What Are the Promises and Challenges of Simultaneous MEG and Intracranial Recordings?

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Abstract (199 words)

Intracranial electroencephalography (iEEG) invasively measures brain activity from neurosurgical patients with higher fidelity and spatial precision than noninvasive electroencephalography (EEG) or magnetoencephalography (MEG) alone. For planning neurosurgical resection, iEEG more robustly detects lower amplitude signals that may distinguish pathological from healthy brain tissue. On the other hand, iEEG can only sample the immediate brain regions implanted for clinical reasons, while MEG synoptically measures the entire brain, albeit with lower fidelity. Relative to scalp EEG, signals recorded by MEG are less distorted by the poorly conducting skull, craniotomies, and neurosurgical hardware. By combining iEEG with simultaneous MEG recordings, we supplement the limited spatial sampling of iEEG

with the superior source localization ability of MEG, yielding a combined interesting technique at two different measurement scales that can cross-validate findings from either.

Setting up such simultaneous MEG-iEEG measurements involves specific considerations, and we review patient selection, patient preparation, and equipment. We then review published studies related to cognition, with emphasis on the sensitivity of MEG to source depth as well as functional connectivity between iEEG and MEG. We end with future directions opened by the unique possibility to record brain signals at different scales simultaneously.

1. Introduction and motivation

Magnetoencephalography (MEG) is a powerful neurophysiological tool for the non-invasive investigation of brain activity at millisecond temporal precision. Clinically, however, electrodes may need to be placed intracranially for higher specificity to assist planning of neurosurgical resection, such as in the presurgical evaluation of epilepsy using electrocorticography (ECoG) and stereo-EEG (sEEG). In other cases, electrodes are chronically implanted in subcortical structures for the purpose of deep brain stimulation (DBS); these same electrodes can be alternatively used to measure local field potentials. DBS is performed most commonly in the basal ganglia for movement disorders such as Parkinson's disease, though increasingly, other applications of DBS are being investigated, such as the thalamus for essential tremor and certain forms of epilepsy.

These invasive procedures, done on purely clinical grounds, provide a unique opportunity to compare the global scale of MEG with the local scale of a ground truth recorded directly above the brain and below the dura (ECoG) or directly within the brain tissues (sEEG, DBS). The simultaneous acquisition of MEG and intracranial EEG (iEEG) represents a significant burden in terms of patient management, acquisition of signals, and data processing. Yet the recording signals of the exact same activity at different scales – local and global – provides key advantages, such as in epilepsy, where interictal discharges are spontaneous and show large variations from one event to another. Similarly, in complex cognitive protocols investigating aspects of memory or different mental strategies, the brain response cannot be assumed to be similar across repetitions of the paradigm. In either case, recording the two modalities at distinctly separate times makes it infeasible to align and average the signals in post-processing. More generally, the simultaneous recording of MEG and iEEG ensures that the brain is in the same state (vigilance, attention, etc.) at both scales.

In methodological terms, simultaneous recordings bring possibilities that are out of reach with separate recordings. In order to understand the links between depth and surface, one can quantify which intracranially observed signals are likely to be measurable extracranially by MEG. This can be detected by identifying signals with

no lag between the iEEG and MEG [1, 2], implying propagation via volume conduction rather than neural connectivity (which would generally involve a lag or phase delay). Another approach is to measure trial-to-trial correlation of amplitude in the time domain (e.g., the inter-trial correlation, ITCOR introduced in [3]) or in the time-frequency domain [4]. Apart from these validation-oriented techniques, simultaneous measurements allow the computation of connectivity index between signals seen intracranially with high spatial specificity and MEG signals [5], providing a powerful means of multi-scale network analysis.

Therefore, in order to compare the exact same brain sources in the same brain states, and to take full advantage of trial-to-trial fluctuations, the invasive and non-invasive signals need to be recorded simultaneously. In this chapter, we review the technical challenges, methods, and findings of simultaneous MEG and intracranial recordings, as well as discuss future venues, with emphasis on cognitive research.

2. Setting up a simultaneous recording

In the last few years, several publications have provided detailed guidelines for the collection of MEG data [6, 7]. Clinical context involves additional challenges and simultaneous recordings require further considerations. Although simultaneous recordings of MEG and iEEG share some aspects of the context and recording procedure with clinical MEG routine [8] and iEEG procedure [9], some characteristics, which we detail here, are very specific to simultaneous recordings.

The present section describes the specific steps required to perform a simultaneous MEG-iEEG recording, including MEG site preparation, patient selection, patient preparation, and we review some of the experimental protocols found in the simultaneous MEG-iEEG literature.

2.1. General considerations

One of the first considerations when deciding to perform a simultaneous recording is the accessibility of the MEG lab, particularly for inpatients in the epilepsy monitoring unit. The proximity of the MEG system facilitates the setup and the preparation of the recording session. Minimal emergency preparation is required for an MEG facility to host a simultaneous MEG-iEEG recording. Depending on the patient safety risk areas, various potential emergency situations may arise and call for best patient safety practices, including specific equipment (e.g. oxygen, suction) and documented procedures (e.g. rescue procedure, crash charts) reviewed by the MEG Medical Director.

In this context, iEEG signals can either be collected from the built-in EEG amplifier of the MEG system [3] or an external one [e.g. 10]. Both configurations have advantages and limitations. The built-in EEG system may have a limited number of

channels (e.g. 64, 128) and the amplitude range may be adapted to record microvolts, whereas the iEEG signals range in the order of millivolts, requiring adjustments to the EEG gain. The built-in EEG system, usually designed for measuring scalp EEG, may need to be certified and approved by the MEG Medical Director and the Institutional Review Board for research using invasive electrodes. Nevertheless, this built-in configuration offers two main advantages: 1) reducing potential noise introduced by an external device (containing metallic parts) within the MEG environment, and 2) reducing post-recording processing, since the EEG data are digitized in the identical MEG environment. Thus a single dataset encapsulates both the MEG and iEEG signals in a single time-aligned dataset.

In other instances, however, an external EEG amplifier may be desirable. In the monitoring unit, for example, the acquisition system is typically certified for invasive clinical applications, which simplifies the procedure for obtaining institutional approval for research. The external unit may also have better gain, noise shielding, jack connectors, and channel count than that offered by the MEG system. In some instances, the analog or digital output of the EEG system can be integrated directly into the MEG system's acquisition. More often, however, the two separate acquisition systems record to two separate files, and the data need to be time-synchronised, typically by providing a periodic timing pulse into a channel of each system. As reviewed in [10], in post processing, the data need to be resampled and aligned to the same time base and filter settings, then merged into a common dataset to ease the simultaneous review of both modalities. As discussed below, the external system must also be arranged to introduce minimal additional noise into the MEG recording.

Planning the stimulation procedure involves preparing the adapted equipment in the MEG facility (e.g. headphones, speakers, relevant display, electrical stimulator). The presentation of the sequence of stimuli must be controlled by a procedure or delivered by a research software package which ensures sub millisecond precision and allows the recording of response time. The MEG facility must validate all timing with calibration measurements for the specific stimulus and computer configuration [11].

Simultaneous recordings involve placing a large amount of recording apparatus (electrodes, wires, connectors), within close reach of the MEG sensors. The presence of metal inside the MEG magnetic shielded room and nearby the sensors may thus result in higher noise levels. SEEG electrodes are usually made of platinum, while ECoG grids may be made of either platinum or nonmagnetic stainless steel. As such, the electrodes themselves, cables, and surgical hardware are typically MRI-compatible, but may nevertheless result in added MEG noise and artifacts arising from electrically conductive materials moving together with the patient's head. An example of this is shown in Figure 1b of [3], where slow oscillatory artifacts arise from the connector placed on the patient's shoulder due to its displacement from breathing. Another source of noise comes from the amplification system that

may not be perfectly isolated, and may be transmitted through the wires to the vicinity of the MEG. An example of this effect is shown in Figure 1d of [3]. Thus, connectors need to be immobilized and removed from the patient body, and the EEG amplifier may need to be isolated from the environment (e.g., powered by battery rather than mains) [10].

2.2. Patient selection

Once the hardware and MEG facility feasibility (as described in previous section) have been established, another constraint in the design of any research study is the likely selection bias of a relatively small number of patients due to their limited availability. Deep brain stimulation studies typically involve the placement of only one or two electrodes with only one pair of contacts activated, and the DBS device may or may not be capable of recording on the other remaining contacts. Thus only a small region of the brain may be available for individual or group studies, depending on the application of DBS used in the patient cohort (e.g., Parkinson's disease, essential tremor, epilepsy, depression, obsessive compulsive disorder, pain).

In contrast, ECoG and sEEG clinical studies generally span wider regions of the brain. ECoG is often performed using a silastic electrode grid placed on the cortical surface and/or sEEG depth electrodes to common targets like the hippocampus and amygdala; when used in epilepsy monitoring, ECoG surface grids can involve more than 100 electrodes spanning entire lobes. sEEG studies typically use between eight and twenty stereotactic depth probes, with five to twenty electrode contacts along each probe [9] such that simultaneous recordings of roughly 200 iEEG channels are common. Unlike DBS patients, however, these are almost always patients with epilepsy that are monitored exclusively in a hospital monitoring unit, with sensitive surgical sites, post-surgery irritability, and reduced medication level to facilitate capturing epileptiform activity. As discussed in the next section, the apparatus of sEEG channels protruding from the head makes it further difficult to find patients that will literally fit inside the rigid MEG helmet. On the other hand, the large craniotomy needed for the implantation of ECoG grids may leave the patient too vulnerable to place inside the rigid MEG helmet.

Another selection bias consideration is the medication level of the patient. The clinical examination of the iEEG patient usually involves the halting/reduction of antiseizure medication, in order to record as many typical seizures (i.e. with typical semiology) as possible during the monitoring unit stay. Once the patient management team is satisfied that an adequate exam has been completed, the patient is returned to their medications, and explantation surgery is scheduled. Research examinations in the MEG are therefore possible in this limited time window, but with an uncertain titration of medication levels in the patient, who may also be tired and subject to brain atypical activities resulting from a series of prior seizures.

The above constraints result in a patient cohort with smaller heads (typically leading to inclusion of more females than males) or a younger pediatric cohort, with various levels of fatigue or alertness on changing medication levels, which can complicate general findings in a group study. Nonetheless, as we review below, these patients provide valuable cross-validation of studies at local and global scales of measurement, from focused invasive studies to synoptic non-invasive measurements, and the possibility to bridge the non-invasive measurements to the much broader class of non-invasive measurements of control research subjects. Put more simply, control studies with electrodes implanted in normal brains are not ethically possible, so these patient studies are invaluable, despite their unavoidable selection bias.

2.3. Patient preparation at the time of the MEG examination

Patients with a DBS implanted may be examined in an outpatient setting, such that the procedure for preparing the patient is nearly identical to the procedures outlined in [8]. If the DBS generator is embedded in the skull, then special care may be necessary regarding any degaussing (i.e. procedure to remove minor magnetic contaminants) of the generator, and the Medical Director for the MEG site must be consulted. If the generator is considered MRI-safe, or if the generator is in the chest, then no other special handling of the patient may be necessary outside of routine preparation for a MEG exam.

Patients with either embedded depth (sEEG) electrodes or a craniotomy with cortical (ECoG) electrodes are being monitored as inpatients in a monitoring unit and therefore require special considerations and handling on the day of the MEG exam. As discussed above in Patient Selection, the opportunity to perform the MEG exam typically comes at the end of the monitoring stay, after adequate clinical data have been gathered to perform the diagnosis and/or the treatment strategy for the patient (see also Chapter 28 on practical issues with recordings in presurgical epilepsy patients). Typically, medications are being resumed, and surgical explantation has been scheduled. We lay out the basic steps that should be considered, with an overall goal to ensure patient safety and comfort by performing many of the tasks bedside in the monitoring unit, before transport to the MEG.

First, the patient should be reconsented to ensure their continuing agreement with any research to be conducted (see also Chapter 9 on Ethical issues). Surgical nursing is then consulted to remove the surgical head dressing, which may have been in place for many days or weeks. With the original headdress removed, the leads of the electrodes can be gathered into a bundle that drapes away from the surgical site and down the neck. The connectors should be arranged such that they land in the nape of the neck and/or outside the MEG helmet. The head can then be rewrapped in a light surgical wrapping, as shown in the figure (Fig. 1A and 1B).

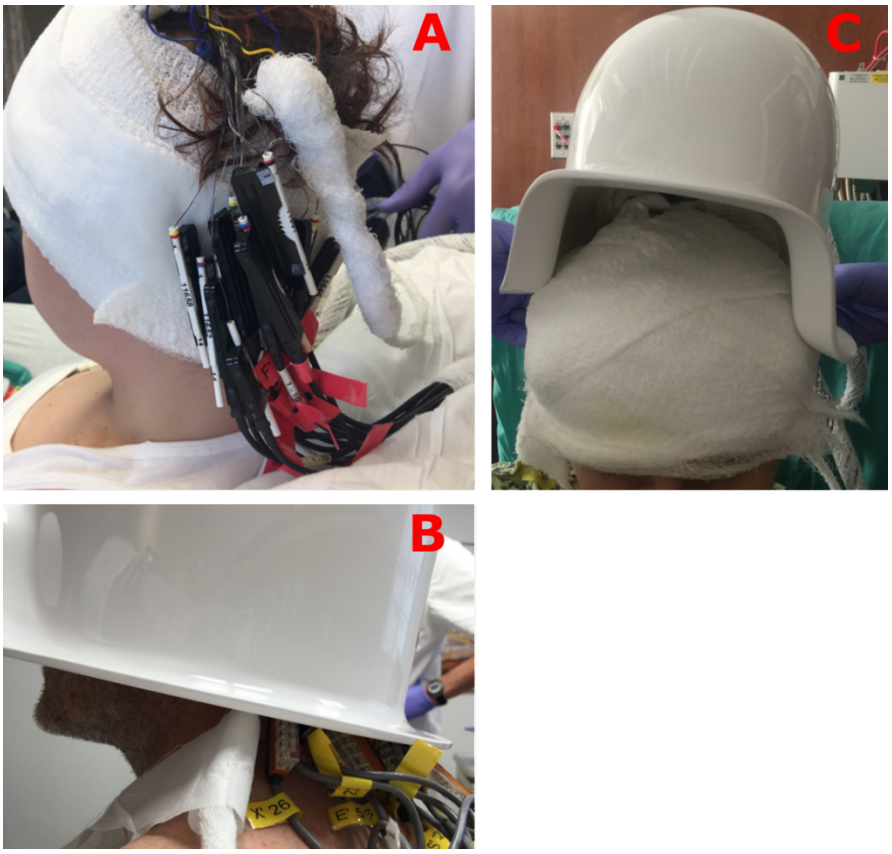

Fig. 1 : (A) The original head dressing is removed and replaced with a light dressing, with the leads and connectors bundled together and draped away from the implantation site. (B) The nape of the neck provides a suitable place to arrange the connectors, such that they nest inside the helmet or extend just below the helmet, depending on the length of the specific brand of electrodes. (C) An exact replica of the MEG helmet is highly useful bedside to ensure that sEEG apparatus and headdress have not made it impossible for the patient to fit, as shown here.

At this point it is imperative to ensure that the patient and their apparatus will fit in the MEG, by using a replica helmet (provided by the MEG manufacturer) at the bedside, as shown in Fig. 1C. Adjustments can be made to the arrangement of the wire bundle and connectors, or it may be determined that the patient cannot fit in the MEG.

Assuming the patient fits the helmet, the MEG technician can begin the bedside process of replacing any heart or muscle (ECG or EMG) electrodes that may not be MEG compatible, then disconnecting the patient from the monitoring room system and connecting the electrodes into the jackbox compatible with the MEG. Since the built-in EEG system of the MEG may have fewer EEG channels than the separate

monitoring unit EEG system, selection of a subset of relevant electrodes has to be coordinated with the researcher, and a careful record of which contacts are retained for the MEG recording must be maintained.

Hospital transport then moves the patient to the MEG suite, with a monitoring unit nurse in attendance, where the usual patient preparation continues [8], albeit under masked (sterile) conditions. Unlike DBS outpatients, however, degaussing may not be approved by the Medical Director, since the introduction of dozens of electrodes into the brain may present unknown coupling considerations. The patient is then placed either supine or upright in the MEG, taking into account the protocols to be run, and taking into account any pressure points of the helmet with the patient's surgical sites.
Immediately after the MEG recording is completed, the patient is directly returned to the monitoring unit for resumed care by the unit staff. Bedside, the MEG jacks and electrodes are removed, and the surgical nurse prepares a final headdress prior to explantation surgery. Depending on the timing before the explantation surgery, reconnection to the recording system in the monitoring unit may not be required.

2.4. Protocols with the iEEG patient in the MEG

In this book, a wide range of possible experimental protocols are discussed, and with the general consideration laid out above, many of them could be run simultaneously with MEG. In this section, we restrict ourselves to citing a few of the published instances that have been used in simultaneous MEG-iEEG, including spontaneous recordings and evoked responses for the study of cognitive functions.

The recording of spontaneous simultaneous MEG-iEEG activity has mainly been focused on the analysis of interictal spikes in epilepsy [2, e.g. 12–14]. Because of the relatively short time of the MEG session, particularly for an sEEG patient, capturing a spontaneous seizure simultaneously with the MEG and sEEG system has not been reported to our knowledge. However, one unique study analyzed a reflexive musicogenic seizure, triggered during the recording by the playing of vocal music [15].
In contrast, studies that measured MEG simultaneously with subcortical LFPs from electrodes implanted for the purpose of DBS often investigate motor movements or associated pathology, which may be expected since DBS is most common in patients with movement disorders such as Parkinson's disease, essential tremor, and dystonia. Similar methods have also been used to examine subcortical-cortical connectivity in resting state networks. For a review, see [16].

As opposed to passive LFP recordings from deep brain electrodes, several more studies have implemented protocols measuring MEG during DBS stimulation, introducing the additional challenge of recording and analyzing the signals despite the presence of high amplitude artefact evoked by the DBS [17, 18][19].

Less commonly, but of particular interest in this book, protocols have been designed to capture the neural activity elicited by various experimental conditions underlying specific cognitive processes, typically using protocols that were originally inspired by earlier experiments from either MEG alone or intracranial EEG alone. We will discuss these studies in greater detail in Section 3.4.

3. What do simultaneous recordings reveal?

3.1. Methodological approaches

Classical MEG and intracranial EEG (iEEG) analyses techniques, such as evoked fields/potentials and time-frequency analysis, can be performed at the level of individual sensors. However, to explore the overall spatial information provided by the multi-sensor recordings source reconstruction techniques are required e.g. spatial filtering technique [20], independent component analysis followed by source localization [21].

Several goals can be pursued with simultaneous recordings. One goal is to assess whether the activity measured with iEEG can be retrieved from MEG signals, either for epileptic discharges [2], evoked fields [3] or time-frequency modulations [1]. When performing correlation analysis, this boils down to finding zero-lag correlation in order to assess whether the same activity is retrieved on MEG in sEEG. Such correlation can be measured across time [2, 22] or across trials [3]. In seminal work, Dalal and colleagues [22] computed and presented the topographic maps of correlation of each sensor data with sEEG electrode in the hippocampus, showing a large-field topography that is compatible with a deep origin of the signals. Another goal is to measure delayed connectivity between an iEEG sensor and MEG signals, in order to retrieve large-scale networks and benefit from the local view of sEEG and large-scale view of MEG. This was performed by [5] using directed phase-lag index, with a seed point in the hippocampus.

3.2. Precision of localization

The first tests of source localization took advantage of measuring fields generated by small currents injected in intracerebral electrodes, thus creating artificial dipoles within the head volume. The great advantage of this technique is to generate a known and well-characterized source, both in terms of location and extent, albeit with a higher amplitude and lesser spatial complexity relative to natural brain activity. Cohen and colleagues [23] injected currents in intracranial EEG electrodes while simultaneously measuring scalp EEG and MEG. No major differences in localization error were found, in contradiction with the hypothesis that MEG would

yield better source localization performance. As noted in [24], the study was initially criticized on methodological grounds [25, 26]. The spatial sampling was low with only 16 channels each for MEG and EEG, which inadvertently prevented the MEG source localization from reaching its full potential; as the skull blurs MEG signals to a far lesser degree than EEG signals, MEG scalp topographies contain more nuances at higher spatial frequencies that can increase the performance of source reconstruction when sensor coverage is optimal. The exclusively radial nature of the implanted sources (due to the electrode implantation scheme) presented a strong bias favoring EEG, since MEG is much less sensitive to radial sources [27]. In [28] and [29], the call was for a careful consideration of the absolute accuracies of either modality under conditions that are fair to both modalities. As noted in (Cohen and Cuffin 1983) and repeated in [29], EEG and MEG provide complementary data, and the use of both modalities can contribute to overall improved accuracy, as confirmed over a large number of theoretical cases [24].
A similar experimental study was conducted by Leahy and colleagues [30] using a human skull phantom implanted with 32 current dipoles and 64 scalp electrodes. A CT scan was used to determine ground truth, and MEG measurements were made. The results yielded a smaller error for MEG (3 mm versus 7-8 mm for EEG) which was attributed to the difficulty of accurately modelling the complexity of the human skull in EEG.
More recently, in a resting state study on patients with epilepsy, [20] measured the distance between 1) the sources found at the peak of the ICA components computed from MEG signals, and 2) the sEEG contact showing maximal correlation with component, and report a mean distance of 20±12.25 mm. Two additional studies used the same localization technique on ICA components putatively corresponding to deep mesial activity, both on epileptic spikes [2] and event related responses [21]. In both cases, the confidence interval of one or two dipole scans included the mesial regions.

3.3. Epileptic discharges

The first report of epileptic discharges in simultaneous MEG-sEEG from [31], compared the epileptic spikes detected on MEG recordings with the ones detected on sEEG signals in terms of detectability, amplitude and localization. The capacity of interictal MEG to detect and localize the epileptogenic zone was found to be comparable with that of sEEG when targeting convexity foci. However, the epileptiform discharges required a higher amplitude and a wider distribution to be detected and localized with only MEG signals.

Shortly after this first report, [32] provided a parametric description of MEG spikes detected thanks to sEEG, aiming at increasing the objectivity of MEG epileptiform events selection.

With a similar strategy, [12] marked the epileptic spikes on sEEG signals, and localized the sources from averaged MEG data (locked on the sEEG events). The

resulting early activity was located in a plausible region, not sampled by sEEG because of physical constraints (a very posterior region where orthogonal electrodes cannot be implanted), confirming clinical hypotheses on this patient.
To investigate the visibility of high gamma oscillations on MEG, [33] performed a time-frequency analysis on the MEG signals locked to epileptic spikes that were detected from sEEG signals. The high gamma oscillations which they observed on the MEG signals were temporally aligned to the ones observed within the same frequency band on the iEEG signals [33 Supp. Fig 2]. The oscillations formed well isolated islands in the time-frequency plane and thus do not correspond to filtered spikes, i.e. 'false ripples' [34]. In a more recent study, [35] have used a beamformer analysis (i.e. a spatial filter applied to the sensor data) in order to detect and localize epileptic ripples (80-120 Hz oscillations) from MEG data. The ripples detected in MEG were validated using sEEG as a gold standard.

Finally, [2] have shown that deep epileptic discharges originating from deep mesial sources can be detected by the MEG sensors. In a first step, independent component analysis was computed on epileptic spikes measured on deep sEEG electrodes (within amygdala and hippocampus). This approach enabled separating focal deep activity from large scale (propagated) networks, whereas the analysis of the MEG signals alone showed only the propagated activity. In a second step, they have shown that in a large proportion of patients the ICA ran on the whole dataset can also extract activity from deep sources, without the prior information arising from sEEG.

3.4. Cognitive potentials and oscillations

3.4.1. Cortical measurements

The first "trimodal" EEG-MEG-sEEG recording reported in a single case study by [3] showed that evoked activity in response to visual presentation of a checkerboard is detected on the three recording modalities, both on average (evoked potentials/fields) and at the single trial level. The simultaneous recording enabled tracking the correlation between depth and surface fluctuations. A source analysis confirmed the consistency between the MEEG sources and the sEEG potentials. In addition, time-frequency analysis could retrieve early beta/gamma band activity (likely evoked) and alpha desynchronization. Induced gamma activations were more scarce, possibly because of the small extent of the sources activated by the experimental task.

With MEG, [5] found that decreases in theta power during spatial encoding predict greater accuracy during subsequent recall. An epilepsy patient with electrodes implanted in temporal regions allowed further investigation of this effect. By simultaneously measuring MEG and intracranial EEG, they further discovered that these

theta oscillations in right anterior hippocampus and left inferior frontal phase-led the left temporal cortex (see Fig. 2).

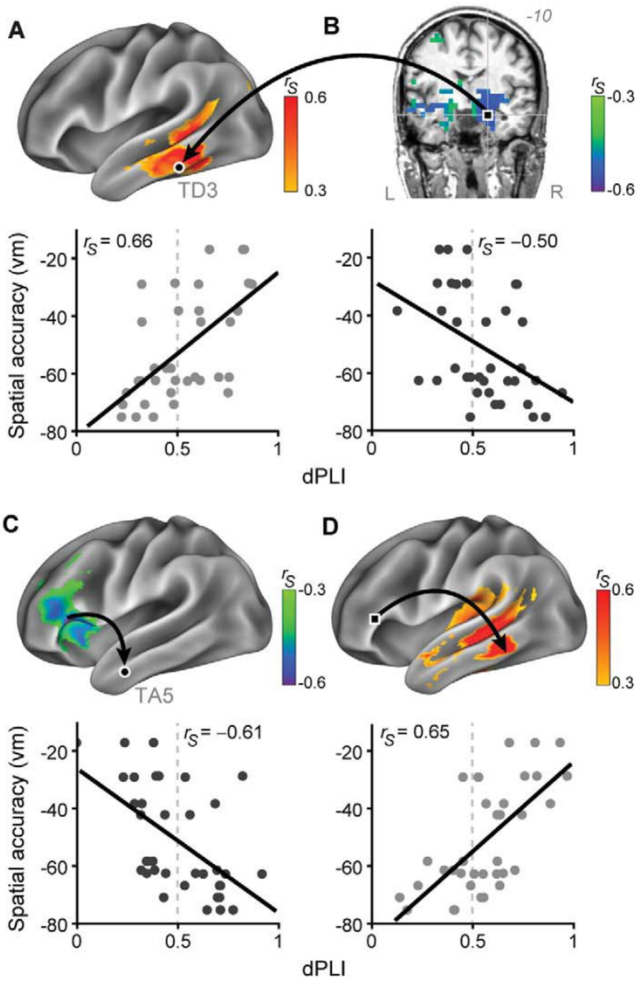

Fig. 2. Simultaneous MEG-iEEG analysis from a single patient to investigate connectivity between MEG sources and left temporal locations sampled directly with intracranial electrodes during a spatial encoding task, and to validate independent MEG findings. A) *directed* phase lag index analysis (see Chapter 36) with MEG beamformer results revealed that task performance was superior when the right hippocampus phase-led the left inferior temporal gyrus. B) A corresponding analysis between intracranial EEG from the left temporal cortex and the right hippocampus from MEG yielded similar findings, validating the MEG results. C) Task performance was also better when left inferior frontal

gyrus, reconstructed with MEG, phase-led the anterior temporal lobe, as sampled by intracranial EEG. D) Subsequently using the left inferior frontal gyrus as a seed for the MEG-based analyses showed that it also exhibited connectivity with the left inferior temporal gyrus, the same area found in (A) that exhibited connectivity with the right hippocampus.
These studies demonstrate different ways in which simultaneous MEG with intracranial EEG can be leveraged to validate MEG-only findings, identify novel connections that may not have been evident with either method alone, and further identify regions of interest for subsequent analyses with MEG alone. Reproduced with permission from [5].

[21] recorded 6 patients with simultaneous MEG-sEEG during a memory task. Patients were instructed to recognize images that they previously memorized ('old/new' paradigm). A blind source separation technique (Second Order Blind Identification, SOBI) revealed MEG components sensitive to the protocol (i.e. showing evoked activity). These components showed consistent topographies across patients and were confirmed in control subjects, presenting a "large" pattern (i.e. topographies with distant positive and negative poles), suggesting the activation of a source originating from a deep origin. The source localization and the correlation analysis of the simultaneous sEEG signals revealed a highest correlation with contacts located in the hippocampus and rhinal cortex, confirming the previous findings.

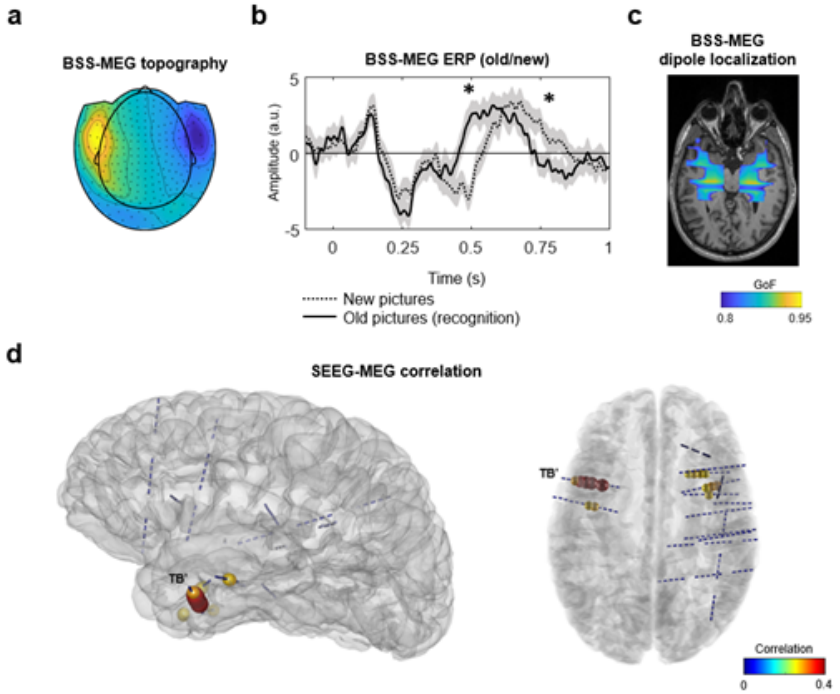

Fig. 3 : Relation between MEG signals and simultaneously recorded intracerebral recordings in one patient [21]. (a) Topography of the deep component obtained with blind source separation (BSS) on MEG signals (BSS-MEG). This topography corresponds to the contribution of the BSS-MEG component to each MEG sensor; its broad distribution is indicative of a deep source. (b) Event-related potential (ERP) on BSS-MEG. Solid and dotted traces are the averaged ERP for old (recognition) and new pictures, respectively. Stars indicate statistically significant differences in amplitude between old and new trials. There is a clear memory-related effect, consistent with what is expected from previous intracerebral studies. (c) Source localization of the BSS-MEG topography with two symmetric dipoles, which confirms the deep origin of the signals (GoF: Goodness of Fit of the two dipoles). (d) Distribution of the correlation of BSS-MEG signals with intracerebral EEG. The highest correlation is visible on the TB (temporo-basal) electrode that targets deep mesial structures, with the peak of correlation located in the rhinal cortex. (Figure courtesy of Victor López-Madrona).

3.4.2. MEG-LFP of basal ganglia / STN via DBS electrodes

DBS electrodes are most commonly implanted in the basal ganglia of patients with movement disorders such as Parkinson's disease. Naturally, the effects of DBS itself on cortical activity and cognition have been investigated in several studies [e.g. 36, 37] and reviews [16, 19]. Before permanent connection to the stimulator, however, DBS electrodes can be alternatively used to measure local field potentials from the implanted structure; a few groups have managed to combine such measurements with MEG.

Most such simultaneous measurements have investigated pathological oscillations or aspects of motor control. However, evidence is mounting that the basal ganglia and other DBS targets such as the thalamus are indeed involved in several other brain functions, including various aspects of cognition.

The first cognitive study employing simultaneous MEG-STN measurements came out recently. [38] employed an expanded judgement task in which participants needed to accumulate multiple observations of a cue with two possibilities, before deciding which of the two possibilities was the accurate choice. The study primarily aimed to investigate whether the STN was involved with "global conflict" – when a cue conflicts with several preceding ones – but did not find evidence to support that role. They found that beta oscillations in both the STN and frontal cortex instead encoded "local conflict" – i.e., when the presented cue differed from the immediately preceding one – but the beta activity in the STN persisted until the next cue, while the cortical activity subsided more quickly. They also specifically found alpha and beta band connectivity between the right dorsal premotor cortex and right STN for these conflicts. Although they could not reliably determine directionality of this relationship, the cortical activity peaked earlier and is in line with other studies which suggest that the cortical activity drives STN activity.

3.4.3. MEG-LFP of thalamus via DBS electrodes

In a pioneering study, [39] combined MEG with thalamic iEEG measurements to investigate corticothalamic circuits mediating visual perception. They found that the phase of low-frequency oscillations in the mediodorsal thalamus (7 - 9 Hz) predicts whether threshold-level visual stimuli were perceived. Leveraging MEG, they furthermore discovered that prefrontal cortex activity precedes these thalamic responses, as assessed by directed connectivity measures, suggesting that corticothalamic interactions ultimately mediate perceptual performance. They also found some evidence that visual cortex activity follows the thalamic responses, though did not have adequate occipital MEG coverage in enough patients to make stronger conclusions. As direct investigations of the human thalamus are rare, this provides important insights into the role of corticothalamic interactions into perceptual cognition, and an impetus for further investigations integrating both thalamic measurements with MEG.

4. Discussion and future avenues

Most effort so far in simultaneous MEG and intracranial recordings has been directed towards epileptic activity, where the spontaneous aspect of the discharges requires simultaneity in order to ensure capturing the exact same brain activity at the two levels. In cognition, the added value of simultaneous recordings may not be so obvious at a first glance. Many studies have performed cognitive protocols in intracerebral EEG alone, and may serve as a basis for assessing MEG results [e.g. 40–43]. Still, simultaneous recordings have distinct qualities that may justify the (significant) added difficulty during acquisition. Firstly, as for epilepsy, they ensure the exact same patient state (vigilance, arousal, level of medication, etc.), which can be important for subtle activity or in protocols where repetition of the same stimuli may result in different brain responses. Secondly, simultaneous recordings allow performing correlation between surface and depth at a single-trial level, which gives a stronger confirmation (in contrast to average across trials) that MEG and iEEG are indeed recording the same brain source. Finally, simultaneous recordings may allow in the future to build a 'meta modality' that combines the local view from iEEG and the global view from MEG, thus improving our knowledge of brain function across spatial scales. Of course, simultaneous recordings can only be performed in patients, thus presenting pathological activity intermingled with physiological one, and potentially reorganized brain networks. Hence the importance of combining the results from multiple patients with varying epileptic sources [44] and confirming the simultaneous MEG results with activity measured in control subjects with MEG only [21].

MEG technology is now rapidly evolving, with next-generation MEG systems employing optically pumped magnetometers (OPM) that operate without liquid helium and allow closer positioning on the head (Brookes et al., 2022). As OPMs can be placed on the head in any desired configuration rather than a rigid unisize helmet, this will relieve some of the challenges with obtaining measurements simultaneously with iEEG. Indeed, the first simultaneous measurements of OPM-MEG and iEEG for detection of interictal spikes were recently presented [45]. The impending proliferation of OPM-MEG systems will surely provide more such opportunities, with the aims of characterizing their sensitivity and source localization accuracy as well as providing further insights into functional connectivity mediating cognitive processes.

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