO	*		III	*
Extratremporal	YES	One touch		II	II
Extratremporal	YES	One touch		I	I
Extratremporal	NO	*		III	III
Extratremporal	YES	One touch		I	*
Extratremporal	YES	Multi-touch	No	IV	*
Multilobar	YES	One touch		I	*

Legend: RD: rotating dipole; MD: moving Dipole; SRC: surgical resected cavity; YEAR 1: 1 Year after the surgery; YEAR 2: 2 Years after the surgery; By analyzing MD method in association to RD solution the overall localizing value of 3D-ESI analysis improved. The outcome of surgical resection improved if SRC followed the MD multi-touch trajectory (blue color) instead of being limited to the result obtained with the RD analysis (orange color); when RD solution was not concordant with SRC the outcome was poor both YEAR 1 and YEAR 2 (violet color).

Table 3: Sensitivity and Specificity of 3D-ESI and iSPECT at 1 and 2 Year follow-up.

Year 1	Sensitivity	Specificity	Year 2	Sensitivity	Specificity
3D-ESI (n=20)	70.60%	100%	**3D-ESI** (n=13)	72.70%	100%
iSPECT (n=13)	75.00%	60.00%	**iSPECT** (n=11)	66.70%	60.00%

Legend: 3D-ESI: 3D-EEG source imaging; iSPECT: ictal single-photon emission-computed tomography

5. Discussion

Our study demonstrates that 3D-ESI contributes meaningful prognostic information in the non-invasive pre-surgical evaluation of children with TSC and pharmaco-resistant epilepsy, and has superior localizing capability compared to iSPECT. 3D-ESI showed an equivalent sensitivity but a superior specificity profile compared to iSPECT when evaluating seizure outcome at 1 and 2 years post-operatively. Improved sensitivity was obtained only when the RD and MD solutions were analyzed together.

Our present findings also provide support for our previous investigations that demonstrated greater sensitivity and specificity of 3D-ESI compared to PET or iSPECT using a RD plus MD solution [37,38]. Because SISCOM has been associated with higher rates of postoperative seizure freedom, it would be interesting in the future to compare 3D-ESI to SISCOM. However, SISCOM data were not available for this study [39-41]. The additive effects of combined RD and MD analysis are best explained by methodological differences between the solutions. A RD is the key dipole parameter that mathematically defines 'goodness-of-fit' from the square root of the summed differences between the measured EEG signal and forward fit of the dipole signal across electrodes. The RD has the advantage of maintaining the SNR of a fixed dipole solution as the 'rotating' vector provides accommodation for the spa-

tiotemporally dynamic nature of epileptiform spikes. In contrast, the MD best represents the temporal properties of a propagating epileptiform discharge.

Epilepsy is currently conceptualized as a system disorder subtended by large-scale networks [42-48]. To understand this theoretical framework, the seizure onset zone is considered the "hub" of brain regions responsible for seizure generation and propagation with "nodes" being remotely involved [49,50]. Therefore, while epileptic activity could involve abnormal neuronal activation in connected regions or by abnormal inter-regional interactions, seizure freedom is unlikely without removing the "hub". Nonetheless, the core relationships of extensive epileptogenic networks remain largely unknown. Whether network perturbations are capable of inducing independent nodal seizure onset is also unresolved and particularly important in TSC because of possible secondary activation of an independent pacemaker tuber. This secondary pacemaker tuber could act as a "false node" or "hidden hub" of the TSC complex epileptic network.

Our findings confirm that 3D-ESI improves seizure outcome if the resection plane followed the MD multi-touch trajectory instead of being limited to the results of RD analysis. Furthermore, when the MD solution was multi-touch and surgery was confined to the RD finding (one tuber), the surgical outcome was unfavorable. Therefore, the MD solution may help define multiple distributed epileptogenic networks in TSC by revealing the presence of multiple potentially epileptogenic tubers or an epileptogenic field that is more extensive and difficult to map. This facilitates "tuber node" excision and prevents the appearance of potential secondary pacemaker tubers ("false node" or "hidden hub") or the lack of consideration of a larger epileptic hub region that are an important potential causes of surgical failure.

We previously demonstrated the importance of MD solutions to map extensive epileptogenic fields in MRI negative patients [38]. Our current experience further supports the recognition of the MD as a marker of epileptic discharge propagation, and implies that MD solutions within the SRC represent stable sources [51]. We therefore hypothesize that the establishment of resection boundaries in cases of epilepsy due to wide and complex networks, as is often the case in patients with focal cortical dysplasia or TSC, should include a MD solution in addition to the RD solution. As the RD and MD solutions are complementary, their combined application increases the localizing power of 3D-ESI, particularly in MRI-negative surgical candidates [37, 38].

Only one retrospective clinical study examined the utility of ESI for source localization in 11 TSC patients (age range: 1-32 Years) [52]. The authors concluded that 3D-ESI was an important tool for the pre-surgical evaluation of TSC patients, complementary to the PET and SPECT results, and improved the management of candidates for surgery when integrated with electro-clinical information. However, unlike our study, high and low resolution EEG was analyzed and a distributed inverse model resulting from an averaging of the IEDs was employed.

We previously demonstrated high sensitivity and specificity of 3D-ESI using fewer than 32 electrodes in conjunction with strategically placed extra-electrodes [37,38,53].

Magnetoencephalography (MEG) and EEG-fMRI are other noninvasive tools that can help to delineate the epileptogenic zone in TSC patients. MEG has shown a comparable ability to identify the epileptogenic zone to the 3D-ESI and ictal-SPECT, but is cost-prohibitive for most centers [54-58]. The differences between the 3D-ESI and MEG were previously analyzed [38]. Only one study analyzed EEG-fMRI data during the pre-surgical evaluation of TSC patients, but the BOLD responses were typically limited to part of the lesion or extended beyond the tuber border [59].

Our study is subject to several limitations, including retrospective design and small study population. This study does not compare the 3D-ESI to the invasive investigations performed for the patients as we focused on the use of 3D-ESI modalities in the non-invasive evaluation and its impact on surgical outcome. Source localization analysis was performed on 3 typical spikes selected on the basis of visual inspection EEG data alone, without more sophisticated analysis. Averaging similar spikes may improve SNR, but should only be performed if voltage topography and spike evolution are utilized and remain similar when selecting the spikes [51]. Spikes were selected based on review of conventional EEG, not on review of the locally dense EEG (LD-EEG) or sub-temporal channels, which were used solely for 3D-ESI analysis. Simulated models with non-uniform sensors increased in the area of suspected dipole generation demonstrated no loss of accuracy [60]. Furthermore, direct comparison of a point-source dipole to an iSPECT may be better served by comparing to the centroid of the iSPECT. Challenges exist in the best definitions for specificity and sensitivity and these have previously been addressed [53,61]. Additionally, none of our temporal cases were multi-touch, suggesting a more restricted epileptic network, and therefore we could not compare temporal to extra-temporal lobe resection.

In conclusion, our limited sample size, short follow-up and reduced statistical power requires further investigation in a larger subject pool before drawing any definitive conclusions. However, while preliminary, our findings suggest the potential importance of 3D-ESI in the evaluation of children with TSC and medically refractory focal epilepsy. The increased accuracy in localization of 3D-ESI when single RD and MD models are analyzed together could reduce surgical failure and lead to a better understanding of epileptogenic networks underlying complex partial epilepsies including focal cortical dysplasia type 1 and TSC.

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