DETECTING EPILEPTIFORM ACTIVITY FROM DEEPER BRAIN REGIONS IN SPATIALLY FILTERED MEG DATA

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LETTER TO THE EDITOR

It is well known that signals from deep sources, such as mesial temporal epileptic foci, are often barely visible in MEG and EEG (Magneto-/Electro-encephalography) recordings. Here we show in two patients how spatial filtering, using a beamforming technique, can be used to identify epileptiform activity. In these patients, this procedure resulted in detection of hippocampal interictal epileptiform discharges, even though these discharges were poorly discernible by visual inspection of the raw MEG time series. The observed interictal epileptiform discharges accurately matched the discharges identified in recordings from depth-electrodes placed in the hippocampi in subsequent invasive measurements. One patient underwent temporal lobe resection, including amygdalohippocampectomy, and has been seizure-free for 3.5 years.

The clinical use of MEG recordings has so far been restricted to mapping of eloquent cortex in brain tumour patients and to localizing epileptiform activity in order to help planning subsequent invasive recordings or neurosurgery. Whole-head MEG has generally better spatial resolution than clinical EEG and is less influenced by the properties of the different tissues in the head. However, the magnetic field strength, and its gradients even more so, decrease faster with distance between source and sensor than the electric potential. As a consequence MEG is more sensitive than EEG for superficial sources, but this reverses at a certain depth (de Jongh et al., 2005).

The most commonly used methods to localise epileptiform activity in epilepsy patients are dipole fitting and beamforming, which can be seen as a spatial filtering technique (Baillet et al., 2001). For each location in the brain separately, the spatial filter parameters (i.e. the beamformer weights) are determined from the data in such a way that signals originating from that particular location are not attenuated, while signals from other locations are maximally attenuated. As an example, the spikiness beamformer (Agirre-Arrizubieta et al., 2014; Kirsch et al., 2006) results in a 3D image, depicting for each voxel the kurtosis of the spatially filtered signal, thereby highlighting locations with sharp (i.e. epileptiform) activity. Similarly, an event-related beamforming approach can be used to create 3D images of source power at the peaks of interictal spikes (Mohamed et al., 2013). Alternatively, beamforming can be used to compute so-called virtual electrodes: the beamformer-based spatial filter is used to determine how the activity, i.e. the electric current density, varies at a particular pre-set location in the head. It has previously been shown that these virtual electrodes allow reliable detection of signals from deep structures, even though the extracranial signals are very weak such that averaging may be required (Mills et al., 2012). A remaining question therefore is whether isolated epileptiform discharges can also be localised to deeper brain regions such as the hippocampus.

In clinical practice the recording of MEG activity in epilepsy patients is always used in
combination with other findings, such as the semiology of seizures, MRI abnormalities, (video-)EEG, and the clinical history. It is often possible to derive a set of possible or probable source regions, and MEG may then be used to discriminate between these possibilities. If, for instance, the MRI of an epilepsy patient shows focal abnormalities, it might be possible by constructing virtual electrode signals from locations near those abnormalities to determine which of these locations is the most likely source of epileptiform activity. We tested this approach in a small sample of epilepsy patients, in whom epileptiform activity was difficult to discern from the raw MEG recordings. We used the basic scalar beamformer construct (Beamformer 2.1, Elekta Neuromag Oy) over the full time window of the recording and a single-sphere model co-registered to the patient’s T1-weighted MRI for the computation of the beamformer weights for locations close to or in regions that were suspected to generate epileptiform activity. Noise normalization was used as the sources were rather deep. These weights were then used to generate the virtual electrode signals.

Figure 1 shows data from a 36-years old female patient with drug-resistant complex partial seizures. The MRI showed sclerosis of the left hippocampus. Because results from imaging and neurophysiological investigations, such as video-EEG, MRI, MEG and PET, did not converge, invasive monitoring with depth electrodes was needed to demonstrate a left temporal origin of the seizures. The intracranial recordings from the left hippocampus showed frequent interictal spike discharges, with spread to medial temporal structures (Figure 1e). The MEG data were subsequently re-analysed using virtual electrodes. The virtual electrode placed in the left hippocampus revealed frequent spikes (Figures 1a,c), which were initially missed when eyeballing the surface recordings because they were difficult to distinguish from noise (Figure 1b). These spikes were subsequently fitted using equivalent current dipoles, which localised to the medial temporal lobe (Figure 1c). However, careful inspection of the virtual electrode time series revealed a hippocampal origin, since the spikes were sharper and of larger amplitude in the hippocampus than in the temporal lobe (Figure 1a), and/or had an earlier onset (Figure 1d), in agreement with the invasive data (Figure 1e). The patient is still seizure-free 3.5 years after left-sided temporal lobe resection, including amygdalohippocampectomy (Engel score 1A).

Figure 2 shows data for a 30-years old male patient with drug-resistant complex partial seizures. He had undergone epilepsy surgery, a lesionectomy in the right fronto-basal cortex, a few years ago. Unfortunately, both seizure semiology and seizure frequency remained the same as prior to surgery, probably due to bilateral independent onset zones. MEG showed spike-waves and sharp waves in left and right temporal channels, which could not be localised, possibly because of a deep (mesial) origin. For the lateralization and localization of the seizure-onset zone, invasive EEG monitoring with depth electrodes was
Figure 1: Patient 1. A) 10 seconds of virtual electrode signals; HCmR: hippocampus right; HCmL: hippocampus left; TL: temporal lobe left. The activity scored as an interictal spike is highlighted. Note that the spike is sharper and of larger amplitude in HCmL than in TL. B) The same 10 seconds of data for magnetometers over the left temporal lobe (after applying tSSS). Note that the marked spike can be identified in these sensor level data, but without the virtual electrode data the spike is difficult to differentiate from the preceding noise. C) Anatomical MRI with the location of the virtual electrodes (green dots), fitted equivalent current dipoles (red dots), and the resection cavity. Note that the virtual electrodes are outside the resected area because the exact location of the resection cavity was unknown at the time of analysis. D) 1 second of virtual electrode signals showing a different spike. Note that the spike in TL is delayed with respect to the one in HCmL, in agreement with the delay seen for a spike in the interictal depth-EEG recordings. E) 4 seconds of interictal depth-EEG signals for 3 bundles. HCmL: middle hippocampus left; T2HCpL: second temporal gyrus through posterior hippocampus left; T3GFuL: third temporal gyrus, fusiform gyrus left. An electrode in an electrographically silent area was used as reference.
Virtual electrodes in deep brain regions

Figure 2: Patient 2. A) 10 seconds of virtual electrode signals; HCmR: hippocampus right; HCmL: hippocampus left. The activity scored as an interictal spike is highlighted. B) The same 10 seconds of data for magnetometers over the right and left temporal lobe (after applying tSSS). C) Anatomical MRI with the location of the virtual electrodes (green dots) and fitted equivalent current dipoles (red dots). Note that some spikes were mainly seen in channels over the right temporal lobes, and others over the left temporal lobe, which localised to the right and left hippocampus, respectively. D) 11 seconds of interictal depth-EEG signals for 3 bundles in the left hemisphere and E) 4 bundles in the right hemisphere. Note that the
indicated. Re-analyses of the MEG data with virtual electrodes in the left and right hippocampi showed marked interictal spikes (Figure 2a), which were recognizable in the surface recordings (Figure 2b). The interictal invasive recordings also showed epileptiform activity in left and right hippocampi, independently (Figures 2d, e). Moreover, three seizures had a left mesial temporal origin and one seizure had a right mesial temporal origin in the invasive EEG. The patient has not undergone further epilepsy surgery.

These two examples demonstrate that the use of virtual electrodes at possible or probable source locations aids the identification of epileptiform activity that would otherwise not be discernible or be missed in surface MEG recordings. This technique must be used with care, as the spatial resolution of virtual electrode signals is a complicated function of signal-to-noise ratio (in the raw MEG data), depth, position and orientation of the sources with respect to the recording array, and the geometry of the head. As a consequence the localizing power may be poor at some locations (Attal and Schwartz, 2013; Wennberg and Cheyne, 2014), such that it is possible to find interictal spikes at a virtual electrode that has been placed at some distance from the real source. We therefore recommend to use the time segments where pathological activity is seen in the virtual electrode signals as input for, for example, conventional dipole localization based on the surface data (Figures 1c, 2c), in combination with a careful inspection of the virtual electrode time series (Figure 1d). Thus, the spatial filtering approach is used to test for epileptiform activity at pre-defined locations, whereas the epileptiform activity is localised using dipole fitting.

In summary, we found that in epilepsy patients for whom there is clinical evidence for possible deep foci, e.g. patients with mesio-temporal epilepsy, it is useful to spatially filter the data, using a virtual electrode beamformer, and to use the signals from these probe sources when scoring the data.

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CONFLICT OF INTEREST STATEMENT
None of the authors have potential conflicts of interest to be disclosed.