



# Addressing a Deep Problem With Magnetoencephalography

Epilepsy Currents  
2019, Vol. 19(5) 289-290

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DOI: 10.1177/1535759719856593

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## Deep Brain Activities Can Be Detected With Magnetoencephalography

Pizzo F, Roehri N, Medina Villalon S, Trébuchon A, Chen S, Lagarde S, Carron R, Gavaret M, Giusiano B, McGonigal A, Bartolomei F, Badier JM, Bénar CG. *Nat Commun.* 2019;10(1):971. doi:10.1038/s41467-019-08665-5

The hippocampus and amygdala are key brain structures of the medial temporal lobe, involved in cognitive and emotional processes as well as pathological states such as epilepsy. Despite their importance, it is still unclear whether their neural activity can be recorded noninvasively. Here, using simultaneous intracerebral and magnetoencephalography (MEG) recordings in patients with focal drug-resistant epilepsy, we demonstrate a direct contribution of amygdala and hippocampal activity to surface MEG recordings. In particular, a method of blind source separation, independent component analysis, enabled activity arising from large neocortical networks to be disentangled from that of deeper structures, whose amplitude at the surface was small but significant. This finding is highly relevant for our understanding of hippocampal and amygdala brain activity as it implies that their activity could potentially be measured noninvasively.

## Commentary

Magnetoencephalography (MEG) with magnetic source imaging is a valuable noninvasive tool in the presurgical evaluation of patients with drug-resistant focal epilepsy.<sup>1</sup> MEG has higher spatial resolution without signal loss by the scalp and skull compared to scalp electroencephalography (EEG), but MEG is typically limited to interictal recordings. Magnetic source imaging with MEG can be achieved using equivalent current dipole modeling of interictal spikes, and the orientation and position of the estimated dipole can be overlaid onto the patient's own coregistered magnetic resonance imaging (MRI).<sup>2</sup> Localization of interictal epileptic spike activity can aid surgical planning,<sup>3</sup> and MEG findings that are concordant with other diagnostic data may help predict a favorable post-operative seizure outcome.<sup>4</sup> Although MEG sensors reside outside of the scalp, several source reconstruction strategies exist to address the "inverse problem" and estimate neural sources of magnetic fields beneath the surface of the brain. But when considering accuracy in localizing signals beneath the surface of the brain, how deep is too deep?

It is known that source localization may be more challenging with deep brain regions, and some investigators have argued that MEG has diminished clinical utility in the evaluation of mesial temporal lobe epilepsy (MTLE) compared to focal neocortical epilepsy.<sup>5</sup> There is also controversy regarding whether spikes recorded using MEG in MTLE truly originate from the mesial structures or simply represent lateral

neocortical spikes, which are also commonly observed in this disorder.<sup>6</sup> This uncertainty presents a substantial problem in this particular patient population, since MTLE is the most common epilepsy syndrome, and potentially the most surgically remediable in properly selected patients. One new sophisticated approach to address this question might be simultaneous recordings with MEG and minimally invasive stereoencephalography (SEEG) with depth electrodes in the mesial temporal structures.

Although MEG is noninvasive and allows whole-brain coverage, direct recordings with either SEEG or subdural electrodes remain the gold standard for high-resolution and reliable delineation of the seizure focus. Recently, Badier and colleagues proposed technical strategies for obtaining high-quality simultaneous recordings from both MEG and SEEG.<sup>7</sup> Now, in their study highlighted here, the authors evaluated spikes from simultaneous MEG and SEEG in 14 focal epilepsy patients with at least one depth electrode in the hippocampus or amygdala (although notably not all patients had MTLE). In each patient, between 16 and 185 spikes were recorded from hippocampal or amygdalar depth contacts, and independent component analysis (ICA) of concomitant MEG recordings was triggered by these detections. In 8 of 14 patients, investigators detected a significant correlation between an ICA component and a mesial temporal spike, and in 7 patients, source localization correctly identified a mesial temporal source. Compared to lateral neocortical sources, the amplitude of



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signals detected in mesial structures was expectedly small. Nevertheless, the results do offer compelling evidence, supported by intracranial recordings, that source localization of isolated mesial temporal spikes is possible with MEG. However, when considering whether a novel diagnostic approach could achieve broad clinical utility, does “possible” necessarily translate to “practical”?

Widespread adaptation of analysis methods utilized in the study may be difficult at many regional centers performing presurgical MEG studies. Dipole modeling using magnetic source imaging requires specialized training and is prone to interpretation error, even without the addition of advanced statistical techniques. Furthermore, mesial temporal lobe source localization using ICA was only successful in a subset of the patients in this study, even when guided by direct intracranial recordings. This level of uncertainty may present a challenge to clinical interpretation, particularly when the interpretation is guided only by scalp EEG together with surface MEG. The current authors also acknowledge the limitation of sparse SEEG spatial resolution in their study, which of course did not sample all deep sources potentially detected by MEG. Despite these limitations, however, the study uses an elegant approach and offers a unique window into the ability of MEG to detect mesial temporal spikes, making significant progress toward improved localization of deep spikes in MTL.

In closing, it is worth noting that the scientific implications of this work extend well beyond spike detect in presurgical evaluations. Noninvasive studies of brain activity during both the resting-state and task-based paradigms are becoming increasingly utilized to understand network dysfunction in epilepsy syndromes. The majority of neuroimaging network studies in epilepsy utilize functional and structural MRI techniques, in part because deep brain structures can be studied with a high level of confidence. However, MEG studies offer the advantage of improved temporal resolution and a more direct reflection of underlying neural sources than functional MRI.<sup>8</sup> Analysis approaches designed to better isolate deep signals in MEG, such as those in this highlighted study, will help to

further advance the role of magnetic source imaging in the study of epileptic networks. While MEG is certainly not a new clinical or research modality in the study of epilepsy, it is likely that we have only begun to scratch the surface of its potential contributions in this disorder.

By Dario J. Englot

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