Interictal and Ictal MEG in presurgical evaluation for epilepsy surgery

Hermann Stefan[1*] and Stefan Rampp[2]

Abstract

Although presurgical evaluation of patients with pharamacoresistent focal epilepsies provides essential information for successful epilepsy surgery, there is still a need for further improvement. Developments of noninvasive electrophysiological recording and analysis techniques offer additional information based on interictal and ictal epileptic activities. In this review, we provide an overview on the application of ictal magnetoencephalography (MEG). The results of a literature research for published interictal/ictal MEG findings and experiences with own cases are demonstrated and discussed. Ictal MEG may provide added value in comparison to interictal recordings. The results may be more focal and closer to the invasively determined seizure onset zone. In some patients without clear interictal findings, ictal MEG could provide correct localization. Novel recording and analysis techniques facilitate ictal recordings. However, extended recording durations, movement and artifacts still represent practical limitations. Ictal MEG may provide added value regarding the localization of the seizure onset zone but depends on the selection of patients and the application of optimal analysis techniques.

Keywords: Ictal MEG, Interictal MEG, Localization of epileptic activity, Presurgical evaluation

Introduction

Epilepsy surgery is an effective treatment option in drug resistant focal epilepsies. A meta-analysis of 78 studies with postoperative follow up (mean of 5 years) has demonstrated seizure control in 66% temporal lobe epilepsy and less in extra temporal lobe epilepsies [1]. A recent study pooling cases from 36 European centers reported an overall postoperative seizure freedom rate of 60.7% in 7 168 patients [2]. This clearly underlines a need for improvement of presurgical evaluation, e.g. by extending the diagnostic spectrum. Magnetoencephalography (MEG) has been shown to significantly improve postoperative freedom rates [3, 4], even though the majority of MEG results rely on interictal epileptic activity. In the following, we review available literature on the added clinical value of ictal MEG for the presurgical evaluation of patients with focal epilepsies.

Interictal MEG

The relation of interictal and ictal focal epileptic activity is an ongoing matter of debate for the use in presurgical evaluation. Interictal spikes of the so-called "irritative zone" can be widely distributed. Hufnagel et al. [5] have a analyzed the seizure-onset localizations by detecting interictal spikes using invasive long-term recordings, and identified the earliest averaged spikes of a spike cluster within zone of < 2 cm from the site of seizure onset in 84% (n = 32) of patients. The question arises if ictal MEG can provide added value to interictal MEG.

MEG recordings usually last between 1 and 2 h. According to the study of De Tiège et al. [6], the mean recording duration in European labs is 90 min, due in a large part to logistical rather than technical reasons. During this time, the interictal epileptic activity is most oftenly detected. The interictal MEG localization corresponds to the invasive seizure onset in 71–100% [7–10].

If the analysis of interictal spikes shows monofocal dense clusters of source localizations and if these are taken into account for resection, postoperative seizure control is good [11, 12].

* Correspondence: hermann.stefan@t-online.de
[1]Department of Neurology - Biomagnetism, University Hospital Erlangen, 6, Schabachanlage, 91054 Erlangen, Germany
Full list of author information is available at the end of the article

In the study of Mu et al. [3] involving 46 patients with presurgical MEG evaluation and intractable frontal lobe epilepsy (FLE) surgery 47.9% became seizure free at a mean follow-up of 5.0 ± 4.0 years. Dipole clusters were completely resected in 70.9% of patients with monofocal activity and resulted in significantly higher seizure free rates compared to partial resection. Complete and extended lesionectomies showed an improved outcome to partial resection. Other studies evaluated resection of areas with increased connectivity based on the resting state network analysis, which showed correlations with postoperative seizure control [13, 14].

In many patients, localizing interictal MEG sources provides information for surgery plans [15, 16]. The accuracy can be increased further by simultaneous MEG/EEG recording and analysis [17], because they have complementary sensitivity regarding source orientation and sensor/electrode coverage, which is useful for identification of artifacts and analysis of epileptic activity of deeper areas. A comparison of interictal MEG, EEG and combined EEG/MEG together with invasively recorded focal epileptic activities is shown in Fig. 1.

Ictal MEG

Among the studies listed in Table 1, compared to the 76–93% frequency of interictal recordings during MEG data acquisition, there was a relatively low frequency of ictal MEG recordings (Table 1). The ictal MEG studies were initially performed only with few channels [22], later with multichannel hemispherical MEG recordings combined with foramen ovale electrodes [23] before

whole head systems became available (Fig. 2). Further ictal MEG studies showed that at seizure onset the signal-to-noise ratio (SNR) for dipole analysis may be rather low or artifacts may obscure the seizure onset. However, in some successfully localized cases, the ictal source localization was demonstrated to be superior to interictal MEG with good correlation to invasively recognized seizure onsets [24, 25]. The ictal movements can be compensated by the development of continuous head localization and correction algorithms [26], thus providing more accurate ictal localizations.

Fujiwara et al. [27] applied different localization algorithms in addition to the classical dipole approach. Seizure onsets were defined by means of short-time fourier transform (STFT), according to the study by Yagyu et al. [28]. The results showed concordant ictal MEG onset source localization and interictal MEG discharge source localizations in the same lobe, and the ictal localizations are closer than the interictal to the seizure onset zone (SOZ) defined by invasive seizure onset. Moreover, the ictal MEG provides clear unilateral source localizations even if interictal MEG spikes are bilateral or missing, and shows better concordance with intercerebral EEG of the SOZ at the sub-lobar level than the interictal MEG. The interictal MEG discharges are useful for lobar localizations but tend to show a wider distribution.

Ictal MEG has also been evaluated by Medvedovsky et al. [20] using extended recording durations. The median time to the first recorded seizure was 5.7 h, range from a few minutes to 40 h (on several days, only daytime seizures). A comparison in twelve patients showed
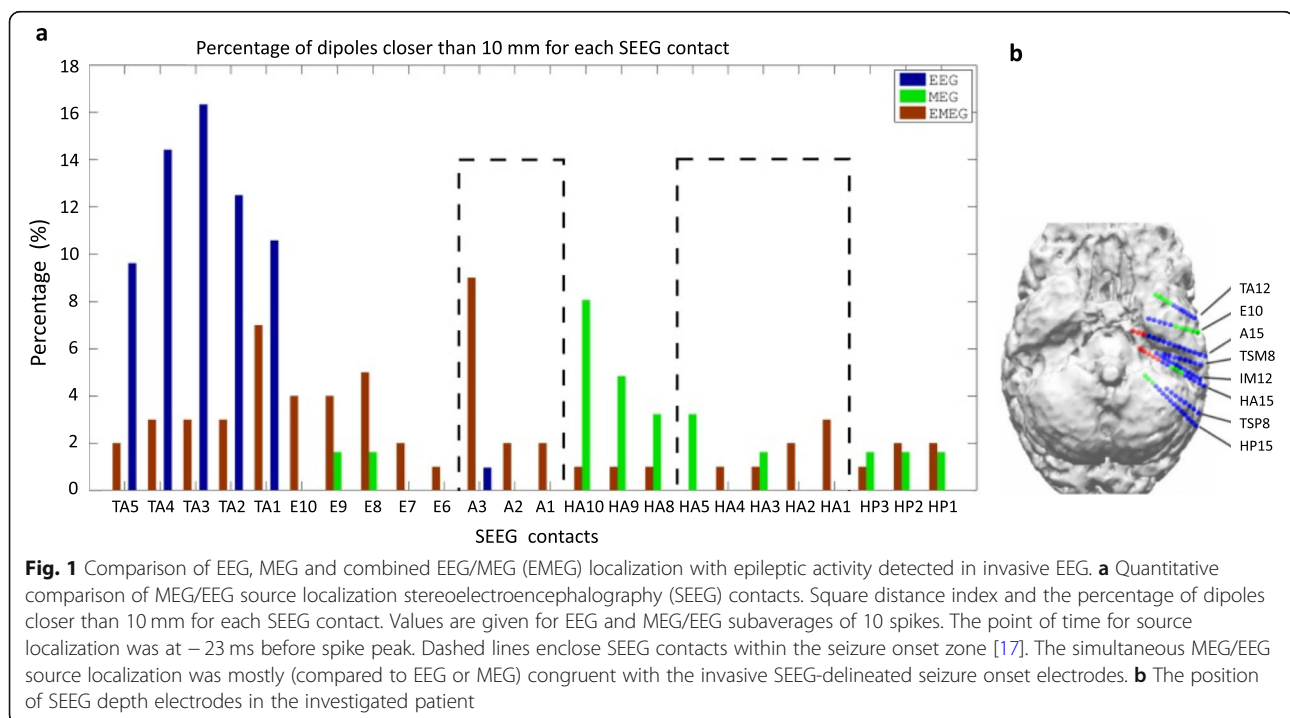
Fig. 1 Comparison of EEG, MEG and combined EEG/MEG (EMEG) localization with epileptic activity detected in invasive EEG. **a** Quantitative comparison of MEG/EEG source localization stereoelectroencephalography (SEEG) contacts. Square distance index and the percentage of dipoles closer than 10 mm for each SEEG contact. Values are given for EEG and MEG/EEG subaverages of 10 spikes. The point of time for source localization was at − 23 ms before spike peak. Dashed lines enclose SEEG contacts within the seizure onset zone [17]. The simultaneous MEG/EEG source localization was mostly (compared to EEG or MEG) congruent with the invasive SEEG-delineated seizure onset electrodes. **b** The position of SEEG depth electrodes in the investigated patient

Table 1 Percentage of ictal recordings in different studies and average recording times

Authors	Year	Average recording time	No. of patients with seizures during MEG recordings (i.e., ictal recordings)	Total No. of patients recorded	Percentage of ictal recordings
Stefan [15]	2003	30 min	31	455	7%
Assaf [18]	2003	120 min	14	57	24%
Alkawadri [19]	2018	51 min	44	377	12%
Medvedovsky [20]	2012	5.7 h	47	246	19%
Ramajunam [21]	2017	90 min	40	310	12.9%
Velmurugan [2]	2018	120 min	67	691	10%

that the ictal data had a high sensitivity of 0.96 and a specificity of 0.9 for the SOZ on a lobar level while the interictal data had a sensitivity of 0.95, but a much lower specificity of 0.75. The positive predictive value (PPV) for the SOZ in dorsolateral areas was 0.765. and for deeper SOZ was 0.786. The negative predictive value (NPV) for the dorsolateral SOZ was 0.625 and for deeper SOZ was 0.692. The PPV for all surfaces was 0.774 and the NPV was 0.655.

The use of MEG has been described in some case reports to evaluate patients with non-convulsive status epilepticus [29, 30]. Figure 3 shows one example.

A 31 year old pharmacoresistant female patient with non-convulsive status epilepticus (NCSE) (open eyes, not able to comply to easy challenges, but able to count and walk without recalling her own activities) EEG showed continuous sharp waves bitemporo-occipital left accentuated. Magnetic source imaging (MSI) revealed focal epileptic activity in left temporal region (infrasylvic, at the posterior portions of the superior and medial temporal gyri and posterior to angular gyrus). The ictal MEG localization was confirmed by invasive presurgical localization [30]. Recordings during NCSE still are rare. A personal observation concerns a female 68 year old patient with pharmacoresistent focal aware and unaware seizures. Some years ago a parietal meningioma left was removed without seizure control. The patient was referred because of status aphasicus over weeks. Because of worse health
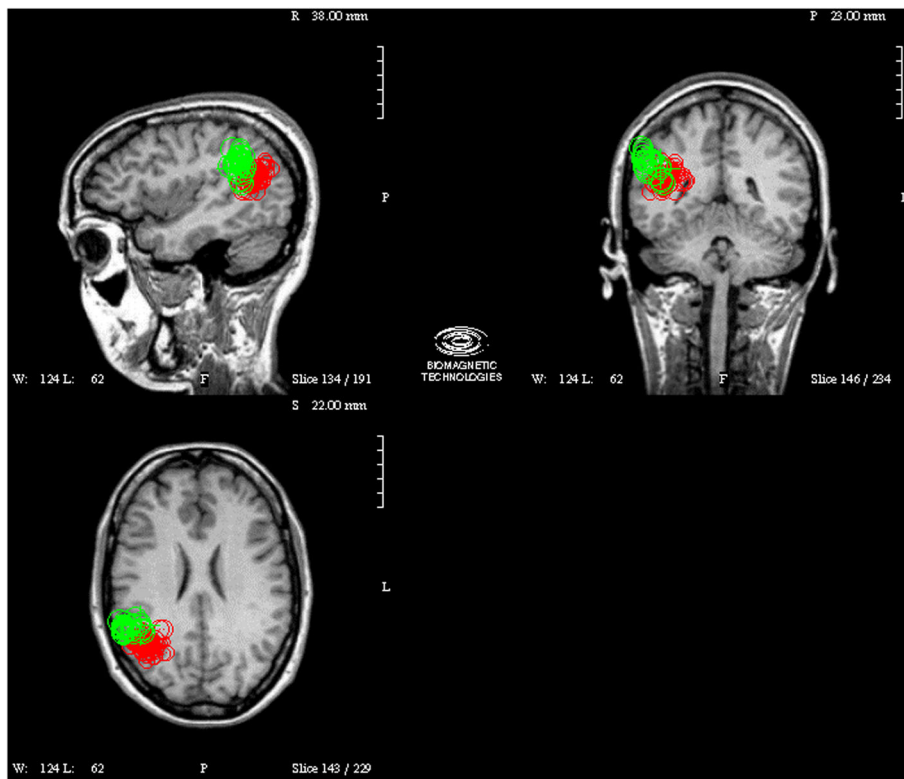
Fig. 2 Interictal and ictal magnetic source imaging (MSI) localizations in a patient with parietal focal cortical dysplasia (FCD) 2 (green: ictal, red: interictal)
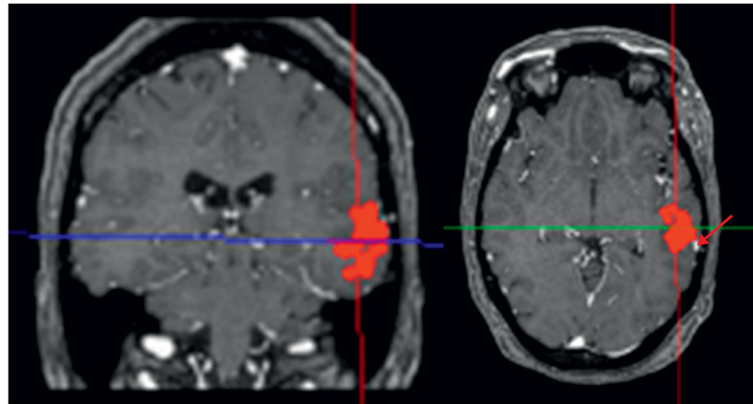
Fig. 3 Recordings during non-convulsive status epilepticus delineated a temporal lobe origin in a patient with unremarkable magnetic source imaging (MRI) [30]

condition no invasive recording for planning epilepsy surgery was possible. Ictal MEG during NCSE revealed focal epileptic activity adjacent to the previous menigioma resection volume. An MEG guided resective epilepsy surgery controlled the NCSE (Stefan, H personal observation).

In refractory status epilepticus [29] ictal MEG spike sources (MEGSSs) were localized in the right rolandic region (1 patient) and right temporal region (1 patient). Interictal MEG revealed unilateral clustered MEGSSs in four patients and bilateral (1 patient). Ictal-onset EEG findings were localized to one region in three patients and two regions in the other two patients. In all five patients, interictal discharges were widespread involving over two lobes (2 patients) or three lobes (3 patients). Suppression burst pattern was detected in one patient. Treatment was performed by cortical excision in two patients (2 patients), hemispherectomy in one and anterior temporal lobectomy in two patients. Two patients became seizure free, the other three patients experienced residual seizures. MEG showed clustered MEGSSs during the refractory status epilepticus (RSE) in the pre-existing epilepsy patients and in an early time window in the acute symptomatic RSE patients. The complete resection of clustered MEGSSs can control refractory status epilepticus and possibly lead to a seizure free outcome.

A study by Alkawadri et al. [19] comparing interictal vs ictal MEG vs EEG reported that in 44 ictal MEGs, equivalent current dipole (ECD) analysis was possible in 29 patients (66%), of whom 8 had no clear interictal discharges in either MEG or EEG. Lobar concordance between ictal and interictal dipoles was seen in all the remaining 21 cases, in whom interictal activity was detected. Sub-lobar concordance was observed in 18 cases (86%). Two patients showed clear MEG ictal patterns
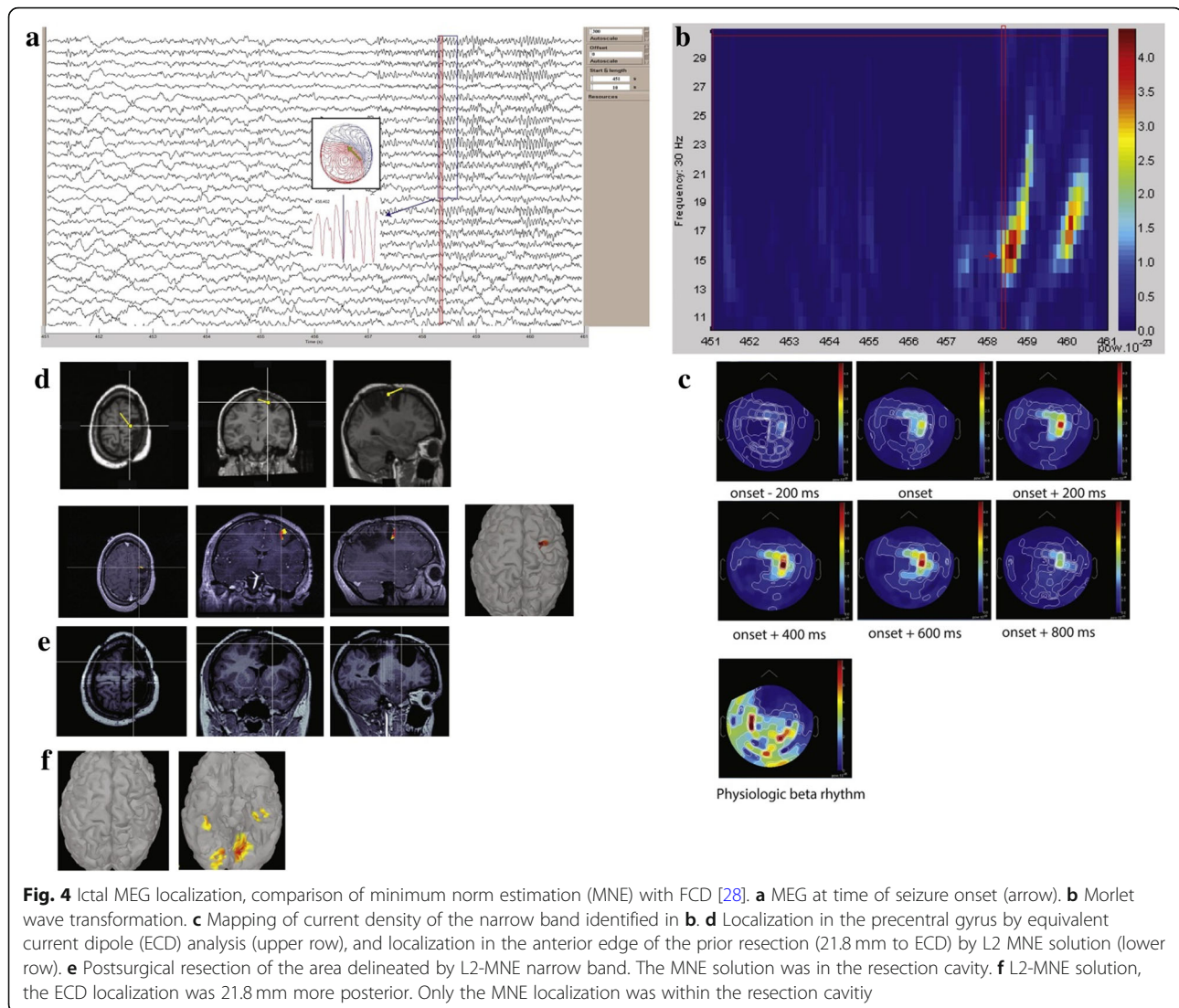
but with no ictal EEG changes, whereas all the cases showing ictal EEG activity also displayed MEG patterns.

In addition to equivalent dipole analysis, other approaches of source localization can also be used, such as minimum norm estimate (MNE), rhythm-based analysis or gradient magnetic-field-topography (GMFT). Exemplary studies comparing interictal and ictal MEG analysis with dipole and multiple frequency band analysis [28] are illustrated in Fig. 4.

Jeong et al. [31] analyzed data from 13 patients with focal drug-resistant epilepsies, of whom 6 patients had normal magnetic resonance imaging (MRI), and 8 received preoperative invasive evaluation. All patients underwent epilepsy surgery with a mean postoperative follow-up of 3.98 years and had seizure outcomes of International League Againt Epilepsy (ILAE) 1 in 9 patients, and 3–6 in the remainder. The authors used sLORETA to analyze different frequency bands in several seconds of preictal data. Then compared the results to the resection cavity in postoperative MRI. Of the 9 seizure free patients, 7 showed sublobar concordance with the resection in gamma activity in a 10-s window before the seizure onset, three of whom had a normal MRI.

In five patients, interictal MEG yielded multilobar localizations, including two with bilateral findings, whereas ictal MEG provided sublobar concordance with the resection in three of these.

Badier et al. [32] have compared different ictal MEG localization approaches (linearly constrained minimum variance [LCMV] beamformer and dipoles) with regard to their ability to localize the epileptogenic zone, as determined by stereoelectroencephalography (SEEG) epileptogenicity index calculations. They found that while both methods could be applied successfully, LCMV was superior to the dipole localization.

Fig. 4 Ictal MEG localization, comparison of minimum norm estimation (MNE) with FCD [28]. **a** MEG at time of seizure onset (arrow). **b** Morlet wave transformation. **c** Mapping of current density of the narrow band identified in **b**. **d** Localization in the precentral gyrus by equivalent current dipole (ECD) analysis (upper row), and localization in the anterior edge of the prior resection (21.8 mm to ECD) by L2 MNE solution (lower row). **e** Postsurgical resection of the area delineated by L2-MNE narrow band. The MNE solution was in the resection cavity. **f** L2-MNE solution, the ECD localization was 21.8 mm more posterior. Only the MNE localization was within the resection cavitiy

Pellegrino et al. [33] utilized wavelet-based maximum entropy on the mean (wMEM) to localize 46 MEG or EEG seizures in 13 patients. The results showed a generally high concordance between ictal and interictal findings. Ictal MEG was concordant on a sublobar level with the invasively identified SOZ in 10 of 11 patients, in whom this information was available. Ictal EEG localization showed sublobar concordance in 6 of 8 patients. Considering all individual seizures, concordance rates were similar for MEG (26/29 seizures) and EEG (9/14). The sublobar differences between ictal and interictal findings did not reach statistical significance. However, the rate of ictal/interictal concordance for MEG was better than that for EEG (90.32% vs 66.67%) and the interictal localizations were closer to the invasively determined seizure onset.

Shirouzu et al. [34] analyzed ictal MEG in patients with neocortical epilepsy. In 13 patients, ictal events were recorded during preoperative MEG. ECD estimation and GMFT were used to detect and localize the ictal MEG onset. Results were compared with the ictal onset zone (IOZ) derived from invasive EEG and the resection. GMFT detected and localized the ictal MEG onset in all patients, whereas ECD estimation showed localized ECDs in only two. The delineation of GMFT was concordant with the invasive localized SOZ at gyral level in 10 of 12 patients (83.3%). The detectability and precision of the delineation of ictal MEG activity by GMFT were significantly superior to those of ECD ($P < 0.05$ and $P < 0.01$). Complete resection of the IOZ in the concordant group provided seizure freedom in 3 patients, whereas seizures remained in 9 patients who had incomplete resections.

Can ictal MEG obviate the need for phase II monitoring in People with drug-refractory epilepsy? A prospective observational study tried to answer this question [21]. In that

study ictal MEG was recorded in 40 of 310 patients with drug refractory epilepsy (12.9%). A focal ECD source localization was available in 32 of them (80%). The difference between numbers of patients cleared for surgery with and without ictal MEG data was statistically significant ($P = 0.0044$). The ictal MEG influenced decisions regarding the possibility of surgery in 9 and converted decisions on phase II monitoring (electrocordicographic) ECoG-guided lesionectomy in 11 patients. Ictal-MEG helped to convert drug-resistant epilepsy patients unsuitable for surgery or planned for phase II monitoring into candidates for surgery and resulted in favorable outcomes in those who were operated.

Selection of brain regions for ictal MEG recordings has to take into account ictal semiology especially if no whole head MEG recording apparatus is available. Otherwise, there is no evidence that the sensitivity of MEG is different for ictal compared to interictal activity. Therefore, especially neocortical areas would be accessible. In addition, also based on the evidence from interictal data, patients with large or multiple lesions, skull defects, asymmetries and complex activity could potentially benefit from MEG recordings also in the interictal case.

In a prospective study of 11 patients with ictal MEG recordings a total of 31 seizures was recorded with EEG and MEG. Ictal MEG turned out positive in 25 of 31 seizures (80.6%) [35]. These findings indicated that early-phase source analysis of interictal and ictal discharges will produce high density EEG (HDEEG)-MEG source solutions that better guide and limit reliance on invasive intracranial monitoring in the pre-surgical diagnosis. Advantages and disadvantages of both interictal and ictal recording techniques are discussed. For the use of combined HDEEG/MEG or separate MEG and HDEEG analysis, the role of different head models have to be taken into account. For combined HDEEG/MEG analysis head volume conduction effects have to be modeled accordingly before a simultaneous analysis can be recommended. Aydin et al. 2015 [17] used individually calibrated 6-compartment finite element model (FEM) forward modeling to leverage the complementary information in EEG and MEG. In this process, the conductivity of the skull compartment was individually calibrated, because variability in skull conductivity is large. It was shown that it is the most important conductivity parameter for the EEG, while it has nearly no influence on the MEG forward modeling [36].

Synopsis of interictal and ictal magnetic source imaging studies

A meta-analysis of published ictal MEG studies in 238 cases revealed 146 patients with ictal and interictal epileptic activity during MEG recording. On a lobar level, ictal and interictal localizations were concordant, i.e.

providing the same localization in 84%. Information regarding concordance on a sublobar level was available in 105 patients and amounted to 73%. In non-concordant cases, interictal localizations usually overlapped with the ictal results, but had more-extended distribution or included additional remote localizations. The comparison of lobar or sublobar concordance between interictal and ictal MEG is summarized in Table 2.

Discussion

Current studies have suggested that ictal MEG can provide additional and useful information in some cases. While ictal and interictal localizations show a high degree of concordance, ictal MEG has increased specificity for the invasively determined SOZ. In many of the studies, interictal localizations are usually overlapping, but show a more extended distribution over neighboring areas and sometimes also remote localizations. When interictal MEG recordings have normal or unclear results, ictal MEG localizes correctly in some cases.

The ictal MEG recordings can be facilitated by some developments. For example, prolonged video-MEG/EEG increase the probabilities to record and identify seizures [51]. Movement compensation [26, 52] and the projection of recorded data to a standard virtual MEG helmet [53] enable the correction of (limited) patient movement during a seizure and increases the percentage of usable MEG recordings. Analytically, the application of STFT [27, 28, 31] for identification of seizure onsets, and the use of distributed source localization approaches [32, 34], especially frequency-based methods [31], seem to improve the localization accuracy in comparison to ECD approaches. Regarding MEG ictal focus localization, there is very little data on specific aspect of localization methodology in lesional subgroups. However, the specific type of lesion will of course only impact source analysis if the generated epileptic activity exhibits any special, potentially limiting features. In ictal source analysis, one of such feature would be fast spread to involve larger areas. In this case, dipole localizations are more susceptible to mislocalization as the assumption is of course that the activity is generated by a single focal source. Distributed source models may be better suited to handle this or suggest propagation if their results deviate from dipole localization. Frequency based source analysis, e.g. using dynamic imaging of coherent sources (DICS), is especially useful if the the seizure exhibits a stable oscillatory component during onset. Then such methods would allow to focus on this while other, e.g. artifact components will have minimal impact. Lesional characteristics may show influence due to the location. E.g. bottom-of-sulcus focal cortical dysplasias (FCDs) may show activity with a dominant radial component, which is not recorded by MEG. Activity may thus

Table 2 Concordance of interictal and ictal magnetic source imaging (MSI) on lobar and sublobar levels

Author	Year	Concordant ictal/interictal		Total		Remarks
		lobar	sublobar	lobar information	sublobar information	
Sutherling [22]	1987	2	NsA	2	NA	
Stefan [23]	1992	1	NA	1	1	
Ishibashi [37]	1998	1	NA	1	NA	
Kirchberger [38]	1998	2	2	2	2	
Ko [39]	1998	2	2	2	2	
Bowyer [40]	2000	1	1	1	1	
Shiraish [41]	2001	4	NA	4	NA	
Eliashev [24]	2002	4	NA	5	NA	
Tilz [25]	2002	5	NA	6	NA	
Oishi [42]	2002	1	1	1	1	
Assaf [18]	2003	2	2	2	2	
Tang [43]	2003	5	5	5	5	
Yoshinaga [44]	2004	2	1	2	2	
Tayah [45]	2006	2	1	3	3	
Vitkainen [46]	2009	2	NA	2	NA	
Xiang [47]	2010	4	3	4	4	HFO
Yagyu [28]	2010	3	3	3	3	Frequency
Kakisaka [48]	2011	1	NA	2	NA	
Medvedovsky [20]	2012	7	6	12	12	
Schmitt & Rampp [30]	2012	1	1	1	NA	
Alkawadri [19]	2018	21	18	21	21	Frequency
Fujiwara [27]	2012	4	0	8	8	Frequency
Jeong [31]	2016	9	8	13	13	Frequency
Pellegrino [33]	2016	13	13	11	13	wMEM
Shirozu [34]	2017	12	10	12	12	GMFT
Velmurugan [49]	2018	12	NA	20	NA	HFO
Total		123	77	146	105	
		84%	73%			
Not included						**Reason**
Badier [32]	2016			6		No interictal information
Koptelova [50]	2018			7		Extended activity
Ramajunam [21]	2017	19	9	32		Indirect information

NA no information available, *HFO* high frequency oscillation, *wMEM* wavelet-based maximum entropy on the mean, *GMFT* gardient magnetic field topography

require slight propagation into the sulcal walls to generate a signal than is visible to MEG. However, our experience [54] shows that this may cause only a minor offset even in the interictal case. It has to be noted however, that these points of discussion are based on localization theory and interictal findings due to the lack of ictal data. More studies would be required to evaluate such specialized aspects.

However, the ictal MEG recordings have some limitations. First of all, the overall probability to record seizures during a routine MEG session can be as low as 7–24% (Table 1). Although recording durations of more than about 60 min may increase the probability to 19–25%, it may be more difficult to achieve the necessary logistics and the patients' comfort may be impaired. Second, while some patient movements during seizures can be compensated, larger movement remains a source of error due the associated artifacts. In extreme cases, patients may completely or partially slip out of the dewar, making it impossible to record anymore. Even if such problems do not occur, the SNR of ictal activity may be low at the seizure onset, resulting in localization issues.

Frequency-based methods, such as STFT [27, 28] or multiple-frequency-band source localization [31] may be helpful in such circumstances. Furthermore, general limitations of MEG, such as artifacts due to metal implants, are of course also relevant for ictal recordings.

Ictal MEG recording in the future may be considerably improved by optically pumped magnetometer (OPM). Since this new type of sensor is directly mounted to the surface of the head, sensitivity is improved and the problem of head movement is considerably reduced. Furthermore, OPM sensors could be placed over the basal areas of the head, improving coverage of temporal areas, a limitation of current MEG systems.

A limitation of our review and, specifically, the evaluation of ictal and interictal results is the lack of standard reporting of localization results regarding brain regions and the different recording and analytical techniques (e.g. head movement compensation, dipole or frequency band based source localization, seizure types). Furthermore, the reviewed literature spanned approximately three decades. While technical and analytical advancements have facilitated ictal recordings and analysis, the same also occurs for interictal recordings. The sublobar concordance rate may be higher than 73%, if up-to-date methods and procedures are applied. A recent EEG study showed that localizations of the spike onset can be in a different sublobar region than localizations of the peak in up to 40% [55]. Comparison to the reference standard of the decision of a multidisciplinary patient management conference ensures that the difference is not only caused by a lower SNR. Localizations of early vs late components may thus already explain a large portion of the differences of ictal vs interictal results.

Due to the technical and logistical requirements, special indications for attempting ictal recordings are required (Table 3). In such specific patient populations, simultaneous prolonged MEG/EEG recordings should be established in order to further enhance the precision of noninvasive source localization for presurgical evaluation.

Conclusion

Ictal MEG has increased specificity for the invasively determined SOZ. In many of the studies, interictal localizations are usually overlapping but show a more extended distribution over neighboring areas and sometimes also remote localizations. When interictal MEG recordings have normal or unclear results ictal MEG localizes correctly in some cases. Special indications, technical and logistical requirements for attempting ictal recordings are required. In such specific patient populations, simultaneous prolonged MEG/EEG recordings should be established in order to further enhance the precision of noninvasive source localization for presurgical evaluation. Ictal MEG recording in the future may be considerably improved by OPM.

Author details
[1]Department of Neurology - Biomagnetism, University Hospital Erlangen, 6, Schabachanlage, 91054 Erlangen, Germany. [2]Department of Neurosurgery, University Hospital Erlangen, 6, Schabachanlage, Erlangen, Germany.

Table 3 Indications for ictal MEG applications

Indications	Reference
High likelihood of seizure recording	Medvedovsky et al., 2012 [20]
MEG interictal scattered, multifocal or no spikes	Fujiwara et al., 2012 [27]
EEG and MRI unclear, MEG interictal lobar	Oishi et al., 2002 [40]
Pharmacoresistent status nonconvulsivus	Schmitt and Rampp, 2012 [30]
Skull defects	Alkawadri et al., 2013 [56]
Suspected frontobasal, mesial occipital or insular localization	Ramanujam et al., 2017 [21]
Noninvasive classification of system epilepsies	Sakurai et al., 2010 [57]

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