Activation of Multiple Cortical Areas in Response to Somatosensory Stimulation: Combined Magnetoencephalographic and Functional Magnetic Resonance Imaging

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Abstract: We combined information from functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to assess which cortical areas and in which temporal order show macroscopic activation after right median nerve stimulation. Five healthy subjects were studied with the two imaging modalities, which both revealed significant activation in the contra- and ipsilateral primary somatosensory cortex (SI), the contra- and ipsilateral opercular areas, the walls of the contralateral postcentral sulcus (PoCS), and the contralateral supplementary motor area (SMA). In fMRI, two separate foci of activation in the opercular cortex were discerned, one posteriorly in the parietal operculum (PO), and one anteriorly near the insula or frontal operculum (anterior operculum, AO). The activation sites from fMRI were used to constrain the solution of the inverse problem of MEG, which allowed us to construct a model of the temporal sequence of activation of the different sites. According to this model, the mean onset latency for significant activation at the contralateral SI was 20 msec (range, 17–22 msec), followed by activation of PoCS at 23 msec (range, 21–25 msec). The contralateral PO was activated at 26 msec (range, 19–32 msec) and AO at 33 msec (range, 22–51 msec). The contralateral SMA became active at 36 msec (range, 24–48 msec). The ipsilateral SI, PO, and AO became activated at 54–67 msec. We conclude that fMRI provides a useful means to constrain the inverse problem of MEG, allowing the construction of spatiotemporal models of cortical activation, which may have significant implications for the understanding of cortical network functioning. *Hum. Brain Mapping* 8:13–27, 1999. © 1999 Wiley-Liss, Inc.

Key words: inverse problem; somatosensory cortex; posterior parietal cortex; supplementary motor area; insula; magnetoencephalography; functional magnetic resonance imaging

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INTRODUCTION

Electrical median nerve stimulation is widely used in clinical neurophysiology for routine diagnostic purposes, as well as in research work to explore the human somatosensory system. Despite this, there are still considerable uncertainties as to which cortical areas are activated in a macroscopically detectable manner by this type of stimulation. In particular, the

timing of activation at different cortical sites is incompletely known.

Magnetoencephalography (MEG) has proven to be superior to electroencephalography (EEG) in locating neuronal events underlying evoked response deflections. Source localization requires solving the inverse problem of electromagnetism, which involves determining the locations, orientations, and strengths of the primary currents from measured electromagnetic fields. The superiority of MEG to EEG is largely based on MEG being practically unaffected by the detailed structure and conductivity of the skull and scalp. In addition, MEG is selectively sensitive to tangential source currents, which makes the inverse solutions more stable than in EEG. The higher spatial frequency content in MEG often enables one to detect source locations by merely observing the field patterns. Although the inverse problem does not have a unique solution [Helmholtz, 1853], in practice the measured field patterns are frequently highly dipolar, suggesting that a single equivalent current dipole (ECD) in that area can be used to model the measured field. ECD modelling has made it possible to disentangle the activities of the primary (SI) and opercular somatosensory cortices from each other [Hari et al., 1984, 1993; see also Okada et al., 1984], the latter containing the second somatosensory cortex (SII). The reliability of localization of short-latency activity at the contralateral SI has been verified by superimposition of the calculated source coordinates on individual magnetic resonance images (MRIs) [e.g., Yang et al., 1993]. Recent studies have suggested that somatosensory evoked magnetic fields (SEFs) also get significant contributions from the contralateral parietal cortex posterior to area 3b [Forss et al., 1994], the ipsilateral SI [Korvenoja et al., 1995], and the wall of the interhemispheric fissure [Forss et al., 1996]. Studies using realistic head models and the signal-space-projection method

[Uusitalo and Ilmoniemi, 1997] have suggested that even SEFs arising at the cerebellum can be identified [Teschke and Karhu, 1997]. However, localization based on MEG only can be problematic, especially at long latencies, when several cortical sites are simultaneously active. The superposition of the magnetic fields from multiple generators may then lead to erroneous localizations. Another problem is that weak sources may be masked by simultaneous strong activity, such as that of SI. In order to circumvent this type of concern, independent information about the plausible source areas is needed from other imaging modalities.

Positron emission tomography (PET) and functional MRI (fMRI) [e.g., Belliveau et al., 1991] provide tomographic images of local blood flow changes secondary to neuronal activation. The localization of activated areas is generally less ambiguous than with MEG. However, low signal-to-noise ratio often limits the sensitivity of these methods. Spatial specificity is limited mainly by movement, nonspecificity to capillary hemodynamics, and image distortions. PET has revealed activation of the contralateral SI, SII bilaterally, and the contralateral supplementary motor area (SMA) after vibrotactile somatosensory stimulation of median nerve territory [Fox et al., 1987; Burton et al., 1993]. Burton et al. [1993] could separate two distinct foci of activation at the opercular region: one anteriorly in the insula, and another posteriorly in the parietal operculum. To our knowledge, activation of the ipsilateral SI or the posterior parts of the contralateral parietal cortex has not been reported in PET studies. Somatosensory studies with fMRI have so far concentrated on delineating the activation of the contralateral SI [e.g., Puce et al., 1995; Sakai et al., 1995; Lin et al., 1996], but activation of the ipsilateral posterior part of SI and the contralateral opercular cortex near SII has been observed as well [Lin et al., 1996]. However, only minimal or no activation of the SMA has been reported to date [Lin et al., 1996].

The temporal resolution of PET and fMRI, being ultimately restricted by the response times of the underlying hemodynamic phenomena [Grinvald et al., 1986; Menon et al., 1995; Frostig et al., 1990], is poor. Indeed, optical imaging of the regional blood flow changes in response to sensory stimulation indicates that the hemodynamic response follows the onset of electrical activity by a delay of several hundred milliseconds [Frostig et al., 1990]. This clearly limits the ability of blood flow-dependent techniques to reveal the temporal sequence of activation of different brain areas in a given experimental situation.

Abbreviations

AO	anterior operculum
EEG	electroencephalography
ECD	equivalent current dipole
fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
PET	positron emission tomography
PoCS	postcentral sulcus
PO	posterior operculum
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
SEF	somatosensory evoked field
SEP	somatosensory evoked potential
SMA	supplementary motor area

In order to better characterize the activation time course, it would be desirable to combine electrophysiological and hemodynamic information in individual subjects. Localization of the hemodynamic responses could then give independent confirmation to electrophysiological source localization, and could be used to constrain the inverse problem solutions of MEG or EEG [Dale and Sereno, 1993; Hämäläinen et al., 1993; George et al., 1995; Ilmoniemi, 1995; Kwong, 1995; Simpson et al., 1995; Liu et al., 1998]. Recently, the location of the hand area of the primary motor cortex has been determined jointly with MEG and fMRI [Beisteiner et al., 1995; Sanders et al., 1996; Stippich et al., 1998]. These studies gave a mean difference in location of less than 10–16 mm between the two techniques.

We assessed with MEG and fMRI the activation of neocortical areas after electrical stimulation of the right median nerve in the same subjects. The objectives were (1) to compare the localizations obtained with MEG and fMRI separately, and (2) to study the time-course of activation at different cortical sites. To achieve our second objective, we used individual fMRI information as a spatial constraint in the solution of the MEG inverse problem. We constructed a model consisting of multiple current dipoles, whose locations were fixed by information from fMRI, but whose orientations and strengths were allowed to vary over time in order to find out the combination that would best explain the complete set of the recorded MEG signals.

MATERIALS AND METHODS

Subjects and experimental setup

In 5 right-handed male subjects (ages 22–38), the right median nerve was stimulated at the wrist with 0.2-msec constant-voltage pulses during both MEG and fMRI experiments. Stimulus intensity was adjusted to be above motor threshold, but clearly below noxious levels. In MEG, the long interstimulus interval (ISI) of 5 sec was chosen, because late components of somatosensory evoked fields are suppressed if the stimulation rate is high [Wikström et al., 1996]. Thus, e.g., as the opercular sources produce visually detectable dipolar field patterns only at latencies >80 msec, these sources could be missed with a short ISI (<1 sec). In fMRI, the stimuli were presented at 4 Hz, because it has been shown that regional cerebral blood flow at SI increases linearly with stimulus frequency up to 4 Hz, then reaching a plateau [Ibañez et al., 1995].

In MEG, the subject was seated in a magnetically shielded room and watched a self-chosen video film.

In fMRI, the subject was instructed to close his eyes and ignore the stimuli. The experimental protocol was approved by the Ethics Committee of the Department of Radiology at Helsinki University Central Hospital.

MEG recordings

SEFs were recorded with the 122-channel helmet-shaped magnetometer (Neuromag, Ltd., Helsinki, Finland) [Ahonen et al., 1993] of the BioMag Laboratory at Helsinki University Central Hospital. Signals were band-pass-filtered between 0.03–310 Hz and sampled at 942 Hz. The sweep duration was 550 msec, including a 150-msec prestimulus baseline. Epochs containing higher MEG amplitudes than 3,000 fT/cm or electric ocular or muscle artifacts exceeding 150 μ V were rejected from the averages. About 200 responses were collected for each averaged trace. The recordings were performed twice to ensure reproducibility of the responses (Fig. 1). The preauricular points and the nasion, which defined the coordinate system, as well as three head position indicator coils attached to the subject's head, were located with a three-dimensional digitizer (Polhemus, Inc., Colchester, VT). The head position within the magnetometer dewar was determined by letting current pass through the indicator coils and by recording the induced magnetic signals.

MRI studies

Magnetic resonance imaging was performed with a 1.5-T Siemens Magnetom Vision system (Siemens AG, Erlangen, Germany) using a standard head coil. To minimize head motion, a dental cast bitten by the subject was attached to the head coil. Head-supporting pillows were used. The magnetic field was globally shimmed prior to imaging. Five localizer images (one transaxial, one coronal, and three sagittal) were acquired for slice positioning. A set of 1-mm-thick sagittal T1-weighted images covering the whole head (field of view, 256 mm; matrix, 256×256) were collected with a 3D-MPRAGE (magnetization prepared rapid gradient echo) sequence (repetition time, TR 9.7 msec; echo time, TE 4 msec; inversion time, TI 20 msec; flip angle 10°). These images were used as the anatomical structure on which the statistical parameter maps and MEG responses were superimposed. Functional imaging was done with a gradient-echo echo-planar sequence (TE 76 msec, except for one subject at 66 msec; TR 3.5 sec; flip angle 90°). Sixteen transaxial 5-mm-thick contiguous slices were obtained to cover the brain from the top to below the level of opercular areas (field of view 256 mm, matrix 128×128). Two consecu-

Figure 1.

MEG responses from subject TM. Enlarged are shown waveforms over the contralateral SI and opercular cortex. Responses from two separate sessions are superimposed (continuous lines) with waveforms predicted by the multidipole model (dashed lines). Vertical line indicates time of stimulus presentation. Note good agreement with measured and predicted waveforms.

tive sets of 120 images were acquired with the baseline and stimulation condition alternating in blocks of 10 images.

Combining fMRI and MEG data

In MEG, the equivalent current dipole (ECD) [see Hämäläinen et al., 1993] was used as the model of local neuronal activity. Dipolar field patterns were searched, and a local subset of 16–58 channels covering both extrema of the field produced by a given single source area was used for dipole fitting. A least-squares dipole search was performed over the whole period of time, during which a given SEF deflection showed a dipolar field pattern. For the contralateral SI, the best-fitting ECDs were found for the short-latency N20m and P35m deflections. For other areas, the best-fitting ECD was chosen regardless of latency, provided that a dipolar field pattern remained stable for a minimum of 10 msec over the source area. A spherical head model was determined individually for each subject from anatomical MRIs best fitting the curvature of the inner surface of the skull over the parietal cortex. Dipoles with a goodness-of-fit value [Hämäläinen et al., 1993]

exceeding 80% were accepted as valid models. Responses peaking at latencies longer than 60 msec were digitally low-pass-filtered at 90 Hz before ECD fitting.

In fMRI, head motion was monitored off-line by viewing the signal-intensity vs. time at the edges of the brain. Some subjects were imaged in several sessions until no motion artifact appeared. Kolmogorov-Smirnov statistical parameter maps were generated on a pixel-by-pixel basis for each slice. The activation threshold of $P < 10^{-6}$ for single voxels was chosen, corresponding to $P < 0.01$ after a Bonferroni correction for 10,000 pixels. The signal-intensity vs. time curves of the significantly activated voxels were inspected for correlation with the stimulation. Mean relative signal changes (%) to stimulation were calculated for each activated area.

Software was developed for the registration of functional images with the anatomical image set, using slice-positioning information. The alignment of MEG coordinates with the anatomical image sets was achieved by locating in the MRIs the fiducial points of the MEG coordinates (the preauricular points and the nasion).

Coordinates of the ECDs and centroids of activated areas in fMRI were transformed to the Talairach coordinate system [Talairach and Tournoux, 1988] with MEDx software (Sensor Systems, Inc., Sterling, VA), and with software written by the authors.

To compare the source locations from MEG and fMRI, the statistical parameter maps were interpolated to volumes consisting of 1-mm³ isotropic voxels. Activation areas were segmented using the *k*-means clustering method [Bow, 1984]. In this procedure, the sum of the squared distances of the activated voxels to the cluster center is minimized, and the between-clusters variance is maximized. The initial centers for the algorithm were selected manually within the activated areas determined by viewing the statistical parameter map overlaid with the three-dimensional (3D) anatomical image set. The distances from ECD locations, as found from MEG, to the nearest activated voxel and to the cluster centroid were calculated.

In order to assess the temporal activation pattern of each source area, a source model consisting of eight dipoles was constructed for the MEG responses. The position of each dipole was fixed to the centroid of the activated area as indicated by fMRI data. In those 6 cases of the total of 40 source areas in the 5 subjects (see Results), where no fMRI activation could be observed for an activation site indicated by MEG, the dipole location was set according to dipole-fitting using MEG alone. The strength and direction of each dipole were allowed to vary so as to produce a least-squares fit to the measured magnetic field pattern at each point of time during the entire sweep. The activation of a given source area was defined as significant if the corresponding ECD strength exceeded the mean strength during prestimulus baseline (normally distributed) by at least 3 standard deviations for at least 5 msec, and if it was apparent from the data that the source amplitude was not due to interference from other sources. Using this criterion, not a single point in the prestimulus baseline reached a significant level for any ECD in any of the subjects.

RESULTS

MEG source localization

Results from the MEG single-dipole fittings alone indicated source areas in both contra- and ipsilateral SI and in opercular regions in all subjects. The ECDs corresponding to the peaks of the short-latency N20m and P35m deflections were contralateral and coincided in the structural MRIs with the Ω -shaped curve of the

central sulcus, which is usually seen in the axial slices and corresponds to the SI hand area [Wood et al., 1988; Yousry et al., 1997]. Over the ipsilateral SI, dipolar field patterns could be observed and thus ECD fittings were performed at latencies between 90–300 msec in different subjects [see also Korvenoja et al., 1995]. These ECDs fell similarly near the Ω -curve. At lateral locations over the opercular cortex, visually detectable dipolar field patterns occurred at 70–120 msec. The corresponding ECD locations were, however, unstable in the anteroposterior direction, shifting at different latencies between a posterior locus in the parietal operculum and a more frontal locus near the insula or frontal operculum. There was no consistent pattern in the temporal behavior of these shifts.

Dipolar patterns about 10 mm posterior and medial to contralateral SI (see Table I for coordinates) could be identified in 3 subjects at latencies of 85–180 msec. In the MRIs these sources were close to the postcentral sulcus (PoCS). Dipolar fields with polarity reversal near the midline were also seen in 3 of the subjects, at latencies of 170–245 msec. The ECDs fitted to these field patterns were anterior to the SI sources, coincident with the location of SMA. These ECDs were in the sagittal sulcus in one subject, and in the contralateral wall of the sulcus in the other 2 subjects.

fMRI results

In fMRI, significant activation of the contralateral SI (mean relative signal increase, 10%; Fig. 2) could be seen in all subjects. In the axial images, the site of activation coincided with the Ω -shaped curve of the central sulcus, where the activation could be seen as a continuous strip covering the whole lateral portion of the Ω -curve, or as 2–3 separate foci (Fig. 3). In 3 subjects, one of the foci extended to the precentral gyrus. The activation coincided with the sulcal wall in all subjects, but in 3 of them, some spread into the sulcus was seen.

Activation near the contralateral PoCS (mean relative signal increase, 13%), SMA (mean relative signal increase, 9%), and ipsilateral SI (mean relative signal change, 11%) was detected in 4 subjects (see Fig. 3). The PoCS activation was seen as separate clusters from those at SI. At the ipsilateral SI, the significant voxels coincided with the posterior wall of the central sulcus or with the postcentral gyrus. At SMA, the activation was on the contralateral wall of the sagittal sulcus in 3 subjects and on the sulcus in one.

Significant activation near the lateral sulcus was discerned in all subjects contralaterally and in 3 subjects ipsilaterally. In this area, the activated voxels were

TABLE I. Mean coordinates in the head frame defined by the preauricular points and nasion (in mm; standard deviations in parentheses) for the different sites of activation as found by MEG and fMRI independently*

Activated area	MEG			fMRI			Mean differences	
	x	y	z	x	y	z	Nearest voxel	Centroid
SII contralateral N20m	-39.6 (4.2)	9.8 (3.4)	91.9 (13.1)	-43.4 (8.4)	5.6 (12.1)	98.0 (13.2)	6 (1-10)	16 (7-25)
SI contralateral P30m	-35.4 (3.8)	9.7 (2.5)	95.5 (12.1)	-43.4 (8.4)	5.6 (12.1)	98.0 (13.2)	6 (1-10)	15 (9-20)
PoCS	-39.3 (4.9)	-3.6 (6.5)	100.4 (9.3)	-32.1 (4.0)	-4.2 (11.3)	110.0 (13.8)	8 (2-11)	19 (18-20)
SII contralateral	-48.6 (4.2)	17.1 (11.7)	57.3 (13.2)	-49.2 (6.7)	5.2 (6.6)	66.0 (12.0)	4 (2-8)	7 (6-31)
Insula contralateral	-51.2 (5.0)	37.1 (0.7)	53.3 (13.1)	-47.5 (6.2)	30.9 (11.6)	48.2 (17.2)	13 (9-15)	24 (12-42)
SII ipsilateral	43.1 (9.1)	15.7 (6.5)	53.3 (16.8)	41.3 (9.2)	2.8 (12.8)	59.4 (15.6)	9 (4-15)	22 (9-36)
Insula ipsilateral	41.4 (6.3)	28.8 (12.1)	45.4 (15.0)	48.4 (8.4)	24.4 (5.3)	54.6 (16.5)	17 (4-19)	30 (9-51)
SI ipsilateral	34.3 (13.1)	15.6 (8.8)	93.1 (17.3)	40.0 (16.2)	1.7 (22.9)	103.8 (8.6)	18 (3-25)	32 (18-41)
SMA	-6.3 (11.3)	23.3 (12.4)	92.3 (17.1)	-4.9 (7.6)	28.9 (13.4)	111.1 (12.2)	11 (4-16)	25 (19-30)

* For contralateral SI, the coordinates of both N20m and P35m are shown; fMRI localizations are compared with these separately. At right are shown the mean differences (in mm) between the ECDs and activated voxels in fMRI. Corresponding ranges are given in parentheses.

widely distributed in the frontoparietal operculum and insular region, being separable into two focal accentuations, one in the parietal operculum, in the vicinity of SII, and the other more anteriorly in the insular region, extending to the frontal operculum (Fig. 4). These locations will be designated as the posterior opercular (PO) and anterior opercular (AO) areas. Mean signal increases for the contralateral PO and AO were 8%, and the mean signal changes for the ipsilateral PO and AO were 7% and 11%, respectively. In 2 subjects, the signal change at all ipsilateral locations was significantly decreased relative to the base-

line rather than increased; in the mean signal changes given above, the absolute values were used.

Comparison of MEG and fMRI localizations

Figure 5 and Table I summarize the activated areas detected with either method alone in each subject. MEG alone could not detect the PoCS source in 2 subjects and the SMA source in one subject, in whom fMRI activation was observed at these areas. On the other hand, there was no discernible fMRI activation of the contralateral PoCS and ipsilateral SI in one subject

Figure 2.

Averages of time courses of fMRI signals at the centroid of each activated area (subject T.M. for SMA, subject S.A. for the other sites). The unit of the horizontal axis is images, 0 denoting onset of stimulation. On the vertical axis is the image signal intensity in arbitrary units.

and ipsilateral operculum in 2 subjects, although these were found in MEG. Comparison of the localization between the two methods shows that the agreement was best for the contralateral SI, where the ECD location was always within 10 mm of the nearest activated voxel. Slightly larger differences were observed for the other sites, the disagreement being greatest for the ipsilateral SI, where the maximum difference between the ECD location and the nearest activated voxel was 25 mm.

At the contralateral SI, an interesting systematic difference was observed, so that the centroids of fMRI activation were always more superficial than the corresponding ECD locations for both the N20m and P35m deflections: the average distance from the origin of the head model was 98 mm for the N20m ECD, 102 mm for the P35m ECD, and 108 mm for the fMRI centroid. At the remaining sites the location differences between MEG and fMRI were not consistently biased to any direction.

Time courses of source currents

Introducing the source locations from fMRI (from MEG alone when no fMRI activation was seen; see Fig. 5) to the time-varying multidipole model allowed characterization of the temporal patterns of activation (Fig. 6). It is noteworthy that the orientations of the ECDs remained stable throughout the analysis period, although these were allowed to change freely in order to find the best fit with the measured data.

As expected, the earliest signal change occurred at the contralateral SI, the mean onset latency for significant activation of the ECD being 20 msec (range, 17–22 msec). However, also other sites showed significant, although weaker, short-latency activation. The mean onset latency for the activation of PoCS source was 23 msec (range, 21–25 msec), of the contralateral PO source 26 msec (range, 19–32 msec), and of the contralateral AO source 33 msec (range, 22–51 msec). The PoCS activation started later than the SI activation in every subject, the delay being 2–4 msec. The PO source was activated later than SI in 4 subjects (delay, 2–11 msec) and earlier in one (2 msec). The AO source was activated after the PO source in 4 subjects (delay, 4–30 msec) and before PO in one (11 msec). The mean onset latency for SMA activation was 36 msec (range, 24–48 msec), being always longer than that for SI and PoCS; however, in one subject the onset latency for SMA (24 msec) was shorter than for PO (27 msec).

Significant activation of the ipsilateral sources at SI, PO, and AO started at 54 (range, 36–70), 60 (42–92), and 67 (32–112) msec, respectively. The PO and AO

sources were activated later than SI in 4 subjects and earlier in one. The ipsilateral AO source was activated later than the PO source in 2 subjects, earlier in 2 subjects, and simultaneously in one.

Because opercular activity was not divided into two separate sources in MEG prior to this study, it was of interest to compare the MEG waveforms predicted by two separate vs. only a single opercular source (as found by dipole fitting alone) with the measured signals over lateral locations. Figure 7 illustrates that the two opercular dipoles PO and AO indeed reproduced the actually recorded signals clearly more accurately than a single opercular dipole.

DISCUSSION

In the present study, we found convergent activation of multiple cortical sites in response to somatosensory stimulation, as studied independently by both hemodynamic and electrophysiological techniques in the same subjects. In addition, activation sites found by fMRI were used as spatial constraints in solving the inverse problem of MEG. The multidipole model thus constructed suggested several previously undetected features in the temporal sequence of activation of the different somatosensory areas.

Comparison of fMRI and MEG localizations: technical aspects

In order to maximize the recorded signals in each recording modality, we used different stimulus presentation rates for fMRI and MEG. Several authors have pointed out that stimulus rates should be the same or as similar as possible for a meaningful comparison [e.g., George et al., 1995]. One of the main concerns is that a high stimulus rate might not activate all areas that are active during a slow rate of stimulus presentation. However, as both methods generally detected activation of the same cortical areas, it can be concluded that the different stimulus rates as used in the present study were not a major concern for the combined use of fMRI and MEG.

It should be emphasized that we used a very simple, passive recording paradigm, in which our only interest was to assess which areas were activated; the equalization of stimulus conditions can be more relevant in situations where the subject is performing a task.

In a few cases, either MEG or fMRI was not successful in detecting the activation of a particular focus. The failure to detect the PoCS or SMA activation in MEG, although these were seen in fMRI, is probably related to the fact that dipolar fields over these regions can be

Figure 3.

visualized at long latencies only, when both SI and opercular areas also show robust activity, potentially masking the weaker SMA and PoCS sources. Concerning missing activation in fMRI, it is noteworthy that the Kolmogorov-Smirnov statistics have the highest specificity and the lowest sensitivity of the commonly used statistics in fMRI [Xiong et al., 1996]. Also, the Bonferroni correction is conservative. Thus, as our analysis emphasized specificity over sensitivity, a weak true fMRI activation could have been missed. The ipsilateral opercular regions, which were not detected in some of the fMRIs, were previously reported to produce weaker blood flow changes than the corresponding contralateral regions [Fox et al., 1987].

There was some disagreement as to the exact localization found independently with MEG and fMRI. For the contralateral SI, the disagreement was of the same order of magnitude as in previous studies comparing fMRI and MEG activation of the motor cortex [Sanders et al., 1996; Beisteiner et al., 1995]. For the other areas, the differences in localization were in some cases larger (see Table I). Functional MRI can be criticized for being sensitive not only to parenchymal changes of blood flow but also to changes in large veins near the site of activation [Lai et al., 1993; Boxerman et al., 1995; Menon et al., 1995]. Beisteiner et al. [1997] suggested that parenchymal activation could be discerned from signals arising in larger vessels, if signals with the highest amplitudes were excluded. Nevertheless, studies using magnetic resonance angiography have indicated fMRI activation of the typical SI areas, even in the absence of large veins over the central sulcus [Puce et al., 1995; Sakai et al., 1995]. It should be further noted that in the present and in previous [Puce et al., 1995] studies, SI activation coincided with the lateral portion of the Ω -shaped curve of the central sulcus, which has been shown to be the site of the SI hand area by means of detailed corticographic mappings [Wood et al., 1988].

In MEG, we used a spherical head model, which is an excellent approximation of the inner surface of the skull at parietal and occipital areas. At frontotemporal areas the inaccuracy of this model may result in notable errors [Hämäläinen and Sarvas, 1987], which could partially explain the relatively large differences

between MEG and fMRI in localization of the opercular sources. Also, for sites outside the contralateral SI, deviation of the magnetic field patterns from ideally dipolar distribution (although the goodness of fit exceeded 80%) probably resulted in localization errors, even though the general area of localization was identified by MEG alone. One difficulty in comparing MEG and fMRI localizations follows from the fact that the ECD is a point source, whereas neuronal mass activation detectable with the present methods always has some spatial extensions, as is in fact suggested by the multiple foci of fMRI activation at the contralateral SI and at opercular areas. If an extended source area is not very large, its magnetic field outside the head can be indistinguishable from that of a point-like ECD [e.g., Hari, 1993], but the ECD location can be erroneously deep. This type of error might, at least in part, account for our finding that the ECD locations were always deeper than fMRI activation at the contralateral SI. Clearly, fMRI signals can also arise at the convexial cortex, while MEG detects fissural activity only, which potentially makes the fMRI sources more superficial than the ECDs. In the future, distributed source models, such as those based on the minimum-norm-estimate [Hämäläinen and Ilmoniemi, 1994; Liu et al., 1998], could possibly reduce MEG localization errors arising from the complexity of source geometry.

Time courses of activation at different areas

Results from multidipole modeling should be interpreted cautiously, because adding a dipole even at an arbitrary location in the brain improves the goodness of fit of a multidipole model. Furthermore, two parallel dipoles placed close to each other can “interact,” which may lead to artificially large ECD amplitudes. In the present study, the dipole locations were constrained to physiologically meaningful locations by fMRI. Further support for the activation sequence predicted by the multidipole model can be found in the anatomic organization of the somatosensory areas and from physiological data from invasive corticographic SEP recordings in human patients.

In addition to the contralateral SI, the multidipole model indicated statistically significant short-latency activation of the contralateral PoCS, PO, and AO. In a recent study, Karhu and Tesche [1999] found evidence of short-latency evoked magnetic fields in the opercular region, using the signal-space-projection method [Uusitalo and Ilmoniemi, 1997]. This activity occurred simultaneously with the earliest SI evoked responses. Because the weak short-latency activation of these locations could not be directly visualized in our data,

Figure 3.

fMRI activation (color-scale maps) and MEG source locations (white circles) calculated from MEG data alone in the contra- and ipsilateral primary sensorimotor cortex (SMIc, SMII), the postcentral sulcus (PoCS), and the supplementary motor area (SMA). ECDs are shown transparently through the brain.

Figure 4.

Figure 5.

Centroids of activated areas detected with fMRI (open symbols) and dipole locations of sources detected with MEG alone (solid symbols) in 5 subjects, displayed in the Talairach coordinate system. Each symbol shape signifies a different subject.

the model indicates that these signals are largely masked by the simultaneous large-amplitude activation of the contralateral SI.

The contralateral SII within the parietal operculum is known to be a target for direct input from the ventrobasal thalamus [e.g., Burton and Robinson, 1981], as well as from SI, both of which routes would be expected to result in short-latency activation at SII. In monkeys, SII appears to be activated serially from SI rather than directly from the thalamus [Pons et al.,

1987]. Consistent with this proposition, Lüders et al. [1985] reported on data from a patient, in whom the presumable SII responses followed the SI responses by a delay of 2.4 msec. Also, our results support the view of serial relay of signals from SI to PO in that the PO source was on average activated slightly later than the SI source. However, PO was activated before SI in one subject.

Several studies in both monkeys [e.g., Ridley and Ettlinger, 1976] and humans [Caselli, 1993] indicate that the opercular somatosensory areas are involved in tactile learning and object recognition. Human opercular responses are enhanced during self-paced movements, which has been taken to indicate a role of these areas in sensorimotor integration [Huttunen et al., 1996]. It has been suggested that a special corticolimbic posterior-to-anterior pathway from SII via the insula

Figure 4.

FMRI activation (color-scale maps) and MEG source locations (dots) calculated from MEG data alone in contra- and ipsilateral posterior (POc, POi) and anterior (AOc, AOi) operculum. ECDs are shown transparently through the brain.

Figure 6.

Time courses of strengths of rotating ECDs placed in the centroids of activated areas seen by fMRI. Grand averages over subjects are shown by the thick lines. Thin lines indicate standard errors of mean. Individual goodness-of-fit curves presented at lower right indicate the amount of variance in the MEG data explained by the multidipole model.

Figure 7.

Left: Recorded SEF waveforms (thick lines) and those predicted by modeling (thin lines) at recording locations indicated by the box at the lower left image. Upper right: Only a single opercular ECD is used for modeling. Lower right: Responses are modelled with two separate opercular sources (AO and PO). Upper left: Goodness of

fit is denoted by g , the continuous and dotted line corresponding to a multidipole model including two and one opercular dipoles, respectively. Note that the recorded signals are better reproduced by two separate dipoles than by just one opercular dipole.

could be the anatomic substrate for the learning of manual skills [Mishkin, 1979]. In the present study, the AO sources (near the insula and frontal operculum) in the contralateral hemisphere appeared to be activated shortly after the PO (SII) source. Hence our results are consistent with the proposed posterior-to-anterior pathway in the opercular areas.

Both fMRI and MEG indicated that PoCS activity was close to the postcentral sulcus. Although there is some uncertainty about the cytoarchitectonic borders in the posterior parts of SI in humans, recent anatomic studies indicate that the walls of the postcentral sulcus are occupied by areas 1 and 2 [Geyer et al., 1997]. These areas receive direct afferents from area 3b [Shanks et al., 1985] and from the ventrobasal thalamus [Jones et al., 1979]. Hence the posterior parts of SI can be expected to be activated either simultaneously with area 3b or only slightly later. In the present study, the multidipole model in fact indicated that PoCS activation followed area 3b activation in every subject by a short delay, which can be taken as evidence for a serial relay of signals from area 3b to more posterior areas. Serial anteroposterior processing within SI is consistent with the increasing complexity of neuronal responses toward the posterior parts of SI [Hyvärinen, 1982].

A number of anatomic routes would allow for the relatively short-latency activation of the SMA, including afferents from the ventrolateral thalamus [e.g., Wiesendanger and Wiesendanger, 1985], from the entire SI excluding area 3b [Jones et al., 1978], and from SII [Jones and Powell, 1969]. Recent epicortical recordings from the mesial wall of the sagittal sulcus showed clear mass responses after median nerve stimulation, peaking at latencies of about 40 msec [Allison et al., 1996]. Although in one of our subjects the SMA source appeared to be activated earlier than that (at 24 msec), generally the present model indicated significant SMA activation at latencies that are remarkably comparable to those found in the invasive electric recordings of Allison et al. [1996].

The ipsilateral SI has also been studied in humans with corticography [Allison et al., 1989]. In these studies, the onset latencies of activation were 40–50 msec, again very similar to those predicted by the multidipole model. The route of activation of the ipsilateral SI remains unknown, but perhaps involves callosal connections [see Korvenoja et al., 1995]. The ipsilateral PO and AO sources were generally activated slightly later than the ipsilateral SI. The ipsilateral SII receives fibers from the contralateral SII and SI [Jones and Powell, 1969], and, of course, from the

ipsilateral SI. Any of these might, in principle, be the route for the activation, but the fact that the main peak of the ipsilateral opercular SEF response occurs 5–20 msec after the corresponding peak at the contralateral operculum [Hari et al., 1993] suggests that callosal connections between the SII cortices are likely mediators of the ipsilateral opercular response.

An interesting finding was the reduction rather than increase of the fMRI signal in 2 subjects at all ipsilateral locations. Previously, Drevets et al. [1995] reported a decrease of regional cerebral blood flow, especially in the ipsilateral hemisphere, when subjects anticipated somatosensory stimulation. Although in the present study the subjects were instructed to ignore the stimulation, we cannot rule out that differences in the attentional or anticipatory states underlie the different polarities of the ipsilateral fMRI signals among subjects.

CONCLUSIONS

We found considerable agreement between the localization results obtained with fMRI and MEG. A model based on combined MEG and fMRI data suggested previously undetected short-latency activation of several somatosensory areas and indicated that the somatosensory evoked fields from the opercular area receive a contribution from two separate sources: a posterior source near SII proper, and a more anterior source near the insula and/or frontal operculum. The activation pattern seen with fMRI gave important a priori information on which areas were involved in the processing of the stimuli. The results suggest that the integrated use of MEG and fMRI can provide information about cerebral functions, with high resolution in both spatial and temporal domains.

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