Cerebral Cortex July 2006;16:960-968
doi:10.1093/cercor/bhj038
Advance Access publication September 21, 2005

Somatosensory and Pain Responses to Stimulation of the Second Somatosensory Area (SII) in Humans. A Comparison with SI and Insular Responses

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Somatosensory and pain responses to direct intracerebral stimulations of the SII area were obtained in 14 patients referred for epilepsy surgery. Stimulations were delivered using transopercular electrodes exploring the parietal opercular cortex (SII area), the suprasylvian parietal cortex (SI area) and the insular cortex. SII responses were compared to those from adjacent SI and insular cortex. In the three areas we elicited mostly somatosensory responses, including paresthesiae, temperature and pain sensations. The rate of painful sensations (10%) was similar in SII and in the insula, while no painful sensation was evoked in SI. A few non-somatosensory responses were evoked by SII stimulation. Conversely various types of non-somatosensory responses (auditory, vegetative, vestibular, olfacto-gustatory, etc.) were evoked only by insular stimulation, confirming that SII, like SI, are mostly devoted to the processing of somatosensory inputs whereas the insular cortex is a polymodal area. We also found differences in size and lateralization of skin projection fields of evoked sensations between the three studied areas, showing a spatial resolution of the somatotopic map in SII intermediate between those found in SI and insula. This study shows the existence of three distinct somatosensory maps in the suprasylvian, opercular and insular regions, and separate pain representations in SII and insular cortex.

Keywords: insula, intracerebral stimulation, pain, second somatosensory area, somesthesia

Introduction

The involvement of suprasylvian opercular and insular cortex in the processing of painful and non-painful somatosensory imputs is supported by numerous data including: anatomical and microelectrodes studies in monkeys (Burton, 1986; Burton *et al.*, 1995; Krubitzer *et al.*, 1995), cortical stimulations (Penfield and Brodley, 1937; Penfield and Jasper, 1954; Penfield and Faulk, 1955; Penfield and Rasmussen, 1957), functional imaging (Casey *et al.*, 1994, 1996; Coghill *et al.*, 1994; Craig *et al.*, 1996; Baron *et al.*, 1999) and scalp recordings of electric and magnetic somatosensory evoked responses in humans (Allison *et al.*, 1989; Kakigi *et al.*, 1989; Valeriani *et al.*, 1996; Mauguière *et al.*, 1997). These studies suggest a replication of somatosensory and pain representations in parietal opercular cortex (SII area), the suprasylvian parietal cortex (SI area) and the insula. Although they combine excellent spatial and temporal resolution, intracerebral depth electrodes have rarely been used to explore the suprasylvian, opercular and insular cortex. Technologic improvements in the stereotactic implantation of depth electrodes using magnetic resonance imaging (MRI) imaging now permit prolonged electrophysiological recordings and direct deep stimulation of SII and insular cortex using transopercular electrodes. This is achieved in patients referred for epilepsy surgery whose seizures are suspected to originate from the perisylvian and insular cortex (Isnard *et al.*, 2000, 2004). In these patients, the intracerebral recording of electrical potentials evoked by painful and non-painful skin stimulations in these regions has recently shown that SII and insular cortex respond to painful and non-painful stimulations with different latencies (Frot and Mauguière, 1999, 2003a,b; Frot *et al.*, 2001). Clinical responses to direct intracerebral stimulation confirmed that the insular cortex is involved in the processing of somatosensory and pain inputs (Ostrowsky *et al.*, 2000, 2002). However, clinical responses to the stimulation of the SII area in the parietal opercular cortex were not detailed in these previous studies. In this study SII stimulations were delivered through contacts of transopercular electrodes which explored, along a single track, SII, the suprasylvian part of SI and the insular cortex, so that it has been possible to compare responses of SII with those of the adjacent SI and insular cortex.

Materials and Methods

Patients

The 14 patients included in this study were stimulated in the SII area. They were selected from a group of 48 patients who underwent a stereo-electroencephalographic (SEEG) exploration of the perisylvian area at the Neurological Hospital of Lyon between March 1997 and May 2003 for presurgical evaluation of drug-resistant epilepsy. The choice of SEEG targets was based on video-EEG recordings of seizures, interictal fluorodeoxyglucose Positron emission tomography (PET), interictal and ictal single photon tomography and cerebral MRI data. The decision to implant insular and opercular cortices was justified by the presence of ictal symptoms suggesting an early ictal involvement of the suprasylvian or insular cortex, such as lips and face paresthesiae, gustatory hallucinations, laryngeal contraction, hypersalivation, facial motor symptoms or facial post-ictal paresis (Isnard *et al.*, 2000; 2004). There were five women and nine men, of whom 11 had electrodes implanted in the right hemisphere and three in the left hemisphere. All subjects understood the purpose of the study, the risks involved, and gave their written consent.

The stimulation sites were determined through x, y and z coordinates. The x coordinate defined the medio-lateral axis, $x = 0$ being the coordinate of the sagittal interhemispheric plane; the y coordinate defined the rostro-caudal axis, $y = 0$ being the coordinate of the frontal plane passing through the vertical anterior commissure (VAC). The z coordinate defined the vertical axis, $z = 0$ being the coordinate of the horizontal plane passing through the anterior and posterior commissure (AC-PC plane). Stimulations were delivered: (i) in the suprasylvian parietal cortex ($48 < x < 63$ mm; $-20 < y < +12$ mm; $8 < z < 14$ mm); (ii) in the parietal operculum ($38 < x < 46$ mm; $-20 < y < +12$ mm; $8 < z < 14$ mm); and (iii) in the insular cortex ($27 < x < 36$ mm; $-22 < y < -3$ mm; $1 < z < 20$ mm). Furthermore we checked on individual brain MRI that contacts were located in either SI, SII or the insula for each patient. For illustrations (Figs 1, 2, 6 and 7) stereotactic positions of contacts were projected onto a standardized T1 weighted MRI used as a template on the SPM2 software (Statistical Parametric

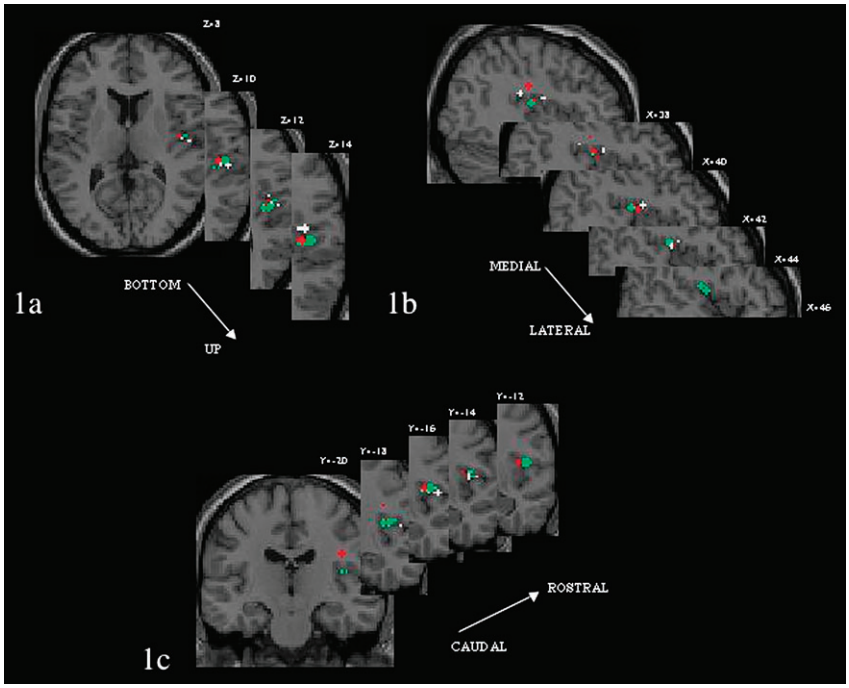

Figure 1. Functional mapping of the SII area obtained by pooling the 30 stimulations of SII in the 14 patients of this study. Stimulation sites were plotted using their *x*, *y* and *z* stereotactic coordinates on a standardized MRI. Each stimulation site is symbolized by a cross: red, painful sensations; green, temperature sensations; white, paresthesiae. Horizontal (*a*), sagittal (*b*) and coronal (*c*) reconstructed MRI slices are represented.

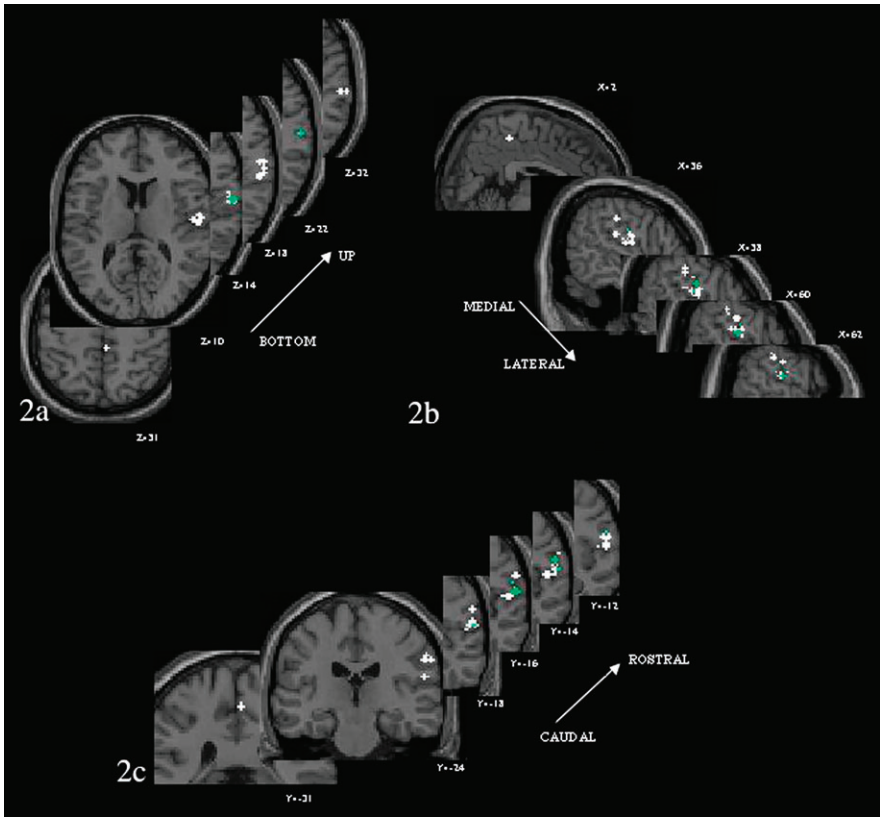

Figure 2. Functional mapping of the SI area obtained by pooling all 45 stimulations of SI. Stimulation sites were plotted using their *x*, *y* and *z* stereotactic coordinates on a standardized MRI. Each stimulation site is symbolized by a cross: green, temperature sensations; white, paresthesiae. Horizontal (*a*), sagittal (*b*) and coronal (*c*) reconstructed MRI slices are represented.

Mapping). Each contact was represented as a sphere (diameter 1 mm). Spheres were introduced into the MRI volume using a home made software (Multifusion) developped with Matlab. Then sagittal, coronal and transversal reconstructions were computed. This explains why, due to inter-individual anatomical differences, some of the contacts may not strictly match with the anatomical structures as represented on standardized brain MRI in illustrations.

The depth (x) coordinates showed no overlap between the three target areas. Moreover the stereotactic coordinates of these targets were the same as those of cortical areas where we have previously recorded intracerebral somatosensory evoked potentials (SEPs) to electric stimulation of median nerve at wrist, with respective latencies of ~20–22, 60–90 and 110–165 ms (Frot and Mauguière, 1999a, 2003; Frot *et al.*, 2001). Based on numerous source modelling studies of evoked potentials and magnetic fields (for reviews, see Hari *et al.*, 1993; Mauguière *et al.*, 1997), somatosensory cortical responses peaking at ~20 and 70 ms are commonly accepted to originate from SI and SII areas, respectively. Thus, in the absence of any systematic mapping study describing the borders between these areas in the human brain, we considered on the basis of our SEP data that the suprasylvian parietal and parietal opercular stimulation sites were located in SI and SII areas, respectively. Similarly the distinction between SII and insular stimulation sites was based on latency differences that we observed between the two areas for responses evoked by CO_2 laser skin stimulation (Frot and Mauguière 2003) since the exact anatomical border between the granular cortex of the inner part of parietal operculum and that of posterior insula cannot be traced on individual human brain MR images.

SII stimulations were performed in 14 patients: 11 patients were stimulated in SII, SI and the insular cortex, three in SII and insula. In this group of 14 patients, 30 stimulations were performed in SII, 22 in SI and 79 in the insular cortex.

SI and/or insular stimulation data in the 34 patients with no SII stimulation were used for a comparative group study of the three areas, including 23 SI stimulations and 141 insular stimulations. Since a single stimulation could evoke either no clinical response or several sensations (e.g. paresthesiae in the left hemibody and speech arrest), the total number of evoked sensations is different from the total number of stimulations. The total number of sensations evoked by stimulations in each of the three areas is given in Table 1 ('Total responses').

Electrodes Stereotactic Implantation

The stereotactic implantation procedure was derived from that first described by Talairach and Bancaud (1973) and is detailed in Ostrowsky *et al.* (2002). A cerebral angiogram was first performed in stereotactic conditions using an X-ray source 4.85 m away from the patient's head, to eliminate the linear enlargement due to X-ray divergence. In order to reach the eloquent cortical target, the stereotactic coordinates (Talairach and Tournoux, 1988) of each electrode were calculated preoperatively on the individual cerebral MRI previously enlarged at scale 1. Cerebral MR and angiographic images were superimposed to avoid any risk of vascular injury during implantation. Electrodes were implanted perpendicular to the mid-sagittal plane and could be left in place chronically for up to 15 days. The electrodes had a diameter of 0.8 mm and 5–15 recording contacts, depending on their length. Contacts were 2 mm long and separated by 1.5 mm from one another. At the end of the surgery, a post-implantation frontal X-ray was performed and superimposed on MR images to check for the final position of each electrode with respect to the targeted anatomical structures. Therefore, contacts could be localized along the tract of transopercular electrodes in the outer and inner aspects of the parietal operculum and in the insular cortex, respectively.

Table 1
Characteristics and type of sensations evoked by SI, SII and insular stimulations

	SI (n)	SII (n)	Insula (n)
Total responses	31	29	207
Somatosensory responses (SSR)	29 (93.5%)	24 (83%)	132 (64%)
Cutaneous paresthesiae	25 (80.6%)	14 (48.3%)	85 (41.5%)
Temperature sensations			
warm	3 (9.7%)	3 (10.3%)	20 (9.7%)
cold	1 (3.2%)	4 (13.8%)	8 (3.8%)
Painful sensations	0 (0%)	3 (10.3%)	19 (9.2%)
Non-somatosensory responses (NSR)	2 (6.5%)	5 (17%)	75 (36%)

Stimulation Paradigm

During this session, patients were sitting in bed and were asked to relax. Electrical stimulations were produced by a current regulated neurostimulator designed for a safe diagnostic stimulation of the human brain (Babb *et al.*, 1980), according to the routine procedure used in our department to map functionally eloquent and epileptogenic areas (Ostrowsky *et al.*, 2000, 2002; Isnard *et al.*, 2004). Square pulses of current were applied between two adjacent contacts (bipolar stimulation). Stimulations characteristics were as follows: frequency of 50 Hz, pulse duration of 0.5 ms, train duration of 5 s, intensity 0.8–6 mA. These parameters were used to avoid any tissue injury [charge density per square pulse < 55 $\mu C/cm^2$ (Gordon *et al.*, 1990)]. This stimulation paradigm, along with the bipolar mode of stimulation using adjacent contacts, ensured a good spatial specificity with respect to the desired structures to be stimulated. The study of current densities in the cortex for bipolar stimulation with 10 mA stimulating current shows that the peak current density occurs in the region immediatly beneath the bipolar electrodes (0.05 A/cm^2) and declines rapidly to 0.02 A/cm^2 0.5 cm away, and that the current density decreases in relation to the square of the distance into the cortex (Nathan *et al.*, 1993). Stimulus intensity was raised from 0.2 mA in steps of 0.4 mA until a clinical response was obtained. We defined efficient stimulation threshold as the minimal intensity necessary to elicit a clinical response. This threshold was 1.87 ± 1.05 mA, 1.6 ± 0.86 and 1.97 ± 1.04 in SI, SII and insula, respectively. No stimulation was delivered at suprathreshold values. These intensities are less than one-fifth of those used in the experiment by Nathan *et al.* (1993) so that there is virtually no current spread out of the stimulation current dipole as defined by the distance of 5.5 mm between the outer and inner limits of the superficial and deep stimulating contacts, respectively (see fig. 4A in Ostrowsky *et al.* 2002).

During the 5 s of stimulations trains, contacts of the transopercular electrode were disconnected from amplifiers but the EEG activity could be monitored on all other recording sites. Stimulation contacts were reconnected within 1 s after the end of the stimulations train. Electrical stimulations producing an after-discharge that spread out of the stimulation site were excluded from analysis.

Collection and Processing of Data

Analysis of clinical responses was performed using the video-taped recordings of stimulation sessions. To estimate and classify the somatosensory responses to electrical stimulation, we analyzed on videotapes spontaneous behavioral manifestations including: (i) facial expression (pain or fear); (ii) verbal complaint (cry, shout, etc.); and (iii) stimulus eviction movements, as well as vegetative changes such as facial pallor or rubefaction. We also collected spontaneous patients' reports and a standardized questionnaire was used to classify the somatosensory responses. Four keywords were proposed to the patient for describing the evoked sensation: (i) pain; (ii) temperature; (iii) non-painful skin sensation; or (iv) 'other type' of sensation. For each of these categories, a list of words was proposed to the patient to further characterize the sensation (pain could be: electric shock, burning, stinging, squeezing, cramp, crushing or pinching; temperature sensation could be warm or cold; non-painful sensation could be: tingling, slight touch, numbness or 'complex', this last category including various individual reports, such as liquid stream, displacement of a limb, that were observed exclusively following insular stimulation (see Isnard *et al.*, 2004). For each of these sensations we asked the patients to evaluate their pleasant or unpleasant nature on a visual analogic scale from 1 (neutral) to 10 (pain). We observed, during stimulation as well as retrospectively on videotapes of the stimulation session, that all responses described by the patient as painful were associated with a facial expression of pain.

The territories of evoked somatosensory responses were drawn on a body sketch and quantified as a percentage of body surface, using a standardized scale (Lund and Browder scale; Miller *et al.*, 1991).

For illustrations, each stimulation site was plotted using its stereotactic coordinates on a standardized MRI.

Group comparisons were done using the χ^2-square, Fischer's exact test or Student's *t*-test. To compare the size of cutaneous projections of somatosensory responses between SI, SII and insular stimulations, we use a non-parametric test (Kruskall–Wallis test).

Results

The rate of ineffective stimulations (i.e. producing no clinical response) in SII was <17% and very similar to that of insular stimulations (18%) while it was slightly higher in SI (31%), thought the difference was not significant. Conversely, the mean response threshold was similar in the three areas and ranged between 1.3 and 2 mA, with a high SD/mean ratio (0.64 in SI, 0.66 in SII and 0.5 in insula).

Somatosensory Responses (Table 1)

Whatever the region stimulated, evoked responses were preferentially somatosensory (SSR), including paresthesiae, temperature sensations (heat or cold) and pains. However, percentages of SSR in SI (93.5%) and SII (83.0%) were significantly higher than that observed in the insula (64.0%) ($P = 0.03$).

Cutaneous Paresthesiae

They were mostly reported as neutral or as unpleasant sensations of tingling, light touch or slight electric current. In SII, these sensations were evoked mostly by stimulating the anterior part of the post-central opercular cortex (Fig. 1), while they were more widely distributed in the insula and SI (Fig. 2).

Temperature Sensations

As shown in Table 1, the SII area was that showing the highest rate of temperature responses with a majority of cold sensations, but, due to the small numbers, these findings do not reach statistical significance. Anatomically, the stimulation sites eliciting temperature sensations in SII were caudal and lateral to those producing cutaneous paresthesiae (Fig. 1).

Painful Sensations

Pains of mild to intolerable intensity were elicited by SII stimulation in three patients after right hemisphere stimulation. The first patient felt painful tingling in the superior part of face, bilaterally but predominating on the left side. The second reported a painful cramp and electric current sensation on the left half of his body and the third felt painful tingling and cramp in his left cheek spreading rapidly to the left half of his body. The degree of pain was independent of stimulation intensity. Anatomically, pain responses in SII seemed mostly evoked after stimulating contacts located more deeply and superiorly than contacts evoking paresthesiae and temperature responses (Fig. 1). The stereotactic coordinates of contacts where paresthesiae, temperature and pain responses were evoked in SII area are reported in Table 2. No statistical difference in the location of contacts evoking pain vs contacts evoking paresthesiae or temperature responses could be evidenced, this might be due to the small number of pain responses (Student's *t*-test: 0.16, 0.83 and 0.22 for *x*, *y* and *z* coordinates respectively).

While the rate of painful responses was equivalent in SII (10.3%) and in the insula (9.2%), no painful sensation was ever elicited by stimulating the SI cortex. Painful responses evoked by Insula stimulation were mostly evoked in its upper-posterior part. They were described as somatosensory (73.7%), including burning sensations, electrical discharges and stinging sensations. The remaining painful sensations (26.3%) were cramps (15.8%), headaches (5.3%) and abdominal pain (5.3%). No difference in pain rating or facial expression of pain sensation could be evidenced between SII and insula.

Non-somatosensory Responses

In SII, only a few non-somatosensory responses (NSR) were obtained, including mostly pharyngo-laryngeal constriction (10.3%) and sudden interruption of speech (6.9%). This contrasts with the multiple types of NSR that were obtained only in the insula, including viscero-sensitive responses, auditory responses, speech disturbances, vestibular sensations such as vertigo or horizontal rotation of the body, fear, sensations of unreality and olfacto-gustatory responses. During SI stimulation, we evoked two NSR that were a vertigo and a speech arrest.

Cutaneous Projections of SSR

In Figure 3, sizes of all cutaneous projections of SSR are plotted showing differences between SI, SII and the insula. The size of skin territories involved by SII responses were intermediate between those of SI and insular responses, the latter ones being the larger. A non-parametric Kruskall–Wallis test showed that differences between the three groups were significant ($P < 0.0001$).

In 7 of the 11 patients in whom SII, SI and the insula were explored, the evoked responses shared a common cutaneous projection, thus offering the opportunity to assess comparatively the somatotopic representations of the same body area in the three structures.

In four of these seven patients, symptoms were perceived in the face area and the extent of the somatotopic representation

Table 2
Stereotactic coordinates (mean ± SD) of the contacts (mm) located in SII area where paresthesiae, temperature and pain responses were evoked (Talairach and Turnoux, 1988)

	x	*y*	*z*
Paresthesiae	43.7 ± 3.4	−12.2 ± 6.7	15.1 ± 3.7
Temperature	45.5 ± 3.6	−12.0 ± 1.8	13.7 ± 1.8
Pain	41.3 ± 2.5	−12.6 ± 3.0	17.7 ± 7.4

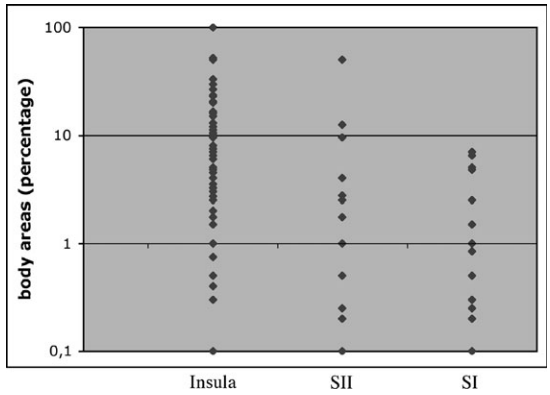

Figure 3. Sizes of all cutaneous projection of somatosensory responses were quantified as a percentage of body surface and plotted respectively for all SI, SII and insular stimulations. The size of skin territories involved by SII responses were intermediate between those of SI and insular responses, the latter ones being the larger. Logarithmic scale.

of the face in SII was intermediate between those in SI and the insula (Fig. 4).

Patient 1 was stimulated in the right hemisphere; he reported an unpleasant tingling of the palate during SI stimulation. During SII stimulation, he felt a very unpleasant and painful tingling in the superior part of face, bilaterally but predominating on the left side. Insular stimulation provoked a discomfort due to a sensation of slight electric current in the throat, mouth and left arm.

Patient 2 also underwent a right-sided stimulation. SI stimulations provoked a cool liquid sensation in the mouth. When SII was stimulated, this cool sensation was felt to be ascending from the sternum up to the throat, whereas insular stimulations evoked a sensation of light touch coming from the left hand and spreading to left arm, with a simultaneous feeling of cool liquid flowing into the throat.

Patient 3 was stimulated in the left hemisphere. A slight touch sensation in the throat was produced by SI stimulations, while SII stimulations provoked an unusual feeling of softening of his tongue, which felt as if it were glued to his palate. Insular stimulation induced a warm shudder going through his throat and whole mouth.

Patient 4 was stimulated in the left hemisphere. SI stimulations evoked tingling in the upper lip on the right side whereas SII stimulation induced a cool liquid sensation flowing into the mouth and on the right upper and lower lips. Insular stimulation induced a strange indefinable sensation on the right side of the face.

In the other three patients, symptoms were perceived in the hand during the three stimulations and the extent of the evoked sensation gradually extended outside the hand area as stimulation moved from SI to SII and to the insular cortex (Fig. 5).

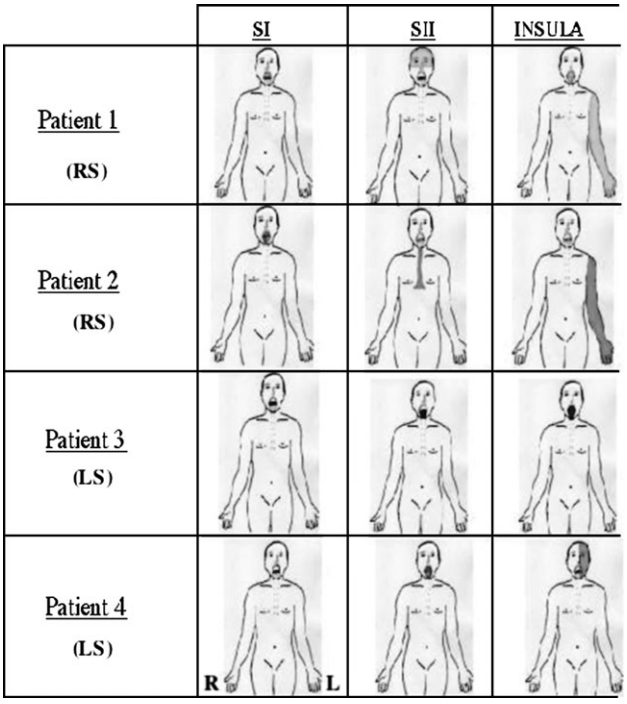

Figure 4. Skin territories involved by evoked sensations in the four patients in whom SI, SII and insular stimulation induced a sensation in the face. The extent of the evoked sensation gradually encompassed the face area as stimulation moved from SI to SII and to the insular cortex. R = right; L = left; RS = stimulation on the right; LS = stimulation on the left.

Patient 1 was stimulated in the right hemisphere. He reported the sensation of a slight electric current in his left hand during SI stimulation. During SII stimulation, he felt a painful cramp and electric current on the left half of his body. Stimulation of the insula produced tingling all over his body.

Patient 2 underwent a left-sided stimulation. SI stimulations induced tingling of the right hand. SII stimulations evoked a warm sensation in his right hand and leg whereas insular stimulations provoked a painful twitching on the right side of his body.

Patient 3 reported a slight electric current in his index and middle fingers during right-sided SI stimulations, while SII stimulations evoked electric current sensation in his left hand. When his insula was stimulated, he felt an electric current in his left arm and face, with an unpleasant feeling of being thrown backward.

Lateralization of Evoked Sensations (Table 3)

Evoked responses affecting limbs were exclusively contralateral to stimulation in SI but could also be bilateral or ipsilateral

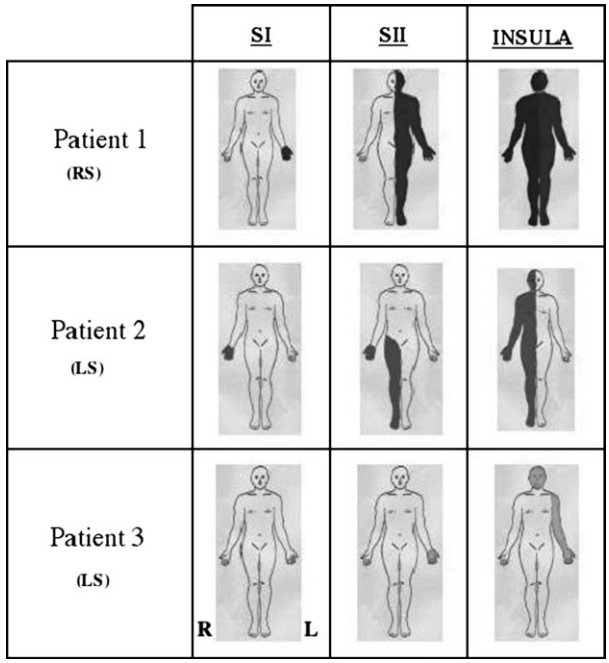

Figure 5. Skin territories involved by evoked sensations in the three patients in whom SI, SII and insular stimulation induced a sensation in the hand. The extent of the evoked sensation gradually encompassed the hand area as stimulation moved from SI to SII and to the insular cortex. R = right; L = left; RS = stimulation on the right; LS = stimulation on the left.

Table 3
Lateralization of evoked somatosensory sensations in SI, SII and insular stimulations

	Bilateral (*n*)	Contralateral (*n*)	Ipsilateral (*n*)
Face or trunk			
SI ($n = 16$)	11	5	0
SII ($n = 11$)	8	3	0
Insula ($n = 66$)	45	16	5
Limbs			
SI ($n = 13$)	0	13	0
SII ($n = 13$)	2	9	2
Insula ($n = 66$)	2	62	2

during stimulations of either SII or the insula. The highest percentage of ipsilateral or bilateral responses was observed after SII stimulation ($P = 0.057$). When the evoked sensation involved the midline part of the body (face or trunk), they were mostly bilateral regardless of the stimulated region. Response lateralization was similar for left and right stimulation.

Somatotopic Organization in SII, SI and Insula

The topography of evoked paresthesiae was used to map the somatotopic representation in SII, SI and the insula. In SII we found that face and hand were over-represented, as compared with other parts of the body, since most of evoked sensations (47% and 33% respectively) were localized in these two areas. The hand area was found to be rostral to the face area while the lower limb representation was located in the upper part of SII (Fig. 6). In SI the somatotopic map reproduced the classical bottom up representations of face, hand and upper limb (Fig. 7). In the insula, face, nose and throat representations were located in the lower posterior part; hand, upper-limb and trunk areas prevailed in the anterior part; and lastly, a representation of the contralateral ear was found in the lower posterior part.

Discussion

The human SII area has rarely been investigated using cortical electrical stimulations because of its anatomical location in the upper bank of the sylvian fissure. Using cortical surface electrodes, Penfield and Jasper (1954) and Penfield and Rasmussen (1957) reported localized feeling of numbness, paresthesiae and movement sensations. Likewise, Lüders (1985) reported 'paralyzing' feelings, inhibition of alternative movements, tingling and speech arrest using subdural electrodes in an area clearly anterior to the parietal suprasylvian cortex. Stimulations in these previous studies were done using surface electrodes; thus, to our knowledge, our study is the first one describing clinical responses to a direct intracortical stimulation of SII in humans.

A first finding of our study is that stimulation of the parietal opercular SII cortex produces almost exclusively somatosensory and pain responses if one includes in this category the 10% of unpleasant pharyngo-laryngeal strangling sensation that we observed when stimulating this area. Indeed, only 6% of our SII responses were clearly non-somatosensory and represented by transient speech disturbances during stimulation. This is very different to what we reported for the insula, which behaves as a polymodal area (Ostrowsky *et al.*, 2000; Isnard *et al.*, 2004). It is noteworthy that a similar percentage of speech disturbances was also observed during insular stimulation.

Although intracerebral stimulations are more focal than those delivered through surface electrodes placed on the cortical surface, the anatomical closeness between the opercular part of SI, SII and the insula, and similarities in stimulation thresholds and response rates between these three structures raise a question about the specificity of our responses according to the stimulated area. Moreover, the possibility that unrecorded or undetected activity in other cortical or subcortical areas may have mediated the elaboration of clinical responses cannot be definitely discarded. However, the stimulation parameters and the bipolar mode of stimulation that we used ensure a satisfying spatial specificity (Nathan *et al.*, 1993; Ostrowsky *et al.*, 2002), and the recording of intracerebral activity during the stimulation increases the specificity of our responses by providing the possibility of detecting diffusing after-discharges that were discarded from analysis. If responses were due to contiguity diffusion of electrical stimulation between SI, SII and the insula, the probability would be very high that we would obtain similar responses by stimulating these three areas. On the other hand, percentages of SSR were different between SI/SII and the insular cortex, pain was elicited in SII and the insula but not in SI, and

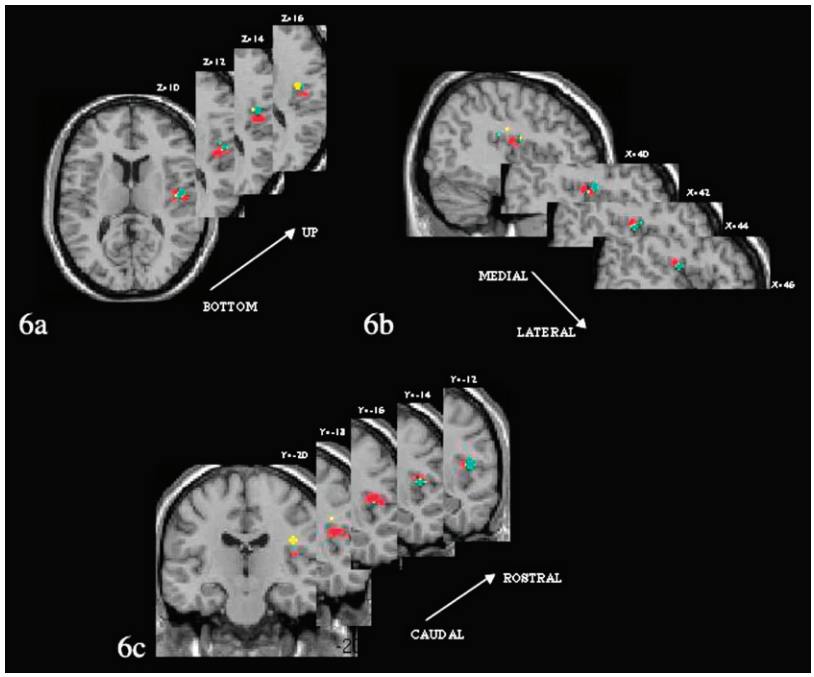

Figure 6. Somatotopic distribution of SII responses obtained by pooling the 30 stimulations of SII in the 14 patients of this study. Stimulation sites were plotted using their *x*, *y* and *z* stereotactic coordinates on a standardized MRI. Each stimulation site is symbolized by a cross: red, face; green, hand; yellow, lower limb. Horizontal (*a*), sagittal (*b*) and coronal (*c*) reconstructed MRI slices are represented.

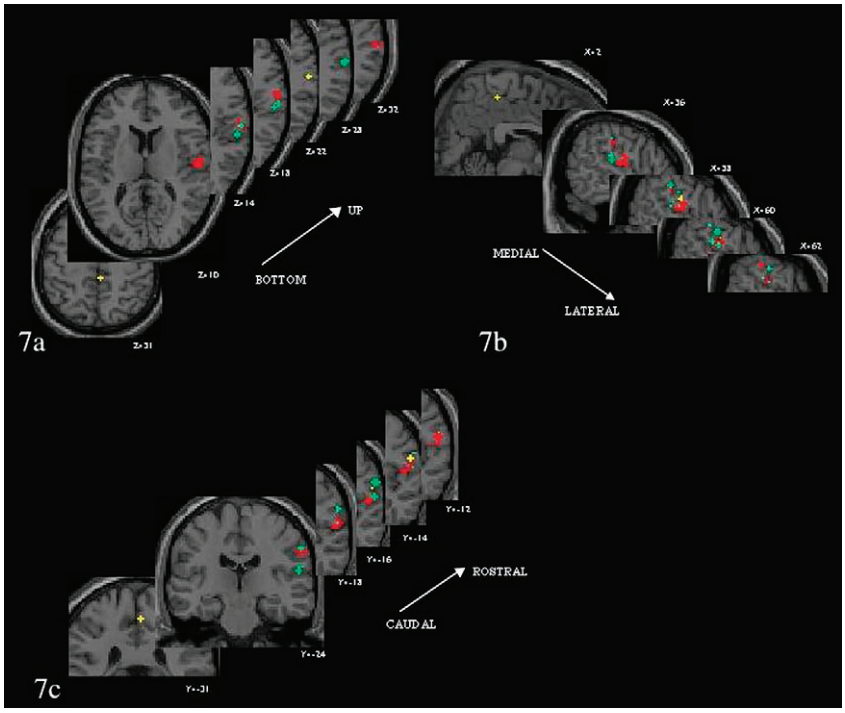

Figure 7. Somatotopic distribution of SI responses obtained by pooling the 45 stimulations of SI. Stimulation sites were plotted using their *x*, *y* and *z* stereotactic coordinates on a standardized MRI. Each stimulation site is symbolized by a cross: red, face; green, hand; yellow, lower limb. Horizontal (*a*), sagittal (*b*) and coronal (*c*) reconstructed MRI slices are represented.

the cutaneous projections of evoked sensations were different in the three explored areas. Moreover, no viscero-motor, auditory, fear, vestibular or olfacto-gustatory responses, which represented one-third of insular responses, were elicited in SI or SII, suggesting a good spatial specificity of our stimulations. Lastly, sensations evoked by electrical stimulation of SI were consistent the with current knowledge of this area in terms of: (i) type of sensations: evoked sensations were principally somatosensory, rarely thermal and never painful (Penfield and Brodley, 1937; Coghill *et al.*, 1994); (ii) lateralization: evoked sensations were mainly contralateral except for face representation (Lamour *et al.*, 1983); and (iii) somatotopic map: localization of evoked responses were consistent with Penfield's homunculus (Penfield and Rasmussen, 1957).

Intracerebral stimulation of SII allowed to address the question of the somatotopic organization of this cortical area in humans. In monkeys, Krubitzer *et al.* (1995) showed the existence of somatosensory maps in lateral parietal cortex. Face representation was located in the superior part. Hand, upper limb, lower limb and trunk were represented in a rostro-caudal sequence in the depth of sylvian fissure. In humans, studies performed in functional MRI and magnetoencephalography suggest a somatotopic organization of SII with the upper limb areas located more anteriorly and more inferiorly than the lower limbs areas (Maeda *et al.*, 1999; Del Gratta *et al.*, 2000). Our results are overall in agreement with these studies although our number of stimulations remains insufficient for a full exploration of SII. As in SI, somatotopic mapping in SII seems disproportionate with an over-representation of face and hand. Eventhough this statement has been matter of debate (Nelson *et al.*, 1980), this finding has already been noticed by Adrian (1941). Because somatotopy was assessed in this study by inter-individual pooling of a limited number of stimulations we were unable to show the latero-medial organization of face, hand, forelimb–shoulder, hip and foot representations in SII, as demonstrated by electrophysiological recording techniques in monkeys and functional imaging in humans (for a review, see Disbrow *et al.*, 2000). Similarly, due to the small number of stimulation sites in the same individual, it was not possible to assess whether the same somatotopic field was represented in multiple distinct areas in the suprasylvian cortex. In the upper bank of monkeys lateral sulcus two adjacent somatosensory areas, one rostral [parieto-ventral (PV) or rostral SII] and the other caudal (SII) contain mirror symmetric maps of the whole body surface, which share a common boundary at the representation of the face, hands and feet (Krubitzer *et al.*, 1995). In humans fMRI studies have suggested a similar organization of somatosensory areas in the upper bank of the sylvian fissure and identified additional somatotopic representations rostral and caudal (possibly area 7b) to the SII-PV area, which are activated less consistently by stimulating large skin areas using moving stimuli (Disbrow *et al.* 2000). In our study SII stimulus sites were scattered between –20 mm and +12 mm along the rostro-caudal axis (*y* Talairach's coordinate) so that one can be sure to have explored the SII-PV area of which center of mass is located between –17.2 ± 1.3 mm (mean ± SD) and –24.4 ± 8 mm according to available human fMRI activation studies (for a review, see Özcan *et al.* 2005). Our explored area also covers the rostral somatotopic representation identified by Disbrow *et al.* (2000), which is located at –15.0 ± 5.4 mm along the *y*-axis. However, in the study by Disbrow *et al.* (2000), only 10 of 16 subjects showed activation of this area of which center of mass overlaps with that of SII/PV in some other fMRI activation studies (Pleger *et al.*, 2003; Özcan *et al.*, 2005). Lastly no firm conclusion can be made as to whether some of our stimulations were located in the somatosensory area caudal to SII/PV

that showed very inconsistent activation (5 of 16 subjects) in the study by Disbrow *et al.* (2000). This possibility remains however unlikely considering the coordinates of this area, which show considerable inter-individual variations along the *y*-axis (–26.1 ± 13.9 mm in Disbrow *et al.*, 2000).

Our data show a significant gradient in the size of sensations evoked on the skin by the stimulation of SI, SII and insular cortex. This observation suggests differences in size of receptive fields between the three cortices, with a lower spatial resolution in insula than in SII, and in SII than in SI. Thus, SII looks less specifically dedicated to spatial discrimination than SI even if spatial analysis is nevertheless possible in this area, especially when hands or face are concerned. This conclusion converges with the observation that, contrary to what is observed for SI, stimuli moved across the skin of large surface areas prove more effective than punctuate stimuli applied to small skin areas in eliciting cortical activation in the lateral sulcus somatosensory areas (Disbrow *et al.*, 2000). Responses to SI stimulations were mostly contralateral (except for face or trunk representation), whereas responses to SII and insular cortex stimulations were more often bilateral. These differences in terms of size and lateralization of receptive fields are in agreement with microelectrodes studies describing SI receptive fields as small and mainly contralateral to stimulus (Lamour *et al.*, 1983) whereas SII and insular receptive fields are larger and more often bilateral (Robinson and Burton, 1980a,b).

Functionally, our data suggest that SII is involved in the processing of both painful and non-painful inputs. The existence of truly painful responses during electrical stimulations of the cortex has been described recently during insular stimulations (Ostrowsky *et al.*, 2000, 2002). In this early study we mentioned that we had been unable to obtain pain responses to SII stimulation, but no systematic sampling of SII responses had been undertaken at that time, so that we missed the 10% of pain responses to stimulation of this area. The present study suggests that the SII area is actually the second cerebral region where pain can be elicited by direct electric stimulation (in addition to the insula). This is concordant with the existence of pain-evoked responses in this area (Frot and Mauguière, 2003) and with anatomical data in monkeys showing that SII cortex receives inputs from both posterior columns (Mufson and Mesulam, 1982; Augustine *et al.*, 1996) and spinothalamic pathways (Stevens *et al.*, 1993). At a given site of stimulation, when pain was elicited in SII, it was the first sensation reported by the subject. We never observed paresthesiae changing into pain when increasing stimulus intensity. This suggests that SII neurons involved in pain responses might behave as a population of nociceptive specific neurons (NS). Single cell recordings demonstrated that SII area contains not only wide dynamic range (WDR) neurons that respond to both nociceptive and non-nociceptive inputs, but also NS neurons (Robinson and Burton, 1980; Cusick *et al.*, 1989), which might be responsible for the pain responses that we observed in our study. However, this question deserves to be addressed by the recording of intracortical potentials evoked by peripheral pain stimulation, which would allow the correlation of the voltage of responses with stimulus intensity and subjective pain rating separately in both SII and the insula.

Thus, our results support the existence of two distinct representations of pain in the operculo-insular region, the first in SII and the second in the insular cortex, while SI stimulation produced only innocuous sensations. Numerous PET and functional MRI studies have shown bilateral pain-related activation in the parietal operculum and the insula (for a review, see Peyron *et al.*, 2000). These studies have highlighted two distinct sites of activation in this region, located in the vicinity of the anterior insular cortex and, more caudally, in the parietal operculum. Moreover, a very recent meta-analysis of 22 PET and 25 fMRI studies of activation by hand somatosensory stimulation suggested that pain responses in the parietal operculum were mostly localized in the OP1 cyto-architectonic subdivision of SII, which is located in the caudal and lateral part of this area (Eickhoff *et al.*, 2005). Lastly, intracerebral recordings of electrical potentials evoked in these regions by painful and non-painful skin stimulations allowed the separation in time and space of SII and insular cortex responses (Frot and Mauguière, 1999a,b, 2003; Frot *et al.*, 2001). Pain responses were shown to peak at 140–170 and 180–230 ms in SII and in the insular cortex, respectively. In this study, although pain could be elicited by stimulation of both areas, it was impossible to distinguish a qualitative difference between painful sensations evoked by SII and insular stimulations, respectively. This raises the question of redundancy and functional specificity of pain representations in SII and insular cortices.

Notes

Authors are thankful to Roland Peyron for his valuable help and advices for the processing and computation of stimulation sites in MRI slices.

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