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The correlation of magnetoencephalography to intracranial EEG in localizing the epileptogenic zone: A study of the surgical resection outcome

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Summary
Objectives: To evaluate the agreement between magnetoencephalography (MEG) and intracranial electroencephalography (ICEEG) results, to determine the characteristics that lead to concordance, and to assess how these factors relate to favorable epilepsy surgery outcome.
Materials: This retrospective study reviewed 50 patients who had positive MEG findings and ICEEG recordings between 2008 and 2010. The anatomical concordance between MEG and ICEEG recordings, the features of the MEG focus, and the relationship between the MEG focus and the surgically resected regions were correlated with the epilepsy surgery outcome.
Results: Thirty-six of the 50 patients with positive MEG and ICEEG findings underwent epilepsy surgery, and 27 (75%) of the patients had an anatomical concordance of MEG/ICEEG. Among the patients with concordant MEG/ICEEG, the seizure free outcome rate was significantly higher compared to the discordant group [18/27 (66.7%) patients concordant vs. 1/9 (11.1%) patients discordant ($p < 0.006$)]. Nineteen (53%) of the 36 patients had complete resection when the MEG focus overlapped with the resection area, and 15 (79%) of these 19 patients became seizure-free following surgery ($p < 0.001$); 17 (47%) of the 36 patients had an MEG focus that was not

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completely resected (the MEG foci of 7 patients partially overlapped the resection areas, and 10 patients had MEG foci that were in a different area from the resection area), and 13/17 (76.5%) patients had seizure recurrences ($p < 0.001$).

Conclusions: Both the anatomical concordance of MEG/ICEEG and the complete resection of the MEG foci significantly increased the chance of seizure-free outcomes following epilepsy surgery.

Introduction

Magnetoencephalography (MEG) is a non-invasive diagnostic tool that is used to record the delicate magnetic signals of the brain and has shown promise in the pre-surgical evaluation of focal epilepsies. MEG has a high temporal resolution (ms), which makes this tool valuable for localizing the epileptogenic zone (EZ) and assessing the spread of epileptic activity. Compared to the electric signals recorded by electroencephalography (EEG), the magnetic signals are minimally distorted, resulting in an improved spatial resolution that can be useful in directing epilepsy surgery resection (Ebersole, 1997; Baumgartner, 2000; Baumgartner and Pataraia, 2006; Pataraia et al., 2002; Knowlton, 2003; Wheless et al., 2004; Wu et al., 2006; Grondin et al., 2006; Ray and Bowyer, 2010). Unlike some pre-surgical procedures, identification of the seizure focus using MEG is not limited by the need for special preparation (e.g., ictal-SPECT) or by the state of recording (e.g., FDG-PET scan).

Prior studies reported a high proportion of concordance between MEG and intracranial EEG (ICEEG) in localizing the EZ, and researchers have investigated whether pre-implantation MEG is useful in guiding the placement of ICEEG electrodes in invasive cases (Sutherling et al., 1988, 2008; Smith et al., 2000; Minassian et al., 1999; Mamelak et al., 2002; Stefan et al., 2003; Barkley and Baumgartner, 2003; Baumgartner, 2004; Knowlton et al., 2006, 2009; RamachandranNair et al., 2007; Agirre-Arrizubieta et al., 2009). Due to the fact that combined MEG and EEG can monitor neuronal activity at different orientation levels, several authors reported an additive value of the combination of both tools during pre-surgical evaluation (Mikuni et al., 1997; Baumgartner, 2000; King et al., 2000; Stefan et al., 2000; Paulini et al., 2007; Ebersole and Ebersole, 2010). Resection of the MEG focus has been associated with a favorable epilepsy surgery outcome (Wheless et al., 1999; Smith et al., 2000; Schwartz and Spencer, 2001; Genoa et al., 2004; Pataraia et al., 2004; Fischer et al., 2005; Schneider et al., 2012). MEG has been shown to be predictive for a favorable epilepsy surgery outcome in temporal lobe epilepsies (Rose et al., 1991; Iwasaki et al., 2002; Assaf et al., 2004), especially when the interictal MEG spikes are tightly clustered (Otsubo et al., 2001; Eliashiv et al., 2002; Oishi et al., 2002; Iida et al., 2005; Ossenblok et al., 2007). Multimodal approach in localizing the EZ was found to be significant when the MEG and other non-invasive modalities such as PET or SPECT were all concordant, that lead to increase in the yield of guidance of the ICEEG electrodes placement; of which Knowlton et al. (1997, 2006, 2008a,b) had concluded that MEG could replace ICEEG in such cases.

This study was conducted to investigate the impact of MEG on pre-surgical evaluation in a group of patients with intractable partial epilepsy. We evaluated the concordance between MEG and ICEEG results, investigated the characteristics that lead to concordance, and assessed how these factors relate to successful epilepsy surgery. This study separately investigated the contribution of various factors, i.e., the anatomic concordance of MEG/ICEEG, the resection of MEG focus, and the characteristics of the dipole cluster among the challenging group of intractable epilepsy patients considered for surgery.

The aim of this study was to validate MEG localizations in epilepsy pre-surgical assessment by utilizing newer advanced technologies in MEG recording with quantitative analysis of MEG findings resection and cluster character (orientation and size) in correlation to the surgical outcome.

Materials and methods

Population

We reviewed the data of 197 patients with intractable partial epilepsy from the Cleveland Clinic Epilepsy Center database that were subjected to MEG between 2008 and 2010 as part of the pre-surgical evaluation. The inclusion criteria were: (1) intractable epilepsy, (2) positive MEG and ICEEG findings, and (3) a minimum of six months of follow-up after epilepsy surgery. Of the 197 patients, 50 fulfilled the inclusion criteria and were included in the study. Among the remaining 147 patients, 132 did not undergo ICEEG, 12 had negative MEG studies, two did not tolerate ICEEG, and one patient had MEG technical difficulties. The same surgical team performed all of the surgeries, ensuring a similar approach.

Technical assessment

MEG recording parameters

We performed 50—60 min of resting-state spontaneous MEG activity in all of the patients using a whole-head, 306-channel Vector View System (Elekta, Helsinki, Finland) in the supine position. Simultaneous EEG was also recorded using the international 10-20-system of electrode placement, with additional anterior electrodes if indicated, e.g., anterior temporal electrodes. Both modalities were acquired together at 1000 samples/s with acquisition filter settings of 0.1 Hz high-pass and 333 Hz low-passes.

The data sets were post-processed with Maxfilter (Elekta, Helsinki, Finland) using the ''tSSS'' algorithm to remove environmental noise and using the head movement compensation algorithm to account for minor head movements. The data were then digitally band-pass filtered from 1 Hz to 55 Hz and were visually examined for abnormal activity, particularly interictal spikes. The spikes were modeled using the vendor's single equivalent current dipole modeling program ''xfit'' and were then co-registered to the individual pre-operative MRIs of each patient.

ICEEG recording parameters

Patients were implanted mostly using subdural (ECoG) grids and depth electrodes (majority of the depth electrodes were placed under stereotactic guidance). A formal patient management conference was held in each case to determine the electrode placement based on information from clinical assessments and other ancillary tests, including the MEG results. The patients underwent inpatient VEEG monitoring for 7—10 days. The ICEEG data were acquired at 500 samples/s with acquisition filter settings of 1 Hz high-pass and 120 Hz low-pass in a referential montage on a Nihon Kohden EEG System (NK, Tokyo, Japan). The data were reviewed on the same system using digital band pass filters of 5—75 Hz and using differential montages.

Cluster index

For this study, we created a ''cluster index,'' using an in-house program, a K-means partitioning method used to separate all of the MEG dipoles into K mutually exclusive clusters, such that the dipoles within each cluster were as close to each other as possible. The location of the centroid of each cluster and the average distance to each dipole in the cluster were then calculated. For display and measurement purposes, a sphere was drawn showing a ''cluster boundary'' based on the mean distance of all of the dipoles from the centroid plus one standard deviation. To calculate the orientation cone, all of the dipoles within a given cluster were translated to a common origin so that the average solid angle could be computed. For visualization, a three-dimensional cone oriented along this axis and with a vertex angle based on the mean angle of deviation from the average, plus one standard deviation, was generated. These graphical elements, namely the cluster diameter and the orientation angle, can be shown for each cluster and are logged in a spreadsheet (Burgess et al., 2011).

Data coding

MEG data

The MEG spike localizations were based on single equivalent current dipole (ECD) localization methods (Sutherling et al., 1988, 2001; Barth et al., 1989; Ebersole, 1997; Knowlton et al., 1997; Wheless et al., 1999). Individual dipole fits were deemed acceptable if: (a) the magnetic field distribution had a dipolar appearance, and (b) the goodness of fit (GOF) was at least 80%. Dipole sources were co-registered to the patient's MRI and the MEG focus was defined as a cluster of at least five dipoles within a circumscribed anatomical area. Factors evaluated in this study included the number of dipoles, the dipole anatomical location, the dipole orientation and the type of dipole cluster (as determined from the cluster diameter distance and the orientation angle of the sphere model).

ICEEG data

The interpretation of the ICEEG was based on the interictal and ictal findings. ICEEG seizure onset zone defined based on the evolving brain activity in frequency, morphology and amplitude over period of time (more 10 s), which is represented by specific anatomical location were the ICEEG grid contact was placed for recording. The localization of the estimated EZ for each patient was determined preferentially from the ictal onset, with the exception of 2 patients with ICEEG localization based only on clearly interictal focus due to the lack of seizures during the ICEEG monitoring.

Epilepsy surgery outcome

The epilepsy surgery outcome was assessed for at least 6 months as part of the regular epilepsy program follow-up. We dichotomized the postoperative outcome according to Engel's classification (Engel et al., 1993): ''Seizure Free Outcome'' (Engel Ia, completely seizure-free); and ''Seizure Recurrence Outcome'' (Engel Ib-IV, not seizure-free). The pathological findings of the resected tissue were correlated with the epilepsy surgery outcome.

Data analysis

MEG/ICEEG anatomical concordance

Concordance of the MEG and ICEEG findings was determined according to previously published criteria by Knowlton et al. (2008a,b). ''Anatomical concordance'' was defined as the similar localization of both MEG and ICEEG based on a defined anatomical region, such as ''sub-lobar'' or ''lobar'' subdivisions (Knowlton et al., 2008a,b). ''Sub-lobar'' concordance was defined as an overlapping of the MEG and ICEEG findings within the same subdivision and at the same lobe (e.g., superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and a similar order in other lobes), such as both localized to left posterior superior frontal gyrus (Fig. 1A); ''lobar'' concordance was defined as an overlapping of the MEG and ICEEG findings within the same anatomical lobe, but not necessarily limited to a subdivision within the lobe, such as both localized to the temporal lobe but with MEG localization posterior to the ICEEG focus (Fig. 1B). ''Anatomical Discordance'' was defined as the anatomical localization of MEG and ICEEG in different lobes (Fig. 1C).

MEG focus resection

An MRI was acquired pre- and post-operatively for each patient on either 1.5 T or 3 T instruments. The MRIs were typically performed on machines within the clinic using standard volumetric protocols that yield nearly isotropic 1 mm^3 voxels. The MEG data were co-registered with the individual MRI of each patient to compare the localization agreement of each modality for the precise brain anatomical concordance location. The MEG focus was coregistered to the post-operative MRI to evaluate the exact extent of the MEG focus localization compared to the surgical resection area. The MEG focus was considered to be ''completely resected''

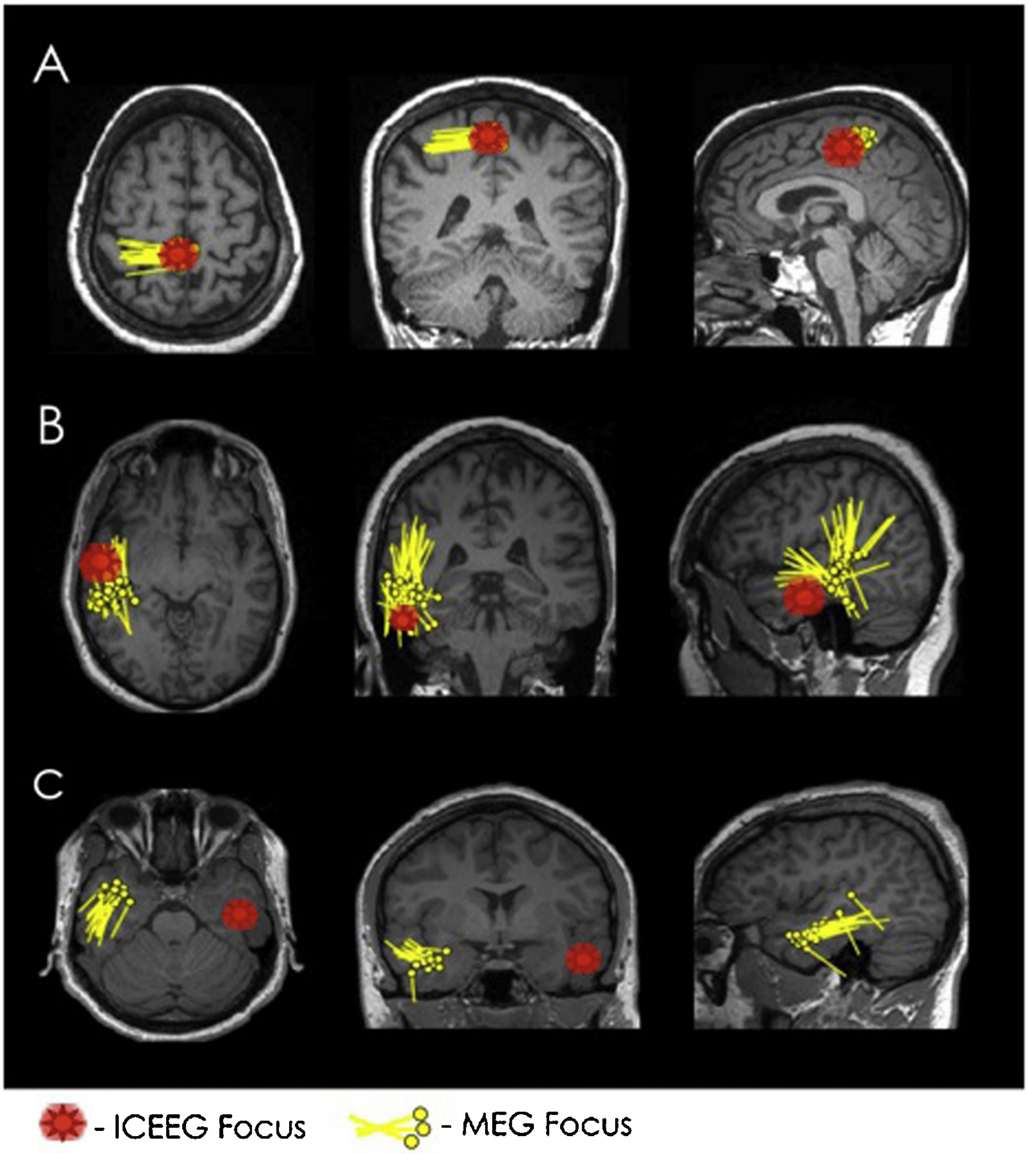

Figure 1 MEG/ICEEG concordance: (A) sublobar concordance on the right frontal superior gyrus where the MEG/ICEEG was completely overlapping (case# 5). (B) Lobar concordance on the right temporal in both MEG/ICEEG but was not completely overlapping (case# 25). (C) Anatomical discordance of both MEG and ICEEG due to different anatomical localization (case# 32).

if the surgically resected area determined by postoperative MRI completely contained the MEG focus. ''Partially resected'' was the incomplete resection of the MEG focus, i.e. not all of the MEG dipoles were included in the surgically resected area. ''Different site resected'' was when the margins of the MEG focus did not overlap with the site of the surgical resection area, such as when the localization was in another anatomical lobe (Fig. 2).

Dipole cluster type

A cluster index was used to estimate the character of the dipole cluster distribution in relation to the diameter distance in the sphere model and the orientation of the dipoles, which was formed by two planes diverging from a center point of the sphere. All of the dipoles were evaluated in relation to these two parameters, and the average of each parameter was estimated. We empirically determined a threshold by looking at past clinical MEG reports that mentioned dipoles judged to be substantially clustered on visual analysis. Based on large number of dipoles in this study, we estimated the average of the two parameters. This estimation showed a group of dipoles that manifested an average diameter distance of less than 10 mm, and an average orientation angle of less than 10 degrees was generally referred to as a ''tight cluster''. Correspondingly, a ''loose cluster'' was defined by a diameter distance and an orientation angle of more than 10 mm and 10 degrees respectively.

Statistical testing

The statistical methods were descriptive, which included frequency and cross tab analysis and mean and standard deviation (SD) calculations in the parametric data.

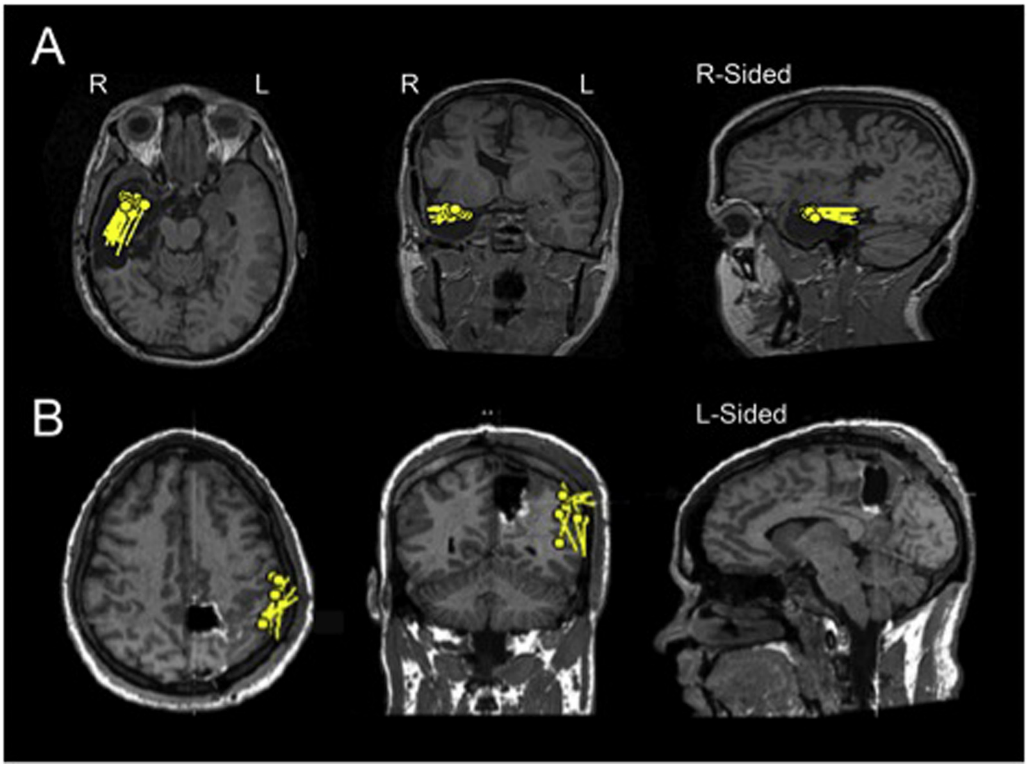

Figure 2 MEG focus resection: (A) excision of the right temporal lobe, MEG focus was completely resected and the patient had seizure-free outcome (case# 30). (B) Excision of left parietal operculum, MEG focus was not resected and the patient had seizure recurrence outcome (case# 13).

Univariate analysis between the surgical resection outcome and each MEG/ICEEG Concordance and MEG focus resection were performed. The chi-square statistical significance level was $p < 0.05$.

Results

Fifty patients had MEG and ICEEG correlations, and of those patients, 33 patients (66%) had anatomical concordance and 17 patients (34%) had discordance. The mean age of the patients was 30 years (SD ±13.8 years, range 11—65 years). The mean age at seizure onset was 11.7 years (SD ±9.5 years, range 1—50 years).

Thirty-six patients were treated surgically based on the pre-surgical evaluation. The mean duration of epilepsy at the time of surgery was 18 years (SD ±12.1, range 2—44). The mean follow-up after surgery was 12 months (SD ±5.4 months, range 6—28 months). Nineteen of the surgically treated patients (53%) had a ''seizure-free outcome'' (SFO), and 17 (47%) of the surgically treated patients had a ''seizure recurrence outcome'' (SRO) (Table 1). The pathological findings were identified for each patient and were focal cortical dysplasia in 22 patients, vascular changes in four patients, inflammatory changes in 4 patients, and gliosis in 6 patients. None of the pathological findings was significantly correlated to the epilepsy surgery outcome ($p = 0.90$).

Among the 14 patients who had no surgery treatment and had MEG and ICEEG, the ICEEG findings were not conclusive due to multifocal seizure onset zones in 7 patients, diffuse seizure onset in 4 patients, EZ overlapped with eloquent cortex in 2 patients, and 1 patient had no ictal event during the pre-surgical evaluation. The MEG findings showed multifocal localization in 8 patients, bilateral foci in 3 patients, fronto-orbital focus in 2 patients, and temporal focus in 1 patient. Six of those 14 patients had MEG and ICEEG concordance (1 localization overlapping eloquent area; 5 showed multifocal localization and there was an overlap on each test), other 8 patients had no significant localization of which epilepsy surgery was not performed.

MEG/ICEEG anatomical concordance

Among the 36 patients who had surgical treatment, 27/36 patients (75%) had anatomical concordance of MEG/ICEEG (18/27 patients (66%) had SFO and 9/27 patients (34%) had SRO), and 9/36 patients (25%) had anatomical discordance (1/9 patients (11%) had SFO, and 8/9 patients (89%) had SRO) ($p < 0.006$) (Table 2). Anatomical concordance was classified as ''Lobar Concordance'' in 14/27 patients (52%) (6/14 patients (42%) had SFO, and 8/14 patients (58%) had SRO), and ''Sub-lobar Concordance'' in 13/27 patients (48%) (12/13 patients (92%) had SFO, and 1/13 patients (8%) had SRO) ($p = 0.013$) (Table 2).

In the 18 patients with MEG/ICEEG concordance, the MRIs were non-lesional in 8 patients (44%) and lesional in 10 patients (56%). The clinical characteristics of these 18 patients (66%) with MEG/ICEEG concordance and a seizure free outcome showed that the concordant MEG focus was localized within the temporal lobe in 8 patients (44%), within

Table 1 The clinical findings of all patients had MEG, ICEEG, and surgical resection outcome.

No.	Age	Gender	Handedness	Seizure onset age	Seizure duration	Lesional/ non-lesional	MEG findings	ICEEG findings	ICEEG type	ICEEG electrodes no.	Concordance type	Surgical resection	Pathology	Post-op follow-up (months)	Seizures freedom
1	17	M	R	8	8	N	R temporal	R temporal	SEEG	132	LB	R frontal	GL	12	Yes
2	27	M	R	24	2	N	L temporal	R temporal	SEEG	82	NC	R temporal-occipital	CD	19	No
3	34	F	R	10	23	LE	R temporal	L parietal	DE	62	NC	L parietal-occipital	NS	9	No
4	13	F	R	8	2	N	L frontal	L frontal	SDE/DE	233	LB	L superior frontal	CD	28	No
5	30	F	R	2	28	LE	L frontal (pre-central)	L frontal (SMA)	SEEG	108	SL	L SMA	VAS	8	Yes
6	53	F	R	16	37	LE	R frontal	R frontal	SEEG	134	LB	R peri-orpecular and orbitofrontal	CD	10	Yes
7	41	M	R	30	10	N	Bi insular	R parietal	SEEG	152	NC	R parietal	GL	12	No
8	27	M	R	15	11	N	R temporal operculum	R tempo-ral/frontal	SEEG	118	NC	R frontal operculum	NS	12	No
9	22	M	L	5	17	LE	R temporal	R temporal	SEEG	158	LB	R temporal	CD	6	Yes
10	23	M	R	14	8	N	R tempo-ral/frontal/insular	R temporal	SEEG	154	NC	R temporal	GL	12	No
11	47	F	R	10	37	LE	L frontal operculum	L frontal operculum	SEEG	106	SL	L frontal operculum	CD	12	Yes
12	27	M	R	8	18	N	L parietal	L parietal	SEEG	136	LB	L superior parietal	CD	7	No
13	19	M	R	2	17	LE	L parietal	L parietal	SEEG	126	LB	L parietal operculum	VAS	15	No
14	12	M	R	2	9	N	L parietal operculum	L parietal operculum	SDE/DE	148	SL	L posterior parietal operculum	CD	16	Yes
15	16	F	L	9	5	N	L frontal	L frontal	SEEG	116	LB	L parietal	VAS	16	No
16	55	F	R	50	4	N	L frontal (pre-central)	L frontal (pre-central)	SDE	140	SL	R mesiofrontal parietal	NS	12	Yes
17	27	M	R	16	9	N	L temporal (anterior pole)	L temporal (anterior pole)	SEEG	94	SL	L temporal	GL	21	Yes
18	53	F	R	39	12	LE	R temporal	R amygdala	SDE/DE	232	NC	R mesial frontal	CD	22	No
19	31	M	R	13	17	LE	L temporal (superior gyrus)	L temporal (superior gyrus)	SDE/DE	120	SL	L lateral temporal	GL	19	Yes
20	39	M	R	16	22	LE	R temporal	R temporal	SDE/DE	224	LB	R temporal parietal	CD	16	No
21	56	M	R	11	43	LE	R frontal operculum	R frontal operculum	SDE/DE	191	SL	R frontal	CD	22	No
22	30	F	R	8	21	LE	L frontal (pre-central)	L frontal (pre-central)	SDE/DE	146	SL	R frontal	CD	12	Yes
23	20	M	R	3	17	LE	R temporal	R frontal	SEEG	130	NC	R frontal	CD	6	No
24	46	F	R	25	20	N	R parietal	L frontal/parietal	SEEG	142	NC	L frontal	CD	8	Yes
25	32	M	R	18	14	N	R temporal	R temporal	SEEG	100	LB	R temporal	CD	12	Yes
26	14	M	R	11	2	N	R temporal	R temporal	SEEG	152	LB	R superior temporal/frontal operculum	NS	6	No
27	30	M	R	14	16	LE	R frontal	R frontal	SEEG	166	LB	R frontal/parietal	CD	12	Yes
28	43	M	R	11	31	N	L temporal (superior gyrus)	L temporal (superior gyrus)	SDE/DE	96	SL	l superior temporal	CD	11	Yes
29	43	M	R	18	25	N	L temporal (middle gyrus)	L temporal (middle gyrus)	SDE/DE	222	SL	L lateral temporal	CD	11	Yes
30	20	F	R	4	15	LE	L temporal operculum	L temporal operculum	SEEG	144	SL	R temporal	CD	9	Yes
31	20	M	R	9	11	LE	R frontal (pre-central)	R frontal (pre-central)	SEEG	132	SL	R frontal	CD	10	Yes
32	16	M	R	12	3	LE	R temporal	L temporal	SEEG	144	NC	L temporal	CD	6	No
33	15	M	R	5	12	LE	L temporal	L temporal	SEEG	138	LB	L temporal	CD	7	No
34	54	M	R	16	37	N	L temporal	L temporal	SEEG	100	LB	L temporal/inferior frontal	NS	6	No
35	31	M	L	12	6	N	R frontal operculum	R frontal operculum	SEEG	92	SL	R frontal operculum	CD	12	Yes
36	54	F	R	18	36	LE	R temporal	R temporal	SEEG	80	LB	R temporal parietal	GL	6	Yes

M: male; F: female; R: right; L: left; Bi: bilateral N: non-lesional; LE: lesional; SEEG: stereotactic EEG; SDE: subdural electrodes; DE: depth electrodes; LB: lobar; SL: Sub-lobar; NC: no concordance; C: complete resection; P: partial resection; D: different site resection; GL: gliosis; CD: cortical dysplasia; VAS: vascular; NS: non-specific.

Table 2 MEG and ICEEG concordance in relation to epilepsy surgery outcome.

MEG/ICEEG localization		*N*	Epilepsy surgery outcome		
			Seizure free	Seizure reoccur	*p*-value
Anatomical	Concordance	27	18	9	0.006
	Discordance	9	1	8	
Subdivision	Lobar	14	6	8	0.013
	Sublobar	13	12	1	

the peri-rolandic and peri-sylvian regions in 8 patients (44%), and within frontal lobe in 2 patients (12%). The MEG findings were localized to the superficial neocortex in 16 patients (89%), and the focus was localized in deep mesial structures in 2 patients (11%). The pathological findings showed that 12 patients (67%) had cortical dysplasia, 4 patients (22%) had gliosis, and 1 patient (6%) had a vascular lesion.

MEG focus resection

The post-operative MRI determined the resected MEG focus. The resection was complete in 19/36 patients (52%) (15/19 patients (79%) had SFO, and 4/19 patients (21%) had SRO) ($p < 0.001$) (Table 3), and the resection was incomplete (partial and different location) in 17/36 patients (48%) (4/17 patients (23.5%) had SFO, and 13/17 patients (76.5%) had SRO) ($p < 0.001$) (Table 3).

The clinical characteristics of the 15 patients (79%) with complete resection and a seizure-free outcome showed that the resected MEG focus was localized within the peri-rolandic and peri-sylvian regions in 8 patients (53%), the temporal lobe in 6 patients (40%), and the fronto-orbital region in 1 patient (7%). The MEG findings were localized to the superficial neocortex in 13 patients (87%) and were localized to the deep mesial structure in 2 patients (13%). The MRI findings were non-lesional in 7 patients (47%) and lesional in 8 patients (53%). The pathological findings included 10 patients (67%) with cortical dysplasia, 3 patients (20%) with gliosis, and 1 patient (1%) with a vascular lesion.

Dipoles cluster types

Tight and loose clusters (determined by the radius distance and orientation angle) were investigated in the 36 patients who underwent resective surgery to determine which cluster characteristics were better correlated with the epilepsy surgery outcome. Of the patients who had surgery, 10 patients (30%) had a tight radius cluster (7 patients (70%) had SFO, and 3 patients (30%) had SRO), and 24 patients (70%) had a loose radius cluster (12 patients (50%) had SFO, and 12 patients (50%) had SRO) ($p = 0.270$) (Table 4). Of the patients who had surgery, 11 patients (33%) had a tight orientation angle cluster (8 patients (73%) had SFO, and 3 patients (27%) had SRO), and 23 patients (67%) had a loose orientation angle cluster (11 patients (48%) had SFO, and 12 patients (52%) had SRO) ($p = 0.161$) (Table 4). The presence of tight cluster based on any of the parameters (radius distance or orientation angle) was associated with the highest chance (70—73%) for seizure freedom after surgery, in compare to the loose cluster where the chance is 48—50%.

Table 3 MEG focus resection in relation to epilepsy surgery outcome.

MEG resection		*N*	Epilepsy surgery outcome		
			Seizure free	Seizure reoccur	*p*-value
Complete	Yes	19	15	4	<0.001
	No	17	4	13	
Different	Yes	10	2	8	0.015
	No	26	17	9	

Discussion

The aim of this study was to investigate the impact of the anatomical concordances of MEG and ICEEG findings to localize the EZ and resection of the MEG focus on the outcome after epilepsy surgery. Furthermore, we tested a model of dipole cluster types to assess if any pattern of EZ localization and complete resection led to increase the chance of a favorable epilepsy surgery outcome.

Several previous studies have explored the concordance between MEG and ICEEG (Smith et al., 2000; Minassian et al.,

Table 4 Cluster type in relation to epilepsy surgery outcome.

Parameters	Cluster type	*N*	Epilepsy surgery outcome		
			Seizure free	Seizure reoccur	*p*-value
Radius	Tight	10	7	3	0.270
	Loose	24	12	12	
Angle	Tight	11	8	3	0.161
	Loose	23	11	12	

1999; Mamelak et al., 2002; Knowlton et al., 2006, 2009; RamachandranNair et al., 2007; Sutherling et al., 2008). In this study, patients with MEG/ICEEG concordance and a seizure free outcome had MEG and ICEEG findings that were mostly localized to the temporal lobe or peri-rolandic and peri-sylvian regions (88%), were isolated to neocortical regions (89%) and were non-lesional (55%). These results confirm previous studies and established the characteristics of concordance MEG/ICEEG based on different model and parameters in the same cohort.

The resection of entire MEG focus was significantly correlated with a seizure-free outcome (15/19 patients (79%) ($p < 0.001$)), which included peri-rolandic and peri-sylvian regions in 53%, temporal regions in 40%, and superficial neocortical and sub-lobar regions in 76%. Different localization of the MEG focus and the surgically resected area was associated with worse seizure outcome (8/10 patients (80%) ($p = 0.02$)), and none of these patients had MEG and ICEEG concordance. Wheless et al. (1999) reported that MEG was successful in 52%, which is second to ICEEG in predicting the EZ for patients with excellent surgical outcomes. Fischer et al. (2005) indicated that a high coverage of the resected volume of the MEG ellipsoid correlated with a favorable outcome. Our findings were similar to those studies and illustrated how MEG significantly affects anatomical resectioning.

Mamelak et al. (2002) reported MEG to be useful in localizing neocortical epilepsies, particularly when the interictal spikes are densely clustered in a single anatomical location. RamachandranNair et al. (2007) found that 8 of the 22 patients had post-operative seizure freedom when the MEG spike clusters were completely resected. Otsubo et al. (2001) found that the removal of MEG spikes clusters within and extending from lesions observed on the MRI prevented seizure recurrence in 12 patients with cortical dysplasia. Additionally, 70—73% of patients who had a tight radius or angle that overlapped with the resected area had a seizure-free surgery outcome. Our findings agree with these previous studies, suggesting that a MEG tight cluster is relatively specific for detecting the EZ and is sensitive for predicting seizure freedom. Importantly, we based our findings on a quantitative tool.

Several limitations must be considered in the interpretation of this retrospective study. In some cases where MEG sources were found in the bilateral hemispheres, the determination of the epileptic focus was based on the localization of the majority of the dipoles (>70% of dipoles), similar to the approach for ICEEG interpretation. This approach could result in a bias of MEG localization. ICEEG placement was based on the proposed logical hypothesis generated from the clinical features of other tests, but if the initial hypothesis were incorrect; the final localization would be inconclusive, possibly leading to an unfavorable epilepsy surgery outcome. ICEEG results cannot be regarded as entirely independent of the MEG findings because MEG might have influenced our electrode placement. Some MEG findings did not reach statistical significance (e.g., dipole cluster type) when correlated with the surgical resection, either due to a small sample or the limitations of the source-localizing model (e.g. single dipole fitting).

In this study the value of MEG localization was validated based on different parameters, such as a systematic approach to guide MEG and ICEEG placement, the resection of the entire MEG focus, and the cluster analysis. Some values were more statistically significant than in other studies. Our findings extend the knowledge of MEG focus characteristics for resection, which is beyond the tentative findings, and all of the findings were based on advanced MEG data interpretation. Our study sets the stage for a study evaluating the prospective use of the MEG localizing tools.

Conclusion

We reviewed multiple factors in relation to MEG results in an effort to provide practical guidance for the evaluation of patients being considered for epilepsy surgery. The predictive value of MEG for successful epilepsy surgery was higher when: (1) there was a sub-lobar concordance of the MEG and ICEEG findings and completely resected; and (2) the epileptogenic zone was localized to the superficial neocortex, and more specifically in the regions where the neocortex was tangential in orientation. When the MEG and ICEEG findings are disconcordant, the localization of the epileptogenic zone should be carefully reviewed. Nevertheless, tight clusters in a context of sub-lobar concordance between MEG/ICEEG could associate with better localization.

References

Agirre-Arrizubieta, Z., Huiskamp, G.J., Ferrier, C.H., van Huffelen, A.C., Leijten, F.S., 2009. Interictal magnetoencephalography and the irritative zone in the electrocorticogram. Brain 132, 3060—3071.

Assaf, B.A., Karkar, K.M., Laxer, K.D., Garcia, P.A., Austin, E.J., Barbaro, N.M., Barbaro, N.M., Aminoff, M.J., 2004. Magnetoencephalography source localization and surgical outcome in temporal lobe epilepsy. Clin. Neurophysiol. 115, 2066—2076.

Barkley, G.L., Baumgartner, C., 2003. MEG and EEG in epilepsy. J. Clin. Neurophysiol. 20, 163—178.

Barth, D.S., Baumgartner, C., Sutherling, W.W., 1989. Neuromagnetic field modeling of multiple brain regions producing interictal spikes in human epilepsy. Electroencephalogr. Clin. Neurophysiol. 73 (5), 389—402.

Baumgartner, C., 2000. Clinical applications of magnetoencephalography. J. Clin. Neurophysiol. 17, 175—176.

Baumgartner, C., 2004. Controversies in clinical neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity. Controv. Clin. Neurophysiol. 115, 1010—1020.

Baumgartner, C., Pataraia, E., 2006. Revisiting the role of magnetoencephalography in epilepsy. Curr. Opin. Neurol. 19, 181—186.

Burgess, R.C., Wang, Z.I., Almubarak, S., Piao, Z., Jin, K., Kakisaka, Y., Mosher, J.C., Dubarry, A.S., Alexopoulos, A.V., 2011. Quantitative characterization of MEG dipole clusters: an objective measurement tool for comparison with intracranial recordings and surgical resection. In: Poster at American Epilepsy Society Sixty-Fifth Annual Meeting, Baltimore, MD.

Ebersole, J.S., 1997. Magnetoencephalography/magnetic source imaging in the assessment of patients with epilepsy. Epilepsia 38 (4), S1—S5.

Ebersole, J.S., Ebersole, S.M., 2010. Combining MEG and EEG source modeling in epilepsy evaluations. J. Clin. Neurophysiol. 27, 360—371.

Eliashiv, D.S., Elsas, S.M., Squires, K., Fried, I., Engel Jr., J., 2002. Ictal magnetic source imaging as a localizing tool in partial epilepsy. Neurology 59, 1600—1610.

Engel, J.J., Van, N.P., Rasmussen, T.B., Ojemann, L.M., 1993. Outcome with respect to epilepticseizures. In: Engel, J.J. (Ed.), Surgical treatment of the epilepsies. Raven Press, New York, pp. 609—621.

Fischer, M.J., Scheler, G., Stefan, H., 2005. Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery. Brain 128, 153—157.

Genoa, A., Hummel, C., Schuler, G., Hopfengärtner, R., Kaltenhäuser, M., Buchfelder, M., Romstöck, J., Stefan, H., 2004. Epilepsy surgery, resection volume and MSI localization in lesional frontal lobe epilepsy. NeuroImage 21, 444—449.

Grondin, R., Chuang, S., Otsubo, H., Holowka, S., Snead, C., Raybaud, C., Rutka, J.T., 2006. The role of magnetoencephalography in pediatric epilepsy surgery. Child. Nerv. Syst. 22, 779—785.

Iida, K., Otsubo, H., Mohamed, I.S., Okuda, C., Ochi, A., Weiss, S.K., Chuang, S.H., Snead 3rd., O.C., 2005. Characterizing magnetoencephalographic spike sources in children with tuberous sclerosis complex. Epilepsia 46 (9), 1510—1517.

Iwasaki, M., Nakasato, N., Shamoto, H., Nagamatsu, K., Kanno, A., Hatanaka, K., Yoshimoto, T., 2002. Surgical implications of neuromagnetic spike localization in temporal lobe epilepsy. Epilepsia 43, 415—424.

King, D.W., Park, Y.D., Smith, J.R., Wheless, J.W., 2000. Magnetoencephalography in neocortical epilepsy. Adv. Neurol. 84, 415—423.

Knowlton, R.C., 2003. Magnetoencephalography: clinical application in epilepsy. Curr. Neurol. Neurosci. Rep. 3, 341—348.

Knowlton, R.C., Laxer, K.D., Aminoff, M.J., Roberts, T.P., Wong, S.T., Rowley, H.A., 1997. Magnetoencephalography in partial epilepsy: clinical yield and localization accuracy. Ann. Neurol. 42, 622—631.

Knowlton, R.C., Elgavish, R., Howell, J., Blount, J., Burneo, J.G., Faught, E., Kankirawatana, P., Riley, K., Morawetz, R., Worthington, J., Kuzniecky, R.I., 2006. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. Ann. Neurol. 59, 835—842.

Knowlton, R.C., Elgavish, R.A., Bartolucci, A., Ojha, B., Limdi, N., Blount, J., Burneo, J.G., Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Riley, K., Kuzniecky, R., 2008a. Functional imaging: II. Prediction of epilepsy surgery outcome. Ann. Neurol. 64, 35—41.

Knowlton, R.C., Elgavish, R.A., Limdi, N., Bartolucci, A., Ojha, B., Blount, J., Burneo, J.G., Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Riley, K., Kuzniecky, R., 2008b. Functional imaging: I. Relative predictive value of intracranial electroencephalography. Ann. Neurol. 64, 25—34.

Knowlton, R.C., Razdan, S.N., Limdi, N., Elgavish, R.A., Killen, J., Blount, J., Burneo, J.G., Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Bartolucci, A., Riley, K., Kuzniecky, R., 2009. Effect of epilepsy magnetic source imaging on intracranial electrode placement. Ann. Neurol. 65, 716—723.

Mamelak, A.N., Lopez, N., Akhtari, M., Sutherling, W.W., 2002. Magnetoencephalography-directed surgery in patients with neocortical epilepsy. J. Neurosurg. 97, 865—873.

Mikuni, N., Nagamine, T., Ikeda, A., Terada, K., Taki, W., Kimura, J., Kikuchi, H., Shibasaki, H., 1997. Simultaneous recording of epileptiform discharges by MEG and subdural electrodes in temporal lobe epilepsy. NeuroImage 5, 298—306.

Minassian, B.A., Otsubo, H., Weiss, S., Elliott, I., Rutka, J.T., Snead 3rd., O.C., 1999. Magnetoencephalographic localization in pediatric epilepsy surgery: comparison with invasive intracranial electroencephalography. Ann. Neurol. 46, 627—633.

Oishi, M., Otsubo, H., Kameyama, S., Morota, N., Masuda, H., Kitayama, M., Tanaka, R., 2002. Epileptic spikes: magnetoencephalography versus simultaneous electrocorticography. Epilepsia 43, 1390—1395.

Ossenblok, P., de Munck, J.C., Colon, A., Drolsbach, W., Boon, P., 2007. Magnetoencephalography is more successful for screening and localizing frontal lobe epilepsy than electroencephalography. Epilepsia 48, 2139—2149.

Otsubo, H., Ochi, A., Elliott, I., Chuang, S.H., Rutka, J.T., Jay, V., Aung, M., Sobel, D.F., Snead, O.C., 2001. MEG predicts epileptic zone in lesional extrahippocampal epilepsy: 12 pediatric surgery cases. Epilepsia 42, 1523—1530.

Pataraia, E., Baumgartner, C., Lindinger, G., Deecke, L., 2002. Magnetoencephalography in presurgical epilepsy evaluation. Neurosurg. Rev. 25, 141, 59, 160—161.

Pataraia, E., Simos, P.G., Castillo, E.M., Billingsley, R.L., Sarkari, S., Wheless, J.W., Maggio, V., Maggio, W., Baumgartner, J.E., Swank, P.R., Breier, J.I., Papanicolaou, A.C., 2004. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? Neurology 62, 943—948.

Paulini, A., Fischer, M., Rampp, S., Scheler, G., Hopfengärtner, R., Kaltenhäuser, M., Dörfler, A., Buchfelder, M., Stefan, H., 2007. Lobar localization information in epilepsy patients: MEG a useful tool in routine presurgical diagnosis. Epilepsy Res. 76, 124—130.

RamachandranNair, R., Otsubo, H., Shroff, M.M., Ochi, A., Weiss, S.K., Rutka, J.T., Snead 3rd., O.C., 2007. MEG predicts outcome following surgery for intractable epilepsy in children with normal or nonfocal MRI findings. Epilepsia 48, 149—157.

Ray, A., Bowyer, S.M., 2010. Clinical applications of magnetoencephalography in epilepsy. Ann. Indian Acad. Neurol. 13, 14—22.

Rose, D.F., Sato, S., Ducla-Soares, E., Kufta, C.V., 1991. Magnetoencephalographic localization of subdural dipoles in a patient with temporal lobe epilepsy. Epilepsia 32, 635—641.

Schneider, F., Alexopoulos, A.V., Wang, Z., Almubarak, S., Kakisaka, Y., Jin, K., Nair, D., Mosher, J.C., Najm, I.M., Burgess, R.C., 2012. Magnetic source imaging in non-lesional neocortical epilepsy: additional value and comparison with ICEEG. Epilepsy Behav. 24, 234—240.

Schwartz, T.H., Spencer, D.D., 2001. Strategies for reoperation after comprehensive epilepsy surgery. J. Neurosurg. 95, 615—623.

Smith, J.R., King, D.W., Park, Y.D., Lee, M.R., Lee, G.P., Jenkins, P.D., 2000. Magnetic source imaging guidance of gamma knife radiosurgery for the treatment of epilepsy. J. Neurosurg. 93 (3), 136—140.

Stefan, H., Hummel, C., Hopfengärtner, R., Pauli, E., Tilz, C., Ganslandt, O., Kober, H., Möler, A., Buchfelder, M., 2000. Magnetoencephalography in extratemporal epilepsy. J. Clin. Neurophysiol. 17, 190—200.

Stefan, H., Hummel, C., Scheler, G., Genow, A., Druschky, K., Tilz, C., Kaltenhäuser, M., Hopfengärtner, R., Buchfelder, M., Romstöck, J., 2003. Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. Brain 126, 2396—2405.

Sutherling, W.W., Crandall, P.H., Cahan, L.D., Barth, D.S., 1988. The magnetic field of epileptic spikes agrees with intracranial localizations in complex partial epilepsy. Neurology 38, 778—786.

Sutherling, W.W., Akhtari, M., Mamelak, A.N., Mosher, J., Arthur, D., Sands, S., Weiss, P., Lopez, N., DiMauro, M., Flynn, E., Leah, R., 2001. Dipole localization of human induced focal afterdischarge seizure in simultaneous magnetoencephalography and electrocorticography. Brain Topogr. 14 (2), 101—116.

Sutherling, W.W., Mamelak, A.N., Thyerlei, D., Maleeva, T., Minazad, Y., Philpott, L., Lopez, N., 2008. Influence of magnetic source imaging for planning intracranial EEG in epilepsy. Neurology 71, 990—996.

Wheless, J.W., Willmore, L.J., Breier, J.I., Kataki, M., Smith, J.R., King, D.W., Meador, K.J., Park, Y.D., Loring, D.W., Clifton, G.L., Baumgartner, J., Thomas, A.B., Constantinou, J.E., 1999. A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. Epilepsia 40, 931—941.

Wheless, J.W., Castillo, E., Maggio, V., Kim, H.L., Breier, J.I., Simos, P.G., Papanicolaou, A.C., 2004. Magnetoencephalography (MEG) and magnetic source imaging (MSI). Neurologist 10, 138—153.

Wu, J.Y., Sutherling, W.W., Koh, S., Salamon, N., Jonas, R., Yudovin, S., Sankar, R., Shields, W.D., Mathern, G.W., 2006. Magnetic source imaging localizes epileptogenic zone in children with tuberous sclerosis complex. Neurology 66, 1270—1272.