Electromagnetic functional brain mapping

in the presurgical evaluation of refractory focal epilepsy

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English abstract

Background: Electroencephalography (EEG) and magnetoencephalography (MEG) are neurophysiological methods used to investigate non-invasively the spatial, temporal and spectral dynamics of human brain functions.

Objectives: This paper reviews data about the use of EEG and MEG for presurgical functional brain mapping in patients with refractory focal epilepsy. Focus is on the localization of the primary sensorimotor (SM1) cortex as well as the verbal language and episodic memory functions.

Material and Methods: The English literature was reviewed based on PubMed search. Relevant references within the selected papers were also included.

Results: Presurgical MEG functional localization of SM1 cortex generally overlaps with intracranial mapping. MEG allows for determination of hemispheric verbal (receptive and expressive) language dominance in neurosurgical patients with a high degree of concordance with the intracarotid amobarbital test. MEG represents an interesting technique to assess postoperative memory outcome in patients with mesial temporal lobe epilepsy. Very few studies have evaluated the yield of EEG in these three clinical indications. High-density EEG might be a promising technique that needs further validation.

Conclusions: MEG is a validated and robust technique for non-invasive functional mapping of SM1 cortex and verbal language hemispheric dominance in patients with refractory focal epilepsy. Data also suggest that MEG is a promising technique to assess the hemispheric dominance of memory function. Further studies are needed to assess the clinical added value of high-density EEG in these clinical indications.

English keywords

Epilepsy surgery, functional brain mapping, sensorimotor cortex, verbal language, episodic memory.

German abstract

Hintergrund: Electroencephalographie (EEG) und Magnetoencephalographie (MEG) sind neurophysiologische Methoden, die für die nicht-invasive Untersuchung der räumlichen, zeitlichen und spektralen Dynamik der menschlichen Hirnfunktion eingesetzt werden.

Zielsetzung: Der vorgestellte Artikel bietet einen Überblick über die Anwendung von EEG und MEG für das prächirurgische funktionelle Mapping bei Patienten mit refraktärer fokaler Epilepsie. Der Fokus liegt auf der Lokalisation des primären sensomotorischen Kortex (SM1), sowie der verbalen Sprach- und episodischen Gedächtnisfunktion.

Material und Methoden: Artikel in englischer Sprache wurden begutachtet, basierend auf einer PubMed-Suche. Relevante Zitate in den ausgewählten Artikel wurden ebenso einbezogen.

Ergebnisse: Die prächirurgische funktionelle Lokalisation des SM1 Kortex mittels MEG überlappt im Allgemeinen mit den Ergebnissen des intrakraniellen Mappings. Die MEG ermöglicht die Bestimmung der hemisphärischen (rezeptiven und expressiven) Sprachdominanz neurochirurgischer Patienten mit einem hohen Grad an Konkordanz mit dem Intrakarotis-Amobarbital-Test (Wada-Test). MEG-Untersuchungen sind auch für die Evaluation der postoperativen Gedächtnisfunktion bei Patienten mit mesialer Temporallappenepilepsie interessant. Sehr wenige Studien haben bisher den Nutzen des EEG im Rahmen dieser drei Indikationen untersucht. Die High-Density-EEG stellt jedoch eine vielversprechende Technik dar, die jedoch weitere Validierung benötigt.

Schlussfolgerungen: Die MEG ist eine validierte und robuste Technik für die nicht-invasive funktionelle Lokalisation des SM1-Kortex, sowie der verbalen hemisphärischen Sprachdominanz bei Patienten mit refraktären fokalen Epilepsien. Die Studienlage weist zudem darauf hin, dass die MEG eine vielversprechende Technik zur Bestimmung der hemisphärischen Gedächtnisdominanz darstellen könnte. Der zusätzliche Nutzen der High-Density EEG im Rahmen dieser Indikationen erfordert weitere Untersuchungen.

German keywords

Epilepsiechirurgie, funktionelles Mapping, Sensormotorischer Kortex, verbale Sprache, episodisches Gedächtnis.

Introduction

The primary aims of presurgical evaluation in patients with intractable epilepsy are to determine the location and the extent of the cortical area generating clinical seizures and to determine its anatomical relationship with functionally eloquent cortex (for a review, see, e.g., [73]). Such evaluation is typically based on a non-invasive approach that includes clinical assessment, prolonged video-electroencephalogram (EEG) monitoring, structural and functional cerebral imaging. Neuropsychological and neuropsychiatric evaluations also form an integral part of the assessment [73]. In some patients, it may be considered that surgery is not a worthwhile option if there is sufficient evidence based on this non-invasive approach that functional deficits will inevitably result from the extent of resection required to alleviate seizures [73]. In other cases where results fail to provide the required information, invasive monitoring using subdural or depth electrodes may be required to accurately localize the seizure onset zone or determine its proximity to eloquent cortices [73].

Functional magnetic resonance imaging (fMRI) of the brain is by far the main functional neuroimaging technique used worldwide to perform non-invasive functional brain mapping in patients with refractory focal epilepsy who are candidate for resective epilepsy surgery (for a review, see, e.g., [25]). In such patients, fMRI has mainly been used to locate primary sensorimotor (SM1) cortices or assess hemispheric dominance for language or episodic memory functions [25]. Thus, in cases where resective epilepsy surgery might compromise motor, language or episodic memory functions and therefore significantly impact on patients' quality of life, fMRI can aid the surgical decision-making process by providing additional non-invasive information about the anatomical relationships between the seizure onset zone to be resected and eloquent brain areas [25]. In addition, fMRI may provide information about possible reorganization of function, which may be critical to determine the surgical strategy (for reviews, see, e.g., [25, 46]). Although numerous studies have validated and highlighted the important role of fMRI in the presurgical evaluation of patients with epilepsy, it must be kept in mind that this technique actually suffers from several limitations and particularly in clinical populations. First, this technique relies on the integrity of the neurovascular coupling that can actually be altered by brain lesions or epilepsy, potentially leading to false positive or negative results [4, 20]. Indeed, apart from lesion-induced neurovascular uncoupling, the neurovascular coupling mechanisms that apply in the normal situation may actually be altered by the epileptic activity *per se* (for a review, see [77]). Second, due to the hemodynamic response time, the relatively poor temporal resolution (at the level of the second) of conventional fMRI hampers fine discrimination of the different neural components (e.g., sensory vs. motor processes) observed in fMRI activation maps [43]. Consequently, fMRI activation maps may be much more challenging to interpret in patients with epilepsy or brain lesions than in healthy subjects [20]. In this context, electrophysiological methods such as magnetoencephalography (MEG) or EEG are increasingly considered as attractive alternatives to fMRI for presurgical functional brain mapping in epileptic patients [3, 16]. EEG and MEG respectively record the scalp electrical potentials and extracranial magnetic fields generated by neuronal electrical activity [33, 67]. Hence, they provide direct information about neuronal activity with a millisecond temporal resolution, and importantly, they do not rely on the neurovascular coupling (for reviews, see, e.g., [33, 67]).

MEG typically uses much more sensors (from 275 to 306 sensors) than conventional EEG systems used in clinical settings (from 21 to 64 electrodes) [67]. Furthermore, magnetic fields, as opposed to electrical potentials, suffer minimum attenuation and distortion from the different tissues they have to cross to reach the scalp surface [33, 67]. Additionally, some data suggest that MEG provides better signal to noise ratio than EEG for most focal neocortical sources [32]. Therefore, MEG is usually considered to have a better spatial resolution (i.e., a few millimetres) than EEG (i.e., about 1 cm) when combined with structural MRI to perform electromagnetic source imaging, i.e., localizing the brain areas at the origin of the recorded signals [33, 67]. This probably explains why functional brain mapping in neurosurgical patients has been performed mainly with MEG rather than EEG. Indeed, source localization based on EEG has seldom been promoted for such clinical applications [45]. Also, the few EEG studies addressing this issue actually used various numbers of scalp EEG electrodes (from 33 up to 256) and various source modelling approaches, which complicates the interpretation of the available data. Still, for a similar number of sensors, some data suggest that localization with EEG could actually be more accurate than that with MEG [48]. The advent of high-density EEG (hdEEG, i.e., from 128 up to 256 scalp electrodes) might therefore challenge the superiority of MEG over EEG in this indication. Of note, the use of hdEEG is becoming *de rigueur* in EEG investigations aiming at performing electrical source imaging [67].

Interestingly, in the surveys of the American Clinical MEG Society (ACMEGS) [2] and of the European MEG Society [23], it appeared that, despite its obvious methodological advantages over fMRI, MEG is clearly underused in this indication in clinical MEG centres compared to the potential number of patients who could benefit from such investigations. Indeed, those surveys reported that the number of MEG recordings performed for functional brain mapping is about half or less of those performed in the context of epilepsy mapping [2, 23]. These data therefore suggest that much effort needs to be done to promote the major interests of electromagnetic source imaging over fMRI for presurgical functional brain mapping [2, 23].

This paper aims at reviewing the available data about the use of MEG and EEG for presurgical functional brain mapping in neurosurgical patients. In particular, we will focus on the use of these techniques to map the SM1 cortex, the areas involved in verbal language, and to assess hemispheric dominance for episodic memory. MEG and EEG can also be used to map auditory and visual cortices but the corresponding data will not be reviewed here, as it is seldom performed in the context of presurgical functional brain mapping. Given the limited number of studies focusing on the use of MEG/EEG in patients with refractory focal epilepsy, we also included studies focusing on neurosurgical patients with brain lesions (e.g., brain tumors) in general.

Preoperative mapping of the sensorimotor cortex

A non-invasive presurgical functional mapping of SM1 cortex is recommended in patients with refractory focal epilepsy due to a lesion located close to or at the central sulcus. In this context, the primary motor (M1) cortex can be at first identified on structural cerebral images on the basis of its anatomical landmarks (i.e., the hand knob), which looks like an omega or epsilon in the axial plane and a hook in the sagittal plane [96]. Still, this approach has been proven to be unreliable due to low inter-rater agreement [85]. It may also be misleading in some patients due to possible anatomic variability, lesion-induced anatomic displacement or plasticity phenomena [11, 22]. It is therefore of clinical importance to use functional mapping procedures to determine as precisely as possible the anatomical relationship between SM1 cortices and the brain lesion to optimally tailor the surgical resection, assess related functional risk(s), and contribute to the decision-making process [22]. Apart from fMRI, MEG has been the main electrophysiological technique used for this clinical indication.

Several studies have demonstrated the ability of MEG to map SM1 cortex in patients with brain lesions (for reviews, see, e.g., [50, 51, 83]). Indeed, MEG mapping of SM1 cortex generally agrees with intracranial mapping of somatosensory or motor cortical areas [51, 83]. The reported mean mislocation is about 10 mm but it should be kept in mind that MEG is mainly sensitive to activity from neurons located within brain sulci, while direct cortical electrical stimulations or recordings are usually performed from the visible gyral surface for which MEG is almost blind [51]. Also, no clear data exist about the spread (i.e., from the stimulation point) of the stimulation current within the cortex [51]. Finally, intracranial electrodes diameter or intercontact distances might not allow proper or exact comparisons [51]. Several studies have also previously shown good anatomical concordance between fMRI- and MEG-based SM1 mapping, but in some cases MEG has proved its superiority to fMRI [7, 8, 37, 38, 42, 43, 53, 54, 72, 79]. These data raise the complex issue of the "gold standard" used to validate non-invasive functional neuroimaging techniques for presurgical brain mapping and, for instance, illustrate that validation of accuracy using intracranial procedures (which is still considered as the gold standard) or fMRI also suffers from several drawbacks.

Several MEG methods have been validated to localize the SM1 cortex and are summarize in Table 1. These are electrical peripheral nerve stimulation [12, 17, 42, 43, 52, 82, 90, 92, 94], tactile stimulation [72, 76], readiness and motor evoked fields [29, 38, 42, 47, 94], rolandic mu rhythm desynchronization/suppression (alpha or beta band components) [12, 55, 93, 94] or cortico-muscular coherence (CMC) [12, 52]. Further information about the practical aspects of functional SM1 cortex mapping using MEG can be found in the ACMEGS guidelines [16]. One of the additional key strengths of MEG over fMRI is its ability to investigate, using the above methods and in a reasonable time for the patient, different neurophysiological processes (i.e., evoked magnetic responses, induced magnetic responses, coupling between peripheral and cortical signals, and cortico-cortical coupling) that can be altered differently by brain lesions or patients' clinical status [12]. Thus, MEG provides a unique opportunity to acquire in one single session several MEG "*functional localizers*" (i.e., a validated MEG method to localize the SM1 cortex, see Table 1) [12]. The anatomical convergence of those different MEG functional localizers at the central sulcus has been demonstrated in healthy subjects and helps building the confidence level in functional mapping results (compared with a uni- or bimodal approach) and determining the clinical need to further undergo intracranial mapping procedures (Figure 1) [12]. Such approach also increases the yield of MEG in case of failure, inaccurate or atypical localization of one MEG functional localizer or fMRI mapping [12].

Combining MEG functional localizers with navigated transcranial magnetic stimulation (nTMS) could be of high clinical interest and should be envisaged in future prospective studies. Indeed, several studies have highlighted the clinical added value of nTMS in presurgical planning with good accuracy compared with direct cortical electrical stimulation [28, 44, 56, 62, 63]. Presurgical functional brain mapping using nTMS could be integrated as an additional non-invasive electrophysiological functional localizer or ultimately, be used to validate the location of fMRI and MEG functional localizers.

Even if MEG has been the main method used for presurgical non-invasive electrophysiological functional SM1 mapping, few studies have addressed the potential clinical value of EEG combined with MEG in patient with refractory focal epilepsy arising from the central area [5, 84]. Those studies mainly focused on primary somatosensory cortex localization. They showed that EEG might be superior to MEG in few cases due to a more radial orientation of primary somatosensory (S1) cortical sources or vice-versa when source orientation was more tangential [5, 84]. These studies also highlight based on these findings that combining MEG with EEG mapping actually helps to resolve some functional mapping ambiguities [5, 84]. Another study compared MEG, hdEEG and fMRI in healthy subjects performing motor and somatosensory tasks [40]. Results showed that, when using individual head models (rather than standard head models), hdEEG localized significantly closer to fMRI (used as a reference for SM1 cortex localization) than MEG [40]. Authors concluded that EEG localization can be more accurate than MEG localization for a similar number of channels [40]. Still, this conclusion can be questioned considering the gold standard (i.e., fMRI) used to validate MEG/EEG localization accuracy and previous studies, which have shown that MEG may be superior to fMRI in localizing the central sulcus (see, e.g., [43]). Finally, one study used hdEEG to localize S1 cortex in healthy subjects and neurosurgical patients, and validated its localization accuracy against fMRI or intracranial cortical stimulation [45]. Results showed good concordance between hdEEG and fMRI with mean Euclidian distances below 15 mm compared with intracranial cortical stimulation [45]. Of note, hdEEG had a source maximum for the first peak of somatosensory-evoked potential that localized deep in the central sulcus (area 3b), whereas fMRI showed maximal signal change on the lateral surface of the postcentral gyrus (area 1) [45]. Actually, hdEEG maximum source localized systematically more medially than the fMRI maximum. These findings suggest that hdEEG and fMRI might be sensitive to different components of S1 cortex activity. The fMRI activation maps are dominated by more integrative somatosensory processes occurring at area 1 of S1 cortex, while hdEEG results are more dominated by the early cortical somatosensory process occurring at area 3b [45]. Another possible explanation would be that fMRI activity follows the topology of the draining veins, which might not necessarily overlap with active neocortical sources [45].

Taken together, the available literature demonstrates that MEG is a validated method and that hdEEG shows great promise for presurgical functional SM1 cortex mapping. Still, further studies are needed to validate hdEEG before promoting its routine clinical use.

Preoperative mapping of verbal language function

In patients with refractory focal epilepsy, functional verbal language mapping is mainly used to assess the hemispheric dominance or the intrahemispheric location of brain areas involved in speech processing and production (for reviews, see, e.g., [25, 64]). Such investigation is typically mandatory to avoid postoperative language deficits in right-handed patients with left-hemisphere perisylvian or anterior temporal lobe epilepsy. It may also be of interest in left-handed patients with similar type of epilepsy over the left or the right hemisphere and clinical signs of speech disturbances during the interictal, the ictal or the postical period. Verbal language mapping is also indicated in the case of early-onset epilepsy that may occasion an epilepsy-induced shift in dominant language hemisphere or rerouting of language pathways from traditional to non-traditional areas within the dominant language hemisphere (for reviews, see, e.g., [18, 21, 34]). Indeed, atypical verbal language networks have been more frequently observed in children than in adults with epilepsy [18, 21, 34]. This might be due to the age-related increase in hemispheric lateralization of verbal language function demonstrated in healthy children [21]. Yet, whether age of seizures onset relates to epilepsy-induced functional reorganization processes is still a matter of debate [21].

Apart from intracranial electrical stimulations, the standard procedure used to assess verbal language hemispheric dominance prior to surgical resection in epilepsy patients is the intracarotid amobarbital test (IAT), also know as the Wada test [91]. The IAT typically involves the injection of sodium amobarbital into a single internal carotid artery via a transfemoral arterial catheterization. This procedure transiently suppresses neuronal activity in the anterior and middle cerebral arteries territories of the injected hemisphere while the patient is presented with various language or memory tasks. It actually challenges the spared vascular territories, in particular in the non-injected hemisphere, for verbal language or memory functions [87]. Still, the IAT procedure suffers from several limitations and drawbacks (for a review, see, e.g., [57]). First, in the context of verbal language mapping, this approach only determines hemispheric lateralization and does not allow for intrahemispheric localization of brain areas involved in the verbal language function. Also, due to the presence of arterial anastomoses via the circle of Willis, it cannot be excluded that non-injected arterial territories are actually also subjected to temporary neuronal activity disturbances, questioning the specificity of IAT results. Finally, this procedure is associated with risks of stroke, infection, and haemorrhage. This explains why non-invasive functional neuroimaging techniques have become nowadays one of the main approaches to assess verbal language networks in patients with refractory focal epilepsy.

Up to now and as for non-invasive functional mapping of SM1 cortex, fMRI has been the main functional neuroimaging technique used for non-invasive functional verbal language mapping in this clinical indication [25]. Studies have demonstrated a high degree (80-90% of patients) of concordance between fMRI and IAT findings [25]. Thus, the consensus in most epilepsy surgery centres with an expertise in verbal language fMRI is that fMRI language lateralization can replace the IAT in most patients to establish hemispheric dominance [6, 25]. Still, the precise intrahemispheric localization of the cortical areas involved in speech processing and production remains suboptimal [25]. Indeed, neocortical areas that do not seem to be activated at the statistical threshold used to build fMRI maps might actually be required for verbal language function, while other areas reaching this threshold may not be functionally relevant for linguistic processes [25]. Therefore, to date, invasive intracranial cortical electrical stimulations or awake surgery remain mandatory when the planned cortical resection overlaps eloquent areas for verbal language function [25].

MEG and EEG have also demonstrated their clinical interest in this indication as they have additional key strengths over fMRI (for a review, see, e.g., [64]). Those techniques indeed allow to characterize the spatial, temporal and spectral dynamics of the successive and largely overlapping cortical processes involved in receptive and expressive speech processes [64]; please see, e.g., [64, 75] for further details regarding language-related successive cortical events in healthy participants which are out of the scope of the present review. MEG has been by far the main electrophysiological technique used in this clinical indication.

A well-known MEG approach used to assess hemispheric dominance for receptive language processes in epileptic patients has been developed by Papanicolaou’s group. This approach is based on a visual or an auditory word-recognition memory paradigm that makes it possible to study event-related fields (ERFs) and their associated successive (few ms time intervals) cortical sources using equivalent current dipole modelling (further methodological details can be found in [60]). Hemispheric dominance is then determined through a laterality index that compares the number of acceptable late (>200 ms post-stimulus onset) cortical activated sources observed in the right and the left hemispheres (mainly within posterior temporal areas) [60]. Using this approach, several studies showed a high degree of concordance (about 86 to 92%) between MEG laterality assessment and IAP both in children and adults [14, 15, 24, 59, 60]. This approach also showed a good concordance with intracranial electrical cortical stimulations [81].

Alternatively, other studies investigated the language hemispheric dominance through the analysis of cortical event-related desynchronization (ERD) processes elicited by silent reading paradigms. Hirata et al. [36] investigated the lateralization patterns of beta or low gamma ERD between left and right frontal areas localized using a spatial filter approach. Using this procedure, concordance of the lateralization index with IAP reached 85%, with a sensitivity of 86.7% and a specificity of 96.7% [36]. Studies that used similar silent reading approaches showed consistent results (see, e.g., [41]). Of note, one study compared IAT, fMRI and MEG using verb generation (fMRI) and silent word reading (fMRI and MEG) in a large group of neurosurgical patients with brain tumors; some of them having refractory focal epilepsy [39]. In that study, the combination of fMRI and MEG reached 100% concordance with IAT results [39].

Finally, other studies used verbal language paradigms with a picture naming or a verb generation task to investigate the hemispheric dominance of frontal language-related brain areas (Figure 2). One study compared these two tasks in 27 patients with refractory focal epilepsy using a multiple source analysis technique called MR-FOCUSS relying on current density mapping [13]. Results showed that picture naming was more concordant than verb generation (96% vs. 82% concordance) with the IAT to lateralize hemispheric dominance [13]. These findings contrast with those of other studies performed in healthy subjects or patients with brain lesions [64]. For example, in a MEG study performed in right-handed healthy subjects that compared three covert verbal language paradigms (verb generation, letter fluency, picture naming) and used a spatial filtering approach to investigate beta band ERD, verb generation was the only task to unveiled a left hemispheric dominance in all subjects [27]. Also and more importantly, in another study that focused on auditory-triggered verb generation and investigated beta band ERD using a spatial filtering approach, correlation with the IAT was 93% in the 14 patients studied prospectively, with a sensitivity of 100% and a specificity of 92% [26].

The verbal language tasks described above typically require the patient to be cooperative. In young children and cognitively impaired patients, this may not be feasible for the patients. Interestingly, successful passive MEG language mapping in small groups of sleeping or sedated children have been reported [70, 88]. For example, one Meg study used a word listening paradigm in 3 children in natural or propofol-induced sleep and successfully lateralized the receptive language areas [88].

Overall, studies have demonstrated the ability of the MEG technique to determine hemispheric verbal language dominance in presurgical patients for both receptive and expressive language processes with a high degree of concordance with the IAT or fMRI [57, 64]. The reliability and the validity of the technique is therefore confirmed for this clinical indication. Considering the advantages of MEG over fMRI (see above), this technique should be considered more frequently for presurgical language mapping, alone or preferably in association with fMRI [57, 64]. Also, as for presurgical SM1 cortex mapping, MEG offers the unique opportunity to investigate using different signal processing and source reconstruction approaches (e.g., ECD, spatial filtering), and in one single MEG session, multiple verbal language tasks triggering specific neuronal processes (e.g., ERFs, ERDs). Such combination appears critical to increase the yield of MEG in this clinical indication [64]. According to the literature, the best task to assess language comprehension both in adults and children appears to be the word recognition task, while the verb generation task can be used to assess language production [64]. As indicated in the ACMEGS guidelines, the use of MEG in presurgical functional verbal language mapping should be restricted to the assessment of language-dominant hemisphere in neurosurgical patients and it is considered that it can replace the IAT in most patients [16]. The use of MEG for the intrahemispheric localization of cortical areas involved in speech processing and production is, as for fMRI, probably not yet optimal. Therefore, MEG cannot replace intracranial cortical electrical stimulations or awake surgery (or both) to guide cortical resection close to eloquent verbal language areas.

To the best of our knowledge, very few studies have addressed the potential role of EEG in this clinical indication. One EEG study investigated, in the sensor space (64 scalp electrodes), the verbal language hemispheric dominance in 36 epileptic patients and 37 healthy subjects using three visually presented language tasks (short-term language memory, phonological, and semantic decision tasks). Results were compared with those of language fMRI (not obtained in all participants) [86]. In patients, the highest concordance with fMRI was obtained with the semantic decision task and reached 87% for the Broca area and 77% for the Wernicke area [86]. This study therefore indicates that EEG might be a promising tool to investigate the lateralization of language function in epilepsy patients but further studies are clearly needed. These future studies should address the additional value of source reconstruction using hdEEG.

Preoperative mapping of episodic memory function

Verbal memory declines in about 30-85% of epileptic patients undergoing left temporal lobe resection while nonverbal memory declines in about 30-50% of the patients when right temporal lobe resection is performed [9, 30, 31, 35].

The standard procedure used to assess the risk of resection-induced loss in memory function prior to surgery in patients with mesial temporal lobe epilepsy is the IAT. During this procedure, the contribution of the non-injected temporal lobe to memory function can be challenged along with language function. Impaired memory performance is observed in about 20–30% of cases after injection on the side of the epileptic hemisphere, whereas this proportion reaches 60–80% after contralateral injection [65, 69, 95]. Based on these data, several authors advocate IAT performance as a way to predict task-specific memory decline after surgery (and possibly to propose surgical abstention if global amnesia is predicted), and as an adjunct to determine seizure focus laterality [61, 74, 95]. However, considering the above mentioned drawbacks of the IAT plus the uncertain proper delivery of the sodium amobarbital to the hippocampal formation [57], several studies have assessed the potential clinical added-value of functional neuroimaging in this clinical indication (for reviews or commentaries, see, e.g., [57, 58, 68]).

Most of the studies performed so far have used fMRI and showed that this non-invasive technique could be of great interest to assess the risk of memory loss associated with anterior temporal lobe resection [25]. To the best of our knowledge, very few MEG studies and no EEG studies at all have been performed and they only involved adult patients [19]. The low number of MEG studies performed in this clinical indication might be due to the fact that MEG is usually considered to have a limited sensitivity to deep brain sources such as the hippocampus. Still, previous studies have shown that it is actually possible to detect hippocampal activity with MEG (see, e.g., [71]).

In a first MEG study that used an auditory word recognition memory task, the mesial temporal lobe activity was assessed using ERFs and equivalent current dipole modelling in a small group of six patients with left medial temporal lobe epilepsy (LMTLE) and seven healthy subjects [89]. This study demonstrated left medial temporal lobe activity in the majority of healthy volunteers (86%) but in only a minority of patients (36%). An opposite pattern was observed for right medial temporal lobe activity as activity within this brain area was observed in all patients but two healthy volunteers (28%). These data suggested the existence of episodic memory reorganization in patients with LMTLE, which is in agreement with some previous fMRI studies [1, 66, 80]. Postsurgical memory outcome was not provided in this first study.

In a second study, similar signal processing and source reconstruction methods were used to evaluate nine patients with left MTLE and nine healthy volunteers during a verbal episodic memory task [49]. MEG data revealed predominant left hippocampal activity in healthy subjects, whereas the clinical group showed mainly activity within the right hippocampus [49]. Three patients with a clear lateralization of memory-related activity towards the right hippocampus underwent a left anterior temporal lobectomy. They showed a significant seizure reduction (Engel 1A/B outcome) after surgery and postoperative memory assessment did not show significant memory loss [49].

These two studies suggest that MEG could be an interesting technique to assess postoperative memory outcome in patients with MTLE. Still, further studies are clearly needed to determine its concordance with fMRI or the IAT.

Main Points

- MEG is a validated and robust method for presurgical functional mapping of SM1 cortex in patients with refractory focal epilepsy.
- MEG is a validated and robust method for verbal language hemispheric dominance in patients with refractory focal epilepsy.
- MEG might be of interest to assess hemispheric dominance for episodic memory in patients with refractory focal epilepsy but further studies are clearly needed.
- hdEEG appears as a promising technique that could challenge the superiority of MEG in these clinical indications.
- Further hdEEG studies are clearly required to assess the respective potential of MEG and hdEEG for presurgical non-invasive functional brain mapping in patients with refractory focal epilepsy.
- Simultaneous MEG and hdEEG studies should be performed to address this critical issue, considering that hdEEG is much more widely available than MEG.
- Harmonization of the methods (i.e., tasks, signal processing approaches, source reconstruction methods) used for presurgical MEG/hdEEG functional brain mapping is mandatory.

Practical Guidelines

MEG should be considered, alone or in combination with fMRI, when functional mapping of SM1 cortex or assessment of the verbal language hemispheric dominance is clinically required in the non-invasive presurgical evaluation of patients with refractory focal epilepsy.

MEG appears mandatory in such patients with atypical fMRI activation patterns.

There is at the moment insufficient available data to promote (i) the use of MEG for hemispheric dominance for episodic memory and (ii) the use of hdEEG for presurgical non-invasive functional brain mapping in patients with refractory focal epilepsy.

Clinical magnetoencephalographers should join forces to:

- Promote the major role that MEG can play in SM1 cortex and verbal language hemispheric dominance mapping.
- Promote the harmonization of the methods (e.g., tasks, signal processing approaches, source reconstruction methods) used for presurgical MEG functional brain mapping.
- Create of MEG data repository that would potentially help predict motor or language outcome after epilepsy surgery (see, e.g., [78]).
- Perform simultaneous MEG/hdEEG studies assessing the respective clinical added value of these techniques to assess the anatomical relationship between the eloquent cortices and the irritative, seizure onset and epileptogenic zones.
- Address the potential role of novel generations of MEG sensors, such as the optically-pumped magnetometers, in these clinical indications. These novel MEG sensors will make it possible to record MEG at room temperature and at a lower cost than currently possible (see, e.g., [10]). This might for sure generalize the use of MEG for non-invasive presurgical functional brain mapping.

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Legend of the figures

Figure 1: MEG and fMRI functional localizers for SM1 cortex mapping. **Top.** Results obtained in one epileptic patient with a rolandic brain tumour. A relative spread of some functional localizers (ERD 10Hz and fMRI) is observed. This indicates that results of non-invasive functional SM1 cortex mapping have to be taken with caution. This case illustrates the clinical added value of combining various functional localizers. **Middle.** Results obtained in another epileptic patient with a brain tumour located at the posterior part of the superior frontal gyrus. A good anatomical concordance of MEG and fMRI functional localizers is observed. This result contributes to increase the confidence level about robustness of non-invasive functional SM1 cortex mapping in this patient. **Bottom.** SEF, somatosensory evoked fields elicited by median nerve electrical stimulations; CMC, cortico-muscular coherence; CKC-TOUCH: cortico-kinetamic coherence with the fingers touching each other during repetitive fingers flexion/extensions; CKC-noTOUCH: cortico-kinetamic coherence with the fingers not touching each other during repetitive fingers flexion/extension; ERD 10 Hz: event related desynchronization of the alpha component of the rolandic mu rhythm; ERD 20 Hz: event related desynchronization of the beta component of the rolandic mu rhythm; fMRI: functional magnetic resonance imaging using classical block-design motor fMRI paradigm; Ellipsoid, assessment of the anatomical convergence of the different functional localizers. Further information can be obtained in [12]. Figure adapted from [12].

Figure 2: Beta band event related desynchronization at the left inferior frontal gyrus during covert verb generation in a right-handed healthy adult subject.