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Functional Magnetic Resonance Imaging Evidence for a Representation of the Ear in Human Primary Somatosensory Cortex: Comparison with Magnetoencephalography Study

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Our previous study (T. Nihashi *et al.*, 2001, NeuroImage 13: 295–304), using magnetoencephalography (MEG), revealed somatotopy of the ear in the human primary somatosensory cortex (SI); that is, the signals following stimulation of the ear reach both the neck and face areas of the SI. However, since this was the first report on somatotopy of the ear in humans, we performed an fMRI activation study to confirm the somatotopic representation, and compared the electrical activity by MEG and the cerebral blood flow change by fMRI. We studied eight healthy subjects using 3-T MRI. We stimulated three parts of the left ear: the helix, the lobulus, and the tragus. First, we identified the location of the ear area in the SI based on our previous MEG study, in which equivalent current dipoles (ECDs) were located in the neck and/or face areas of the SI. Then, we determined the search volume as a sphere with a 15-mm radius, which was placed in the neck and/or face area. We analyzed whether or not fMRI activation occurred inside such spheres. Stimulation of the helix activated the neck area of the SI in four of eight subjects, and both the neck and face areas in two. No activation was observed in two subjects. Stimulation of the lobulus activated the neck area in one subject, the face area in two, both in four, and neither in one. Stimulation of the tragus activated the face in four, both in three, and neither in one. These fMRI findings confirm the result of MEG that the representation of the ear in the SI is separated into neck and face areas.

Key Words: **somatosensory; functional magnetic resonance imaging; ear; human; magnetoencephalography.**

INTRODUCTION

Penfield and his colleagues were the pioneers in showing the somatotopic representation in the human primary somatosensory cortex (SI), termed the somatosensory homunculus, during neurosurgery (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1957). They used electrical stimulation of the cortical surface. Thereafter, existence of the somatosenosry homunculus was confirmed by the recording of somatosensory evoked potential (SEP), or by averaging the signals of electroencephalography (EEG), directly from the cortical surface (Woolsey *et al.*, 1979; Wood *et al.*, 1988; Allison *et al.*, 1989a,b; Baumgartner *et al.*, 1991a). Recently, technical developments have enabled investigation of the human brain by noninvasive methods. Studies have examined somatotopy by functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and positron emission tomography (PET). By the use of fMRI, the hand, face, and foot areas of the SI have been examined and median nerve stimulation has been reported (Stippich *et al.*, 1998; Spiegel *et al.*, 1999; Servos *et al.*, 1999; Boakye *et al.*, 2000; Kurth *et al.*, 2000; Francis *et al.*, 2000; Gratta *et al.*, 2000). Studies of somatosensory evoked magnetic fields (SEFs) by averaging MEG signal have since revealed the homunculus structure of the SI (Brenner *et al.*, 1978; Hari *et al.*, 1984; Sutherling *et al.*, 1988; Baumgartner *et al.*, 1991b; Suk *et al.*, 1991; Kakigi, 1994; Kakigi *et al.*, 1995, 2000; Mogilner *et al.*, 1994; Hoshiyama *et al.*, 1995, 1996, 1997a; Shimojo *et al.*, 1996; Nakamura *et al.*, 1998; Itomi *et al.*, 2000, 2001; Nihashi *et al.*, 2001). The homunculus has also been studied by PET (Fox *et al.*, 1987; Ibanez *et al.*, 1995; Bittar *et al.*, 1999).

The site for ear stimulation has not, however, been clarified, probably because it is difficult to examine the ear area during neurosurgery. Interestingly, although the neck and face are next to each other on the human

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FIG. 1. Three points stimulated on the left ear. The black circle, black triangle, and black square indicate the stimulus point on the helix, lobulus, and tragus, respectively.

body, Penfield's homunculus shows that the neck and face areas of the SI are separated. Therefore, where the boundary between two areas is located is of interest. In addition, the ear is unique in terms of developmental anatomy. The external ear develops from six mesenchymal proliferations at the dorsal ends of the first and second pharyngeal arches, surrounding the first pharyngeal cleft. These six parts fuse and form the definitive auricle. The innervations of the nerves differed between the anterior three parts and the posterior three parts. The anterior three are innervated by a branch of the trigeminal nerve and the posterior three by a branch of the cervical nerve. Therefore, the innervation of the ear might involve both the trigeminal and cervical nerves. In most adults, cervical nerve innervation is dominant (Moore, 1992; Sadler, 1995). Our previous study (Nihashi *et al.,* 2001), using MEG, revealed somatotopy of the ear in human SI; that is, the signals following stimulation of the ear reached both the neck and face areas of the SI in terms of electrical activity. However, as there have been no other reports on the representation of the ear in the SI, there is a need to confirm this result with another modality.

PET and fMRI have excellent spatial resolution, but relatively poor temporal resolution. On the other hand, MEG can detect electrical responses and has high spatial and temporal resolution; however, source localization requires solving the inverse problem of electromagnetism. In addition, when many cortical areas are activated simultaneously, the estimation of multiple sources is difficult and complicated. Actually in our previous study, when a double dipole existed in both the neck and face areas of the SI simultaneously, we had to use a multidipole model, brain electric source analysis (BESA) (Scherg and Buchner, 1993) (Neuro-Scan, McLean, VA) to make a model with two dipoles under some conditions. The combined use of MEG and PET or fMRI enables us to understand brain function in more detail than with a single modality (George *et al.,* 1995; Puce, 1995; Sanders *et al.,* 1996; Grimm *et al.,* 1998; Korvenoja *et al.,* 1999; Roberts *et al.,* 2000).

Therefore, the object of the present study was to confirm our previous finding (Nihashi *et al.,* 2001) that the ear area of the SI was located near both the neck and face areas, by using fMRI following stimulation of three parts of the ear, the helix, lobulus, and tragus, by comparing the results of fMRI and MEG.

MATERIALS AND METHODS

Subjects

Eight healthy volunteers (6 males, 2 females; ranging from 25 to 45 years old) participated in this study. We determined the topography of the ear area of the SI with MEG before the fMRI study. Four of the subjects had participated in our previous study and four were new. Therefore, we compared the results from fMRI

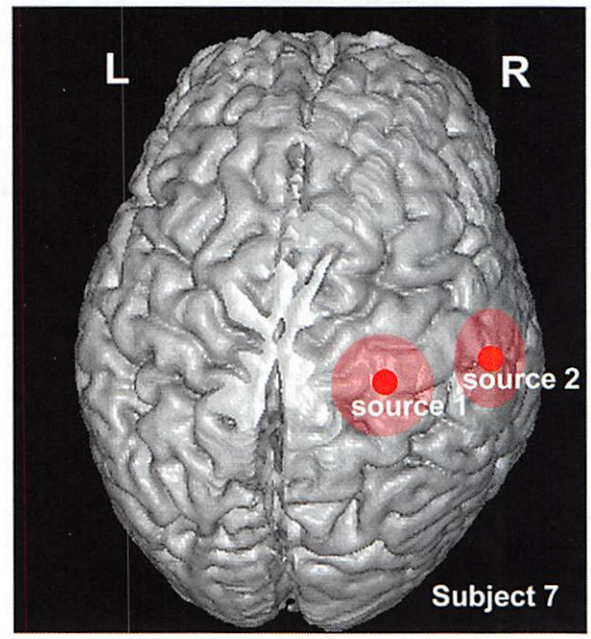

FIG. 2. Method used to analyze our data. We searched for fMRI activation only in the sphere. We made a sphere with a 15-mm radius, centered by the ECD location. Sources 1 and 2 were located in the neck and face areas of the SI, respectively. A small red circle shows the location of the ECD and a large red circle shows the search volume in subject 7 following stimulation of the tragus.

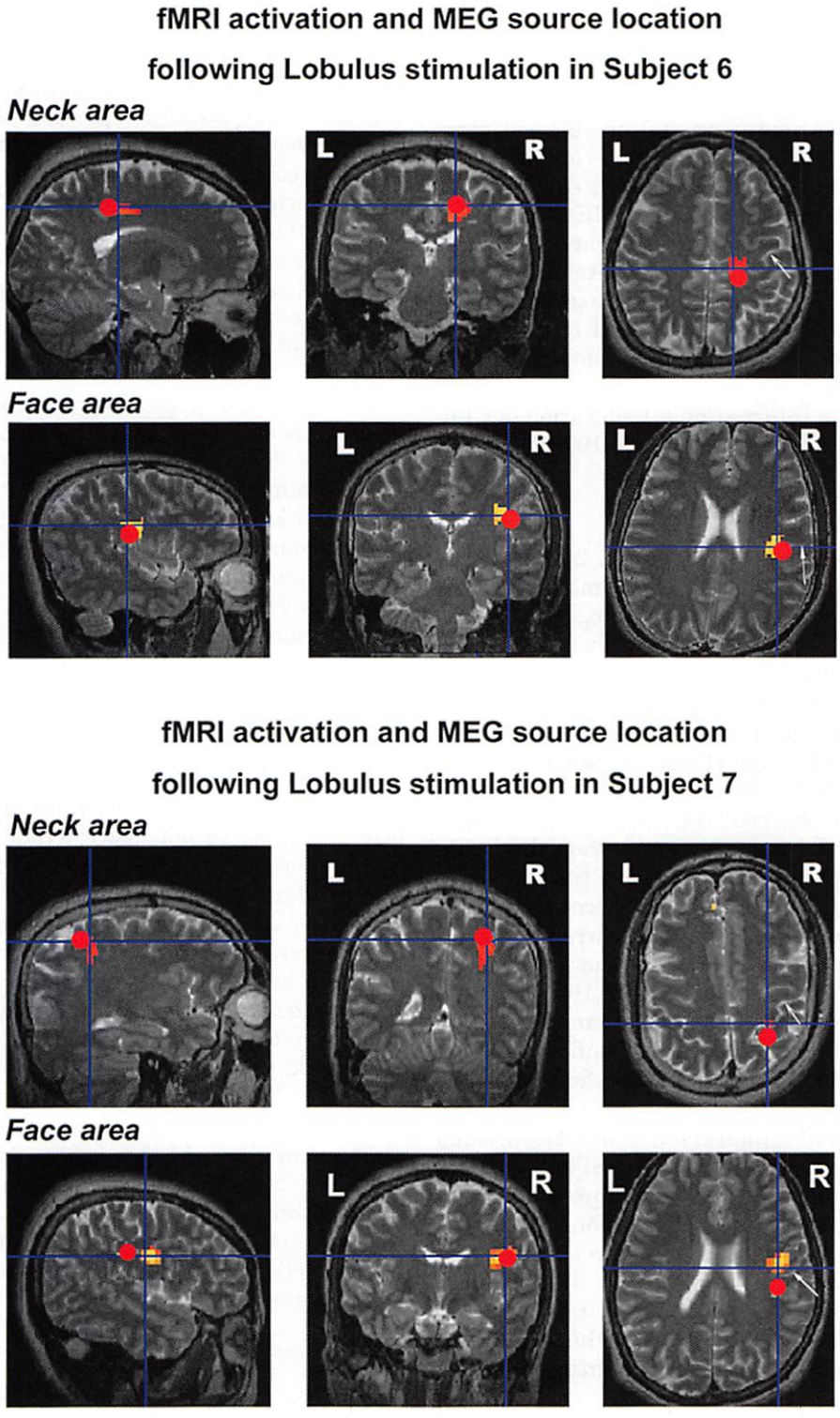

FIG. 3. Activation sites in the neck and face areas of the SI following stimulation of the lobulus in subjects 6 and 7. White arrows show the central sulcus. Red circles show the ECD locations. fMRI activation is shown by a color scale.

with those from MEG in eight subjects. Informed consent was obtained from all subjects prior to the study, which was first approved by the ethics committee at our institution.

Ear Stimulation Procedure

We stimulated 3 sites on the left ear (24 stimulus conditions: 3 conditions × 8 subjects): (1) the helix

(posterior), (2) the lobulus (middle) and (3) the tragus (anterior) (Fig. 1). A pair of silver ball electrodes was used for stimulation. The stimulus electrodes were clipped onto the ear and fixed into position with a nose clip for swimming (Arena, Canada) or surgical tape. For fMRI, the electrical stimulus was a constant-voltage square wave pulse delivered at the rate of 2 Hz. We used a 0.5-ms stimulus duration. For MEG, the stimulus rate was 1 Hz and the stimulus duration 0.05 ms. There was no difference in experimental conditions between the fMRI and MEG studies except for the duration and rate of the stimulus. The stimulus intensity was approximately three times the sensory threshold (4–9 mA, mean 6.2 mA) according to the guidelines for SEP issued by the International Federation of Clinical Neurophysiology (Mauguiere *et al.* 1999).

MEG Acquisition and Analysis

In our previous study (Nihashi *et al.,* 2001), we recorded SEFs with a 37-channel biomagnetometer (Magnes, Biomagnetic Technologies Inc., San Diego, CA) following stimulation of the ear electrically. The MEG signals were filtered with a 1- to 80-Hz bandpass filter and digitized at the sampling rate of 2048 Hz. The analysis window was from 100 ms before to 200 ms after stimulation, and the prestimulus period was used as the baseline. At first, we estimated the location of the single equivalent current dipoles (ECDs), using a single-dipole model. In some subjects, when the ECDs were estimated to be in unlikely areas (in the white matter or the hand area of SI), the isocontour maps showed a two-dipole pattern, or a low correlation coefficient was obtained, we examined the data using BESA with a two-dipole model, one in the neck and face areas of the SI. We defined the neck and face areas based on the homunclus reported by Penfield and colleagues (Penfield and Boldley, 1937; Penfield and Rasmussen, 1957) and our previous MEG studies (Hoshiyama *et al.,* 1996; Itomi *et al.,* 2001). Hoshiyama *et al.* (1996) showed the face area of the SI following lip stimulation, and Itomi *et al.* (2001) showed the neck area following posterior neck stimulation. Most subjects in the present study participated in our previous MEG studies (Hoshiyama *et al.,* 1996; Itomi *et al.,* 2001). First, we located two dipoles near the defined face and neck areas of the SI, and then searched nearby for the best location and orientation, using BESA.

In single-dipole analyses, we estimated dipole fitting at a point with a goodness of fit (GOF) above 0.97. In multiple-dipole analyses, we considered the fit of the dipoles to be significant when the GOF was larger than 0.90 (Toro *et al.,* 1993; Valeriani *et al.,* 1997; Watanabe *et al.,* 1999a,b). We could not obtain data from the ipsilateral hemisphere due to the stimulus artifacts in our previous MEG study (Nihashi *et al.,* 2001).

fMRI Acquisition and Analysis

For brain functional imaging, a rest condition (10 images) was alternated with a stimulated condition (10 images) every 30 s (3 s per image) during the fMRI measurement, and 106 volumes of gradient echo single-shot echo planar imaging (EPI) images was acquired with a time of repetition (TR) of 3 s, time of echo (TE) of 30 ms, field of view (FOV) of 19 cm, and matrix size of 64 × 64, in 26 transaxial slices of 2.7 mm with a 0.3-mm gap, using 3-T MR imagers (General Electric, Milwaukee, WI). The first 6 volumes was discarded because of unsteady magnetization. The remaining data were analyzed by statistical parametric mapping with SPM99 (Welcome Department of Cognitive Neurology, London, UK) on Matlab (Mathworks, Sherborn, MA). The EPI images were realigned, and smoothed with 8-mm full width at half-maximum isotropic Gaussian kernel. The resulting set of voxel values for comparison of the stimulus condition constituted a statistical parametric map (SPM) of the t statistics (SPM{t}). SPM{t} was transformed to the unit normal distribution SPM{Z}. Using MEG data, first, we decided on the location of the ECDs in the neck and face areas of the SI before fMRI analysis. Based on the locations, we determined the search volume as a sphere with a 15-mm radius, which was placed on the neck and face areas of the SI (Fig. 2). The center of the search volume was the location of the ECD. We analyzed whether or not fMRI activation occurred inside such spheres. Korvenoja *et al.* (1999) reported that the mean difference between the ECDs and activated voxel in fMRI was 15 mm following stimulation of the median nerve electrically. In our previous MEG study (Nihashi *et al.,* 2001), the mean value of the Euclid distance between the neck and face areas of the SI was approximately 33 mm. Therefore, the search sphere was made as wide as possible to examine the areas around each hand and neck region of the SI while reducing overlap as much as possible. Because of this anatomical a priori information, the statistical threshold was set at $P < 0.05$, and not corrected for multiple comparisons. For anatomical imaging, 112 slices of fast spin-echo images were acquired with a TR of 6 s, TE of 68 ms, FOV of 19 cm, and matrix size of 256 × 256, in 26 transaxial slices of 1.5 mm, with no slice gap.

Integration of fMRI and MEG

MEG coordinates were determined from the five fundamental anatomical points, bilateral preauricular points, the nasion, the inion, and the vertex. The same anatomical landmarks used to create the MEG head-based 3D coordinate system (the nasion and bilateral preauricular points) were visualized in the MRI by affixing to these points high-contrast cod liver oil capsules (3 mm in diameter) whose short relaxation time provided a high-intensity signal in the T1-weighted

TABLE 1

Activation of Contralateral SI by fMRI and MEG

		Helix stimulation		Lobulus stimulation		Tragus stimulation	
Subject	Location	fMRI	MEG	fMRI	MEG	fMRI	MEG
1	Neck	○	○				○
	Face	○	○	○	○	○	○
2	Neck		○		○	○	○
	Face			○	○	○	○
3	Neck		○	○	○	○	○
	Face			○	○	○	○
4	Neck	○	○	○	○		○
	Face					○	○
5	Neck	○	○			○	○
	Face				○	○	○
6	Neck	○	○	○	○		○
	Face			○	○		○
7	Neck	○	○	○	○		○
	Face		○	○	○	○	○
8	Neck	○	○	○	○		
	Face	○	○	○	○	○	○

Note. This table shows the pattern of the activation by fMRI and MEG. When we could obtain location data by MEG (Nihashi *et al.*, 2001), we used the data to determine the center of the search sphere of fMRI analysis. The activation by fMRI was defined as significant ($P < 0.05$, uncorrected).

MR images. The common anatomical landmarks allowed easy transformation of the head-based 3D coordinate system (nasion and entrance of the auditory meati of the left and right ears) used by the MEG source analysis to the MRI. The MEG source locations were converted into pixels using the MRI transformation matrix and overlayed onto the corresponding MR image. We determined the voxel in the anatomical MRI, which showed the point of the ECD. In fact, we regarded the voxel decided by the above procedure in the anatomical MRI as the location of the ECD.

RESULTS

Contralateral SI Response (fMRI)

Stimulation of the helix activated only the neck area of the SI in four subjects, and both the neck and face areas in two. We could find no activation in two subjects by fMRI. Stimulation of the lobulus activated only the neck area of the SI in one subject, only the face area in two subjects, and both the neck and the face areas in four subjects. We could find no activation in one subject. Stimulation of the tragus activated only the face area of the SI in four subjects, and both the neck and face areas in three. We could find no activation in one subject. Table 1 shows the pattern of activation in the contralateral SI by fMRI.

The receptive fields of the ear in the SI showed variability among subjects and the site of stimulus. The patterns of activation of SI by fMRI were divided into three types: activation of (1) both the neck and face areas, (2) only the face area, and (3) only the neck area. Each pattern was seen in nine, six, and five stimulus conditions, respectively. Pattern 3, in which only the neck area was activated, was present mainly in the helix stimulus condition but not at all in the tragus stimulus condition.

Comparison between MEG and fMRI Studies on Contralateral SI

By MEG, following stimulation of the helix, the ECDs were estimated to lie in the neck area of the SI with the single-dipole model in five subjects, and in both the neck and face areas with the double-dipole model in three. When the lobulus was stimulated, the ECDs were estimated to lie in the neck area in one subject, in the face area in two, and in both the neck and face areas in five. On stimulation of the tragus, the ECDs were estimated to lie in the face area in one subject, and in both the neck and the face areas in seven. The activated regions detected by fMRI and MEG are summarized in Table 1. There were similar patterns of activation in 15 of 24 conditions.

First we note that the middle (lobulus) of the ear showed a pattern intermediate to those of the anterior (tragus) and posterior (helix) parts. In fact, the condition "neck only" was observed mainly when the helix was stimulated, and not at all following stimulation of the tragus. When the lobulus was stimulated, "neck only" was observed in only one case. The condition "face only" was observed mainly in the lobulus and tragus stimulus conditions.

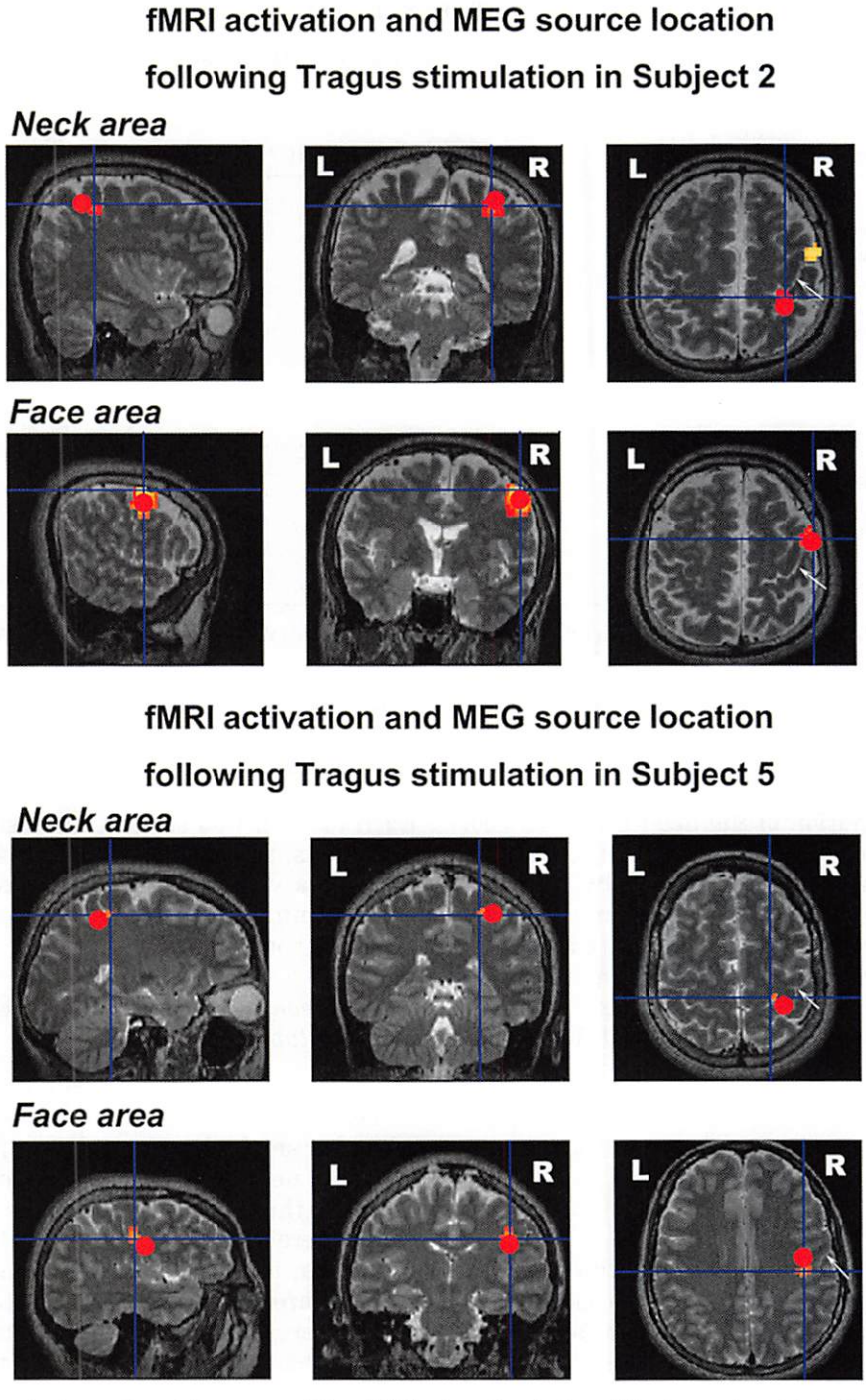

FIG. 4. Activation sites in the neck and face areas of the SI following stimulation of the tragus in subjects 2 and 5. White arrows show the central sulcus. A red circle shows the ECD location. fMRI activation is shown by a color scale.

Figure 3 shows representative double-activation maps following stimulation of the lobulus in two subjects. Figure 4 shows representative double-activation maps following stimulation of the tragus in two subjects. The distance between the location of the ECD and the centroid of fMRI activation was within 10 mm in most cases. Figure 5 is a representative activation map of 3D MRI following stimulation of the lobulus and tragus. The locations of the ECDs and the activation by fMRI were almost the same in the SI.

DISCUSSION

In our previous study (Nihashi *et al.,* 2001), we reported that the ear area of the SI was located near the neck area, but the receptive fields of some parts of the

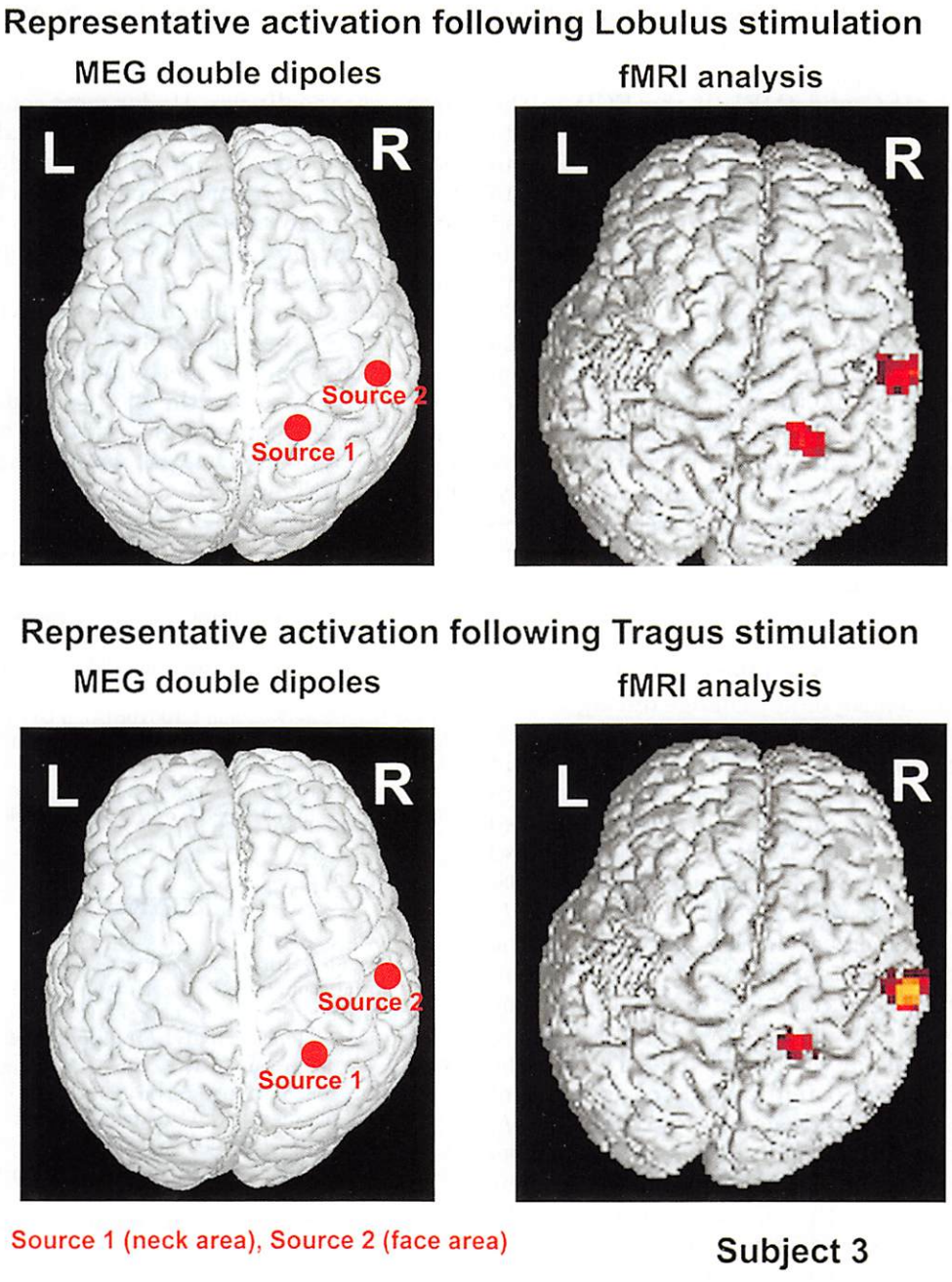

FIG. 5. Map of activation by fMRI and the ECD location by MEG (double-dipole model) in subject 3 following stimulation of the lobulus and the tragus. Both the neck and face regions of the SI are activated. fMRI activation is shown by a color scale.

ear, such as the lobulus and tragus, were estimated to lie in both the neck and face areas of the SI.

We found fMRI activation to occur around the ECDs under most conditions. However, we could not find the same pattern of activation in eight conditions. We considered three possible reasons for this. First, in the MEG study, we measured electrical activity and analyzed the time-locked electrically stimulated SEF, that is, the early responses within 40 ms of stimulation. In the fMRI study, we measured cerebral blood flow, as BOLD signal, continuously during the entire stimulus period. The fMRI signal begins to increase 2 or 3 s after the stimulation and the level of signal reaches a plateau after 7 to 10 s. When the activity ends, the level of signal returns to baseline after about 10 s (Logothetis *et al.,* 2001; Bandettini and Ungerleider, 2001). Therefore, the analysis window was much longer for fMRI than MEG, and not only the primary responses but all

the activated regions were evident. We speculated that this analysis window might lead to the difference in the results. The second explanation involves mainly the disadvantages of MEG and fMRI. If the ECD in the neck or face area of the SI is directed mainly radial to the surface of the cortex, it is very difficult for MEG to record such an ECD. In contrast, fMRI was sensitive to changes in blood flow in large veins near the activated site. Therefore, if there was a cortical vein around the SI, we could not identify the site of activation accurately (Lai *et al.,* 1993; Beisteiner *et al.,* 1995, 1997; Menon *et al.,* 1995). Third, the difference might be due to the stimulus site, "the ear." That is, the intensity of electrical stimulation, at three times the sensory threshold, might be insufficient to stimulate the ear, where there are fewer cutaneous fibers than in the limbs. However, we could not use a larger intensity, because it caused intolerable pain. In fact, in our previous MEG study, it was also difficult to obtain sufficient responses following electrical stimulation of the ear.

The direct relationship between neural activity and the fMRI response is not yet understood. fMRI BOLD signal reflects the hemodynamic change during activation of the brain; that is, when blood flow increases, blood oxygeneration increases and deoxyhemoglobin decreases. Consequently, this mechanism leads to an increase in fMRI signals. Many studies have reported on the connection between fMRI signals and neural activity (Boynton *et al.,* 1996; Matheiesen *et al.,* 1998; Arthurs *et al.,* 2000; Ogawa *et al.,* 2000). Arthurs *et al.,* (2000) recorded an increase in the amplitude of the somatosensory evoked potential and a change in intensity of fMRI BOLD signal following stimulation of the median nerve electrically. They showed that the intensity of the BOLD signal correlated linearly with the amplitude of the evoked potential and speculated that the signal reflected neural activity (Arthurs *et al.,* 2000). Logothetis *et al.* (2001) showed a relation between neural activity and BOLD signal directly. They recorded simultaneously the neural signals and fMRI responses from the visual cortex of anesthetized monkeys while stimulating them with a rotating checkerboard and analyzed local field potentials (LFPs). LFPs were related to synaptic activity, which consumed more energy than the action potential. Therefore, their findings suggested that synaptic activity reflected the BOLD fMRI signal.

With MEG, when many cortical areas were activated simultaneously, the estimation of multiple sources was difficult and complicated as many authors have reported (Hoshiyama *et al.,* 1997a,b; Valeriani *et al.,* 1997, 1998; Watanabe *et al.,* 1998). Previously (Nihashi *et al.,* 2001), we used a multiple-dipole analysis for some conditions. In general we had to be careful with the results from multiple-dipole modeling, because adding a dipole in the cortex improves the goodness of fit. In the present study, we determined the location of the neck and the face areas of the SI using MEG data, and then searched for the fMRI activation area near the dipoles. Under most conditions, we could find the activation as a BOLD signal around the dipoles estimated by multidipole modeling. Therefore, we ascertained our previous results obtained by MEG and confirmed that the electrical activities on MEG and the cerebral blood flow changes on fMRI occurred near each other.

In conclusion, although the receptive fields of the ear in the SI showed variability among subjects and the site of the stimulus, these findings strongly suggested that the "ear area" of the SI is located in both the neck and face areas under many stimulus conditions. These results obtained by fMRI were compatible with our previous MEG results.

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