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Somatotopic organization of human somatosensory cortices for pain: a single trial fMRI study

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The ability to locate pain plays a pivotal role in immediate defense and withdrawal behavior. However, how the brain localizes nociceptive information without additional information from somatotopically organized mechano-receptive pathways is not well understood. To investigate the somatotopic organization of the nociceptive system, we applied Thulium-YAG-laser evoked pain stimuli, which have no concomitant tactile component, to the dorsum of the left hand and foot in randomized order. We used single-trial functional magnetic resonance imaging (fMRI) to assess differential hemodynamic responses to hand and foot stimulation for the group and in a single subject approach. The primary somatosensory cortex (SI) shows a clear somatotopic organization ipsi- and contralaterally to painful stimulation. Furthermore, a differential representation of hand and foot stimulation appeared within the contralateral opercular–insular region of the secondary somatosensory cortex (SII). This result provides evidence that both SI and SII encode spatial information of nociceptive stimuli without additional information from the tactile system and highlights the concept of a redundant representation of basic discriminative stimulus features in human somatosensory cortices, which seems adequate in view of the evolutionary importance of pain perception.

Keywords: Pain; Nociception; Single trial fMRI; Laser; Neuroimaging; Somatotopy; Sensory coding; SI; SII

Introduction

The ability to locate the origin of a noxious stimulus is essential for the individual to withdraw or escape, which in many instances requires the adoption of spatially oriented withdrawal actions. Previous work demonstrated that a very basic form of spatial coding—that of stimulus laterality of pain stimuli—is not only preserved in target regions of the afferent neuraxis such as thalamus, SI, SII, and posterior insula (Bingel et al., 2003; Brooks et al., 2002; Coghill et al., 2001), but also in subcortical structures of the motor system, such as the putamen, red nucleus, and cerebellum (Bingel et al., 2002). Previous psychophysical data from studies in humans using intraneural electrical microstimulation have demonstrated an impressive capability to localize nociceptive stimuli, even when evoked by C-nociceptors (Ochoa and Torebjork, 1989). Similarly, selective nociceptive laser stimuli are precisely localizable (Kanda et al., 1999). These findings suggest the existence of a somatotopic representation for pain within the central nervous system. However, knowledge about the cortical representation of spatial coding of nociceptive stimuli in humans is comparably sparse.

The major candidate to subserve spatial discrimination of painful stimuli is the primary somatosensory cortex (SI) given its pronounced somatotopic organization of mechano-receptive afferents. The postulate of SI's major role in the sensory-discriminative aspects of pain processing goes back to the early observations of Head and Holmes (1911) in patients with parietal lesions and has been substantiated by animal data demonstrating nociceptive afferents from lateral thalamic nuclei into SI cortex and by human data using PET (Andersson et al., 1997).

Another major cortical site of early pain encoding comprises a broad region surrounding the Sylvian fissure including insula and secondary somatosensory cortex (SII). Data from animal studies and recent imaging studies in humans suggest that SII has a somatotopic organization for tactile stimuli (Burton and Carlson, 1986; Disbrow et al., 2000; Ruben et al., 2001). However, previous imaging studies failed to demonstrate a somatotopic organization of nociception within SII that goes beyond stimulus laterality (Andersson et al., 1997; Xu et al., 1997). Thus, the role of SII in discriminating stimulus location of painful stimuli remains ambiguous (Treede et al., 2000).

This study aims to investigate the contribution of primary and secondary somatosensory cortices to the encoding of stimulus location of nociceptive stimuli that lack a concomitant mechanical component. Therefore, we used a Thulium(Tm)-YAG-laser to apply sudden unexpected and selective nociceptive stimuli in a randomized order to hand or foot of the left body side. To test the hypothesis of a somatotopic organization in primary and secondary

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somatosensory cortices, we studied BOLD responses using an event-related fMRI design.

Methods

Subjects

Eighteen healthy subjects (16 male, 2 female) all right-handed, aged 20 to 33 years (mean 27) gave written informed consent to participate in the study, which was conducted in accord with the declaration of Helsinki and approved by the local Ethics committee. All subjects had normal pain thresholds for both sites of stimulus application, no history of neurological or psychiatric disease, and were free to withdraw from the study at any time.

Laser stimulation

A Tm:YAG infrared laser (Neurolaser, BAASEL Lasertech, Starnberg Germany) was used to apply computer-controlled brief radiant pain stimuli. The Tm:YAG laser emits near-infrared radiation (wavelength 1.96 μm, spot diameter 5 mm, pulse duration 1 ms) with a penetration depth of 360 μm into the human skin, where it activates heat-sensitive A-delta and C-nociceptors. The laser stimulus allows precise restriction of the deposited heat energy to the termination area of primary nociceptive afferents (20–570 μm), without damaging the epidermis or affecting the subcutaneous tissue. Although the pulse length is short (1 ms), the profile of the temperature increase in the skin is depth-dependent delayed (maximum around 50 ms) and much longer due to heat conduction, active heat absorption, and passive cooling. The different conduction velocities of A-delta and C-fibers ($\approx$15 vs. $\approx$1 m/s) leads to sequential pain sensations (Spiegel et al., 2000). Psychophysical measurements of the pain increase over time after a Tm-Laser impulse of 1 ms indicates a maximum pain after 1 s followed by a slow decay (Ploner et al., 2002).

All ferromagnetic components belonging to the laser head used inside the scanner room were replaced by brass parts. The main laser device was in the MR control room, and connected to the laser head in the magnet room with an optical fiber of 10 m length, transmitting the laser light. Individual pain thresholds for the sites of stimulus application were determined outside the scanner at a separate occasion, but within 1 week before the MR experiment.

Experimental protocol

Fifty selective nociceptive cutaneous laser stimuli were randomly applied to the dorsum of the left hand or foot (25 stimuli each) in a single fMRI session. Stimulus application was computer controlled (Software Presentation; www.neurobehavioralsystems.com), and unpredictable, invisible, and inaudible for the subject. The laser probe was positioned manually to either stimulate hand or foot as signaled by a vocal command only to be heard for the experimenter. The laser probe was held at a distance of about 5 cm above the skin. A helium-neon pilot-laser spot illuminated the area to be stimulated. To avoid sensitization and habituation, the stimulus site was systematically varied (at least 1 cm) after each stimulus. For hand-stimulation an energy level of 600 mJ was used. This choice was based on previous fMRI and psychophysical experiments, indicating that 600 mJ stimuli applied to the dorsum of the hand evoke a brief but clearly ‘‘pin prick-like’’ painful sensation without any warmth or tactile components (Bromm and Lorenz, 1998; Buchner et al., 2000; Spiegel et al., 2000). This intensity reliably activates SI, SII, and the insula (Bornhovd et al., 2002; Buchner et al., 2000). To account for an increased pain-threshold of the foot using the Tm:YAG-laser (Devos et al., 2000), a 650 mJ stimulus was used for foot stimulation. The inter-stimulus interval was fully randomized between (8 and 12 s). Rating of the perceived pain-intensity was not requested to minimize additional motor or working memory components. After scanning, all subjects reported that the stimuli were moderately and comparably painful for both sites of stimulus application.

Image acquisition

MR scanning was performed on a 1.5-T MRI system (Siemens Vision). A high resolution ($1 \times 1 \times 1$ mm voxel size) T_1-weighted structural MRI was acquired for each volunteer using a 3-D FLASH sequence. A total of 382 fMRI scans (20 axial, 3 mm thick slices each, 1 mm gap) were acquired using a gradient echo echo-planar (EPI) T2*-sensitive sequence (TR 1.6 s, TE 40 ms, flip angle 90°, matrix 64×64, field of view 210×210 mm). The images were oriented slightly tilted toward the AC-PC line and aligned so that the sample included primary as well as secondary somatosensory cortex. The subjects’ head was positioned in a standard head coil with foam pads.

Image processing and statistical analysis

Image processing and statistical analysis were carried out using SPM99 (Friston et al., 1995b; Worsley and Friston, 1995) (http://www.fil.ion.ucl.ac.uk/spm). All volumes were realigned to the first volume (Friston et al., 1995c), spatially normalized (Friston et al., 1995a) to a standard EPI template (Evans et al., 1993) and finally smoothed using a 6-mm isotropic Gaussian kernel. The T_1-weighted structural data was co-registered to the functional scans by normalizing it to a T_1-weighted template in the same space as the T_2* EPI template used to normalize the functional data set. Data analysis was performed by modeling the different trials (pain foot, pain hand) as delta functions convolved with a canonical hemodynamic response function as implemented in SPM99. Inspection of the plotted responses revealed that responses evoked by laser stimuli at the foot were delayed by 1–1.5 s on average, which reflects the difference in conduction velocity of C- and A-delta-fibres (Chung et al., 1979; LaMotte and Campbell, 1978). We therefore also delayed the HRF model for foot responses by 1 scan (1.6 s). Voxel-wise regression coefficients for both regressors were estimated using least squares within SPM99 (Friston et al., 1995c). Movement parameters derived from the realignment procedure were included as covariates of no interest. Effects were tested with appropriate linear contrasts of the regression coefficients (parameter estimates), resulting in a t statistic for each voxel. These t statistics constitute a statistical parametric map (SPM), which are interpreted by referring to the probabilistic behavior of Gaussian random fields (Worsley, 1994). SPMs were computed for each of the stimulus conditions (hand and foot) for each individual and for the group using random effects analysis. In our regions of interest, namely SI and SII, whose involvement in pain processing has been clearly established by previous functional imaging studies (for review, see Peyron et al., 2000), a region of interest approach was used. In the group (random effects) analysis, activations in SI and SII were corrected for a

sphere of 20/15 mm radius, respectively. Significance is reported according to classical criteria namely $P < 0.05$ corrected for multiple comparisons. The data of three subjects were excluded from data analysis due to gross movement artifacts.

Assessment of somatotopic organization

Hand stimulation resulted in significantly stronger activation compared to foot stimulation throughout the whole volume sampled. This parallels experiences from a recent fMRI study comparing tactile stimulation of hand and foot stimulation (Ruben et al. personal communication) and previous ERP and MEG studies, also indicating that laser stimulation of the foot evokes significantly smaller signal than hand stimulation (Spiegel et al., 2000; Lorenz et al. and Ploner et al. personal communication). Consequently, a somatotopic organization could not be assessed by simply statistically contrasting hand with foot stimulation. Therefore, to investigate the somatotopic organization in SI and SII, the MNI-coordinates of the most significant voxel (activation peak) within SI and SII were determined for each stimulus condition. This was done for the group and for each individual. To identify the activation peak in the single individual, a region of interest (ROI) approach for all four sites of interest—that is, ipsilateral and contralateral SI and SII cortex was used. To allow for the identification of activation peaks in each individual, a rather liberal threshold of $P < 0.01$ uncorrected was chosen for the activation in the single subject.

In SI, there was an obvious difference regarding the locations of activations evoked by hand and foot painful stimulation in the group analysis—with the foot being represented more medially along the postcentral sulcus (see Table 1). This was true for both ipsilateral and contralateral hemisphere. Therefore, for the single subject analysis the ROI (20 mm sphere) was placed around the different peak activation derived from the group analysis for each stimulus condition. A rather large ROI (sphere with radius 20 mm) was chosen to cover a broad area along the postcentral gyrus and to not artificially restrict/bias the results of the single-subject analyses.

Since the random effects analysis (RFX) revealed rather similar peak activations in contralateral and ipsilateral SI (see Table 1), homologous ROIs were used for ipsilateral and contralateral SI and centered around the peak activation of contralateral SI. Voxels revealed by the ROI analysis, which could not be assigned to SI, were excluded from data analysis. First of all, the revealed voxels had to relate to the hemisphere investigated (a ROI with 20 mm radius around the foot coordinate may also reveal voxels belonging to the other hemisphere). Secondly, such peak voxels were excluded which are clearly in the motor cortex (precentral gyrus) or the cingulate. For this decision, activations were overlaid on the individual structural T_1-weighted image in each single subject. To validate this procedure, additional inspection of peak activations within SI was performed in each single subject to account for the possibility that these peaks fell outside the respective ROI.

In SII, the activation (and the peak activation) of hand and foot painful stimulation overlapped in the random effects (group) analysis (see Table 1). Both hand and foot pain evoked a significant activation peak in contralateral SII-cortex at the same location. In ipsilateral SII, the coordinates of peak activation somewhat differed from that. Accordingly, the contralateral coordinate, which was identical for hand and foot stimulation appeared representative for SII cortex. Subsequently, this same representative coordinate [± 39, −18, 18] was chosen as center of the 15-mm radius ROI to identify the peak activation in the single individual for both stimulus conditions in ipsi- and contralateral SII. This choice was further supported by the results of our recent study, which showed that stimulus laterality is represented in contralateral SII at a similar coordinate (38, −18, 15—see Bingel et al., 2003). To statistically test for the differences between peak activation sites between hand and foot, we used a multivariate linear model (Hotellings T_2^2 test) for dependent samples. To further investigate differences in individual directions, the coordinates of each orthogonal direction (x, y, z) were compared separately with a t test. A difference was accepted to be significant at $P < 0.05$.

Table 1
Peak activation in primary (SI) and secondary (SII) somatosensory cortex for hand and foot (random effects analysis)

Region		Coordinate (x, y, z in mm)		Voxel-level (T)
		Hand Stimulation	Foot Stimulation	H/F
SI	R	36, −36, 48	9, −36, 66	6.3*/3.8o^{+}
	L	−39, −30, 51	−9, −39, 57	7.6*/4.2^{+}
SII	R	39, −18, 18	39, −18, 18	6.9*/5.0*
	L	−33, −18, 12	−42, −24, 6	7.5*/4.5^{+}

L = left hemisphere, R = right hemisphere.
* <0.05 corrected.
$^{+}$ <0.001 uncorrected for region of interest (SI sphere with 20 mm diameter, SII 15 mm).

Results

Painful laser stimulation of hand and foot led to statistically significant increases in fMRI signal intensity in several cortical areas. In this report, we focus on pain-related responses in SI and SII cortices. The results of the group analysis are reported first, followed by the results that we obtained in individual subjects.

Group analysis

In both the contra- and ipsilateral SI cortices the representation sites of hand and foot were different, with the foot being located more medially and cranially than the hand. This was not the case for SII, where the representation sites greatly overlapped for both body sites (see Table 1). Painful foot stimulation evoked significantly weaker activation than painful hand stimulation. Therefore, the foot did not lead to significant activation in SI and ipsilateral SII cortex according to our criteria of significance, while the hand clearly evoked significant activation in both areas, importantly also ipsilateral SI cortex.

Single subject analysis

SI

Laser stimulation of the foot failed to evoke SI activation in two subjects (3 and 11) even at very low statistical thresholds. Therefore, these subjects could not be included in statistical comparison of the coordinates of peak activation of hand and foot stimulation. Comparison of both sites of stimulus application for the single subjects peak activation revealed a differential representation of hand and foot pain in contra- and ipsilateral SI, with the foot being

Table 2
Peak activation in contralateral primary somatosensory cortex of hand and foot pain in individual subjects

Subject	Coordinate (x, y, z in mm)		Voxel-level (T)
	Hand stimulation	Foot stimulation	
1	45, −30, 57	3, −24, 66	4.9/10.3
2	42, −30, 66	18, −39, 63	3.8/2.6
4	45, −36, 45	0, −39, 60	4.5/4.9
5	39, −30, 66	6, −30, 75	7.5/5.1
6	15, −48, 66	15, −48, 66	3.6/2.7
7	39, −54, 48	3, −45, 66	5.4/5.7
8	42, −33, 48	15, −42, 78	5.9/3.5
9	54, −30, 48	0, −30, 60	3.6/4.1
10	45, −30, 51	24, −39, 63	3.2/2.7
12	36, −39, 72	9, −30, 60	3.7/2.8
13	36, −42, 69	21, −39, 69	6.2/4.7
14	33, −51, 60	15, −39, 75	5.3/2.7
15	39, −27, 57	12, −27, 72	3.4/3.2
Mean (±SD)	39 (±9), −37 (±9), 58 (±9)	11 (±8), −36 (±7), 67 (±6)	

The coordinates of peak activation of hand and foot painful stimulation differ significantly in contralateral SI (Hotellings T_2^2 $F(3,10) = 15.0$, $P < 0.05$) with the foot being represented medially ($T(12) = 7.3$, $P < 0.05$) and cranially ($T(12) = 3.1$, $P < 0.05$) to the hand. No significant effect in the anterior posterior direction was observed ($T(12) = 0.4$, P = n.s.). Please note that subjects 3 and 11 are not included in this analysis.

represented medially and cranially to hand stimulation (Tables 2 and 3 and Fig. 1).

SII

All subjects showed bilateral SII activation in response to hand and foot stimulation. Comparison of peak activation for both sites of stimulus application for the single subjects revealed a differential representation of hand and foot pain in the contralateral operculo-insular region. Here, the foot is represented medially and anteriorly to hand stimulation (Tables 4 and 5 and Fig. 2a/b). Additionally, the foot appears to be located slightly more caudally/inferiorly to the hand, however, this difference was not significant. No segregation was observed within the ipsilateral operculo-insular region (Tables 4 and 5 and Fig. 2a/b).

Discussion

To investigate the somatotopic arrangement in SI and SII, touchless laser pain stimuli were randomly applied to the dorsum of the left hand and foot and BOLD activity reflecting cortical neuronal response assessed with event-related fMRI. Statistical comparison of peak activation revealed different peak-coordinates for hand and foot within ipsi- and contralateral SI as well as contralateral SII cortex. These differential activation patterns in response to the laser stimulus illustrate that these areas have the capacity to encode and process stimulus location in the absence of tactile information and elucidate a differential, namely somatotopically organized representation for selective nociceptive information within multiple sites of somatosensory cortex.

Table 3
Peak activation in ipsilateral primary somatosensory cortex to hand and foot pain in individual subjects

Subject	Coordinate (x, y, z in mm)		Voxel-level (T)
	Hand Stimulation	Foot Stimulation	H/F
1	−33, −27, 48	−9, −39, 69	4.1/8.3
2	−27, −39, 72	−12, −39, 69	3.1/2.9
4	−48, −36, 57	−12, −48, 66	5.2/5.2
5	−33, −54, 63	−9, −30, 63	6.7/3.2
6	−39, −36, 51	−33, −39, 48	2.3/2.6
7	−48, −30, 45	−9, −45, 69	4.7/3.7
8	−12, −33, 63	−6, −30, 78	5.0/2.8
9	−39, −42, 66	−6, −42, 57	3.3/4.9
10	−48, −30, 51	−24, −45, 54	4.1/2.7
12	−48, −42, 42	−6, −27, 69	2.3/3.4
13	−21, −39, 69	−12, −45, 63	3.7/3.3
14	−51, −39, 54	0, −30, 54	4.3/3.0
15	−33, −33, 60	−12, −48, 75	4.5/2.7
Mean (±SD)	−38 (±12), −37 (±7), 57 (±9)	−12 (±9), −39 (±7), 64 (±9)	

The coordinates of peak activation of hand and foot painful stimulation differ significantly in ipsilateral SI (Hotellings T^2 $F(3,10) = 12.1$, $P < 0.05$), with the foot being represented medially ($T(12) = 6.4$, $P < 0.05$) and cranially ($T(12) = 2.1$, $P < 0.05$) to the hand. No significant effect in the anterior posterior direction is observed ($T(12) = 0.6$, P = n.s.). Please note that subjects 3 and 11 are not included in this analysis.

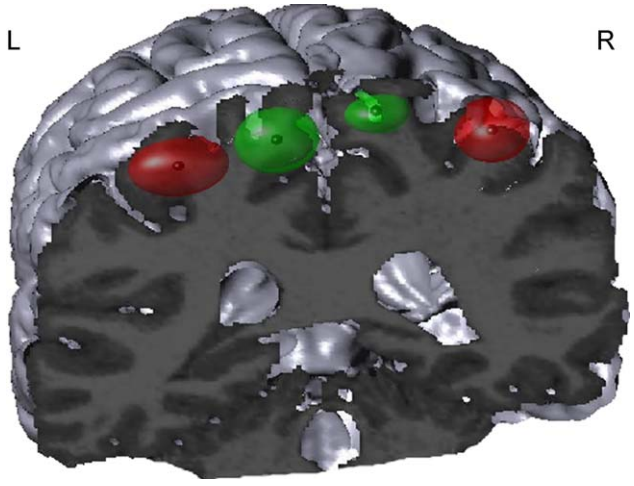

Fig. 1. Differential representation sites of hand and foot related laser-evoked pain in SI. Hand- and foot representation of laser-evoked fMRI responses in ipsilateral and contralateral SI-cortices overlaid on a normalized rendered T_1-weighted image. Mean distributions of peak activation are illustrated by a sphere centered around the mean coordinate (dot), with the extensions of the standard deviation of each coordinate (x, y, z) for each stimulus condition. Foot-related distribution is depicted in green, hand-related responses in red.

Pain stimulus and experimental design

The laser-stimulus does not reflect typical clinical pain, which is longer and involves greater emotional reactions. However, the stimulus quality of the laser is ideal for the evaluation of a distinct discriminative aspect of pain, as the central processing of nociceptive spatial information. It exclusively activates nociceptive pathways (Bromm and Lorenz, 1998; Spiegel et al., 2000), and avoids bias of concurrent activation of tactile fibers (e.g., Aβ), which could bias or contribute to a somatotopic representation of pain stimuli in the brain. A painful stimulus inevitably engages attention, memory, and the motor system. However, we aimed at minimizing top down effects, by randomly applying unpredictable (location + time) laser stimuli and not requesting pain-ratings. Since we were interested in the spatial coding of nociceptive stimuli, it was of particular importance to preclude the subjects from developing spatially oriented expectancy, which has been shown to alter both pain-perception and representation (Buchner et al., 2000; Sawamoto et al., 2000). Since we randomly applied touchless and spatially unpredictable laser stimuli to either hand or foot, we think we can be sure that the spatial segregation for hand and foot painful stimulation found in our study is indeed related to somatotopically ordered nociceptive input into the brain.

SI

The role of SI in perception has been controversial due to the inconsistent activations of SI across different imaging studies on pain (Bushnell et al., 1999). However, to date, several imaging studies of pain using pure nociceptive (e.g., laser) stimuli have substantiated the involvement of SI in pain processing irrespective of concomitant tactile stimulation. (Bingel et al., 2003; Bornhovd et al., 2002; Kanda et al., 2000; Timmermann et al., 2001). Our study provides first evidence that a somatotopic organization of purely nociceptive stimuli is represented in both contra- and ipsilateral SI, irrespective of associated tactile stimulation. The localizing properties of SI for pain processing are supported by experimental animal data: nociceptive neurons in SI of cat and monkey receiving projections of the lateral thalamic nuclei are somatotopically organized (Follett and Dirks, 1994; Kenshalo and Willis, 1991; Lamour et al., 1983). Furthermore, evidence arises from the clinical observation that patients with SI surgically removed or injured show impaired pain localization ability (Marshall, 1951; Penfield and Jasper, 1954). Our finding of a somatotopic arrangement in SI for pain complements previous PET data demonstrating differential activation along the contralateral postcentral gyrus for capsaicin-induced cutaneous pain comparing hand and foot stimulation (Andersson et al., 1997), even though in this

Table 4
Peak activation in contralateral secondary somatosensory cortex for hand and foot pain in individual subjects

Subject	Coordinate (x, y, z in mm)		Voxel-level (T)
	Hand stimulation	Foot stimulation	
1	54, −21, 15	33, −12, 3	4.9/8.3
2	54, −15, 18	54, −12, 18	3.8/3.8
3	39, −12, 15	27, −21, 3	6.5/3.1
4	54, −33, 21	54, −12, 6	5.3/4.7
5	39, −18, 15	45, −6, 3	6.8/4.5
6	54, −30, 33	36, −18, 18	3.9/4.3
7	45, −18, 18	54, −3, 6	6.1/10.0
8	54, −3, 3	51, −3, 3	6.3/6.3
9	54, −12, 3	39, −3, 30	4.4/4.2
10	45, −6, 6	45, −3, 3	3.2/2.9
11	54, −24, 18	36, −18, 6	4.6/4.0
12	54, −21, 18	45, −33, 30	2.8/3.9
13	39, −12, 21	39, −12, 18	9.8/8.2
14	39, −15, 15	39, −18, 15	4.7/4.3
15	54, −21,21	39, −15, 3	3.8/2.7
Mean (±SD)	49 (±7), −17(±8), 16 (±8)	42 (±8), −13 (±8), 11 (±10)	

The coordinates of peak activation of hand and foot painful stimulation differ significantly in the contralateral operculo-insular region (Hotellings T^2_2 $F(3,12) = 3.8$, $P < 0.05$), with the foot being represented medially ($T(14) = 2.6$, $P < 0.05$) and anteriorly ($T(14) = 2.1$, $P < 0.05$) to the hand. The foot appears to be located slightly more caudally/inferiorly to the hand, however, this difference was not significant ($P = 0.06$).

Table 5
Peak activation in ipsilateral secondary somatosensory cortex for hand and foot pain in individual subjects

Subject	Coordinate (x, y, z in mm)		Voxel-level (T)
	Hand stimulation	Foot stimulation	
1	−36, −3, 9	−33, −15, 3	4.1/6.3
2	−45, −30, 33	−42, −18, 12	3.2/4.1
3	−39, −12, 18	−51, −33, 33	5.5/4.0
4	−39, −18, 15	−51, −9, 3	5.7/5.7
5	−51, −30, 6	−42, −24, 24	4.4/3.6
6	−36, −18, 18	−54, −3, 6	3.6/3.3
7	−33, −18, 21	−54, −27, 24	6.3/7.6
8	−51, −18, 9	−39, −21, 15	5.5/3.9
9	−42, −21, 9	−42, −21, 6	5.2/3.8
10	−54, −24, 15	−51, −3, 3	4.7/3.7
11	−45, −3, 6	−48, −27, 18	3.6/4.0
12	−54, −9, 3	−54, −6, 3	2.7/3.7
13	−54, −3, 3	−54, −3, 3	7.7/9.5
14	−39, −3, 12?	−48, −27, 15	5.6/4.4
15	−54, −24, 27	−54, −3, 3	4.3/3.3
Mean (±SD)	−45 (±8), −16 (±10), 14 (9)	−48 (±7), −16 (±11), 11 (±10)	

The locations of peak activation do not differ for hand and foot painful stimulation (Hotellings T_2^2 $F(3,12) = 0.6$, $P = 0.6$).

study localizing information might have been biased by mechanoreceptive afferents and cognitive factors like pain anticipation evoked by the predictable long lasting pain sensation (Bushnell et al., 1999; Porro et al., 2002). The representation sites for hand and foot pain in SI revealed in our study reflects the known medial to lateral somatotopic organization of human SI that has been repeatedly demonstrated for the tactile modality (Kurth et al., 1998; Penfield and Boldrey, 1937; Ruben et al., 2001; Wood et al., 1988). The SI x coordinate for hand stimulation appeared to correspond to area 3b, which does not exclude extension into the more cranial area 1, where the dominant nociceptive input appeared to project to in the monkey (Kenshalo et al., 2000), recently also suggested in man (Ploner et al., 2000) based on comparisons of tactile and nociceptive MEG responses. However, our hand-coordinate is compatible with numerous other fMRI studies, especially with respect to the x coordinate (Brooks et al., 2002; Coghill et al., 2001; Peyron et al., 1999; Talbot et al., 1991).

An interesting finding of our study is the demonstration of a somatotopic organization of nociceptive input to the ipsilateral SI cortex. Although EEG and MEG of laser-evoked activity consistently failed to localize ipsilateral SI activity (Ploner et al., 1999; Tarkka and Treede, 1993; Timmermann et al., 2001), we observed it in both of our previous fMRI studies (Bingel et al., 2003; Bornhovd et al., 2002). Activation in ipsilateral sensory-motor cortex has also been observed in a 3T fMRI study in anesthetized rats subjected to intense electrical and noxious chemical stimuli (Tuor et al., 2000). Generally, ipsilateral SI activity could result from uncrossed afferent or transcallosal excitatory pathways. Evidence for the existence of the latter using electrical stimuli has been demonstrated in humans by MEG (Schnitzler et al., 1995), combined MEG and fMRI (Korvenoja et al., 1999) and in rats by cortical surface potentials (Heppelmann et al., 2001). Notably, ipsilateral SI activity appeared suppressed during anticipation of painful stimuli (Porro et al., 2002) and during focussed attention to the site of vibro-tactile stimulation suggesting its strong context dependency and modulation by prefrontal top-down mechanisms (Staines et al., 2002). Disinhibition of transcallosal excitatory pathways has been suggested to underlie an unusual ipsilateral SI MEG activity in response to passive movement stimuli applied to an affected index finger contralateral to a centro-parietal stroke (Druschky et al., 2002).

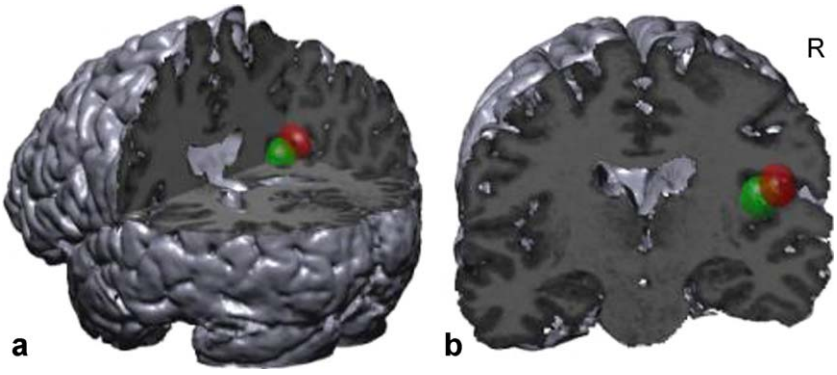

Fig. 2. (a/b) Differential representation sites of hand and foot related laser-evoked pain in contralateral SII. Hand- and foot representation of laser-evoked fMRI responses in contralateral SII overlaid on a normalized rendered T_1-weighted image. Mean distributions of peak activation are illustrated by a sphere centred around the mean coordinate (dot), with the extensions of the standard deviation of each coordinate (x, y, z) for each stimulus condition. Foot-related distribution is depicted in green, hand-related responses in red.

Detailed investigations, including electrophysiology techniques with superior temporal resolution will be needed to determine (i) how nociceptive afferents reach this region and (ii) to characterize the functional relationship of ipsilateral and contralateral SI cortex depending on specific paradigms.

SII

Bilateral activation in the neocortex surrounding the Sylvian fissure is most consistently found in functional imaging studies of pain (Peyron et al., 2000). The significance of the SII region for the processing of sensory discriminative aspects of pain is supported by clinical observations: Greenspan et al. (1999) reported contralateral impaired sensory-discriminative ability including tactile and nociceptive modalities in patients with lesions involving the operculo-insular region. Epileptic seizures originating in SII can evoke pain sensation localized to special body parts (e.g., arm) (Scholz et al., 1999). Recent neuroimaging studies of pain in humans have substantiated the role of SII in sensory-discriminative aspects demonstrating that this area is considerably involved in intensity coding of applied and perceived pain (Bornhovd et al., 2002; Coghill et al., 1999; Porro et al., 1998).

However, evidence from single cell recordings is limited and has failed to sufficiently characterize the ability of SII in discriminating the location of nociceptive stimuli (Dong et al., 1989; Robinson and Burton, 1980b). Single nociceptive neurons identified in this area mainly had large bilateral receptive fields. However, this should be seen with caution because these studies usually employed mechanical search stimuli (Burton and Carlson, 1986). There has been increasing evidence for a closely located but separate representation of pain in the parasylvian cortex, which might be an explanation why these studies missed nociceptive neurons in the SII complex (Treede et al., 2000). Two recent studies using subdural electrodes have demonstrated very early responses to laser-evoked pain in the parasylvian cortex indicating its predominant involvement in the processing of nociceptive stimuli (Frot and Mauguiere, 2003; Vogel et al., 2003). Our previous study highlights that stimulus laterality is represented in contralateral SII cortex provides first evidence that a sub-region of SII comprises at least a broad body scheme of selective nociceptive information (Bingel et al., 2003).

Our present study demonstrates different representation sites within SII for hand and foot nociception and therefore complements these findings by the existence of another aspect of somatotopy, namely the distinct representation of upper and lower body parts in SII cortex. Our SII coordinates were relatively medial and may therefore extend into areas of the posterior insula. Together with our recent finding that stimulus laterality is also represented in the contralateral posterior insula (Bingel et al., 2003), this may support the notion that SII and the posterior insula represent a functional unit. Despite the relatively high spatial resolution of fMRI, this somatotopic arrangement was not visible in the group analysis as in SI, but was detected in the single subject analysis. This may be explained by the larger receptive fields in SII than in SI (Robinson and Burton, 1980a,b,c). This difficulty might also explain why two previous studies using PET failed to find a somatotopic arrangement for pain in SII (Andersson et al., 1997; Xu et al., 1997).

The finding of a somatotopic order within contralateral SII parallels previous work on the human tactile modality and results obtained from non-human primates (Disbrow et al., 2000; Ruben et al., 2001). The foot being represented more medially and caudally than the hand equivalents a recent human fMRI study by Ruben et al. (2001), who compared different fingers and toe I of one body side with electrical stimuli. Accordingly, studies on the tactile modality in non-human primates revealed the representation site of the lower limb within the parietal operculum located medially to the representation of the hand, more adjacent to the fundus of the lateral sulcus (Robinson and Burton, 1980c; Whitsel et al., 1969). In further accordance with these authors, we failed to observe a consistent somatotopy within ipsilateral SII.

Anatomical and human electrophysiological data indicate that nociceptive input into SII can largely bypass the primary sensory cortex. A recent MEG study performed by Ploner et al. (1999) demonstrated that nociceptive input reaches SII mostly parallel to SI probably by direct projections from VPI, whereas tactile input reaches this region sequentially through projections from SI. This direct access of nociceptive information into SII might reflect a "collateral security-system" of nociceptive processing in contrast to the sequential highly differentiated network for tactile stimuli and indicates crucial importance of this area in human pain processing. In this context, it is biologically plausible that the SII-region encodes not only stimulus intensity but also spatial stimulus information.

Conclusion

In conclusion, using randomized application of laser pain stimuli in combination with event-related fMRI, we provide evidence that both SI and SII encode spatial information of nociceptive stimuli without additional information from the tactile system. This highlights the concept of a redundant representation of basic discriminative stimulus features in human somatosensory cortices, which seems adequate in view of the evolutionary importance of pain perception.

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