FULL-LENGTH ORIGINAL RESEARCH

The diagnostic utility of 3D electroencephalography source imaging in pediatric epilepsy surgery

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Summary

Objective: **The aim of this study was to investigate the utility of three-dimensional electroencephalography source imaging (3D-ESI) with low-resolution electroencephalographic data in the pediatric noninvasive presurgical evaluation, and to compare the findings with positron emission tomography (PET) and ictal single-photon emission computed tomography (iSPECT).**

Methods: **We retrospectively selected 60 patients from a database of 594 patients who underwent excisional surgery for drug-resistant epilepsy. Patients were <18 years at time of surgery, had at least one presurgical volumetric brain magnetic resonance imaging (MRI), and at least 1 year of outcome data. 3D-ESI was performed with NeuroScan software CURRY V.7.0. For each patient the surgical resection was planned utilizing 3D-ESI as an adjunctive tool to supplement MRI and electrocorticographic data. Our analyses addressed three critical variables: pathology (focal cortical dysplasia vs. other pathologies), imaging (MRI negative vs. positive cases), and surgery (temporal resection vs. extratemporal and multilobar resections). We also compared the localizing utility and surgical outcome of 3D-ESI findings with PET, iSPECT, and the colocalized surgical resection. Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 20.**

Results: **Mean age at surgery was 11.18 years (range 1–18 years). 3D-ESI showed a strong correlation with the surgical resection cavity (65.0%), particularly within the temporal lobe. 3D-ESI demonstrated better localization in MRI-negative cases (78.6%), which was not statistically significant. 3D-ESI also correlated with a superior surgical outcome profile compared to PET and iSPECT.**

Significance: **Our findings demonstrate that 3D-ESI data obtained with low-resolution electroencephalography achieves reasonably accurate noninvasive localization of epileptic spikes in pediatric focal epilepsy, especially in temporal lobe and MRI-negative cases, and is comparable to iSPECT and PET. Given its lesser expense and lack of radiation exposure, 3D-ESI is a useful and efficient tool for evaluating surgical candidacy in pediatric epilepsy surgery centers, particularly if PET and iSPECT are unavailable.**

KEY WORDS: **EEG, Electric source imaging, Focus localization, Temporal lobe epilepsy, Epilepsy surgery.**

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Three-dimensional electroencephalography source imaging (3D-ESI) is a computer-assisted mathematical technique to provide dipolar and distributed source modeling of coregistered electroencephalography (EEG) potentials and magnetic resonance imaging (MRI). Detailed overviews of the different source reconstruction methods are available.[1,2] 3D-ESI has been employed successfully to noninvasively localize the epileptogenic zone,[3–12] and is generally found

Key Points

- 3D-ESI analysis can contribute meaningful noninvasive localizing data in the presurgical evaluation of children with intractable focal epilepsy
- The localizing power of 3D-ESI in patients undergoing temporal resection was particularly significant and showed superiority compared to PET and iSPECT
- 3D-ESI was an attractive option in the MRI-negative population showing a superior localizing level compared to iSPECT or PET
- 3D-ESI demonstrated higher sensitivity and specificity compared to PET or iSPECT at 2 years' postoperatively
- 3D-ESI data are acquired at considerably less expense and with lower radiation exposure, so this technique may be especially valuable in resource-poor epilepsy surgery centers

to be complementary to magnetoencephalography. However, there are few comparisons to other presurgical evaluation modalities such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT), or studies of 3D-ESI in the pediatric population. Furthermore, most clinical 3D-ESI studies report <20 subjects, analyzed 3D-ESI with a high-resolution EEG technique that limits its widespread clinical utility, or did not correlate findings with surgical outcome.

We herein report our experience with 3D-ESI analysis in a large cohort of children undergoing surgical resection for intractable focal epilepsy. We had three goals: (1) to investigate whether 3D-ESI utilizing routine electrode placement could generate meaningful localizing information in the pediatric noninvasive presurgical evaluation (feasibility); (2) to establish whether 3D-ESI analysis of only three highly selected interictal spikes could identify the surgical cavity (localizing level), and (3) to correlate 3D-ESI with surgical outcome (efficacy level). We also compared the localization and efficacy of 3D-ESI to PET and ictal SPECT (iSPECT).

Methods

Patient population

We retrospectively selected 60 patients from a database of 594 patients undergoing excisional surgery for drug-resistant epilepsy at our institution from 2007 to 2013. Patients were included if they were 18 years or younger at the time of surgery, had at least one presurgical volumetric brain MRI, and at least 1 year of follow-up. Patients with prior surgery were excluded. Our presurgical evaluation protocol for MRI-negative patients has been published previously.[13] The database analysis was conducted in accordance with an institutional approved human subject protection protocol.

Our population was divided into three study cohorts: (1) focal cortical dysplasia (FCD) versus other pathologies, (2) MRI-negative versus MRI-positive cases, and (3) temporal lobe versus extratemporal and multilobar resection. Cases with FCD had a confirmed tissue diagnosis according to the recent International League Against Epilepsy (ILAE) classification or a confirmed radiologic diagnosis.[14,15] The "other pathology" group was confirmed by tissue histopathologic diagnoses.

EEG and MRI acquisition

EEG data were recorded using a 32-channel digital XLTEK system (Neuroworks Ver. 7.1.1) containing 19 channels and a sampling frequency of 512 Hz. Electrodes were placed according to the standard 10–20 system. Based on review of the seizure semiology, interictal discharges identified on prior studies, and MRI findings, an additional 4–10 electrodes were applied over the suspected epileptogenic region in each patient to increase localizing accuracy during ESI analysis. Multi-planar MRI sequences, including volumetric axial T1 sequences, were obtained on a Signa Horizon LX 3 Tesla MRI scanner (GE Healthcare, Little Chalfont, United Kingdom).

3D-ESI analysis

ESI for each patient was performed with NeuroScan software CURRY V.7.0 using scalp EEG data and volumetric axial T1 images. Representative interictal spikes were selected by experienced epileptologists (AR, IM) by review of EEG in standard bipolar and referential montages from the 10–20 system. Discharges that were bilaterally synchronous were not selected for analysis. After the interictal activity was confirmed to be typical for the patient and recorded in artifact-free periods, three spikes or sharp waves analyzed in the CURRY software were selected without preference from the results of any computerized preprocessing for analysis. For each patient, volumetric axial T_1 MRI sequences were used to construct realistic subject-dependent head models and a Boundary Element Model (BEM) consisting of skin, skull, and brain tissue compartments.

3D-ESI analysis was calculated from the onset of the spike or sharp wave to the highest amplitude or peak.[2] For purposes of analysis, this time interval was further subdivided into three segments: (1) initial phase of deviation, (2) midpoint of the negative phase, and (3) peak. In the presurgical evaluation, moving dipoles as well as Independent Component Analysis were used to evaluate for propagation that would not be apparent on visual analysis of the waveform and to evaluate the validity of the single dipole model versus multiple independent sources. A single rotating dipole (RD) model was constructed for each spike or sharp wave. Only the single rotating dipole was used in this analysis (Fig. 1).

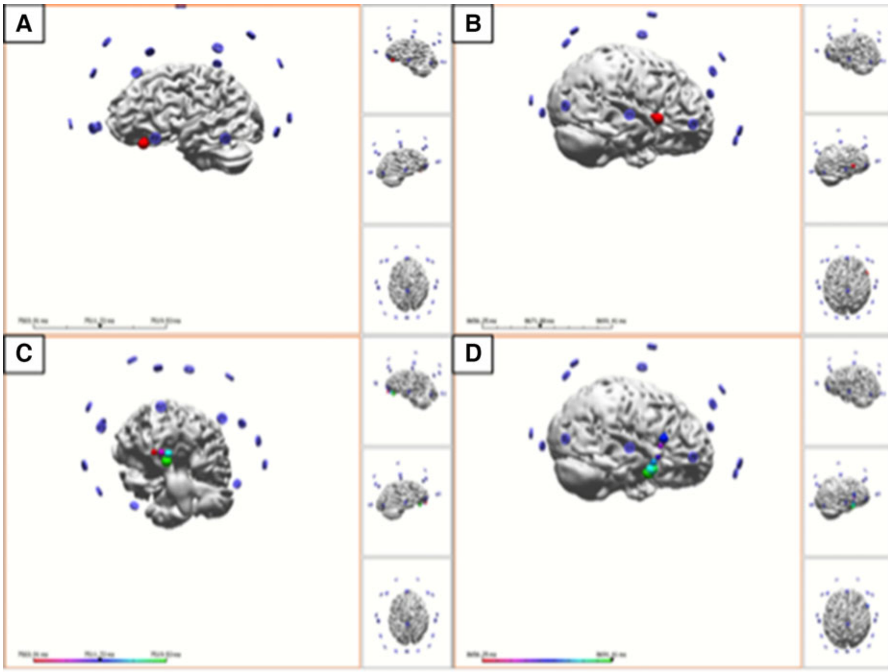

Figure 1.
Three-dimensional electroencephalography source imaging. 3D-ESI of single spikes using a rotating dipole model (**A** and **B**) reveals two possible sources in the inferior deep frontal region that is difficult to lateralize. A moving dipole model (**C** and **D**) helps differentiate interhemispheric propagation of a single source from potentially bilateral independent sources.

Comparison of 3D-ESI to surgical resection

Surgical resection was planned individually utilizing 3D-ESI as an adjunctive tool in the presurgical evaluation that included ictal semiology, EEG, MRI, PET, and iSPECT data.

Two experienced epileptologists (AR, PJ) visually determined whether the rotating dipole model solution localized within the surgical resection cavity (SRC) (Fig. 2). As three spikes or sharp waves were evaluated for each patient, the rate of SRC concordance in each model was calculated as 0%, 33%, 66%, or 100%. RD findings were considered localizing if they achieved 66% or 100% concordance, and nonlocalizing for 0% or 33% concordance. If the two primary reviewer's assessments disagreed, a third reviewer (AH) reviewed the images and a final determination was based on agreement between the third reviewer and one of the primary reviewers.

PET and ictal SPECT data

PET scans were performed after intravenous injection of 4.9 mCi of F-18 fluorodeoxyglucose in patients with normoglycemia. Ictal SPECT imaging was performed following administration of 14.2 mCi of 99mTc-hexamethylpropylene amine oxime at the onset of a typical seizure, verified by review of simultaneous video-EEG recording. All injections were performed within 30 s of electrographic seizure onset, and the SPECT images were acquired within 4 h of radiotracer injection.[16] Subtraction of ictal SPECT coregistered to MRI (SISCOM) data was not utilized in our analysis, as it was not frequently performed.

Comparison of PET and ictal SPECT imaging to surgical resection

Neuroradiologists blinded to the clinical histories interpreted all PET and ictal SPECT scans. Images were independently reevaluated by two reviewers (AR and PJ), and each scan was categorized as localizing if the functional abnormalities identified on PET or ictal SPECT were resected completely (Fig. 3). PET and SPECT functional abnormalities that were outside the SRC or demonstrated multifocal functional abnormalities were considered nonlocalizing.

Surgical procedure and outcome

For each patient, the surgical resection was planned utilizing 3D-ESI only as an adjunctive tool in the presurgical evaluation, which was based primarily on MRI and electrocorticographic data.

Surgical resections were categorized as temporal, extratemporal, or multilobar. Postoperative seizure outcomes at 1 year and 2 years were obtained via clinical assessment or telephone interview. Surgical outcome was classified according to Engel's classification criteria: (I) completely seizure free, auras only or only atypical early postoperative seizures, (II) 90% seizure reduction or nocturnal seizures only, (III) 50% seizure reduction, and (IV) <50% seizure reduction. Seizure outcomes were classified as favorable (Engel I and II groups) or unfavorable (Engel III and IV groups).

We also analyzed the sensitivity and specificity of 3D-ESI, PET, and iSPECT studies.

Sensitivity was defined as the ratio of patients with source localization within the SRC and favorable

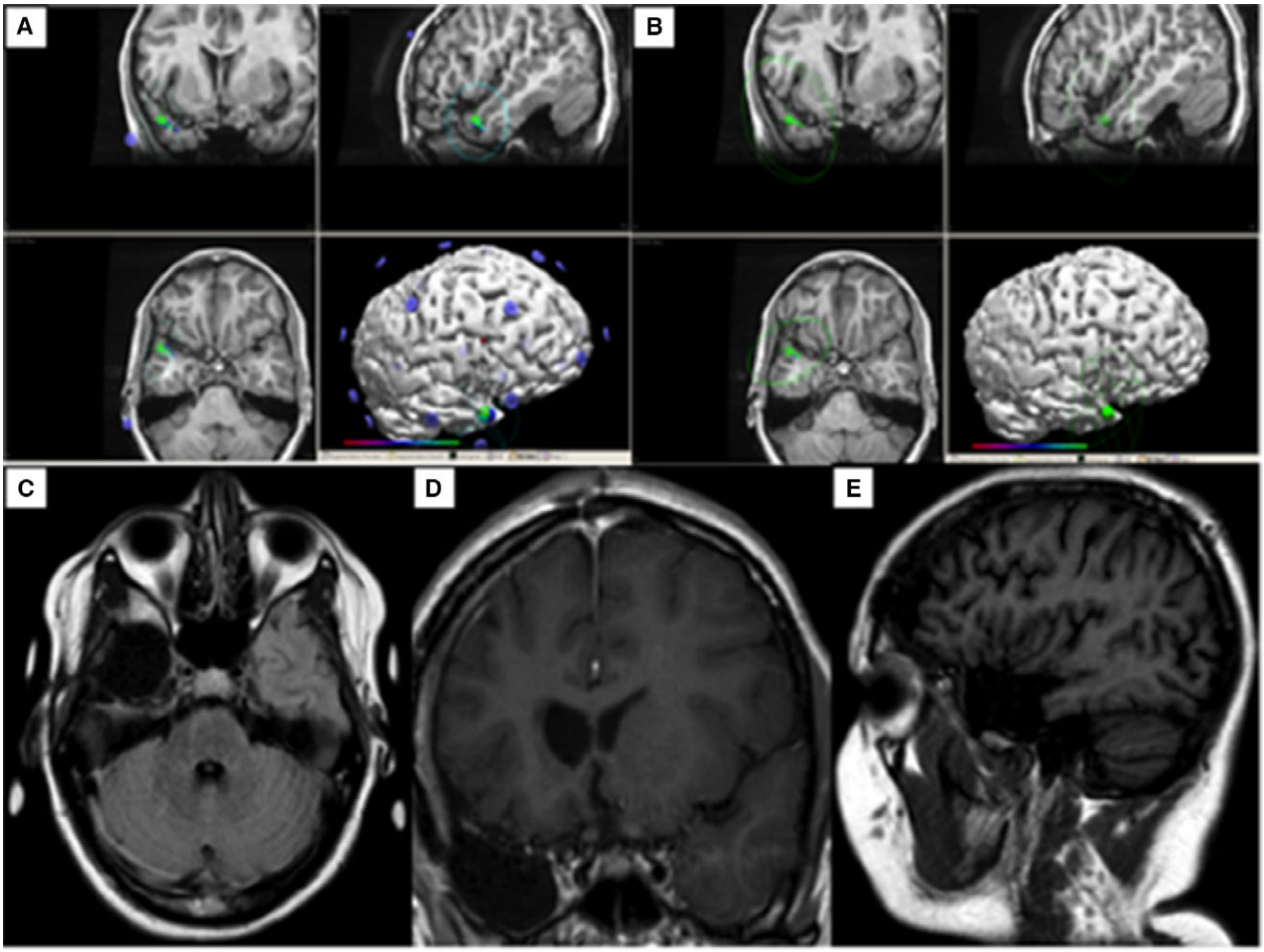

Figure 2.
Comparison of 3D-ESI to surgical resection. 3D-ESI sources using the rotating dipole (**A**) model and moving dipole model (**B**) were both localized within the surgical resection cavity (**C**–**E**).
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outcome to all patients with favorable outcome after surgery.

Specificity was defined as the ratio of patients with source localization outside the SRC and poor outcome to all patients with an unfavorable outcome after surgery.

Statistical methods

The dependent variable was defined as 3D-ESI co-localization of the seizure-onset zone. Analysis of variance was used to determine significant predictors of 3D-ESI as a continuous variable, defined by concordance with the resection cavity. Statistical assumptions for analysis of variance (ANOVA) were evaluated (i.e., normality, homogeneity of variance) with no violations found. Finally, sensitivity and specificity characteristics were calculated for Rotating Dipole, PET, and iSPECT relative to surgical outcomes at 1- and 2-year intervals. Dipole localization was collapsed into a dichotomous variable to calculate receiver-operating characteristics. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 20.

Results

Patients

Sixty patients who underwent surgical resection for intractable focal epilepsy met inclusion criteria. All underwent video-EEG monitoring, brain MRI, and 3D-ESI analysis, whereas 36 also had PET and 25 had ictal SPECT scans. Fourteen patients had a normal brain MRI. Forty patients had an FCD, whereas 20 patients had other pathologies including tuberous sclerosis (7), tumor (5), encephalomalacia (3), infection (2), hemangioma (1), Rasmussen's syndrome (1), and gliosis (1). No patient had prior excisional surgery. Mean age at surgery was 11.18 years (range 1–18 years).

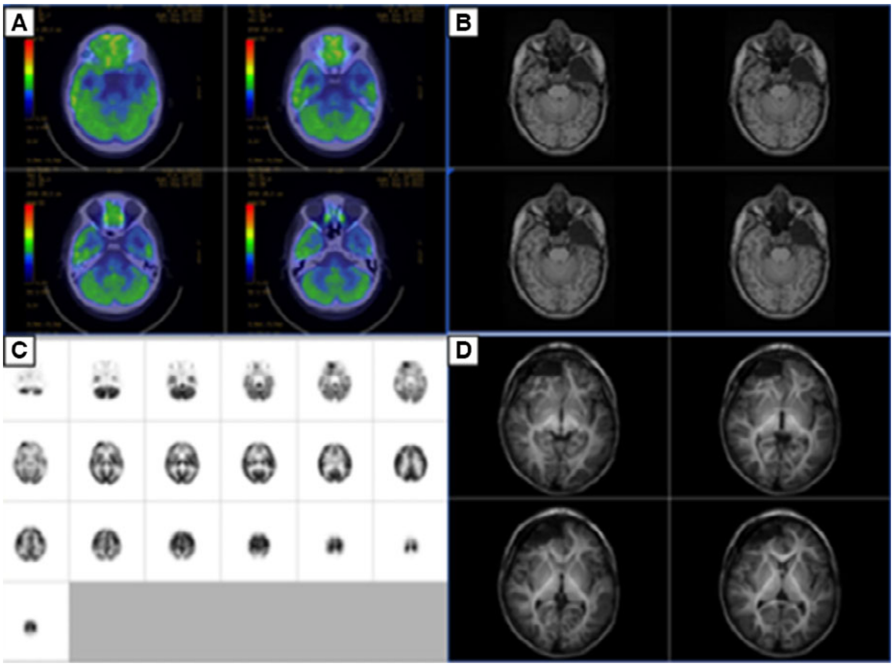

Figure 3.
Comparison of PET and iSPECT to surgical resection. Each PET scan (**A**) and iSPECT study (**C**) was categorized as localizing if the functional abnormalities identified were resected completely (**B** and **D**).
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3D-ESI analysis and the surgical cavity

Table 1 gives the results for analyzed variables. 3D-ESI analyses were considered localized to the SRC in 65% of all patients, whereas 35% were considered nonlocalized to the SRC. Among different resection types, localization to the SRC was more frequently achieved in patients undergoing temporal lobe resection compared to either extratemporal ($p = 0.004$) or extratemporal combined with multilobar resection ($p = 0.01$). 3D-ESI more frequently localized to the SRC in MRI-negative (78.6%) compared to MRI-positive cases (60.9%), but this difference did not achieve statistical significance. There were no differences in 3D-ESI localization to SRC between FCD (67.5%) and other pathologies (60.0%), or between FCD type I (63.1%) and type II (71.4%).

Localization to the SRC between 3D-ESI, PET, and iSPECT

Table 2 summarizes the overall findings obtained with 3D-ESI, PET, and iSPECT analysis. Thirty-six patients (60%) had at least one presurgical interictal PET study, and 25 patients (40%) underwent at least one iSPECT. Of these, 12 patients underwent both PET and iSPECT, 24 had only PET, and 13 had only iSPECT. Strong concordance between ictal semiology, EEG, and MRI findings obviated the need for functional neuroimaging in an additional 11 cases.

3D-ESI localized to the SRC in 65% of patients, comparable to iSPECT (68%) and superior to PET (55.5%), although this difference did not achieve statistical significance. Similar findings were noted when we compared the three techniques to patients with FCD versus other pathologies.

3D-ESI localized to the SRC more frequently than PET and iSPECT in patients undergoing temporal lobe resection, but this small subgroup did not reach statistical significance.

We also found that 3D-ESI showed a superior localization in MRI-negative patients compared to PET or iSPECT. By comparison, iSPECT demonstrated slightly better findings in MRI-positive cases compared to the other two techniques, but neither of these findings was statistically significant.

3D-ESI, PET, and iSPECT and surgical outcome

Table 3 summarizes the sensitivity and specificity values for 3D-ESI, PET, and iSPECT with regard to surgical outcome. 3D-ESI showed a sensitivity of 65.9% at 1-year postoperatively and 60.6% at 2 years, and a specificity of 36.8% at 1 year and 50.0% at 2 years. PET demonstrated a lower sensitivity but higher specificity at 1 and 2 years compared to 3D-ESI, whereas the reverse was true with iSPECT, which had a higher sensitivity but lower specificity at 1 and 2 years compared to 3D-ESI.

Discussion

The findings of our retrospective study demonstrate that 3D-ESI analysis may contribute meaningful noninvasive localizing data in the presurgical evaluation of children with intractable focal epilepsy. 3D-ESI enhanced scalp EEG data with only a small number of extra electrodes in the suspected epileptogenic zone and analysis of three interictal spikes. We found that 65% of the patients who underwent 3D-ESI using this EEG model evidenced a clearly localized

Table 1. Relation of 3D-ESI analysis with the surgical cavity (localizing level)

	3D-ESI localizing	3D-ESI nonlocalizing	p-Value
Overall population (n = 60)	n = 39 65.0%	n = 21 35.0%	
Pathology			
FCD (n = 40) 66.7%	n = 27 67.5%	n = 13 32.5%	
Other pathologies (n = 20) 33.3%	n = 12 60.0%	n = 8 40.0%	
Type of surgery			
Temporal (n = 13) 21.7%	n = 11 84.6%	n = 2 15.4%	0.004[a] 0.01[b]
Extratemporal (n = 25) 41.7%	n = 12 48.0%	n = 13 52.0%	
Multilobar (n = 22) 36.6%	n = 15 68.2%	n = 7 31.8%	
MRI			
Positive (n = 46) 76.7%	n = 28 60.9%	n = 18 39.1%	
Negative (n = 14) 23.3%	n = 11 78.6%	n = 3 21.4%	

FCD, focal cortical dysplasia; 3D-ESI localizing, 3D electroencephalography source imaging with SRC concordance from 66% to 100%; 3D-ESI nonlocalizing, 3D electroencephalography source imaging with SRC concordance from 0% to 33%; n, number of the patients.

[a]p-Value obtained by comparison temporal resection versus extratemporal resection.

[b]p-Value obtained by comparison temporal resection versus extratemporal combined with multilobar resection.

Table 2. Relation of PET and iSPECT analysis with the surgical cavity (localizing level)

	PET loc.	PET non-loc.
Population with PET (n = 36)	n = 20 55.0%	n = 16 45.0%
Pathology		
FCD (n = 29) 80.6%	n = 15 51.7%	n = 14 48.3%
Other pathologies (n = 7) 19.4%	n = 5 71.4%	n = 2 28.6%
Type of surgery		
Temporal (n = 8) 22.2%	n = 4 50.0%	n = 4 50.0%
Extratemporal (n = 15) 41.7%	n = 6 40.0%	n = 9 60.0%
Multilobar (n = 13) 36.1%	n = 10 76.9%	n = 3 23.1%
MRI		
Positive (n = 26) 72.2%	n = 15 57.7%	n = 11 42.3%
Negative (n = 10) 27.8%	n = 5 50.0%	n = 5 50.0%
	iSPECT loc.	**iSPECT non-loc.**
Population with iSPECT (n = 25)	n = 17 68.0%	n = 8 32.0%
Pathology		
FCD (n = 19) 76.0%	n = 13 68.4%	n = 6 31.6%
Other pathologies (n = 6) 24.0%	n = 4 66.7%	n = 2 33.3%
Type of surgery		
Temporal (n = 3) 12.0%	n = 2 66.7%	n = 1 33.3%
Extratemporal (n = 11) 44.0%	n = 6 54.5%	n = 5 55.5%
Multilobar (n = 11) 44.0%	n = 9 81.8%	n = 2 18.2%
MRI		
Positive (n = 16) 64.0%	n = 12 75.0%	n = 4 25.5%
Negative (n = 9) 36.0%	n = 5 55.6%	n = 4 54.4%

FCD, focal cortical dysplasia; loc., localizing; non-loc., nonlocalizing; n, number of patients.

source dipole (rotating dipole) that was located directly within the surgical cavity.

Previous 3D-ESI studies have been performed in adults utilizing high-resolution EEG. One of the few pediatric studies examined 3D-ESI accuracy in interictal EEG recordings with 19–29 scalp electrodes but employed a distributed inverse model (depth-weighted minimum norm, MN).[7] Although the authors reported a localizing value of 90%, their methodology differed from ours in several ways: only subjects with a favorable outcome were selected, the study was not blinded, no postoperative MRI data were consistently available, the epileptogenic region was mapped from surgical notes, and 3D-ESI accuracy was determined by the degree of overlap (arbitrary 50% minimum) between the resection and a statistically deconstructed depth-weighted MN map, which the authors defined as the region of "discharge onset."

Our findings revealed a localizing sensitivity of 3D-ESI that was superior to PET (55.5%), and comparable to iSPECT (68.0%). This supports the findings of our previous study reporting a favorable localizing level of iSPECT in the pediatric mild malformation of cortical development (mMCD)/FCD population.[15] Because SISCOM has been associated with higher rates of postoperative seizure freedom,[17–19] it would be interesting in the future to compare 3D-ESI to SISCOM. However, SISCOM data were not available for this study. In comparison, previous PET studies (conducted mainly in nonoperated adults) demonstrated 43–68% localization of the anatomic location of a structural lesion over MRI data.[20–22]

The localizing power of 3D-ESI in patients undergoing temporal resection was particularly significant. 3D-ESI in temporal lobe patients showed superior localizing power compared to PET and iSPECT. Although our sample size is too small to obtain statistical significance, the finding is nonetheless intriguing. Previous 3D-ESI studies in patients with temporal lobe seizures have only indirectly addressed its reliability and validity.[2,6] Utilizing high-density EEG arrays (128–256 channels) and volumetric brain MRI, Brodbeck et al.[3] found that 3D-ESI was more localizing in

Table 3. 3D-ESI, PET, and iSPECT and surgical outcome

FU1	Sensitivity (%)	Specificity (%)	FU2	Sensitivity (%)	Specificity (%)
3D-ESI (n = 60)	65.9	36.8	3D-ESI (n = 49)	60.6	50.0
PET (n = 36)	58.3	50.0	PET (n = 29)	55.0	55.0
iSPECT (n = 25)	66.7	28.6	iSPECT (n = 23)	64.3	33.3

FU1, 1 year after the surgery; FU2, 2 years after the surgery; n, number of patients.

temporal foci than PET or SPECT were. These results underscore a potentially important and specific role of 3D-ESI in pediatric patients with intractable temporal lobe epilepsy.

We found no comparative studies investigating 3D-ESI in MRI-negative and MRI-positive cases. Our localizing level of 3D-ESI in MRI-negative subjects (78.0%) compared to MRI-positive cases (60.9%), makes 3D-ESI an attractive option in the MRI-negative population, as 3D-ESI showed a superior localizing level compared to iSPECT or PET. A recent study confirmed the same high localizing level (80%) of 3D-ESI in 10 MRI-negative adults but the authors used a linear distributed inverse solution (LAURA - local autoregressive average) for their source estimation.[4]

The superiority of 3D-ESI in MRI-negative cases is not unexpected, as the occurrence of a lesion often guides the resection and functional abnormalities are deemed "less" reliable. It is well known that structural lesions may be falsely localizing, although the presence of a lesion often correlates with surgical success.[15,23,24] Because MRI-negative patients are challenging surgically,[23–27] the added power of a supportive localizing methodology is a welcome addition.

Our study demonstrated a higher sensitivity and specificity of 3D-ESI findings compared to PET or iSPECT at 2 years postoperatively. These findings are similar to those of a previous study in adults with temporal lobe epilepsy (mean age at surgery, 26.8 years) utilizing a different linear distributed inverse solution (local autoregressive average [LAURA]) and high-resolution EEG.[3]

This retrospective study is subject to several limitations. Until recently, 32 electrodes was considered the minimum to study scalp topography and source localization in sufficient detail.[5] More recent studies suggest that at least 64 electrodes should be used and that evenly spaced electrodes at 64 or 128 improve spike detection and localization.[1–6] The data presented are based on our practice since 2007 of locally increased electrodes at areas of interest. To avoid bias in spike identification, review of EEG is only performed with standard electrodes of the 10–20 system. Limited additional electrodes are used only for 3D-ESI analysis, and additional electrodes in uninvolved areas would likely contribute additional noise than signal. Simulated dipoles have been tested with nonuniform sensors increased in the area of suspected dipole generation and demonstrated no loss of accuracy.[28] In addition, high-density electrode numbers typically involve the use of electrode caps that we do not use in our practice for prolonged monitoring. Furthermore, because bilateral synchronous discharges were not included in analysis, no statement can be made about additional localizing ability in this scenario.

In conclusion, we have shown that 3D-ESI may play an important role in the noninvasive presurgical evaluation of pediatric patients with intractable focal epilepsy using only low-resolution EEG and three interictal sharp waves or spikes. 3D-ESI has at least a comparable localizing level and a better efficacy level profile than iSPECT and PET. Furthermore, 3D-ESI was particularly localizing in patients with temporal lobe epilepsy and in MRI-negative patients. Because 3D-ESI data is acquired without radiation exposure and at considerably less expense, especially when considering freely-available open source software, this methodology is attractive at pediatric epilepsy surgery centers and may be especially valuable in resource-poor epilepsy surgery centers that lack PET or iSPECT.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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