Representation of Pain and Somatic Sensation in the Human Insula: a Study of Responses to Direct Electrical Cortical Stimulation

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We studied painful and non-painful somaesthetic sensations elicited by direct electrical stimulations of the insular cortex performed in 43 patients with drug refractory temporal lobe epilepsy, using stereotactically implanted depth electrodes. Painful sensations were evoked in the upper posterior part of the insular cortex in 14 patients, mostly in the right hemisphere. Non-painful sensations were elicited in the posterior part of the insular cortex in 16 patients, in both hemispheres. Thus, painful and non-painful somaesthetic representations in the human insula overlap. Both types of responses showed a trend toward a somatotopic organization. These results agree with previous anatomical and unit recording studies in monkeys indicating a participation of the posterior part of the insular cortex in processing both noxious and innocuous somaesthetic stimuli. In humans, both a posterior and an anterior pain-related cortical area have been described within the insular cortex using functional imaging. Our results help to define the respective functional roles of these two insular areas. Finally, lateralization in the right hemisphere of sites where painful sensations were evoked is coherent with the hypothesis of a preponderant role of this hemisphere in species survival.

Introduction

Based on numerous anatomical and microelectrode studies in monkeys, the involvement of the insular cortex in processing painful as well as non-painful somatosensory inputs has been increasingly contemplated (Burton and Jones, 1976; Robinson and Burton, 1980; Mufson and Mesulam, 1984; Friedman and Murray, 1986; Apkarian and Hodge, 1989; Hodge and Apkarian, 1990; Schneider *et al*., 1993; Apkarian and Shi, 1994; Craig *et al*., 1994; Dostrovsky and Craig, 1996; Blomqvist *et al*., 2000). Laser-evoked potentials in humans have shown bilateral dipolar sources in the second somatosensory area (SII) or the insular cortex (Tarkka and Treede, 1993; Bromm and Chen, 1995; Kakigi *et al*., 1995; Valeriani *et al*., 2000; Opsommer *et al*., 2001). Furthermore, functional imaging in humans have confirmed these data by showing an activation of the insular cortex in response to painful and non-painful somaesthetic stimuli (Burton *et al*., 1993; Casey *et al*., 1994, 1996, 2001; Coghill *et al*., 1994; Hsieh *et al*., 1995b; Craig *et al*., 1996, 2000; Vogt *et al*., 1996; Andersson *et al*., 1997; Antognini *et al*., 1997; Derbyshire *et al*., 1997; Rainville *et al*., 1997; Svensson *et al*., 1997, 1998; Xu *et al*., 1997; Davis *et al*., 1998a,b; Derbyshire and Jones, 1998; Disbrow *et al*., 1998; Iadarola *et al*., 1998; May *et al*., 1998; Oshiro *et al*., 1998; Paulson *et al*., 1998; Bushnell *et al*., 1999; Gelnar *et al*., 1999; Peyron *et al*., 1999; Ploghaus *et al*., 1999; Tölle *et al*., 1999; Kwan *et al*., 2000) [for a review see Peyron *et al*. (Peyron *et al*., 2000)]. Studies on direct electrical stimulation of the insular cortex remain scarce. Respiratory, somato-motor and circulatory effects have been reported in primates and carnivores during insular cortex stimulation (Kaada *et al*., 1949; Babkin and Van Buren, 1951; Hoffman and Rasmussen, 1953). In humans, it has long been a challenge to stimulate the insular cortex during the presurgical assessment of epilepsy, due to its anatomic location, buried under the frontal, temporal and parietal opercular cortices and covered by a dense wall of vessels. Thus, only a few studies have reported non-nociceptive somaesthetic symptoms, cardiovascular effects as well as viscero-motor and viscero-sensitive sensations consecutive to direct electrical stimulation of the insular cortex (Penfield and Faulk, 1955; Wieser, 1983; Oppenheimer *et al*., 1992; Ostrowsky *et al*., 2000). No painful sensation was so far described except in two patients we previously mentioned (Ostrowsky *et al*., 2000).

In this study, we report both painful and non-painful somaesthetic sensations elicited by cortical stimulation of the insular cortex in patients undergoing a depth stereotactic recording (stereo-electroencephalography, SEEG) in the course of the presurgical evaluation of their temporal lobe epilepsies. Our data show that the posterior part of the insular cortex is involved in the processing of both painful and innocuous somaesthetic inputs. Furthermore, their respective topographical distributions overlap within this cortical area.

Materials and Methods

Patients

The 43 patients included in this study (29 women and 14 men) were investigated at the Neurological Hospital in Lyon between January 1996 and November 2000. Language lateralization was assessed by intracarotid amobarbital test in all patients. Among the 36 right-handed patients, 35 had a left language representation and one a bilateral language representation. Among the seven left-handed patients, four had a left language representation, two had a bilateral language representation and one had a right language representation. All patients suffered from a drug-resistant temporal lobe epilepsy (TLE) and underwent a SEEG in the course of their presurgical investigation. Cortical structures to be explored were chosen according to video-EEG recordings of seizures, interictal [^{18}F]fluoro-deoxyglucose positron emission tomography (18-FDG PET), interictal and ictal single photon emission tomography (SPECT) and cerebral magnetic resonance imaging (MRI) data. The decision of insular implantation in the patients of this study was based on the existence of ictal symptoms (such as lip and face paraesthesiae, auditory or gustatory hallucinations, laryngeal contraction, hypersalivation, simple motor signs and post-ictal paresis) suggesting an early spread of the discharge to perisylvian structures (Isnard *et al*., 2000). Twenty-four patients presented a right TLE and 19 a left TLE.

Stereotactic Implantation and Insular Site Location

The stereotactic implantation technique used is that described by Talairach and Bancaud (Talairach and Bancaud, 1973). A cerebral angiography is first performed in stereotactic conditions using an X-ray source 4.85 m away from the patient's head, eliminating the linear enlargement due to X-ray divergence. In order to reach the pertinent cortical target, the stereotactic coordinates (Talairach and Tournoux, 1988) of each electrode [x for the medio-lateral axis, with $x = 0$ being the coordinate of the sagittal interhemispheric plane; y for the rostro-caudal axis, $y = 0$ being the coordinate of the frontal plane passing through the

vertical anterior commissure (VAC); z for the vertical axis, $z = 0$ being the coordinate of the horizontal plane passing through the anterior and posterior commissures (AC–PC plane)] are calculated preoperatively on the individual cerebral MRI previously enlarged at scale 1. Cerebral MRI and angiographic images are easily superimposed to avoid any risk of vascular injuries during implantation.

At the end of the surgery, a post-implantation frontal X-ray was taken and superimposed on MRI images to verify the final position of each implanted electrode with respect to targeted anatomical structures.

Electrodes are implanted perpendicular to the mid-sagittal plane and can be left in place chronically up to 15 days. The electrodes have a diameter of 0.8 mm and 5–15 recording contacts, depending on their length. Contacts are 2 mm long and are separated by 1.5 mm from one another. The insular cortex was investigated using trans-opercular electrodes. In all cases, only the first and second deepest contacts of the trans-opercular electrode were found to be strictly located in the thickness of the insular cortex as checked on superimposed MRI and X-ray images (Fig. 1*A*). A total of 93 insular sites were explored, 49 in the right and 44 in the left insular cortex. Each of these insular sites was localized using the stereotactic coordinates of the deepest contact of the corresponding trans-opercular electrodes. The x coordinate (depth of implantation) was verified on the post-implantation frontal X-ray whereas the strict perpendicular trajectory of the electrode, verified on both the frontal and sagittal post-implantation X-rays, ensured that the preoperatively calculated y and z coordinates had been preserved. The estimated spatial error of this insular site location technique is ±2 mm in the three dimensions due to several factors: MRI slice thickness of 1 mm, MRI definition (pixel size) of 0.9 mm; pooling of sites of all patients on a single MRI saggital slice of the insular cortex, whether this slice was extracted from a standardized atlas (Montreal National Institute standard brain) or from the individual MRI of one of our patients (see below).

Stimulation Paradigm

A current regulated neurostimulator designed for a safe diagnostic stimulation of the human brain was used (Babb *et al*., 1980). Square pulses of constant polarity were applied between the two deepest contacts of the trans-opercular electrodes located in the insular cortex (see Fig. 1*A*). Two modes of stimulation were used; low frequency stimulation (LFS): 1 Hz, 1–3 ms, 1–5 mA applied during 5–10 s and high frequency stimulation (HFS): 50 Hz, 0.1–0.5 ms, 0.8–6 mA applied during 5 s. These parameters were chosen to avoid any tissue injury [charge density per square pulse <55 $\mu C/cm^2$; see Gordon *et al*. (Gordon *et al*., 1990)]. These parameters, along with the bipolar mode of stimulation using adjacent contacts, ensured a good spatial specificity with respect to the desired structure to be stimulated (Nathan *et al*., 1993). HFS was used in all patients and at least once on each insular site. LFS was only performed in the first 20 patients and then abandoned due to its poor efficiency in terms of evoked clinical responses. Stimulation of cortical areas is a routinely applied procedure used in our unit during SEEG recordings to map functionally eloquent cortex and epileptogenic areas. Patients were fully informed of the aim of this investigation and gave their consent before entering this phase of the presurgical evaluation of their epilepsy. During stimulation, patients were sitting in bed and were asked to relax.

Results

A total of 188 stimulations (61 LFS and 127 HFS) were performed in the 93 insular sites in the 43 patients. Clinical responses (of different modalities) were evoked in only 35 of the patients (35/43; 81%), in 67 of the sites (67/93; 72%), and during 111 of these stimulations (59% of the stimulations, 14 LFS and 97 HFS). These responses were reported during the stimulation period and disappeared either immediately or very shortly (a few seconds) then after. The electrical stimulations could be followed by an after-discharge (AD) which either remained localized to the stimulation site (localized AD) or spread to other insular or extra-insular sites that were not directly stimulated (diffusing AD). In 52 sites, the clinical responses were evoked in the absence of AD. In 12 sites, the elicited responses were followed by a localized AD. The three sites where responses

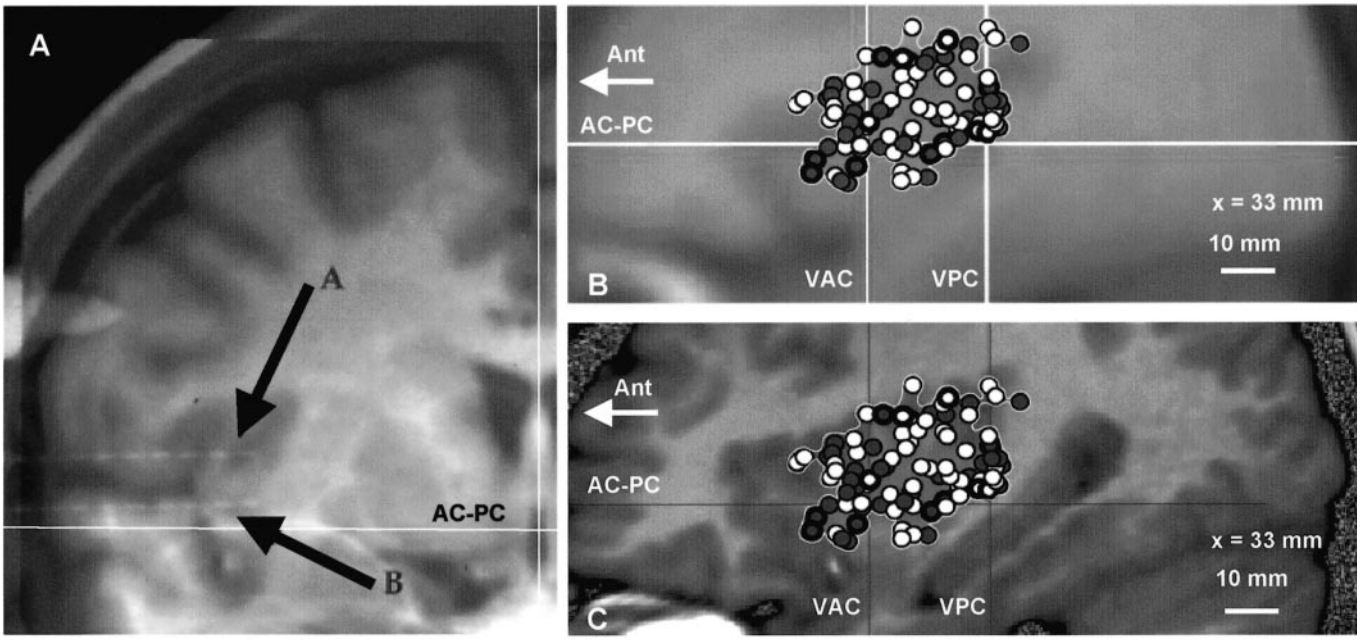

Figure 1. (*A*) Immediate post-implantation frontal X-ray showing the trajectory of the electrodes superimposed on the corresponding coronal section of the MRI. As can be seen, the first and second deepest contacts of the trans-opercular electrodes A and B (indicated by the arrows) are in the depth of the insular cortex. (*B*) A plot of all (93) stimulated insular sites on a sagittal section ($x = 33$ mm) of the insular cortex of the MNI standard brain. (*C*) A plot of all (93) stimulated insular sites on the corresponding sagittal section of the insular cortex of one of our patient's cerebral MRI, showing a similar sampling. Circles represent sites of stimulation, thick contours indicate sites where stimulation evoked a localized AD. AC–PC: horizontal plane passing through the anterior and posterior commissure; VAC: frontal plane passing trough the anterior commissure, perpendicular to the AC–PC plane; VPC: frontal plane passing through the posterior commissure, perpendicular to the AC–PC plane. The white line is the contour of the stimulated insular area. Open circles: insular sites in the right hemisphere; hatched circles: insular sites in the left hemisphere.

were followed by a diffusing AD were excluded from the topographical and somatotopic analysis, and therefore not represented on the figures.

Because only one to three insular sites were stimulated per patient, individual data remained poorly informative. Thus, the topographic and somatotopic analysis of our responses were performed by pooling sites where responses were obtained on a single sagittal insular image. In Figure 1 all stimulated sites, whether right or left, are plotted on a sagittal section of the insular cortex of the MNI (Montreal National Institute, Canada) standard brain (Fig. 1*B*) and on the corresponding slice of one of our patients (Fig. 1*C*). Due to inter-individual variations, the borders and anatomical details of the MNI brain slice are blurred as compared with those of the individual MRI slice. However, as can be seen in Figure 1, the sampling of the insular cortex was very similar using either of these two types of brain section. This plotting shows that most of the insular surface has been explored except the most anterior part of the insular cortex (y > to 15 mm). For illustration's sake, we plotted sites of stimulation on the individual sagittal MRI slice in other figures.

Painful Sensations Evoked by Insular Cortex Stimulation

Painful sensations were elicited in 17 insular sites (17/93; 18.2%) in 14 patients (14/43; 32.5%). Mean intensity of stimulation was 2.2 mA ± 0.9. Twelve sites were located in the right and five in the left insular cortex. Pain was elicited only during HFS, without AD on 13 sites (11 patients) and with a localized AD in two sites (in two patients). The two sites, both located in the left insular cortex of one patient where the painful sensations were followed by a diffusing AD, are excluded from the following discussion.

The 15 sites where pain was elicited in the absence of AD or with a localized AD were located in the upper posterior part of the insular cortex (Figs 2*A* and 4*A*). Pain intensity could vary from mild to intolerable but was not related to the presence or absence of a localized AD, nor to stimulation intensity. The occurrence of an intolerable painful sensation led us to immediately stop the stimulation, which then only lasted for about 1 s instead of 5 s. Pain disappeared as soon as the stimulation was interrupted except in a few cases where the intense pain was followed by a sore feeling that could last up to 1 min after the end of the stimulation. Painful sensations were located contralateral to the stimulation site or bilaterally when midline parts of the body were involved. Whereas limb sensations were elicited across the posterior part of the insular cortex, face, ear and nose painful sensations (the cephalic representation) were mostly elicited in a limited area in the upper anterior part of the posterior section of the insular cortex (Fig. 2*B*). Qualities of the evoked pain were described as a burning, a stinging or a disabling sensations. Electrical shocks or discharges were also reported (Fig. 2*C*). Since all elicited sensations comprised a part of the contralateral body and since the anatomical location of the right and left reactive sites within the insular cortex did not differ significantly (Mann–Whitney test; two-tailed $P > 0.66$), coordinates of insular sites of both hemispheres were pooled to calculate mean coordinates of the insular pain representation. These mean coordinates were x = 31.2 ± 4.9 mm, y = –16.4 ± 6.3 mm, z = 13.2 ± 7.6 mm (Table 1).

Most sites where painful sensations occurred were located in the right hemisphere (Fig. 2*A*). Although based on a limited number of sites (15), this higher proportion of sites inducing pain is statistically significant (Fisher's exact test; two-tailed $P = 0.02$). Moreover, the three sites located in the left insular cortex correspond to stimulation sites in three different patients: the first patient was left-handed and had a bilateral language representation, the second one was left-handed with a left language representation and the third one was right-handed with a left language representation. The 12 right insular sites where painful sensations occurred were stimulated in 10 different patients of whom nine were right-handed (eight with a left language representation and one with a bilateral language representation) and one was left-handed with a bilateral language representation. Therefore, only once was a painful sensation elicited during stimulation of the insular cortex on the side of a hand and language dominant hemisphere.

Non-painful Somaesthetic Sensations Evoked by Insular Cortex Stimulation

Non-painful somaesthetic sensations were elicited in 21 insular sites (21/93; 22.5%) in 16 patients (16/43; 37.2%). Nine sites were located in the left and 12 in the right insular cortex. Three of these 16 patients also reported painful evoked sensations described in the preceding section. Painful and non-painful somaesthetic sensations were evoked on different sites except for one site where a first LFS induced a non-painful cold somaesthetic sensation in the contralateral arm and a second HFS stimulation induced an extremely painful electric shock in the contralateral half of the body. All non-painful somaesthetic-evoked responses but one were obtained using HFS. Sensations were elicited in the absence of AD in 18 sites (13 patients) and with a localized AD in three sites (in three patients). No diffusing AD was observed during non-painful somaesthetic sensations. Mean intensity of stimulation was 2.4 ± 1.8 mA.

Most reactive sites were located in the posterior part of the insular cortex (Figs 3*A* and 4*A*). These non-painful sensations were felt contralateral to the stimulation or bilaterally when midline parts of the body were concerned. They involved the face, the ear and/or the throat when stimulated sites were located in the upper part of the posterior section of the insular cortex and the limbs when sites were distributed in its inferior part (Fig. 3*B*). They were reported as warmth, cold or tingling sensations. Tingling and warmth sensations were evoked throughout the posterior part of the insular cortex. The only cold sensation was obtained by stimulating the upper posterior part of the insula (Fig. 3*C*). Since all sensations comprised at least a part of the contralateral body and since anatomical locations of right versus left reactive sites within the insular cortex did not differ significantly (Mann–Whitney test; two-tailed $P > 0.23$), coordinates of insular sites of both hemispheres were pooled to calculate mean coordinates of the non-painful insular somaesthetic representation. These mean coordinates were x = 32 ± 3.5 mm, y = –13.1 ± 10.6 mm, z = 7.8 ± 8.3 mm (see Table 2), values that did not differ significantly from those of the insular pain representation (Student's t-test; two-tailed $P > 0.05$; Fig. 4*B*).

The proportion of the reactive sites found in the left versus the right hemisphere were not found statistically significant (Fisher's exact test; two-tailed $P = 0.8$).

Discussion

The major finding of this study is the possibility to induce painful and non-painful somaesthetic sensations by direct stimulation of the posterior part of the human insular cortex. We further demonstrate that both painful and non-painful somaesthetic insular representations overlap and tend to be somatotopically organized. Finally, an unexpected lateralization of painful sensation induced by stimulating the right hemisphere is disclosed.

Insular stimulations in our study were performed in epileptic

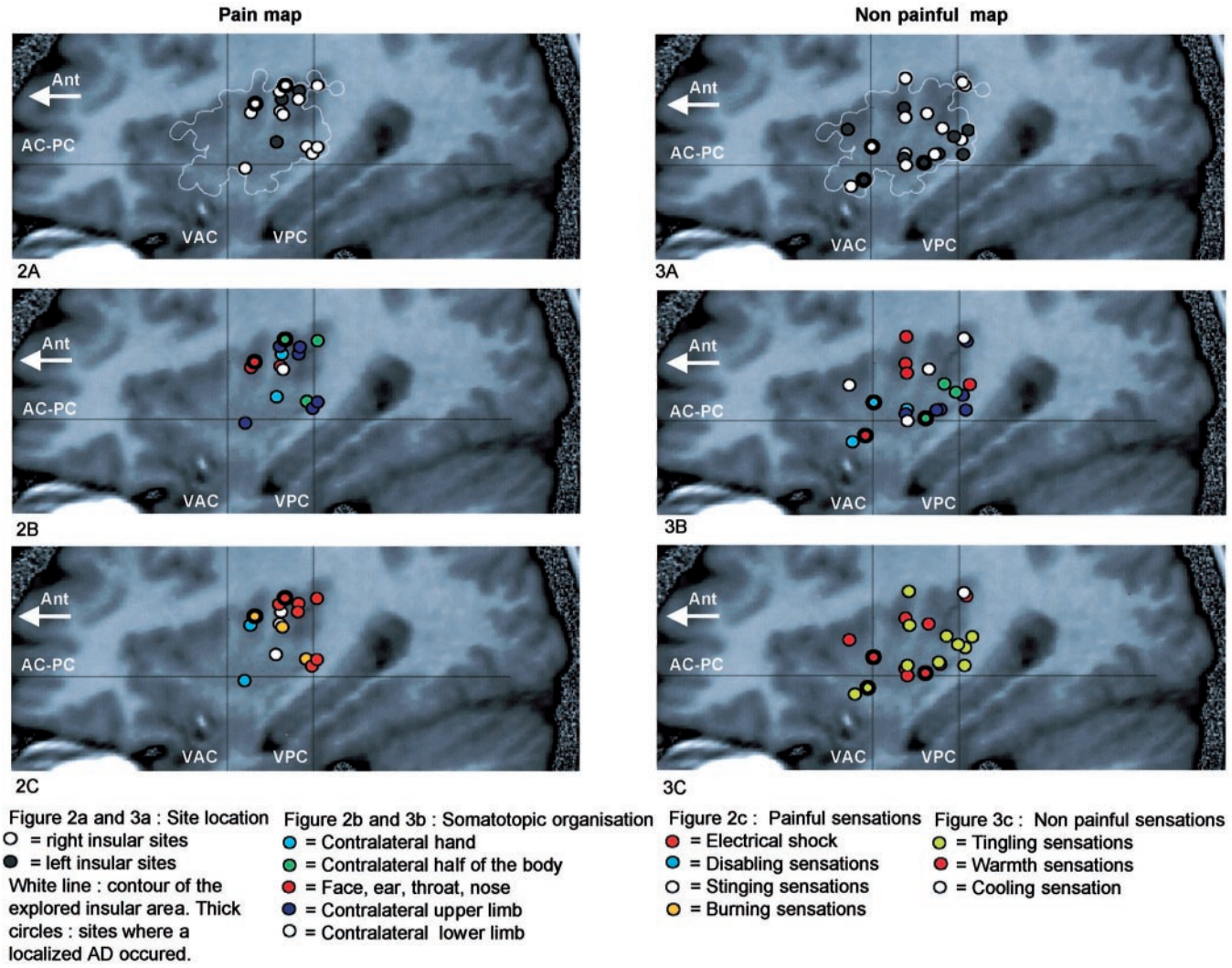

Figure 2. A plot of sites where painful sensations occurred in 14 patients; (*A*) most sites are located in the upper posterior part of the insular cortex, in the right hemisphere; (*B*) somatotopic organization of the responses: the cephalic representation is more rostral than that of the limb and hand representation; (*C*) location of different pain qualities.

Figure 3. Plotting of sites where non-painful sensations occurred in 16 patients; (*A*) most sites are located in the posterior part of the insular cortex, in both hemisphere; (*B*) somatotopic organization of the responses: the cephalic representation is similar to that of pain representation whereas limb and hand representations are more scattered across the posterior part of the insular cortex; (*C*) location of warmth, cold and tingling sensations.

patients. One could therefore argue that the responses we obtained are related to an abnormal (epileptogenic) cortex, or a cortex that has been submitted to repetitive fits leading to plastic changes (Gloor, 1990; Fish *et al*., 1993). Nonetheless, and concerning the painful responses, these were not reported in previous studies which were also performed in epileptic patients.

The proximity of the second somatosensory area (SII) with respect to the insula also raises the question as to the specificity of our responses. Even considering the current density spatial distribution during bipolar stimulation (Nathan *et al*., 1993), the threshold value leading to an effective stimulation of SII would have to be known in order to evaluate a possible involvement of SII by stimulations of the neighbouring insular cortex. The main argument favouring the specificity of our insular stimulations is that painful responses could never be obtained when stimulating directly SII using identical stimulation parameters (personal observations). This is coherent with the fact that Penfield and Jasper also never reported such painful responses when stimulating SII (Penfield and Jasper, 1954). Furthermore, the recording of the intracerebral activity during the stimulus paradigm gives us confidence in the specificity of our responses by providing the possibility to detect diffusing AD. It has been demonstrated that no significant cerebral blood flow change occurs during direct electrical cortical stimulation carried out with our paradigm of stimulation in the absence of AD (Kahane *et al*., 1999). As most of the responses reported in this study were obtained in this condition, one can assume that the spatial resolution of our functional mapping is not blurred by some remote effects of the stimulation on neighbouring structures. This assumption seems also acceptable for responses associated with a localized AD which remained confined to the stimulation site. Conversely, responses associated with a diffusing AD were discarded from our functional mapping study. In summary, according to the above considerations, pain and non-painful somaesthetic evoked responses obtained in this study can be reliably considered as specific of the stimulation of the posterior part of the insular cortex.

Table 1
Stereotactic coordinates of the 15 insular sites where painful sensations were elicited in absence of AD or with a localized AD in our study (*site located in left hemisphere)

	x	y	z
	26	–22	5
	30	–8	17
	27	–15	20
	40	–5	–1
	31	–7	14
	30	–24	3
	28	–16	22
	40	–25	22
	32	–15	15
	31*	–14	6
	29	–25	5
	30	–20	18
	27*	–20	20
	40*	–15	18
	27	–16	14
Mean	31.2	–16.4	13.2
SD	4.9	6.3	7.6

Table 2
Stereotactic coordinates of the 21 sites where non-painful somaesthetic sensations were elicited in absence of AD or with a localized AD in our study (*site located in left hemisphere)

	x	y	z
	40	–25	22
	31	0	5
	33*	7	10
	36*	–15	1
	33	–9	3
	32	–9	23
	32*	–27	9
	30*	–9	16
	34	–9	0
	33	–15	14
	36	6	–6
	31	–25	7
	33*	–9	2
	29*	–18	3
	29	–9	13
	37*	2	–4
	27*	–27	3
	31	–20	10
	28	–18	3
	25	–24	23
	32*	–23	8
Mean	32	–13.1	7.8
SD	3.5	10.6	8.3

Pain Representation

Apart from two patients we already reported (Ostrowsky *et al.*, 2000), truly painful responses have not been previously described during stimulation of any area of the cerebral cortex in humans. This can be attributed to different reasons: (i) studies of insular stimulation in monkeys and dogs were performed under anaesthesia (Kaada *et al.*, 1949; Babkin and Van Buren, 1951; Hoffman and Rasmussen, 1953) thus precluding any study of pain-evoked responses. (ii) In humans, Penfield and co-workers extensively stimulated all cortical areas of the human brain, using surface electrodes, during cortectomies under local anaesthesia (Penfield and Brodley, 1937; Penfield and Jasper, 1954), including the insular cortex (Penfield and Faulk, 1955). However, they only explored the upper posterior part of the insula in rare cases after removal of the fronto-parietal operculum. As can be seen in our results, painful sensations could not be elicited from all sites situated in the upper posterior part of the insular cortex and a large number of stimulation sites in this area must therefore be sampled in order to disclose the insular pain representation.

The existence of a pain representation in the posterior insular cortex is coherent with anatomical connectivity and electrophysiological properties of this area in monkeys. Indeed, a major source of insular inputs originates from thalamic nuclei receiving spino-thalamic-tract fibres (STT) which carry nociceptive information (Burton and Jones, 1976; Mufson and Mesulam, 1984; Friedman and Murray, 1986; Apkarian and Hodge, 1989; Hodge and Apkarian, 1990). Furthermore, Burton and Jones showed a preferential thalamic input to the posterior part of the insular cortex from the supragenicular-limitans nucleus (SG-Li) and the posterior complex (Po) in monkeys (Burton and Jones, 1976). In humans, Craig *et al.* described a thalamic structure specifically relaying painful and thermal stimuli: the posterior portion of the ventral medial nucleus, i.e. the VMpo (Craig *et al.*, 1994). As the latter nucleus is embedded in the Po, one can assume that its efferent fibres terminate in a similar insular area. These connections have moreover been described by Craig (Craig, 1995), who showed tracing studies indicating the anatomical projection of the VMpo to the same part of the insular cortex associated in this study with pain and cold sensations. The ventral posterior inferior nucleus (VPI) is another relevant structure since it contains a high proportion of nociceptive neurons (Apkarian and Shi, 1994) and also projects to the posterior part of the insula (Burton and Jones, 1976; Mufson and Mesulam, 1984). Finally, and in agreement with all these possible inputs, single-unit recordings performed in monkeys have revealed nociceptive responses in neurons of the posterior part of the insular cortex (Robinson and Burton, 1980).

In humans, our results can be compared with previous clinical observations and studies using different techniques: evoked potential, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Brain injuries located in the superior/posterior portion of the insula have led to impairment in pain perception (Greenspan and Winfield, 1992; Schmahmann and Leifer, 1992; Greenspan *et al.*, 1999). In healthy volunteers, all dipolar source models of the earliest lateralized evoked potential to CO_2 laser stimulation include bilateral sources in SII or the insular cortex (Tarkka and Treede, 1993; Bromm and Chen, 1995; Kakigi *et al.*, 1995; Valeriani *et al.*, 2000; Opsommer *et al.*, 2001). Although these results are in rough agreement with ours, further more accurate comparisons are impeded by the limited spatial resolution of this technique.

Most PET studies reveal a bilateral activation of the insular cortex during peripheral painful stimuli. Since most of our responses were contralateral to the cortical stimulation we will only consider contralateral insular PET activation. When the mean coordinates of the insular sites eliciting painful sensations are compared with those obtained in PET studies, they are significantly different in each spatial dimension (Student's *t*-test; two-tailed $P < 0.006$). In the x (lateral–medial) and z (vertical) dimensions, the mean PET coordinates depart from ours by 5.8 mm and 6.7 mm, respectively (see Tables 1 and 3, and Fig. 4*B*). This could be due to the simultaneous activation of SII which is difficult to discriminate from that of the insula using PET technique allowing no more than a 4 mm spatial resolution with the most advanced tomographs. Thus, the significance of the statistical difference obtained for these two dimensions remains highly questionable. In the y (rostro-caudal) dimension, the difference increases to 15.2 mm (see Tables 1 and 3, and

Table 3
Stereotactic coordinates of mean peaks of activation found in the insular cortex contralateral to the noxious peripheral painful stimuli described in previous PET studies performed in humans (*site located in left hemisphere)

Reference	*x*	*y*	*z*
(Casey *et al.*, 1994)	37	–19	14
(Coghill *et al.*, 1994)	38	6	9
(Hsieh *et al.*, 1995b)	33*	9	8
(Casey *et al.*, 1996)	37	–19	14
(Vogt *et al.*, 1996)	36	0	4
(Craig *et al.*, 1996)	37*	–9	3
(Craig *et al.*, 1996)	37*	5	3
(Rainville *et al.*, 1997)	42	–6	12
(Andersson *et al.*, 1997)	36*	6	1
(Svensson *et al.*, 1997)	44	5	9
(Xu *et al.*, 1997)	36	–6	0
(Xu *et al.*, 1997)	32	16	–4
(Iadarola *et al.*, 1998)	38	6	8
(Derbyshire *et al.*, 1997)	30*	–2	4
(May *et al.*, 1998)	36*	6	2
(Svensson *et al.*, 1998)	38	5	11
(Svensson *et al.*, 1998)	43	5	2
(Svensson *et al.*, 1998)	46	1	–2
(Derbyshire and Jones, 1998)	40*	–20	16
(Paulson *et al.*, 1998)	39	–22	16
(Paulson *et al.*, 1998)	33	1	0
(Tölle *et al.*, 1999)	35*	–6	7
(Peyron *et al.*, 1999)	34*	–2	4
(Casey *et al.*, 2001)	33	23	7
(Casey *et al.*, 2001)	33	–15	9
(Casey *et al.*, 2001)	39	1	11
Mean	37	–1.2	6.5
SD	3.8	11.1	5.5

The mean *y* coordinate of these PET studies (–1.2 mm) departs from ours (–16.4 mm) by 15.2 mm.

Table 4
Separate stereotactic coordinates of the anterior and posterior peaks of activation reported in recent PET studies showing two distinct peaks of activation within the insular cortex contralateral to the peripheral noxious stimulation (*site located in left hemisphere)

Reference	*x*	*y*	*z*
	Anterior peaks		
(Craig *et al.*, 1996)	37*	5	3
(Xu *et al.*, 1997)	32	16	–4
(Paulson *et al.*, 1998)	33	1	0
(Casey *et al.*, 2001)	33	23	7
(Casey *et al.*, 2001)	39	1	11
Mean	34.8	9.2	3.4
SD	3	9.8	5.8
	Posterior peaks		
(Craig *et al.*, 1996)	37*	–9	3
(Xu *et al.*, 1997)	36	–6	0
(Paulson *et al.*, 1998)	39	–22	16
(Casey *et al.*, 2001)	33	–15	9
Mean	36.2	–13	7
SD	2.5	7	7

Fig. 4*B*). Even if some of the earliest PET studies were performed with a spatial resolution of ~8 mm, this difference could be considered as truly significant. However, recent PET studies (Craig *et al.*, 1996; Xu *et al.*, 1997; Paulson *et al.*, 1998; Casey *et al.*, 2001) are more and more showing two separate foci of maximal activation within the insular cortex: one located in its antero–inferior part, the other in its postero-superior extent (Table 4). Thus, not discriminating these two peaks of activation would lead to a biased mean *y* value shifted anteriorly with respect to our data. To overcome this bias, one can consider only the mean coordinates of the posterior peak of activation of these recent PET studies (x = 36.2 ± 2.5 mm, y = –13 ± 7 mm, z = 7 ± 7 mm, Table 4). Doing this, the coordinate differences between the posterior peak of PET activation and our sites of stimulations for x, y and z are 5, 3.5 and 6.2 mm, respectively. According to the technical limitations already mentioned, one can consider that these differences are not significant. Furthermore, a recent study (Casey *et al.*, 2001) has demonstrated that the pattern of structures activated by a persistent thermal nociceptive stimulus could evolve in time with respect to the beginning of the stimulation. In the early period (0–60 s), an anterior insular activation was observed (y = 23 mm) while two more caudal peaks of activation appear during following scans (y = 1 mm and –15 mm, respectively). This phenomenon could also explain the discrepancies along the rostro-caudal axis of data reported in previous PET studies. Also worth noting is the comparison made by Casey's group between their results obtained with a conventional protocol in 1994 and those obtained in the late phase of the nociceptive stimulation in their more recent study. In very similar stimulus conditions, a difference of 18 mm in the antero-posterior dimension stands between the two activated peaks in the contralateral insula [see table 3 in Casey *et al*. (Casey *et al.*, 2001)]. For all the above reasons, one can consider that comparisons between our data and those obtained by the PET technique is at this time very questionable.

Nonetheless, it remains to be determined the functional role of the antero-inferior pain representation disclosed in PET studies which is located in an area that was sampled by our electrodes but in which we could not evoke any pain responses (mean coordinates of the antero-inferior peak in recent PET studies showing two peaks of activation: x = 34.8 ± 3 mm, y = 9.2 ± 9.8 mm, z = 3.4 ± 5.8 mm, Table 4). The presence of such an antero-inferior peak of activation is not surprising *per se* since a projection from the VPI to the anterior part of the insula has been described (Burton and Jones, 1976). One can thus postulate that although both anterior and posterior parts of the insular cortex receive nociceptive inputs via the VPI, the anterior part is not involved in exteroceptive pain perception itself but in other related functions. This hypothesis would fit with the viscerosensitive, visceromotor and autonomic reactions previously observed when stimulating this particular anterior insular area (Penfield and Faulk, 1955; Oppenheimer *et al.*, 1992; Ostrowsky *et al.*, 2000).

Finally, the more recent introduction of fMRI with its improved spatial resolution could have led to a more precise topographic location of activated brain structures. To this date, only a few studies in the field of pain processing are available (Antognini *et al.*, 1997; Davis *et al.*, 1998a,b; Disbrow *et al.*, 1998; Oshiro *et al.*, 1998; Bushnell *et al.*, 1999; Gelnar *et al.*, 1999; Ploghaus *et al.*, 1999; Kwan *et al.*, 2000; Moulton *et al.*, 2000). Three of them deserve special attention since they directly addressed the question we are interested in. Gelnar *et al*. who, unfortunately, did not explore the anterior part of the insula, reported an activated peak in its posterior part, mean coordinates of which (x = 42 mm, y = –10 mm, z = 14 mm) are in fairly good agreement with our data (Gelnar *et al.*, 1999). Results obtained by Davis *et al*. are more puzzling, showing a large interindividual variability in activated insular areas which are distributed throughout its rostro-caudal axis with some preponderance in its anterior part (Davis *et al.*, 1998b). A similar result is obtained by Ploghaus *et al*. who, in addition, found a distinct peak of activation in the anterior insular cortex specifically related to the expectation of painful stimuli (Ploghaus *et al.*, 1999). Together with our data, this last observation tends to

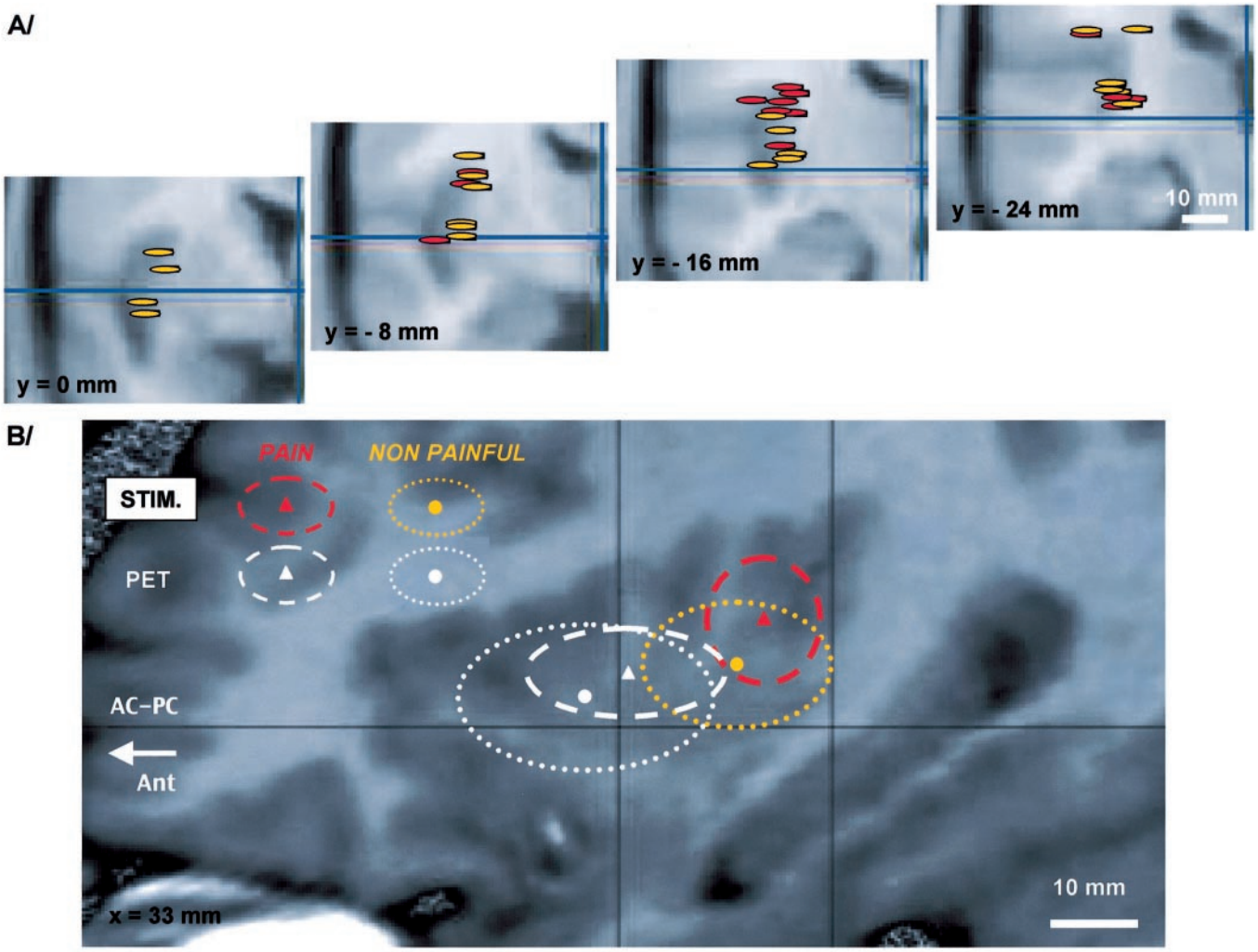

Figure 4. (*A*) Projections of all insular stimulation sites on selected coronal sections of the MNI standard brain. The *x*-axis 5.5 mm dimension of each ellipse has been traced between the two contacts used for stimulation using as limits the inner side of the deepest insular contact and the outer side of the neighbouring contact. This representation illustrates the coronal projection of the estimated stimulation current dipole. Even using an average standard brain representation, some of these ellipses appear located deeper, in the external capsule, or overlap with the external capsule. This is due to rather large interindividual anatomical differences and the fact that some of the insular stimulation sites are located on coronal sections adjacent to those illustrated. However, note that for each stimulated site, the location of the corresponding two contacts of the trans-opercular electrode was checked to be strictly located in the thickness of the insular cortex on superimposed MRI and X-ray images in each patient. Non-painful sites are in yellow, painful sites are in red. (*B*) Respective location of painful and non-painful representations within the insula defined according to direct electrical stimulations (this study) or resulting from previous PET studies (see Tables 3 and 5). Centres of these areas correspond to mean *y* and *z* coordinates and their extents are defined from the associated *y* and *z* standard deviations.

attribute to the anterior insula a functional role not directly related to pain perception.

Non-painful Sensation Representation

It is generally accepted that tactile sensation is supported by the medial lemniscal system. However, according to its known connectivity, the ventral posterior lateral nucleus which receives its major input from the medial lemniscal tract does not project to the insular cortex in monkeys (Burton and Jones, 1976). The sensations we obtained in the posterior part of the insular cortex can nonetheless be divided into two types. Thermal ones (mainly warm) can be explained in the light of recent studies describing a STT component coding specifically not only for painful but also for thermal stimuli. It originates in the superficial lamina I of the spinal dorsal horn and terminates in a subdivision of the Po, the VMpo (Craig *et al.*, 1994; Dostrovsky and Craig, 1996; Blomqvist *et al.*, 2000). The projections of the latter nucleus on the posterior part of the insula (Burton and Jones, 1976) should thus ensure a thermal representation within the insula which can be activated by direct electrical stimulation. Similar considerations can account for the tingling sensations we observed. It has been demonstrated that wide dynamic range neurons located deeper in the dorsal horn (laminae III–IV) are able to carry tactile information beside pain related signals (Zhang *et al.*, 1991). The STT recipient nuclei (Po, SG-Li, VPI) are thus able to supply the insula with non-nociceptive somaesthetic information through the limited but consistent proportion of wide-dynamic neurons they contain (Apkarian and Shi, 1994). This is supported by single-cell studies in monkeys showing a high percentage (nearly two-thirds) of neurons in the posterior insula responding to non-nociceptive stimulations (Robinson and Burton, 1980; Schneider *et al.*, 1993). The above considerations refer to the most direct route for non-painful stimuli to the insular cortex. However we cannot exclude that somaesthetic inputs reach the insular cortex via area SII, which sends direct projections to the posterior insular cortex (Mufson and Mesulam,

Table 5
Stereotactic coordinates of mean peaks of activation in the insular cortex contralateral to peripheral non-painful stimuli disclosed in previous PET studies in humans (*site located in left hemisphere)

Reference	*x*	*y*	*z*
(Burton *et al.*, 1993)	39.9	6	5.9
(Burton *et al.*, 1993)	30.4*	25.6	2.2
(Burton *et al.*, 1993)	39.2	16.1	6.2
(Burton *et al.*, 1993)	38.2*	7.1	11.1
(Coghill *et al.*, 1994)	38	–13	–5
(Craig *et al.*, 1996)	37*	–9	3
(Craig *et al.*, 1996)	37*	5	3
(Derbyshire *et al.*, 1997)	30*	–2	4
(Iadarola *et al.*, 1998)	38	20	–8
(Iadarola *et al.*, 1998)	34	8	–8
(Craig *et al.*, 2000)	36*	–22	24
Mean	36.1	3.8	3.5
SD	3.3	14.4	9.1

The mean *y* coordinate of these PET studies (3.8 mm) departs from ours (–13.1 mm) by 16.9 mm

1982) and responds to non-painful stimulation of the median nerve in humans (Frot and Mauguière, 1999).

The non-painful representation we obtained can also be compared in terms of location with previous studies in humans using different techniques. Dipolar source modelling of somatosensory evoked potentials in humans have revealed dipoles, deep in the upper bank of the Sylvian fissure, posterior to the central fissure, compatible with generators in SII or the insular cortex (Baumgartner *et al*., 1991; Hari *et al*., 1993; Forss *et al*., 1996; Mauguière *et al*., 1997). Unfortunately, the limited spatial resolution of this technique does not allow more precise comparisons. Cerebral blood flow increases in the insular cortex contralateral to innocuous somaesthetic stimulation have been reported in PET studies (Burton *et al.*, 1993; Coghill *et al.*, 1994; Craig *et al.*, 1996, 2000; Derbyshire *et al.*, 1997; Iadarola *et al.*, 1998) but with mean coordinates of activation peaks significantly more rostral (16.9 mm; Student's *t*-test: two-tailed $P = 0.0007$) and lateral (4 mm; Student's *t*-test: two-tailed $P = 0.003$) than mean coordinates of sites where non-painful somaesthetic sensations were evoked in our patients (see Tables 2 and 5, and Fig. 4*B*). Although statistically significant, these differences remain highly questionable for the technical reasons already evoked for the insular pain representation. More puzzling is the fact that the non-painful somaesthetic area activated in PET studies was sampled in our study and no corresponding sensations were herein evoked. Looking carefully at the data previously obtained with the PET technique [see fig. 1 of Craig *et al*. (Craig *et al*., 1996) for 20 and 40°C thermal stimuli], it seems that the global insular activation can be constituted of two distinct peaks of activation, similar to the ones induced by painful stimuli. However, the same group, in a later study carried out in very similar stimulation conditions (Craig *et al.*, 2000), did not confirm this pattern at least for the 20°C stimulus, mentioning only a posterior insular peak of activation, coordinates of which are in perfect agreement with our results. On the ipsilateral side of stimulation, an anterior peak of activation that was not present in the earlier study (Craig *et al.*, 1996) was this time observed. Facing such data variability implies that we should show caution in more precise comparisons with our results. Finally, fMRI studies (Davis *et al.*, 1998b; Gelnar *et al.*, 1999; Disbrow *et al*., 2000; Sawamoto *et al*., 2000) do not allow direct comparisons since none of them gives the mean coordinates of an insular area activated by non-painful somaesthetic stimuli. Nevertheless, it is worth noting the distribution of responses following tactile stimuli reported by Davis *et al.* and found selectively in the posterior part of the insula, a location which tightly fits with our results (Davis *et al*., 1998b). However, in the same study, innocuous temperature-related activations in the insula were not segregated consistently in any particular region.

Somatotopic Organization of the Responses

Another original contribution of this study concerns a possible somatotopic organization of pain representation in the human insula. To our knowledge, this question has not been addressed before in single-cell studies in monkeys (Robinson and Burton, 1980), and only once in a PET study which failed to demonstrate distinct representations for hand and foot painful stimulation (Xu *et al.*, 1997). Concerning the non-painful somaesthetic representation, no precise topography within the insular cortex can be found in Wieser's data (Wieser, 1983) whereas Penfield and Faulk (Penfield and Faulk, 1955) already noticed some somatotopic organization within the insular cortex with responses located to the limbs (and usually better lateralized) when stimulating insular sites located posteriorly and to the midline structures (lips, tongue, mouth and throat) when stimulating insular sites located more anteriorly. A similar trend is observed in our study.

Overlap Between Painful and Non-painful Representations

As can be seen in Figure 4*B*, insular areas where painful and non-painful somaesthetic responses were obtained, overlap. This is in agreement with the connectivity described above allowing somaesthetic inputs, whether painful or not, to converge to the posterior part of the insular cortex via direct STT-thalamocortical projections. At the cellular level, Robinson and Burton showed that the same insular neuron in the posterior insula was able to respond to both painful and non-painful somaesthetic stimuli (Robinson and Burton, 1980). The receptive fields of these insular neurons were found to be large, in agreement with our observations that responses obtained when stimulating the posterior part of the insular cortex included extensive parts of the body. This is an additional factor which could participate in the overlap between the representation of the two somaesthetic modalities. Finally, PET data showing similar activated regions in the insular cortex during painful and non-painful somaesthetic stimuli (Coghill *et al.*, 1994; Craig *et al.*, 1996; Derbyshire *et al.*, 1997; Iadarola *et al.*, 1998) are coherent with this overlapping location of the pain and non-painful somaesthetic representations within the human insular cortex.

Lateralization of the Painful Representation

Whereas non-painful somaesthetic sensations were evoked in similar proportion by stimulation of right or left insular sites, pain was mostly elicited when stimulating the insula of the non-dominant language and/or manual hemisphere, i.e. the right insular cortex. Previous authors have also mentioned some asymmetrical features concerning the human insula. Thus, Clarke found that the volume of the left insula was larger than that of the right (Clarke, 1896). Later, Oppenheimer *et al*. demonstrated, a right-sided dominance of sympathetic effects (increased cardiac frequency and blood pressure) after insular cortex stimulation as opposed to a left-sided dominance for parasympathetic effects (Oppenheimer *et al.*, 1992). The right-sided dominance of sites where painful sensations were evoked in our study would be therefore physiologically coherent, a sympathetic tone increase being expected during painful sensations. A right hemispheric dominance has also been described in PET studies for the

affective–emotional component of pain with a preferential increased cerebral blood flow in the right anterior cingulate gyrus (Hsieh *et al*., 1995a, 1996, 1999). Furthermore, studies on cerebral lateralization have emphasized the fact that the right hemisphere is more involved in spatial as well as in attentional process and many aspects of emotion (Mesulam, 1981; Silberman and Weingartner, 1986; Gainotti, 1996). Attentional process and visuo-spatial integration for directing the individual's attention towards threatening external stimuli are of great importance for survival. Finally, the precocious and faster development of the right hemisphere during fetal life accounts for what is referred to as the right hemisphere 'conservatism' (Geschwind and Galaburda, 1985). Our data are in line with this theory, suggesting that pain integration, which is a determinant factor in species survival, could be preferentially dependent on the right hemisphere.

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