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Can ictal-MEG obviate the need for phase II monitoring in people with drug-refractory epilepsy? A prospective observational study

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ABSTRACT

Purpose: To determine if ictal-magnetoencephalography (ictal-MEG) source localization (SL) added information towards delineating the ictal-onset zone (IOZ), whether and how it helped final decision-making in epilepsy-surgery.
Methods: Definite focal clusters on ictal-MEG were available for 32 DRE-patients, data was analyzed (single equivalent current dipole (ECD) model), SL done. Clinical history, long-term video-EEG (VEEG) monitoring, epilepsy-protocol MRI, FDG-PET, ictal-SPECT and interictal-MEG were discussed at the multispeciality Epilepsy Surgery Case-conference (ESC). Cases were reviewed with ictal-MEG SL presented only at the last ESC (after decision using other available modalities). Patients were grouped as VEEG localization and MRI-lesion concordant (Group-A), discordant (Group-B), and no MRI-lesion (Group-C). Final hypothesis or decision, surgical outcome in those operated, and how ictal-MEG data influenced them were recorded.
Results: Five lesion-negative patients had identification of lesions after review of MRI with ictal-MEG SL. The difference between numbers of patients cleared for surgery without and with ictal MEG data was statistically significant ($p = 0.0044$); but the difference in those cleared for phase II monitoring was not ($p = 1.00$). Ictal MEG influenced decisions on possibility of surgery in 9 and converted decisions of phase II monitoring in 11 patients to electrocorticography-guided lesionectomy (20 in all; Group A-11, Group B-4, Group C-5); five were operated, with good seizure-control on follow-up.
Conclusions: Delineation of IOZ by ictal-MEG helped convert DRE patients unsuitable for surgery or planned for phase II monitoring into candidates suitable for surgery, even ECoG-guided resections, and resulted in favorable outcomes in those who were operated.

1. Introduction

Persons with drug refractory epilepsy (DRE) need to undergo multiple investigations in order to have their ictal onset zones (IOZ) correctly delineated. This is of utmost importance as it determines the operative outcome of these patients. In several such patients, the non-invasive investigations done routinely: epilepsy-protocol magnetic resonance imaging (MRI), long-term video electroencephalographic (VEEG) monitoring, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) do not clearly identify the epileptogenic focus, and these patients are either planned for the invasive phase II monitoring or palliative procedures. Magnetoencephalography (MEG) has certain known advantages over the scalp electroencephalography (EEG): its signals are less affected by the intervening brain, scalp and other tissues, and also it is better able to detect tangential dipoles not picked up by EEG. MEG has been shown to add value to other investigations in the pre-surgical evaluation of DRE patients- of the 455 who underwent MEG, the sensitivity for specific epileptic activity was 70%; of the 131 who had surgeries, 89% had lobar concordance [1]. In a recent retrospective analysis of 132 post-surgical patients by Englot et al., a highly significant number with MEG dipoles concordant with the region of resection achieved seizure-freedom after a minimum follow-up of one-year [2]. MEG has been shown to be helpful in more accurate

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localization in patients with tuberous sclerosis, insular, mesial frontal lobe and even non-lesional epilepsies [3–7]. Based on these and several other studies, the American Clinical MEG Society (ACMEGS) issued a 'Position Statement' in favor of MEG being used as a non-redundant method of localizing the IOZ in people with DRE that is localization-related, especially if the established modalities provide insufficient information [8].

Investigative modalities which have ictal-recordings may be more accurate in localizing the IOZ. MEG data is acquired for a short period, as the head position is required to be fixed, so it is usually interictal; an ictal MEG is available if a patient happens to have a seizure during the acquisition. There are retrospective studies, case reports and series in which the ictal MEG has been shown to yield useful information in delineating the IOZ, where the source localizations (SLs) have been compared with electrocorticography (ECoG) and intracranial EEG findings, and surgical outcomes [9–13].

In this study, the objective was to see if ictal MEG SL could be of additional use in accurately localizing the IOZ, and whether it could positively influence the decisions in epilepsy-surgery.

2. Methods

This was a prospective, observational study done at the Centre of Excellence for Epilepsy, All India Institute of Medical Sciences, New Delhi, and the MEG facility at the National Brain Research Centre, Manesar, Haryana, between June 2014 and April 2016. DRE patients who (1) had failed to achieve sustained seizure-freedom with two appropriately chosen, well-tolerated and used AEDs schedules; (2) had one or more seizures during the MEG data acquisition, and whose ictal source analysis showed definite focal clustering (5 or more dipoles in 1 cm^2) were recruited and followed-up [14]. Patients who had ictal-MEG data but without definite focal clustering on preliminary analysis, were not included.

A patient of DRE selected for work-up for epilepsy surgery undergoes a long-term VEEG, in which a minimum of three habitual seizures are recorded, and an MRI of the brain (epilepsy protocol on a 3-Tesla machine). The MRI is discussed with the neuroradiologists alongside the clinical history, semiology and VEEG localization. If there is a lesion seen (for example, mesial temporal lobe sclerosis (MTS), dysembroblastic neuroepithelial tumor, hypothalamic hamartoma) concordant to the VEEG findings, no further investigation is planned till the multidisciplinary Epilepsy Surgery Case-conference (ESC), in which neurologists, neurosurgeons, neuro-radiologists, nuclear medicine specialists and neuropsychologists participate. If, however, there is encephalomacia, suspected dual pathology, subtle lesion like focal cortical dysplasia (FCD) or more than one lesion- a PET-brain (except in large gliotic lesions), ictal and interictal SPECT, and MEG are carried out. The analysis and reporting of MEG SLs are carried out by clinical neurophysiologists blinded to the VEEG localization and the MRI, PET, and SPECT findings.

2.1. MEG data acquisition

Simultaneous MEG and EEG were recorded inside a magnetically shielded room with Elekta Neuromag Triux system, containing 102 magnetometer and 204 gradiometer sensors. Simultaneous EEG was recorded with size appropriate 64 channel Elekta Neuromag EEG Cap. The position of the patient's head in the helmet relative to the MEG sensors was determined using continuous head position indicator (HPI) coils. Average 1.5–2 h of simultaneous MEG and EEG recording was performed during which spontaneous magnetic brain activity (eyes-closed, rest, supine position), activation procedure of hyperventilation for 3 min and sleep (whenever achieved) was recorded, sampling frequency 1 kHz, 330 Hz low pass antialiasing filter. Spatio-temporal signal space separation method (tSSS) was applied to the recordings (Taulu and Simola, 2006), by including the artifactual bad channels. Raw data buffer length was 10 s and subspace correlation limit was 0.98.

2.2. Co-registration

The MRI of each patient was registered with the MEG fiducials and sensors using the Dicom Access version 1.5.11 and MRILab version 1.7.25.

2.3. Analysis

Analysis of MEG data was performed using data analysis software with Elekta Neuromag Triux version 2.94. The data was off-line band-pass filtered 1–50 Hz for visual inspection. Artifactual channels were removed from analysis. For EKG and eye-blink artifacts, corrections were done.

Epileptiform discharges in the form of spikes and sharp waves in MEG were identified independently, which were visually identified by a certified EEG technologist and were then confirmed by a certified clinical neurophysiologist and epileptologist.

2.4. Interictal analysis

The interictal epileptiform discharges with similar magnetic field distribution maps were categorized together. Equivalent current dipole (ECD) on spherical head modelling method was applied to individual epileptiform signal beginning from the onset of the discharges at every 1 ms time points until the peak. Only those dipoles which got fit on the cortex and which met the criteria (dipole amplitude 150–450 nA m, reduced chi square $<$1.5, confidence volume (cv) $<$150 mm cubed, goodness of fit (GOF) >70%) were considered to be part of the epileptogenic focus. The localizations thus obtained for each set of categorized signals was counted as one focus.

2.5. Ictal analysis

The equivalent current dipole (ECD) on spherical head modelling method was employed to the independent epileptic discharge noted within 10 s prior to the generalized spreading of the discharges. The analysis was performed on the individual epileptiform signal so obtained as mentioned above, beginning from the onset of the discharges at every 1 ms time points until the peak. Only those dipoles which got fit on the cortex and which met the criteria (dipole amplitude 150–450 nA m, reduced chi square $<$1.5, confidence volume (cv) $<$150 mm cubed, goodness of fit (GOF) >70%) were considered to be part of the ictal epileptogenic focus.

2.6. Localization of the IOZ

All these patients were discussed at the ESC after completion of at least VEEG and the epilepsy-protocol MRI and, if not cleared for surgery, again after the next set of investigations planned at the initial ESC were available. When a hypothesis regarding the IOZ was arrived at after looking at results of all the appropriate investigations (including PET and/or SPECT, and SL of the interictal MEG), the ictal MEG SLs were presented at another ESC (henceforth referred to as the last ESC). The decisions made at each ESC were duly recorded in the individual patient's ESC-file.

The lesion on MRI which was concordant with the VEEG localization was taken as the 'gold standard', to which the IOZ as

determined by the ictal-MEG was compared. Concordance was when the lateralization and the lobar localization were the same, in all comparisons between modalities. Sub-lobar concordance, if noted, will be specifically mentioned.

Patients were grouped after the last ESC, according to VEEG and MRI-lesion concordance, into three groups: Group A—in which there was concordance of the two; Group B where there was discordance; and, Group C, with patients who had no lesion on MRI. In those patients where the MRI and VEEG were discordant, concordance was checked for with the MRI lesion and VEEG localization separately, and if lesion-negative, with the VEEG localization only.

2.7. Statistical analysis

The McNemar test for paired proportions was used to find the differences in the numbers of patients cleared for surgery, and the number of patients cleared for phase II monitoring before and after the ictal MEG data was presented for decision-making.

3. Results

Out of 310 patients of DRE who underwent MEG as part of pre-surgical evaluation during the study period, 40 had one or more seizures during the acquisition of MEG data; seizures were focal in 33, and 7 patients had secondarily generalized seizures. Source analysis with the ECD model showed definite focal clustering in 32 (19 males, age range 6–45years) patients, so these were followed-up further and the others were excluded from this study. Out of these 32, 5 patients were being evaluated due to unfavorable outcomes after their initial surgeries for DRE.

Lesion on the MRI was seen in 20 patients in the initial assessment; in 5, re-look at the MRI after VEEG and ictal MEG concordance, at the last ESC led to identification of a lesion (an example in Fig. 1). After the last ESC, the patients were grouped into Groups A (VEEG and MRI findings concordant-18), B (VEEG and MRI findings discordant-7) and C (MRI-negative-7).

Temporal lobe localizations were in 9 among Group A, 7 among Group B and 1 out of the Group C cases. The lesions on MRI were as follows: focal cortical dysplasia (FCD)-18, mesial temporal sclerosis (MTS) being evaluated after surgery-1, FCD + MTS-4, encephalomalacia-2, calcified granuloma-1.

Concordance of ictal MEG source localization with (MRI + VEEG), MRI, and VEEG are presented in Table 1; concordance of interictal MEG, PET and ictal SPECT are also compared. Ictal MEG gave a localization opposite to the lesion on the MRI in 2 patients of Group A, 3 from Group B, and opposite to the VEEG localization in 3 patients of Group B, and 1 from group C. In 18 patients, there was concordance of ictal and interictal MEG localizations; out of these, 13 were from Group A, 3 from Group B, and 2 from Group C. Notably, 11 of the 13 Group A patients had concordance with the 'Gold Standard'; all five cases of Groups B and C had concordance with VEEG. Ictal SPECT and ictal MEG had similar localizations in 11 patients: Group A-8 of 13, Group B-1 out of 7, and Group C-2 out

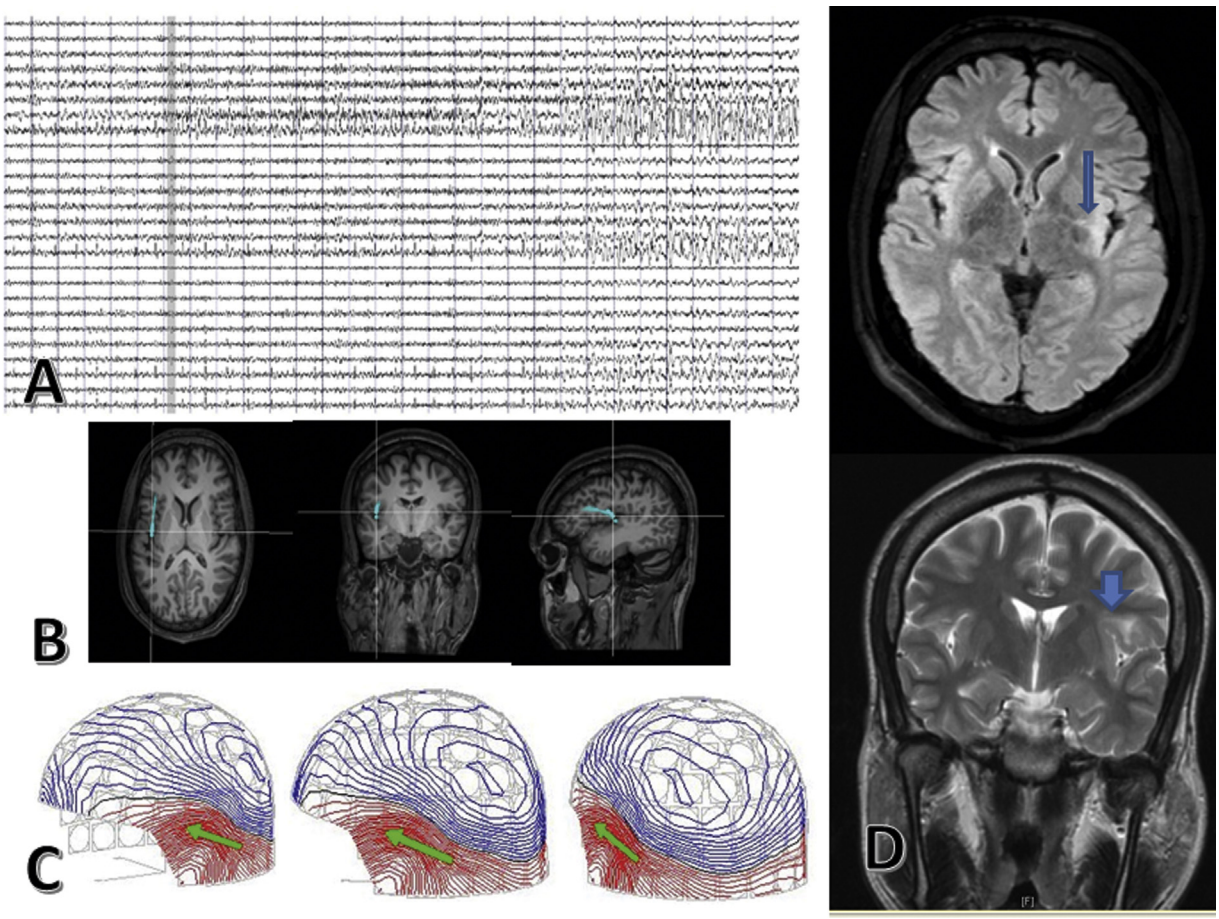

Fig. 1. Magnetoencephalography (MEG) data and source localization (SL) results of patient number 10. (A) MEG discharges recorded at seizure onset over the left hemisphere. (B) Ictal MEG localization results (blue arrow = dipole sites) projected onto magnetic resonance imaging (MRI); showed dipole cluster at the left insula.(C) Ictal MEG localization demonstrates three-dimensional orientation. (D) MRI (Fluid Attenuated Inversion Recovery {FLAIR}—axial and T2-weighted coronal views) of the patient with insular cortex thicker than the opposite side and a Taylor Band, marked by arrow, identified with help of ictal MEG- SL. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Concordance of MEG SLs, SPECT and PET data with VEEG and MRI.

		Ictal MEG	Interictal MEG	SPECT	PET
Group A (n = 18): concordance with MRI-VEEG		12 (66.6%) Sublobar concordance in 10	11 (55.5%) Sublobar concordance in 8	10/13[a]	6/8[a]
Group B (n = 7)	Concordance with MRI	1 Sublobar concordance in 1	3 Sublobar concordance in 3	4/7[a]	4/6[a]
	Concordance with VEEG	4	5	1/7[a]	3/6[a]
Group C (n = 7): concordance with VEEG		4	3	2/4[a]	3/3[a]

[a] Number in whom SPECT and PET were either not done or non-localizing.

of 3 patients (rest of the patients either had no localization on ictal SPECT or could not have the test done).

Temporal lobe localizations were in 9 among Group A, 7 among Group B and 1 out of the Group C cases. The lesions on MRI were as follows: focal cortical dysplasia (FCD)-18, mesial temporal sclerosis (MTS) being evaluated after surgery-1, FCD + MTS-4, encephalomalacia-2, calcified granuloma-1.

Concordance of ictal MEG source localization with (MRI + VEEG), MRI, and VEEG are presented in Table 1; concordance of interictal MEG, PET and ictal SPECT are also compared. Ictal MEG gave a localization opposite to the lesion on the MRI in 2 patients of Group A, 3 from Group B, and opposite to the VEEG localization in 3 patients of Group B, and 1 from group C. In 18 patients, there was concordance of ictal and interictal MEG localizations; out of these, 13 were from Group A, 3 from Group B, and 2 from Group C. Notably, 11 of the 13 Group A patients had concordance with the 'Gold Standard'; all five cases of Groups B and C had concordance with VEEG. Ictal SPECT and ictal MEG had similar localizations in 11 patients: Group A-8 of 13, Group B-1 out of 7, and Group C-2 out of 3 patients (rest of the patients either had no localization on ictal SPECT or could not have the test done). Ictal MEG influenced changed decisions in the type of epilepsy-surgery to be performed in 20 patients; in five others already cleared for phase II monitoring, ictal MEG also helped in planning of intracranial lead-placement.

The difference between numbers of patients cleared for surgery without and with ictal MEG data was statistically significant ($p = 0.0044$); but the difference in those cleared for phase II monitoring was not ($p = 1.00$).

4. Discussion

In our study, though ictal MEG SL has helped convert patients from 'not cleared for surgery' status to suitable surgical candidates ($p = 0.0044$), the number in whom decision of phase II monitoring was changed to lesionectomy, did not change significantly. The reason being, there were an almost equal number converted from 'not cleared' to 'cleared for phase II monitoring'.

There is good concordance of ictal MEG findings with VEEG localization and with the MRI lesion, especially when they are concordant with each other (in more than 66% Group A patients), which helps validate the investigative modality. In patients with discordance of VEEG and MRI, the ictal MEG SLs were concordant with either of the two in five of the eight patients, but matched more often with the VEEG localization. Even in the group that was lesion-negative, ictal SLs coincided with VEEG lateralization and lobar localization in the four out of seven cases. Ictal MEG SLs and ictal SPECT also had similar localization in eleven of the twenty-four cases the latter investigation was done or gave localizations. Assaf et al. also found similar patterns of ictal discharges in both MEG and EEG, in two temporal and three extra-temporal lobe epilepsy patients. Two each of the TLE and ETLE patients got operated and, except for one, and all had favorable outcomes [11].

There was also good concordance of SLs of ictal and interictal MEG data, and both together (patients 7, 8, 9, 18) and ictal alone (patients 11, 12) helped in identification of the lesion. This is because MEG is better for sub-lobar localizations, and therefore for abnormalities located in the deeper regions of the brain-like basifrontal, mesial occipital, insula etc. Shiraishi et al. in 2001 reported four cases in whom interictal in all, and ictal EEG in three had sharp activity in the midline, but ictal MEG SL in three patients, in the mesial frontal regions [6]. Though MRI showed no lesion in three of these patients, they had a suspicion of FCD in all four in the areas of the cortex indicated by the ictal MEG. A more detailed localization is possible with MEG, ictal greater than interictal as has been discussed in a report of two pediatric patients by Yoshinaga et al. where they found an FCD in the mesial occipital region in one patient [13]. Among our patients, the five whose lesions were identified with the help of ictal MEG data went on to be cleared for ECoG-guided resection. All were, expectedly, diagnosed with FCD on MRI by neuro-radiologists. One patient (number 7) was operated and has only occasional visual auras now, and histopathology showed FCD type IC (International League Against Epilepsy classification).

This has also been the observation in two cases by Tilz et al., they retrospectively compared ictal MEG SLs of six patients to

Table 2
Decisions of the penultimate and last epilepsy surgery case-conference, and influence of ictal MEG on the decisions.

		Group A (n = 18)	Group B (n = 7)	Group C (n = 7)
Cleared for surgery *before* last ESC	ECoG-guided resection	7	0	0
	Intracranial EEG monitoring	10	1	0
	Not cleared[a]	1	6	7
Cleared for surgery *after* last ESC	ECoG-guided resection	17	1	0
	Intracranial EEG monitoring	1	3	5
	Not cleared[a]	0	3	2
Ictal MEG influenced decisions	Phase II monitoring → ECoG-guided resection	10	1	0
	Not cleared → phase II monitoring	1	3	5
	Lesion identification	5	1	0

[a] Planned for palliative procedure or continued medical management and diet therapy measures.

localizations by other modalities and, in some patients, with surgical outcomes. It was also noted in this study that ictal, at times along with interictal MEG, was of help in patients evaluated after a previous surgery, as it gave a much more precise location of the IOZ with respect to the operated site, hence guiding further resections, as in our patients (Table 2) [9]. Similarly, delineation of the EZ was more precise in 13 patients with porencephalic lesions, where resection of the regions with interictal MEG-clusters resulted in favorable outcomes on follow-up, in the study by Bennett-Back et al. [15]. Two of our patients had porencephalic lesions: patient 10, with ictal onsets on ictal MEG at different regions, so the decision was to do a hemispherotomy rather than an ECoG-guided resection; another (patient 17) with a smaller lesion, is planned for resection of the area anterior to the it, as his ictal MEG showed a cluster there (Fig. 2).

Another study by Fujiwara et al. found that the interictal and ictal SLs were similar in the ECD model and two other, extended source algorithms—standardized low resolution brain electromagnetic tomography (sLORETA), and multiple signal classification (MUSIC) [10]. We used the single ECD model, but Tanaka et al. found the dynamic statistical parametric model superior to ECD model for the ictal analysis of five frontal lobe epilepsy patients [16].

Fujiwara et al. also compared the ictal and interictal MEG localizations with intracranial EEG and found ictal analysis to be more accurate, as although both had lobar concordance- the ictal localization was found to be structurally closer to the intracranial EEG onsets [10]. Stefan et al. in 1992 were the first to report ictal MEG, and they also noted good accordance of ictal and interictal MEG localizations with ECoG in their three DRE patients [17]. In the study by Ishii et al., three patients of FCD had highest kurtosis value of both ictal and interictal localizations within the dysplastic areas, corroborated by ECoG and histopathology [18]. A cardinal study by Medvedovsky et al. also comparing the ictal MEG SLs with intracranial EEG findings calculated the sensitivity and specificity for deep cortical locations and for hemisphere-lobe-surface localizations of over 70%, and for hemisphere-lobe localization of over 90% [19].

In three of our patients, intraoperative ECoG showed high amplitude spikes in the regions with ictal MEG clusters, and the surgical outcome was favorable after it was included in the resection (patients 6, 7 and 9, Table 2), and in all three, the histopathological diagnosis was FCD. Among patients of Groups B and C, there was good concordance of ictal (and, in many cases, interictal) MEG findings with VEEG localization; patients not initially cleared for surgery were, with ictal MEG data, planned for either ECoG-guided resections or phase II monitoring (Table 3) Magnetic Source Imaging results modified intracranial-EEG electrode coverage in 18 of the 77 cases of the study cohort, seven out of these 18 patients in whom additional electrodes were

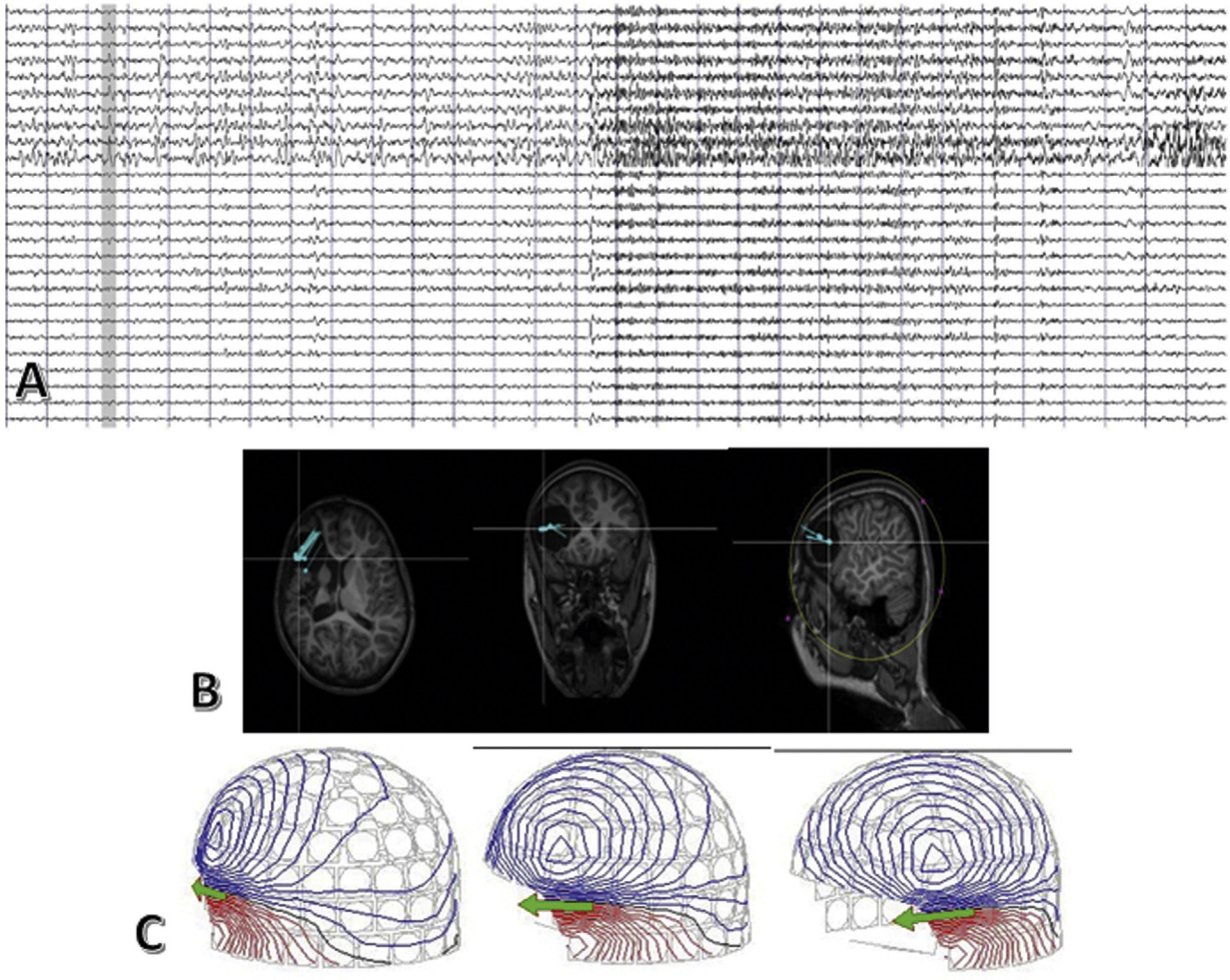

Fig. 2. Magnetoencephalography (MEG) data and source localization (SL) results of patient number 16. (A) MEG discharges recorded at seizure onset over the left hemisphere. (B) Ictal MEG localization results projected onto MRI, (blue arrow = dipole sites) showed dipoles cluster antero-inferior to the cavity. (C) Ictal MEG localization with three-dimensional orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Details of patients evaluated after surgeries (*) and those operated after ictal MEG study (**). The decisions influenced by the ictal MEG data are marked (†).

Patient number	VEEG	MRI	Ictal MEG	Inter-ictal MEG	PET	SPECT-SISCOS	Surgery performed/ECoG grade (if available)	Outcome/decision
6*	F4	Right MFG residual FCD, posterior to cavity	Right MFG anterior to cavity	Right IFG posterior to cavity	Right perisylvian region, just posterior to cavity	Right frontal, posterior to cavity	Operated again for removal of residual dysplasia	No seizures for one and a half years†
7**	C4 T6O2	Right mesial occipital FCD	Right mesial occipital	Bilateral mesial occipital	No localization	No localization	ECoG guided resection, ECoG grade III	Only auras for the last over one year†
9**	F4 T4	Right MFG FCD, insula not involved	Right IFG	Right IFG	Right frontal	Right frontal	ECoG guided resection-ECoG-spikes in IFG, resected	Seizure-free for the last six months†
10**	F4,C4	Right frontal, parietal, occipital gliosis	Right high parietal/ frontal- lateral wall of lesion	Right parietal	Right frontal, parietal, lateral occipital	Right cerebral hemisphere	Right hemi-spherotomy	Seizure-free for the last ten months
14*	FP2F4C4	Operative cavity right STG, MTG + atrophied body and tail of hippocampus	right high parietal	right parietal	Not done	no localization	Resection of atrophied body and tail of hippocampus	Plan to operate again to resect residual body and tail†
15*	F4T4	Residual dysplasia right IFG, insula	Right IFG	Right frontal anterior to cavity	Right posterior frontal lobe	Right basifrontal	ECoG-guided resection done earlier for right basifrontal FCD	Plan to operate again to resect residual FCD right insula, IFG
25**	FP1F3	Left SFG, posteriorly, parietal lobe, opercular FCD	Left MFG, posteriorly	Left posterior insula	Not done	Left parietal lobe	Left hemisphero-tomy done	Seizure-free for over 6 months
26*	C3F7	Residual FCD just posterior to motor leg area in left parietal lobe	Right IFG	Left IFG	Left hemisphere	No localization	ECoG-guided resection for left frontal FCD done earlier	Decision not to operate again, due to high possibility of deficit, seizures being mild and relatively infrequent†

MFG—middle frontal gyrus; IFG—inferior frontal gyrus; FCD—focal cortical dysplasia; ECoG—electrocorticography.

placed using MEG source localization (SL) had seizures originating from these electrodes, in the study by Knowlton et al. [20].

Out of 32 patients with ictal MEG data, a significant number have been cleared over this period of 2 years. However, only five have managed to get operated (patients 6, 7, 9, 10, 25; Table 3). This is because of the long waitlist, being the only government-center providing comprehensive epilepsy-surgery services in North India. At our MEG-facility, we use 306 channels, compared to the older studies on ictal MEG, which used fewer channels. Higher number of gradiometers increases the signal-to noise-ratio, and more magnetometers improve the spatial resolution of MEG. Also, continuous head position indicators may be used to increase the duration of data acquisition, to increase the possibility of recording a seizure. MEG is done at no cost at the patient's end, whereas depths and grids for invasive monitoring are extremely expensive, and many are unable to afford them.

To conclude, ictal MEG data, if available, must be analyzed, and may be used one step before the decision of intracranial EEG placement is made, especially if other modalities give inconclusive results. Ictal and interictal MEG together can help by identification of lesion in MRI-negative cases, thereby decision-making on the type of surgery (resection versus intracranial EEG placement), guiding repeat surgeries, and in encephalomacic lesions, ECoG-grid placement and extent of resection, choice of surgery in multi-lobar lesions, and intracranial EEG lead-placements, all due to better sub-lobar localization.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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