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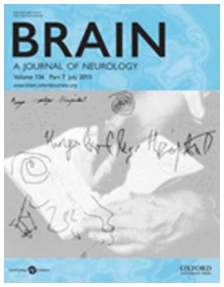

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Localization of the epileptogenic zone using magnetoencephalography predicts seizure freedom in epilepsy surgery

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Abstract

The efficacy of epilepsy surgery depends critically upon successful localization of the epileptogenic zone. Magnetoencephalography (MEG) enables non-invasive detection of interictal spike activity in epilepsy, which can then be localized in three dimensions using magnetic source imaging (MSI) techniques. However, the clinical value of MEG in the pre-surgical epilepsy evaluation is not fully understood, as studies to date are limited by either a lack of long-term seizure outcomes or small sample size. We performed a retrospective cohort study of focal epilepsy patients who received MEG for interictal spike mapping followed by surgical resection at our institution. We studied 132 surgical patients, with mean post-operative follow-up of 3.6 years (minimum 1 year). Dipole source modelling was successful in 103 (78%) patients, while no interictal spikes were seen in others. Among patients with successful dipole modelling, MEG findings were concordant with and specific to: i) the region of resection in 66% of patients, ii) invasive electrocorticography (ECoG) findings in 67% of individuals, and iii) the MRI abnormality in 74% of cases. MEG showed discordant lateralization in ~5% of cases. After surgery, 70% of all patients achieved seizure-freedom (Engel class I outcome). Whereas 85% of patients with concordant and specific MEG findings became seizure-free, this outcome was achieved by only 37% of individuals with MEG findings that were non-specific or discordant with the region of resection ($\chi^2 = 26.4$, $p < 0.001$). Localizing MEG findings predicted seizure freedom with an odds ratio of 5.71 (2.30-14.2, 95% CI), and had a positive predictive value (PPV) of 91.9% in temporal lobe and 77.4% in extra-temporal/multi-lobe cases. In conclusion, MEG is a valuable tool for non-invasive interictal spike mapping in epilepsy surgery, and localization of the epileptogenic zone using MEG is associated with improved seizure outcomes.

Key words: epilepsy surgery, epileptogenic zone, imaging, magnetoencephalography (MEG), refractory

Essential abbreviations: ECoG: electrocorticography; EEG: electroencephalography; GTCS: generalized tonic-clonic seizures; MEG: magnetoencephalography; MSI: magnetic source imaging; MRI: magnetic resonance imaging; OR: odds ratio; PET: positron emission tomography; TLE: temporal lobe epilepsy.

Introduction

Seizures are resistant to anti-epileptic drugs in one third of patients with focal epilepsy, leading to significant morbidity (Cascino, 2008). Resective epilepsy surgery leads to seizure-freedom in approximately two-thirds of patients with temporal lobe epilepsy (TLE), and in more than one-half of individuals with an extra-temporal epileptogenic zone (Engel *et al.* , 2012, Englot *et al.* , 2013, Spencer and Huh, 2008). Despite these successes, there is substantial room for improvement in the localization and surgical treatment of drug-resistant epilepsy. While invasive electro-diagnostic techniques such as electrocorticography (ECoG) are the gold standard for seizure focus localization, recordings require additional surgical intervention and are limited to the area of electrode coverage (Yuan *et al.* , 2012). Improved methods for non-invasive mapping of epileptogenic networks across the whole brain remain critically important to the pre-surgical evaluation, as adequate localization of the seizure focus is the most important predictor of seizure freedom in epilepsy surgery (Englot *et al.* , 2014).

Magnetoencephalography (MEG) is a non-invasive tool that can help delineate the epileptogenic zone, in part by localizing interictal epileptic spikes (Kirsch *et al.* , 2007, Tovar-Spinoza *et al.* , 2008). MEG possesses high spatio-temporal resolution without signal deterioration from the skull and scalp that may limit signal propagation with EEG (Zumer *et al.* , 2007). Brain source imaging with MEG can be achieved using equivalent current dipole (ECD) modeling of interictal spikes, and the position and orientation of the estimated dipole can be overlaid onto the patient's own co-registered magnetic resonance imaging (MRI) to aid surgical planning (Funke *et al.* , 2009, Kirsch *et al.* , 2007). This process of interictal spike modeling of MEG data and dipole map overlay is often referred to as magnetic source imaging (MSI). However, despite advances in source localization techniques, MEG is performed in only a

minority of pre-surgical epilepsy evaluations. While cost and regional availability contribute to relatively low rates of utilization, the clinical value of MEG in surgical epilepsy treatment has also been less well established compared to diagnostic modalities such as EEG, ECoG, MRI, and other functional neuroimaging methods (Stefan *et al.* , 2011).

Previous studies have compared interictal MEG to other diagnostic modalities for epileptogenic zone localization (Pataraia *et al.* , 2004, Paulini *et al.* , 2007). Stefan and colleagues report the largest series of MEG in epilepsy to date, describing a 70% sensitivity of MEG for detecting epileptic activity in 455 patients, of which 131 had epilepsy surgery (Stefan *et al.* , 2003). However, without detailed analysis of post-operative seizure outcome, only limited conclusions can be drawn regarding the predictive value of MEG in achieving long-term seizure-freedom. While other studies have directly related MEG findings to surgical outcome, their statistical conclusions have been limited by small sample size (Fischer *et al.* , 2005, Knowlton *et al.* , 2006, Mu *et al.* , 2014, Paulini *et al.* , 2007). After systematic review of relevant studies, one group suggested there is insufficient evidence in the literature to support a relationship between MEG use and seizure outcome after epilepsy surgery (Lau *et al.* , 2008). Furthermore, given the additional technical challenges of source localization with deeper brain structures such as the mesial temporal lobe, some have argued that MEG has diminished clinical utility in TLE compared to neocortical epilepsy (Leijten *et al.* , 2003, Shigeto *et al.* , 2002). Thus, the predictive value of MEG spike mapping in epilepsy surgery remains incompletely understood.

Here we report a retrospective cohort study including 132 patients with focal epilepsy who underwent MEG followed by resective epilepsy surgery at our institution, with seizure outcomes determined at mean post-operative follow-up of 3.6 years (minimum 1 year). We examine the concordance of spike activity mapped by MSI with the area of resection and with

the results of other diagnostic modalities, and relate MEG findings to seizure outcome. To our knowledge, this represents the largest reported series of MEG in surgical epilepsy patients with comprehensive long-term seizure outcome data.

Materials and Methods

Patients

We retrospectively examined 348 MEG recordings performed in 310 epilepsy patients referred for studies at the University of California, San Francisco (UCSF) Biomagnetic Imaging Laboratory (BIL) between June 1, 2004 and June 30, 2013. Among these, we identified 144 patients who underwent resective surgery for focal epilepsy at our institution following MEG recordings. Twelve patients without at least one year of post-operative follow-up were excluded, and 132 patients were analyzed. Overall, 43% of patients who underwent extra-temporal resection and 36% of those who received temporal lobectomy for intractable epilepsy at our institution during the study period received MEG. While no strict referral criteria exist in our practice, MEG is typically performed on patients in whom surgical intervention is being considered, but there is some uncertainly with regard to seizure focus localization after long-term scalp EEG and anatomical MRI. Patients who underwent only non-resective epilepsy surgery, such as a device implantation or disconnection procedure, were not included. Only the last MEG session prior to surgery was considered in patients who underwent multiple recording sessions. All procedures and patient consents in the study were in full compliance with UCSF clinical research policies, with research protocol approval by the UCSF Committee on Human Research.

MEG data acquisition and analysis

Simultaneous EEG and MEG recordings were performed inside a magnetically shielded room, with a 275 channel whole-head axial gradiometer system (VSM MedTech, Port Coquitlam, British Columbia). Data were recorded from each patient in a passband of 0–75 Hz (300 Hz sample rate) using a CTF 275 channel whole cortex MEG helmet. Twenty-one channel scalp EEG was recorded simultaneously using a modified international 10–20 system that includes subtemporal electrodes. Thirty to forty minutes of spontaneous data were obtained in 10–15 min intervals with the patient asleep and awake. The position of the head in the MEG dewar relative to the MEG sensors was determined via indicator coils before and after each interval to ensure adequate sampling of the entire magnetic field. The data were bandpass filtered offline at 1–70 Hz.

Spikes were visually identified by a certified EEG technologist (MM) and were confirmed by a board-certified clinical neurophysiologist and epileptologist (HEK). EEG spikes were identified based on the criteria defined by the International Federation of Clinical Neurophysiology (IFCN) for EEG epileptiform discharges (Deuschl and Eisen, 1999). MEG spikes were chosen for analyses based on duration (< 80 ms), morphology, field map, and lack of associated artifact. The onset of each spike, defined as the rising deflection of the first sharp negativity from the baseline, was marked and ECDs were fit using commercial software provided by CTF Systems (VSM MedTech, Port Coquitlam, British Columbia). Only sources with a goodness of fit higher than 90% were accepted. Co-registration of dipoles to MRI scans was performed using fiducials (nasion and preauricular points) to produce magnetic source images (MSI) of dipoles superimposed on anatomic images. The authors then inspected these results and classified the spike dipoles according to their location and orientation.

We estimated the concordance between the lobe or lobar regions(s) indicated by spike dipoles localization and three separate reference regions: i) the lobe (or sublobar region) of resection determined by examination of post-operative MRI and operative reports, ii) the epileptogenic zone as estimated by epileptologist review of invasive intra-operative (interictal) and extra-operative (ictal and interictal) ECoG recordings, when available, and iii) the region of abnormality, if present, seen on MRI. Dipoles were considered concordant with the reference region if the dipole location and orientation indicated spike source in the same lobe or lobar region. If the region indicated by spike dipoles indicated more than one lobar region of epileptogenic tissue extent, but the reference region also overlapped these multiple regions (e.g., left lateral parieto-occipital spikes preceding a parieto-occipital cortical resection), findings were considered concordant. Spike activity was considered concordant and specific if no appreciable (>10%) dipole source estimates were observed in other lobes, but considered non-specific in the setting of another distal region with >10% dipoles. Other scenarios included cases in which dipoles were ipsilateral but in a different region compared to the reference area (concordant lateralization only), and cases of discordant lateralization in which >50% of dipoles were contralateral. Spike localization and the determination of concordance between regions were performed while blinded to the patient's seizure outcome.

Evaluation of clinical data and seizure outcomes

For all patients, we retrospectively reviewed outpatient and inpatient provider notes, diagnostic and laboratory reports, operative records, and pathology reports. Clinical and demographic data including patient gender, age, handedness, epilepsy duration, surgical history, medication

history, MRI results, EEG findings, PET results, use of implanted electrodes for long-term recording, side and region of surgery, as well as the use of intra-operative ECoG were recorded. Details regarding patients' epilepsy history and seizure semiology, including seizure type and frequency, were obtained from pre-operative and post-operative assessments by epileptologists. Epilepsy risk factors were recorded, including a history of: i) cerebral palsy or birth injury, ii) developmental delay or static encephalopathy, iii) febrile seizures, iv) head trauma, v) central nervous system infection, vi) epilepsy family history, vii) drug or alcohol abuse, viii) cerebral ischemia, and/or ix) status epilepticus. Seizure outcome was determined by the latest patient follow-up with the epileptologist using a modified Engel classification system (Engel *et al.* , 1993). Except where specified, "seizure freedom" is used here to refer to an Engel class I outcome, signifying freedom from all disabling seizures.

Surgical decisions were made by a comprehensive team of epileptologists, neurosurgeons, neuropsychologists, neuroradiologists, and other practitioners. Standard pre-operative evaluation included magnetoencephalography (MEG), scalp EEG, and structural MRI, and often included neuropsychological evaluation, positron emission tomography (PET), and long-term video-EEG monitoring with or without extra-operative ECoG using surgically implanted subdural and/or depth electrodes. Intra-operative interictal ECoG was also performed in the majority of cases. Resections were customized to incorporate epileptogenic regions and cerebral lesions, and to preserve eloquent cortex, where applicable. For cases of mesial TLE, anterior temporal lobectomy was performed, including tailored resection of the lateral temporal cortex, amygdala, and hippocampus. Surgical specimens were analyzed by neuropathologists.

Statistical analysis

Individual chi-square (χ^2) tests were used to evaluate potential associations between MEG findings defined above (concordant and specific versus non-specific, lateralized only, or discordant) and location of resection (temporal lobe versus extra-temporal), and between MEG findings and epilepsy pathology (lesional versus non-lesional). To identify associations between various factors of interest and post-operative seizure outcome (Engel I versus Engel II-IV), univariate analysis was performed using a χ^2 test for categorical variables (eg., gender) or an unpaired Student's *t*-test for continuous variables (eg., age). Variables displaying a p value < 0.20 on univariate analysis were then entered into a multivariate logistic regression model in a backwards fashion, in order to identify potential predictors of seizure-freedom (Engel I outcome). Potential interactions between variables were examined. Odds ratios (ORs) were calculated for variables significantly associated with seizure-freedom and reported with a 95% confidence interval (CI). The positive predictive value (PPV) for forecasting seizure-freedom was calculated for interictal MEG, ictal EEG, MEG, and PET. Statistical significance was assessed at $p < 0.05$. Statistical analyses were performed using SPSS version 22 (IBM, Somers, NY).

Results

We identified 132 patients with drug-resistant focal epilepsy who were referred for MEG for localization of the epileptogenic zone, followed by resective epilepsy surgery at our institution, and with at least 1 year post-operative follow-up (mean, 3.6 years). Mean age (± SEM) at the time of surgery was 27.3 years (range, 3-68 years), and 73 (55%) individuals were male. Other

patient characteristics are provided in Table 1.

Interictal spike dipole modelling

Among 132 patients, 103 (78%) had successful modelling of MEG dipole activity corresponding to interictal spikes. Spike activity was not observed during recordings in 25 (19%) patients, and metallic artifact (e.g., dental implants) limited MEG interpretation in 4 (3%) cases. No differences in patient age, seizure frequency, or duration of epilepsy were observed between patients with or without successful dipole modelling ($p > 0.05$, unpaired *t*-tests).

An example of successful dipole localization is displayed in Figure 1. In this 12-year-old female with drug-resistant focal epilepsy, simultaneous MEG/EEG recordings demonstrated interictal spikes in the right frontal/central region (Fig. 1A), localized by equivalent current dipole modelling to the right anterior cingulate cortex (Fig. 1B). MRI revealed a subtle blurring of gray-white matter differentiation at this location (Fig. 1C), which was resected under the guidance of intra-operative ECoG (Fig. 1D). Post-operatively, neuropathological examination suggested FCD type IIA, and the patient remains seizure-free (Engel I outcome) two years after surgery.

Concordance between MEG findings and the epileptogenic zone

To estimate the accuracy and reliability of MEG, we examined the concordance between MEG spike localization with three reference regions: the region of resection, the epileptogenic zone delineated by intra-operative or extra-operative ECoG, and the area of abnormal MRI findings (Fig. 2). These reference regions coincided with each other in most, but not all, cases. MEG

findings were concordant with and specific to: i) the lobe of resection in 68 (66%) of 103 patients with successful MEG dipole modelling, ii) ECoG findings in 62 (67%) of 92 patients who had invasive recordings, and iii) an MRI abnormality in 65 (74%) of 87 cases with a radiological lesion. Across all reference categories, MEG dipoles were concordant with the reference region but non-specific (i.e., spikes also seen in another lobe) in 9-13% of comparisons, dipoles localized to the same side but not region as the reference area in 11-17% of cases, and MEG was discordant, with most dipoles localizing to the contralateral hemisphere, in 5% of cases.

We also asked whether MEG accuracy and reliability might differ with epileptogenic zones in different anatomical regions or caused by various epilepsy etiologies (Table 2). The rate of concordant and specific MEG results (i.e., first group in Fig. 2) was similar in patients with a temporal lobe (64%) versus extra-temporal/multi-lobe (69%) seizure focus ($\chi^2 = 0.3$, $p = 0.7$), and between those with lesional (67%) versus non-lesional (64%) epilepsy pathology ($\chi^2 = 0.1$, $p = 0.8$). These results suggest that across various epilepsy etiologies and anatomic locations, MEG provides accurate and specific localization of the involved lobe in two-thirds of cases, and have some localizing or lateralizing value in 95% of patients.

MEG concordance in predicting seizure outcome

After surgery, 92 (70%) patients were free of disabling seizures (Engel IA-D), including 67 (51%) individuals who achieved complete seizure-freedom (Engel IA). Other seizure outcomes were Engel II, Engel III, or Engel IV in 13 (10%), 17 (13%), and 10 (8%) patients, respectively. We examined the relationship between post-operative seizure outcome and MEG concordance

with the area of resection (Fig. 3). Among patients with successful dipole modelling, Engel I outcome was achieved by 85% of 68 individuals with concordant and specific MEG findings, but in only 37% of 35 patients with spike dipoles that were lateralized-only, non-specific, or discordant ($\chi^2 = 26.4$, $p < 0.001$). Also, concordant and specific MEG was associated with seizure-freedom in both patients with localized ictal scalp EEG (n = 79, $\chi^2 = 6.4$, $p = 0.02$) and with non-localized EEG (n = 50, $\chi^2 = 9.8$, $p = 0.002$). Only one of five (20%) patients with MEG spike lateralization discordant with the area of resection became seizure-free. These findings suggest that seizure freedom is significantly more likely when resection is performed in agreement with dipole localization than in cases without concordance between the lobe of resection and MEG.

Seizure outcomes were stratified across various other factors of interest, as listed in Table 3. Although no relationship between demographics and seizure outcome was observed (Table 3A), patients who became seizure-free had tried slightly fewer anti-epileptic drugs than those with persistent seizures (Table 3B). Also, fewer patients with a history of generalized tonic-clonic seizures became seizure-free (62%) than those with only partial seizures (82%). Seizure freedom was more common among individuals with lesional pathologies – such as mesial temporal sclerosis (84%), malformation of cortical development including focal cortical dysplasia (79%), and tumor (77%) – than among patients with the non-specific finding of gliosis only (55%). Examining pre-operative diagnostic studies, individuals with a localized ictal EEG were more likely to achieve Engel I outcome than those with non-localized EEG (Table 3C). Finally, among those patients with a well-defined radiological lesion, outcomes were more favorable with gross-total over subtotal resection (Table 3D).

Multivariate analysis was performed to further evaluate predictors of seizure outcome

and potential interactions. As shown in Figure 4, significant predictors of seizure-freedom included concordant and specific MEG, the absence of pre-operative generalized seizures, and localized ictal scalp EEG. Although seizure-freedom was more common in patients with abnormal MRI than those with normal imaging (OR = 2.02; 0.80-5.10, 95% CI), this was not significant on multivariate analysis. Finally, we calculated the PPV for each non-invasive, whole-brain diagnostic modality in predicting post-operative Engel I outcome (Table 4). MEG exhibited a PPV of 85.3% overall, comparable to ictal scalp EEG (79.8%) and anatomical MRI (72.5%). The PPVs for MEG in temporal lobe and extra-temporal/multilobe cases were 91.9% and 77.4%, respectively, suggesting that MEG has predictive value in TLE as well as focal neocortical epilepsy.

Discussion

Here we report MEG dipole mapping results and long-term seizure outcomes in 132 patients who underwent MEG prior to resective epilepsy surgery at our institution. Interictal MEG spike activity was observed in 78% of patients, and spike localization was concordant with and specific to the lobe of resection in two-thirds of these individuals, with discordant lateralization in 5% of cases. Post-operative seizure-freedom was achieved in 85% of patients with MEG findings concordant with and specific to the region of resection. In contrast, only 37% of individuals became seizure-free when resection was performed in the setting of non-specific or discordant MEG results. Finally, MEG predicted seizure freedom on multivariate analysis, along with localized ictal scalp EEG and a lack of generalized seizures. Our results suggest that although MEG dipole mapping is not without limitations, it represents a valuable non-invasive

tool to help localize the epileptogenic zone in pre-surgical epilepsy patients, and may assist with outcome prognostication.

Previous studies have examined the sensitivity and accuracy of MEG in epilepsy surgery planning. In the largest series of MEG recordings in epilepsy, Stefan and colleagues reported a 70% sensitivity of MEG for epileptic activity across 455 patients, with localization of the correct lobe to be treated in 89% of 131 surgical cases (Stefan *et al.* , 2003). Some groups have reported that MEG may be more likely to localize to the epileptogenic zone than interictal or ictal scalp EEG (Pataraia *et al.* , 2004, Paulini *et al.* , 2007). Knowlton et al. and Jung et al. have reported good agreement between MEG and invasive electrodiagnostic modalities in separate series of patients with implanted grid/strip electrodes or stereo-electroencephalography, respectively (Jung *et al.* , 2013, Knowlton *et al.* , 2006). Other investigators have described an important role of MEG in planning surgical placement of intracranial electrodes (Knowlton *et al.* , 2009, Sutherling *et al.* , 2008). Finally, various groups have reported clinical utility of MEG in planning resection for focal neocortical epilepsy (Kim *et al.* , 2013, Mamelak *et al.* , 2002, Mu *et al.* , 2014), hemispheric epilepsy (Torres *et al.* , 2011), and re-operation after failed epilepsy surgery (Mohamed *et al.* , 2007). Our results confirm the utility of MEG spike localization described in these prior reports, and extend these findings by demonstrating the value of MEG in predicting long-term surgical outcome.

MEG in temporal lobe epilepsy

Given that source localization may be more challenging with deeper regions such as mesial temporal structures, some have argued that MEG has diminished clinical utility in TLE (Leijten

et al. , 2003, Shigeto *et al.* , 2002). Our group previously reported a series of 25 patients with mesial TLE, in which MEG interictal spikes were observed in 86% of patients, including well-localized spikes in two-thirds of individuals with a non-localized MRI (Kaiboriboon *et al.* , 2010). Other studies have also demonstrated favorable dipole localization with MEG in TLE patients (Baumgartner *et al.* , 2000, Stephen *et al.* , 2005). In the present series, concordance between MEG dipoles and the lobe of resection was comparable between TLE and extra-temporal lobe epilepsy patients, and between patients with mesial temporal sclerosis versus other pathologies. However, our study does not address the localizing value of mesial versus lateral temporal dipoles in patients with mesial TLE, as temporal lobectomies in our series were performed anatomically, including resection of both mesial structures and lateral temporal cortex. Also, MEG referrals for typical cases of mesial temporal sclerosis are less common in our practice, which may contribute to selection bias in this study. While our results suggest MEG can be a clinically useful in confirming TLE, the predictive value of mesial temporal spike localization warrants further attention. Potentially, this issue could be addressed by examining mesial versus lateral temporal MEG spikes in patients who receive selective amygdalo-hippocampectomy with preservation of the lateral temporal cortex.

Technique limitations and future directions

While our results support a role for MEG interictal dipole mapping, there are limitations to the technique, highlighted by patients in which spikes were not encountered, and those with non-specific localization. MEG has higher spatial resolution without signal loss by the skull and scalp compared to scalp EEG, but MEG is typically limited to interictal recordings, and thus cannot

replace video/EEG monitoring of ictal events. Localization of interictal spikes with either MEG or electrodiagnostic studies can help to identify the irritative zone, but this may not always coincide with the epileptogenic zone required for seizure generation (Ray *et al.* , 2007). Also, although MEG is noninvasive and allows whole-brain coverage, direct recordings with invasive ECoG remains the gold standard for accurate and reliable delineation of the seizure focus (Yuan *et al.* , 2012). As with other diagnostic modalities, MSI dipole modelling requires specialized training and is prone to interpretation error. Although advanced adaptive spatial filtering techniques can be employed for automated spike localization, further validation is required before such methods can replace manual dipole fitting (Kirsch *et al.* , 2006).

Beyond dipole mapping, other potential roles for MEG in epilepsy evaluation warrant exploration. Given favorable spatio-temporal resolution, MEG is well positioned to investigate high frequency oscillations (HFOs), of which the localizing value has become increasingly appreciated in epilepsy (Bragin *et al.* , 2010). Also, MEG has been used successfully to explore resting-state functional connectivity in numerous brain disorders (Guggisberg *et al.* , 2008), and a better understanding of connectivity reorganization in epilepsy may further aid our ability to map epileptic networks (Centeno and Carmichael, 2014). Finally, beyond localization, MEG is a valuable tool for non-invasive mapping of eloquent cortex including language, somatosensory, motor, and visual function in patients with epilepsy or other neurosurgical disorders (Findlay *et al.* , 2012, Tovar-Spinoza *et al.* , 2008).

Study design limitations

The most notable limitation of the present study design is its non-randomized, retrospective

nature. While we can ascertain the statistical relationship between MEG results and seizure outcome in hindsight, we cannot directly access the effect that MEG had on planning the resection, and thus, on seizure outcome. Furthermore, our study population is diverse, including a wide age range and various pathologies and resection types, which may limit the generalizability of our findings to certain patient groups. Clearly, a randomized, controlled trial examining the effects of pre-surgical MEG use on seizure outcome in epilepsy surgery would be ideal, but such a study is very unlikely because of highly problematic design challenges and ethical concerns. Nevertheless, the strength of our study is that it is the largest series to date, to our knowledge, examining MEG results in epilepsy patients with long-term seizure outcomes.

Conclusions

MEG represents a useful tool for interictal spike localization in pre-surgical epilepsy patients, given high spatio-temporal resolution and lack of signal deterioration by the skull and scalp. Although interictal spikes are not always observed with MEG, dipole modelling was successful in 78% patients in the present study, providing accurate and specific localization of the region for resection in two-thirds of those individuals. Seizure freedom was common (85%) in patients with localizing and specific MEG findings, but uncommon (37%) when the resection was performed with non-specific or discordant MEG results. Although the technique has its limitations, MEG dipole mapping can provide valuable information for surgical planning, and other potential uses for MEG in the evaluation of epilepsy patients warrant further attention.

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References

Baumgartner C, Pataraia E, Lindinger G, Deecke L. Neuromagnetic recordings in temporal lobe epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2000 Mar;17(2):177-89.

Bragin A, Engel J, Jr., Staba RJ. High-frequency oscillations in epileptic brain. Current opinion in neurology. 2010 Apr;23(2):151-6.

Cascino GD. When drugs and surgery don't work. Epilepsia. 2008 Dec;49 Suppl 9:79-84.

Centeno M, Carmichael DW. Network Connectivity in Epilepsy: Resting State fMRI and EEG-fMRI Contributions. Frontiers in neurology. 2014;5:93.

Deuschl G, Eisen A. Recommendations for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology. Electroencephalography and clinical neurophysiology Supplement. 1999;52:1-304.

Engel J, Jr., McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA : the journal of the American Medical Association. 2012 Mar 7;307(9):922-30.

Engel J, Van Ness P, Rasmussen T, Ojemann L. Outcome with respect to epileptic seizures. In: Engel J, editor. Surgical Treatment of the Epilepsies, ed 2. New York: Raven Press; 1993. p. 609-21.

Englot DJ, Lee AT, Tsai C, Halabi C, Barbaro NM, Auguste KI, et al. Seizure types and frequency in patients who "fail" temporal lobectomy for intractable epilepsy. Neurosurgery. 2013 Nov;73(5):838-44.

Englot DJ, Raygor KP, Molinaro AM, Garcia PA, Knowlton RC, Auguste KI, et al. Factors associated with failed focal neocortical epilepsy surgery. Neurosurgery: in press. 2014.

Findlay AM, Ambrose JB, Cahn-Weiner DA, Houde JF, Honma S, Hinkley LB, et al. Dynamics of hemispheric dominance for language assessed by magnetoencephalographic imaging. Annals of neurology. 2012 May;71(5):668-86.

Fischer MJ, Scheler G, Stefan H. Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery. Brain : a journal of neurology. 2005 Jan;128(Pt 1):153-7.

Funke M, Constantino T, Van Orman C, Rodin E. Magnetoencephalography and magnetic source imaging in epilepsy. Clinical EEG and neuroscience. 2009 Oct;40(4):271-80.

Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, et al. Mapping functional connectivity in patients with brain lesions. Annals of neurology. 2008 Feb;63(2):193-203.

Jung J, Bouet R, Delpuech C, Ryvlin P, Isnard J, Guenot M, et al. The value of magnetoencephalography for seizure-onset zone localization in magnetic resonance imaging-negative partial epilepsy. Brain : a journal of neurology. 2013 Oct;136(Pt 10):3176-86.

Kaiboriboon K, Nagarajan S, Mantle M, Kirsch HE. Interictal MEG/MSI in intractable mesial temporal lobe epilepsy: spike yield and characterization. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2010 Mar;121(3):325-31.

Kim H, Kankirawatana P, Killen J, Harrison A, Oh A, Rozzelle C, et al. Magnetic source imaging (MSI) in children with neocortical epilepsy: surgical outcome association with 3D post-resection analysis. Epilepsy research. 2013 Sep;106(1-2):164-72.

Kirsch HE, Mantle M, Nagarajan SS. Concordance between routine interictal magnetoencephalography and simultaneous scalp electroencephalography in a sample of patients with epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2007 Jun;24(3):215-31.

Kirsch HE, Robinson SE, Mantle M, Nagarajan S. Automated localization of magnetoencephalographic interictal spikes by adaptive spatial filtering. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2006 Oct;117(10):2264-71.

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. Annals of neurology. 2006 May;59(5):835-42.

Knowlton RC, Razdan SN, Limdi N, Elgavish RA, Killen J, Blount J, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. Annals of neurology. 2009 Jun;65(6):716-23.

Lau M, Yam D, Burneo JG. A systematic review on MEG and its use in the presurgical evaluation of localization-related epilepsy. Epilepsy research. 2008 May;79(2-3):97-104.

Leijten FS, Huiskamp GJ, Hilgersom I, Van Huffelen AC. High-resolution source imaging in mesiotemporal lobe epilepsy: a comparison between MEG and simultaneous EEG. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2003 Jul-Aug;20(4):227-38.

Mamelak AN, Lopez N, Akhtari M, Sutherling WW. Magnetoencephalography-directed surgery in patients with neocortical epilepsy. Journal of neurosurgery. 2002 Oct;97(4):865-73.

Mohamed IS, Otsubo H, Ochi A, Elliott I, Donner E, Chuang S, et al. Utility of magnetoencephalography in the evaluation of recurrent seizures after epilepsy surgery. Epilepsia. 2007 Nov;48(11):2150-9.

Mu J, Rampp S, Carrette E, Roessler K, Sommer B, Schmitt FC, et al. Clinical relevance of source location in frontal lobe epilepsy and prediction of postoperative long-term outcome. Seizure : the journal of the British Epilepsy Association. 2014 Aug;23(7):553-9.

Pataraia E, Simos PG, Castillo EM, Billingsley RL, Sarkari S, Wheless JW, et al. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? Neurology. 2004 Mar 23;62(6):943-8.

Paulini A, Fischer M, Rampp S, Scheler G, Hopfengartner R, Kaltenhauser M, et al. Lobar localization information in epilepsy patients: MEG--a useful tool in routine presurgical diagnosis. Epilepsy research. 2007 Sep;76(2-3):124-30.

Ray A, Tao JX, Hawes-Ebersole SM, Ebersole JS. Localizing value of scalp EEG spikes: a simultaneous scalp and intracranial study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2007 Jan;118(1):69-79.

Shigeto H, Morioka T, Hisada K, Nishio S, Ishibashi H, Kira D, et al. Feasibility and limitations of magnetoencephalographic detection of epileptic discharges: simultaneous recording of magnetic fields and electrocorticography. Neurological research. 2002 Sep;24(6):531-6.

Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol. 2008 Jun;7(6):525-37.

Stefan H, Hummel C, Scheler G, Genow A, Druschky K, Tilz C, et al. Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. Brain : a journal of neurology. 2003 Nov;126(Pt 11):2396-405.

Stefan H, Rampp S, Knowlton RC. Magnetoencephalography adds to the surgical evaluation process. Epilepsy & behavior : E&B. 2011 Feb;20(2):172-7.

Stephen JM, Ranken DM, Aine CJ, Weisend MP, Shih JJ. Differentiability of simulated MEG hippocampal, medial temporal and neocortical temporal epileptic spike activity. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2005 Dec;22(6):388-401.

Sutherling WW, Mamelak AN, Thyerlei D, Maleeva T, Minazad Y, Philpott L, et al. Influence of magnetic source imaging for planning intracranial EEG in epilepsy. Neurology. 2008 Sep 23;71(13):990-6.

Torres CV, Fallah A, Ibrahim GM, Cheshier S, Otsubo H, Ochi A, et al. The role of magnetoencephalography in children undergoing hemispherectomy. Journal of neurosurgery Pediatrics. 2011 Dec;8(6):575-83.

Tovar-Spinoza ZS, Ochi A, Rutka JT, Go C, Otsubo H. The role of magnetoencephalography in epilepsy surgery. Neurosurgical focus. 2008 Sep;25(3):E16.

Yuan J, Chen Y, Hirsch E. Intracranial electrodes in the presurgical evaluation of epilepsy. Neurol Sci. 2012 Aug;33(4):723-9.

Zumer JM, Attias HT, Sekihara K, Nagarajan SS. A probabilistic algorithm integrating source localization and noise suppression for MEG and EEG data. NeuroImage. 2007 Aug 1;37(1):102-15.

Tables

Table 1: Patient characteristics

Age at surgery	*years*	27.3 ± 1.3
Gender	Male	73 (55)
	Female	59 (45)
Handedness	Right	97 (74)
	Left	18 (14)
	Ambidextrous	4 (3)
	Not yet lateralized or unknown	13 (10)
Duration epilepsy	*years*	14.0 ± 1.0
Lobe involved	Temporal	75 (57)
	Frontal	27 (21)
	Parietal	7 (5)
	Occipital	5 (4)
	Multiple	18 (14)
Seizure frequency	*no. per week*	11.0 ± 1.9
History of generalized seizures	Yes	78 (59)
	No	54 (41)
Side of surgery	Right	55 (42)
	Left	77 (58)
Previous resection	No	112 (85)
	Yes	20 (15)

Data are N (%) for categorical variables or mean ± SEM for continuous variables. N = 132 patients. MCD: malformation of cortical development; MTS: mesial temporal sclerosis.

Table 2: MEG concordance with the area of resection by location and pathology

A) Lobe	Concordant and specific	Non-specific, lateralized-only or discordant	B) Primary Pathology	Concordant and specific	Non-specific, lateralized-only or discordant
Temporal	37 (64)	21 (36)	Gliosis only	19 (66)	10 (34)
Frontal	11 (55)	9 (45)	MCD	18 (72)	7 (28)
Parietal	6 (86)	1 (14)	MTS	15 (63)	9 (37)
Occipital	3 (100)	0 (0)	Tumor	14 (78)	4 (22)
Multi-lobe	7 (64)	4 (36)	Ischemia/infarct	1 (33)	2 (67)
Hemispherectomy	4 (100)	0 (0)	Other	1 (25)	3 (75)
Total	68 (66)	35 (34)		68 (66)	35 (34)

Data are N (%). N = 103 patients with MEG spikes modelled. MCD: malformation of cortical development; MEG: magnetoencephalography; MRI: magnetic resonance imaging; MTS: mesial temporal sclerosis.

Table 3: Seizure outcomes and associated factors

		Engel I	Engel II-IV	*p* value
A) Patient demographics				
Age at surgery	*years*	26.3 ± 1.5	29.5 ± 2.4	0.26
Gender	Male	54 (74)	19 (26)	0.26
	Female	38 (64)	21 (36)	
Handedness	Right	66 (68)	31 (32)	0.91
	Left	13 (72)	5 (28)	
	Ambidextrous	3 (75)	1 (25)	
	Not yet lateralized or unknown	10 (77)	3 (23)	
B) Epilepsy characteristics				
Duration epilepsy	*years*	13.4 ± 1.2	15.5 ± 1.8	0.34
Seizure frequency	*no. per week*	10.2 ± 2.3	13.0 ± 3.5	0.50
AED regimen tried	*no.*	4.5 ± 0.3	5.7 ± 0.5	0.03*
Epilepsy risk factors	*no.*	0.78 ± 0.10	0.85 ± 0.12	0.69
Lobe involved	Temporal	55 (73)	20 (27)	0.43
	Frontal	16 (59)	11 (41)	
	Parietal	5 (71)	2 (29)	
	Occipital	4 (80)	1 (20)	
	Multi-lobe	8 (57)	6 (43)	
	Hemispherectomy	4 (100)	0	
Primary Pathology	Gliosis only	23 (55)	19 (45)	0.05
	MCD	26 (79)	7 (21)	
	MTS	21 (84)	4 (16)	
	Tumor	17 (77)	5 (23)	
	Ischemia/infarct	3 (60)	2 (40)	
	Other	2 (40)	3 (60)	
History of generalized seizures	Yes	48 (62)	30 (38)	0.02*
	No	44 (82)	10 (18)	
C) Pre-operative diagnostics				
MEG	Concordant and specific	58 (85)	10 (15)	< 0.001*
	Non-specific or discordant	13 (37)	22 (63)	
	No spikes modelled	21 (72)	8 (28)	
MRI	Abnormal	79 (73)	30 (27)	0.14
	Normal	13 (57)	10 (43)	
Ictal scalp EEG	Localized	63 (80)	16 (20)	< 0.01*
	Not localized	26 (52)	24 (48)	
Implanted ECoG	Performed	35 (60)	23 (40)	0.06
	Not performed	57 (77)	17 (23)	
PET (when performed)	Abnormal	17 (65)	9 (35)	0.12
	Normal	12 (92)	1 (8)	

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D) Operative factors				
Side of surgery	Right	39 (71)	16 (29)	0.85
	Left	53 (69)	24 (31)	
Intra-operative ECoG	Performed	76 (70)	32 (30)	0.81
	Not performed	16 (67)	8 (33)	
Extent of resection (Tumor, vascular malformation, tuber, cyst only)	Gross-total	16 (80)	4 (20)	0.05
	Subtotal	2 (33)	4 (67)	
Previous resection	No	80 (71)	32 (29)	0.30
	Yes	12 (60)	8 (40)	
TOTAL		92 (70)	40 (30)	

Data are N (%) for categorical variables or mean ± SEM for continuous variables. *Statistically significant value ($p < 0.05$) from χ^2 test (categorical) or *t*-test (continuous) comparing patients with Engel I versus II-IV seizure outcomes. AED: anti-epileptic drug; ECoG: electrocorticography, EEG: electroencephalography; MCD: malformation of cortical development; MEG: magnetoencephalography; MRI: magnetic resonance imaging; MTS: mesial temporal sclerosis; PET: positron emission tomography.

Table 4: Positive predictive value of non-invasive, whole-brain diagnostic modalities

	All cases (n = 132)		Temporal lobe (n = 75)		Extra-temporal and multilobe (n = 57)	
	PPV (%)	95% CI	PPV (%)	95% CI	PPV (%)	95% CI
Interictal MEG	85.3	74.6-92.7	91.9	78.1-98.2	77.4	58.9-90.4
Ictal scalp EEG	79.8	69.2-88.0	80.0	66.3-90.0	79.3	60.3-92.0
MRI	72.5	63.1-80.6	75.8	63.3-85.8	68.1	52.9-80.9
Interictal PET	65.4	44.3-82.8	68.8	41.4-88.9	60.0	26.4-87.6

N = 132 (MEG and MRI), 129 (EEG), 39 (PET). CI: confidence interval; EEG: electroencephalography; MEG: magnetoencephalography; PET: positron emission tomography; PPV: positive predictive value.

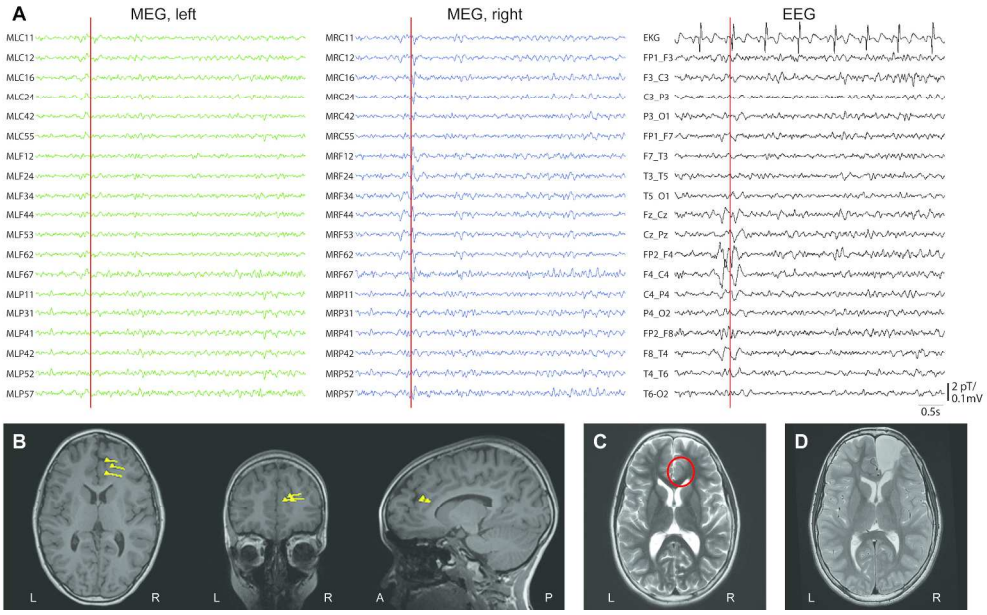
Figure Legends

Figure 1: Example of MSI dipole modelling with simultaneous MEG/EEG recordings. A) Recordings from selected MEG channels and simultaneous EEG in a 12-year-old female with drug-resistant focal epilepsy. A representative interictal spike is seen in both MEG and EEG recordings localizing to the right frontal/central region. B) Localization of single dipole sources corresponding to the spike in A, and similar spikes during the recording, shown as triangles with vector tails superimposed on T1-weighted anatomical MRI. C) Pre-operative T2-weighted axial MRI showing a subtle abnormal blurring of gray-white matter differentiation in the right anterior cingulate region (circle), proximal to the location of MEG dipoles. D) Post-operative T2-weighted axial MRI demonstrating the resection cavity. Neuropathological examination revealed FCD type IIA, and the patient remains seizure-free two years after surgery. EEG: electroencephalography; FCD: focal cortical dysplasia; MEG: magnetoencephalography; MRI: magnetic resonance imaging; MSI: magnetic source imaging.

Figure 2: MEG concordance with the area of resection, ECoG, and MRI. Shown is the number of patients with concordance between the region of MEG spike activity to three reference regions: i) the region of resection, ii) the epileptogenic zone delineated by ECoG, and iii) MRI abnormality. Cases are classified as concordant and specific, concordant but non-specific (same region, but >10% spikes also noted elsewhere), concordant lateralization only (same side, different region), and discordant lateralization (>50% spikes contralateral). Only 103 (78%) of 132 patients are included in this graph, as no spikes were modelled with MEG in 29 patients. ECoG: electrocorticography; MEG: magnetoencephalography; MRI: magnetic resonance imaging.

Figure 3: Relationship between MEG findings and seizure outcome. A) Post-operative seizure-freedom (Engel I outcome) was significantly more common in patients with concordant and specific MEG (85% seizure-free) than in patients with non-specific, lateralized-only, or discordant MEG (37% seizure-free overall, $\chi^2 = 26.4$, $p < 0.001$). Among patients with no spikes modelled, 72% were seizure-free after surgery. B) MEG findings stratified by seizure outcome. For details of these categories, see Fig. 2 legend. N = 132 patients. MEG: magnetoencephalography.

Figure 4: Predictors of seizure-freedom from multivariate analysis. Significant predictors of seizure-freedom include concordant and specific MEG, the absence of pre-operative GTCS, and localized ictal scalp EEG. Results are from multivariate logistic regression analysis, represented as OR with 95% confidence interval. Dashed line represents OR = 1. EEG: electroencephalography; GTCS: generalized tonic-clonic seizures; MEG: magnetoencephalography; OR: odds ratio.



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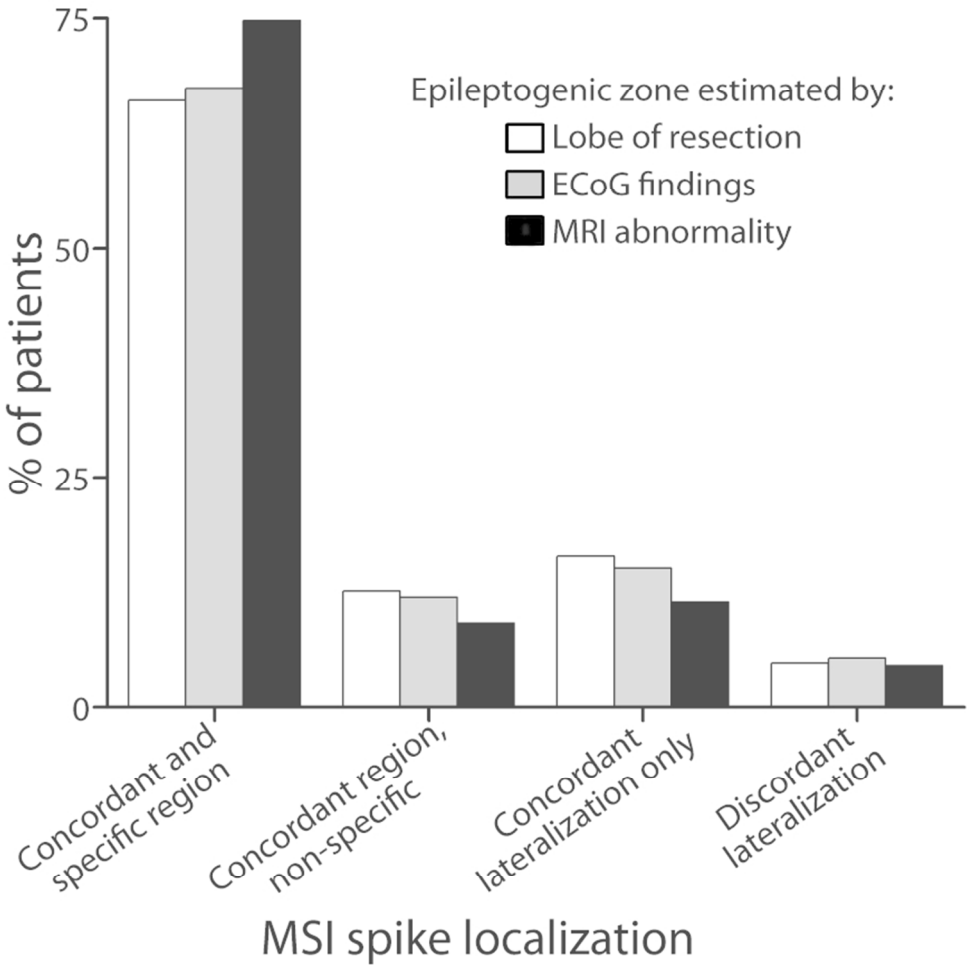

Figure 2: MEG cojavascript: document.forms[0].JUST_SAVED_FL.value='Y'; if(document.forms[0]['ATTRIBUTE_LIST_NAME'] eld('ATTRIBUTE_LIST_VALUE',document.forms[0][document.forms[0]['ATTRIBUTE_LIST_NAME'].value].value);} setD ETAILS');ncordance with the area of resection, ECoG, and MRI. Shown is the number of patients with concordance between the region of MEG s ction, ii) the epileptogenic zone delineated by ECoG, and iii) MRI abnormality. Cases are classified as concordant and specific, concordant but n where), concordant lateralization only (same side, different region), and discordant lateralization (>50% spikes contralateral). Only 103 (78%) , as no spikes were modelled with MEG in 29 patients. ECoG: electrocorticography; MEG: magnetoencephalography; MRI: magnetic resonance
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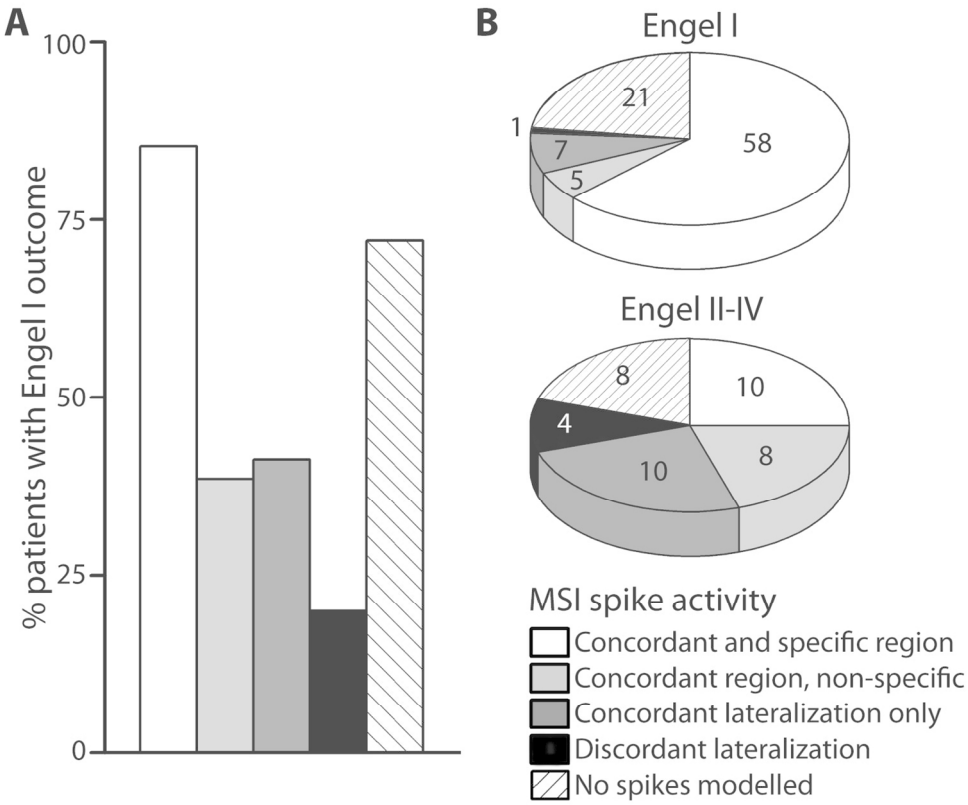

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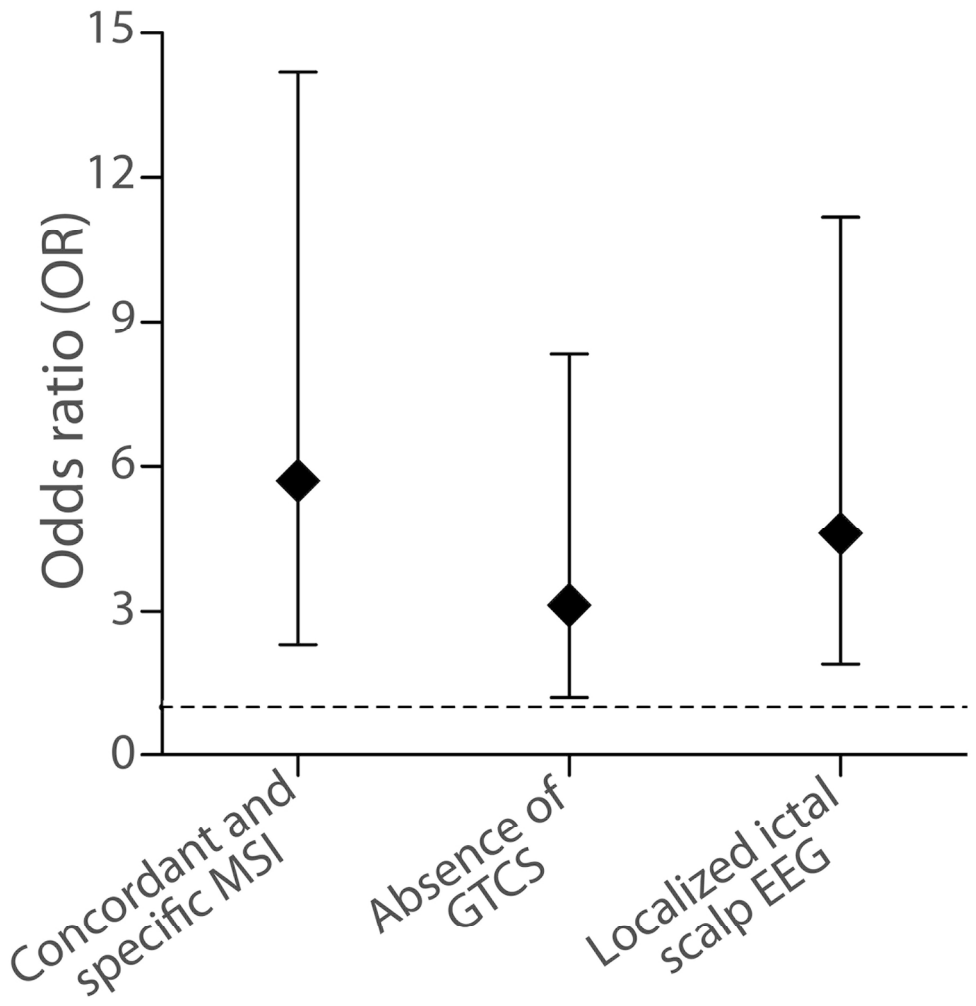

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