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Virtual localization of the seizure onset zone: Using non-invasive MEG virtual electrodes at stereo-EEG electrode locations in refractory epilepsy patients

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ABSTRACT

In some patients with medically refractory epilepsy, EEG with intracerebrally placed electrodes (stereo-electroencephalography, SEEG) is needed to locate the seizure onset zone (SOZ) for successful epilepsy surgery. SEEG has limitations and entails risk of complications because of its invasive character. Non-invasive magnetoencephalography virtual electrodes (MEG-VEs) may overcome SEEG limitations and optimize electrode placement making SOZ localization safer. Our purpose was to assess whether interictal activity measured by MEG-VEs and SEEG at identical anatomical locations were comparable, and whether MEG-VEs activity properties could determine the location of a later resected brain area (RA) as an approximation of the SOZ. We analyzed data from nine patients who underwent MEG and SEEG evaluation, and surgery for medically refractory epilepsy. MEG activity was retrospectively reconstructed using beamforming to obtain VEs at the anatomical locations corresponding to those of SEEG electrodes. Spectral, functional connectivity and functional network properties were obtained for both, MEG-VEs and SEEG time series, and their correlation and reliability were established. Based on these properties, the approximation of the SOZ was characterized by the differences between RA and non-RA (NRA). We found significant positive correlation and reliability between MEG-VEs and SEEG spectral measures (particularly in delta [0.5–4 Hz], alpha2 [10–13 Hz], and beta [13–30 Hz] bands) and broadband functional connectivity. Both modalities showed significantly slower activity and a tendency towards increased broadband functional connectivity in the RA compared to the NRA. Our findings show that spectral and functional connectivity properties of non-invasively obtained MEG-VEs match those of invasive SEEG recordings, and can characterize the SOZ. This suggests that MEG-VEs might be used for optimal SEEG planning and fewer depth electrode implantations, making the localization of the SOZ safer and more successful.

1. Introduction

Epilepsy surgery is a treatment option in selected patients with medically refractory focal epilepsy. It aims at rendering the patient seizure-free by removing tissue that is responsible for seizure generation and/or propagation. This region is referred to as the epileptogenic zone (EZ), and is only know unequivocally after surgery if the patient becomes seizure-free (Luders et al., 2006). Preoperatively, surrogate markers of the EZ can be obtained by non-invasive techniques. A proportion of patients need additional invasive stereo-electroencephalography (SEEG) monitoring of seizures to substantiate the hypothesis about the location of the EZ by establishing the seizure onset zone (SOZ). In resection cases, the area that is to be resected (resection area, RA) usually includes the SOZ as it is a well-established surrogate marker of the EZ (Luders et al., 2006).

Successful SOZ identification by SEEG depends upon correct planning and placement of intracerebral electrodes. The hypothesis regarding the SOZ location used for electrode placement needs to be focused, since SEEG coverage of brain structures is limited and the risk of complication rises with increasing number of electrodes implanted. Although SEEG provides essential information in selected cases, some of its disadvantages – such as high costs, risks and patient burden involved in implantation of the electrodes and the long-term invasive monitoring– apply to all patients. In addition, SEEG fails to reveal the SOZ in some cases, despite using all conventional non-invasive studies, such as video-EEG and MRI. Additional information from non-invasive

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studies is needed to improve the SEEG placement and to limit the number of required electrodes.

By using magnetoencephalography (MEG) for assessment of epileptiform activity, as well as for more advanced source localization and network analysis, one might overcome some SEEG limitations. With spatial filtering (beamforming) it is possible to reconstruct time series of neuronal activation at a-priori defined target locations –so called virtual electrodes (MEG-VEs) (Hillebrand and Barnes, 2005; Hillebrand et al., 2005). MEG-VEs have provided information on epilepsy, e.g. interictal spikes location concordant to the SOZ (Mohamed et al., 2013). Moreover, MEG-VEs allow detection of epileptiform discharges in deep structures, like the hippocampus, and have been used to assess functional connectivity and brain network properties in epilepsy (Hillebrand et al., 2016; Nissen et al., 2017; Nissen et al., 2016). Simulated SEEG recordings are feasible, since the location and number of MEG-VEs can be varied and MEG-VEs can be placed in user-defined locations.

Our group and others have previously used resting-state functional brain network characteristics, established from pre- and postoperative fMRI and MEG to increase prediction of success of surgery in addition to conventional interictal measures such as interictal spikes and spectral power (Quraan et al., 2013; Stam, 2014; van Diessen et al., 2013a). Epilepsy-related disturbances include both increases and decreases in mean functional connectivity, decreased long distance efficiency, altered distribution of regions with high centrality (hubs), and presence of hubs in or near the EZ (Stam, 2014; van Diessen et al., 2013a; Wendling et al., 2010). Removal of these hubs correlates with favorable outcome after epilepsy surgery (Nissen et al., 2017; Ortega et al., 2008). These measures are essentially assumption-free, meaning they involve all brain regions without focusing on the specific regions that were thought to be involved in seizure generation and propagation. The value of subnetwork analysis involving only specific brain areas needs to be established further.

To aid the planning of SEEG placement, we investigated whether interictal activity measured by MEG and SEEG at identical anatomical locations corresponded with respect to spectral, functional connectivity and network properties in patients with medically refractory epilepsy. Furthermore, we determined whether the spatial distributions of these properties were indicative of the later RA.

2. Methods

2.1. Patient selection

We retrospectively included nine patients with refractory epilepsy who underwent resective surgery at the VU University Medical Center. The inclusion criteria included availability of MEG and SEEG data that had been recorded as part of their presurgical evaluation, postoperative MRI and CT (Computed Tomography) with implanted depth electrodes. All patients gave informed consent to use their data for research purposes and the local Medical Ethical Review Committee at VUmc (in accordance with the Declaration of Helsinki) approved the study. One year postoperative surgery outcome was recorded using the Engel score (Engel Jr et al., 1993).

2.2. SEEG recordings

Implantation of intracerebral electrodes with multiple contacts (Ad-Tech, Medical Instrument Corporation, USA, 10–15 contacts, electrode diameter: 1.12 mm, intercontact spacing 5 mm) was performed with a stereotactic procedure and planned individually based on the hypothesized SOZ from non-invasive pre-operative studies, including video-EEG, structural MRI, MEG, Positron Emission Tomography (PET) and in selected cases ictal Single Photon Emission Computed Tomography (iSPECT). The number of electrodes per patient varied between 10 and 15 and the total number of contacts between 64 and 121, resulting in SEEG with 64–121 channels (see supplementary Table S1 for details of individual patients). Recordings were performed with a sampling frequency of 1024 Hz and downsampled by a factor of 2, except for one patient (500 Hz). From the recorded data, 10 consecutive interictal broadband (0.5–70 Hz) epochs of 4096 samples (8–8.2 s each) of the first day of the recording with the patient awake, at rest and with eyes open were selected for further analysis. No changes to anti-epileptic medication was indicated at the time of this part of the SEEG recording, hence SEEG did not differ from MEG recordings with regards to medication.

2.3. MEG recordings

A whole-head MEG system with 306 channels (102 magnetometers and 204 gradiometers, Elekta Neuromag Oy, Helsinki, Finland), placed in a magnetically shielded room (VacuumSchmelze GmbH, Hanau, Germany), was used to obtain the MEG recordings. Patients were in a supine, no-task, eyes-closed resting-state condition. A sampling frequency of 1250 Hz, an anti-aliasing filter of 410 Hz, and a high-pass filter of 0.1 Hz were used online for the recordings. Four head position indicator (HPI) coils were used to determine the head's position during the recordings. The scalp outline and HPI coil positions were digitized using a 3-D digitizer (Fastrak, Polhemus, Colchester, VT, USA). The temporal extension of Signal Space Separation (tSSS) (Taulu and Simola, 2006) (subspace correlation limit of 0.9 and a sliding window of 10 s) using MaxFilter software (Elekta Neuromag Oy, v. 2.2.15) was used to remove artifacts. The MEG data were co-registered with the patient's anatomical preoperative MRI using surface-matching software. A single sphere was fitted to the outline of the scalp and used as a volume conductor model for the beamforming approach.

2.4. MEG-VE reconstruction at SEEG electrode locations

Broadband (0.5–48 Hz) MEG-VEs were reconstructed at the locations of the SEEG contact points using a scalar beamforming method (Elekta Neuromag Oy; beamformer; v. 2.2.10), with normalized broadband beamformer weights that were computed using the broadband data covariance, a unity noise covariance matrix, and an equivalent current dipole (ECD) as the source model. The coordinates of the SEEG contact points were obtained from the post-implantation CT scan (containing the SEEG electrodes) that had been fused (linear coregistration) with the preoperative MRI scan (iPlan Net 3.0.0, BrainLab Ag, Germany) (Hillebrand and Barnes, 2005; Hillebrand et al., 2005): Fig. 1 (upper left image) shows that the SEEG contacts have a high signal density relative to brain tissue. Signal density was also higher than other high density structures, such as blood vessels. By setting a threshold, all contacts were isolated and stored. Subsequently, the x-, y- and z-coordinates for these contacts were used as input locations for the manual placement of the MEG-VEs. MEG signals at each VE location was reconstructed with beamforming: The beamforming methodology is described in detail in Hillebrand et al., 2005 (Hillebrand and Barnes, 2005; Hillebrand et al., 2005). In summary, for a particular location (in our case, the locations of the SEEG contacts) and source orientation) a set of beamformer weights are computed. The weights are chosen such that the activity at that location is reconstructed without the contribution from noise (or signal from other locations). The beamformer output at a target location for a source is the weighted sum of the output of all signal channels, and is called virtual electrode:

$$VE = W \cdot B \quad (1)$$

where VE is the beamformer output or virtual electrode, W is the $1 \times N$ weight vector and B an NxM matrix containing the magnetic field at the N sensor locations at all M latencies (Hillebrand and Barnes, 2005; Hillebrand et al., 2005). The choice of weights determines how accurate the signal for a region is reconstructed and these are determined by the formula: