

## Clinical significance of ictal magnetoencephalography in patients undergoing epilepsy surgery



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### HIGHLIGHTS

- Resection should include ictal single equivalent current dipole (SECD), interictal SECD and MRI lesion localization, when feasible.
- Concordant ictal and interictal SECDs can be a favorable predictor of seizure freedom if the areas can be safely resected.
- Among SECD, dynamic statistical parametric mapping, and linearly constrained minimum variance, SECD should be considered the first line of analysis for ictal MEG when the data is amenable to SECD source localization.

### ABSTRACT

**Objective:** The significance of ictal magnetoencephalography (MEG) is not well appreciated. We evaluated the relationships between ictal MEG, MRI, intracranial electroencephalography (ICEEG), surgery and postoperative seizure outcome.

**Methods:** A total of 45 patients (46 cases) with ictal MEG who underwent epilepsy surgery was included. We examined the localization of each modality, surgical resection area and seizure freedom after surgery.

**Results:** Twenty-one (45.7%) out of 46 cases were seizure-free at more than 6 months follow-up. Median duration of postoperative follow-up was 16.5 months. The patients in whom ictal, interictal single equivalent current dipole (SECD) and MRI lesion localization were completely included in the resection had a higher chance of being seizure-free significantly ( $p < 0.05$ ). Concordance between ictal and interictal SECD localizations was significantly associated with seizure-freedom. Concordance between MRI lesion and ictal SECD, concordance between ictal ICEEG and ictal and interictal SECD, as well as concordance between ictal ICEEG and MRI lesion were significantly associated with seizure freedom.

**Conclusions:** Ictal MEG can contribute useful information for delineating the resection area in epilepsy surgery.

**Abbreviations:** DE, depth electrode; dSPM, dynamic statistical parametric mapping; EZ, epileptogenic zone; FLAIR, Fluid-attenuated inversion recovery; FCD, focal cortical dysplasia; ICEEG, intracranial electroencephalography; IOZ, ictal onset zone; LCMV, linearly constrained minimum variance; MEG, magnetoencephalography; SDE, subdural electrode; SECD, single equivalent current dipole; SEEG, stereo-electroencephalography.

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**Significance:** Resection should include ictal, interictal SECDs and MRI lesion localization, when feasible. Concordant ictal and interictal SECDs on MEG can be a favorable predictor of seizure freedom.

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## 1. Introduction

Magnetoencephalography (MEG) is widely used as part of pre-surgical evaluation in patients with intractable epilepsy. MEG provides epileptic source localization with high temporal and spatial resolution (Knowlton and Shih, 2004). MEG also gives a broad view of whole-head activities non-invasively, therefore has the potential to contribute important information to guide implantation for intracranial recordings (Agirre-Arrizubieta et al., 2014; Murakami et al., 2016). Generally, MEG has been performed to detect and localize interictal discharges, because, until the recent development of continuous head position monitoring, the patient head position was required to be fixed in the sensor helmet, and movement artifacts associated with seizures would interfere with accurate magnetic source localization. However, ictal MEG may yield useful information if patients happen to have a seizure during the acquisition without substantial head movement. Previous ictal MEG studies suggested that ictal MEG has better concordance with intracranial electroencephalography (ICEEG), (Fujiwara et al., 2012) and has better sensitivity than interictal MEG for estimating ictal onset zone (Medvedovsky et al., 2012).

There is little consensus on the methodology of choice for ictal MEG analysis. The equivalent current dipole (ECD) model is currently the most common and accepted method for modeling sources of interictal epileptic discharges for epileptic focus localization (Bagić et al., 2011). For ECD modelling, the single ECD (SECD) model is the most commonly used (Badier et al., 2016; Kakisaka et al., 2012a, 2012b, 2011; Medvedovsky et al., 2012; Mohamed et al., 2007; Ramanujam et al., 2017). Recently, several methodologies for MEG source localization that model extended sources and do not require the investigator to choose a priori the number of separate sources to be localized, have been developed. Some groups used distributed source modeling (Alkawadri et al., 2018; Fujiwara et al., 2012; Pellegrino et al., 2016; Tanaka et al., 2009) and beamformers (Badier et al., 2016) for ictal MEG analysis. If the ictal onset consists of repetitive spikes, sharp waves, or a higher amplitude ictal rhythm, consideration should be given to the fact that ictal activity can propagate rapidly into adjacent cortex. Accordingly, the earliest ictal potentials should be used for source modeling in order to best identify the location of seizure origin (Bagić et al., 2011). On the other hand, SECD analysis is accurate only when the source can be explained as a single relatively focal source. The differences between these methodologies for ictal MEG analyses warrant a dedicated study to assess their clinical value.

In this study, we examined the relationships between ictal MEG, MRI, ICEEG, surgery, and postoperative seizure outcome. We also examined three algorithms including SECD, dynamic statistical parametric mapping (dSPM), and linearly constrained minimum variance (LCMV) to elucidate which methodology yields the most accurate localization for ictal MEG analysis.

## 2. Materials and methods

### 2.1. Informed consent and ethical standards

This study was approved by the Cleveland Clinic institutional review board. Informed consent was obtained in the form of opt-out on the website. Those who opted out were excluded.

### 2.2. Patient selection criteria

Patients were included if: (i) they underwent preoperative MEG and had epileptic aura or magnetoencephalographic seizures, (ii) they underwent epilepsy surgery (resective surgery or laser ablation), then followed up for at least six months, and (iii) their preoperative ictal MEG data were amenable to source localization using SECD modeling. If the same patient underwent several epilepsy surgeries, the presurgical ictal MEG recordings were considered separately for each surgery. More detailed patient selection protocol is available in [Supplementary Material \(Supplementary Fig. 1\)](#).

### 2.3. Pre-surgical evaluation and surgical strategy

The strategies for ICEEG implantation were discussed during a multidisciplinary patient management conference (PMC) based on review of multiple modalities. Detailed description of the surgical planning process can be found elsewhere (Bulacio et al., 2012; Gonzalez-Martinez et al., 2013), and more detailed information is available in [Supplementary Methods](#).

### 2.4. MEG data acquisition

A 1-hour MEG scan was performed for each patient using a 306 (204 planar gradiometers and 102 magnetometers) channel whole-head MEG system (Vector-View, Elekta, Helsinki, Finland). Scalp EEG was recorded simultaneously (21-channels, 10–20 system). Recordings were carried out in the supine position, and the patients were made comfortable and encouraged to relax in a magnetically shielded room. No procedures facilitating/evoking seizures (e.g., withdrawal of antiepileptic medication, sleep deprivation) were included in the MEG protocol. Data were sampled at 1000 Hz and filtered from 0.03 Hz to 330 Hz. Head position was determined with five head-position indicator (HPI) coils. Continuous HPI was recorded to allow slow movement during MEG recordings and to make long recordings easier for patients. The MEG data were postprocessed by spatial-temporal signal space separation (tSSS) (Taulu and Simola, 2006) to suppress interference originating outside the brain, and by signal space separation (SSS)-based movement compensation (MC) (Taulu et al., 2005) using Maxfilter 2.0 software (Elekta-Neuromag, Helsinki, Finland). Artifact suppression using the default parameters of the tSSS algorithm implemented within the Elekta Maxfilter system (10-s time window, subspace correlation 0.980) was applied to the data. We confirmed that MaxFilter's movement compensation accurately corrected for the head rotation within the dewar (Kakisaka et al., 2012a). Total recording time varied for each patient due to interruption by an ictal event or prolongation for capture of ictal events. Identification of ictal events was obtained by observation of patients using a monitoring camera (equipped with remote tilt, pan, and zoom) inside the magnetically shielded room. (Video recording, for post hoc evaluation of the ictal events was not consistently available.).

### 2.5. MEG analysis by SECD

For ictal and interictal SECD analysis, we used x-fit software from the vendor (Elekta-Neuromag, Helsinki, Finland). Interictal

SECDs were fitted at the peak of the discharges. Individual spike analysis was performed on data segments containing epileptiform discharges which had been visually identified from either MEG or EEG channels (Iwasaki et al., 2005). Source modeling was based on MEG data only. The acquired data were low-pass filtered at 60 Hz. High-pass filtering was used at appropriate settings between 2 and 8 Hz to extract the spike component from the slower background activity. The ECD model was fitted to the patient's spherical head model using the recorded signals from a total of 306 channels (204 planar gradiometers and 102 magnetometers). The following statistical criteria were used when reviewing the SECD results: goodness of fit > 80%, confidence volume < 1500 mm<sup>3</sup>, reduced  $\chi^2$  < 1.5, and dipole moment between 100–500 nAm. The dipoles were fitted to a multiple-sphere head model at the sensor level and co-registered to the patient's MRI using routine fiducial points, along with > 200 digitized scalp points to outline the head using Mrilab software from the vendor (Elekta-Neuromag, Helsinki, Finland). We defined positive interictal SECD as a cluster when there were at least 5 localizable dipoles. The choice of five dipoles as a threshold was based on the American Clinical Magnetoencephalography Society Clinical Practice Guideline (Bagić et al., 2011). Interictal dipole clusters were categorized into three types based on their 'tightness' as follows: A tight cluster was defined by five or more dipoles located within a single sulcus and the two adjacent gyri bordering this sulcus. A loose cluster was defined by five or more dipoles located within one sub-lobar region. Sub-lobar regions were defined using a common scheme (e.g. frontopolar, superior frontal, inferior frontal, mesial frontal, superior parietal, inferior parietal, mesial parietal, lateral occipital, mesial occipital, temporopolar, superior lateral temporal and mesial temporal) (Knowlton et al., 2008, 2006; Schneider et al., 2012). A scattered cluster was defined by five or more dipoles involving more than one sub-lobar region.

For ictal MEG analysis, stability of the magnetic influx and efflux was verified visually from the magnetic field distributions by expert readers. We defined the ictal onset as the first evolving rhythmic oscillations in MEG temporally related to the clinical or EEG onset. The earliest ictal discharge within 5 seconds from the beginning of the ictal onset was used for dipole fitting (Fig. 1F), and dipoles were accepted if they met the appropriate criteria listed above. For rhythms other than spikes, we fit the dipoles at the time of the peak of waveforms (Alkawadri et al., 2018). We then performed sequential dipole fits over the time epoch which contained 80% of the rising slope of each waveform (Lantz et al., 2003). If dipole fitting failed because they were generalized discharges, focal discharges but had no dipoles meeting the statistical criteria, showed no MEG change, or movement artifacts, we defined the ictal study as 'non-localizable'. Positive ictal SECD studies were defined if one or more ictal dipoles which satisfied the above criteria were localized ('localizable' study).

## 2.6. MEG analysis by dSPM and LCMV

As the first step for ictal MEG analysis using dSPM, and LCMV, we performed Morlet wavelet transformation (<https://neuroimage.usc.edu/brainstorm/Tutorials/TimeFrequency>) using Brainstorm software (Tadel et al., 2011). Epochs lasting 8 s (from –3 to 5 s, 0 being the time of ictal onset) were imported into the software. Preprocessing included 2–80 Hz band-pass filter, 60 Hz and 120 Hz notch filter, and DC correction (baseline window from –3 s to –1 ms). We computed a time frequency decomposition in a frequency window ranging from 2 Hz to 80 Hz on a linear scale and with a frequency resolution of 1 Hz over the full time window (–3 s to +5 s) as reported before (Pellegrino et al., 2016) (Supplementary Figs. 2–5). An example of this processing workflow is shown in Fig. 1A. The time–frequency decompositions of all sensors using

Morlet Wavelet transformation (MWT) were displayed to check and possibly refine the time of seizure onset, to exclude possible artifacts using a band-pass filter, and to select the frequency band (yellow box in Fig. 1A) to consider for the ictal source imaging by identifying the largest energy change at the onset (Alkawadri et al., 2013; Fujiwara et al., 2012). Detailed information is available in [Supplementary Methods](#).

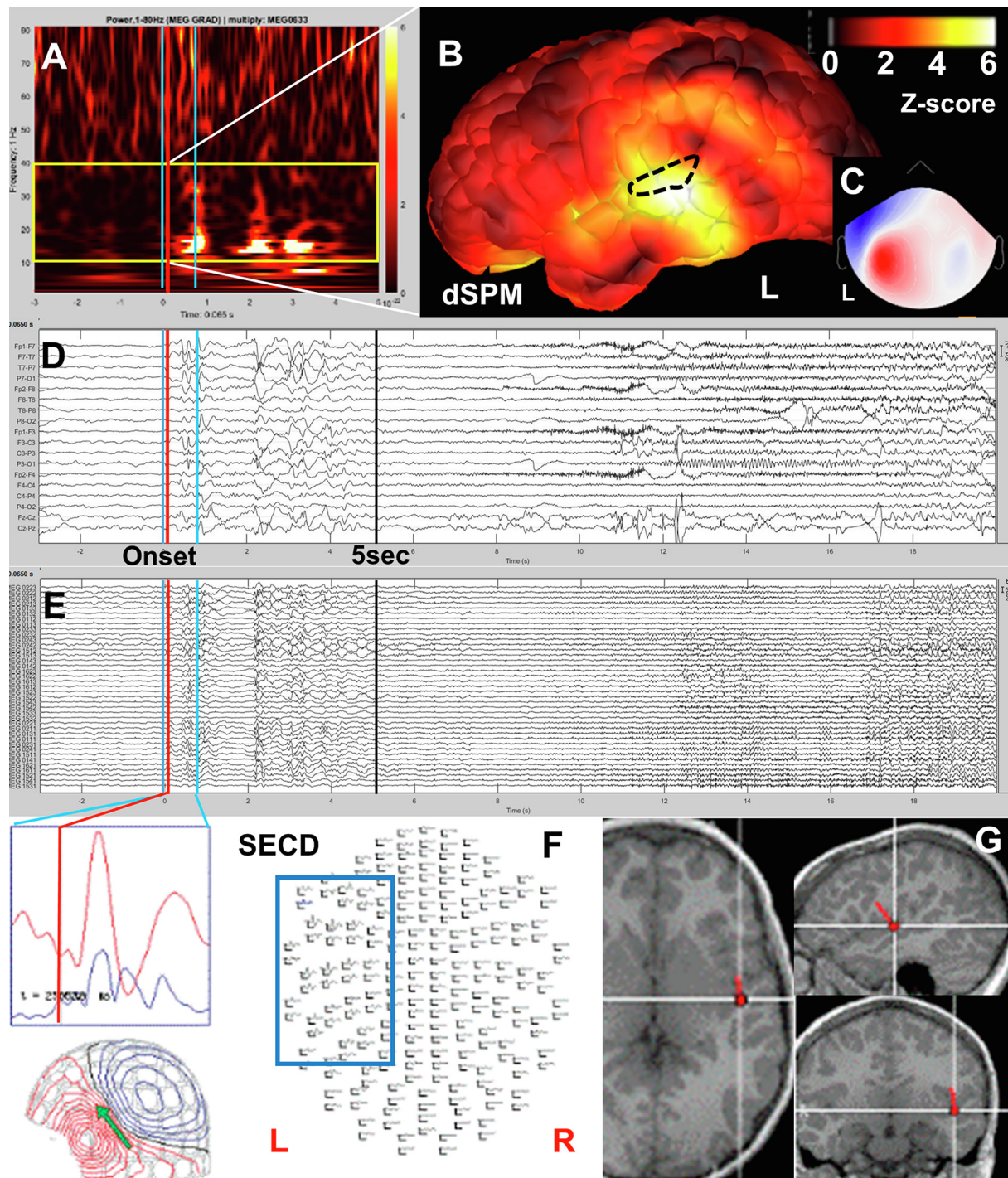
The cortical surface of the brain was extracted using BrainSuite (<https://brainsuite.org/>) from the patient's individual MRI. After having identified the frequency band of interest, we ran the dSPM and LCMV (<https://neuroimage.usc.edu/brainstorm/Tutorials/SourceEstimation>) to compute the inverse solution within the –3 s to 5 s time window as shown in Fig. 1A–E. Detailed procedures and settings for dSPM and LCMV are available in [Supplementary Methods](#) and [Supplementary Figs. 6–11](#). Brainstorm computes the standard deviation for normalization as a Z-score. We defined the IOZ from dSPM and LCMV localizations as regions with Z-score > 4 after MWT showing ictal oscillation, and we defined the results of ictal dSPM and LCMV analysis as negative, if (i) no obvious ictal oscillation was seen in the time frequency analysis, (ii) the activity with Z-score more than 4 was not seen after ictal onset (0 to +5 s).

## 2.7. Resection and concordance analysis

The locations of the ictal and interictal SECDs were exported from the Neuromag vendor software in DICOM format, as high-intensity voxels imprinted on the preoperative MRI. Subsequently, three image volumes were co-registered using Curry software (version 7, Neuroscan Inc., Charlotte, NC, USA): the preoperative MRI with SECDs imprinted, the CT obtained immediately after SEEG implantation, and the postoperative MRI. All SECDs were segmented from the imprinted preoperative MRI and overlaid on the postoperative MRI to determine complete or incomplete resection of the SECDs (Murakami et al., 2016). Resection of the ictal and interictal SECDs was deemed to be "complete", when  $\geq 70\%$  of both ictal and interictal SECDs was localized within the resection cavity (Iwasaki et al., 2002). If there were multiple isolated populations of interictal SECDs,  $\geq 70\%$  of dipoles in all populations should be resected to be considered "complete" resection, to avoid selection bias of which type of interictal dipole clusters (e.g. multiple-/bilateral- isolated tight clusters) should be resected. Resection of  $\geq 70\%$  of the area with Z-score more than four in dSPM and LCMV was deemed to be "complete". Individual SECDs and ICEEG contacts located within, or no further than 5 mm beyond, the resection margins were considered as resected, taking into account the expected displacement of tissue around the resected area along with the unavoidable MRI distortion and minor image coregistration errors. Blinded reviewers (TH, MA, and TA) analyzed whether ictal and interictal SECDs, MRI lesion, ictal SEEG contacts, dSPM, and LCMV IOZ were resected completely or not.

We defined the relationship between two tests as 'concordant' when: i) the two compared tests both had sub-lobar localization that overlapped by  $\geq 30\%$ , or ii) when one test showed sublobar localization and the other lobar localization, and there was  $\geq 70\%$  overlap, or iii) when the two compared tests both had lobar localization, and there was  $\geq 70\%$  overlap (schematic shown in [Supplementary Fig. 12](#)). If multiple clusters of ictal SECDs were localized over multi-lobar regions, we only analyzed the first cluster estimated from the earliest component. If multiple clusters of interictal SECDs were localized, we analyzed concordance between the area of interest and the closest and tightest interictal SECD cluster. If the patients had multiple seizure types, we analyzed the same type of seizure captured in MEG and ICEEG. Blinded reviewers (TH, MA, and TA) analyzed the concordance of the results including MEG, MRI, and ICEEG.





**Fig. 1.** Overview of ictal source localization by single equivalent current dipole (SECD) and dynamic statistical parametric mapping (dSPM). L; left, R; right. (A) Morlet wavelet time–frequency decomposition of data (2–80 Hz). Yellow square indicates the frequency band (10–40 Hz) for dSPM and linearly constrained minimum variance (LCMV). There are alpha to beta oscillations corresponding with ictal discharges. (B) dSPM shows ictal onset zone in the left superior temporal. Black dotted line delineates surgical area. (C) Magnetic field topography shows a dipolar pattern over the left temporal region. (D) EEG in longitudinal bipolar montage, and (E) MEG over the left temporal sensors (gradiometer). First blue line and red line in A, D, E, and F indicate the ictal onset (0 ms) and analysis point (65 ms after seizure onset), respectively. (F) Blue square in the top view of all sensors is the region of interest (ROI) selected to increase signal-to-noise ratio and improve SECD fitting. (G) Localization of ictal onset using SECD analysis. Ictal SECD was localized over the left Heschl's gyrus. (No. 2 in [Supplementary Table 1](#)).

## 2.8. Epilepsy surgery outcome

The epilepsy surgery outcome was assessed after at least 6 months as part of the regular epilepsy program clinical follow-up. Seizure outcomes at the most recent follow-up were categorized

into seizure-free (Engel class Ia) or not seizure-free (Ib–IVc) based on Engel's classification (Engel and Palm Desert International Conference on the Surgical Treatment of the Epilepsies (2nd: 1992: [Indian Wells Calif](#), 1993). Histopathological specimens were reviewed by a dedicated neuropathologist. Focal cortical dys-

plasia was subdivided according to the International League Against Epilepsy (ILAE) classification (Blümcke et al., 2011).

## 2.9. Statistical analysis

Statistical analyses were done with JMP version 14 software (SAS Institute, Cary, NC, USA). ANOVA was used to compare the association of continuous variables with outcomes. Fisher's exact test or Chi-square test were used to compare the association of categorical variables with outcomes. Cochran-Armitage trend test for analysis was used for the ordinal variables. We used Fisher's test to assess the relationship of parameters, complete resection of regions of interest, concordance between modalities and seizure-freedom. First, we performed univariate logistic regression models to compare the association of complete resection of ictal, interictal SECDs, and MRI lesion association with seizure-freedom after surgery. Then, we computed receiver operating characteristic curves (ROC) predicting seizure-freedom regarding these three parameters. We compared each area under the ROC (AUC) to test the accuracy of these models by the Delong method (DeLong et al., 1988). The significance level was set at  $P < 0.05$ .

## 2.10. Data availability

The data that support these findings are available upon reasonable request from the corresponding authors.

## 3. Results

### 3.1. Patient selection

We retrospectively reviewed ten years of MEG data from 1794 epilepsy cases studied in the Cleveland Clinic Epilepsy Center from April 2008 to April 2018. Seizures occurred during MEG in 156 cases (9.1%). In 105 out of the 156 (105/156, 67.3%) cases, MEG recorded positive ictal SECD. Sixty-two out of the 156 cases underwent ICEEG. Forty-four out of the 62 cases subsequently underwent epilepsy surgery after ICEEG. Thirty-one out of the 156 cases underwent epilepsy surgery without ICEEG. In the total 75 epilepsy surgical cases, two cases with follow-up less than 6 months and 27 cases where ictal MEG data were not amenable to SECD analysis were excluded. Finally, 46 (45 patients) cases were included in our study (29 with ICEEG, 17 without ICEEG). Details are described in [Supplementary Fig. 1](#).

### 3.2. Patient background and surgical outcome

Twenty-one (45.7%) out of 46 cases were seizure-free at more than 6 months follow-up. Median duration of postoperative follow-up was 16.5 months. Details are shown in [Table 1](#).

In the total 46 included cases, 11 out of 28 cases with MRI lesions underwent ICEEG (Group A, [Fig. 2A](#)); the remaining 17 out of 28 cases with MRI lesions underwent epilepsy surgery without ICEEG (Group B, [Fig. 2B](#)); all 18 cases without MRI lesions underwent ICEEG (Group C, [Fig. 3](#)) before epilepsy surgery. There were 4/11 (36.4%), 11/17 (64.7%), and 6/18 (33.3%) patients who achieved seizure-freedom after epilepsy surgery in Group A, B, and C, respectively. There were 7 patients who had temporal lobe and 39 extratemporal resections; and of those 4 out of the 7 (57.1%) temporal and 17 out of 39 (43.6%) extratemporal cases became seizure-free after surgery ([Table 1](#)). The results of each modality and surgical area are shown in [Supplementary Table 1](#).

Twenty-nine (21 male, 8 female) out of 46 cases were followed up more than one year; median follow-up duration was 39 (12–102) months. Eleven out of 29 cases were seizure free at one-

year follow-up. Details are shown in [Supplementary Results and Table 1](#).

### 3.3. Resection of MEG, MRI and ICEEG localizations versus seizure outcome

Patients in whom the ictal, interictal SECDs and MRI lesion were completely resected had a significantly higher chance of achieving seizure freedom as compared to the partial or no resection cases ( $P = 0.0024$ ,  $P = 0.045$  and  $P = 0.011$ ). Details are in [Table 2](#), and [Figs. 2 and 3](#) show illustrative cases. In contrast, the same analyses applied to ictal ICEEG ( $P = 0.13$ ), ictal dSPM ( $P = 0.32$ ) or ictal LCMV ( $P = 0.52$ ) localizations did not show significance.

MRI had the highest sensitivity (93.3%) in predicting seizure-freedom after complete resection of the MRI lesion, followed by ICEEG (80%), and ictal SECD (66.7%). ROCs for complete resection of ictal, interictal SECDs and MRI lesion in predicting seizure-freedom are shown in [Supplementary Fig. 13](#). There were no significant differences in any of the AUC measures overall. However, the most accurate parameter predicting seizure-freedom was complete resection of ictal SECDs in 41 patients who had ictal (AUC = 0.75) and interictal (AUC = 0.65) SECDs and in 25 patients who had ictal (AUC = 0.76), interictal (AUC = 0.67) SECDs, and MRI lesion (AUC = 0.73) as shown in [Supplementary Table 2](#).

In 29 out of 46 patients with more than one year follow-up, those whose ictal SECDs were completely resected had a significantly higher chance of achieving seizure freedom, as compared to the partial or no resection cases ( $P = 0.048$ ). Details are in [Supplementary Table 2](#).

### 3.4. Concordance between MEG, MRI and ICEEG localizations versus seizure outcome

Among 46 cases with positive ictal SECD, nine out of the 11 cases who had concordant ictal SECD and interictal SECD localizations became seizure-free ([Table 3](#), [Figs. 2 and 3](#)); concordance between ictal and interictal SECD localizations was significantly associated with seizure freedom ( $P = 0.0031$ ).

Among the 28 cases with MRI lesions (groups A and B combined), all seven of the cases in whom the MRI lesion was concordant with ictal SECD localization became seizure-free. Concordance between MRI lesion and ictal SECD localization was significantly associated with seizure freedom ( $P = 0.0069$ ) ([Table 3](#), example in [Fig. 2A](#)). The same analysis applied to concordance between MRI lesion and interictal SECD localization did not show significance ( $P = 0.073$ ).

Among the 29 cases with ictal ICEEG (group A and C combined), seven out of 11 cases in whom ictal ICEEG showed concordant results with ictal SECD became seizure-free, and four out of five cases in whom ictal ICEEG showed concordant results with interictal SECD became seizure-free, and all three cases in whom ictal ICEEG showed concordant results with MRI lesion became seizure-free. Concordance between ictal ICEEG versus ictal, interictal SECD localization and MRI lesion was significantly associated with seizure freedom ( $P = 0.017$ , 0.01 and 0.024 in [Table 3](#), [Figs. 2A and 3A](#)).

Concordance between ictal ICEEG and MRI had the highest sensitivity (75%) for predicting seizure-freedom after surgery, followed by concordance between ictal ICEEG and ictal SECD (70%), and concordance between ictal and interictal SECD (52.9%) as shown in [Table 3](#).

In 29 out of 46 patients with more than one year follow-up, concordance between ictal versus interictal SECD ( $P = 0.038$ ) and ictal ICEEG versus interictal SECD ( $P = 0.033$ ) localization was significantly associated with seizure freedom, respectively, as shown in [Supplementary Table 4](#).

**Table 1**  
Clinical profiles of 46 cases.

|  | Total (N = 46, 100%)        | Seizure-free (N = 21, 45.7%) | Non-seizure free (N = 25, 54.3%) | P-value |
|--|-----------------------------|------------------------------|----------------------------------|---------|
| <b>Gender</b>                                |                             |                              |                                  |         |
| Male   | 31 (67.4%)                  | 13 (61.9%)                   | 18 (72%)                         | 0.54*   |
| Female                                       | 15 (32.6%)                  | 8 (38.1%)                    | 7 (28%)                          |         |
| <b>Handedness</b>                            |                             |                              |                                  |         |
| Right  | 35 (76.1%)                  | 15 (71.4%)                   | 20 (80%)                         | 0.52*   |
| Left   | 7 (15.2%)                   | 3 (14.3%)                    | 4 (16%)                          |         |
| Ambidexterity                                | 4 (8.7%)                    | 3 (14.3%)                    | 1 (4%)                           |         |
| <b>Seizure history</b>                       | Mean $\pm$ SD (Range) years |                              |                                  |         |
| Age at seizure onset                         | 9.5 $\pm$ 11.1 (0–50)       | 9.7 $\pm$ 13.4 (0–50)        | 9.4 $\pm$ 8.9 (0–30)             | 0.93**  |
| Age at surgery (epilepsy surgery or ICEEG)   | 21 $\pm$ 13.4 (0.7–56)      | 18.6 $\pm$ 15 (0.7–56)       | 23 $\pm$ 11.8 (4–47)             | 0.27**  |
| Duration of epilepsy before surgery (N = 45) | 10.5 $\pm$ 10.3 (1–44)      | 8.0 $\pm$ 7.6 (0.7–29)       | 12.7 $\pm$ 11.8 (1–44)           | 0.13**  |
| <b>Epilepsy surgical history</b>             |                             |                              |                                  |         |
| Resective surgery                            | 8 (17.4%)                   | 2 (9.5%)                     | 6 (24%)                          | 0.67*   |
| Resective surgery + VNS                      | 3 (6.5%)                    | 1 (4.7%)                     | 2 (8%)                           |         |
| VNS  | 2 (4.4%)                    | 1 (4.7%)                     | 1 (4%)                           |         |
| None   | 33 (71.7%)                  | 17 (81%)                     | 16 (64%)                         |         |
| <b>MRI findings</b>                          |                             |                              |                                  |         |
| Lesional                                     | 28 (61%)                    | 15 (71.4%)                   | 13 (52%)                         | 0.23*   |
| Non-lesional                                 | 18 (39%)                    | 6 (28.6%)                    | 12 (48%)                         |         |
| <b>Number of seizure type</b>                |                             |                              |                                  |         |
| 1  | 35 (76.1%)                  | 17 (80.9%)                   | 18 (72%)                         | 0.62*** |
| 2  | 8 (17.4%)                   | 3 (14.3%)                    | 5 (20%)                          |         |
| 3  | 3 (6.5%)                    | 1 (4.8%)                     | 2 (8%)                           |         |
| <b>Seizure semiology during ictal MEG</b>    |                             |                              |                                  |         |
| NCS  | 15 (32.6%)                  | 5 (23.8%)                    | 10 (40%)                         | 0.47*   |
| Tonic or clonic                              | 14 (30.4%)                  | 6 (28.6%)                    | 8 (32%)                          |         |
| Epileptic aura                               | 11 (23.9%)                  | 7 (33.3%)                    | 4 (16%)                          |         |
| Automotor                                    | 5 (10.9%)                   | 2 (9.5%)                     | 3 (12%)                          |         |
| Hypermotor                                   | 1 (2.2%)                    | 1 (4.8%)                     | 0 (0%)                           |         |
| <b>Seizure frequency before surgery</b>      |                             |                              |                                  |         |
| Daily  | 25 (54.4%)                  | 14 (66.7%)                   | 11 (44%)                         | 0.15*** |
| Weekly                                       | 10 (21.7%)                  | 3 (14.3%)                    | 7 (28%)                          |         |
| Monthly                                      | 11 (23.9%)                  | 4 (19%)                      | 7 (28%)                          |         |
| <b>Type of ICEEG</b>                         | N = 29                      | N = 10                       | N = 19                           |         |
| SEEG   | 19 (65.5%)                  | 6 (60%)                      | 13 (68.4%)                       | 0.68*   |
| SDE/DE                                       | 10 (34.5%)                  | 4 (40%)                      | 6 (31.6%)                        |         |
| <b>Surgical area</b>                         |                             |                              |                                  |         |
| Temporal                                     | 7 (15.2%)                   | 4 (19%)                      | 3 (12%)                          | 0.7*    |
| Extra-temporal                               | 39 (84.8%)                  | 17 (81%)                     | 22 (88%)                         |         |
| <b>Postoperative follow-up duration</b>      | Median (range) months       |                              |                                  |         |
|  | 16.5 (6–102)                | 14 (6–102)                   | 18 (6–102)                       | 0.7**   |
| <b>Pathology</b>                             |                             |                              |                                  |         |
| FCD I  | 16 (34.7%)                  | 6 (28.6%)                    | 10 (40%)                         | 0.06*   |
| FCD II                                       | 9 (19.6%)                   | 7 (33.3%)                    | 2 (8%)                           |         |
| Gliosis                                      | 9 (19.6%)                   | 6 (28.6%)                    | 3 (12%)                          |         |
| Not significant                              | 5 (10.9%)                   | 1 (4.8%)                     | 4 (16%)                          |         |
| Not available (laser ablation)               | 4 (8.7%)                    | 0 (0%)                       | 4 (16%)                          |         |
| Encephalitis                                 | 2 (4.3%)                    | 1 (4.8%)                     | 1 (4%)                           |         |
| Glioma                                       | 1 (2.2%)                    | 0 (0%)                       | 1 (4%)                           |         |

SD, standard deviation; ICEEG, intracranial electroencephalography; MEG, magnetoencephalography; SEEG, stereo-electroencephalography; SDE, subdural electrode; FCD, focal cortical dysplasia; NCS, non-clinical seizure; Seizure-free = Engel class Ia. \*Fisher's exact test; \*\*ANOVA, Analysis of Variance; \*\*\*Cochran-Armitage trend test. The significance level was set at  $P < 0.05$ .

## 4. Discussion

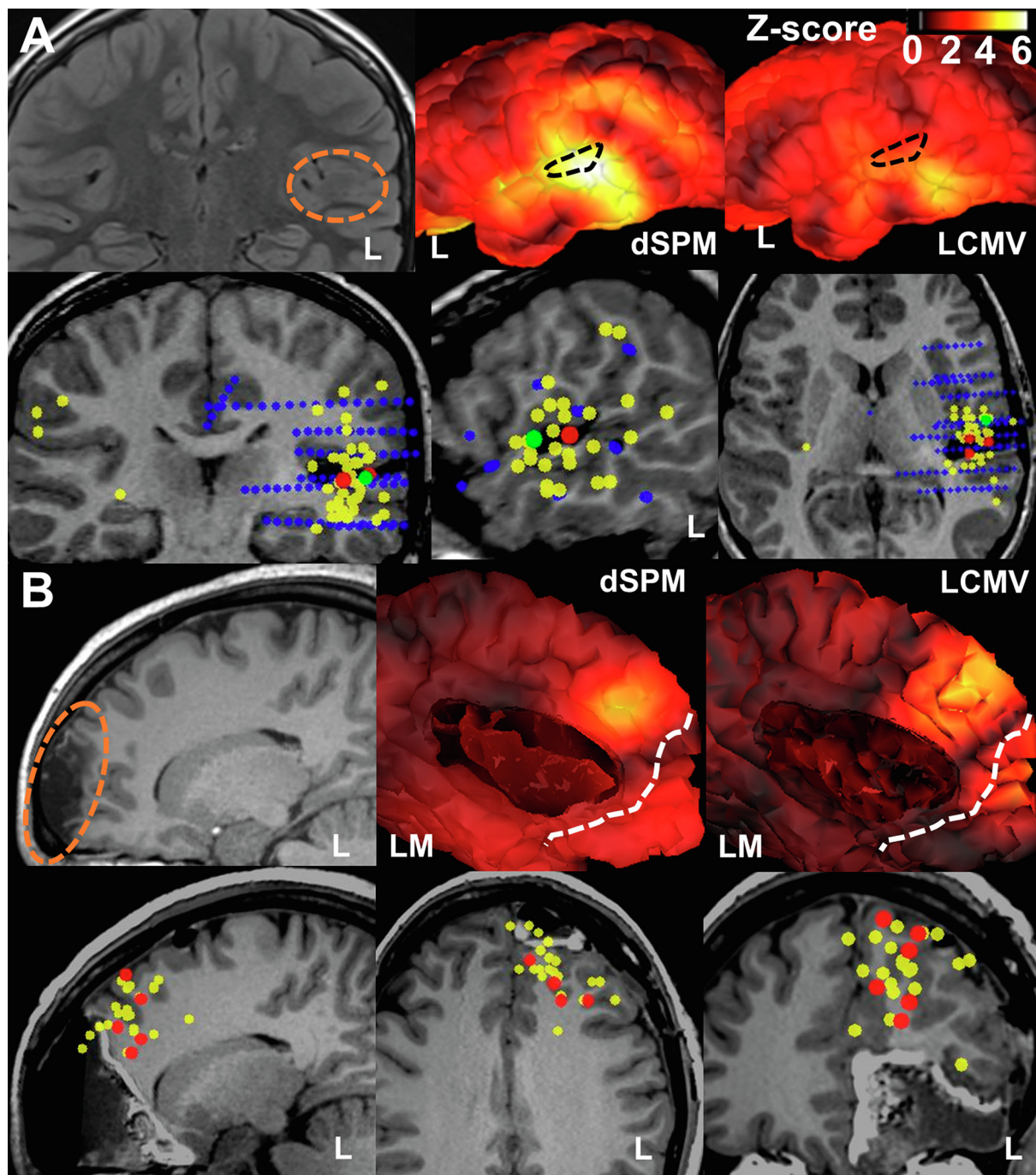
### 4.1. Ictal and interictal SECDs

One of the most important findings from our study is that complete resection of ictal and interictal SECDs was significantly associated with postoperative seizure-freedom. Complete resection of ictal SECDs showed a better ability to predict postoperative seizure-freedom than complete resection of interictal SECDs based on the ROC analysis. There are a couple of points which warrant emphasis:

First, the number of analyzable interictal events is much larger than the ictal ones. And the time scale of a seizure renders its spatiotemporal development much more readable. Ictal SECDs tended

to be localized as a smaller number of dipoles confined to a smaller area than the interictal SECDs (Supplementary Table 1). This is also consistent with the customary finding that the “irritative zone” is a superset of the “seizure onset zone” (Lüders et al., 2006). Complete resection of ictal SECDs will more likely result in seizure freedom, as noted above, than resection of interictal sources. Moreover, resection of the SECD cluster was deemed to be “complete” in our study, only when  $\geq 70\%$  of all ictal and interictal dipoles were resected to avoid selection bias of which type of interictal dipole clusters should be resected. Complete interictal SECD resection might be harder to achieve than in previous studies due to the stricter definition for “complete resection” in our study compared with definitions in previous studies (Knowlton et al., 2009; Murakami et al., 2016; Oishi et al., 2006). As we continue to gather



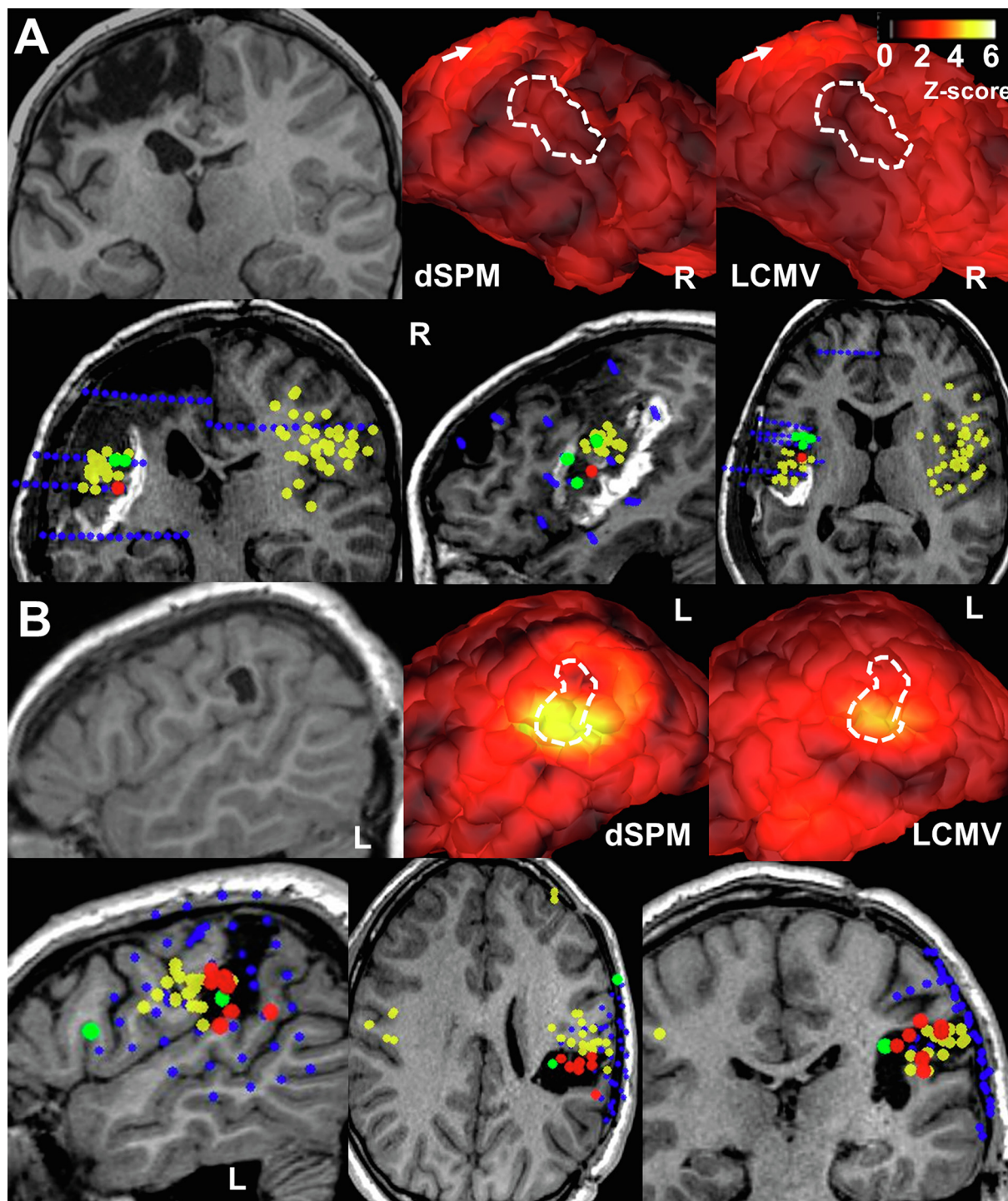


**Fig. 2.** MRI lesional cases illustrating the various scenarios of the relationships between magnetoencephalography (MEG), MRI, intracranial electroencephalography (ICEEG) and resection area. L; left, LM; left mesial, Red dot; ictal single equivalent current dipole (SECD), yellow; interictal SECD, green; ictal ICEEG (SEEG) contact, blue; ICEEG contact. (A) MRI shows blurred borderline between cortex and white matter in orange dotted-lined area in T1-weighted coronal image. Dynamic statistical parametric mapping (dSPM) and linearly constrained minimum variance (LCMV) show ictal onset zone (IOZ) in the left superior temporal and inferior temporal regions respectively. Black dotted line delineates resection area. dSPM IOZ was resected partially (i.e. < 70% resection). LCMV IOZ was not resected. Ictal SECDs, ictal ICEEG electrode, and MRI lesion were completely resected. The patient (No. 2 in [Supplementary Table1](#)) achieved seizure freedom > 6 months after surgery. Surgical pathology showed gliosis. (B) MRI (T1-weighted sagittal image) shows encephalomalacia over the left frontal pole in orange dotted-lined area. dSPM and LCMV IOZs were localized over the left mesial frontal region respectively. Ictal and interictal SECD were concordant over the posterior area of MRI lesion. Only MRI lesion was completely resected. White dotted line indicates posterior margin of resection area. The patient (No. 12) became seizure-free > 7 months after surgery. Surgical pathology showed gliosis.

data, a more sophisticated strategy for deciding what type of interictal SECD cluster should be resected might be needed for seizure control, especially when a surgical candidate has widely distributed interictal SECDs and/ or multiple-/ bilateral- isolated interictal SECD tight clusters.

Second, our result should be interpreted in the context of the rapid and complicated propagation of spike activity. We fitted

interictal SECDs at the peak of epileptic spikes (in contrast to ictal SECDs fitted at the rising slope of each waveform). At this point, the spike activities may have already spread to a broader area than the epileptogenic zone. The patient in [Fig. 2B](#) achieved seizure freedom after resection of encephalomalacia over the left frontal pole, even though the ictal and interictal dipoles were not completely resected. Takayama et al. reported on 10 epilepsy patients with



**Fig. 3.** MRI non-lesional cases illustrating the various scenarios of relationships between magnetoencephalography (MEG), intracranial electroencephalography (ICEEG) and resection area. L; left, R; right. Red dot; ictal single equivalent current dipole (SECD), yellow; interictal SECD, green; ictal ICEEG contact, blue; ICEEG contact, white dotted circle; resection area. (A) MRI (T1-weighted image) shows post-operative change of prior epilepsy surgery over the right precentral region. Dynamic statistical parametric mapping (dSPM) and linearly constrained minimum variance (LCMV) IOZs were localized over the right inferior parietal region respectively (white arrow). Ictal, interictal SECD and ictal ICEEG (SEEG) were concordant. Ictal SECDs and ictal ICEEG contacts were completely resected. The patient (No. 34 in [Supplementary Table 1](#)) achieved seizure-freedom > 8 months after surgery. Pathology showed gliosis. (B) MRI (T1-weighted image) shows post-operative change of prior epilepsy surgery over the left supramarginal gyrus. Ictal and interictal SECD, ictal dSPM, ictal LCMV, ictal ICEEG (depth electrode and subdural electrode) were all concordant. Ictal SECDs, dSPM and LCMV IOZs were completely resected. The patient (No. 9–2) became seizure-free > 65 months after second surgery. Pathology showed focal cortical dysplasia (FCD) type II.

ulegyria who underwent ICEEG prior to resective surgery. In their 10 case series ([Takayama et al., 2019](#)), there was discordance of localization between interictal MEG (localized over the bilateral fronto-temporo parietal and fronto-parietal regions) versus ICEEG IOZ and localization of ulegyria (localization of ICEEG IOZ and ule-

gyria were both in the parieto-occipital region) in 2 out of 4 patients who became seizure-free after surgery, as seen in our case. Our case ([Fig. 2B](#)) and these findings suggested that rapid spread of depolarizing activities arising from ulegyria over the regions (e.g. frontal, parietal and occipital) that are supposed to have rich con-



**Table 2**

Resection of MEG, MRI and ICEEG localizations versus seizure outcome.

|                           | Number<br>Y/ N | Epilepsy surgery outcome |                          | Sensitivity<br>(%) | Specificity<br>(%) | P-value |
|---------------------------|----------------|--------------------------|--------------------------|--------------------|--------------------|---------|
|                           |                | Seizure-free<br>(Y/N)    | Non-seizure free<br>Y/N) |                    |                    |         |
| Ictal SECDs (N = 46)      | 19/27          | 14/7                     | 5/20                     | 66.7               | 80                 | 0.0024* |
| Interictal SECDs (N = 41) | 12/29          | 8/9                      | 4/20                     | 47.1               | 83.3               | 0.045*  |
| MRI lesion (N = 28)       | 20/8           | 14/1                     | 6/7                      | 93.3               | 53.8               | 0.011*  |
| ICEEG IOZ (N = 29)        | 17/12          | 8/2                      | 9/10                     | 80                 | 52.6               | 0.13    |
| dSPM IOZ (N = 41)         | 14/27          | 8/10                     | 6/17                     | 44.4               | 73.9               | 0.32    |
| LCMV IOZ (N = 43)         | 14/29          | 8/12                     | 6/17                     | 40                 | 73.9               | 0.52    |

MEG, magnetoencephalography; ICEEG, intracranial electroencephalography; SECD, single equivalent current dipole; IOZ, ictal onset zone; dSPM, dynamic statistical parametric mapping; LCMV, linearly constrained minimum variance; Y, Yes; N, No. P-value by Fisher's exact test. \*The significance level was set at  $P < 0.05$ .

**Table 3**

Concordance between MEG, MRI, and ictal ICEEG localizations versus seizure outcome.

|                      |                          | N<br>C/D | Epilepsy surgery outcome |                           | Sensitivity (%) | Specificity<br>(%) | P-value |
|----------------------|--------------------------|----------|--------------------------|---------------------------|-----------------|--------------------|---------|
|                      |                          |          | Seizure-free (C/D)       | Non-seizure free<br>(C/D) |                 |                    |         |
| Ictal SECD (N = 46)  | Interictal SECD (N = 41) | 11/30    | 9/8                      | 2/22                      | 52.9            | 91.7               | 0.0031* |
| MRI lesion (N = 28)  | Ictal SECD (N = 28)      | 7/21     | 7/8                      | 0/13                      | 46.7            | 100                | 0.0069* |
|                      | Interictal SECD (N = 25) | 6/19     | 5/7                      | 1/12                      | 41.7            | 92.3               | 0.073   |
| Ictal ICEEG (N = 29) | Ictal SECD (N = 29)      | 11/18    | 7/3                      | 4/15                      | 70              | 78.9               | 0.017*  |
|                      | Interictal SECD (N = 26) | 5/21     | 4/4                      | 1/17                      | 50              | 94.4               | 0.01*   |
|                      | MRI lesion (N = 11)      | 3/8      | 3/1                      | 0/7                       | 75              | 100                | 0.024*  |

MEG, magnetoencephalography; ICEEG, intracranial electroencephalography; SECD, single equivalent current dipole; N, number; C, concordant; D, discordant. P-value by Fisher's exact test. \*The significance level was set at  $P < 0.05$ .

nections to other regions may cause complexity and misinterpretation of interictal MEG. In Fig. 2B, the patient became seizure-free even after incomplete ictal SECDs resection as well. The magnetic field attenuates rapidly as the distance from focus to MEG sensors increases, typically distant sources in the mesial temporal cortex (Enatsu et al., 2008). SECDs in the basal temporal, basal frontal and deep interhemispheric areas might be undetected. It is important to carefully interpret SECD localization in these deeper areas distant from the MEG sensors.

#### 4.2. Methodology for ictal MEG analysis

Our data showed that complete resection of the SECD ictal localization was significantly associated with seizure freedom, while dSPM and LCMV did not, supporting the clinical superiority of SECD analysis compared to dSPM and LCMV in our cohort.

One important caveat is that picking the time for analysis for each algorithm could be challenging and may critically affect the results. If the ictal onset consists of repetitive spikes, sharp waves, or a higher amplitude ictal rhythm, consideration should be given to the fact that ictal activity can propagate rapidly into adjacent cortex (Bagić et al., 2011) as shown in Supplementary Fig. 8. We analyzed peaks of ictal changes only from 0 to 5 s after ictal onset for SECD analysis. If the first discharge had acceptable fitting statistics, we then performed sequential dipole fitting to find the earliest activities which could be explained as a 'single source'. On the other hand, for dSPM and LCMV, we analyzed the areas showing Z-score  $> 4$  consistently and reproducibly after the start of ictal oscillation. It is possible that at this point ictal oscillation might already be spreading outside of the epileptogenic zone (EZ) (Lüders et al., 2006). This may explain the inferiority of dSPM and LCMV localization. Choosing the analysis time point for dSPM and LCMV is challenging as there is no direct statistical measure, and they do not require the investigator to choose *a priori* the number of separate sources to be localized. Multiple sources with Z-

score  $> 4$  by dSPM and LCMV can be localized at the same time point where it may be difficult for these two methods to distinguish real ictal activities from noisy background activities as shown in Supplementary Fig. 8.

Importantly, SECD modeling may be misleading when the source is very large and cannot be explained by a single source (Kobayashi et al., 2005). And ictal patterns with small SNR such as low amplitude fast, diffuse flattening, or obscured pattern, may be statistically problematic for SECD. Distributed source modeling and beamforming should perhaps be considered in patients in whom MEG shows an ictal pattern with small SNR/ large distribution, because these methods may better optimize the sources estimated from such activities.

#### 4.3. Surgical strategy based on ictal & interictal MEG, MRI, and ICEEG

Our data suggest that if an ictal MEG is (fortuitously) recorded, concordance between ictal and interictal SECD is a favorable sign for seizure freedom. This result was also observed in previous ictal MEG analysis (Fujiwara et al., 2012). A systematic review and meta-analysis revealed that the odds of becoming seizure-free after surgery were 2.5 times higher in patients with lesions on MRI or histopathology (Téllez-Zenteno et al., 2010) than in those with no lesions. These reports support our results. Patients with complete resection of ictal ICEEG contacts did not always achieve seizure freedom in our data, a result also seen in a previous report from our group (Murakami et al., 2016). However, ictal ICEEG showed higher sensitivity than ictal SECD. There were significant relationships between ictal ICEEG concordant with ictal, interictal SECD, MRI and seizure-freedom after epilepsy surgery. It is very important to include ICEEG contacts in the surgical area when ictal ICEEG is concordant with MEG and/ or MRI lesion.

Focusing on the patients who were followed up more than one year in our data, concordance between ictal versus interictal SECD, and ictal ICEEG versus interictal SECD localization, were both sig-

nificantly associated with seizure freedom. This result indicates that concordance between ictal and interictal epileptic MEG activity in pre-surgical evaluation is a positive predictive factor for seizure-freedom after epilepsy surgery.

Our findings suggest that ictal SECD may be able to play a role similar to ictal ICEEG in patients with MRI lesions. In the setting of other congruent non-invasive data (including seizure semiology, scalp EEG, and nuclear medicine imaging) when the ictal SECD is concordant with a convincing MRI lesion that is in a non-eloquent brain region, our analysis shows that ICEEG might not be needed.

#### 4.4. Limitations

Our study is inherently limited by its retrospective nature and relatively short post-surgical follow-up of at least 6 months. This follow-up time, however, was probably adequate for demonstrating localization accuracy; previous studies of patients with early recurrence due to mislocalization have typically shown recurrence within the first six postoperative months (Jehi et al., 2010; Najm et al., 2013). In addition, the majority of the patients in our study had follow-up times of much more than six months (with a median of 16.5 months).

The relatively small number of 46 cases (although the largest cohort in the literature), and the smaller subgroup of only 29 cases with more than one year follow-up, raises the possibility of type II errors.

Ictal onset was defined by visual inspection of MEG or simultaneous EEG data without consistent video recording of the seizures. Hence, we could not be certain of the exact starting time of clinical seizures. Therefore, it is possible that some pre-ictal activities may have been misidentified as the first ictal changes.

Our surgical strategy was to remove the minimum area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures (Lüders et al., 2006), and the surgical plan was determined in a consistent fashion by the group during a PMC. Nevertheless, there were different surgeons involved in this study, and slight differences in surgical approach may have influenced the results of concordance analysis.

#### 5. Conclusions

Our data suggest that when both interictal and ictal epileptic discharges were present during MEG recording, and when ictal events were localizable using SECD, the accuracy of ictal SECD was higher than interictal SECD in predicting seizure-freedom. In addition, the complete resection of ictal SECDs and MRI lesion, and concordance between ictal and interictal SECD, were associated with postoperative seizure freedom. When ictal MEG activities are localizable by SECD, SECD analysis should be considered first line for ictal MEG analysis compared to dSPM or LCMV.

#### CRedit authorship contribution statement

**Masaya Katagiri:** Conceptualization, Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing. **Z. Irene Wang:** Conceptualization, Supervision, Visualization, Writing – review & editing. **Tugba Hirfanoglu:** Data curation, Validation. **Mubarak M. Aldosari:** Data curation, Validation. **Thandar Aung:** Data curation, Validation. **Shan Wang:** Visualization. **Katsuya Kobayashi:** Data curation, Formal analysis. **Juan Bulacio:** Resources. **William Bingaman:** Resources. **Imad M. Najm:** Resources. **Andreas V. Alexopoulos:** Resources, Supervision.

**Richard C. Burgess:** Conceptualization, Resources, Supervision, Writing – review & editing.

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#### Conflicts of interest

The authors report no competing interests.

#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2022.10.005>.

#### References

- Agirre-Arrizubieta Z, Thai NJ, Valentín A, Furlong PL, Seri S, Selway RP, et al. The value of Magnetoencephalography to guide electrode implantation in epilepsy. *Brain Topogr* 2014;27:197–207. <https://doi.org/10.1007/s10548-013-0330-x>.
- Alkawadri R, Burgess RC, Kakisaka Y, Mosher JC, Alexopoulos AV. Assessment of the Utility of Ictal Magnetoencephalography in the Localization of the Epileptic Seizure Onset Zone. *JAMA Neurol* 2018;75:1264. <https://doi.org/10.1001/jamaneurol.2018.1430>.
- Alkawadri R, Krishnan B, Kakisaka Y, Nair D, Mosher JC, Burgess RC, et al. Localization of the ictal onset zone with MEG using minimum norm estimate of a narrow band at seizure onset versus standard single current dipole modeling. *Clin Neurophysiol* 2013;124:1915–8. <https://doi.org/10.1016/j.clinph.2013.03.016>.
- Badier J-M, Bénar C-G, Woodman M, Cruto C, Chauvel P, Bartolomei F, et al. Ictal Magnetic Source Imaging in Presurgical Assessment. *Brain Topogr* 2016;29:182–92. <https://doi.org/10.1007/s10548-015-0445-3>.
- Bagić AI, Knowlton RC, Rose DF, Ebersole JS. ACMEGS Clinical Practice Guideline (CPG) Committee. American Clinical Magnetoencephalography Society Clinical Practice Guideline 1: recording and analysis of spontaneous cerebral activity. *J Clin Neurophysiol* 2011;28:348–54. <https://doi.org/10.1097/WNP.0b013e3182272fed>.
- Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission1. *Epilepsia* 2011;52:158–74. <https://doi.org/10.1111/j.1528-1167.2010.02777.x>.
- Bulacio JC, Jehi L, Wong C, Gonzalez-Martinez J, Kotagal P, Nair D, et al. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. *Epilepsia* 2012;53:1722–30. <https://doi.org/10.1111/j.1528-1167.2012.03633.x>.
- Enatsu R, Mikuni N, Usui K, Matsubayashi J, Taki J, Begum T, et al. Usefulness of MEG magnetometer for spike detection in patients with mesial temporal epileptic focus. *Neuroimage* 2008;41:1206–19. <https://doi.org/10.1016/j.neuroimage.2008.03.038>.
- Engel J. *Palm Desert International Conference on the Surgical Treatment of the Epilepsies* (2nd : 1992 : Indian Wells Calif. Surgical treatment of the epilepsies. Raven Press; 1993.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–45.
- Fujiwara H, Greiner HM, Hemasilpin N, Lee KH, Holland-Bouley K, Arthur T, et al. Ictal MEG onset source localization compared to intracranial EEG and outcome: Improved epilepsy presurgical evaluation in pediatrics. *Epilepsy Res* 2012;99:214–24. <https://doi.org/10.1016/j.epilepsyres.2011.11.007>.
- Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. Stereoelectroencephalography in the “difficult to localize” refractory focal epilepsy: Early experience from a North American epilepsy center. *Epilepsia* 2013;54:323–30. <https://doi.org/10.1111/j.1528-1167.2012.03672.x>.
- Iwasaki M, Nakasato N, Shamoto H, Nagamatsu K, Kanno A, Hatanaka K, et al. Surgical implications of neuromagnetic spike localization in temporal lobe epilepsy. *Epilepsia* 2002;43:415–24.

- Iwasaki M, Pestana E, Burgess RC, Lüders HO, Shamoto H, Nakasato N. Detection of epileptiform activity by human interpreters: blinded comparison between electroencephalography and magnetoencephalography. *Epilepsia* 2005;46:59–68. <https://doi.org/10.1111/j.0013-9580.2005.21104.x>.
- Jehi L, Sarkis R, Bingaman W, Kotagal P, Najm I. When is a postoperative seizure equivalent to “epilepsy recurrence” after epilepsy surgery? *Epilepsia* 2010;51:994–1003. <https://doi.org/10.1111/j.1528-1167.2010.02556.x>.
- Kakisaka Y, Alexopoulos AV, Gupta A, Wang ZI, Mosher JC, Iwasaki M, et al. Generalized 3-Hz spike-and-wave complexes emanating from focal epileptic activity in pediatric patients. *Epilepsy Behav* 2011;20:103–6. <https://doi.org/10.1016/j.yebeh.2010.10.025>.
- Kakisaka Y, Wang ZI, Mosher JC, Dubarry AS, Alexopoulos AV, Enatsu R, et al. Clinical evidence for the utility of movement compensation algorithm in magnetoencephalography: Successful localization during focal seizure. *Epilepsy Res* 2012a;101:191–6. <https://doi.org/10.1016/j.epilepsyres.2012.03.014>.
- Kakisaka Y, Wang ZI, Mosher JC, Nair DR, Alexopoulos AV, Burgess RC. Magnetoencephalography's higher sensitivity to epileptic spikes may elucidate the profile of electroencephalographically negative epileptic seizures. *Epilepsy Behav* 2012b;23:171–3. <https://doi.org/10.1016/j.yebeh.2011.09.019>.
- Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, et al. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: A prospective study. *Ann Neurol* 2006;59:835–42. <https://doi.org/10.1002/ana.20857>.
- Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, et al. Functional imaging: II. Prediction of epilepsy surgery outcome. *Ann Neurol* 2008;64:35–41. <https://doi.org/10.1002/ana.21419>.
- Knowlton RC, Razdan SN, Limdi N, Elgavish RA, Killen J, Blount J, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. *Ann Neurol* 2009;65:716–23. <https://doi.org/10.1002/ana.21660>.
- Knowlton RC, Shih J. Magnetoencephalography in Epilepsy. *Epilepsia* 2004;45:61–71. <https://doi.org/10.1111/j.0013-9580.2004.04012.x>.
- Kobayashi K, Yoshinaga H, Ohtsuka Y, Gotman J. Dipole Modeling of Epileptic Spikes Can Be Accurate or Misleading. *Epilepsia* 2005;46:397–408. <https://doi.org/10.1111/j.0013-9580.2005.31404.x>.
- 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;20:311–9. <https://doi.org/10.1097/00004691-200309000-00003>.
- Lüders HO, Najm I, Nair D, Widdess-Walsh P, Bingman W. The epileptogenic zone: General principles. *Epileptic Disord*. 2006;8:S1–9. <https://doi.org/10.3109/9780203091708-107>.
- Medvedovsky M, Taulu S, Gaily E, Metsähonkala E-L, Mäkelä JP, Ekstein D, et al. Sensitivity and specificity of seizure-onset zone estimation by ictal magnetoencephalography. *Epilepsia* 2012;53:1649–57. <https://doi.org/10.1111/j.1528-1167.2012.03574.x>.
- Mohamed IS, Otsubo H, Donner E, Ochi A, Sharma R, Drake J, et al. Magnetoencephalography for surgical treatment of refractory status epilepticus. *Acta Neurol Scand Suppl* 2007;186:29–36.
- Murakami H, Wang ZI, Marashly A, Krishnan B, Prayson RA, Kakisaka Y, et al. Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. *Brain* 2016;139:2935–47. <https://doi.org/10.1093/brain/aww215>.
- Najm I, Jehi L, Palmini A, Gonzalez-Martinez J, Paglioli E, Bingaman W. Temporal patterns and mechanisms of epilepsy surgery failure. *Epilepsia* 2013;54:772–82. <https://doi.org/10.1111/epi.12152>.
- Oishi M, Kameyama S, Masuda H, Tohyama J, Kanazawa O, Sasagawa M, et al. Single and Multiple Clusters of Magnetoencephalographic Dipoles in Neocortical Epilepsy: Significance in Characterizing the Epileptogenic Zone. *Epilepsia* 2006;47:355–64. <https://doi.org/10.1111/j.1528-1167.2006.00428.x>.
- Pellegrino G, Hedrich T, Chowdhury R, Hall JA, Lina J-M, Dubeau F, et al. Source localization of the seizure onset zone from ictal EEG/MEG data. *Hum Brain Mapp* 2016;37:2528–46. <https://doi.org/10.1002/hbm.23191>.
- Ramanujam B, Bharti K, Viswanathan V, Garg A, Madhavi T, Bal C, et al. Can ictal-MEG obviate the need for phase II monitoring in people with drug-refractory epilepsy? A prospective observational study. *Seizure* 2017;45:17–23. <https://doi.org/10.1016/j.seizure.2016.10.013>.
- Schneider F, Alexopoulos AV, Wang Z, Alnubarak S, Kakisaka Y, Jin K, et al. Magnetic source imaging in non-lesional neocortical epilepsy: Additional value and comparison with ICEEG. *Epilepsy Behav* 2012;24:234–40. <https://doi.org/10.1016/j.yebeh.2012.03.029>.
- Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci* 2011;2011:879716. <https://doi.org/10.1155/2011/879716>.
- Takayama Y, Ikegaya N, Iijima K, Kimura Y, Muraoka N, Kaneko Y, et al. Is intracranial electroencephalography useful for planning resective surgery in intractable epilepsy with ulegyria? *J Neurosurg* 2019;1–6. <https://doi.org/10.3171/2019.8.JNS.191642>.
- Tanaka N, Cole AJ, von Pechmann D, Wakeman DG, Hämäläinen MS, Liu H, et al. Dynamic statistical parametric mapping for analyzing ictal magnetoencephalographic spikes in patients with intractable frontal lobe epilepsy. *Epilepsy Res* 2009;85:279–86. <https://doi.org/10.1016/j.epilepsyres.2009.03.023>.
- Taulu S, Simola J. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys Med Biol* 2006;51:1759–68. <https://doi.org/10.1088/0031-9155/51/7/008>.
- Taulu S, Simola J, Kajola M. Applications of the signal space separation method. *IEEE Trans Signal Process* 2005;53:3359–72. <https://doi.org/10.1109/TSP.2005.853302>.
- Téllez-Zenteno JF, Ronquillo LH, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: A systematic review and meta-analysis. *Epilepsy Res* 2010;89:310–8. <https://doi.org/10.1016/j.epilepsyres.2010.02.007>.