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Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited

Laure Mazzola,[1,2,3] Jean Isnard,[2,4,5] Roland Peyron[1,2,3] and François Mauguière[2,4,5]

1 Department of Neurology, University Hospital, St-Etienne, 42055 cedex 2, France
2 Team 'Central Integration of Pain' Lyon Neuroscience Research Centre, INSERM U 1028, CNRS UMR 5292, 69677 Bron, France
3 Jean Monnet University, St-Etienne, 42055 cedex 2, France
4 Claude Bernard University Lyon 1, 69622 Villeurbanne cedex, France
5 Department of Functional Neurology and Epilepsy, Neurological Hospital, Hospices Civils de Lyon, 69677 Bron, France

Correspondence to: François Mauguière,
Department of Functional Neurology and Epilepsy,
Hôpital Neurologique,
59 Boulevard Pinel,
69677 Bron cedex, France
E-mail: mauguiere@univ-lyon1.fr

Thanks to the seminal work of Wilder Graves Penfield (1891–1976) at the Montreal Neurological Institute, electrical stimulation is used worldwide to localize the epileptogenic cortex and to map the functionally eloquent areas in the context of epilepsy surgery or lesion resections. In the functional map of elementary and experiential responses he described through >20 years of careful exploration of the human cortex via stimulation of the cortical surface, Penfield did not identify any 'pain cortical area'. We reinvestigated this issue by analysing subjective and videotaped behavioural responses to 4160 cortical stimulations using intracerebral electrodes implanted in all cortical lobes that were carried out over 12 years during the presurgical evaluation of epilepsy in 164 consecutive patients. Pain responses were scarce (1.4%) and concentrated in the medial part of the parietal operculum and neighbouring posterior insula where pain thresholds showed a rostrocaudal decrement. This deep cortical region remained largely inaccessible to the intraoperative stimulation of the cortical surface carried out by Penfield after resection of the parietal operculum. It differs also from primary sensory areas described by Penfield *et al.* in the sense that, with our stimulation paradigm, pain represented only 10% of responses. Like Penfield *et al.*, we obtained no pain response anywhere else in the cortex, including in regions consistently activated by pain in most functional imaging studies, i.e. the first somatosensory area, the lateral part of the secondary somatosensory area, anterior and mid-cingulate gyri (mid-cingulate cortex), anterior frontal, posterior parietal and supplementary motor areas. The medial parietal operculum and posterior insula are thus the only areas where electrical stimulation is able to trigger activation of the pain cortical network and thus the experience of somatic pain.

Keywords: Penfield; pain; electrical stimulation; human cortex; insula; parietal operculum
Abbreviations: SI = primary somatosensory area; SII = secondary somatosensory area

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Introduction

Wilder Graves Penfield and his colleagues were the first to use direct cortical stimulation for intraoperative cortical functional mapping in the context of epilepsy surgery. Between his first descriptions of the functional organization of the sensory–motor strip (Penfield and Boldrey 1937; Rasmussen and Penfield, 1947) and his last published Gold Medal lecture given at the Royal Society of Medicine in 1968, Penfield produced an exhaustive functional map of the human cortex based on electrical stimulation while patients are conscious (Penfield, 1968). He distinguished motor, sensory and speech areas, where stimulation produces responses that can be seen as distortions or caricatures of the normal specialized function of each stimulated area, from lateral temporal lobe areas, the stimulation of which produces 'experiential responses' combining complex auditory or visual hallucinations, sometimes reported by the subject as a recollection of a past personal experience in an experiential flashback and/or in an interpretive signalling context (Penfield and Jasper, 1954; Penfield and Perot, 1963). It is noteworthy that somatic pain was absent both from the list of elementary responses to stimulation of the somatosensory cortex, including the primary (SI) and secondary (SII) somatosensory areas and the insula (Penfield and Faulk, 1955), and from that of the 'experiential responses' reported by the Montreal School. Penfield and Jasper (1954) noted that some pricking or tingling sensations evoked by stimulation of the somatosensory areas were exceptionally reported as 'unpleasant', but considered that 'the degree of pain was so slight as to cause one to wonder if the use of the term is not a misnomer'.

More recently, functional imaging studies have identified several cortical areas activated by painful stimuli. These brain regions, which are often referred to as the 'pain matrix' in the literature, include the insula, the secondary somatosensory area located in the suprasylvian parietal operculum, the anterior and mid-cingulate cortex, the primary somatosensory area, the anterior frontal and posterior parietal cortices and the supplementary motor area (Peyron *et al*., 2000; Apkarian *et al*., 2005). They are generally considered as forming a network that integrates several pain-associated functions such as pain intensity coding, pain localization, emotional and vegetative reaction, and motor withdrawal from a painful stimulus.

The notion that pain cannot be produced by focal stimulation of a localizable area of the human cortex, which has prevailed for years since the seminal studies of the Montreal School, and the complexity of the cortical network activated by painful stimuli brought into question the very existence of a 'primary pain area' receiving specific pain inputs from the periphery that could play the same role as other primary sensory areas for visual, auditory or non-painful somatic sensations. Because recent stimulation and evoked potential studies, which will be discussed later in this article, have suggested that the deep parietal operculum and posterior insular cortex might be involved in the primary processing of pain inputs, we undertook the task of revisiting the observations of Penfield by reviewing the responses we have obtained over the past 12 years in the context of epilepsy surgery using intracortical electrical stimulations covering the entire human cortical mantle.

Patients and methods

Patients

Subjective and videotaped behavioural responses to 4160 cortical stimulations from 164 consecutive epileptic patients were carefully analysed. Patients who reported pain sensations during their spontaneous epileptic seizures, patients with defined lesions of the pain system on brain MRI (spinothalamic tract, thalamus and/or cortical pain matrix) and patients receiving opioid therapy had been previously excluded from this group.

All patients (81 females, 83 males; age range 21–59 years) included in this study had undergone intracortical depth recordings using the stereo-electroencephalographic procedure for presurgical evaluation of their drug refractory epilepsy over the 12-year period between January 1997 and December 2008. During this period, 1116 multi-contact electrodes were implanted for mapping the epileptogenic and functionally eloquent cortical areas, 440 in the left hemisphere and 676 in the right. Analysis of the data was carried out between January 2009 and December 2010.

As the aim of depth electrode implantation was to locate the epileptogenic and functionally eloquent areas in various types of partial epilepsies, the set of stimulation sites as a whole was distributed all over the cortical mantle (Fig. 1A and B, Table 1).

All patients were fully informed of the aims of the stereo-electroencephalographic recording and stimulation procedures and gave their written informed consent in agreement with the Declaration of Helsinki.

Stereotactic electrode implantation

The stereotactic implantation procedure was adapted 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 magnetic resonance and angiographic images were superimposed to visualize vessel positions in order to minimize the risk of vascular injury during implantation. Electrodes were implanted perpendicular to the mid-sagittal plane and were left *in situ* for 7–15 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 from one another by 1.5 mm. In order to check for the final position of each electrode with respect to the targeted anatomical structures, a post-implantation frontal X-ray was performed and superimposed on MRIs.

Stimulation paradigm

During the stimulation 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 (Isnard *et al*., 2004). Square pulses of current were applied between two adjacent contacts (bipolar stimulation). Only pairs of contacts located in the grey matter were used for stimulation.

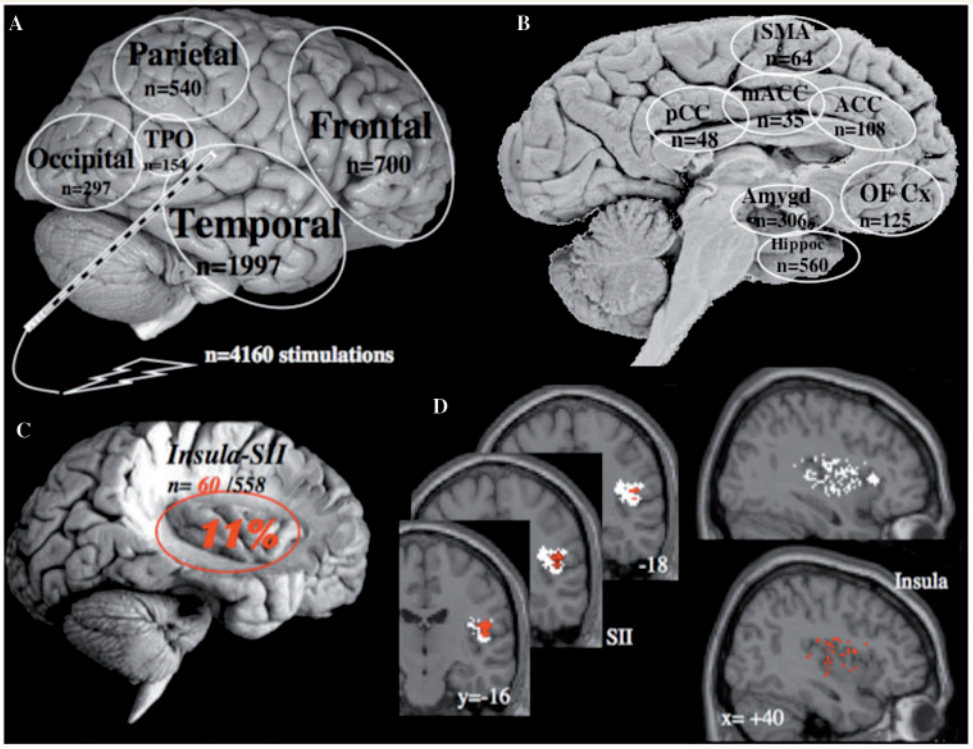

Figure 1 Cortical sampling of electrodes. (**A–C**) Cortical sampling of electrodes (diameter: 0.8 mm, 5–15 recording contacts per electrode), implanted perpendicular to the mid-sagittal plane (**A**: convexity, **B**: medial wall). Contacts (2 mm long) were separated by 1.5 mm from one another. (**C**) Pain sensations were exclusively obtained by stimulations in the SII and insular cortex (n = 60/558, incidence of pain = 10.8%). (**D**) Normalized 3D representation of contacts whose stimulation did (red) or did not (white) induce pain sensations. Coordinates: x = lateral/medial, y = anterior/posterior, z = top/bottom. n = number of stimulations. Amygd = amygdala; Hippoc = hippocampus; MCC = mid-cingulate cortex; OF Cx = orbito-frontal cortex; pCC = posterior cingulate cortex; SMA = supplementary motor area; TPO = temporo-parieto-occipital cortex.

Stimulation characteristics were as follows: frequency 50 Hz, pulse duration 0.5 ms, train duration 5 s, intensity between 0.2 and 4 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 (Nathan *et al*., 1993). Stimulus intensity was raised from 0.2 mA in increments of 0.4 mA to obtain a clinical response. We defined the efficient stimulation threshold as the minimal intensity necessary to elicit a clinical response. No stimulation was delivered at supra-threshold values.

During the 5 s stimulations trains, contacts of the stimulated electrode were disconnected from amplifiers but the EEG activity could be monitored on all other recorded sites. Stimulation contacts were reconnected within 1 s after the end of the stimulations train. The test–retest reliability when stimulating the same electrode at different times in the same patient, with respect to the consistency of subjective reports, was good for non-painful-evoked sensations, except for stimulations evoking a diffusing post-discharge that were excluded from the analysis. However, painful stimulations were not replicated for ethical reasons.

Collection and processing of data

Analysis of clinical responses was performed using the videotaped recordings of stimulation sessions. Concerning somatosensory responses, spontaneous reports by the patients and their answers to a standardized questionnaire were used to classify the evoked sensation into pain, temperature sensation, non-painful paraesthesiae or other types of response. For each of these categories, a list of words was proposed to the patient in order to characterize the sensation. Behavioural manifestations evoked by the stimulation were also carefully studied on videotaped recordings, in particular to assess motor, visceral and pain responses.

The territories of evoked somatosensory pain responses were drawn on a body sketch and quantified as a percentage of body surface (Mazzola *et al*., 2009), using the standardized Lund and Browder scale (Miller *et al*., 1991). To compare the size of cutaneous projections of pain responses after SII and insula stimulations, we used a non-parametric test (Mann–Whitney test).

Since 2003, the study has been prospective and when painful sensations were evoked, patients were additionally asked to evaluate pain intensity by a visual analogue scale from 0 to 10.

The stimulation sites were determined through Talairach x, y and z coordinates along lateral–medial, rostrocaudal and superior–inferior axes, respectively (Talairach and Tournoux, 1988). We checked on individual brain MRI that contacts were located in the targeted structure, for each patient. The anterior commissure–posterior commissure distance was normalized for each patient, and for illustrations the stereotactic positions of contacts were projected onto a standardized T_1-weighted MRI used as a template in the Statistical Parametric Mapping (SPM2) software (Wellcome Trust Centre for Neuroimaging).

Table 1 Distribution of implanted electrodes and stimulated contacts

Stimulated regions	Electrodes (*n*)	Stimulated contacts (*n*)
Frontal lobe	**292**	**700**
Frontal pole	24	59
Orbitofrontal region	*40*	*125*
Anterior cingulate gyrus	*49*	*108*
Medium cingulate gyrus	*21*	*35*
Posterior cingulate gyrus	28	48
SMA	*34*	*64*
Others	80	222
Temporal lobe	**519**	**1997**
Amygdala	86	306
Hippocampus	149	560
Temporal pole	51	174
Others	233	957
Parietal lobe	**170**	**540**
SI	*89*	*128*
SII	*78*	*86* *Pain = 11 (12.8%)* *Right-sided stimulation contacts (8/11; 73%)* *Characteristics of evoked pain:* *Contralateral (7/11; 64%)* *Bilateral (4/11; 36%)* *Extent = 7% (1–50%) of the skin surface** *VAS = 7/10 (range 5–9)*
Others	**81**	**326**
Insula	*273*	*472* *Pain = 49 (10.4%)* *Right-sided stimulation (25/49; 51%)* *Contralateral (26/49; 53%)* *Bilateral (14/49; 29%)* *Ipisilateral (6/49; 12%)* *Undefined (3/49; 6%)* *Extent = 13% (0.5–50%) of the skin surface** *VAS = 6.4/10 (range 4–9)*
Occipital lobe	73	297
Temporo-parieto-occipital junction	62	154
Total	1116	4160

Italics refers to the 'pain matrix'. VAS = Visual Analogue Scale; **P* = 0.02.

Each contact was represented as a cube (1 mm^3). Cubes were mapped onto the MRI volume using homemade software (Display slices) developed in Matlab. Then sagittal and coronal reconstructions were computed.

To make visual representation easier, all insular contacts were projected onto a single plane ($x = 40$ mm from the midline sagittal plane), passing through the whole rostrocaudal extent of insular cortex in Fig. 1D. This explains why some of the contacts may not strictly match with the chosen anatomical slice of insula in the figure. Likewise, painful contacts located in the SII area were projected onto three coronal planes ($y = 16$; 17; 18) for illustration (Fig. 1D).

As described in a previous study, the suprasylvian (SI), parietal opercular (SII) and insular cortex can be differentiated using trans-opercular electrodes for stimulating the cortex (Mazzola *et al*., 2006). The type of clinical responses, the size and lateralization of skin projection fields of evoked sensations, clearly differentiate these three cortical areas showing distinct somatosensory maps in the three of them, and separate pain representations in SII and insular cortex. The depth (*x*) coordinates showed no overlap between these three target areas. Moreover, the stereotactic coordinates of the SI, SII and insular stimulation sites were included in the separate clusters of sites where somatosensory responses are evoked by electric stimulation of the median nerve, with latencies of 20–22 ms in SI, 60–90 ms in SII and 110–165 ms in the insula (Frot and Mauguière, 1999, 2003; Frot *et al*., 2001). Based on numerous source modelling studies of evoked potentials and magnetic fields (for a review see Hari *et al*., 1993 and Mauguière *et al*., 1997), somatosensory responses peaking at ~20 and 70 ms are commonly accepted to originate from 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) and in 17 of the 52 patients in whom stimulation evoked a pain sensation in SII or in the insula we checked that contacts where we produced pain by electrical stimulations were the same as those where we recorded laser pain evoked potentials. Lastly, we also checked the position of contacts on individual MRI ('Collection and processing of data' section) with the limitation that the anatomical border between the granular cortex of the inner part of the parietal operculum and the posterior granular insular cortex cannot be precisely delineated on visual analysis of MRI slices.

Results

The most salient and original observations stemming from our systematic review of the clinical effects of cortical stimulation on pain sensations are presented below.

Pain response occurs very rarely after intracortical stimulation. A painful somatic sensation was evoked by cortical stimulation in only 60 of the 4160 stimulated sites (1.4%) without hemispheric dominance (51% in the right and 49% in the left hemisphere).

Sites where stimulation produced pain were exclusively concentrated in the medial part of the SII area or in the posterior and upper part of the insular cortex, which are anatomically contiguous (Fig. 1C and D). The percentage of pain responses was low in both SII and insular cortex: 12.8% (11/86) for SII stimulation and 10.4% (49/472) for insular stimulation. All patients who reported a painful sensation also had spontaneous behavioural manifestations of pain including facial expression of pain, verbal complaints including shouts and cries, movements to avoid the stimulus or vegetative changes such as facial pallor or rubefaction (see a representative video in the Supplementary material). Non-painful paraesthesiae represented 35% of responses to insular stimulation ($n = 151$) and were described as 'tingling', 'feeling of pulsation',

'feeling of vibration', 'feeling of numbness' or unpleasant non-painful paraesthesiae such as pins and needles or slight electric current. Numbness represented 6.6% of non-painful somatic responses ($n = 10$).

In pooled data, the pain-threshold stimulation intensity decreased along the rostro-caudal axis of the insula (Fig. 2A), with a significant correlation between pain threshold intensities and the rostro-caudal (y) coordinates of the stimulation sites ($P = 0.01$; $R = 0.46$). As illustrated in Fig. 2B, all contacts where pain responses were obtained at very low current intensities (0.2–0.9 mA) were concentrated in the upper and caudal quadrant of the insular cortex. Individual analysis of responses in the 25 patients with >1 electrode (2–4) implanted in the insular cortex also showed that pain was most often (23/25) evoked by stimulating the most superior and posterior sites (Fig. 3). Due to the low number of pain responses obtained in SII ($n = 11$), we were unable to show a similar rostro-caudal gradient of pain threshold in the parietal operculum.

As shown in Table 1 and illustrated in Fig. 1, no somatic pain sensation was ever collected after any of the 3602 stimulations performed outside of SII and the insular cortex. We did not include as pain responses 14 sensations of headache (0.3%) ipsilateral to stimulation in sites located close to the surface of temporal pole or temporo-basal cortex, considering that headache was likely to result from meningeal current leak in these cases, and five abdominal auras (0.1%) reported as 'unpleasant' after stimulation of amygdala, anterior hippocampus or entorhinal cortex.

None of the somatosensory responses to stimulation of the cortical areas involved in painful sensations in functional imaging studies, other than SII and insular cortex, were painful. Seventy-five per cent of SI stimulations evoked non-painful paraesthesiae in restricted body areas that were exclusively contralateral to stimulations in the limbs and mostly bilateral (69%) in the face or trunk. Of the 108 stimulations performed in the anterior cingulate cortex, 105 (97.2%) did not evoke any clinical sensation. Two of the three remaining stimulations evoked paraesthesiae and one an indefinable cephalic feeling. Of 184 stimulations of the lateral pre-motor frontal cortex, four produced an epigastric sensation. Lastly, no somatic sensation was obtained after any of the 64 stimulations delivered to the supplementary motor area.

This retrospective review of our database also confirmed, in a much larger set of data and now covering the entire brain, our previous observations regarding the features of pain sensations produced by stimulation of the SII-insular cortex (Ostrowsky *et al*., 2002; Mazzola *et al*., 2006, 2009): (i) pain was elicited at similar low current intensities of 0.9 ± 0.3 mA in SII and 1.4 ± 0.9 mA in the insula (no significant difference); (ii) in both areas, the descriptive terms used by the patients for qualifying their pain were similar: burning, painful sensation of electricity or electric shock; stinging, painful pins and needles, crushing or cramp sensation without visible movement; (iii) no significant difference was observed between SII and insula in terms of pain intensity. VAS mean scores were 7/10 in SII (range 5–9/10) and 6.4/10 in the insula (range 4–9/10); (iv) in both areas, pain was most often contralateral to stimulation but could also be bilateral or ipsilateral to stimulus when the painful sensation concerned parts of the body close to midline, such as face or trunk; and (v) in spite of large pain projection areas on the body surface, a somatotopic organization of painful responses was found in the caudal insula, the face area being rostral to the upper limb area, and the latter being located above the lower limb representation.

Discussion

This review of our experience of cortical stimulation provides some clues for understanding why Penfield and his collaborators failed to elicit pain responses by stimulating the human cortex. The first is that their surgical access to the areas where we obtained pain responses, which are deeply located in the cortical fissures and buried under the dense wall of sylvian vessels, was limited both in time and space. The limitation in time pertains to the fact that Penfield *et al*. could stimulate the cortical surface only for a few minutes during the surgical procedure. This short access minimized their chances to obtain pain responses that we observed so rarely, despite stimulating patients chronically implanted with depth electrodes, which allowed repeated testing over several days if required. The main limitation, however, was spatial in that they had access to the insula and neighbouring parietal opercular cortex only after surgical removal of the temporal operculum or, more exceptionally, after removal of the outer part of the fronto-parietal operculum. Thus, the map of insular somatosensory responses drawn using cortical stimulations through surface electrodes by Penfield and Faulk (1955), which did not include a pain representation, shows that most of the stimulation sites were located in the lower half of the insula (Fig. 4) thus leaving unexplored the upper and caudal part of the insula where we obtained most of our pain responses using intracortical electrodes implanted stereotactically for stimulation. This part of the insula was also where we found the lowest pain thresholds, compared with those measured in more rostral and inferior insular sites (Fig. 2A and B).

A second and intriguing reason for the failure of Penfield's team to produce pain by stimulating the cortex is the low frequency of pain responses obtained following stimulation of the operculo-insular cortex, which remains largely unexplained but clearly differentiates this cortical region from primary sensory cortical areas that readily produce corresponding sensations when stimulated, as observed in this study after stimulation of the SI area. The stimulations we have used were set at threshold intensities and did not aim at producing pain responses; thus our stimulation parameters were not necessarily optimal for the activation of clusters of insular cortical projection neurons. Therefore, the rate of painful responses (10.8%) that we observed in the insular cortex, although consistent with other recently published stimulation data (9.6% in Afif *et al*., 2010), might be underestimated compared with those theoretically obtainable. Furthermore, our study reveals that the pain threshold is not homogeneous in the insular cortex and is lower in the posterior insula, so that pain responses might have been more frequent if higher stimulus intensities had been used when exploring the whole extent of the granular insular cortex. Moreover, for obvious ethical reasons, we never increased the stimulus current intensity over response threshold in sites where non-painful somatic sensations had been

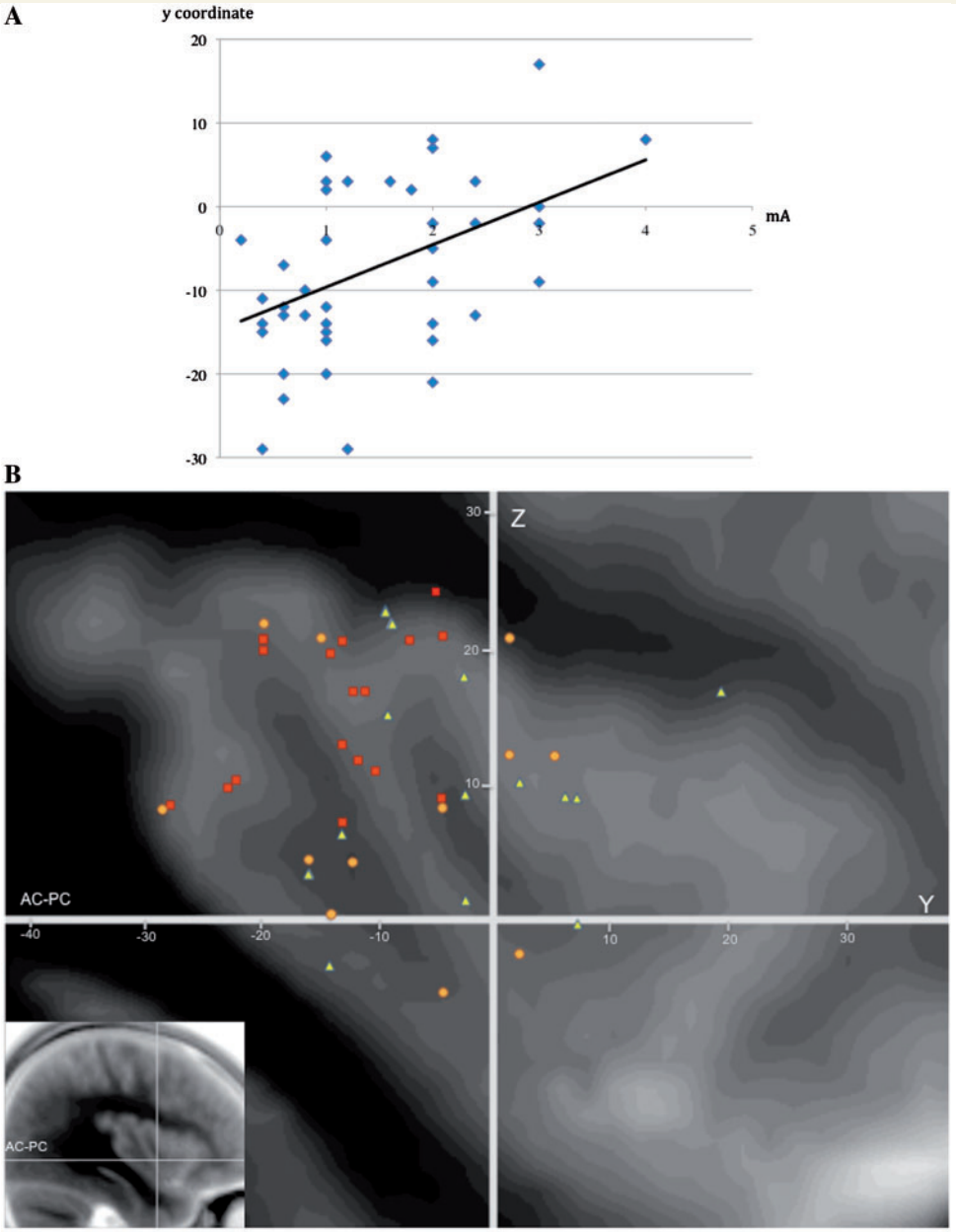

Figure 2 Anteroposterior pain threshold gradient in insular cortex. (**A**) Correlation between pain threshold stimulus intensity (mA) and *y* coordinates of the stimulation sites in the insular cortex ($P = 0.01$; $R = 0.46$). The more caudal the stimulation site in the insula, the lower is the pain threshold stimulus intensity. (**B**) Distribution of pain thresholds in the insula according to their *y* and *z* coordinates. The *y*-axis is the projection of the anterior commissure–posterior commissure (AC–PC) horizontal plane; the *z*-axis is the projection of the coronal plane passing through the anterior commissure and perpendicular to the anterior commissure–posterior commissure horizontal plane in Talairach and Tournoux (1988) stereotactic system of coordinates. To make easier visual representation and to illustrate the interindividual variation of insular projection in the stereotactic system of coordinates, a sagittal insular mean image (MNI space), averaged from 24 subjects, acquired in our group was superimposed to the spatial distribution of stimulation sites stereotactic coordinates. The pain stimulation threshold was between 0.2 and 0.9 mA (red squares), 1–1.9 mA (orange circles) and 2–3 mA (yellow triangles). The distribution of low pain threshold sites (red squares) in the insula is to be compared with that of somatosensory response somatosensory response sites drawn by Penfield and Faulk (1955) reproduced in Fig. 4.

obtained. One of the reasons for the variation of pain threshold along the rostro-caudal axis of the insula might be the cyto-architectonic heterogeneity of the operculo-insular cortex. The SII region is known to include at least four distinct cortical areas identified by somatotopic mapping and connectivity in monkeys (Robinson *et al*., 1980; Krubitzer *et al*., 1995) and by cyto-architectonic and functional MRI studies in humans (Disbrow *et al*., 2000; Eickhoff et *al*., 2006*a*, *b*). Similarly, recent data

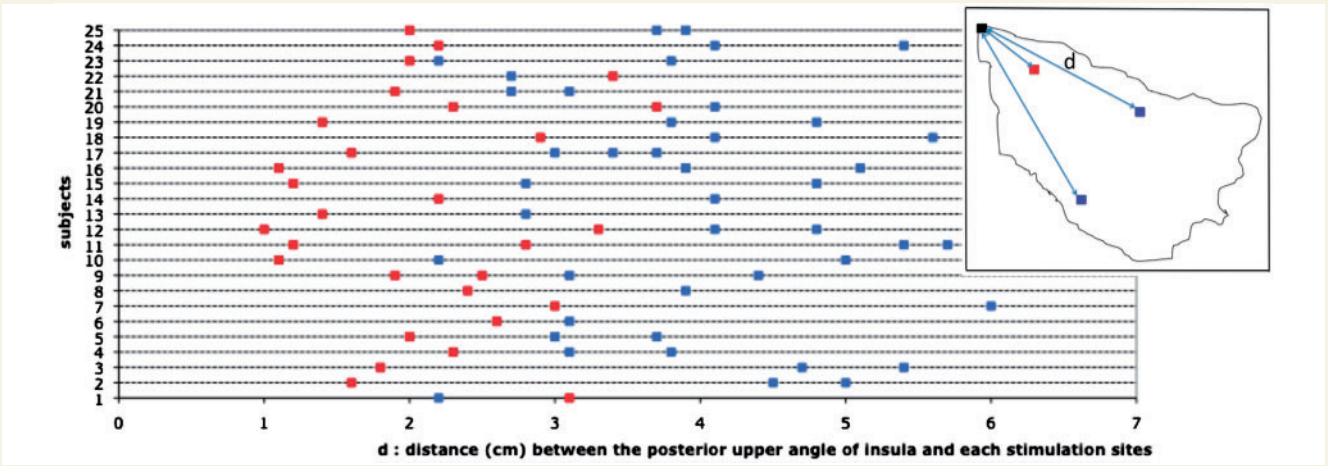

Figure 3 Location of painful stimulation sites in patients implanted with several insular electrodes. This figure shows the distance in centimetres between the posterior upper angle (black square) of the insula and each of the stimulation sites in the same individual subject, for the 25 patients in whom several electrodes were implanted in the insula. The more this distance is short, the more the stimulation site is located in the postero-superior part of insula. Red squares = sites where stimulation evoked pain; blue squares = sites where stimulation evoked a non-painful response. With the exception of Subjects 1 and 22 (ordinates axis), the site where stimulation produced a pain sensation was the one most posteriorly located in the insula.

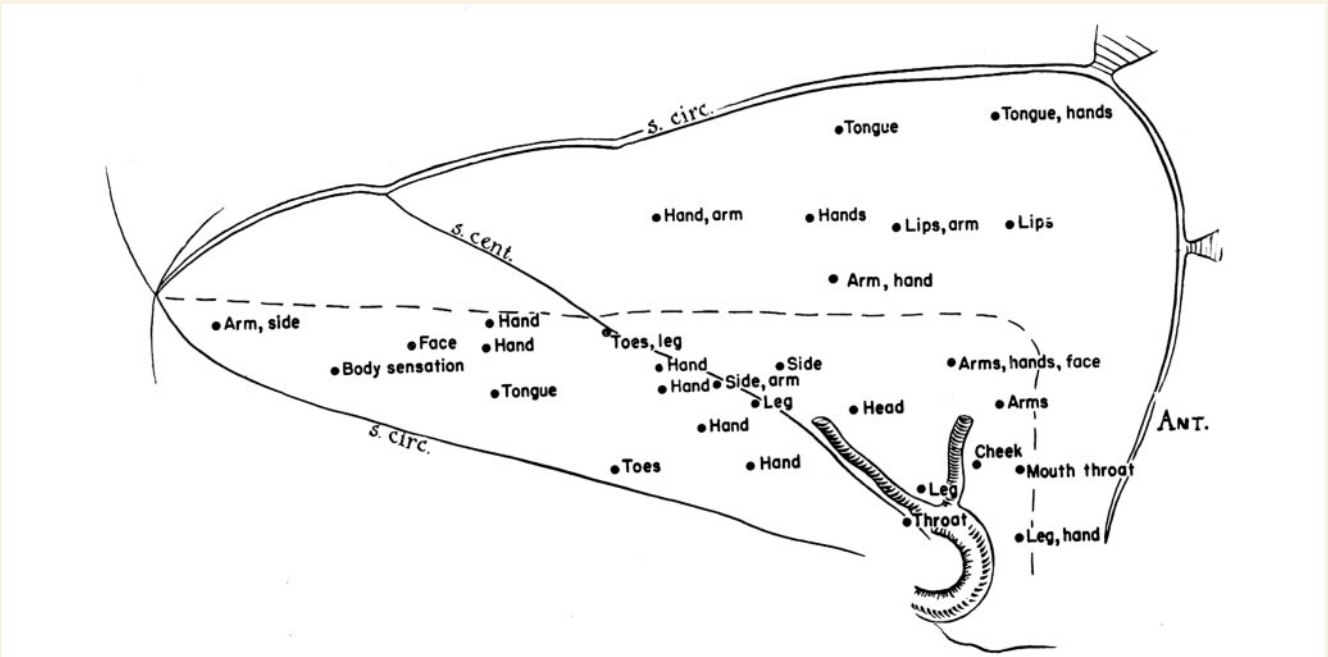

Figure 4 Map of somatosensory responses in the insula drawn by Penfield and Faulk (1955). In their article entitled: 'The insula: further observation on its function' published in *Brain* in 1955, Penfield and Faulk described the somatosensory responses to stimulation of the insular cortex as follows: 'The sensations produced by stimulation of the insula were variously described by the patients as "tingling," "warmth," "numbness," "tightness," "vibration," "shock," and simply as "sensation".' These sensations were usually contralateral, but were on occasion ipsilateral or bilateral. The quality of somatic sensation produced by stimulation of the insula does not differ very much from that elicited from Rolandic and supra-Sylvian sensory areas. According to the authors: 'The broken line separates the portion of the insula covered by the parietal and frontal opercula, above and in front, from the portion covered by temporal operculum below'. Although the orientation of the insula in this drawing differs from that represented using stereotactic coordinates in Fig. 2B, it appears clearly that no somatosensory responses were obtained by Penfield and Faulk in the upper and posterior quadrant of the insular cortex, where we found the lowest pain response thresholds. The reason for this unexpected finding is that this region remained unexplored in most cases reported by Penfield and Faulk who themselves regretted that their analysis was 'greatly handicapped by the fact that the superior portion of the insula has been so rarely exposed'. ANT = anterior; s.circ = circular sulcus.

(Kurth *et al*., 2010) showed three distinct areas in the posterior insula. These subregions are probably differently involved in the processing of pain, explaining why not all stimulations in SII and posterior insula are able to evoke a pain sensation. The existence of some somatotopic organization of pain responses to stimulation of the posterior insular cortex (Mazzola *et al*., 2009) in spite of large and overlapping pain projection fields on the skin surface was confirmed in this study, in agreement with pain laser-evoked potentials (Vogel *et al*., 2003; Baumgärtner *et al*., 2006) and functional imaging studies (Brooks *et al*., 2005; Henderson *et al*., 2007, 2011; Bjornsdotter *et al*., 2009). These converging data, in spite of some non-confirmative functional MRI studies (Bingel *et al*., 2004; Ferretti *et al*., 2004), favour the view that the insular cortex might contain a single somatotopic representation of pain in spite of its cyto-architectonic heterogeneity. Since the somatotopic representation was obtained in our study by pooling, at the group level, pain responses in patients who each had a very limited number of insular contacts, increasing the spatial sampling of insular stimulation sites in the same individual could theoretically solve this apparent contradiction between multiple cyto-architectonic areas and a single somatotopic pain map. The use of oblique implantation tracts parallel to the surface of the insular cortex, as recently proposed (Afif *et al*., 2010; Stephani *et al*., 2011), might help to clarify this issue without increasing the number of implanted electrodes above that strictly needed for presurgical exploration. However, the parietal operculum is not explored with this type of electrode trajectory.

Interestingly, we also obtained thermal sensations after stimulation of the posterior part of the insula [warmth ($n = 52$) and cold ($n = 15$)] and deep parietal opercular cortex [warmth ($n = 6$) and cold ($n = 3$)], where pain responses could be elicited, suggesting that this cortical region may be the site of a primary representation of 'protopathic' feelings subserving interoception (Craig, 2002). The finding that the medial part of the parietal opercular cortex and the posterior insula are the only areas where electrical stimulation is able to evoke either pain or thermal sensations is consistent with: (i) the existence of a specific spinothalamic relay nucleus for pain and temperature (Blomqvist *et al*., 2000; Craig, 2004) that projects to the posterior insula in monkeys and humans (Craig, 1995); (ii) the clinical observation that lesions in the posterior insula and the inner parietal operculum can be associated with an increase of cold, warm and pain detection thresholds and also with spontaneous pain and allodynia (Schmahmann and Liefer, 1992; Greenspan *et al*., 1999; Birklein *et al*., 2005; Garcia-Larrea *et al*., 2010); (iii) the data from a PET study showing a linear increase of posterior and dorsal insular activation with increasing cold levels of stimulation (Craig *et al*., 2000) and those of Hua *et al*. (2005) showing that, as pain responses, the representation of cold sensations, as assessed by functional MRI, is somatotopically organized (see above).

Another explanation for the rarity of pain responses to cortical stimulation might be that focal cortical stimulation of the operculo-insular region is *per se* insufficient to consistently reproduce the global 'experience' of pain, but can only initiate the aversive sensation qualified as 'pain' in some privileged circumstances. We have recently reported the case of a patient with a cortical dysplasia of the posterior insula who experienced spontaneous painful epileptic seizures, and in whom ictal fast low voltage activity and repetitive spiking in the lesion area produced a pain sensation that could be reproduced by focal stimulation (Isnard *et al*., 2011). Interestingly, in this patient, during painful seizures, the high frequency ($\geqslant 40$ Hz) energy of the signal recorded by intracortical electrodes increased in parietal operculum and mid-cingulate gyrus, and spikes in the posterior insula preceded by 80 ms those recorded in these two regions. This observation suggests that the 'experience' of pain can be triggered in the posterior insular cortex and also depends on the subsequent activation of the network of cortical areas most consistently reported as activated by external painful stimuli. The fact that clinical responses to cortical stimulation reflect activation of distributed cortical areas distant from, but interconnected with, the stimulation site was first proposed by Penfield (1968) to explain what he called 'experiential responses'. However, the reason why stimulation of the posterior-insular cortex may, or may not, reproduce such a pain experience remains unknown.

Our finding that pain could not be elicited by cortical stimulation anywhere else than in the operculo-insular cortex corroborates the opinion of Penfield and colleagues who, for the reasons discussed above, missed the operculo-insular pain responses and concluded that stimulating the human cortex in awake patients is not painful. This statement holds in particular for all cortical regions of the 'pain matrix', including SI, supplementary motor area, anterior frontal and posterior parietal cortices. A paradigmatic case is that of the mid-cingulate cortex (Vogt, 2005), which is consistently activated by pain in functional imaging studies (see Peyron *et al*., 2000 for a review) and is included in all source imaging models of pain-evoked electrical potentials or magnetic fields (see Garcia-Larrea *et al*., 2003 for a review). The mid-cingulate cortex and the operculo-insular region both receive pain inputs from the periphery. Both regions receive fibres from thalamic nuclei relaying spinothalamic inputs in monkeys, namely the central lateral and centromedian parafascicular complex for mid-cingulate cortex (Baleydier and Mauguière, 1980; Hatanaka *et al*., 2003; Vogt *et al*., 2005); the ventral posterior complex for parietal operculum and insula (Burton and Jones, 1976; Mufson and Mesulam, 1984; Friedman and Murray, 1986; and Weiss *et al*., 2005, for projections to insula in humans); and the posterior part of the ventromedial nucleus of the thalamus for dorsal posterior insula (Craig, 1995, 2003; Craig *et al*., 1994). Moreover, pain-evoked, responses were recorded after skin laser stimulation using intracortical recordings of the human brain with latencies of the first negative peak that are similar in parietal operculum and mid-cingulate cortex (120–140 ms) and 40 ms longer (180 ± 16 ms) in the insula (Frot and Mauguière, 2003; Frot *et al*., 2008). In spite of these similarities and contrary to what we have observed in the operculo-insular cortex, there is no report in the literature of any pain response to stimulation of the cingulate gyrus including the mid-cingulate cortex, although this area has been explored and stimulated for years in the context of epilepsy surgery.

Hutchinson *et al*. (1999), who recorded and stimulated the mid-cingulate cortex in awake humans using microelectrodes, were also surprised to observe that electrical stimulation, even

with high currents, failed to elicit painful or unpleasant sensations at sites in the mid-cingulate cortex where they had recorded pain sensitive neurons. In fact, our data show that this dissociation between activation by pain and absence of pain response to direct stimulation is not an exception but is the rule in all cortical areas involved in building the 'experience of pain', except for the posterior insular cortex and the deep part of the parietal operculum. Whether Penfield and his colleagues, had they had easier access to this cryptic region of the brain, which will remain as a missing piece in their functional map of the human cortex, would have considered it as a 'primary cortical pain area' or would have classified the evoked pain as an 'experiential' response is a conjectural issue that remains debated among pain physiologists and clinicians.

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Supplementary material

Supplementary material is available at Brain online.

References

Afif A, Minotti L, Kahane P, Hoffmann D. Anatomofunctional organization of the insular cortex using intracerebral electrical stimulation in epileptic patients. Epilepsia 2010; 51: 2305–15.

Apkarian AV, Bushnel MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005; 9: 463–84.

Babb TL, Mariani E, Seidner KA, Mutafyan G, Halgren E, Wilson CL, Crandall PH. A circuit for safe diagnostic electrical stimulation of the human brain. Neurol Res 1980; 2: 181–97.

Baleydier C, Mauguière F. The duality of cingulate gyrus in monkey. Neuroanatomical study and functional hypothesis. Brain 1980; 103: 525–54.

Baumgärtner U, Tiede W, Treede RD, Craig AD. Laser-evoked potentials are graded and somatotopically organized anteroposteriorly in the operculoinsular cortex of anesthetized monkeys. J Neurophysiol 2006; 96: 2802–8.

Bingel U, Lorenz J, Glauche V, Knab R, Glascher J, Weiller C. Somatotopic organization of human somatosensory cortices for pain: a single trial fMRI study. NeuroImage 2004; 23: 224–32.

Birklein F, Rolke R, Müller-Forell W. Isolated insular infarction eliminates contralateral cold, cold pain, and pinprick perception. Neurology 2005; 65: 1381.

Blomqvist A, Zhang ET, Craig AD. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain 2000; 123: 601–19.

Björnsdotter M, Löken L, Olausson H, Vallbo A, Wessberg J. Somatotopic organization of gentle touch processing in the posterior insular cortex. J Neurosci 2009; 29: 9314–20.

Brooks JCW, Zambreanu L, Godinez A, Craig AD, Tracey I. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. Neuroimage 2005; 27: 201–9.

Burton H, Jones EG. The posterior thalamic region and its cortical projection in new world and old world monkeys. J Comp Neurol 1976; 168: 249–302.

Craig AD. Distribution of trigeminothalamic and spinothalamic lamina I terminations in the macaque monkey. J Comp Neurol 2004; 477: 119–48.

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002; 3: 655–66.

Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci 2003; 26: 1–30.

Craig AD. Supraspinal projections of lamina I neurons. In: Guilbaud JM, Ollat G, editors. Forebrain areas involved in pain processing. Montrouge: John Libbey Eurotext; 1995. p. 13–26.

Craig AD, Bushnell MC, Zhang ET, Blomqvist A. A thalamic nucleus specific for pain and temperature sensation. Nature 1994; 372: 770–3.

Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000; 3: 184–90.

Disbrow E, Roberts T, Krubitzer L. Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. J Comp Neurol 2000; 418: 1–21.

Eickhoff SB, Schleicher A, Zilles K, Amunts K. The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb Cortex 2006a; 16: 254–67.

Eickhoff SB, Amunts K, Mohlberg H, Karl Zilles. The Human parietal operculum II. Stereotaxic maps and correlation with functional imaging results. Cerebral Cortex 2006b; 16: 268–79.

Ferretti A, Del Gratta C, Babiloni C, Caulo M, Arienzo D, Tartaro A, et al. Functional topography of the secondary somatosensory cortex for nonpainful and painful stimulation of median and tibial nerve: an fMRI study. Neuroimage 2004; 23: 1217–25.

Friedman DP, Murray EA. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the Macaque. J Comp Neurol 1986; 252: 348–73.

Frot M, Garcìa-Larrea L, Guenot M, Mauguière F. Responses of the supra-sylvian SII cortex in humans to painful and innocuous stimuli. A study using intra-cerebral recordings. Pain 2001; 94: 65–73.

Frot M, Mauguière F. Dual representation of pain in the operculo-insular cortex in humans. Brain 2003; 126: 438–50.

Frot M, Mauguière F. Timing and spatial distribution of somatosensory responses recorded in the upper bank of the sylvian fissure SII area in humans. Cereb Cortex 1999; 9: 854–63.

Frot M, Mauguière F, Magnin M, Garcia-Larrea L. Parallel processing of nociceptive A inputs in SII and midcingulate cortex in humans. J Neurosci 2008; 28: 944–52.

Garcia-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin 2003; 33: 279–92.

Garcia-Larrea L, Perchet C, Creac'h C, Convers P, Peyron R, Laurent B, et al. Operculo-insular pain (parasylvian pain): a distinct central pain syndrome. Brain 2010; 133: 2528–39.

Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. Pain 1999; 81: 273–82.

Gordon B, Lesser RP, Rance NE, Hart J Jr, Webber R, Uematsu S, et al. Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation. Electroencephalogr Clin Neurophysiol 1990; 75: 371–7.

Hari R, Karhu J, Hämäläinen M, Knuutila J, Salonen O, Sams M, et al. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. Eur J Neurosci 1993; 5: 724–34.

Hatanaka N, Tokonu H, Hamada I, Inase M, Ito Y, Imanishi M, et al. Thalamocortical and intracortical connections of monkey cingulate motor areas. J Comp Neur 2003; 462: 121–38.

Henderson LA, Gandevia SC, Macefield VG. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study. Pain 2007; 128: 20–30.

Henderson LA, Rubin TK, Macefield VG. Within-limb somatotopic representation of acute muscle pain in the human contralateral dorsal posterior insula. Hum Brain Mapp 2011; 32: 1592–601.

Hua LH, Strigo IA, Baxter L, Johnson SC, Craig AD. Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. Am J Physiol Regul Integr Comp Physiol 2005; 289: R319–25.

Hutchinson WD, Davis KD, Lozano AM, Tasker RR, Dostrowsky JO. Pain-related neurons in the human cingulate cortex. Nat Neurosci 1999; 2: 403–5.

Isnard J, Guénot M, Sindou M, Mauguière F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. Epilepsia 2004; 45: 1079–90.

Isnard J, Magnin M, Jung J, Mauguière F, Garcia-Larrea L. Does the insula tell our brain that we are in pain? Pain 2011; 152: 946–51.

Krubitzer L, Clarey J, Tweedale R, Elston G, Calford M. A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. J Neurosci 1995; 15: 3821–39.

Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 2010; 214: 519–34.

Mauguière F, Merlet I, Forss N, Vanni S, Jousmäki V, Adeleine P, et al. Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: location and activation timing of SEF sources. Electroencephalogr Clin Neurophysiol 1997; 104: 281–9.

Mazzola L, Isnard J, Mauguière F. Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses. Cereb Cortex 2006; 16: 960–8.

Mazzola L, Isnard J, Peyron R, Guenot M, Mauguiere F. Somatotopic organization of pain responses to direct electrical stimulation of the human insular cortex. Pain 2009; 146: 99–104.

Miller SF, Finley RK, Waltman M, Lincks J. Burn size estimate reliability: a study. J Burn Care Rehabil 1991; 12: 546–59.

Mufson EG, Mesulam MM. Thalamic connections of the insula in the rhesus monkey and comments on the paralimbic connectivity of the medial pulvinar nucleus. J Comp Neurol 1984; 227: 109–20.

Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV. Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. Electroencephalogr Clin Neurophysiol 1993; 86: 183–92.

Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex 2002; 12: 376–85.

Penfield W. Engrams in the human brain: Mechanisms of memory. Proc Roy Soc Med 1968; 61: 831–40.

Penfield W, Boldrey E. Somatic motor and sensory representations in the cerebral cortex of man as studied by electrical stimulation. Brain 1937; 60: 389–443.

Penfield W, Faulk M. The insula, further observation on its function. Brain 1955; 78: 445–70.

Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston: Brown L; 1954.

Penfield W, Perot P. The brain's record of auditory and visual experience. A final summary and discussion. Brain 1963; 86: 595–696.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000; 30: 263–88.

Robinson CJ, Burton H. Somatic submodality distribution within the second somatosensory SII, 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. J Comp Neurol 1980; 192: 93–108.

Rasmussen T, Penfield W. Further studies of the sensory and motor cerebral cortex of man. Fed Proc 1947; 6: 452–60.

Schmahmann JD, Leifer D. Parietal pseudothalamic pain syndrome: clinical features and anatomic correlates. Arch Neurol 1992; 49: 1032–37.

Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M, Lüders H. Functional neuroanatomy of the insular lobe. Brain Struct Funct 2011; 81: 716–8.

Talairach J, Bancaud J. Stereotactic approach to epilepsy: methodology of anatomo-functional stereotaxic investigations. Prog Neurol Surg 1973; 5: 297–354.

Talairach J, Tournoux P. Coplanar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Vogel H, Port JD, Lenz FA, Solaiyappan M, Krauss G, Treede RD. Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. J Neurophysiol 2003; 89: 3051–60.

Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. Nature Rev Neurosci 2005; 6: 533–44.

Weiss N, Lawson C, Greenspan J, Ohara S, Lenz FA. Studies of the human ascending pain pathways. Thalamus Relat Syst 2005; 3: 71–86.