Somatotopy in Human Primary Somatosensory Cortex in Pain System

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Background: Compared with somatotopical organization (somatotopy) in the postcentral gyrus in the tactile system, somatotopy in the pain system is not well understood. The aim of this study is to elucidate whether there is somatotopy in the human pain system.

Methods: To elucidate the somatotopy of nociceptive neurons in the postcentral gyrus, the authors recorded pain-evoked cortical responses to noxious intraepidermal electrical stimulation applied to the left hand and left foot in 11 male subjects, using magnetoencephalography.

Results: Brief painful stimuli evoked sustained cortical activity in the primary somatosensory cortex (SI) in the hemisphere contralateral to the stimulated side and in the secondary somatosensory cortex in both hemispheres. In SI, representations of the hand and foot were distinctly separated, with a more medial and posterior location for the foot, whereas no significant difference was found in the locations for the secondary somatosensory cortex dipole. The SI arrangement along the central sulcus was compatible with the homunculus revealed by Penfield using direct cortical stimulation during surgery.

Conclusions: The human pain system contains a somatotopical representation in SI but with less somatotopical organization in the secondary somatosensory cortex. The current results provide supporting evidence of SI involvement in human pain perception and suggest that human SI subserves the localization of the stimulated site in nociceptive processing.

THE human postcentral gyrus is associated with somatic sensation, as is represented by the well-known "penfieldian homunculus" (a bizarre-shaped human body projected to the brain cortical section). Since the landmark study of Penfield and Boldrey,[1] somatotopy (an orderly representation of the skin surface) has been demonstrated by various methods, such as the direct stimulation of the cortical surface,[1] the recording of somatosensory-evoked responses on the cortical surface,[2–4] and magnetoencephalographic approaches.[5,6] However, all of these somatotopy-related studies were performed in the processing of innocuous tactile somatosensory information.

Pain processing in humans, particularly in terms of primary somatosensory cortex (SI) involvement in pain perception, remains largely unknown in contrast to the processing of innocuous tactile sensation. Recent functional imaging studies in humans have provided evidence that multiple regions of the brain are involved in pain perception. For example, the secondary somatosensory cortex (SII), insula, and anterior cingulate cortex have been shown to be activated by noxious stimuli.[7] Bushnell *et al.*[8] reported SI to be activated in approximately one half of all pain imaging studies (see table 1 in Bushnell *et al.*), and its contribution to pain perception is still controversial[7,8] since Tarkka and Treede[9] first reported activity in the vicinity of SI using electroencephalography. Only a few recent magnetoencephalography studies have demonstrated pain-induced SI activity.[10–12] The probable reason half of the studies did not identify the SI activity is that early SI components are very weak and easily overlooked.[13]

As for the location of noxious stimulation–evoked activation in SI, only a few studies, such as somatosensory-evoked potential[9,14] and positron emission tomography[15] studies, have indicated an arrangement along the central sulcus consistent with somatotopical organization. However, these indications regarding somatotopy in pain perception remains to be confirmed, because SI involvement in pain perception is still controversial and somatotopical investigation essentially requires high spatial and temporal resolutions. In addition, it has been technically difficult to record cortical activities in humans noninvasively, and selectively apply painful stimulation.

Magnetoencephalography noninvasively records weak magnetic fields produced by electric currents flowing in neurons in the human brain.[16] Multichannel magnetoencephalography has an advantage of detecting cortical activities at higher spatial resolutions (on the millimeter order) than those of somatosensory-evoked potential (recorded by electroencephalography), and at much higher temporal resolutions (on the millisecond order) than those of functional magnetic resonance imaging and positron emission tomography.

The aim of this study is to elucidate whether there is somatotopy along the central gyrus in the human pain system by recording pain-evoked somatosensory-evoked magnetic field (pain SEF). In this study, we used two methods to detect SI activities along the central gyrus in human pain perception: One is magnetoencephalography, and another is noxious intraepidermal electrical stimulation that preferentially provides Aδ-fiber nociceptive stimuli without tactile sensations. We recorded pain SEF by whole-head–type magnetoencephalography after acute pain evoked by noxious intraepidermal electrical stimulation inflicted to the dorsum of the left hand and left foot in healthy human subjects.

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Materials and Methods

Subjects

The experiment was performed on 11 healthy male volunteers, aged 24–35 yr (mean age ± SD, 29.0 ± 3.6). The study was approved by the Gunma University Hospital Clinical Investigation and Research Unit (ethics committee; Maebashi, Japan), and written consent was obtained from all of the subjects. All of the subjects were right-handed, none had a history of neurologic disease, and all had normal magnetic resonance (MR) brain images.

Painful Electrical Stimulation

For painful stimulation, an intraepidermal stimulation method developed by Inui *et al.*[12,17] was used. However, the original method was modified slightly to provide a higher selectivity for the activation of nociceptors.[18] We used a concentric bipolar needle electrode (patent pending: inventors, Koji Inui and Yasuyuki Takeshima; assignee, National Institute for Physiologic Sciences, Okazaki, Japan; date patent applied for, November 30, 2004) for intraepidermal stimulation in this study with its inventors' permission. The anode was an outer ring 1.2 mm in diameter, and the cathode was an inner needle that protruded 0.2 mm from the outer ring. By gently pressing the electrode against the skin, the needle tip was inserted in the epidermis, while the outer ring was attached to the skin surface.

This method has some major advantages as follows: (1) Aδ fibers can be selectively stimulated. The method has been shown to be useful in pain SEF studies in humans[12,18] to detect signals ascending through Aδ fibers without the contamination of tactile responses due to fast conducting fibers, such as Aβ fibers. (2) Its stimulation induces sharp and well-defined pricking pain sensations without any innocuous sensations in humans. (3) It is a noninvasive and simple method involving only electrical stimulation and therefore activates skin nociceptors directly without a time delay, unlike laser stimulation. The method provides a constant activation time, which is the condition required for stimulus-locked averaging in somatosensory-evoked magnetic field (SEF) studies.

Using such a method, we could evoke sharp-pain stimulus preferentially without any tactile sensation. The electric stimulus was a current-constant square wave pulse delivered at random intervals of 0.2–0.4 Hz. The stimulus duration was 1.0 ms. Current intensity was scaled sufficient to produce a definite pain sensation and a pain intensity from 3 to 5 on a visual analog scale, where 0 represents not painful and 10 represents extremely painful in each subject. Stimulus intensity was determined before the recordings.

We stimulated the left hand and left foot. The hand site was the dorsum of the left hand between the first and second metacarpal bones. The foot site was the instep of the left foot between the first and second metatarsal bones. The mean stimulus intensities were 0.58 ± 0.08 mA (mean ± SD) for the hand stimulation and 0.59 ± 0.16 mA for the foot stimulation. The mean visual analog scale scores were 3.6 ± 0.6 for the hand stimulation and 3.8 ± 0.6 for the foot stimulation. The insertion of the needle electrode caused no bleeding or visible damage to the skin.

Experimental Protocol

Two different conditions were used for each subject: conditions under which the pain stimuli were applied to the left hand (hand condition) and left foot (foot condition). The first stimulus place (the hand or foot) was randomized across subjects. The subjects were required to relax and count the stimuli applied silently, *i.e.*, to pay attention to the stimuli. Each condition contains 130 stimuli. To avoid habituation and maintain the subject's vigilance, we took three intervals of 2–3 min randomly under each condition and divided one condition into four sessions. During the interval between sessions, the subjects were asked how many stimuli were applied in the preceding session to confirm their arousal and whether they recognized definite pain stimuli without tactile sensation.

Data Acquisition and Analysis

Somatosensory-evoked magnetic fields were recorded with a helmet-shaped 306-channel detector array (Vectorview; ELEKTA Neuromag, Helsinki, Finland) comprising 102 identical triple sensor elements in a magnetically shielded room. Each sensor element consisted of two orthogonal planar gradiometers and one magnetometer coupled to a multisuperconducting quantum interference device, thus providing three independent measurements of magnetic field. The signals were recorded at a band-pass of 0.1–100 Hz and digitized at 600 Hz. The analysis period of 550 ms included a prestimulus baseline of 50 ms. Pain SEF data, *i.e.*, the averaged magnetoencephalographic values after painful somatosensory stimulation, were collected and averaged after 130 stimuli for each condition. The signals recorded from the 204 gradiometers were used for source localization.

To identify the sources of the evoked activities, the equivalent current dipole (ECD), which best explained the measured data, was computed using a least-squares search method.[16] A subset of 10–18 channels including the local signal maxima were used for the estimation of ECDs. These calculations gave the three-dimensional location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MR images to determine the source location. The x-axis passed through preauricular points pointing to the right, the positive y-axis traversed the nasion, and the positive z-axis pointed up. The goodness of fit of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field vari-

ance. We used the goodness of fit to determine whether the model was an appropriate one. Only ECDs explaining more than 90% of the field variance (goodness of fit > 90%) at selected periods of time were used for further analysis.

The analysis period was extended to the entire time period, and all of the channels were taken into account in computing a time-varying multidipole model because several cortical activities after painful stimulation overlapped temporally. The strengths of the previously found ECDs were allowed to change while their locations and orientations were maintained. The resulting source strength waveforms were used in the determination of peak and onset latencies and dipole strength (peak amplitude). The data acquisition and analysis followed Hamalainen *et al.* [16]

On the basis of point markers, MR image and magnetoencephalography coordinate systems were aligned, and source locations were superposed on the individual MR images. MR image scans were obtained from all the subjects with a 3.0-T Siemens Allegra scanner (Siemens Medical Systems, Erlangen, Germany). T1-weighted coronal, axial, and sagittal image slices obtained every 2.0 mm were used for rendering the three-dimensional reconstruction of the brain's surface.

After confirming the dipole moments between two different conditions, to determine the statistical significance of the source location on a three-dimensional coordinate system, we adopted a discriminant analysis, using the x-, y-, and z-coordinates as variables. Furthermore, the Wilcoxon paired signed rank test was used to assess the difference in the coordinates (x, y, and z) of the dipole source, onset latency, peak latency, and dipole moment strength between the hand and foot conditions. $P < 0.05$ was considered to be significant. Data were expressed as mean $\pm$ SD.

Results

The epidermal stimulation elicited well-defined pricking sensations without tactile sensations in all of the subjects. There was no significant difference in visual analog scale score or stimulus intensity between the hand and foot conditions.

Figure 1 shows representative data obtained from subject 1 and its analysis procedure. Under both the hand and foot conditions, clear and consistent evoked magnetic fields were detected in three spatially segregated areas, namely the right centroparietal area and the right and left frontotemporal areas, which are shown in figure 1a as circles *A*, *B*, and *C* under the hand condition, and as circles *A'*, *B'*, and *C'* under the foot condition, respectively. By the ECD analysis, circles *A* and *A'* in figure 1a were estimated to be located in the right posterior wall of the central sulcus, corresponding to SI in the hemi-

sphere contralateral to the stimulated side (fig. 1b). Similarly, circles *B* and *B'* and *C* and *C'* were estimated in the upper bank of the sylvian fissure, corresponding to SII in the right and left hemispheres, respectively (fig. 1b). We termed the three ECDs cSI (contralateral SI), cSII (contralateral SII), and iSII (ipsilateral SII) under each condition. The SI sources were located in or around the crown of the postcentral gyrus under both the hand and foot conditions, corresponding to Brodmann's area 1 or 2 (figs. 1b and 2). Their x-, y-, and z-coordinates are shown in table 1. The traces in figure 1c indicate the time course of these activities in both the hand and foot.

Figure 2 shows the locations of cSI and cSII under the hand and foot conditions of four representative subjects, respectively, superimposed on three-dimensional brains constructed from each subject's brain MR images. There was a significant difference between the hand and foot cSI locations based on three-dimensional cluster analysis (discriminant analysis, $P = 0.0014$). On the other hand, the source locations of cSII (discriminant analysis, $P = 0.548$) and iSII ($P = 0.547$) did not differ significantly between the hand and foot conditions. Using the Wilcoxon paired signed rank test on the coordinates (x, y, and z) of ECD (cSI, cSII, iSII) locations between the hand and foot conditions, significant differences in the x- and y-coordinates in cSI were found. The cSI location under the foot condition was significantly medial ($P < 0.005$) and posterior ($P < 0.05$) to that under the hand condition (table 1), whereas the bilateral SII (cSII and iSII) coordinates did not differ significantly between the two conditions (table 1 and figs. 1b and 2).

Then, we compared the onset latencies, peak latencies, and dipole strengths of cSI, cSII, and iSII between the hand and foot conditions. Time course waveforms recorded in a representative subject under both the hand and foot conditions are shown in figure 1c. The onset and peak latencies were significantly longer under the foot condition than under the hand condition in all the cSI, cSII, and iSII sources (table 2). They were significantly longer in iSII than in cSII ($P < 0.01$) under both conditions. In the iSII, the dipole strength under the foot condition was significantly smaller than that under the hand condition ($P < 0.05$); there were no significant differences in the dipole strengths of cSI and cSII between the two conditions (table 2).

Discussion

This is the first magnetoencephalographic study that showed somatotopy in the human pain system. Using magnetoencephalography, which has high temporal and spatial resolutions, we verified somatotopy in SI activities along the central sulcus in early responses to noxious intraepidermal electrical stimulation. In contrast, bilateral SII shows less somatotopy. The current results provide
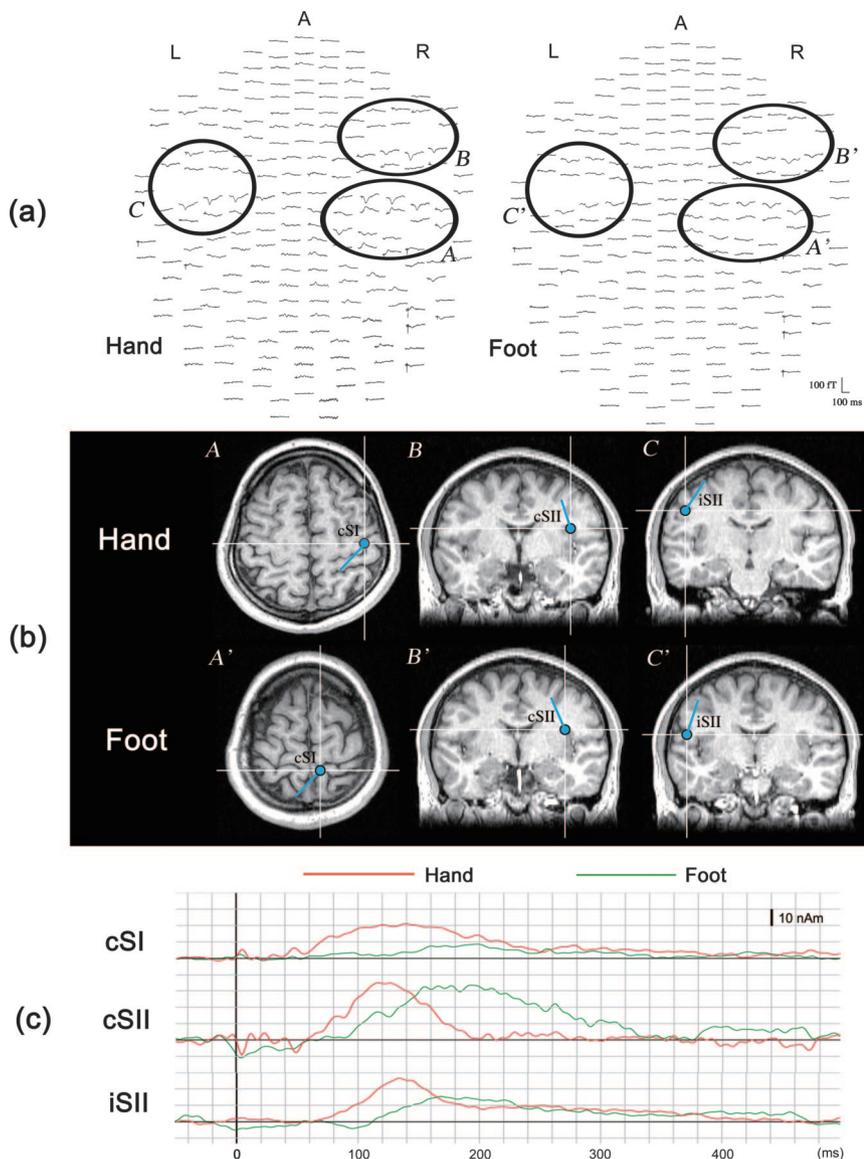
Fig. 1. Primary cortical response to pain applied to hand and foot in representative single subject, drawn by magnetoencephalography. A = anterior; cSI = contralateral primary somatosensory cortex; cSII = contralateral secondary somatosensory cortex; Hand = hand condition; iSII = ipsilateral secondary somatosensory cortex; Foot = foot condition; L = left; R = right. (*a*) Pain-evoked magnetic fields of subject 1 after intraepidermal electrical stimulations applied to dorsum of left hand and left foot. The head is viewed from the top, and in each response pair, the *upper trace* illustrates the field derived along the latitude, and the *lower trace* illustrates that along the longitude. Clear consistent magnetic fields were detected in three spatially segregated areas, circles *A*, *B*, and *C*, under the hand condition, and circles *A'*, *B'*, and *C'* under the foot condition, respectively. (*b*) Location and orientation of main responses (*A*, *B*, and *C* under the hand condition; *A'*, *B'*, and *C'* under the foot condition) superimposed on magnetic resonance image sections of subject 1. Under each condition; *left*, horizontal slice at primary somatosensory cortex level; *center*, coronal slice at cSII level; *right*, coronal slice at iSII level. (*c*) The figure shows the time-varying dipole strengths of cSI, cSII, and iSII activities under the hand (*red line*) and foot (*green line*) conditions. The *horizontal line* indicates the time (ms) from the stimulus onset, and the *vertical line* indicates electrical potential (nAm) at the source locations.

supporting evidence of SI involvement in human pain perception and suggest that human SI subserves the localization of the stimulated site in nociceptive processing.

Pain Evoked by Intraepidermal Electrical Stimulation

We confirmed in all the subjects under both hand and foot conditions that brief, pricking, and well-localized pain sensations are evoked by intraepidermal electrical stimulation, which reflects preferential Aδ-fiber stimulation by this method. We consider this to be the greatest advantage of intraepidermal electrical stimulation, *i.e.*, it enables selective technical stimulation of the nociceptive system with ordinary parts. There has been a problem with conventional transcutaneous electric stimulation methods such as that using a bipolar felt-tip electrode, which although is an easy method of producing painful sensations, activates large myelinated fibers (Aα fibers or Aβ fibers) related to tactile, vibration, and proprioception sensations, which are not "pure" pain-related components.

First pain is a brief, pricking, and well-localized pain, which mediate mainly Aδ fibers. The pain SEFs observed were generally compatible with results of previous studies using intraepidermal electrical stimulation[12,19,20] and laser stimulation;[11,21] they showed no activities during a 0- to 60-ms latency period in all subjects. For example, the activities of well-known 20- and 30-ms responses mediating Aβ-fiber inputs, which are known as the earliest cortical responses evoked by tactile stimulation, were completely lacking (fig. 1c).[19–22] This observation could be well explained by the difference between the conduction velocities mediating Aβ fiber (innocuous) and Aδ fiber (noxious) inputs in both peripheral and spinal processing.[19,23]
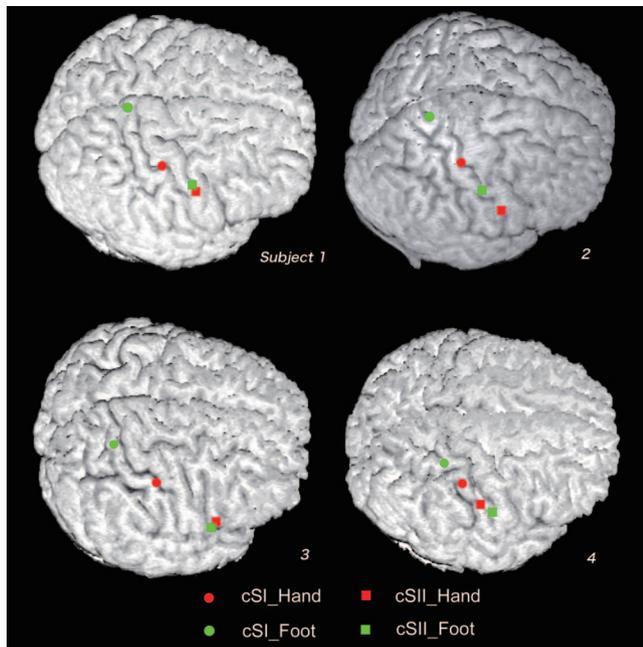
Fig. 2. Source locations of contralateral primary somatosensory cortex and secondary somatosensory cortex in four subjects. cSI = contralateral primary somatosensory cortex; cSII = contralateral secondary somatosensory cortex; Hand = hand condition; Foot = foot condition. Source locations are superimposed on individual three-dimensional magnetic resonance images. The three-dimensional brain image was reconstructed using the magnetic resonance images of each subject. The *red filled circle and square* indicate the source locations of cSI and cSII under the hand condition, respectively. The *green filled circle and square* indicate the source locations of cSI and cSII under the foot condition, respectively. There was a significant difference between the hand and foot cSI locations based on three-dimensional cluster analysis (discriminant analysis, *P* = 0.0014). On the other hand, the source locations of cSII (discriminant analysis, *P* = 0.548) and iSII (*P* = 0.547) did not differ significantly between the hand and foot conditions.

Somatotopy in SI

The SI sources between the hand and foot in the current study are clearly separated along the central sulcus, and their spatial relationship is compatible with

Table 1. Mean Coordinates of Sources under Each Condition

	x, mm	y, mm	z, mm
Hand			
cSI	39.4 ± 9.8	8.0 ± 8.2	100.7 ± 10.3
cSII	50.0 ± 5.5	25.8 ± 7.7	63.5 ± 7.4
iSII	-46.7 ± 3.7	18.8 ± 6.6	68.9 ± 7.3
Foot			
cSI	24.6 ± 9.6*	-1.4 ± 8.0†	101.2 ± 9.8
cSII	53.5 ± 5.6	25.0 ± 7.9	62.5 ± 11.9
iSII	-49.6 ± 5.0	19.8 ± 5.9	67.6 ± 11.1

The x-axis passed through the preauricular points, pointing to the right; the positive y-axis traversed the nasion; the positive z-axis pointed up. The contralateral primary somatosensory cortex (cSI) location under the foot condition was significantly medial (Wilcoxon paired signed rank test, $P < 0.005$) and posterior ($P < 0.05$) to that under the hand condition.

* $P < 0.005$.   † $P < 0.05$.

cSII = contralateral secondary somatosensory cortex; iSII = ipsilateral secondary somatosensory cortex.

Table 2. Mean Onset Latencies, Peak Latencies, and Dipole Strengths under Each Condition

	Onset Latency	Peak Latency	Dipole Strength
Hand			
cSI	69.5 ± 8.1	135.7 ± 30.0	14.0 ± 9.8
cSII	67.8 ± 11.9	128.9 ± 24.5	19.3 ± 13.1
iSII	75.0 ± 14.1	152.3 ± 32.1	24.7 ± 9.0
Foot			
cSI	91.0 ± 13.7*	170.2 ± 51.1†	15.7 ± 7.0
cSII	90.6 ± 23.8*	171.6 ± 44.5*	14.4 ± 8.3
iSII	103.7 ± 13.1†	190.4 ± 44.2*	17.4 ± 8.7‡

Significant differences between the hand and foot conditions were found at * $P < 0.005$, † $P < 0.01$, and ‡ $P < 0.05$ with the Wilcoxon paired signed rank test. The onset and peak latencies under the foot condition were significantly longer than those under the hand condition in all contralateral primary somatosensory cortex (cSI), contralateral secondary somatosensory cortex (cSII), and ipsilateral secondary somatosensory cortex (iSII) sources. The dipole strength of iSII under the foot condition was significantly smaller than that under the hand condition, whereas there was no significant difference in cSI and cSII dipole strengths between the two conditions.

the penfieldian homunculus (fig. 2). We consider our results to qualify as appropriate candidates for analyzing somatosensory areas in the human pain system. However, further studies are required to establish the entire body map in SI for the human nociceptive system. There were more individual variations in the foot source locations than in the hand source locations. This observation is compatible with those of previous studies investigating lower limb representations with tactile stimulation, suggesting complicated anatomical problems of the lower limb area in SI.[14,24]

In terms of SI activity, ECDs were found located in the anterior crown of the postcentral gyrus under both the hand and foot conditions in the MR images, suggesting that they correspond to Brodmann's area 1 or 2 (figs. 1b and 2). The current ECD locations are generally in accord with pain-induced SI source locations that recent magnetoencephalographic data have shown, different from those of tactile stimulation that originates from area 3b.[11,20,21,25] To our knowledge, there are three magnetoencephalographic studies[11,19,21] in which the locations of SI activation after noxious and innocuous stimuli were directly compared. All of these studies found the location of noxious stimulus-evoked SI activation probably in area 1 slightly more medial and superior than that of early SI activation in area 3b evoked by tactile stimuli. These studies clearly showed that the processing of noxious signals differed from tactile processing in SI. Within subdivisions in SI, area 3a is also suggested to be involved in the nociceptive system.[26,27] Kenshalo *et al.*[28] suggest that nociceptive neurons are located in area 1 of SI in monkeys, which is somatotopically organized. Therefore, it is presumed that subdivisions except 3b are involved in the nociceptive system.

SI in Nociceptive Processing

Kenshalo *et al.*[29,30] clearly showed that a pathway from the ventral spinothalamic tract to SI *via* the ventroposterior lateral nucleus of the thalamus plays a role in nociception in unitary recording studies in monkeys. Nociceptive neurons in both the ventroposterior lateral nucleus and SI have restricted contralateral receptive fields and are somatotopically organized.[28–30] They also demonstrated that the activity of SI nociceptive neurons correlates with the monkey's detection speed of noxious stimuli.[31] These results suggest that nociceptive neurons in SI possess the ability to provide information on the sensory-discriminative component of nociceptive processing.

Accumulating evidence from human imaging studies[9,10,15,32–35] also indicates the essential role of SI in the sensory-discriminative aspects of pain, such as localization, intensity, and temporal attributes of a noxious stimulus. The localization of painful laser-induced stimuli applied to the hand and foot areas was almost the same as that of tactile stimuli, with a mean error of 14 ± 3 mm.[36] A recent study clearly showed that the spatial discrimination capacity does not differ between nociceptive and tactile systems in humans.[37] These findings suggest that the human nociceptive system has a neural mechanism that provides precise spatial information. Among possible brain areas responsible for such mechanism, SI is the most frequently suggested area involved in stimulus localization for the nociceptive system.[7]

Despite these data, the role of SI in the discriminative aspect of pain remains controversial.[27,38–40] In this study, we showed the somatotopical representations of the hand and foot in SI after painful stimulations, which are consistent with the evidence of small restricted receptive fields of SI nociceptive neurons that receive projections from somatotopically organized neurons in the ventroposterior lateral nucleus in monkeys.[29,30] Our results suggest that human SI subserves the localization of the stimulated site in nociceptive processing. A case report of a patient with a lesion in SI also supports this notion; this patient had a selective loss of first pain sensation and pain localization, but a preserved pain affect.[41]

Somatotopy in SII

Our current data did not indicate a clear somatotopy in SII, for which we found strong responses from the hand and foot stimulations. Somatotopy in SII has been reported in monkeys[2,42,43] and humans.[44–46] Although no study has shown a clear topographic order of SII in humans, unlike the homunculus in SI, Maeda *et al.*[47] have shown a tendency of the SII topographic order in humans as follows: medial–lateral direction: tibial nerve–middle finger–thumb–upper lip–lower lip. Our results of SII in pain perception showed a tendency of the topographic order hand–foot in the medial–lateral direction, opposite that reported by Maeda *et al.* in tactile sensation.

Three magnetoencephalographic studies[11,19,21] demonstrated no significant difference between the locations of tactile and nociceptive sources in human SII. In contrast, Vogel *et al.*[48] suggested that the nociceptive SII area in humans activated by noxious stimulations may be separate from the tactile SII area. It is unclarified whether the tactile and nociceptive processings are both in the same SII areas or whether they exhibit different neuronal activities despite their being adjacent each other. In the current study, because bilateral SII locations showed no significant differences between the hand and foot conditions, we conclude that SII in the pain system does not have a strong somatotopy, unlike SI.

SII in Nociceptive Processing

The secondary somatosensory cortex has been suggested to be part of the cognitive-evaluative components of pain perception.[10,32–35] Our result of no significant somatotopy in SII activities supports the suggestion that SII is associated more with the cognitive-evaluative aspects of the painful nature of a stimulus, such as pain-related emotion, learning, and memory, rather than with the sensory-discriminative aspects of pain.

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