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# Time Course of Activity in Itch-Related Brain Regions: A Combined MEG–fMRI Study

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**Mochizuki H, Inui K, Tanabe HC, Akiyama LF, Otsuru N, Yamashiro K, Sasaki A, Nakata H, Sadato N, Kakigi R.** Time course of activity in itch-related brain regions: a combined MEG–fMRI study. *J Neurophysiol* 102: 2657–2666, 2009. First published August 26, 2009; doi:10.1152/jn.00460.2009. Functional neuroimaging studies have identified itch-related brain regions. However, no study has investigated the temporal aspect of itch-related brain processing. Here this issue was investigated using electrically evoked itch in ten healthy adults. Itch stimuli were applied to the left wrist and brain activity was measured using magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). In the MEG experiment, the magnetic responses evoked by the itch stimuli were observed in the contralateral and ipsilateral frontotemporal regions. The dipoles associated with the magnetic responses were mainly located in the contralateral (nine subjects) and ipsilateral (eight subjects) secondary somatosensory cortex (SII)/insula, which were also activated by the itch stimuli in the fMRI experiment. We also observed an itch-related magnetic response in the posterior part of the centroparietal region in six subjects. MEG and fMRI data showed that the magnetic response in this region was mainly associated with itch-related activation of the precuneus. The latency was significantly longer in the ipsilateral than that in the contralateral SII/insula, suggesting the difference to be associated with transmission in the callosal fibers. The timing of activation of the precuneus was between those of the contralateral and ipsilateral SII/insula. Other sources were located in the premotor, primary motor, and anterior cingulate cortices (one subject each). This study is the first to demonstrate part of the time course of itch-related brain processing. Combining methods with high temporal and spatial resolution (e.g., MEG and fMRI) would be useful to investigate the temporal aspect of the brain mechanism of itch.

## INTRODUCTION

Itch is an unpleasant sensation and a particularly severe problem for patients with atopic dermatitis. Therefore clarification of the mechanism of itch is clinically important. The itch sensation is associated with the excitation of C-fibers induced by pruritogens such as histamine (Simone et al. 1987; Torebjörk 1974; Tuckett and Wei 1987) and, in the past, was considered to be a perception of weak pain. However, it was found that certain C-fibers and spinothalamic tract neurons are selective to pruritogens (Andrew and Craig 2001; Schmelz et al. 1997, 2003). The finding indicates that there are some ascending pathways specific to or selective for itch, suggesting that itch is not a perception of weak pain. Recently, researchers have tried to clarify how our brains create the sensation of itch using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies have shown that the prefrontal cortex, basal ganglia, cingulate cortex, insula, somatosensory cortex, motor cortex, premotor cortex, (pre-) supplementary motor area, parietal cortex, and cerebellum are associated with itch (Darsow et al. 2000; Drzezga et al. 2001; Herde et al. 2007; Hsieh et al. 1994; Leknes et al. 2007; Mochizuki et al. 2003, 2007; Valet et al. 2008; Walter et al. 2005). In addition, it was also reported that the itch–scratch cycle, a serious problem among patients with atopic dermatitis, is partly due to enhanced activity in the striato-thalamo-orbitofrontal circuit (Leknes et al. 2007; Schneider et al. 2008). These previous studies mainly focused on the spatial aspect of the brain mechanism of itch (i.e., which brain regions are associated with itch). On the other hand, its temporal aspect (e.g., the sequence in which itch-related brain regions are activated) is still unclear. Magnetoencephalography (MEG) and electroencephalography (EEG) can measure brain activity in the order of milliseconds. Histamine induces a long-lasting and dull itch sensation. Thus histamine is not useful for measuring stimulus-locked brain activity using MEG and EEG. Recently, Ikoma et al. (2005) established a new way to elicit an itch sensation (i.e., electrically evoked itch). Mochizuki et al. (2008) confirmed that electrically evoked itch is useful for MEG and EEG experiments and also reported that the stimulus, as well as histamine-induced itch, activates C-fibers. The rather low spatial resolution of MEG/EEG and a problem due to resolving an inverse problem in dipole estimates (i.e., the answers to an inverse problem are infinite) can be compensated for by using a method with high spatial resolution such as fMRI. By combining these methods, more reliable and precise information concerning itch-related brain processing can be obtained. Thus in this study, we investigated the time course of itch-related activity in the brain using electrically evoked itch, MEG, and fMRI. This is the first study to focus on the temporal aspect of the brain mechanism of itch.

## METHODS

### *Subjects*

Ten healthy male volunteers (mean ± SD: 32 ± 6 yr) participated in this study. Subjects with a history of allergy, atopic eczema, or

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other dermatological diseases were excluded. The study was approved by the Ethics Committee at the National Institute for Physiological Sciences (NIPS). Written informed consent was obtained from each subject and the study was performed in compliance with the relevant laws and guidelines of NIPS.

### *MEG experiment*

ITCH STIMULI. An itch sensation was induced by using electrically evoked itch (Ikoma et al. 2005; Mochizuki et al. 2008). Two electrodes for the electrical stimulation (Mochizuki et al. 2008) and two reference electrodes were attached to the lateral and medial sides of the left wrist (Fig. 1). Constant-current square-wave pulses (pulse duration, 2 ms; frequency, 50 Hz) were applied to the skin through the electrodes using an electrical stimulator (SEN-7203, Nihon kohden, Tokyo). The current intensity used in the MEG experiment was 0.1–0.7 mA. Twenty pulses were given in one stimulus. Thus it took 400 ms to apply 20 pulses in one stimulus. An itch sensation is appreciably reduced when the stimuli are repeatedly applied to one site and the interstimulus interval (ISI) is $<$30 s (Mochizuki et al. 2008). Thus in this study, two different sites (i.e., the lateral and medial sides) were stimulated sequentially with intervals of 15–20 s so that the ISI at each site was $>$30 s. Ten stimuli were given in a session and there were 10 sessions in this experiment. Thus 100 stimuli in total were applied. In addition, even with a long ISI, repeated stimulation of one site without a rest can lead to a dramatic decrease in the itch sensation. Thus the subjects had rested for 5–10 min between sessions to maintain a clear itch sensation across sessions. The intensity of itch stimuli was determined using the visual analog scale (VAS): a score of 0 indicates that the subjects felt no itch sensation; a score of 10 indicates that the subjects felt an intense itch sensation with a strong desire to scratch.

Before each session, we asked the subjects whether they felt a clear itch sensation on stimulating the wrist with the current used in the previous session. If the subject reported that an itch sensation was absent or markedly decreased compared with the previous session, then the current intensity and location within the wrist was changed to induce an itch sensation similar to that in the previous session. After each session, the subjects reported the mean VAS score of the 10 stimuli applied during a session. We averaged the mean VAS scores of all sessions and used the average for the data analysis.

MEG RECORDINGS. Evoked magnetic fields were recorded with a helmet-shaped 306-channel detector array (Vectorview, Elekta Neuromag Oy, Helsinki, Finland), comprised of 102 identical triple-sensor elements. Each sensor element consisted of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID (superconducting quantum interference device) and thus provided three independent measurements of the magnetic fields. The signals were recorded with a band-pass of 0.03–200 Hz and digitized at 600 Hz. As in previous MEG studies, MRI and MEG data were coregistered using the locations of four head position indicator (HPI) coils placed at specific sites on the scalp (e.g., Akatsuka et al. 2007; Nakata et al. 2005, 2008; Wasaka et al. 2003). In detail, before the recording of MEG, four HPI coils attached to the subject's head were measured with respect to three anatomical landmarks (nasion and bilateral preauricular points) using a three-dimensional (3D) digitizer. The locations of the HPI coils were superimposed on MRI. We also measured the location of the HPI coils with respect to the MEG sensors and the resulting magnetic fields, by feeding a current from the MEG machine into the HPI coils. The locations of MEG sensors and resulting magnetic fields were superimposed on MRI so that the locations of the HPI measured using the MEG machine corresponded to those measured using the 3D digitizer. This processing was performed using the MEG and MRI coordinate systems (Vectorview).

DATA ANALYSIS. The period of analysis was 2,000 ms, including a prestimulus baseline of 100 ms. A band-pass filter of 0.1–100 Hz was used. The baseline correction was done using the mean activity 100 ms before the presentation of the electrical stimulus. Artifacts including eye blinks and eye movements were excluded from the analysis. The source modeling (see Hämäläinen et al. 1993) was based on signals recorded by 204-channel gradiometers. To identify the sources of the evoked activities, an equivalent current dipole (ECD), which best explains the measured data, was computed by using a least-squares search. A subset of 12–22 channels including the local signal maxima was used for the estimation of ECDs. These calculations gave the 3D location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's high-resolution structural MRI (see FMRI MEASUREMENT) to show the source locations. The goodness-of-fit value of an ECD was calculated to indicate in percentage terms how much the dipole contributes to the measured field variance. Only ECDs explaining $>$80% of the field variance during selected periods of time were used for further analysis. The

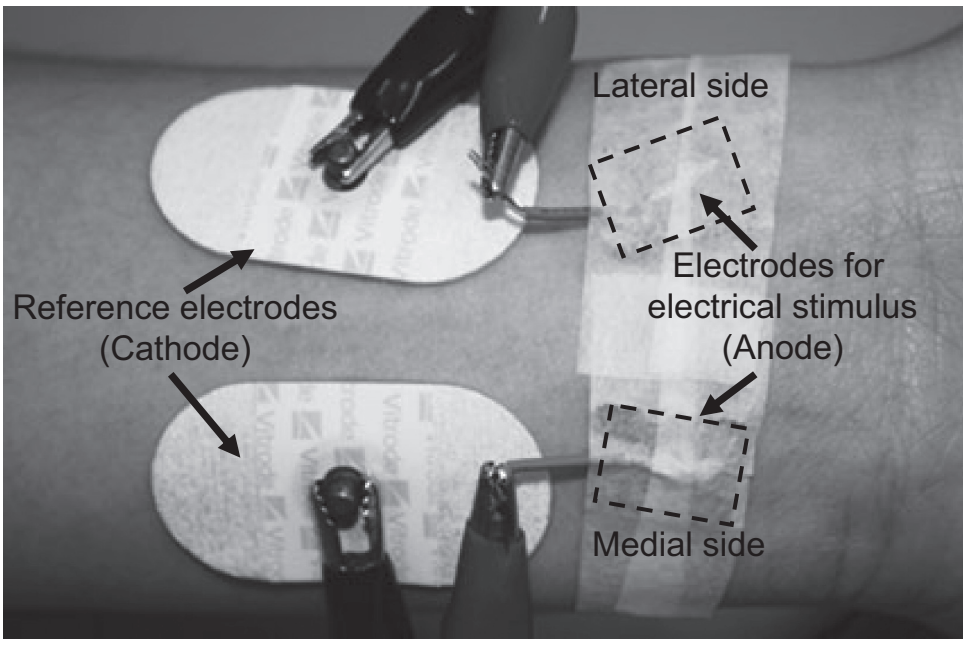


FIG. 1. The left wrist with electrodes delivering the electrical stimuli.

period of analysis was extended to cover the entire duration and all channels were taken into account in computing a time-varying multidipole model. We calculated the areal mean signals to obtain the latency of each brain region where the dipole was located. First, we identified an area of interest, which included four gradiometer pairs that showed strong responses. We used these four gradiometer pairs to analyze the areal mean signals. We calculated vector sums by squaring MEG signals of gradiometer pairs and summing these signals together; we then recalculated the square root of this sum. The areal mean signals were computed by averaging these vector sums for an area of interest. The areal mean signals were computed from 100 ms before to 1,900 ms after stimulus onset, individually for each subject. This method of data analysis followed some previous studies using the same MEG system as that in the present study (Akatsuka et al. 2007; Bonte et al. 2006; Nakata et al. 2005, 2008; Tarkiainen et al. 2003). In this study, we used the areal mean signals to measure the latency of each brain region. The peak latency of the magnetic response to electrically evoked itch obtained from each subject was used to clarify the sequence in which itch-related brain regions were activated.

### *fMRI experiment*

ITCH STIMULI. As in the MEG experiment, two electrodes for the electrical stimulation and two reference electrodes were attached to the left wrist. The electrical stimuli were sequentially applied to the lateral and medial sides of the wrist (ISI, 15–20 s; pulse duration, 2 ms; frequency, 50 Hz) using the same electrical stimulator as that used in the MEG experiment. The current intensity used in the fMRI experiment was 0.1–0.6 mA. In a preliminary fMRI experiment, we used the same itch stimulus as that used in the MEG experiment. Although the subjects felt a clear itch sensation and the VAS score in the preliminary experiment was similar to that in the MEG experiment (VAS scores: 3–4), we did not observe any significant activation during the itch stimuli in the preliminary fMRI experiment. Therefore in the fMRI experiment, the number of pulses was increased. In a preliminary psychophysical experiment, we also confirmed that the itch sensation tended to decrease or disappear due to habituation when the number of pulses was >250. Thus 250 pulses were given in one stimulus. Ten stimuli were given in a session. There were three sessions in this experiment. Therefore 30 stimuli were applied in total. Intervals between sessions were 5–10 min. As in the MEG experiment, the intensity of the current was determined for each subject before each session. After a session, the subjects reported the mean VAS score of the 10 stimuli applied. We averaged the mean VAS scores of all sessions and used the average for the data analysis.

FMRI MEASUREMENT. The fMRI experiment was conducted using a 3-tesla MRI scanner (Allegra, Siemens, Erlangen, Germany). For functional imaging during the sessions, a series of 108 volumes was acquired using T2*-weighted, gradient-echo, echo-planar imaging (EPI) sequences. Each volume consisted of 38 transaxial slices, each having a thickness of 3.5 mm with a 0.5-mm gap between slices to cover the entire cerebrum and cerebellum (repetition time [TR] = 2,500 ms; echo time [TE] = 30 ms; flip angle [FA] = 80°; field of view [FOV] = 192 mm; 64 × 64 matrix). Oblique scanning was used to exclude the eyeballs from the images. To acquire a finer structural whole-head image, magnetized prepared rapid gradient echo (MP-RAGE) images were also obtained (TR = 2,500 ms; TE = 4.38 ms; FA = 8°; FOV = 230 mm; number of slabs = 1; number of slices per slab = 192; voxel dimensions = 0.9 × 0.9 × 1.0 mm).

MAKING AN ITCH-RELATED FUNCTIONAL BRAIN MAP. The first two EPI volumes (i.e., functional images) of each session were eliminated to allow for the stabilization of the magnetization. Data were analyzed using statistical parametric mapping 5 (SPM5 revision 1782; The Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2007b (The MathWorks, Natick, MA). To reduce head-motion artifacts, all functional image volumes were realigned to the third scan volume. Then, the MP-RAGE image volume was coregistered with the image volume of the third scan. The whole-head image volume was normalized to the Montreal Neurological Institute (MNI) T1 image template using an affine transformation and a nonlinear basis function. The same parameters were applied to all of the EPI volumes, which were spatially smoothed in three dimensions using an 8-mm full width at half-maximum Gaussian kernel.

The statistical analysis was conducted at two levels. First, individual itch-related activity was evaluated (first-level analysis). Second, to make inferences at a population level, individual data were summarized and incorporated into a random-effects model (second-level analysis) (Holmes and Friston 1998).The resulting set of voxel values for the contrast (to evaluate itch-related activity) constituted a statistical parametric map (SPM) of the $t$ statistic (SPM{$t$}). The brain regions activated by the itch stimuli were identified using the voxel-level analysis in SPM5 and the statistical threshold for a significant activation was set at $P = 0.05$, with a false discovery rate (FDR) correction for multiple comparisons for the entire brain (Genovese et al. 2002).

TRANSFORMATION OF THE COORDINATES OF DIPOLES IN EACH SUBJECT INTO TALAIRACH COORDINATES. This is the first MEG study concerning itch. Thus it was not known which brain regions were associated with itch-related magnetic responses and whether the brain regions from which these responses originated were the same among subjects. Therefore the coordinates of dipoles in each subject's brain were transformed into a common coordinate system (i.e., the MNI template), to confirm to what extent the dipoles obtained from the subjects were assembled in the same areas. In detail, we obtained a structural MRI, including the dipoles estimated in the MEG experiment for each subject. The structural MRI with the dipoles was normalized with the MNI template using the parameters determined earlier (see MAKING AN ITCH-RELATED FUNCTIONAL BRAIN MAP). The normalization was done using SPM5. Even if the dipoles were assembled in the same brain regions, it was unclear whether these regions were actually activated by the itch stimuli because of the low spatial resolution of MEG and an inverse problem. In fact, it was unknown which brain regions were activated by electrically evoked itch, since no previous fMRI and PET studies have used electrically evoked itch. Thus we compared the brain regions where the dipoles were assembled and the itch-related functional brain map obtained in the fMRI experiment.

Most previous fMRI and MEG studies showed Talairach coordinates of peak activations (fMRI) and dipoles (MEG). Thus the coordinates of each dipole on the MNI template were further transformed into the stereotaxic coordinates of Talairach and Tournoux (1988) using an established formula (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) (Brett et al. 2002).

## RESULTS

### *VAS scores*

All subjects reported a clear itch sensation in this study. The VAS scores in the fMRI experiment and MEG experiment were 4.5 ± 0.9 (mean ± SD) and 3.0 ± 0.6, respectively, and were statistically significantly different ($P < 0.0001$, paired $t$-test). The current intensities in the fMRI and MEG experiments were 0.32 ± 0.12 and 0.34 ± 0.1 mA, respectively, not statistically significantly different ($P = 0.2$, paired $t$-test).

### *fMRI experiment*

The group data analysis (i.e., second-level analysis) in the fMRI experiment showed significant activations in the second-

ary somatosensory cortex (SII), insula, precuneus, posterior parietal cortex (PPC), anterior parietal cortex (APC), prefrontal cortex, premotor cortex, supplementary motor area (SMA), thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and cerebellum (Fig. 2 and Table 1).

### *MEG experiment*

MEG WAVEFORMS. Figure 3 shows a typical magnetic response of the brain elicited by electrically evoked itch. There were three main magnetic responses (i.e., in the right frontotemporal region, left frontotemporal region, and posterior part of the centroparietal region). The magnetic response in the right frontotemporal region was observed in all subjects. The responses in the left frontotemporal region and the posterior part of the centroparietal region were observed in nine and six subjects, respectively.

SOURCE LOCALIZATION. Seven of ten subjects showed itch-related magnetic responses in three different regions. Thus three dipoles were used to explain the measured MEG data. In the rest of the subjects (three subjects), itch-related magnetic responses were observed in one, two, and four regions. Thus one, two, and four dipoles were used to explain the measured MEG data, respectively (see also Table 2). Figure 4 shows the typical results obtained from a single subject. The dipoles associated with the magnetic responses in the bilateral frontotemporal region were located near the Sylvian fissure around Brodmann's area (BA) 43/BA 40 (corresponding to SII) and the insula (light blue circles and bars in MRI in Fig. 4, *top*), so we termed this area SII/insula. In addition, the dipole associated with the magnetic response in the posterior part of the centroparietal region was located in the precuneus (light blue circles and bars in Fig. 4, *bottom*). The locations of the dipoles were almost the same as the area significantly activated in the same subject in the fMRI experiment (red region in Fig. 4).

All subjects' dipoles were superimposed on the itch-related functional brain map obtained from the group data analysis in the fMRI experiment (Fig. 5). Most of the dipoles overlapped with the red-colored brain regions significantly activated by the itch stimuli in the fMRI experiment. The dipoles associated with the bilateral frontotemporal regions were mainly located in the bilateral SII/insula (blue and yellow circles in Fig. 5; also see Table 2). In two subjects, there were two magnetic responses in the left frontotemporal region (pink and orange circles in Fig. 5). The dipole associated with the posterior part of the centroparietal region was mainly located in the precuneus, which was also significantly activated by the itch stimuli in the fMRI experiment (light blue circles in Fig. 5; Table 2). The number of subjects who had dipoles in the contralateral SII/insula, ipsilateral SII/insula, and precuneus was nine, eight, and six, respectively. In addition, the estimated dipoles were also located in the right premotor cortex (BA 6), right primary

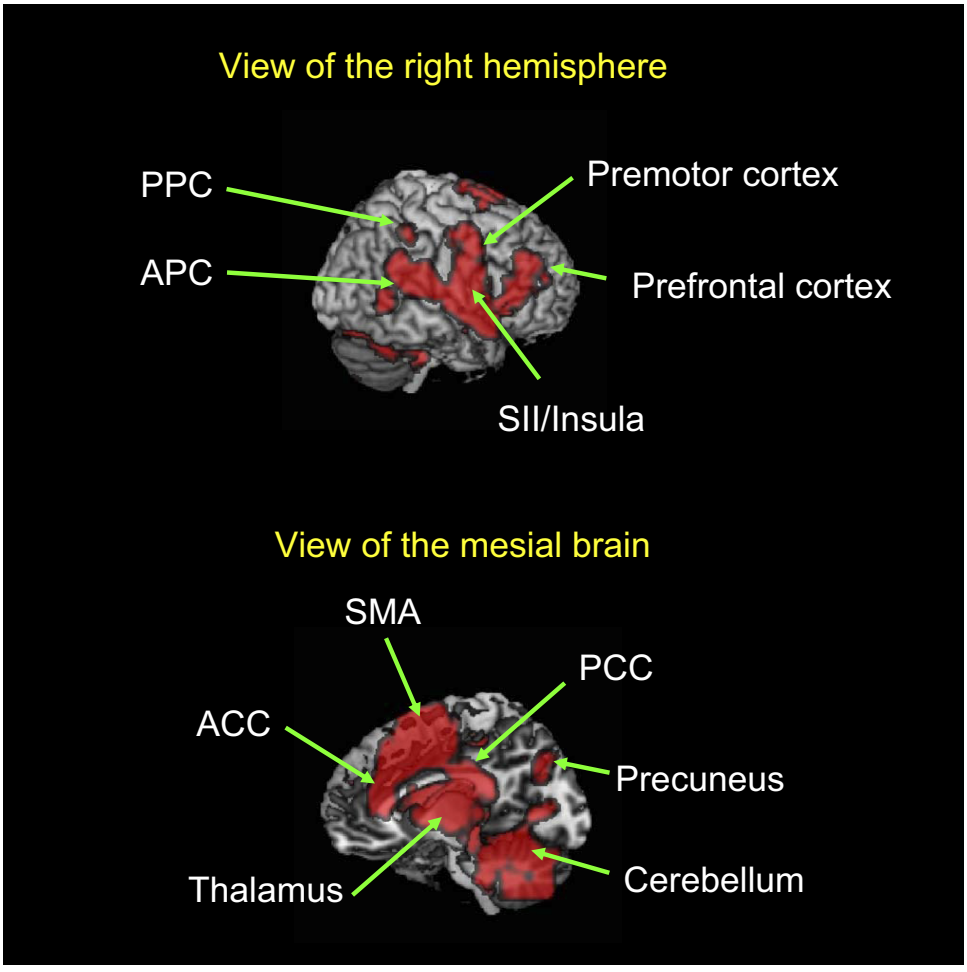


FIG. 2. The brain regions activated by the itch stimuli in the fMRI experiment. The statistically significantly activated areas by 30 itch stimuli were superimposed on a surface-rendered image (2nd-level analysis, statistical threshold: $P = 0.05$ with FDR correction for multiple comparisons). FDR, false discovery rate; fMRI, functional magnetic resonance imaging; SMA, supplementary motor area; SII, secondary somatosensory cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; APC, anterior parietal cortex; PPC, posterior parietal cortex.

TABLE 1. *Brain regions significantly activated by the itch stimuli in the fMRI experiment*

| Brain Region | BA | Talairach Coordinates x | y | z | Z-Score |
|---|---|---|---|---|---|
| Prefrontal cortex | 45 | 30 | 38 | 17 | 3.88 |
| Premotor cortex | 6 | 30 | −4 | 46 | 3.55 |
| SMA | 6 | 16 | 7 | 55 | 4.27 |
| Insula | | 42 | −3 | 11 | 4.46 |
| | | −42 | −2 | 7 | 4.15 |
| SII | 43/40 | 53 | −19 | 12 | 4.02 |
| | | −50 | −24 | 6 | 3.66 |
| Thalamus | | 0 | −19 | 5 | 3.50 |
| ACC | 24/32 | −4 | 21 | 34 | 4.78 |
| PCC | 23/30 | −6 | −30 | 25 | 4.37 |
| Precuneus | 7/31 | 12 | −68 | 38 | 3.01 |
| APC | 39/40 | 65 | −37 | 30 | 4.21 |
| | | −48 | −46 | 26 | 3.86 |
| PPC | 7/40 | 39 | −52 | 43 | 3.61 |
| Cerebellum | | −20 | −72 | −35 | 4.14 |

BA, Brodmann's area; SMA, supplementary motor area; SII, secondary somatosensory cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; APC, anterior parietal cortex; PPC, posterior parietal cortex.

motor cortex (M1), and right ACC (BA 24/BA32) (green, black, and white circles in Fig. 5, respectively).

LATENCY. There were seven subjects who showed dipoles in the contralateral and ipsilateral SII/insula. The latency was significantly delayed in the ipsilateral SII/insula, compared with the contralateral SII/insula [$P = 0.004$ (paired $t$-test), the ipsilateral side (mean ± SD): 740 ± 76 ms; the contralateral side: 785 ± 76 ms]. The difference in latency was 46 ± 27 ms between the contralateral and ipsilateral SII/insula. One subject (subject 4 in Table 2) had two responses in the left frontotemporal region and so the early response was used for this test. We compared the latency (paired $t$-test) for six subjects who showed dipoles in the precuneus and contralateral SII/insula and found no significant difference between them ($P = 0.19$; the precuneus: 783 ± 76 ms; the contralateral SII/insula: 772 ± 86 ms). We also performed a paired $t$-test for five subjects who showed dipoles in the precuneus and ipsilateral SII/insula. There was no significant difference ($P = 0.1$; the precuneus: 769 ± 76 ms; the ipsilateral SII/insula: 804 ± 83 ms). One subject (subject 4) had two responses in the left frontotemporal region and so the early response was used for this test.

## DISCUSSION

In this study, we investigated the temporal aspect of brain mechanism of itch using electrically evoked itch, MEG, and fMRI. Itch-related magnetic responses were observed in the bilateral frontotemporal regions and posterior part of the centroparietal region in the MEG experiment. The sources of these responses were mainly estimated to be in the bilateral SII/insula and precuneus, consistent with the fMRI experiment. The latency was significantly shorter in the contralateral than that in the ipsilateral SII/insula. The latency of the precuneus was between that in the contralateral and that in the ipsilateral SII/insula. This is the first study to demonstrate part of temporal information of itch-related brain processing.

### *Source localization*

The estimated dipoles associated with the magnetic responses in the bilateral frontotemporal regions were located near the Sylvian fissure (SII/insula) in this study. A similar

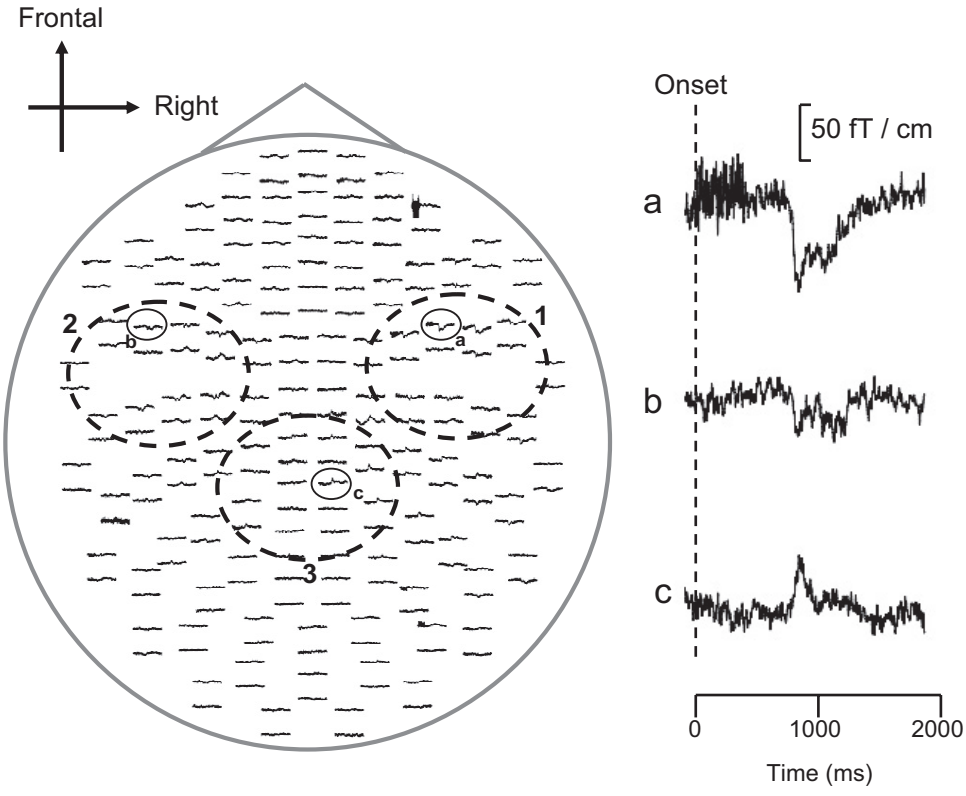


FIG. 3. Spatial distribution of magnetic responses of the planer gradiometers evoked by electrically evoked itch in a single subject. Magnetic responses were observed in 3 distinct regions: the right frontotemporal region, left frontotemporal region, and posterior part of the centroparietal region, numbered 1, 2, and 3, respectively. A typical magnetic response for each region on the scalp map (a, b, and c) is enlarged and shown on the *right*. The average number was 100. In the graphs on the *right*, the dashed vertical line indicates the time of stimulus onset. The bar in the graph indicates the scale of the ordinate. The scale bar 50 fT/cm refers to the amplitude of the magnetic response.

TABLE 2. *Locations of dipoles and latencies of the magnetic responses associated with the itch stimuli in the MEG experiment*

| | SII/Insula | | | | | |
|---|---|---|---|---|---|---|
| Subject | Right Hemisphere [48, −12, 20] | Left Hemisphere [−46, −11, 20] | Precuneus [6, −52, 49] | Premotor Cortex [37, −7, 38] | M1 [−52, −15, 27] | ACC [1, 42, 14] |
| 1 | 897 | 912 | 897 | | | |
| 2 | 759 | 854 | 766 | | | |
| 3 | 754 | 809 | 751 | | | |
| 4 | 686 | 708 (1,202) | 698 | | | |
| 5 | 686 | 738 | 733 | | | |
| 6 | 848 | | 853 | | 861 | |
| 7 | 691 | 724 | | | | |
| 8 | 704 | 753 | | | | 1,032 |
| 9 | 982 | | | | | |
| 10 | | 869 (1,167) | | 1,104 | | (Order: ms) |

Mean coordinate of each brain region in the Talairach coordinate system is denoted in brackets [x, y, z]. There were two responses in the left frontotemporal region in subjects 4 and 10, The later response is denoted in parentheses.

result was reported in previous pain and tactile studies using MEG and EEG (Forss et al. 2005; Frot and Mauguière 2003; Kakigi et al. 2003; Kanda et al. 2000; Mauguière 2004; Nakata et al. 2008; Ploner et al. 1999, 2000, 2002; Raij et al. 2003; Timmermann et al. 2001; Tran et al. 2002; Treede et al. 1999, 2000). Our fMRI data also showed that the bilateral SII/insula and precuneus were significantly activated by the itch stimuli. The estimated dipole associated with the magnetic response in the posterior part of the centroparietal region was mainly located in the precuneus. In contrast, no previous pain and tactile studies using MEG and EEG reported dipoles in the precuneus (e.g., Forss et al. 2005; Inui et al. 2003; Kakigi et al. 2005; Kanda et al. 2000; Nakata et al. 2008; Opsommer et al. 2001; Ploner et al. 1999, 2000), implying some differences in parietal processing between itch and pain.

As mentioned earlier, itch-related magnetic responses were mainly associated with the activation of SII/insula and the precuneus. In contrast, just a few previous PET and fMRI studies observed significant itch-related activation of SII and the precuneus (Herde et al. 2007; Mochizuki et al. 2003, 2007). The discrepancy may be associated with differences in methodology. Previous studies used histamine to elicit itch (e.g., Drzezga et al. 2001; Hsieh et al. 1994; Leknes et al. 2007; Valet et al. 2008), whereas this study used electrically evoked itch. Actually, histamine-induced itch and electrically evoked itch differ in axon reflex flare and electrical threshold (Andrew and Craig 2001; Ikoma et al. 2005; Schmelz et al. 1997). In particular, the steep rise and short-lived nature of electrically evoked itch used in this study might be the most important reason for the discrepancy. SII/insula and the precuneus might adapt substantially during a long-lasting itch sensation induced by histamine.

Some pain and tactile studies also observed activation of the precuneus (de Leeuw et al. 2006; Iadarola et al. 1998; Kitada et al. 2005; Niddam et al. 2008). Thus the activation of the precuneus is not specific to itch in somatosensory processing. Unfortunately, the precise role of the precuneus in somatosenory processing is little understood. Some neuroimaging studies concerning pain reported that the precuneus was associated with the empathy of pain, pain hallucination, and modulation of pain by hypnosis, speculating that the precuneus might have some role in the interaction between internal or psychological states and somatic sensations (Bär et al. 2002; Faymonville et al. 2006; Jackson et al. 2006; Ochsner et al. 2008; Schulz-Stübner et al. 2004).

The ACC is a region of the brain important to itch perception. Actually, activation in this region was observed in previous itch studies using fMRI and PET (Darsow et al. 2000; Drzezga et al. 2001; Herde et al. 2007; Hsieh et al. 1994; Leknes et al. 2007; Mochizuki et al. 2003, 2007; Valet et al. 2007). However, an itch-related magnetic response of the ACC was observed in only one subject in this study. The main reason for this discrepancy is that MEG is not sensitive to activities deep in the brain or activities with a dipole direction radial to the brain's surface. However, EEG can measure the activation of the ACC (e.g., Bentley et al. 2002, 2003; Bromm 2004; Kakigi et al. 2005; Opsommer et al. 2001; Tarkka and Treede 1993). Thus itch-related activation of the ACC would be observed using EEG.

### *Time course of itch-related activations*

The latency of the response was significantly longer in the ipsilateral (785 ± 76 ms) than that in the contralateral (740 ± 76 ms) SII/insula. The mean of the difference in latency was larger in this study (46 ± 27 ms) than that in previous pain and tactile studies (10–30 ms) (e.g., Forss et al. 2005; Ploner et al. 1999, 2000; Qiu et al. 2004; Tran et al. 2002). However, the difference in latency of the SII/insula between the hemispheres differed greatly between subjects (this study: 15–95 ms; other studies: −1 to 94 ms) (e.g., Ploner et al. 1999; Qiu et al. 2004). Considering this point, it is not surprising that the mean of the difference in latency in this study was slightly different from that reported previously. The difference in latency between the ipsilateral and contralateral SII/insula is considered to be due to a delay of transmission through the callosal fibers (Forss et al. 1994; Kakigi et al. 2003). Thus the difference in latency of the SII/insula between the hemispheres observed in this study could also be due to the conduction time for transcallosal transmission.

The latency of the precuneus was between that in the contralateral and that in the ipsilateral SII/insula (Table 2). However, there were no significant differences in latency between the contralateral SII/insula and precuneus or the ipsilateral SII/insula and precuneus. Human and animal anatomical studies reported that SII and insula receive projections from the

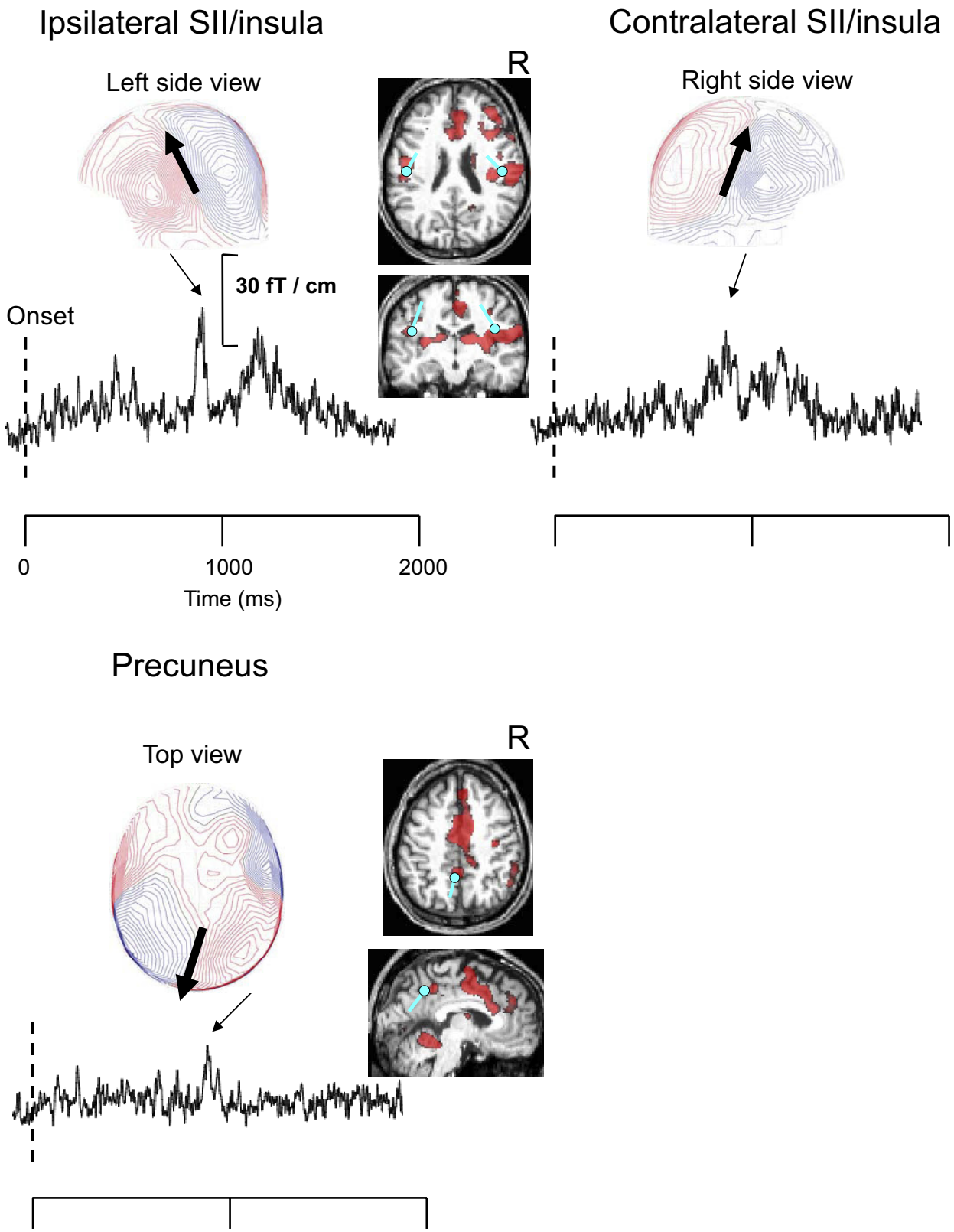


FIG. 4. Typical images of the source locations, a 3-dimensional (3D) isocontour map of magnetic fields and typical areal mean signals of a single subject. The sources located in the bilateral SII/insula and precuneus (light blue circles and bars) were superimposed on the subject's normalized MRI. Red regions in the MRI are areas significantly activated by the itch stimulus in the subject in the fMRI experiment (1st-level analysis, statistical threshold: $P = 0.05$ with FDR correction for multiple comparisons). Areas surrounded by red and blue contour lines in the 3D isocontour map show the outflux and influx of magnetic fields recorded from the gradiometers of the subject, respectively (right side, left side, and top views). The arrows in the graphs indicate when the 3D isocontour map and dipoles were obtained. In each graph, the dashed vertical line indicates the time of stimulus onset. The bar in the *top left* graph indicates the scale of the ordinate. The scale bar 30 fT/cm refers to the amplitude of the magnetic response. R, the right hemisphere.

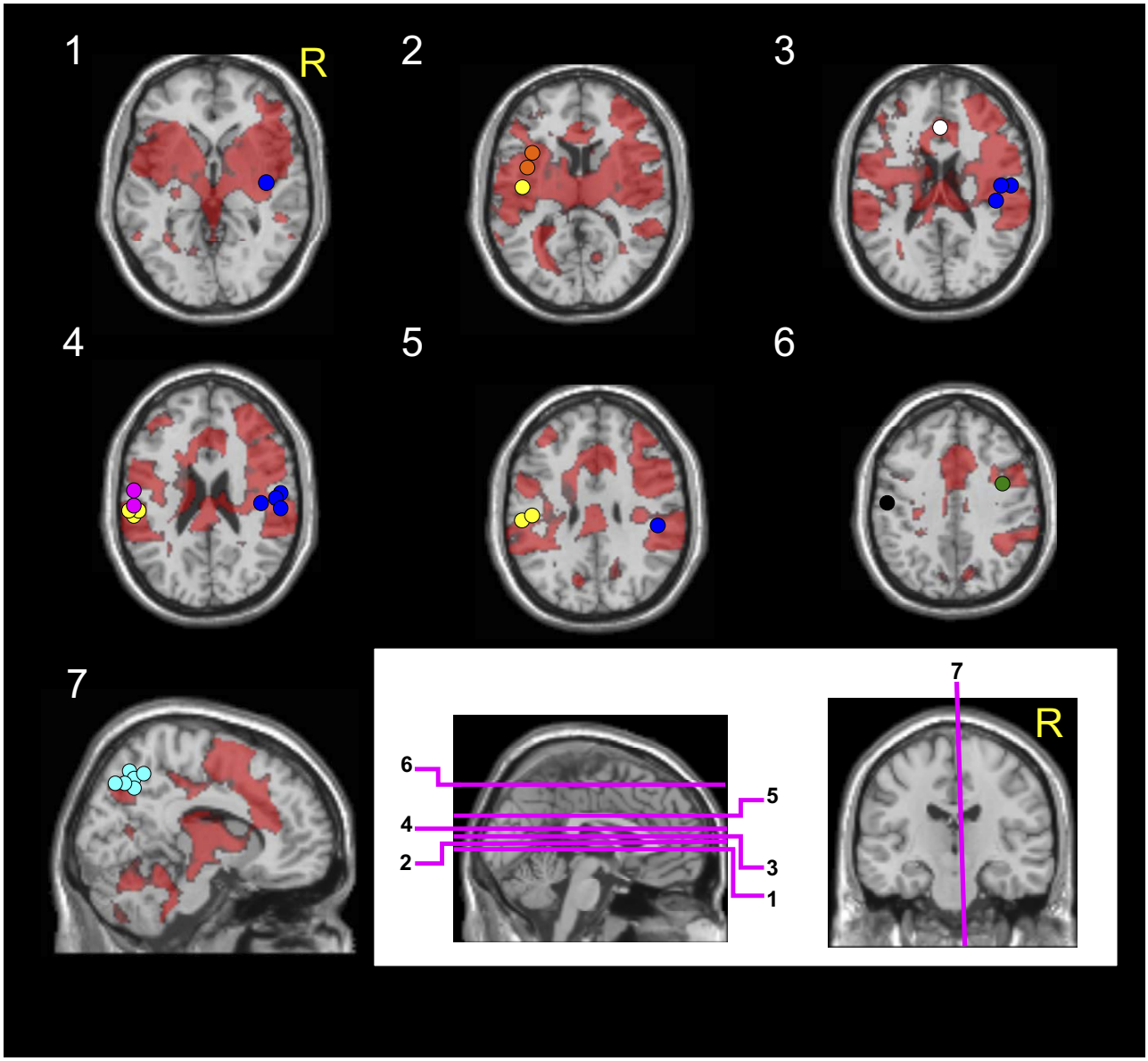


FIG. 5. The dipoles of all the subjects. Dark blue circles: the contralateral SII/insula; yellow circles: the ipsilateral SII/insula. There were 2 distinct responses in the left hemisphere in 2 subjects. The dipoles of these subjects are indicated by pink (SII) and orange (the anterior insula) circles. Light blue circles: the precuneus; white circle: the anterior cingulate cortex; green circle: the premotor cortex; black circle: the primary motor cortex. Red regions were activated by the itch stimuli in the fMRI experiment (2nd-level analysis, statistical threshold: $P = 0.05$ with FDR correction for multiple comparisons). R, the right hemisphere.

lateral thalamus, which are part of the spinothalamic terminations of itch (Andrew and Craig 2001; Simone et al. 2004), whereas the precuneus does not have such projections (Nieuwenhury et al. 1988; Schmahmann and Pandya 1990; Yeterian and Pandya 1985, 1988). However, the precuneus receives projections from the medial thalamus (Schmahmann and Pandya 1990), which are also the spinothalamic terminations associated with C-fibers (e.g., Ammons et al. 1985; Dong et al. 1978). Thus the activation of the precuneus observed in this study might be associated with projections from the medial thalamus to the precuneus. The precuneus also has anatomical connections with itch-related brain regions such as the cingulate cortex, parietal cortex, premotor cortex, supplemetary motor area, prefrontal cortex, and basal ganglia (Cavada and Goldman-Rakic 1989; Goldman-Rakic 1988; Leichnetz 2001; Petrides and Pandya 1984). Thus there are still several possibilities for the brain region from which the precuneus receives projections. It seems that the precuneus does not have anatomical connections with SII and the insula (Nieuwenhury et al. 1988; Schmahmann and Pandya 1990; Yeterian and Pandya 1985, 1988). Thus the activation of the precuneus may be independent of the neural circuit composed of the lateral thalamus-contralateral SII/insula-ipsilateral SII/insula.

### *Functional brain map associated with electrically evoked itch*

Previous itch studies using fMRI and PET used histamine to induce an itch sensation. Thus this is the first fMRI study to show the brain activity associated with electrically evoked itch.

The brain regions activated by electrically evoked itch were almost the same as those observed in studies using histamine-induced itch. However, our fMRI experiment did not reveal activation of the basal ganglia and orbitofrontal cortex, whereas several neuroimaging studies using histamine did (Herde et al. 2007; Leknes et al. 2007; Mochizuki et al. 2007; Schneider et al. 2008; Walter et al. 2005). These brain regions might be less sensitive to phasic stimuli than a long-lasting itch sensation such as that induced by histamine. As mentioned earlier, SII and precuneus were observed in this study, whereas only a few previous itch studies observed the significant activation of these brain regions. In this regard, the brain mechanisms may differ slightly between histamine-induced itch and electrically evoked itch.

### *Difference in pulse between fMRI and MEG experiments*

The VAS score was significantly higher in the fMRI experiment than that in the MEG experiment. However, the difference was not associated with the current intensity, since the current intensity was not statistically significantly different between the fMRI and MEG experiments. Therefore the difference in VAS scores would mainly be attributable to the number of pulses (fMRI experiment: 250 pulses; MEG experiment: 20 pulses). In addition, we found that a 20-pulse stimulus was enough to observe itch-related magnetic responses in MEG but not sufficient to induce large enough changes in blood oxygen level–dependent signals in fMRI. Repeated stimulation of the same site using our electrodes induces habituation/adaptation. Thus we asked each subject to report the subjective sensation of itch before each session. Although we did not record details, we changed the current intensity and location of the electrodes within the wrist more frequently in the fMRI experiment (three sessions in total) than in the first three sessions of the MEG experiment. Considering this point, the effect of habituation/adaptation would become larger with the increase in the number of pulses. However, a clear itch sensation was always obtained after changing the intensity and location of the stimulus in the fMRI and MEG experiments.

### *Conclusion*

This is the first study to show the time course of activity in itch-related brain regions using electrically evoked itch, MEG, and fMRI. The magnetic responses of the bilateral frontotemporal regions were mainly derived from the activation of the bilateral SII/insula. The ipsilateral SII/insula was activated significantly later than the contralateral SII/insula, suggesting that the difference in latency was associated with transmission in the callosal fibers. The magnetic response in the posterior part of the centroparietal region was mainly associated with the activation of the precuneus, whereas no previous pain and tactile studies using MEG and EEG reported dipoles in the precuneus. This interesting result may indicate the uniqueness of itch perception in humans. The activation of the precuneus occurred in between that of the contralateral and that of the ipsilateral SII/insula. The findings indicate that combining methods with high temporal (e.g., MEG) and spatial (e.g., fMRI) resolution would be useful to investigate the temporal aspect of the brain mechanism of itch.

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