

Phantom study supports claim of accurate localization from MEG data

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Abstract. To evaluate the localization accuracy and precision of magnetoencephalography (MEG) for cortical and deep neural sources, we conducted a phantom experiment. We have used MEG data generated by current dipole-like sources in a spheroidal phantom. MEG signals were recorded by activating superficial and deep current generators implanted in the phantom, which were driven separately by weak, transient currents of varied strengths. The data were analyzed by four different modeling techniques. We evaluate and compare the localization accuracy obtained with the phantom data from previous studies of our laboratory. In these previous studies, we have demonstrated, by using fMRI sub-millimeter spatial resolution as a reference point that the localization accuracy of MEG with MFT, at least at the level of V1, is within a few millimeters. For the phantom data, overall high spatial resolution was demonstrated for isolated weak, transient, cortical and sub-cortical neural sources for each of the four source localization techniques. The differences between the methods were typically only a few millimeters. As expected localization, accuracy was reduced for deep sources.

Keywords: MEG, localization accuracy, phantom, fMRI

1. Introduction

Magnetoencephalography (MEG) is a non-invasive technique that records the extra-cranial magnetic field produced by mass neuronal activity using super-conducting quantum interferences devices (Cohen, 1972). While the temporal resolution of MEG is unparalleled, its spatial resolution and precision is often questioned on theoretical and practical grounds.

The magnetic signals from the human brain are extremely weak (typically 50-500 fT) compared with ambient magnetic-field variations (Hamalainen et al., 1993), effective pre-processing techniques, such as bandpass filtering, are necessary to isolate the signal of interest from environmental noise and biological artifacts generated by human body. Besides band-pass filtering, averaging is a simple and powerful way of improving the signal-noise-ratio (SNR) of MEG signal. Averaging has become the choice method for extracting high-SNR signals from noisy MEG data to reveal significant signals that are not readily identifiable in single trials. However, recent studies challenged the foundation of averaging (Laskaris et al., 2003; Makeig et al., 2002), namely that the MEG signal can be separated into contributions evoked by the stimulus and noise from unrelated signals.

At the more practical level, standard MEG experimental procedures that restrict subject's head motion become very demanding, when the relative location of brain (and hence the subject) and the sensors must be kept constant for the duration of a run to about a millimeter. On the theoretical side, MEG localization faces what appears an impossible task; to solve a problem that is known for well over a century to have a non-unique solution (von Helmholtz, 1853). This is less of a problem in practice because even mild constraints are sufficient to select one out of the infinite available solutions. The question then becomes one of estimating plausible sources given the data. Such estimation uses as input the solution of the forward problem, which involves the calculation of the magnetic field generated by known current sources for a given head model. Inaccuracies in the forward model can lead to reduced localization accuracy for MEG.

The precision and accuracy with which neural sources can be localized within human brain can be assessed with experiments in which the true location and temporal activity of the sources are known. A simple and effective way is with computer or phantom-generated data. The computer-generated data are however of limited use because they do not take into account errors due to head modeling

inaccuracies and imperfections in instrumentation and noise. Studies with skull or skull-like phantoms take into account these parameters and test test localization at different parts of the brain. Introducing into the phantoms features similar to those of a real human head allows studying the deviations of the physical system from the model and inaccuracies in the forward model (e.g. approximations of the head geometry). Phantom studies with dipoles implanted in a human skull filled with conducting gelatin (Baillet et al., 2001; Leahy et al., 1998; Yamamoto et al., 1988) or a cadaver head (Barth et al., 1986) have so far been used to determine the expected accuracy of EEG and MEG source localizations. These studies presented single-source localization errors as small as approximately 3 mm for cortical and sub-cortical dipole positions. Although, such localization accuracy is satisfactory for the assessment of the underlying neural sources, these studies exhibit many limitations. The examined dipoles strengths were either too high (Leahy et al., 1998), or not specified (Sutherling et al., 2001; Wang and Oertel, 2000), while when low dipole strengths (as low as 52 nA-m) were used, the analysis was performed on the averaged magnetic fields derived from a large number of repetitions (Yamamoto et al., 1988).

Here, we conducted a phantom experiment building on previous studies, motivated by the desire to produce realistic data corresponding to complex spatio-temporal current sources and to examine MEG ability in accurate localization of weak, transient neural sources. Multiple isolated, superficial and deep sources were implanted into a realistically shaped phantom, which were driven either separately or simultaneously by weak, transient, currents of varied strengths. The results of our phantom study are interpreted in the light of earlier studies from our lab (Moradi et al., 2003; Ioannides and Fenwich, 2005; Poghosyan and Ioannides, 2007).

2. Material and Methods

It is widely assumed that functional magnetic resonance imaging (fMRI) can serve as a gold standard for MEG in terms of localization accuracy, though it does not provide accurate temporal detail of the underlying neural activity. The tomographic localization of activity within primary visual cortex (striate cortex or V1) was examined using whole-head MEG and 4T functional magnetic resonance imaging (fMRI) in four male subjects (age: 27-35). Circular check-board pattern stimuli with radii from 1.8 to 5.2° were presented at eccentricity of 8° and angular position of 45° in the lower quadrant of the visual field to excite the dorsal part of V1. The MEG data were analyzed by Magnetic Field Tomography (MFT). The MFT estimates for each time slice were smoothed by averaging the current density vector over a 6.4 ms window. A paired t-test was made between distributions from each subject and each of the three baselines. Using fMRI sub-millimeter spatial resolution as a reference point, the study demonstrated that the localization accuracy of MEG with MFT, at least at the level of V1, is within a few millimeters of the fMRI loci (Moradi et al., 2003).

Although, these studies are ideal for testing the localization accuracy of MEG, it seems extremely hard to do. That is because it is extremely difficult for fMRI to provide accurate localization at sub-millimeter accuracy (with no distortions) throughout the brain, and partly because of the very slow hemodynamic response that limits the interpretation of the fMRIs results beyond the early retinotopic visual areas. Another approach to assess the MEG localization accuracy is to perform the same experiment at different days. Repetition of the experiment allowed to assess not only the precision of the source localization but also the reproducibility of the entire experimental procedure and analysis. In a previous study of our lab (Poghosyan and Ioannides, 2007), we used MEG to record brain responses while subjects were presented with circular checkerboard pattern stimuli in peripheral and parafoveal locations in all four visual field (VF) quadrants. The experiment for each subject was repeated on three different days. The precision of the localization was defined as the SD of the activation locations across the three days measurements. Sources of MEG signal for each experimental day were localized using the same approach as in Moradi et al. (2003). To corroborate the localization accuracy in V1 and provide an indication of accuracy in the visual cortical areas beyond it we used computer simulations with known sources.

The excellent localization demonstrated for superficial activity in V1 cannot be generalized to the entire brain because the MEG sensitivity is reduced with depth and brain areas like the cerebellum and brainstem are not well covered by the sensor array of modern MEG devices. The localization accuracy of MEG was tested for deep areas, like the amygdala (Ioannides et al., 2004) and especially eye movements (Ioannides and Fenwich, 2005). Although the evidence from these studies is clear, they do not provide a gold standard. To assess the localization accuracy of MEG for different parts of the brain experimental studies can be performed in which the true location and temporal activity of the dipoles are known. Computer stimulation of head shape phantom studies can thus be performed examining the

localization accuracy of MEG. Computer generated data are however of limited use because assume simplified models for the head, instrumentation and noise, and thus the source configuration may be very different from neuronal sources in real brain. For this study we used a spheroidal phantom designed by one of us (AAI) to have realistic features with exaggerated departure from spherical symmetry and uniformity. Four dipoles were placed in one of four locations inside the spheroidal phantom, referred to hereafter as PhS1, PhS2, PhS3, and PhS4. These four locations were chosen to represent the full range of difficulties for localizing generators in the brain. We will focus on results for the most superficial (PhS1) and a moderately deep (PhS3) sources. The phantom dipoles were driven by current sources with pulse strength varied in different runs from 1 to 20 μA , with one μA steps, so that the range of MEG signal strength produced covers the range of typical MEG values recorded in MEG experiments with human subjects. Eighty-four runs were collected in total, twenty datasets for each single dipole position (one for each dipole strength: 1-20 μA), three runs with two simultaneously active dipoles, and one run with three dipoles that were activated simultaneously. In each run, 60 sec data were collected containing 360 current pulses, with inter-stimulus interval of 100 msec. MEG data were processed using different modeling techniques: Equivalent Current Dipole (ECD), Synthetic Aperture Magnetometry (SAM), Multiple Signal Classification (MUSIC) and Magnetic Field Tomography (MFT).

3. Results

In our previous fMRI/MEG study (Moradi et al., 2003), both fMRI and MEG identified spatially well-overlapped activity within the targeted area in each subject (Fig 1). Figure 1 shows that these early V1 activations were very focal and in excellent agreement with the fMRI V1 localization. We compared time-dependent statistical parametric mapping (SPM) images derived from our MFT solutions with similar images derived from fMRI data using identical stimuli and the same subjects. The accuracy of just a few millimeters reported in this study is almost an order of magnitude better than most previously reported comparisons of fMRI and MEG localization. In this study, fMRI served as a gold standard, but the fMRI actually had to be mapped in MRI slices identified for each subject in a separate fMRI experiment. This restricted the targeted area to just one part of V1.

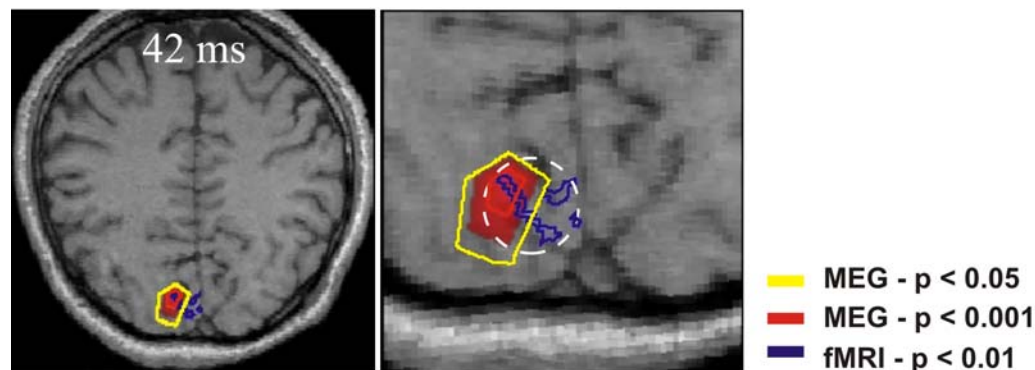


Figure 1. Comparison of V1 activation between fMRI at the onset of M50 (42 ms). The results are shown in the paracalcarine slice best covering V1 for one subject. Blue outlines mark the boundary of statistically significant fMRI activations, while with yellow and red are marked the MEG activations. The dashed white circle represents the expected (targeted) area based on a separate retinotopic exploration of the V1 area of the subject.

In Poghosyan and Ioannides (2007), we used a similar protocol but with eight separate stimuli to cover all foveal and parafoveal quadrants of the visual field. The results showed the expected retinotopic response, with the earlier stimulus-evoked responses registered in V1. Then, activity with largely overlapping latencies spread rapidly to V2, V3 and throughout the whole visual system. Unambiguous and focal activations with precise onset, peak latencies, and peak amplitudes for each one of the three subjects and each day of the three days were identified in retinotopic areas. Activations in all areas were consistent in location and timing across subjects and for each subject they were highly reproducible across three experimental days (Fig. 2). Localization precision was typically within a few millimeters in all areas. The localization accuracy was as predicted by computer simulations and consistent with our earlier fMRI/MEG study.

In our phantom study, the most superficial dipole (PhS1) was localized with an accuracy of 2-3 mm at strengths as low as 3-5 μA (Fig. 3). The differences in localization accuracy between these four methods were only a few millimeters. The ECD fit applied to the single trial data by using either all sensors or a subset of sensors failed to fit the data for strengths below 10 μA . The performance of the modeling techniques varied for the sources away from the surface and/or close to sharp discontinuities. For the dipole position PhS3, the best results were obtained using ECD and MFT on averaged data (Fig. 3).

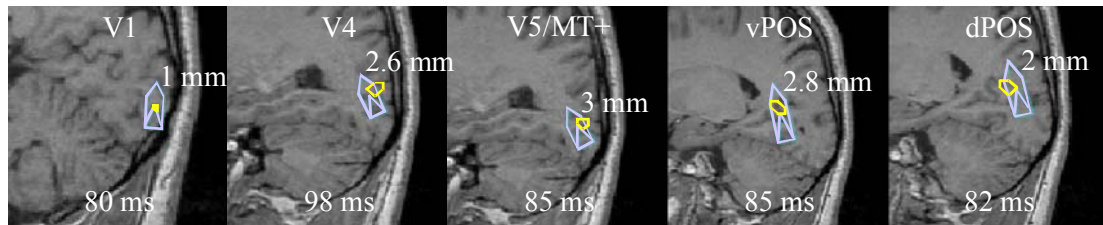


Figure 2. Source dipoles (light blue arrows) together with their MFT-SPM estimates (yellow contours). Sagittal slices of MR images where the dipoles were placed are shown. Yellow contours encopass the regions with a statistical significance ($p < 0.001$). Names of the areas are given on top of each MRI. The distance between the dipole's location and the centroid of its estimate is indicated next to each dipole. Latencies of the estimated activations are shown at the bottom of each MRI.

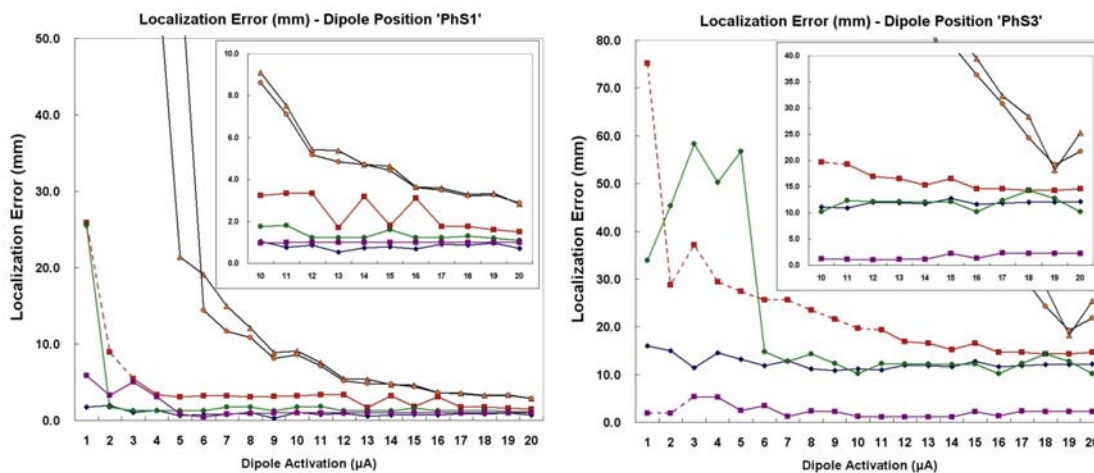


Figure 3. The localization error (in mm) versus the dipole strength (in μA) for the two out of four different dipole locations (PhS1 and PhS3). The dash lines represent values with no statistically significant t -values for SAM. For MFT, the dash lines represent localization error of MFT applied to averages, and are presented when the technique did not give statistically significant t -values. Abbreviations of Av-ECD and ECD(S) are respectively corresponding to the ECD applied to averaged data and ECD fit applied to data that were derived by using a subset of sensors.

4. Discussion

MEG data elicited by visual and somatosensory stimuli from human subjects can be localized in the expected primary sensory areas with accuracy of a few millimeters. Satisfactory results are obtained with a fine spatial detail when monitoring the real-time brain activity by using MEG signal. This finding is in accordance with our findings from the visual evoked responses study that was performed in the same subjects at different days (Poghosyan and Ioannides, 2007). At this level of precision, MEG becomes a powerful tool for studying spatial as well as temporal details of human brain activity, and specifically, as we have demonstrated here, the dynamics of early visual responses.

Our phantom data indicate that weak (as small as 8 nA-m) neuronal activity can be located in real-time with high accuracy (of 1-2 mm) within the cortical regions for field strengths at physiological levels. In terms of difficulty, MEG has an excellent spatial resolution for primary sensory neural sources located at cortical areas. The performance was similar for all techniques, with the only exception of ECD on single-trials. As expected, dipolar sources that were positioned more deeply in

the phantom were localized less accurately than the dipole at the superficial position. The PhS3 source was localized with an accuracy of approximately 5 mm by using dipole fitting on averaged data, MFT and MUSIC, while SAM revealed slightly worst results than the other modeling techniques.

The preceding results indicate that MEG can localize with an accuracy of 1-2 millimeters real-time neuronal activity at cortical areas. The choice of the modeling technique is not critical for superficial cortical sources. For deeper sources, different techniques are more advantageous than others for specific locations and strengths, and at least for MFT localization accuracy well within one centimeter seems possible even for deep sources, provided that SNR is sufficient high.

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