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The advantage of combining MEG and EEG: comparison to fMRI in focally-stimulated visual cortex

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Abstract

To exploit the high (millisecond) temporal resolution of magnetoencephalography (MEG) and electroencephalography (EEG) for measuring neuronal dynamics within well-defined brain regions, it is important to quantitatively assess their localizing ability. Previous modeling studies and empirical data suggest that a combination of MEG and EEG signals should yield the most accurate localization, due to their complementary sensitivities. However, these two modalities have rarely been explicitly combined for source estimation in studies of recorded brain activity, and a quantitative empirical assessment of their abilities, combined and separate, is currently lacking. Here we studied early visual responses to focal Gabor patches flashed during subject fixation. MEG and EEG data were collected simultaneously, and compared with the functional MRI (fMRI) localization produced by identical stimuli, in the same subjects. This allowed direct evaluation of the localization accuracy of separate and combined MEG/EEG inverse solutions. We found that the localization accuracy of the combined MEG+EEG solution was consistently better than that of either modality alone, using three different source estimation approaches. Further analysis suggests that this improved localization is due to the different properties of the two imaging modalities, rather than simply due to increased total channel number. Thus, combining MEG and EEG data is important for high-resolution spatiotemporal studies of the human brain.

Introduction

EEG and MEG offer the highest temporal resolution available in non-invasive brain imaging, on the order of milliseconds (Hämäläinen et al., 1993). In order to determine the location of the cerebral current sources giving rise to signals recorded outside the head with EEG electrodes or with MEG sensors, one has to calculate the solution to an ill-posed inverse problem. That is, there are an infinite number of current distributions that can explain the EEG and MEG signals recorded. This property of EEG and MEG, together with the relatively large distance between the sensors and sources, limits the accuracy with which signal sources can be localized, making the interpretation of activation time-courses difficult whenever multiple sources are

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active simultaneously, which is often the case. Thus, a signal which seems to arise from a given single location may actually be a superposition of several activations that are in reality 1–3 centimeters apart (Liu et al., 2002), thus possibly originating in functionally different cortical areas. To obtain accurate spatiotemporal activation profiles, it is therefore important to assess the localization errors in the inverse solutions obtained from EEG and MEG measurements.

EEG and MEG arise from the same sources in the brain: synchronized postsynaptic currents in and around apical dendrites of pyramidal cells over an area of at least 1 cm² are the most easily detectable sources (Hamalainen et al., 1993). However, differences in the physical properties of the electric and magnetic fields arising from the same current source may help improve the source localization using both measurements, relative to using either of them alone (Cohen and Cuffin, 1983; Cuffin and Cohen, 1979). The spatial pattern of the electric potential and that of the normal component of the magnetic field produced by a focal tangential current source are rotated by 90 degrees relative to each other, so that the axes that give the best localization accuracy are also orthogonal (Cohen and Cuffin, 1983). Furthermore, the contribution of radially oriented sources, prominent in EEG, is very weak in MEG (Baule and McFee, 1965). These complementary properties of EEG and MEG allowed the disambiguation of the early evoked potential in response to median nerve stimulation, and its identification as a single tangential source in somatosensory cortex, rather than a pair of radial sources in motor and somatosensory cortices (Wood et al., 1985). In addition, the sensitivity pattern of MEG decreases more rapidly with source depth than that of EEG (Cuffin and Cohen, 1979). Finally, the high resistivity of the skull in combination with the more conductive scalp smears and attenuates the electrical potential distribution (Cooper et al., 1965; Delucchi et al., 1962; Geisler and Gerstein, 1961), whereas it does not affect the magnetic fields (Grynspan and Geselowitz, 1973); this confers a localization advantage for MEG, for those sources that it is able to detect (Cuffin and Cohen, 1979).

These factors have long suggested that better localization can be obtained by combining EEG and MEG, compared to either measurement alone. Theoretical and simulation studies have shown the complementary nature of their sensitivity and field patterns (Cohen and Cuffin, 1983; Cuffin and Cohen, 1979), and the advantage of combining them (Fuchs et al., 1998; Liu et al., 2002). However, to date, few studies have combined EEG and MEG data in recordings of real brain activity. The few reported experimental results (Cohen and Cuffin, 1983; Fuchs et al., 1998; Wood et al., 1985) lacked a comparison to independent data, separate from the MEG/EEG, regarding true source location. One study measured both MEG and EEG in response to artificial dipoles placed in known locations in patients' heads, and quantitatively compared localization results, but did not combine MEG and EEG (Cohen et al., 1990). A rigorous comparison of EEG, MEG, and combined MEG+EEG to other physiological recordings, would allow to systematically test the localization accuracy of the combined data and each of the single modalities.

Here, we evaluated the localization errors of EEG, MEG, and combined MEG+EEG, by comparing each to BOLD fMRI responses, using identical focal visual stimuli presented in an identical event-related paradigm. It is particularly apt to assess localization accuracy in the visual system, where multiple retinotopic visual areas (each ~1 cm wide; (Sereni et al., 1995)) reside in close proximity, making MEG/EEG localization particularly challenging. Moreover, the retinotopic organization of the visual system is well-understood based on prior fMRI studies. Thus, appropriately-placed visual stimuli should evoke a separate local response patch in each retinotopic visual area, and changing the stimulus location should change cortical response location in a predictable way. Retinotopic field-sign mapping can objectively reveal visual area borders in each subject, allowing one to define an fMRI region-of-interest specific to the first visual area, V1. Since V1 is the earliest cortical area to receive visual input (Nowak et al., 1995; Raiguel et al., 1989; Schmolesky et al., 1998), the earliest cortical visual MEG/EEG

responses to static stimuli may be assumed to arise from V1. BOLD fMRI localization does not depend on the solution of an inverse problem as do MEG/EEG, and it offers millimeter spatial resolution.

Therefore, in this study we took the BOLD fMRI as an estimate for true activity location and calculated the distance between the fMRI V1 response, isolated using the field-sign area border map (Serenio et al., 1995), and the EEG, MEG or MEG+EEG V1 response, identified as the earliest response. Stimulus location was moved to verify that response location moved appropriately with it. We used three inverse approaches: anatomically-constrained (Dale and Sereno, 1993) dynamic statistical parametric mapping (dSPM (Dale et al., 2000)) and depth-weighted minimum-norm estimation (MNE) (Hamalainen and Ilmoniemi, 1984), as well as equivalent current dipole fitting (Lin et al., 2006b; Tuomisto et al., 1983). We found that combined MEG+EEG gave smaller localization errors than either modality alone for all inverse solutions evaluated.

Materials and methods

Stimuli

In both fMRI and MEG/EEG sessions, a single 100% contrast Gabor patch was presented in one of four locations (upper or lower visual quadrant, at 5 or 10 degrees eccentricity) for 500 ms while the subject fixated a central fixation cross (see Fig. 1A). A blank condition (gray except for the fixation cross) was additionally presented. The carrier spatial frequency of the Gabor patch was 2 cycles/degree, and the Gaussian full-width at half-maximum was 1.2 and 1.7 degrees for the 5 and 10 degree-eccentricity stimuli, respectively. These sizes equal twice the mean size of receptive-fields in V1 at these eccentricities, as determined by electrophysiology in macaque (Dow et al., 1981). Each arm of the black fixation cross was 0.17 degrees long and 0.11 degrees wide in the MEG sessions, and 0.09 degrees long and 0.04 degrees wide in the fMRI sessions. The gray level of the background was equivalent to the mean of the Gabor patches. The background extended horizontally to an eccentricity of 23 degrees in the MEG/EEG sessions and 11.5 degrees in the fMRI sessions. Stimuli were presented using Presentation (Neurobehavioral Systems, Albany, CA).

To monitor fixation and facilitate subject arousal, one arm of the fixation cross disappeared for 33 ms as soon as the stimulus epoch ended, and the subject indicated with a button-press whether it was the upper or lower arm. Subjects performed at >90% correct, and incorrect/missed trials were discarded. The interstimulus interval was randomized between 1–6.5 secs at 500 ms intervals (mean: 1.56 secs), a schedule which was optimized for rapid-presentation event-related fMRI acquisition using FreeSurfer (<http://www.surfer.nmr.mgh.harvard.edu>) (Dale, 1999).

Each session included 20 scans of 4:16 minutes for a total of 500 repetitions per stimulus condition (excepting one subject's fMRI session, which lasted only 13 scans). A rest interval of 1 minute preceded each new scan. The four Gabor patch stimuli were presented to each subject in the hemifield contralateral to the hemisphere for which that subject's retinotopic map was of higher quality. For four subjects this was the left hemifield, and for two it was the right hemifield.

For fMRI retinotopic mapping (Serenio et al., 1995), contrast-reversing black and white scaled-checkerboard rotating wedges and expanding rings were presented. Four scans (two for the wedge stimulus and two for the ring stimulus) were acquired, each of 8:32 minute duration. Each scan consisted of 8 stimulus cycles of 64 seconds each, during which the wedge stimulus rotated counter-clockwise from vertical and the ring stimulus expanded from the central fixation cross out to the edge of the display (approximately 10 degrees eccentricity).

Data acquisition

Six subjects underwent four scanning sessions each: an MEG/EEG session and an fMRI session using Gabor patch stimuli, an fMRI retinotopic mapping session, and a structural MRI scan. The fMRI retinotopic session was used to delineate the V1 border, as shown in Fig. 1B. All results were registered to the cortical surface reconstructed from the structural scan, which also provided data for setting up the MEG/EEG BEMs. Informed written consent was obtained from participants before each scanning session, and the Massachusetts General Hospital Human Studies Committee approved all procedures under protocols 1999P-010946, 2000P-001155, 2000P-001318.

fMRI—Functional imaging was performed in a 3T Trio scanner (Siemens Medical Solutions, Erlangen, Germany), using an echo-planar imaging pulse sequence. In the Gabor patch experiment, 20 scans were performed; in each 128 brain volumes were acquired with TR=2 s and TE=30 ms, totaling 4:16 per scan. Thirty-four 3-mm thick slices oriented approximately horizontally (parallel to the plane touching the lowest point in occipital cortex and the lowest point in the temporal lobe), were acquired with no spacing and an in-plane resolution of 3.125×3.125 mm. This slice prescription covered the entire brain, or missed some very dorsal frontal cortex. An 8-channel head coil was used. In the retinotopic mapping session an occipital 8-channel coil was used. Four scans of 8:32 min were performed with TR=4 s, TE=30 ms. Thirty-two slices at the same resolution as in the Gabor patch experiment were acquired, oriented perpendicular to the calcarine sulcus.

MEG/EEG—The MEG data were acquired with a Vectorview (Neuromag-Elekta Oy, Helsinki, Finland) MEG 306-sensor array arranged in 102 triplets of one magnetometer and two orthogonal planar gradiometers. For simultaneous EEG recording, a 70-electrode EEG cap was applied. To monitor eye-movements, two bipolar electrode pairs were employed for vertical and horizontal electro-oculogram (EOG) recordings. These were placed above and below the left eye for vertical EOG, and laterally to each eye for horizontal EOG. Four head position indicator (HPI) coils were attached onto the EEG cap. Next, the 3D locations of three cardinal landmarks (nasion, left and right periauriculars), EEG electrodes, HPI coils and additional points on the scalp were digitized using a Fastrak system (Polhemus, Colchester, VT) to allow subsequent registration of the MEG/EEG data to the structural MRI. The subject was then seated in a magnetically-shielded room (Cohen et al., 2002) with the upper jaw resting on a bite-bar that was pre-constructed for each individual using dental care materials (Marinkovic et al., 2004). Before recording, current was passed in the HPI coils in order to determine the position of the subject's head relative to the MEG sensor array during subsequent data analysis. After every 5 scans (4:16 min each), recording was stopped and an additional HPI reading was taken, including at the very end of the session, for a total of 5 HPI readings. The MEG/EEG data were acquired and saved continuously at a sampling rate of 600 Hz with a recording passband set to 0.1–200 Hz. For quality control purposes, the data were also averaged online.

Structural MRI—Data were collected with a 1.5 T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) and included 4 scans, each lasting approximately 8 min. Two standard structural magnetization-prepared rapid gradient echo (MPRAGE) scans (190 Hz/pixel, flip angle = 7 degrees, TR/TE/TI = 2.73 s/3.31 ms/1 s), and two multi-echo multi flip angle (5 and 30 degrees) fast low-angle shot (FLASH) scans (651 Hz/pixel, TR = 20 ms, TE = $(1.8 + 1.82 * n)$ ms, $n = 0-7$) were run. 128 contiguous 1.33 mm-thick sagittal slices were acquired at an in-plane resolution of 1×1 mm. The FLASH sequences were used for constructing the boundary element model surfaces for each subject because they provide different tissue contrast from the standard MPRAGEs (Fischl et al., 2004).

Data analysis

fMRI data were analyzed using the FS-FAST toolbox within FreeSurfer (<http://www.surfer.nmr.mgh.harvard.edu>). EPI images were motion corrected by aligning to the first EPI scan in each session (Cox and Jesmanowicz, 1999) using the AFNI motion correction tool (<http://afni.nimh.nih.gov/afni/>), and spatially smoothed using a Gaussian filter of 5 mm full width at half-maximum. After averaging, hemodynamic responses were fit using a gamma function with $\delta=2.25$ and $\tau=1.25$. The fMRI activity reported here is thus an integral over the entire response duration. The response to the blank condition was subtracted from each of the four Gabor patch conditions. The significance level of this difference ($-\log_{10}(\text{P value})$) was used in subsequent calculations, and is shown in Figs. 2–3 and in Sup. Fig. 1.

Polar angle and eccentricity maps were computed from the retinotopy scans by phase-mapping of the responses at the fundamental stimulus frequency, as described in (Serenó et al., 1995). Visual area borders were determined from the gradients in the polar angle and eccentricity maps using the visual field sign technique (Serenó et al., 1994), resulting in mirror-image (e.g. V1, V3) and non-mirror-image (e.g. V2, V4) visual field representations.

V1 activation—An anatomical label was created for each subject by manually tracing the V1 border obtained from the field sign map (see Fig. 1B), so that the vertices within this label all belong to V1. The V1 fMRI response to each Gabor patch stimulus was defined as the fMRI response within this label, as shown in Fig. 1D. Peak response location was calculated as the center-of-mass of the 2% highest-responding V1 vertices ($\sim 0.1\%$ of total hemispheric cortical surface per hemisphere). See Sup. Fig. 1.

MEG/EEG data were analyzed using the in-house MNE software (<http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php>). Data were low-pass filtered at 200 Hz. Signal-space projection with a three-dimensional noise subspace (Tesche et al., 1995), computed from an empty-room recording, was applied to the magnetometer data. Noisy MEG/EEG channels were identified by inspection of the raw data and online averages, and ignored in all subsequent processing. Using the 5 HPI readings, scans with head translation of less than 3 cm were determined, for a total of 15–20 4:16 min scans per subject. During offline averaging, trials were rejected for incorrect subject response, large EOG reading (150 μV) and large sensor reading (10 pT for magnetometers, 3 pT/cm for gradiometers). In each stimulus condition, the total number of trials averaged was 300 – 480. A noise covariance matrix was calculated from the individual epochs using 300-ms baseline periods prior to stimulus onset.

The MEG/EEG data were registered to the structural data using MRILab (Elekta-Neuromag Oy, Helsinki, Finland) with help of the fiducial landmark locations, the digitized EEG electrode locations, and additional scalp surface points. The locations of possible dipole sources were constrained to the gray/white matter boundary segmented from the structural MRI data (see below), and a forward solution for this source space was constructed using three-layer BEMs with the linear collocation approach (Hamalainen and Sarvas, 1989; Mosher et al., 1999). Conductivities used for the intracranial tissue (brain, CSF), skull and scalp were chosen as 0.3, 0.006 and 0.3 S/m, respectively. The forward solution matrix and the data were whitened using the noise covariance matrix (Lin et al., 2006a; Lutkenhoner, 1998), rendering the data unitless. The unitless data obtained in this way from MEG gradiometers, MEG magnetometers, and EEG electrodes can thus be combined into a single inverse solution without further normalization steps.

Anatomically-constrained dSPM inverse solution—The noise covariance matrix and the whitened forward solution were used to create a linear inverse operator as described in

(Dale et al., 2000), using the anatomical constraint only. The inverse operator was applied to the whitened data vector at each time-point. A loose orientation constraint (Lin et al., 2006a) of 0.6 was employed. An orientation constraint (Lin et al., 2006a; Liu et al., 1998) value of 0 allows only current components normal to the local cortical surface, i.e. enforces a strict orientation constraint, and a value of 1 corresponds to no orientation constraint. Orientation constraints of 0.2 and 0.4 were tested in addition to the 0.6 value used; by visual inspection these constraints provided less satisfactory results. The current estimate at each cortical location was normalized to the estimated baseline (pre-stimulus) variance. If a strict orientation constraint is employed, this results in a z -score. In the case of loose orientation constraint employed here, the variances of the three current components are summed, resulting in an F -like statistic (Dale et al., 2000). The output is given as the square-root of the F statistic, which is thus essentially a signal-to-noise ratio estimate, analogous to a z -score. dSPM is a variant of the L_2 MNE that alleviates the latter's strong superficial bias in source localization. In contrast to the other two methods (below), which estimate the strength of the currents, the dSPM provides an indication of locations where the estimates are most reliable based on their signal-to-noise ratio.

Some low-SNR measurements resulted in huge localization errors (see Fig. 4B). Thus, when comparing between MEG, EEG and MEG/EEG measurements, we used a threshold criterion to produce a more conservative comparison. The maximum over the entire cortex of each measurement's dSPM is plotted on the X axis in Fig. 4B for each modality selection. The p value of this peak dSPM was calculated from the F probability distribution function using the FPDF function in Matlab (MathWorks, Inc., Natick, MA) with degrees of freedom equal to $3 \times$ the number of time points used in calculating the noise covariance matrix (>400000). Three such p values were calculated for each measurement (for MEG, EEG, MEG/EEG) and averaged to give the average peak p value. Only measurements for which this value was lower than 0.01 were included in subsequent calculations.

Anatomically-constrained depth-weighted MNE inverse solution—To compensate for the inherent superficial bias of the MNE, depth-weighting has been suggested (Fuchs et al., 1999; Lin et al., 2006b). The results shown in Sup. Fig. 2A were obtained as in (Lin et al., 2006b) with depth-weighting parameter $\gamma = 0.8$, although values between 0.6 and 1.5 were also explored, producing similar results.

Equivalent current-dipole fitting—The same boundary-element model was used as in the other inverse calculations. An initial guess for the dipole location was obtained by scanning through a grid of dipoles within the brain volume, followed by a non-linear search for the optimal dipole location using the Nelder-Mead Simplex Algorithm (Nelder and Mead, 1965). The dipole amplitude parameters were determined by a linear fit as described in (Mosher et al., 1992).

V1 activation—The V1 MEG/EEG response was defined as activity at or slightly before the earliest peak in the temporal waveform, as shown in Fig. 1C. This latency was determined for each subject, ranging between 72–76 ms following stimulus onset. At this early latency the cortical response presumably arises primarily in V1, though we cannot rule out some contribution from other areas (e.g. V2). We did not spatially restrict the MEG/EEG inverse locations. To keep the cortical area included in the MEG/EEG peak calculation at $\sim 0.1\%$ of the total hemispheric surface area as in fMRI, the five highest-responding vertices (out of ~ 5000) were used in peak calculation. Peak location for dSPMs and for depth-weighted MNEs was calculated similarly to the fMRI data (See Sup. Fig. 1).

Localization error—Localization error was defined as the peak-to-peak distance to the fMRI V1 data, and was calculated for each modality selection – EEG alone, MEG alone, and

combined MEG+EEG – and each measurement (response to a single stimulus condition in a single subject, of which there were 24). The distances between the peak locations were computed in the original 3D volume (not on the inflated surface used for visualization purposes).

Structural MRI: The cortical surface, to which fMRI and MEG/EEG data were registered, as well as the skin, outer skull and inner skull surfaces, used for the MEG/EEG BEM forward modeling, were reconstructed from the MPRAGE and FLASH images with FreeSurfer (<http://www.surfer.nmr.mgh.harvard.edu>) (Dale et al., 1999; Fischl et al., 1999; Fischl et al., 2001). The cortical surface (gray/white matter boundary) comprised approximately 130000 vertices per hemisphere, spaced at ~1 mm. The MEG/EEG source space was constrained to this cortical surface, and was decimated at 5 mm spacing, resulting in ~5000 current locations per hemisphere.

Results

Comparison between fMRI and MEG/EEG

We presented small (full width at half-maximum of 1.2 or 1.7 degrees) high-contrast Gabor patches for 500 ms at variable inter-stimulus intervals while subjects, six in total, gazed at a central fixation cross (see Materials and methods and Fig. 1A). Borders of subjects' visual areas were mapped (Fig. 1B). Gabor patches were presented in two different sessions: an fMRI scan, and an MEG/EEG recording session (Fig. 1C). The BOLD fMRI response of subject 1 to each of the four Gabor patches is shown in Fig. 1D on the inflated cortical surface. A patch of activation representing the stimulus was evoked in each cortical visual area. Consistent with the known retinotopic organization (Serenio et al., 1995; Whitteridge and Daniel, 1961), the more central stimuli – 1 and 3 – evoked more posterior responses than the more peripheral stimuli – 2 and 4. Upper vs. lower visual field stimuli – 1 and 3 vs. 2 and 4 – activated ventral vs. dorsal occipital regions, respectively. Fig. 2A shows the fMRI responses of subject 2.

The dSPM inverse solutions of the MEG, EEG and combined MEG+EEG data of subject 2 at 74 ms after stimulus onset are shown in Fig. 2B. Visual inspection reveals that the best correspondence to fMRI (Fig. 2A) is obtained by the MEG+EEG dSPM. The MEG solution for stimulus 1 is mostly in the correct general vicinity but also assigns activation to the parieto-occipital sulcus and nearer to the occipital pole. The EEG dSPM incorrectly assigns the activity to parietal cortex, while the MEG+EEG dSPM shows the most compact response pattern around the location corresponding to the fMRI activation. For stimulus 2, BOLD activation is ventral to the calcarine sulcus, while MEG alone and EEG alone both incorrectly indicate primarily dorsal activation. Combining the two modalities results in the only dSPM indicating significant ventral activation, thereby giving the smallest localization error. For stimulus 3, while some portion of the response is ascribed by all three dSPMs to the location indicated by the BOLD activation, only for MEG+EEG is this the main activation. For stimulus 4, the response location indicated by MEG alone is too ventral and by EEG - too dorsal, whereas the location given by combined MEG+EEG is the most faithful to the BOLD response.

To facilitate comparison of each inverse solution to the fMRI V1 response, in Fig. 3A we present them on the same inflated surface, for all stimulus conditions. In the MEG+EEG panel the plus signs (indicating the highest-responding vertices) are visibly clustered around the dots of each condition more tightly than in the other panels; thus a better correspondence to the fMRI is obtained in this subject using the combined modalities, compared to either alone. Fig. 3B presents data from another subject, again showing the same combined MEG+EEG localization superiority.

We next quantified the localization error of MEG, EEG and MEG+EEG by determining the distance between the V1 fMRI response and the early dSPM. The peak of each response was calculated as its center-of-mass, with the weight at each vertex taken as its response significance (see Materials and methods and Sup. Fig. 1). The distance between the V1 fMRI peak and the early dSPM peak serves as an estimate of the localization error for each dSPM. Table 1 shows the peak-to-peak distances to fMRI obtained for each dSPM at each stimulus condition, for the subject shown in Fig. 3A. The smallest distances were achieved by the MEG+EEG dSPM estimate.

The distribution of localization errors of the early dSPMs over the six subjects and four stimulus conditions is shown in Fig. 4A for each modality selection (MEG, EEG and MEG+EEG). The MEG+EEG solution of 12 of the 24 measurements is at the lowest bin of 0–10 mm localization error, with rapidly decreasing numbers at larger error bins. MEG alone has a shallower peak at the lowest bin, with more measurements at higher localization errors, and for EEG alone the peak of the distribution is at the 10–20 mm error bin. Therefore, the MEG+EEG distribution is tightest around zero distance to fMRI.

Dependence of localization error on SNR

In simulation studies, localization accuracy depends strongly on SNR (Cuffin, 1986; Liu et al., 1998). Here, our use of real MEG/EEG/fMRI data makes it possible to gauge the effect of SNR on inverse solution localization errors relative to an external dataset, the fMRI results. Since the dSPM is essentially an SNR estimate (see Materials and methods), we used the maximal dSPM value obtained over the brain for each measurement as its SNR. Fig. 4B plots localization error as a function of this SNR estimate for the 24 measurements, for each of the 3 modality selections. The exponential-like decay of localization error with SNR indicates the crucial importance of high SNR measurements in localization of real MEG and EEG data. At $\text{SNR} \leq 4$, localization errors of 40 mm and more represent over 20% of our measurements, whereas at $\text{SNR} \geq 5$, all localization errors were less than 20 mm. In addition, it is clear from this figure that high-SNR measurements are obtained more readily by combining MEG and EEG, since the combined modality dominates the range $\text{SNR} \geq 10$ (7 measurements as opposed to 1 each for the single modalities).

Comparison between MEG, EEG and MEG+EEG

We next used the p value corresponding to the maximal dSPM value to set a 0.01 threshold level for inclusion in further analysis (see Materials and methods). Sixteen of the 24 measurements met this criterion, and for them we calculated the mean localization error and its standard error for each modality selection, shown in Fig. 4C left. We obtained an $8.3 (\pm 0.7)$ mm mean ($\pm$ SE) localization error in our MEG+EEG measurements, which was significantly smaller than both the mean MEG error (10.8 ± 0.8 mm; $p = 0.0146$) and the mean EEG error (16.6 ± 2.9 mm; $p = 0.0230$) (two-tailed paired t -tests). The difference between MEG and EEG did not reach statistical significance in our sample ($p = 0.0672$). We conclude that the combined MEG+EEG solution gives superior localization to either modality alone.

We verified that the superior localization performance of combined MEG+EEG (relative to either modality alone) is not specific only to the dSPM inverse calculation, by testing two additional inverse approaches: anatomically-constrained depth-weighted MNE, and equivalent current dipole fitting. Fig. 4C (middle, right) shows the localization errors obtained by these inverse methods for the 16 measurements that met the above 0.01 criterion level. Sup. Fig. 2 details the distribution of localization errors obtained for each method. While overall the errors were larger than for the dSPM inverses, the same trend of an advantage for the combination over the single modalities exists here as well. A 2-way ANOVA testing the effect of modality selection (MEG, EEG, MEG+EEG) and inverse method (dSPM, dipole fitting, depth-weighted

MNE) was performed on the 9 possible combinations and the 16 thresholded measurements. This analysis revealed a main effect for inverse method ($p=0.0005$), confirming that of the methods used here dSPM gave the lowest localization errors. A main effect for modality selection with $p<0.0001$ confirms the advantage of combined MEG+EEG over MEG and EEG, for all inverse methods.

To test whether the improved localization obtained by combining MEG and EEG merely reflects the larger total number of sensors, 70 MEG channels were removed by randomly choosing 70 of the 102 MEG sensor triplets and randomly omitting one channel from each. The performance of all the inverse solutions, MEG, EEG, the full MEG+EEG-376 and the new MEG+EEG-306, is shown in Fig. 4D, for all 24 measurements. The new combined solution has a number of channels equal to MEG alone, yet it performs very similarly to the full MEG+EEG-376 solution. This is also evident in the distribution of errors shown in Fig. 4A. These results suggest that the improved localization is indeed due to the complementary properties of MEG and EEG, rather than just to the larger total number of data channels.

Discussion

Summary and relationship to the existing literature

Our results show that in visual cortex, localization results obtained by combining MEG and EEG are superior to those obtained by either modality alone. This result holds for the three different source localization approaches we tested: dSPM, dipole modeling and depth-weighted MNE. To the best of our knowledge, this is the first work to study localization of MEG/EEG data recorded during sensory stimulation using fMRI as an independent, external estimate of activity location. A combined MEG+EEG inverse solution with the same total number of channels as our MEG apparatus, obtained by random removal of 70 MEG channels, resulted in localization errors similar to those of the full MEG+EEG solution. This shows that increasing the total number of channels is not the only reason the MEG+EEG solution is better than the MEG-alone solution; it suggests that the improved localization is also due to the different sensitivity patterns of the two imaging modalities. Finally, the dSPM inverse solution gave localization results for our data that were superior to dipole fitting and depth-weighted MNE.

While fMRI is not subject to the same localization problems inherent in MEG/EEG, there are still questions regarding the coupling of the hemodynamic BOLD signal and electrical activity. If the BOLD signal does not colocalize with electrical activity, using it as an estimate for true activity location may lead to distorted error estimates. In general, the controversy over the coupling between hemodynamic and electrical activity revolves around the issue of signal amplitude of the different hemodynamic and electrical components and their spread (Devor et al., 2003; Logothetis et al., 2001; Niessing et al., 2005; Rees et al., 2000; Vanzetta and Grinvald, 1999), whereas there seems to be general agreement that the location of the peak response is consistent between the two signal types (Devor et al., 2005; Grinvald et al., 1986; Puce et al., 1997; Shmuel et al., 2006; Shoham et al., 1999; Thompson et al., 2003). For example, orientation tuning curve peaks derived from spiking and hemodynamic responses in cat visual cortex differ by less than 10 degrees, which corresponds to a cortical distance of less than 1 mm (Grinvald et al., 1986; Thompson et al., 2003). In addition, stimulation of a rat whisker evokes larger spiking and hemodynamic responses in the corresponding cortical barrel than in a neighboring barrel less than 1 mm away (Devor et al., 2005). Furthermore, recent studies suggest that the BOLD signal from veins draining electrically active cortex decreases in amplitude when the vein's distance from the activated site is over a few millimeters (Kim et al., 2004; Turner, 2002). Optical imaging using intrinsic signals measured at 570 nm, i.e. emphasizing cerebral blood volume (CBV; one of the major hemodynamic components in BOLD fMRI), has consistently shown that differential orientation maps in cat and monkey visual cortex reveal the same cortical orientation and ocular dominance columns as differential maps from signals

measured at 605 nm (the deoxygenation, 'initial dip', component) (Frostig et al., 1990; Vanzetta et al., 2004; Vanzetta and Grinvald, 2001). Even single-condition maps, i.e. maps obtained by contrasting a single orientation to a blank rather than to an orthogonal orientation, have recently been demonstrated at 570 nm, although they are much noisier than those at 605 nm (Vanzetta et al., 2004). These results indicate that, even though CBV has a much less selective spread than the initial dip, the peaks of the two components colocalize. Since the initial dip has itself been shown to colocalize with electrical activity (Grinvald et al., 1986; Thompson et al., 2003), this further suggests colocalization of BOLD fMRI with electrical activity. In summary, BOLD fMRI is currently one of the best non-invasive, widely-available approaches for obtaining estimates of the location of neural activity.

Two aspects of the current study further strengthen the assumption underlying our use of fMRI as a basis for comparison. First, human retinotopic organization as revealed by BOLD fMRI in low-level visual areas is similar to monkey retinotopic organization as revealed by both BOLD fMRI and electrophysiology, which are highly similar among themselves (Brewer et al., 2002; Fize et al., 2003; Sereno et al., 1995). Thus, the retinotopic stimuli we used are likely to evoke colocalized electrical and hemodynamic responses in low-level visual areas. Second, we were careful to compare localization of response peaks only, rather than the spatial extent of the responses, to ensure that the hemodynamic BOLD signals are maximally comparable to the electrical activity measured by MEG/EEG (see above regarding the better colocalization of peak responses than spatial extent). While there are inevitably residual errors in the fMRI localization (such as due to slight misregistration to the structural data, and finite signal-to-noise ratio), and there may even be gross errors on the order of 10 mm (Disbrow et al., 2000), the above considerations mean that these residual errors were not consistently biased. Thus, for local stimuli such as those we used here, within retinotopic visual areas such as V1, the peak fMRI response may serve as an unbiased estimate of the true activity location. At this point it is difficult to estimate the localization error in the fMRI data itself, but a somatosensory study in macaque cortex comparing fMRI and electrophysiological mapping found a mean distance between the two datasets' centroids of 5 and 5.6 mm for the face and hand area, respectively (Disbrow et al., 2000). Although a better correspondence might have been achieved in that study if a 3 T rather than 1.5 T magnet was used and if the drug doses were more similar in the two sessions, these results suggest that the mean MEG+EEG localization error obtained here (8.3 mm) are not far from the accuracy level of fMRI results.

In this study we determined the first-order difference between the fMRI and MEG/EEG activity distributions, calculated as the peak-to-peak distance between them. We did not look at higher-order differences arising from the distributions' spread, for two reasons: 1) we do not have reliable knowledge about the relationship between the spread of neural activity and the spread of the BOLD signal (see above), and 2) the MEG/EEG inverse solutions are by nature not very informative regarding the actual extent of the underlying sources. The two MNE variants used (dSPM and depth-weighted MNE) both have the property of producing more distributed cortical activation patterns than the underlying sources, so as to minimize the L_2 norm of the solution. On the other hand, dipole fits concentrate all the activity to a single point, by definition. We therefore concentrated on a first-order analysis, although further higher-order analyses may reveal additional interesting effects.

Limitations of the current study

Several factors could potentially further improve the localization results obtained here. First, more accurate electrical conductivity values determined for each subject individually could be employed (Fuchs et al., 1998; Gonçalves et al., 2003; Huizenga et al., 2001) instead of the values available in the literature that we have used for each of the three homogenous boundary-element model (BEM) layers (Geddes and Baker, 1967). However, the conductivity measurements

require either acquiring electrical impedance tomography data or, e.g., somatosensory evoked responses, which is not always feasible. A second potential improvement to our results could be obtained by accounting for conductivity inhomogeneities and anisotropies within the layers of the head model (Peters and De Munck, 1991; Rudy et al., 1979), using e.g. finite-element methods (Haueisen et al., 1997). Each subject's conductivity tensor could be calculated from an additional, diffusion tensor MRI scan (Tuch et al., 2001). Furthermore, distinguishing between more tissue types than we have done here, e.g. between white matter, gray matter and CSF, and between layers of the skull, will also improve the inverse solution (Ramon et al., 2006; Wolters et al., 2006). Today these methods are not yet available for routine multi-subject studies (e.g. Ramon et al. (2006) and Wolters et al. (2006) studied a single subject each). However, when implemented, these enhancements will improve localization accuracy. Most likely, localization will improve mainly for EEG and for the combination of MEG and EEG. Thus, the current results provide a lower bound for the superiority of combined MEG and EEG over MEG alone.

The spatial sampling of the fMRI data was at 3 mm (slice thickness) or 3.125 mm (in-plane) resolution, which is considered standard, rather than high resolution in current studies. Although smaller than any of the MEG/EEG localization errors observed in this study, as a basis for comparison it would have been preferable to have higher-resolution spatial sampling (e.g. 1 mm). While the Gabor patch stimuli were identical in the two imaging sessions, the gray background extended 11.5 degrees in the fMRI experiment and 23 degrees in the MEG/EEG recording, which seems like a large difference. However, from a physiological standpoint this is not likely to be a source of significant difference between the two sessions. First, for neurons with a peripheral receptive field that does not overlap with the Gabor patch, the onset of the stimulus will not entail any change within their receptive field. This is true both for the 11.5 and the 23-degree backgrounds, e.g. in one case a neuron may 'see' constant black in its receptive field and in the other – constant gray. Thus no difference between prestimulus and poststimulus times is expected for these neurons. Second, the magnitude of response to the onset of the high-contrast Gabor patch for neurons whose receptive field overlaps with it is much larger than any contextual modulation that may arise from an area in the receptive field that does not change. Therefore neural responses in the two setups are not significantly different.

Outlook

An important goal for future work is to generalize the error estimation approach employed here to later latencies, when multiple cortical areas are simultaneously active. This is more challenging because currently we do not know which visual areas are activated at any given latency of the response, other than our V1-only assumption for response onset. This information is needed to decide which fMRI response patches to include; thus we cannot establish fMRI "ground truth" for late time-points. The good experimental agreement shown in this work between MEG/EEG and fMRI increases the likelihood that adding fMRI constraints (Dale et al., 2000) will be beneficial in revealing the dynamic pattern of activations evoked in visual cortex and recorded with MEG/EEG. The current data indicate that combining MEG and EEG from actual sensory recordings results in superior source localization accuracy over either modality alone, implying that it will be useful to combine the two modalities in future spatiotemporal imaging studies to increase the precision with which activation temporal waveforms are reported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. V1 responses to focal visual stimuli: fMRI, MEG, EEG

A. Stimulation paradigm. A Gabor patch was flashed for 500 ms in one of 4 locations (upper-left 5-degree eccentricity stimulus shown here), immediately followed by 33 ms of the fixation cross task. The subject indicated by a button press whether the upper or lower arm of the cross disappeared. The interstimulus interval varied between 1–6.5 seconds, during which only the fixation cross was present. The isoluminant gray background extended farther into the periphery than shown here.

B. V1 labeling using retinotopic mapping in subject 1. Field sign is either mirror image (yellow) or non-mirror image (blue). The mirror image representation abutting the calcarine sulcus is V1, delineated in black. Note that the anterior segment of the border is due to the peripheral limit of the visual stimulation. Gray dashed box indicates zoom-in region for D. White arrows indicate 3D directions: a – anterior, p – posterior, d – dorsal, v – ventral, m – medial, l – lateral. cs: fundus of the calcarine sulcus, occ: occipital pole. Dark gray: sulci; light gray: gyri.

C. Evoked MEG/EEG responses in occipital sensors, for the same subject as in B. All the analysis in this study was performed at the early peak, indicated by the dashed line (76 ms in this subject). Two upper panels: example traces from the two MEG planar gradiometer sets, third panel: MEG magnetometer, fourth panel: EEG electrode. Solid line: stimulus onset. Horizontal scale bar: 100 ms; vertical scale bars (from top): 20 fT/cm; 20 fT, 2 microvolt.

D. fMRI responses to the 4 stimulus conditions, for the same subject as in B and C. A focal response patch is evoked in V1 (and in each adjacent retinotopic visual area). The response pattern follows predictions from retinotopic mapping. The black line indicates the V1 border, as in B. Schematic representations of the stimuli, fixation cross and Gabor patch (not drawn to scale), are shown in the top left corner of each response panel.

Figure 2. Comparison of spatial response patterns from fMRI and MEG/EEG in subject 2
 Each column shows responses to a stimulus condition (schematically presented at the top). The medial posterior view shown here includes the full response pattern. The inflated cortical surface is used for visualization. Threshold for presentation: 1% highest-responding vertices.
 A. fMRI. Dashed line: fundus of the calcarine sulcus.
 B. dSPM inverse solutions for MEG (top), EEG (middle), and MEG+EEG (bottom) data 74 ms after stimulus onset.

Figure 3. MEG+EEG gives best correspondence to fMRI: single subjects

MEG (left), EEG (middle) and MEG+EEG (right) dSPMs and fMRI responses of all stimuli shown on the same inflated cortical surface for enhanced visual comparison. Dots and plus signs denote fMRI responses and dSPMs, respectively, color-coded for different stimulus conditions (similarly to Fig. 1). Each dot/plus sign corresponds to an activated vertex. Note that this is simply an alternative presentation format to the usual format, shown e.g. in Fig. 2, where activation level is interpolated between the vertices. The data are identical, but this format allows multiple activation patterns to be presented on the same surface. For thresholding details, see Materials and methods.

A. Subject 2 (same subject as Fig. 2). Note that the EEG response to stimulus condition 1 is completely outside the zoom region (blue plus signs missing from middle panel, see Fig. 2B middle row left panel). The best clustering of dSPM vertices next to the appropriate fMRI vertices occurs in the MEG+EEG response (right panel).

B. Subject 3.

Figure 4. Quantitative comparison of localization errors between MEG (purple), EEG (orange) and MEG+EEG (cyan), calculated for six subjects

A. Distribution of dSPM localization errors, showing the number of measurements (from a total of 24) exhibiting a peak-to-peak distance to fMRI within 10 mm bins, the centers of which are indicated on the X axis. Of the three, the distribution of MEG+EEG is tightest around the lowest error bin. The 306-channel MEG+EEG dSPM (gray; see text) performs similarly to the full 376-channel MEG+EEG dSPM.

B. dSPM localization error as a function of SNR, estimated as the maximal dSPM value over the whole brain. Black line: $y = 530e^{-0.9x} + 8.6$. Symbols as in A.

C. Mean localization errors over the 16 (of 24) measurements for which $p < 0.01$ (where p is the average peak P value; see text) for MEG, EEG and MEG+EEG, for three inverse calculations: dSPM, dipole fitting and depth-weighted MNE (see text). Within each inverse calculation, asterisks indicate significant difference ($p < 0.05$). Bars: standard errors.

D. dSPM localization errors for all 24 individual measurements, showing that the 306-channel MEG+EEG solution performs very similarly to the full 376-channel MEG+EEG solution. Symbols as in A.

Table 1

Localization errors in mm for all stimulus conditions (dSPMs), for the subject shown in Figs. 2, 3A and 6.

	MEG	EEG	MEG+EEG
1	13.2885	53.3229	5.1475
2	9.6815	12.0999	5.7134
3	12.767	15.3172	8.158
4	13.7057	12.8559	5.7228