FULL-LENGTH ORIGINAL RESEARCH

The diagnostic utility of 3D-ESI rotating and moving dipole methodology in the pre-surgical evaluation of MRI-negative childhood epilepsy due to focal cortical dysplasia

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Summary

Objective: This study investigates whether a combined rotating dipole (RD) and moving dipole (MD) solution enhances three-dimensional electroencephalography (EEG) source imaging (3D-ESI) localization in magnetic resonance imaging (MRI)–negative pediatric patients with focal cortical dysplasia (FCD).

Methods: We retrospectively selected 14 MRI-negative patients with FCD from a cohort of 60 pediatric patients previously used to evaluate the diagnostic utility of 3D-ESI in epilepsy surgery. Patients were younger than 18 years at time of surgery and had at least 1 year of outcome data. RD and MD models were constructed for each interictal spike or sharp wave, and it was determined whether each inverse algorithm localized within the surgical resection cavity (SRC). We also compared the 3D-ESI findings and surgical outcome with positron emission tomography (PET) and ictal single photon emission computed tomography (iSPECT).

Results: RD analyses revealed a high concordance with the SRC (78.6%), particularly for temporal lobe resection (100.0%), and showed superior localization compared to PET and iSPECT, with the highest correlation in FCD type I and temporal lobe resection. Furthermore, the RD method was superior to iSPECT in FCD type II cases and to PET in extratemporal resections. RD and MD results were comparable, but in 18.2% of patients with FCD type I with localizing RDs, the MD solution was only partially within the SRC; in all of these patients 3D-ESI also correlated with superior surgical outcome compared to PET and iSPECT, especially when RD and MD solutions were analyzed together.

Significance: 3D-ESI in MRI-negative cases showed superior localization compared to iSPECT or PET, especially in FCD type I and temporal lobe epilepsy, and correlated with superior surgical outcome compared to iSPECT and PET at 1 year and 2 years postoperatively, especially when RD and MD solutions were analyzed together. These findings suggest that 3D-ESI based on a combined RD-MD solution improves surgical accuracy in MRI-negative patients with FCD.

KEY WORDS: Source localization, Epilepsy surgery, MRI-negative, Focal cortical dysplasia.

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Key Points

- 3D-ESI is an important tool in the noninvasive presurgical evaluation of MRI-negative patients with FCD
- Combining 3D-ESI RD and MD dipolar solutions provides localizing information in MRI-negative patients with FCD
- This combined approach is superior for seizure-focus localization compared to PET or iSPECT
- Analysis of combined RD and MD solutions helps to define dysplastic epileptogenic networks

Focal cortical dysplasia (FCD) is the most common substrate in children with medically refractory focal epilepsy undergoing excisional surgery and often occurs in the absence of a visible lesion on magnetic resonance imaging (MRI).[1–6] The presurgical evaluation of this cohort is therefore particularly challenging and associated with high rates of surgical failure.[7–11] This subgroup is therefore often excluded from surgical consideration. A preoperative evaluation mandates a comprehensive approach that typically includes systematic analyses of all available clinical, electrophysiologic, anatomic, and functional imaging data.[12]

Three dimensional (3D) electroencephalography (EEG) source imaging (3D-ESI) is a recently described tool to localize the seizure-onset zone in focal epilepsy.[13–22] Although 3D-ESI has been used to successfully identify the epileptic focus in adult patients,[21] experience in children is more limited.[23] The ability of 3D-ESI to provide localizing information in MRI-negative patients has obvious implications for surgical candidacy in children with MRI-negative FCD.

To evaluate the utility of 3D-ESI in pediatric magnetic resonance imaging (MRI)–negative patients, we analyzed 14 MRI-negative patients with FCD selected from a cohort of 60 pediatric subjects previously studied to assess the role of 3D-ESI in pediatric focal epilepsy surgery.[24] We now report a more specific sub-group analysis restricted to MRI-negative patients. Our study had the following two objectives: (1) to assess the localizing ability of 3D-ESI in the absence of a structural lesion, and (2) to evaluate whether a combined analysis of moving dipole (MD) and rotating dipole (RD) enhances the accuracy of 3D-ESI localization in this specific patient subgroup.

Methods

Patient population

We retrospectively selected 14 MRI-negative patients with FCD from a published cohort of 60 pediatric patients at our institution who underwent excisional surgery for drug-resistant epilepsy between 2007 and 2013.[24]

Inclusion criteria were the following: (1) 18 years or younger at time of surgery, (2) pre-surgical negative volumetric brain MRI, (3) brain MRI 6 months after surgical resection, (4) tissue diagnosis of FCD according to the International League Against Epilepsy (ILAE) classification,[25] and (5) at least 1 year of surgical follow-up. Patients with prior surgery were excluded. Our pre-operative protocol for MRI-negative patients has been reported previously.[26]

Our analyses focused on the following two variables: pathology (FCD type I vs. FCD type II), and surgical localization (temporal vs. extratemporal and multilobar resection). Multilobar cases were characterized by continuous areas and not by separated epileptogenic foci.

Database analysis was conducted in accordance with an institutionally approved human subjects protection protocol.

EEG and MRI acquisition

EEG data were recorded using a 32-channel digital XLTEK system (Neuroworks Ver.7.1.1) containing 19 channels, placed according to 10–20 system, and a sampling frequency of 512 Hz. To increase localizing signal for 3D-ESI analysis, we applied an additional 4–10 electrodes over the suspected epileptogenic region on the basis of seizure semiology and interictal discharges examined on prior EEG. Volumetric axial T1 sequences were obtained on a Signal Horizon LX 3 Tesla MRI scanner.

3D-ESI analysis

3D-ESI analysis was performed with NeuroScan software CURRY V.7.0 using scalp EEG data and volumetric axial T1 images. A volumetric axial T1 MRI sequence was used to construct realistic subject-dependent Boundary Element Model (BEM) for each subject. The BEM segmentation was performed automatically in the CURRY software and was used for each dipole analysis. Electrode positions were determined by idealized label-matching within the CURRY software.

Experienced epileptologists (AR, IM) selected three interictal spikes or sharp waves for each patient that were believed to be typical by review of the EEG in standard bipolar and referential montages during artifact-free periods. The three spikes or sharp waves were selected for dipolar analysis without computerized preprocessing.

3D-ESI findings were calculated from the onset of the discharge to the peak of negative phase.[27] The bandwidth for analysis was from 1 to 30 Hz. RD and MD models were constructed for each spike or sharp wave to maximize the signal-to-noise ratio and account for propagation effects (Fig. 1). For the RD, the position of the dipole is maintained fixed over the time window analyzed, whereas the vector is allowed to rotate in space as a function of time throughout this window. For the MD solution, the positions, orientations, and strengths of the dipole are calculated

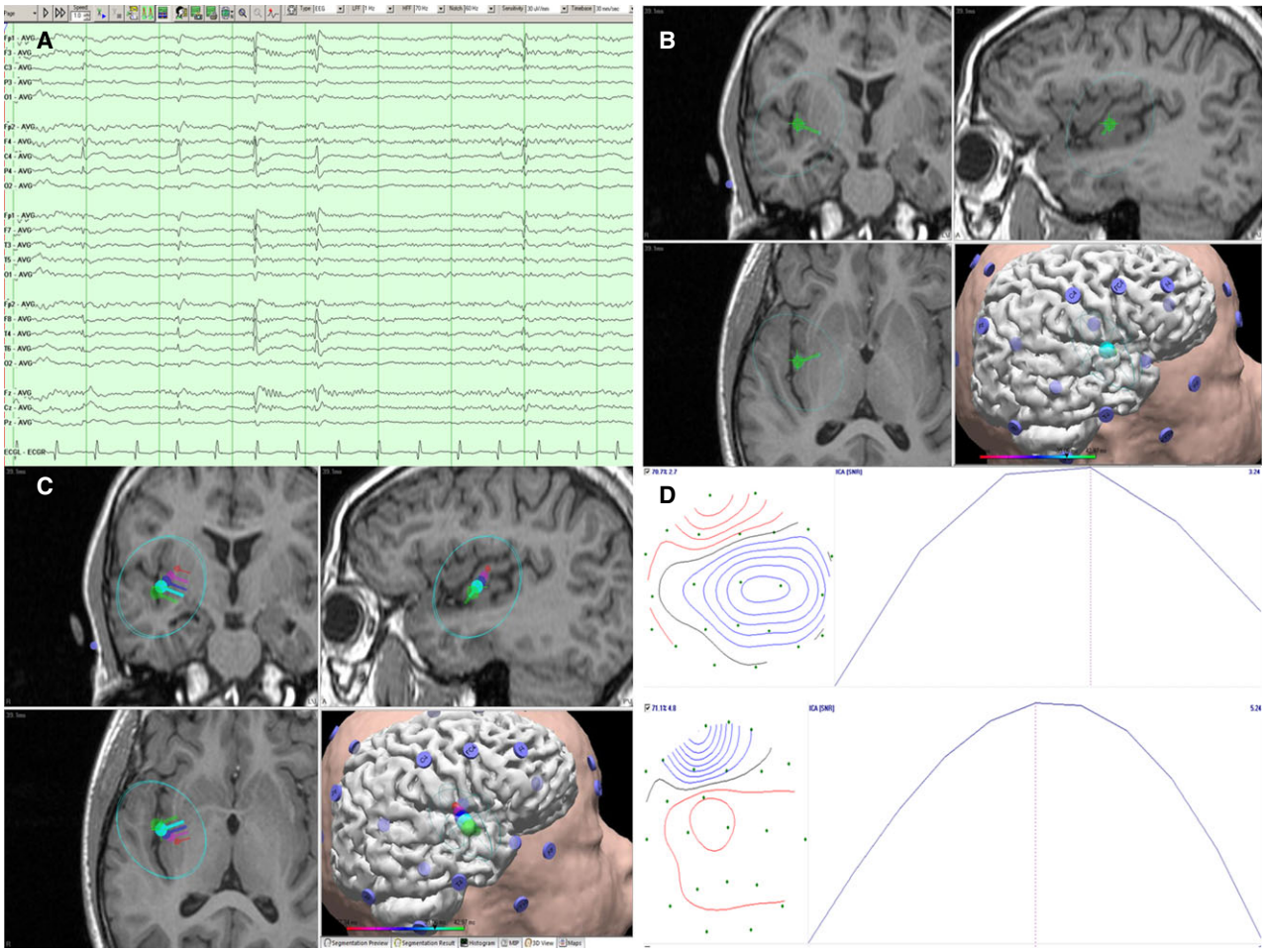

Figure 1.
Electroencephalography source imaging. 3D-ESI of single spikes (**A**) using a rotating dipole (RD) (**B**) moving dipole (MD) (**C**) models reveals one possible source in the right insula. MD and independent component analysis (**D**) were used to evaluate for propagation and to evaluate the validity of the single dipole model.
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independently for every time point analyzed, thereby resulting in a trace of dipoles. MD and independent component analysis (ICA) were used to evaluate for propagation and to evaluate the validity of the single dipole model (Fig. 1). Single RD and MD models were selected for each interictal epoch, and both were used in this analysis.

Comparison of 3-D ESI to surgical resection

Two experienced epileptologists (AR, PJ) visually determined whether RD and MD dipole models localized within the surgical resection cavity (SRC) (Fig. 2). Because three spike or sharp waves were evaluated for each patient, the rate of SRC concordance of RD was calculated as 0%, 33%, 66%, or 100%, and the findings were considered localizing if they achieved 66% or 100% concordance or nonlocalizing for 0% or 33% concordance.

MD findings were considered "inside" if the solution localized completely within the surgical resection planes, "partially inside" when the solution was partially resected, and "outside" when the entire solution did not overlap the resected cavity.

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

Positron emission tomography (PET) scans were performed after intravenous injection of 4.9 mCi of F-18 fluorodeoxyglucose (FDG) in patients with normoglycemia. Ictal single photon emission computed tomography (iSPECT) imaging was performed with administration of 14.2 mCi of 99mTc-hexamethylpropyleneamine oxime (HMPAO) within 30 s of electrographic seizure onset. iSPECT images were acquired within 4 h of radiotracer injection.[28]

Subtraction of ictal SPECT co-registered to MRI (SISCOM) data were not utilized in our analysis, as it was not frequently performed.

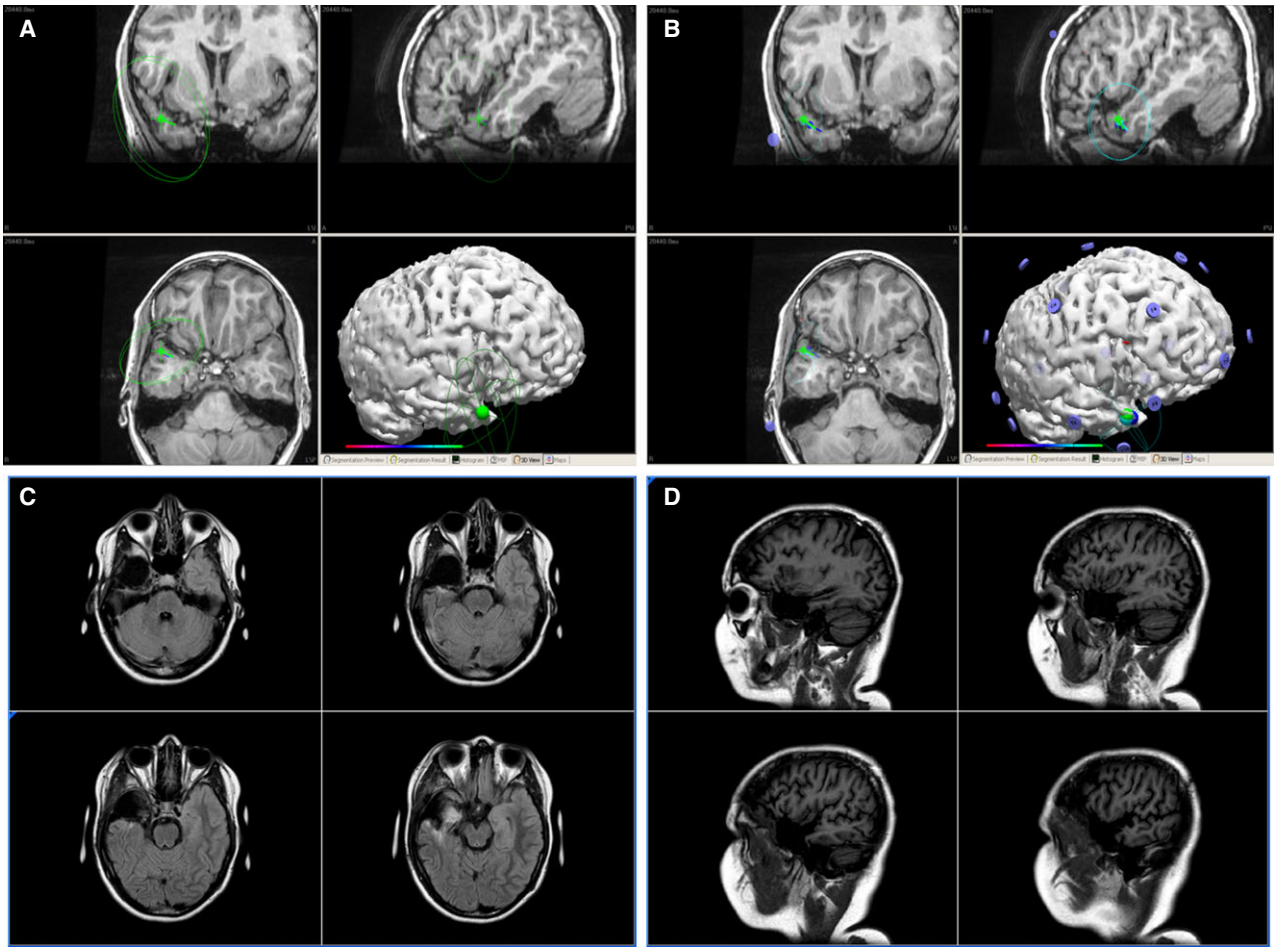

Figure 2.
Comparison of 3-D ESI to surgical resection. 3D-ESI sources using the rotating dipole (RD) (**A**) and moving dipole (MD) (**B**) models were both localized within the surgical resection cavity (**C**, **D**).
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Comparison of PET and iSPECT imaging to surgical resection

Neuroradiologists blinded to the clinical histories interpreted all PET and iSPECT scans and the images were independently reevaluated by two reviewers (AR and PJ).

Each scan was classified as localizing if the functional abnormalities were resected completely. PET and SPECT scans that demonstrated either abnormalities outside the SRC or multifocal functional abnormalities were considered nonlocalizing.

Surgical procedure and outcome

Surgical resection was based primarily on MRI and EEG data with 3D-ESI, PET, and SPECT employed as adjunctive tools.

Surgical resections were categorized as temporal, extratemporal, or multilobar. Surgical outcome data obtained via direct clinical assessment or telephone interview and were classified according to Engel's classification criteria at 1 and 2 years after surgery.

We calculated the sensitivity and specificity of 3D-ESI, PET, and iSPECT findings. We defined sensitivity as the percentage of patients with focus localization within the SRC in patients with Engel class I or II outcomes among all patients with favorable outcomes. We defined specificity as the percentage of patients with focus localization outside the resected zone in patients with Engel class III or IV outcome among all patients with unfavorable outcomes.

Results

Patients

Fourteen patients (10 female, four male) met study criteria. Mean age at surgery was 12.35 years (range 5–18 years). All patients had video-EEG monitoring and brain MRI. Ten patients had PET scans and nine underwent ictal SPECT. There were two temporal (14.2%), six extratemporal (43.9%), and six multilobar (43.9%) resections. Nine patients (64.3%) had FCD type I and five (35.7%) had FCD type II.

3D-ESI, PET, and iSPECT findings in relation to the resection cavity

Table 1 summarize the RD and MD findings of 3D-ESI analyses as well as PET and iSPECT findings. RD analyses were highly correlated with SRC (78.6%), the highest correlation being achieved in patients undergoing temporal lobe resection (100.0%) compared to either extratemporal (66.7%) or multilobar resection (83.3%). There were no differences in RD localization between FCD type I (77.7%) or type II (80.0%).

Ten patients (71.4%) had at least one pre-surgical interictal PET study, and nine patients (64.3%) underwent at least one iSPECT. Five patients underwent both PET and iSPECT.

Although our study population is small, potentially making conclusions from statistical analysis less robust, the RD method was more localizing (78.6%) than iSPECT (55.6%) or PET (50.0%). The greatest differences were found with FCD type I and temporal lobe resection.

The RD method also revealed superior localization compared to iSPECT in FCD type II cases and to PET in extratemporal resections.

3D-ESI and surgical outcome

Table 2 summarizes the relationships between 3D-ESI, histopathology, resection area, and surgical outcome at 1 and 2 years.

When the RD solution was nonlocalizing, the MD solution was always located outside the resection margins; Among patients with a localizing RD solution, 81.8% evidenced an MD classified as inside the surgical cavity. The remaining 18.2% evidenced a MD solution that was only partially inside. This group uniformly evidenced FCD type I on tissue histopathology.

Comparative sensitivity and specificity of different localizing tests

Table 3 presents the respective sensitivity and specificity of 3D-ESI, PET, and iSPECT for surgical outcome. 3D-ESI showed superior sensitivity and specificity compared to PET and iSPECT at both 1 year and 2 years postoperatively, especially with combined RD and MD models. RD modeling had a sensitivity of 63.6% at 1 year postoperative and 62.5% at 2 years, and a specificity value of 100% at 1 year and 75.0% at 2 years. The combined MD and RD solution increased 3D-ESI sensitivity to 77.7% at 1 year and 2 years postoperatively.

Discussion

The results of this study confirm that 3D-ESI is an important tool in the noninvasive presurgical evaluation of MRI-negative children with FCD. 3D-ESI was superior to iSPECT or PET and showed an enhanced sensitivity and specificity profile compared to iSPECT and PET at 1 year and 2 years postoperatively, especially when RD and MD solutions were analyzed together.

Although the MD best represents the temporal properties of a propagating epileptiform discharge, the RD has the advantage of maintaining the signal-to-noise ratio of a fixed dipole solution, as the "rotating" vector allows some accommodation for the spatiotemporally dynamic nature of epileptiform spikes. The RD is the key dipole parameter, as it mathematically defines "goodness-of-fit" from the square root of the summed differences between the measured EEG signal and forward fit dipole signal across electrodes. The combined dipole approach therefore yields information that enhances our ability to localize the epileptogenic hub of MRI-negative patients with FCD and assists surgical decision-making.

Few clinical studies have assessed the surgical cavity with combined dipolar methods, and there is even less information regarding 3D-ESI in MRI-negative patients[21]or comparisons to PET and iSPECT. Brodbeck recently found a highly accurate localization (80%) of 3D-ESI in the MRI-negative population.[21] In this study, a linear-distributed inverse solution was applied to a heterogeneous population of adults, half of whom underwent 3D-ESI with high-resolution EEG.

We previously showed that the RD solution in MRI-negative patients is highly localizing (78.6%) and superior to PET (50.0%) and iSPECT (55.6%).[24] The present

Table 1. Relation of 3D-ESI analysis, PET, and iSPECT with the surgical resection cavity

	Overall population n (%)	Pathology		Type of surgery		
		FCD-I	FCD-II	Temporal	Extratemporal	Multilobar
3D-ESI		9 (64.3)	5 (53.7)	2 (14.2)	6 (43.9)	6 (43.9)
RD localizing	11 (78.6)	7 (77.7)	4 (80)	2 (100)	4 (66.7)	5 (83.3)
MD inside	9 (64.2)	5 (55.5)	4 (80)	1 (50)	3 (50)	5 (83.3)
PET	10 (71.4)	6 (66.7)	4 (80)	1 (50)	5 (83.3)	4 (66.7)
Localizing	5 (50)	3 (50)	3 (75)	0 (0)	1 (20)	4 (100)
iSPECT	9 (64.3)	7 (77.8)	2 (40)	1 (50)	4 (66.7)	4 (66.7)
Localizing	5 (55.6)	4 (57.2)	1 (50)	0 (0)	2 (50)	3 (75)

FCD, focal cortical dysplasia; 3D-ESI, 3D-EEG source imaging; RD, rotating dipole; MD, moving dipole; PET, positron emission tomography; iSPECT, ictal single photon emission computed tomography; n, number of patients.

Table 2. Outcome for 3D-ESI with regard to surgical outcome

Etiology	Surgery type	RD localizing	MD inside	MD partially inside	FU 1Y	FU 2Y
FCD I	Extratemporal	Yes	Yes		Favorable	Favorable
FCD I	Temporal	Yes	No	Yes	Unfavorable	Unfavorable
FCD I	Multilobar	Yes	Yes		Favorable	*
FCD II	Extratemporal	Yes	Yes		Favorable	Favorable
FCD I	Extratemporal	Yes	No	Yes	Unfavorable	Unfavorable
FCD II	Extratemporal	Yes	Yes		Unfavorable	Unfavorable
FCD II	Temporal	Yes	Yes		Favorable	Favorable
FCD II	Multilobar	Yes	Yes		Favorable	*
FCD I	Multilobar	Yes	Yes		Unfavorable	*
FCD I	Extratemporal	No	No		Unfavorable	Unfavorable
FCD II	Multilobar	No	No		Unfavorable	Unfavorable
FCD I	Multilobar	Yes	Yes		Favorable	Favorable
FCD I	Multilobar	Yes	Yes		Favorable	Favorable
FCD I	Extratemporal	No	No		Unfavorable	Favorable

FCD, focal cortical dysplasia; RD, rotating dipole; MD, moving dipole; n, number of patients; FU 1Y, 1 year after the surgery; FU 2Y, 2 years after the surgery. Gray color: by analyzing MD method in association with RD solution, the overall 3D-ESI sensibility increased both at 1 year and 2 years postoperatively.

Table 3. Sensitivity and specificity of 3D-ESI, PET, and iSPECT at 1 year and 2 years of follow-up

FU1	Sensitivity, %	Specificity, %	*FU2*	Sensitivity, %	Specificity, %
3D-ESI (n = 14)	63.6–77.7[a]	100.0	3D-ESI (n = 11)	62.5–77.7[a]	75.0
PET (n = 10)	60.0	40.0	PET (n = 7)	50.0	40.0
iSPECT (n = 9)	60.0	50.0	iSPECT (n = 8)	50.0	25.0

FU 1Y, 1 year after the surgery; FU 2Y, 2 years after the surgery; 3D-ESI, 3D-EEG source imaging; PET, positron emission tomography; iSPECT, ictal single photon emission computed tomography; n, number of patients.
[a]Increased sensitivity secondary to combined analysis of RD and MD both at 1 year and 2 years postoperatively.

investigation extends these findings because the RD method was shown to be highly localizing and particularly efficacious in temporal lobe epilepsy (100%) compared to either extratemporal (66.7%) or multilobar (83.3%) cases. Furthermore, the RD solution in temporal lobe and FCD type I cases was superior to PET and iSPECT. The RD method also revealed superior localization compared to iSPECT in FCD type II cases and PET in extratemporal patients. The localizing value of 3D-ESI in MRI-negative FCD patients was not pathology sub-type specific, as there were no differences between FCD I (77.7%) and FCD II (80.0%).

Our previous study demonstrated a higher sensitivity and specificity of RD compared to PET or iSPECT at 1 year and 2 years after the surgery.[24] The present analyses utilizing combined RD and MD analyses further enhanced 3D-ESI sensitivity at both 1 year (63.6–77.7%) and 2 years (62.5–77.7%) after surgery. This finding suggests that RD and MD are complementary when utilized together and synergistically increase the localizing power of 3D-ESI in MRI-negative children.

We have previously called attention to the limitations of 3D-ESI analysis using <32 electrodes and strategically placed extraelectrodes around the suspected epileptogenic zone.[24] These limitations apply to our current study, which is also limited by the small population and retrospective study design.

It is important to note that whenever the RD was nonlocalizing, the MD was always located outside the resection cavity, and increased sensitivity was achieved only when the RD was localizing and MD was at least partially within the surgical cavity. This agrees with the assumption that the MD acts as an indicator of propagation of the epileptic discharge and implies that MD solutions inside the SRC represent more stable sources.[14] It is not surprising that all subjects with a localizing RD and a MD partially within the surgical cavity had FCD type I, which typically is associated with an epileptogenic field that is more extensive and difficult to map than in FCD type II.[29,30] We therefore suggest that the proposed resection boundaries in MRI-negative cases should include consideration of the MD solution as well as the RD solution.

Although the complete removal of the MRI-detected structural lesion is the most important factor determining seizure freedom following surgery, caution should be exercised when proposing any cause–effect relationship between an MRI-detected abnormality and the seizures.[31–33] In some cases, an MRI lesion introduces a bias into the presurgical evaluation through false localization that influences the surgical plan negatively.[34]

Magnetoencephalography (MEG) is another noninvasive tool, clinically available since 2002, that can help to delineate the epileptogenic zone.[35–38] Brain source imaging with

MEG can be achieved using equivalent current dipole modeling of interictal spikes.[39,40] This process of interictal spike modeling of MEG data and dipole map overlay is often referred to as magnetic source imaging. Because MEG detects tangential sources, it would be ideal to perform in combination with EEG for source localization, which is better suited for radial sources. However, cost considerations prevent MEG from being performed in more than a minority of presurgical epilepsy evaluations, and its clinical value in surgical epilepsy treatment has been less well established compared to other diagnostic modalities.[41] Notably, 3D-ESI is performed with software added to standard equipment, whereas MEG requires a separate device, facilities, and expertise**.** Our retrospective study is subject to several limitations. To obtain the 3D-ESI analysis, we selected three spikes that we defined as typical on the basis of visual inspection of EEG trace morphology without more sophisticated analysis, such as voltage topography over the time course of the spike. Recent studies suggest that at least 64 electrodes should be used to define scalp topography and source localization in sufficient detail.[17,18,27,42–44] Since 2007 we have added electrodes at regions of interest because additional electrodes in uninvolved areas add noise to the analyses. To avoid bias in spike identification, review of EEG was performed exclusively with standard 10–20 system electrodes placement. The limited number of additional electrodes was used solely for 3D-ESI analysis. In addition, simulated dipoles have been tested with nonuniform sensors increased in the area of suspected dipole generation and demonstrated no loss of accuracy.[45] Furthermore, any direct comparison of a point-source dipole to an extended PET or SPECT solution has some limitations. PET or SPECT findings could more likely extend beyond the resection site. An alternative in future analyses could employ the centroid of the PET or SPECT result in comparison to the 3D-ESI dipole solution. In conclusion, we confirm the important role of 3D-ESI in MRI-negative patients with FCD[24] and we demonstrate an increased accuracy in localization of 3D-ESI when single RD and MD models are analyzed together. Therefore, we speculate that by analyzing both RD and MD solutions, epileptologist could utilize 3D-ESI to better understand the extent of epileptogenic networks underlying FCD.

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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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