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# Detection and localization of deep sources in magnetoencephalography: a review

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## *Abstract*

Magnetoencephalography (MEG) is a non-invasive technique for exploring the spatio-temporal dynamics of brain networks with high temporal resolution as well as good spatial capacities thanks to relative insensitivity to low skull conductivity. It is a tool of choice both for neuroscience research and for clinical applications, and is used routinely in epilepsy for localizing the sources of epileptiform discharges.

Still, the capacity of capturing deep sources, such as hippocampus and amygdala that are key players in memory and emotion, has been for long a topic of debate. Thus, the fine characterization of deep structures has been up to now the reserved domain of intracerebral EEG, performed during presurgical evaluation of patients with epilepsy. We review here the evidence for the detection of deep sources in MEG, with emphasis on simultaneous recordings of MEG and intracerebral EEG.

In this review, we discuss how simultaneously recording depth and surface signals enables to investigate the correlation between MEG and invasive signals actually recorded in deep structures. We also discuss new venues in analysis and recording methods for reconstructing deep activities from MEG.

## *Introduction*

Magnetoencephalography (MEG) measures neuronal activity in a non-invasive manner, with a temporal resolution of the order of the millisecond and weak dependence on the electrical conductivity of the underlying structures. This gives MEG a very good spatial discrimination power [1], thanks in particular to its low sensitivity to skull conductivity. MEG is widely used to localize the brain regions underlying cognitive tasks, during functional mapping of eloquent and language regions before surgery, and is one of the key pre-surgical evaluation tools in patients with drug-resistant epilepsy [2].

Among all regions that can be investigated with MEG, deep brain structures such as hippocampus, amygdala and thalamus are of primary interest. Indeed, these structures are key players in memory, emotion, cognition, and in pathologies such as neurodegenerative disorders and epilepsy [e.g; 3,4]. They have however long been considered as difficult if not impossible to see from EEG/MEG surface sensors as signals attenuate rapidly as a function of the distance to sensors. Further attenuation arises from the fact that deep structures such as hippocampus, amygdala and thalamus are considered as the epitome of “closed fields” generators, i.e., producing little field outside the structure itself [5]. To make things even more difficult, activity in deep “closed fields” structures propagate very fast to the nearby (neocortical) structures [6], and what is visible on the surface

signals could be in fact propagated activity or activity generated solely in lateral cortices [7]. Finally, deep activity can be overshadowed by that of more superficial concurrent generators that have much higher signal to noise ratio at the surface [8]. See Figure 1 for a schematic representation of these configurations.

A very important venue for better understanding deep activity arises from intracerebral recordings performed clinically during presurgical evaluation of epilepsy (stereo-electroencephalography, SEEG [9]) as well as during deep brain stimulation. About 15 to 18 SEEG depth electrodes can be implanted, each electrode having between 5 and 15 contacts. They permit to obtain signals with exquisite spatial specificity, and to target directly deep brain structures. They are orthogonally or obliquely implanted through a small burr hole in the scalp, on sole clinical criteria. The number of electrodes required to insert depends on the underlying anatomic-electro-clinical hypotheses and on the hospital [10-13]. Some centers use subdural grids with the advantage of higher spatial sampling, as they cover large areas of the brain. However, requirement of craniotomy, impracticality of bilateral monitoring, and inability to record from deeper cortical or subcortical sources are limitations of this approach.

Intracerebral recordings give a formidable opportunity for validating non-invasive results [14] and for ensuring the deep origin of signals. Importantly, for spontaneous activity such as interictal epileptic spikes, it is necessary to record simultaneously surface and deep signals in order to ensure that the exact same activity is captured at the two levels [8,15]. Indeed, the occurrence of epileptic discharges is unpredictable, and the frequency and spatial distribution may fluctuate depending on brain state and level of medication. Simultaneous recordings are also crucial if one wants to measure trial-to-trial coupling between deep structures and surface signals [16,17] or to trigger surface analysis based on activities marked in depth [18,19]. We review here studies that have performed simultaneous recordings of both deep structures and surface MEG signals, as well as new venues in analysis and recording methods for reconstructing deep activities from MEG. Previous reviews focussing on the hippocampus can be found in [20,21].

### *Simultaneous MEG and intracerebral recordings*

The first combined use of intracerebral electrodes and EEG/MEG was done by Cohen and Cuffin, who created artificial dipoles in the head by injecting current between consecutive electrodes [22]. They did not find a significantly better localization error for MEG than EEG, but it is to be noted that the injected dipoles were radial, which is the most unfavourable condition for MEG. Simultaneous recordings of MEG with intracranial signals were later performed with electrocorticography in patients during presurgical evaluation of epilepsy [23-27].

In order to confidently determine the deep origin of signals, it is useful to use the intracerebral technique that directly records within deep structures. The first simultaneous MEG and intracerebral recordings were performed at Centro Médico Teknon in Barcelona [28] and at the LENA laboratory at Pitié-Salpêtrière in Paris [29,30]. Santiuste and colleagues recorded from a single depth electrode and showed that mesial spikes, despite their lower amplitude, can be detected on MEG (25 to 60% for deep spikes versus 95% for neocortical spikes); they considered signals to be concordant if they presented a delay less than 25 ms [28]. In another study, Dalal and colleagues showed a map of zero-lag correlation between the hippocampus and the MEG signals with a dipolar topography that strongly suggests a deep source [31], even though no actual source reconstruction was performed on these signals. The superimposition of the intracerebral signal in the hippocampus and the most correlated MEG sensor shows clearly a theta oscillation with zero phase difference. This is in favour of a direct recording of hippocampus on MEG, even if zero-lag phase synchrony cannot be ruled out

(see for example [32], noting however that in this latter study the hippocampus is the third-party driver leading to zero phase synchrony between *neocortical* structures).

We have shown in the MEG Centre of Marseille that it is possible to push the recording capacities in order to obtain signals from three modalities (MEG-EEG-SEEG) at the single trial level [17] and with high SEEG sampling [33]. Thanks to the high sampling (containing both mesial structures and surrounding neocortex) and to independent component analysis (ICA), we investigated the differential implication of subcortical structures and neocortex [19]. Specifically, ICA allowed separating large-scale networks that correspond to propagated activity towards the neocortex from actual activity from deep structures, this latter being overshadowed by the former at the sensor level. Several tests were performed, including single-trial correlation between ICA components and SEEG, as well as source localization on the ICA components. Taken together, these results suggest that signals from deep structures can be captured on MEG – at least for epileptic activity. We are currently working on detectability of deep mesial structures in MEG within the context of a memory paradigm [34].

Another important venue for simultaneously recording MEG and SEEG at deep structure arises from the possibility to record patients implanted with deep brain stimulation (DBS) electrodes [35]. As DBS targets the thalamus, it will be possible to investigate the thalamic contribution to MEG signals, which has been suggested to be visible in MEG [19,36,37]. To elucidate the therapeutic effects of DBS, simultaneous MEG-LFP recordings were carried out in patients with Parkinson's disease (PD). These studies were able to delineate two key networks between sub-thalamic nuclei and cortical structures (motor area and fronto-parietal regions) [38,39], where the cortico-sub-cortical coupling could be modulated by DBS [35].

#### *Source localization and forward modelling*

Simultaneous recordings have shown that deep sources visible on SEEG can be reflected on the MEG signals. However, in most cases, only surface MEG signals are available, and one needs to ensure that deep activity can be recovered without the help of intracerebral recordings. Several difficulties arise. Generally, MEG recordings consist of signals with low signal to noise ratio, and this is especially true for deep sources. Moreover, there is a linear superposition of superficial sources at the channel level that may mask the activity from deep sources. One option to overcome these limitations is to use a source localization algorithm directly targeting deep sources [40].

To estimate brain sources based on MEG data, solution to both the forward and inverse problem must be addressed. The forward model is implemented by a gain matrix, which estimates the contribution of each dipole, i.e. each elementary source within the brain, to the sensors. The computation of the gain matrix is based on a volume conductor (head) model that defines the head geometry and tissue resistive properties. Depending on the topographical patterns computed using forward solution, the sources associated to the activity recorded with MEG are determined with inverse solution techniques. While constructing head model, it would be ideal to consider the electrical and geometrical features of subcortical structures. When a detailed head model is considered, the simulation study in [41] showed that MEG is more sensitive than EEG for detecting tangential cortical sources and can also detect subcortical sources that are sufficiently tangential [41].

One of the simplest ways to find the origin of the recorded activity of deep sources is by using one or a few equivalent current dipoles (ECD) that reproduce the magnetic field observed at the surface [42]. The actual source configuration is likely to be non-dipolar (for example in the case of the convoluted fine structure of the hippocampus, see Fig. 1), but it is important to note that potential

multi-dipolar contribution to signals attenuate very rapidly with distance. Dipolar localization has thus been used to identify hippocampal activations during memory tasks [43,44]. Some researchers advocate to investigate also monopolar sources (see [45] discussed in [46])

Another approach consists in estimating sources distributed over the brain, for example the Minimum Norm Estimate (MNE) [47,48]. The distributed sources model does not require any prior on the number of active sources, and can incorporate additional spatial information [40]. It also permits to consider the possibility of extended neocortical networks which activity can overlap in time with deep sources.

In distributed sources approaches, sources can be modelled as a very large number of dipolar sources located on a grid or constrained to lie on a mesh of the neocortex. Attal and colleagues have proposed to use additional compartments that model deep structures, in order to compensate for the bias introduced by the simultaneous activation of cortical and sub-cortical regions, specifically the hippocampus, amygdala and thalamus [36,40]. Such framework was subsequently used to reconstruct amygdala time course [49,50]. The results indicate that hippocampus and amygdala can be localized with good accuracy when activated alone. However, regional specificity is reduced when there are simultaneous activations of cortical and subcortical sources, making it hard to differentiate deep regions without further assumptions. An additional difficulty arises from the fact that neocortical structures surrounding the hippocampal /amygdala can be activated and difficult to distinguish from the latter because of the proximity relative to the distance to sensors. Thus, it seems important to assess the volume of confidence of a given localization result [19], and verify whether hippocampal, amygdala and neighbouring neocortex are included or not within the confidence interval. This confidence interval is more tractable for dipoles than for distributed sources [51,52] although solutions have been proposed for patches [53].

Another extensively used method in source reconstructions is adaptive spatial filtering (or "beamforming") [54]. This method is based on a spatial filter computed for each source location independently and can reconstruct the time series throughout the brain, including the hippocampus or amygdala [55]. Beamforming estimates the activity recorded at a given location, incorporating biophysical constraints (typically a regional basis of dipoles). When the activity is temporally overlapping with cortical fields, leakage originating from the inverse problem [56] may obscure the signal originating from deep sources. Subtraction of several conditions with different activities may be used to mitigate this effect [57]. On the other hand, beamforming reconstructs the activity at the desired location, instead of finding the point that better reproduces the recorded field. Therefore, this approach is complementary to the other methods for source localization. Different source localization algorithms could reconstruct deeper subcortical sources from MEG data by suppressing the high SNR signals from the neocortex. In general, source reconstruction from beamformer seems to be more focal and localized to hippocampus, compared to MNE images, but this requires further investigation as estimation of source extent is a difficult task [58].

Krishnaswamy and colleagues proposed a method based on sparse representations for recovering deep sources. Based on the analysis of the forward field, they show that in the presence of largely distributed cortical sources (full cortical space) it is impossible to unambiguously estimate simultaneously active subcortical sources. On the contrary, if cortical generators are sparse, then it is possible to recover separately cortical and sub-cortical activities [37], which they do based on a subspace pursuit greedy algorithm. Sparse source localization is in general difficult, but is certainly a promising path for source localization and mitigation of source leakage effects [59] (review in [37]).

Beyond source localization biophysical/mathematical models, one can use computational models in order to infer hidden variables. In other words, one can perform an inverse problem on a variable that is in the computational model but not directly visible from the data, as done for example in dynamic causal modeling [60], or in the 'virtual epileptic patient' [61]. This was done in the context of distant subcortical-cortical networks where effective connectivity based on DCM allowed inferring subcortical activity [62].

### ***Blind source separation***

One option for disentangling deep and cortical sources mixed on sensors is ICA, performed on the continuous signals [19]. ICA was successfully applied to EEG and MEG in order to separate different processes mixed on the signals, either in cognition [63] or in epilepsy [64-66]. This was the strategy used in the study of Pizzo and colleagues in order to separate deep activity from that of superficial networks, then comparing it to simultaneously acquired SEEG [19] (Figure 2). ICA aims at separating the activity of  $N$  sources mixed on  $M$  sensors (where  $N \leq M$ ), assuming that the sources have different spatial distributions and that their time-series are independent [67]. After reconstructing the time-course of the sources, their origin can be inferred using ECDs to reproduce the ICA topography of each source. As pointed earlier, one difficulty that arises when solving the inverse problem is that activities from deep sources can be mixed with neocortical sources [19]. If the ICA manages to fully disentangle the sources, then one component can actually correspond to a single brain region [68] and thus be reasonably modelled with a single dipole (assuming the activity is not too extended, which is not guaranteed). In some cases, two symmetric sources can be observed that correspond to homologous brain regions, and can be modelled by symmetric dipoles [69]. Bayesian source localization is also an interesting path to explore [52], as well as sparse methods such as L1 on the spatial gradient of the sources (total variation) [65]. For more complex source configurations and in particular for extended brain areas, distributed sources including patch modelling can be considered; a difficulty to overcome is that the definition of noise covariance for ICA topography is not straightforward (there is not temporal dimension one which to estimate covariance, only one data vector). Moreover, the ICA approach has been challenged recently, showing that source localization of single ICA components does not improve the localization results in MEG (and can on the contrary be detrimental) [70], a potential explanation for these results is the above-mentioned difficulty for modelling the source of a single topography when it is not purely dipolar, and also in the fact in some cases several ICs may need to be taken in to account [66].

We noted above the importance of sparsity constraints in source localization. It is interesting to note that ICA can be seen as another way to obtain sparse representations [71]. Potentially, the patterns seen on ICA topographies could be used in order to gain information on the underlying sources, as was done on EEG patterns in epilepsy [72].

The computation of ICA or covariance matrices that are used in source localization require large amount of time samples which increases with the square of number of channels. To be noted, there are signal space separation (SSS) [73] and beam-space dual signal space projection (bDSSP) [74] algorithms where dimensionality reduction is obtained by projecting the data into a low dimensional subspace. Moreover, these methods decompose the MEG signals into superficial and deep source components and suppress the stronger interference from superficial sources, as performed in the cortical signal space suppression (CSS) method [75] that preserves the subcortical signals while suppressing the cortical contributions. This latter method is completely data-driven and does not require forward modelling or inverse solutions.

## **Detectability of deep sources according to MEG configuration**

The significance of MEG sensor design on the depth sensitivity of MEG is still under investigation. Conventional MEG systems have either any of the three types of pickup coil configurations: magnetometers (with single loop of wire), axial, and planar gradiometers (two or more loops spaced at a distance with opposite orientation). Overall, axial gradiometers were able to deliver optimal brain SNRs compared to magnetometers, while planar gradiometer is sensitive to superficial sources by suppressing environmental noise. Although axial gradiometers have an added advantage, any sensor type can measure subcortical activity relative to the square of the distance and the amount of noise in the background of other brain activity [76].

In another (complementary) line of research, Tzovara and colleagues have identified the difficulty of localizing deep sources, and propose to use a head cast to ensure minimal head movement and therefore optimal localization precision [77] – which should be useful for both deep and superficial sources.

### ***Conclusion and New venues***

There is now several converging evidence that deep signals can be recorded in MEG, in line with EEG findings [78,79], thus opening new exciting new venues for the non-invasive investigation of brain networks in physiology and pathology, a fast growing field in neuroscience [80].

Simultaneous recordings of intracerebral EEG and MEG recordings provide perhaps the strongest evidence that MEG can reliably measure deep activity in patients [19,81,82]. Reliability of deep sources detection with source localization and source separation methods (ICA/bDSSP/CSS) can be assessed if simultaneous ground truth such as SEEG electrode recordings are available. More progress is thus expected from such simultaneous acquisitions.

An important future path is the advent of a new generation of MEG sensors. As opposed to conventional SQUID system, optically pumped magnetometers (OPMs; [83]) does not require liquid helium. They have lower sensitivity, but a four-fold increase in SNR could be achieved as OPMs can be brought closer to scalp surface and allow head movements [84]. A question that still remains to be investigated is whether being close to the surface does not ‘blind’ the OPM to the deeper sources by being overwhelmed by the strong activity of superficial sources [37,75]. As OPM sensors are mobile, it has been proposed to record directly within the mouth in order to obtain a recording of hippocampal activity dorsally from within the mouth [85]. This could help in more accurately to determine the actual deep origin of the signals.

Another interesting possibility is to use simultaneous recording of surface and depth signals as a combined “meta-modality”, i.e. to fuse them into a joint analysis [18,38,82]. In any case, the continuous or single trial analysis is crucial in order to extract the covariation between depth and surface signals, either at zero lag (reflecting the same activity) or at different lags (network analysis) [17,86].

Future progress in simultaneous recordings (number of modalities, type of sensors) and in the inverse problem of both MEG and intracerebral EEG [87-89] should also allow refining the definition of the links between surface measures and cerebral activity.

### ***Figure Legends***

Figure 1: Schematic view of different source configurations and their reflection on MEG. a) only deep sources are active (hippocampus and amygdala). As activation is of a ‘closed field’ type, no visible

signal is recorded from the surface. b) Activity from hippocampus propagates to nearby neocortex, which has a structured source geometry (open field) and can be seen as a signal at the surface (small because of the depth). c) only subparts of hippocampus and amygdala are active, producing an open field and small signal at the surface. d) The activity from deep structures is overshadowed by activity from the superficial neocortex that has a higher amplitude due to shorter distance to the sensors.

Figure 2: Results of simultaneous MEG/intracerebral recordings (methods in [19]). a) Example of an ICA component corresponding to a deep source (note the “wide” topography), found on data triggered on spikes visible in mesial temporal SEEG contacts b) Source localization performed on the topography (confidence interval of equivalent dipole), within right mesial temporal regions c) SEEG implantation (only left side is shown) d) Superimposition of average ICA time course (in color, based on SEEG triggers) and SEEG contacts for which there is significant correlation (in black). Contacts are located in left amygdala (Ap), left hippocampus (Bp) and left basal temporal regions (TBp) and are shown on the right of the panel, with the same color convention as the traces.

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This is the first attempt to record hippocampus from within the mouth, which is now possible thanks to the new generation of OPM MEG sensors that are mobile. This gives the opportunity to improve the sampling of the topography deep activity, by providing a measure from below. This is very relevant for deep sources that can have a widespread topography, and in which surface sensors may miss important parts of the fields. This should in turn improve the localization of deep sources and help disentangling them from superficial measures

\* Sekihara K, Adachi Y, Kubota HK, Cai C, Nagarajan SS. Beam-space dual signal space projection (bDSSP): A method for selective detection of deep sources in MEG measurements. *Journal of Neural Engineering* 2018;15(3).

This study addresses the difficult challenge of separating deep and superficial sources from surface measures, as the former can be overwhelmed by the activity of the latter on non-invasive sensors. Here, the approach is based on the beamformer signal processing technique, a spatial filter that suppresses the activity of sources other than the source of interest. The authors show that by using a signal subspace approach specific to deep sources, they can obtain better suppression of the superficial contribution to the recorded signals than with a classical method.



\* Seeber M, Cantonas LM, Hoevels M, Sesia T, Visser-Vandewalle V, Michel CM. Subcortical electrophysiological activity is detectable with high-density EEG source imaging. *Nature Communications* 2019;10.

This study uses for the first time simultaneously recorded DBS electrodes and surface EEG for assessing the detectability of thalamus on EEG. The authors have correlated the time courses of source reconstructed signals and that of DBS electrodes, and found highest correlation for sources close to the DBS electrodes recording the thalamus. This suggests that thalamic activity can indeed be reconstructed from the surface signals.

\* Pizzo F, Roehri N, Medina Villalon S, Trebuchon A, Chen S, Lagarde S, Carron R, Gavaret M, Giusiano B, McGonigal A, Bartolomei F *et al*: Deep brain activities can be detected with magnetoencephalography. *Nat Commun* (2019) **10**(1):971.

This study investigates the possibility of retrieving deep brain sources in MEG (magnetometers), thanks to simultaneously recorded intracerebral EEG (stereoencephalography, SEEG). Epileptiform events were marked on SEEG, and independent component analysis was used in order to disentangle deep sources from superficial (propagated) sources. Importantly, there was a high spatial sampling of depth electrodes that allowed probing nearby neocortex. The origin of the putative deep components was assessed by several methods in order to strengthen confidence in the results: (i) the deep aspect of the MEG topography (“wide” field) (ii) correlation of MEG-ICA and SEEG across time along trials (testing for general resemblance of the time courses) or at a given time point across trials (testing whether trial-to-trial fluctuations correlate in depth and surface), as well as (iii) dipolar source reconstruction with a confidence interval (which is expected to be large for deep sources).

\* Samuelsson JG, Khan S, Sundaram P, Peled N, Hämäläinen MS. Cortical Signal Suppression (CSS) for Detection of Subcortical Activity Using MEG and EEG. *Brain Topography* 2019;32(2):215-28. Tailoring of the source reconstruction for specifically targeting deep sources.

This article presents a signal subspace approach that is tailored for suppressing neocortical signals and emphasizing the deep contribution to the surface sensors. It takes advantage of the presence of both gradiometers and magnetometers, using the (more short-sighted) gradiometers for the estimation of superficial activity.

\* López-Madróna VJ, Medina Villalon S, Jayabal V, Trébuchon A, Alario FX, Bartolomei F, et al. Detection of mesial networks with magnetoencephalography during cognition. *LiveMEG 2020: a cutting EEG event2020*.

This study applied ICA on MEG during a memory task to explore the signature of the hippocampal formation on MEG. They found a common ICA-MEG component across subjects, with the same “deep” topography. Using simultaneous SEEG recordings and partial correlation, they confirmed the origin of the ICA-MEG as a network composed solely by the hippocampus and rhinal cortex. These results confirmed that hippocampal activity can be seen on MEG in cognition. Importantly, they identified a specific fingerprint of this network on MEG recordings, facilitating future studies based on this activity without an intracranial confirmation of its origin.

\* Hosseini SAH, Sohrabpour A, He B: Electromagnetic source imaging using simultaneous scalp eeg and intracranial eeg: An emerging tool for interacting with pathological brain networks. *Clin Neurophysiol* (2018) 129(1):168-187.

Intracranial EEG (iEEG) can be used for validating results from non-invasive source reconstruction algorithms. Such recordings possess good spatial precision, as they are not blurred by the skull. However, at a fine level, there can be discrepancy between the true location of cortical sources and the actual position of the contacts recording them. Here, both signals are used together during source localization, which can take advantage of the large field of view of on-invasive signals, and the high signal to noise and spatial capacities of iEEG signals.

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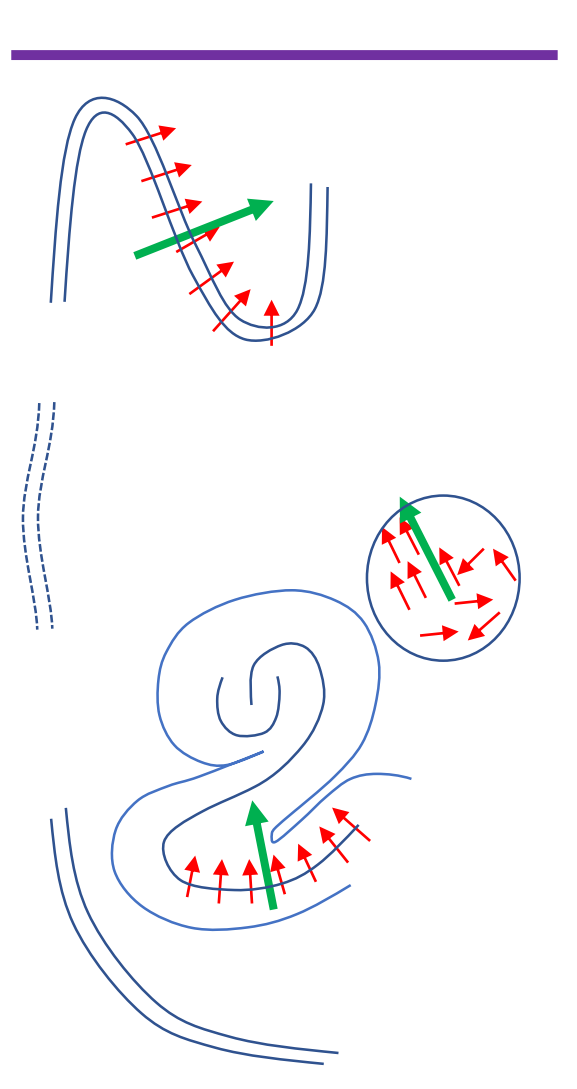
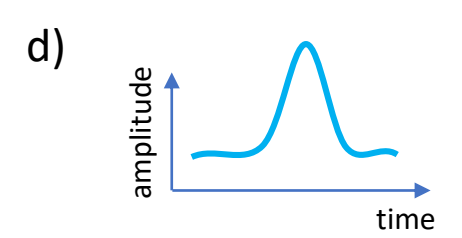
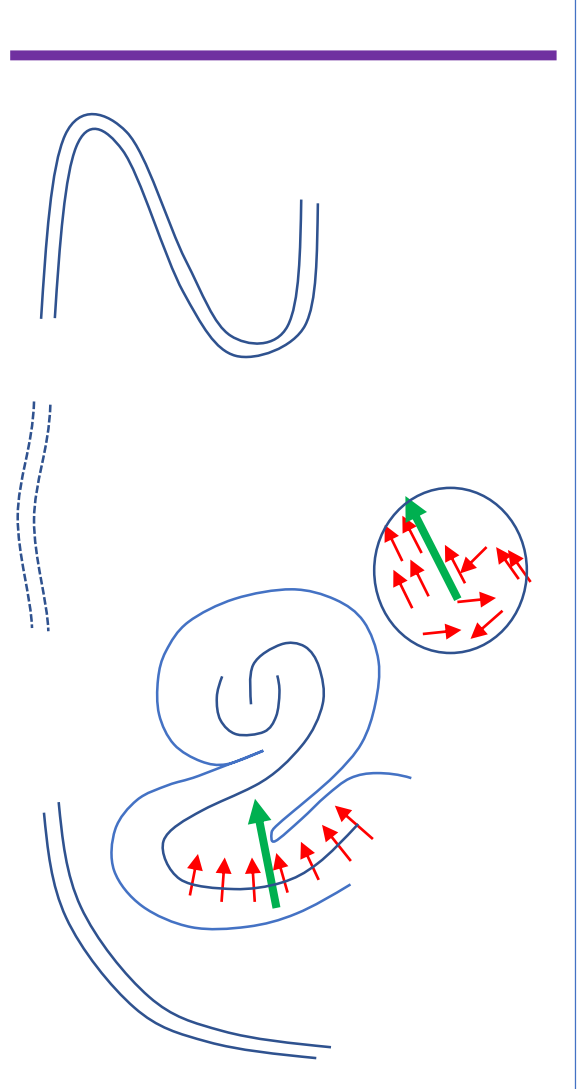
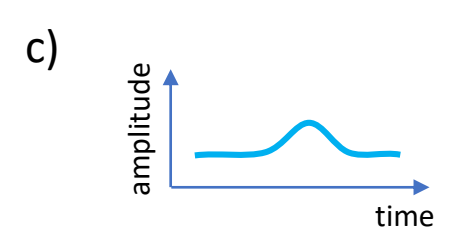
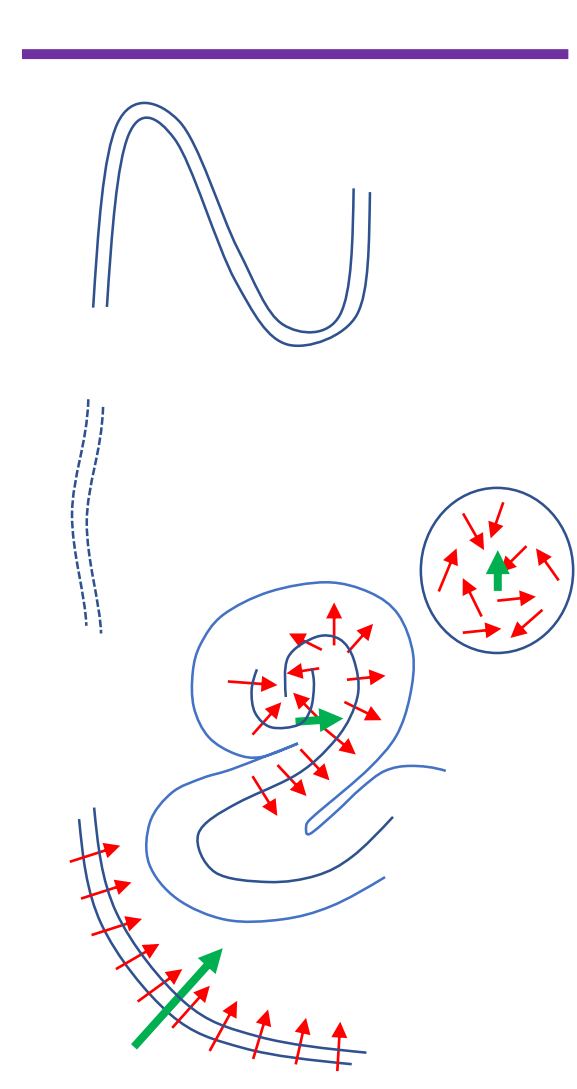
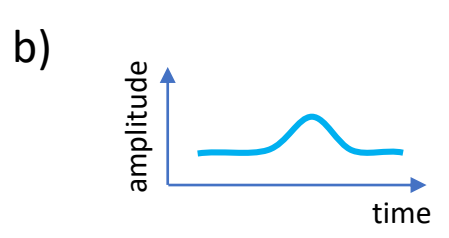
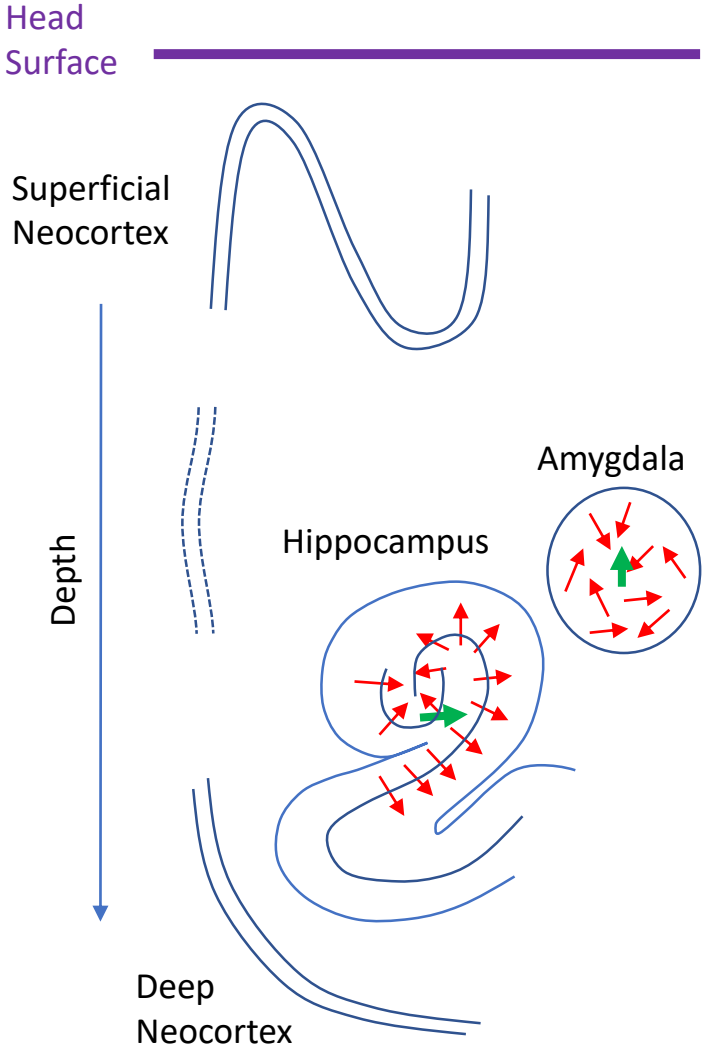
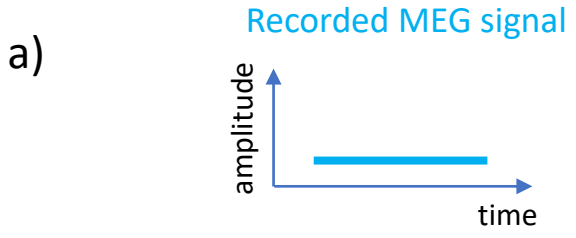
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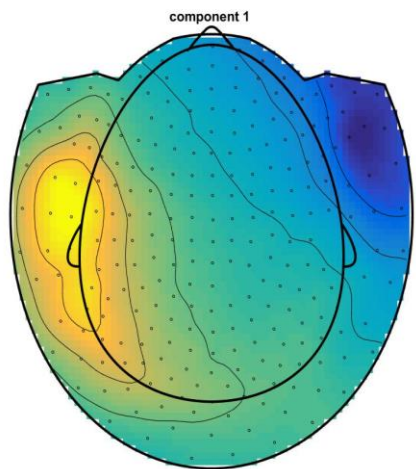
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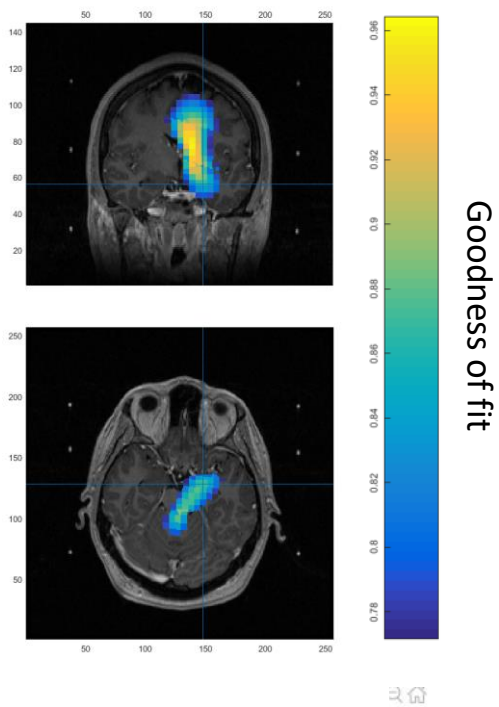
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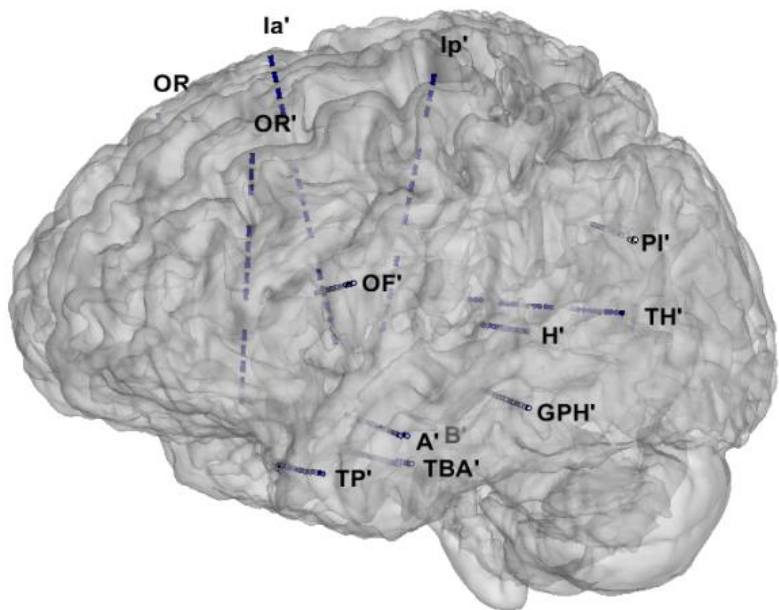
a)



b)



c)



d)

