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MEG-based identification of the epileptogenic zone in occult peri-insular epilepsy

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ABSTRACT

Introduction: Presurgical work-ups of patients with pharmacoresistant epileptic seizures can require multiple diagnostic methods if magnetic resonance imaging (MRI) combined with video-EEG monitoring fails to show an epileptogenic lesion. Yet, the added value of available methods is not clear. In particular, only a minority of epilepsy centres apply magnetoencephalography (MEG). This study explores the potential of MEG for patients whose previous sophisticated work-ups missed deep-seated, peri-insular epileptogenic lesions.
Patients and methods: Three patients with well documented, frequent, stereotypical hypermotor seizures without clear focus hypotheses after repeated presurgical work-ups including video-EEG-monitoring, 3 Tesla (3 T) magnetic resonance imaging (MRI), morphometric MRI analysis, PET and SPECT were referred to MEG source localisation.
Results: In two out of three patients, MEG source localisation identified very subtle morphological abnormalities formerly missed in MRI or classified as questionable pathology. In the third patient, MEG was not reliable due to insufficient detection of epileptic patterns. Here, a 1 mm × 1 mm × 1 mm 3 T fluid-attenuated inversion recovery (FLAIR) MRI revealed a potential epileptogenic lesion. A minimal invasive work-up via lesion-focused depth electrodes confirmed the intralesional seizure onset in all patients, and histology revealed dysplastic lesions. Seizure outcomes were Engel 1a in two patients, and Engel 1d in the third.
Discussion: MEG can contribute to the identification of epileptogenic lesions even when multiple previous methods failed, and when the lesions are located in deep anatomical structures such as peri-insular cortex. For epilepsy centres without MEG capability, referral of patients with cryptogenic focal epilepsies to centres with MEG systems may be indicated.

1. Introduction

Epilepsy surgery delivers the best results when the presurgical work-up indicates the existence of an epileptogenic lesion that matches the seizure onset hypothesis created from video-electroencephalography (EEG)-monitoring. A 90% success rate has been reported in patients that underwent complete resections of focal cortical dysplasias type IIB.[1] In contrast, surgical outcomes are significantly worse for patients considered non-lesional following the preoperative work-up.[2–4]

If an epileptogenic lesion is not evident after standard 1.5 Tesla (1.5 T) MRI examinations, diagnostic methods such as positron emission tomography (PET), single photon emission computed tomography (SPECT), sophisticated 3 T magnetic resonance imaging (3 T MRI) including morphometric analysis (MA), and magnetoencephalography (MEG) can be applied to generate a focus hypothesis. Benefits have been described for each of these methods.[4–8] However, their application to individual patients depends on their availability at epilepsy centres.

MEG is the least likely to be available; this is probably due to the high cost of obtaining and maintaining the equipment and in Germany the lack of reimbursement. This restriction stands in contrast to reports about reliable MEG focus detection at epilepsy centres that routinely apply this method during presurgical work ups.[5,7,9–11] To demonstrate the potential added value of MEG in patients, who underwent their presurgical work-up in a centre

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without routine access to MEG, we report three consecutive patients in whom multiple previous techniques failed to localise peri-insular dysplastic lesions.

2. Materials and methods

2.1. Patients

In 2008 and 2009, three patients were referred from the epilepsy surgery program of the University of Bonn to the Epilepsy Centre Erlangen to localise their epileptogenic zones by MEG. All three patients had undergone comprehensive work-ups that failed to yield a focus hypothesis that would have allowed either a direct resection of the epileptogenic zone or the creation of a clear hypothesis for invasive work-up. Because focus identification is necessary to surgically treat epilepsy, they opted to take part in a clinical MEG evaluation at the Epilepsy Centre Erlangen. For clinical data and the applied diagnostics before the MEG-examination see Tables 1 and 2. Preoperative patient MRIs and morphometric MRI analyses are shown in Fig. 1.

2.2. Magnetoencephalgraphy/electroencephalgraphy (MEG/EEG) data acquisition and source localisation

MEG was recorded with simultaneous EEG (MEG/EEG) using a 74 channel MEG system (4D Neuroimaging, San Diego, CA, USA) in a magnetically shielded room (Vakuumschmelze, Hanau, Germany). The system consisted of 2 sensors (sensors A and B) with 37 first-order axial gradiometers with a 5 cm baseline. Distance between the channels was 2.8 cm on average. Simultaneous 32-channel EEG with an electrode cap with electrode localisations according to the International 10/20 system was recorded in all three patients. For combined MEG/EEG-recordings, patients were positioned in a supine position with their eyes closed. No provocation methods for interictal epileptic activity were applied. MEG-sensors were repositioned bilaterally allowing investigation of multiple brain regions during recording sessions, which were 20 min long for each sensor position ('run'). The MEG/EEG signal was processed by an analogue bandpass filter (1–120 Hz) and digitised with a sampling rate of 520.8 Hz. Afterwards, MEG-recordings were digitally bandpass-filtered (3–70 Hz, notch filter 50 Hz). These settings were based on in-house standards for routine clinical investigations.

MEG/EEG recordings were manually inspected by experienced evaluators for the occurrence of epileptic spikes according to the criteria of the International Federation of Clinical Neurophysiology, taking special characteristics of MEG spikes into account.[12,13] All recorded epileptic MEG spikes and their EEG correlates were averaged in each patient. Moving equivalent current dipoles (moving ECD) were calculated from averaged MEG spikes using a single sphere head model. Moving ECD of the EEG correlates of the

Table 1
Clinical data of the three patients show characteristics typical for patients with epilepsy due to dysplasic lesions. AED, antiepileptic drugs; SPS, simple partial seizures; CPS, complex partial seizures; SGTCS, secondary generalised tonic clonic seizures.

Patient	Age at seizure onset (years)	Seizure type/ frequency	Number of applied AED/number of AED at workup	Age at first/final work-up (years)
1	6	CPS: 4/d	7/3	14/19
2	9	SPS: 10/m CPS: 9/m	9/3	37/44
3	6	CPS: 2/d sGTCS: 1/m	11/3	39/45

Table 2
Results of the presurgical work-ups and hypotheses of the epileptic focus before referral of the patients to MEG. MRI, magnetic resonance imaging; MAP, morphometric analysis program; DVA, developmental venous anomaly; fMRI, functional MRI; PET, positron emission tomography; SPECT, single photon emission computed tomography; SISCOM, subtraction ictal SPECT coregistered to MRI; SMA, supplementary motor area.

Patient	Non-invasive video-EEG: interictal/ictal/semiology	MRI/MAP	Language dominance (fMRI, Wada test)	PET	SPECT	Focus hypothesis prior to MEG
1	Interictal: no spikes; ictal: bifrontopolar seizure pattern; semiology: rising of both arms, at times pronounced on the right, hypermotor body swinging. Occasionally seizures initiated by fear or micropsia	MRI (1.5 and 3 Tesla): DVA left fronto-lateral suprasylvic; MAP: junction and extension image pathologic left frontal suprainsular (understood to be caused by DVA)	Left (fMRI, WADA)	Hypometabolism temporopolar and temporomesial right	Ictal: hyperperfusion superior frontal gyrus left	No clear hypothesis
2	Interictal: no spikes; ictal: high amplitude rhythmic activity bifrontotemporal for 4–25 s, then muscle artefacts; doubling of heart rate; semiology: from sleep ascending feeling of heat, dysaesthesia right arm, then sudden tonic elevation of arms and tonic legs	MRI (1.5 and 3 Tesla): normal; MAP: junction image pathologic left frontal and temporal operculum	Atypical bilateral (fMRI, Wada) DTI: arcuate fascicle mesial and superior of the lesion	Normal; questionable hypometabolism temporo mesial right (two PET)	Ictal: hyperperfusion temporo-mesial and lateral left	Left insula or postcentral with propagation to SMA. Relevance of suspicious MAP-lesion in temporal operculum uncertain
3	Interictal: left temporal low amplitude spikes; ictal: initial left centro-temporal delta-activity for 5 s then bifrontal propagation; semiology: (1) from sleep tonic flection of the arms, then hypermotor arm and leg movements, swinging of the trunk (2) burning dysaesthesia of the palate and the face, speech-arrest	MRI (1.5 and 3 Tesla): questionable, not clearly circumscribed FLAIR signal alteration of the left insula (no definite pathology). MAP: only unspecific alterations	Left hemispheric language dominance	Normal	Ictal: hyperperfusion inferior frontal gyrus right; interictal: hypoperfusion inferior frontal gyrus right SISCOM: left frontal opercular and left parietal hyperperfusion	Frontal lobe epilepsy, possibly left insula

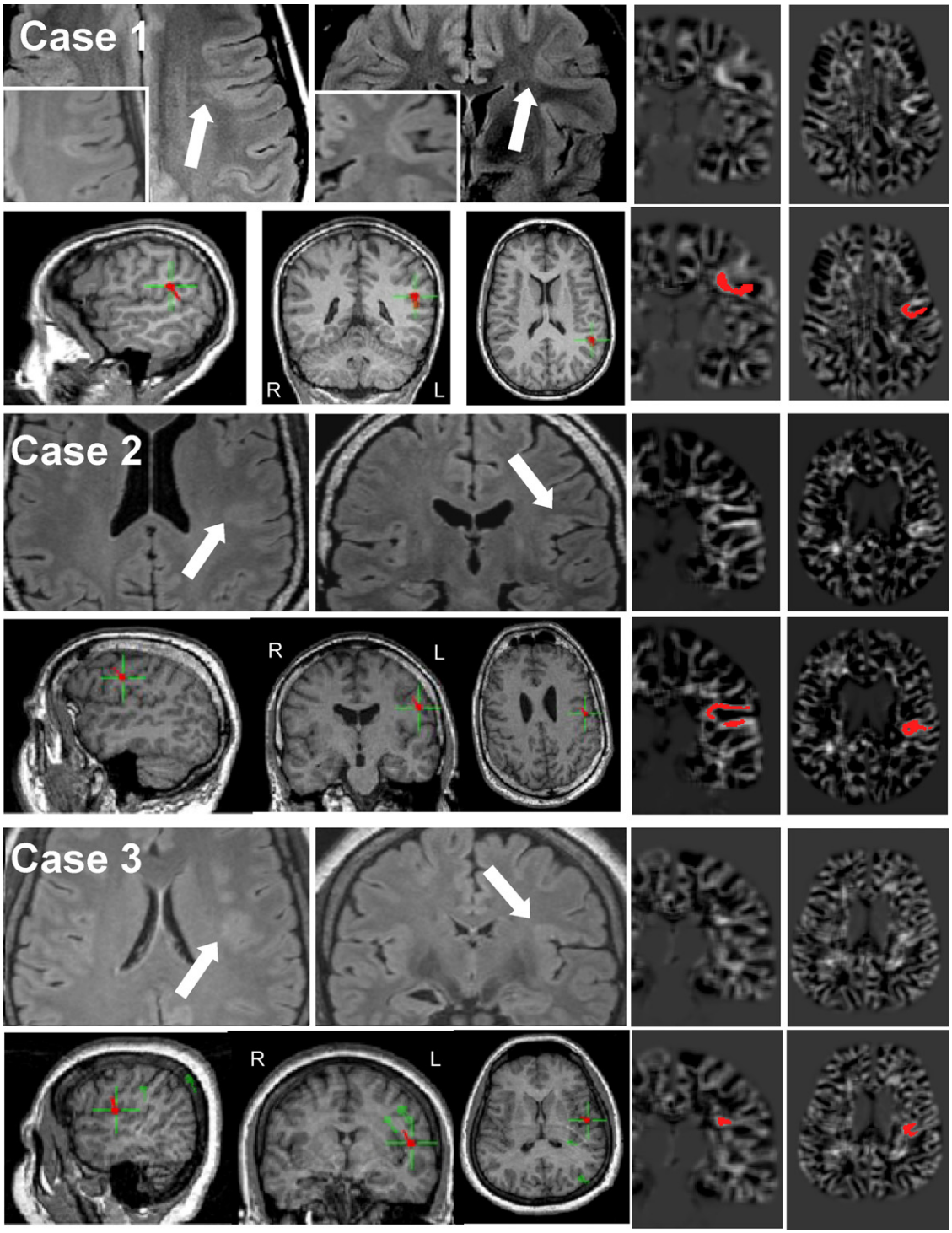

Fig. 1. Pre-implantation imaging of the three patients. Upper left panels: 3 Tesla FLAIR images (1 mm × 1 mm × 1 mm) of the epileptogenic lesions; upper right panels: morphometric analysis derived from a 3 Tesla 3D-T1 magnetisation-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MPRAGE) (1 mm × 1 mm × 1 mm). Lower left panels: illustration of magnetocephalography (MEG)-derived source localisation, red: MEG-moving equivalent current dipole (ECD) (spherical head model), residual variance patient 1: ≤16%, patient 2: ≤9%, patient 3: ≤14%, green: moving ECD of simultaneous electroencephalography (EEG) signal (diffuse localisation as signal to noise ratio is low: residual variance ≤54%); lower right panels: regions of interest (red) derived from morphometric analysis program (MAP) which finally served for minimal invasive implantation, L: left, R: right, left/right orientation of all coronal and axial figures is the same. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

averaged MEG spikes were localised using a 3-shell boundary element model. CURRY software (versions 4.6 and 6, Compumedics Neuroscan, Victoria, Australia) was used for MEG and EEG source localisation. The coregistered datasets were provided to the referring epilepsy centre in Bonn where the results were the basis for continued presurgical work-ups.

3. Results

3.1. MEG/EEG-results

MEG detected interictal epileptic activity in all three patients. In patient #1, only one interictal epileptic spike was recorded, and it

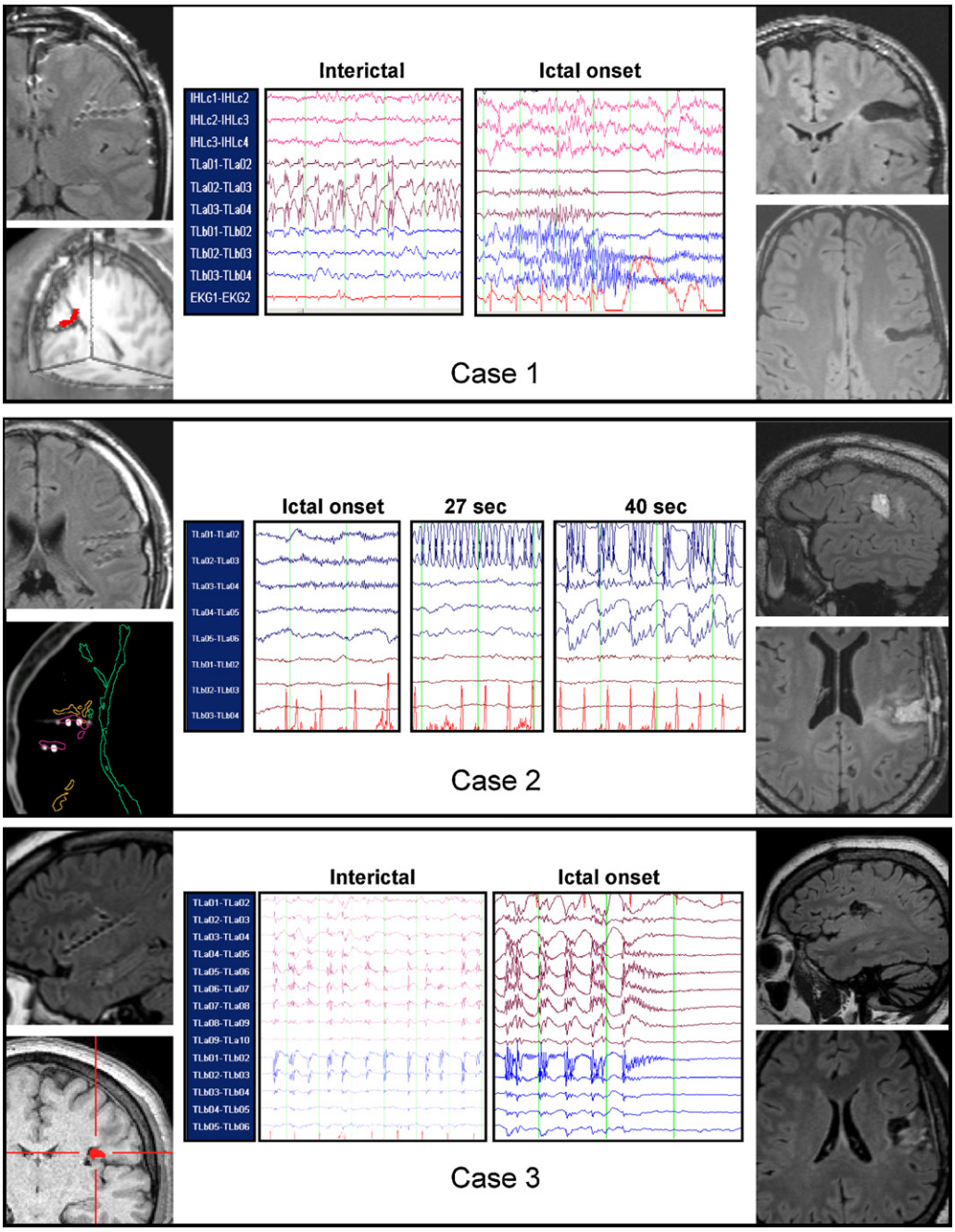

Fig. 2. Left MRI and CT panels: the stereotactically implanted depth electrodes penetrate the presurgically defined regions of interest in each patient with at least some contacts. Subsequent invasive EEG (middle panels) shows interictal and ictal discharge patterns highly typical for dysplasic cortical lesions. Following the proof of epileptogenicity of the suspected lesions, narrowly extended lesionectomies were performed (right MRI panels). Seizure outcomes are Engel 1a in cases one and three, and Engle 1d in case two.

gave discrete hints of left perisylvic to parietal epileptic activity origin. Three hypermotor seizures occurred during MEG acquisition, which could not be used for further evaluation due to movement artefacts. Continuous head position tracking was not available, which could have diminished these artefacts. Simultaneous EEG did not record a clear correlate of an epileptic spike, so source localisation was not performed.

In patient #2, eight interictal epileptic spikes suggested an origin of epileptic activity in the premotor area of the left inferior frontal gyrus. Source localisation was not performed because simultaneous EEG did not show a clear correlate.

MEG recorded 39 epileptic spikes in patient #3. MEG localisations were clearly monofocal in the left peri-/suprasylvic area. Only discrete spikes could be recorded in simultaneous EEG. However, EEG activity averaged on MEG interictal spikes could be used to firm MEG localisations. Results of the MEG source localisation are shown in Fig. 1.

3.2. Contribution of MEG/EEG results to the generation of the focus hypothesis

In patient #1 the MEG-source localisation indicated a focus in the left peri-insular to parietal region, but a repeated examination was recommended due to the insufficient number of detected spikes. However, a 3 Tesla MRI including a 3D-FLAIR sequence with a resolution of 1 mm × 1 mm × 1 mm substantiated the

morphometric analysis program (MAP)-derived focus hypothesis and indicated a left suprainsular cortical and subcortical signal increase, slight cortical thickening and a hyperintense extension directed to the wall of the lateral ventricle, making a focal cortical dysplasia (FCD) Type IIB very likely. The MEG dipole was remote from this lesion, yet in the respective area no morphological abnormality was detectable.

In patient #2, the MEG-dipoles localised to the left suprasylvian area. This supported the hypothesis of an epileptogenic lesion in the frontal operculum MAP-abnormality. MEG did not suggest epileptogenic activity in the infrasylvian operculum, which was also highlighted by MAP.

In case #3, MEG localised dipoles in the posterior left insula. This finding led to a focused re-evaluation of the MAP, which subsequently identified a MAP abnormality that corresponded to a subtle cortex signal increase and blurring of the grey/white matter junction that was not previously regarded as pathologic.

In patients #2 and #3, a high-resolution 1 mm × 1 mm × 1 mm FLAIR was also performed, but the morphological lesion was difficult to recognise even with MEG and MAP.

3.3. Minimally invasive EEG confirmation of the focus hypothesis

All three patients underwent a minimally invasive region of interest (ROI) targeted EEG following previously described methodology that details the electrode implantation in case #1.[14] The abnormalities detected by MAP served to define the ROIs, which were targeted with two depth electrodes in each patient. Because of some semiological details not clearly attributable to suspected epileptogenic lesion site (micropsia, chin jerks, hypermotor movements), patient #1 was also implanted with two subdural strip electrodes over the left hemispheric convexity and three in the left interhemispheric cleft to exclude a seizure origin distant to the suspected lesion.

In all three patients, interictal repetitive spike-patterns typical for cortical dysplasia[15] were recorded by the electrode contacts penetrating the ROIs (Fig. 2), and the sites of first ictal rhythmic activities could be attributed to the suspected lesions. In patient #1 the additionally implanted strip electrodes did not suggest a second epileptogenic zone. Electrical stimulation mapping via the depth electrodes in patients 2 and 3 revealed motor and sensory function in the cortex adjacent to the intended resection.

3.4. Surgery and outcome

Narrow lesionectomies were performed in each patient because of the localisation of the epileptogenic zone in the eloquent regions of the left insula and peri-insular cortex. The extents of the surgeries are depicted in Fig. 2.

Tissue resected from patient #1 confirmed a FCD type IIB. More than 36 months after surgery the patient remains free of neurological deficits and seizures, and their medication regimen has been discontinued. Patient #2 underwent a narrow resection of a supra-insular ROI, and the histological analysis showed a grey-white differentiation disorder with heterotopic neurons in the white matter but no well defined dysplastic entity. Immediately after surgery, the patient was free of neurologic deficits. However, a bleed into the resection cavity on postoperative day three made a revision surgery necessary, and the patient subsequently developed aphasia and high-grade paresis of the right hand. At the last follow up (24 months postsurgical) the paresis of the right hand persisted, but aphasia was reduced to word retrieval difficulties. After initial seizure persistence with an approximate 70% reduction in frequency, the patient is now secondarily seizure-free for 19 months with the exception of one seizure during medical malcompliance. He continues a four-fold anticonvulsive medication regimen. The histological examination of patient #3 also revealed a FCD IIB. The patient remains seizure-free (12 months postsurgical), suggesting that the hypothesis regarding the localisation of the epileptogenic zone was correct. However, the patient suffers from word retrieval disturbances and residual coordination problems of the right hand.

4. Discussion

In this study of a small series of patients with suspected cryptogenic epilepsy, MEG-enabled focus hypotheses were confirmed in two out of three cases. The relevance of this study is three-fold:

Firstly, MEG can be helpful in detecting epileptogenic zones even if several other techniques have failed. This is not novel; many studies have reported positive MEG findings during the presurgical work-ups of epilepsy patients.[5–9] However, most of these studies are published by epilepsy centres that routinely apply MEG early in the work-up, usually before all other available methods have been used. This context obscures the true *additive* value of MEG. All patients in the current series had at least one previous noninvasive presurgical evaluation in addition to the current extensive work up, including MRI, video-EEG monitoring, PET, and SPECT that failed to define a clear focus hypothesis. In the current work-up, even morphometric analysis[17] of a 3 T MRI magnetisation-prepared rapid acquisition with gradient-echo sequence (MPRAGE) was applied before the epileptogenic lesion was localised. Therefore, these patients are among the most challenging surgical candidates. Despite the difficulties, MEG uncovered new information that finally led to the identification of the epileptogenic zones in two out of three cases. Of course, the small size of the study cannot qualify the true additive value of MEG in the presurgical work-up, but it can promote further studies in larger groups of comparable patients and motivate referral of pharmacoresistant patients without clear focus hypotheses to an MEG examination.

Secondly, in the two patients with corresponding MEG-dipoles and suspicious morphological structures in MRI or MAP (#2 and #3), the use of MEG prevented unnecessary extensive and invasive work-ups. Regarding the intolerable preoperative seizure frequency in all three patients, the lack of clear foci hypotheses would have necessitated stereo-EEG[18] or the implantation of multiple strip and grid electrodes.[19] MEG is particularly promising for identifying deeply seated lesions, which are difficult to access by subdural electrodes and can require multiple depth electrodes, which increases the risk for implantation-associated complications.

Thirdly, after the MEG-based focus hypothesis and subsequent detection of potential epileptogenic lesions, both patients became candidates for a minimally invasive presurgical work-up[14] that finally confirmed the suspected lesions. In patient #1, the final focus hypothesis was made by MRI (3-dimensional high-resolution FLAIR), not MEG, because the MEG-dipole localisation did not correspond to a morphologic abnormality in MRI or MAP. The most convincing explanation might be that only one spike was detected for MEG source localisation, and this may have represented propagated epileptic activity rather than the focus itself. Alternatively, suboptimal sensor position during the MEG recording might explain why the epileptogenic lesion was missed in this case. The sensitivity of MEG to interictal epileptic discharges is estimated to be around 70%[5,20]; therefore one missed focus out of three patients would be in the expected range.

In contrast to EEG, MEG reasonably localised deep epileptogenic zones in two out of three patients. MEG ECDs were tangentially oriented in all patients. The signal to noise ratio is higher for tangentially oriented sources in MEG compared to EEG, and might

explain why the yield of simultaneous EEG is low, especially in patients with a low number of epileptic spikes.

It is disputed in the literature if MEG is able to localise epileptic activity from deep cerebral structures, such as the Sylvian fissure[21]; however, some authors reported that brain stem activity is detectable with MEG systems.[22] The present study results also support the hypothesis that MEG can localise deep epileptogenic foci. These results underscore the rationale to reevaluate patients with suspected monofocal seizure onset, which are negative even after extensive, multimodal work-ups. Future studies should also evaluate the ability of high-resolution 7 T MRI of the MEG-based region of interest to uncover subtle lesions.

5. Limitations

There are several limitations of this study. Firstly, a small number of patients were included. The positive results of our study suggesting a true additive value of MEG show the need for larger, prospective studies.

Secondly, no clear-cut inclusion criteria were used. However, all three patients underwent extensive presurgical evaluations without a clear focus hypothesis prior to MEG evaluation, and all of them suffered from occult perisylvic epilepsy.

Finally, a whole head system was not used in the MEG recordings and a head movement tracking system was unavailable. Thus, the sensitivity might be lower compared to currently available MEG systems. In particular, seizure onsets in patient 1 might have been localised using a head movements tracking system.[16]

6. Conclusion

This small case series suggests that MEG is a valuable addition to other methods applied during the presurgical work-up. Even in (peri-) insular areas, it can help identify or confirm potentially epileptogenic lesions on MRI/MRI-postprocessing and thereby make a lesion-oriented surgical approach possible. The substantial proportion of MRI-negative patients, even under optimal 3 Tesla MRI conditions, indicates that an additive value of MEG can be expected. Larger studies addressing the value of MEG imaging in inconclusive cases should be performed. For centres without direct access to MEG, referral of patients with cryptogenic focal epilepsy to a centre providing MEG examinations might be indicated.

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