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# **DUAL REPRESENTATION OF PAIN IN THE OPERCULO-INSULAR CORTEX IN HUMANS.**

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## Summary

In this study, we report on response properties of the supra-sylvian opercular and insular cortices to a painful stimulation delivered by a CO<sub>2</sub> laser recorded by depth intracerebral electrodes in epileptic patients. We defined two cortical areas of activation in the operculo-insular cortex in response to a painful laser stimulation: a supra-sylvian opercular area where we recorded responses peaking at 140-170 ms after a painful stimulation (N140-P170) and a deeper insular area where responses with a similar pattern were peaking 180-230 ms after the stimulus (N180-P230). The average delay of 50 ms measured between the opercular and insular responses can reflect either a sequential activation of the supra-sylvian cortex then of the insula via cortico-cortical connections or a direct activation of the insula by inputs conveyed via thalamo-cortical projections through distinct fibers with different conduction times. We also recorded similar insular and opercular responses in the hemisphere ipsilateral to the stimulation peaking 15 ms later than contralateral responses ; this delay is compatible with a trans-callosal input transmission between these cortices. The mean stereotactic coordinates of the supra-sylvian opercular N140-P170 and insular N180-P230 responses were found very similar to those of the maximal blood-flow responses to pain reported by PET and fMRI studies in these cortical areas. We were able to distinguish the supra-sylvian opercular and insular cortices in terms of response latencies evoked by a painful stimulus and in terms of stereotactic coordinates of the sources of these responses. The sequential timing of activation of supra-sylvian and insular cortices shown in this study thus complements in the time domain the spatial information provided by neuro-imaging studies of pain cortical processing. It strongly suggests that these cortical areas are those responding with the shortest latency to peripheral pain inputs in the human brain.

## 1. Introduction

Based on numerous anatomical and microelectrode studies in monkeys (Burton 1986, Burton et al. 1995, Krubitzer et al. 1995), it is now well accepted that the second somatosensory area (SII) and the insular cortex play a major role in the processing of painful and non-painful inputs (Robinson et Burton 1980a,b,c, Mesulam and Mufson 1982, Friedman and Murray 1986, Cusik et al. 1989, Burton and Sinclair 1990, 1991, Schneider et al. 1993, Zhang et al. 1999). Several clinical observations confirmed these data. Some observations of ictal pain sensation have been indeed reported in patients with epileptic seizures originating in SII (Young et al. 1986). The team of Greenspan (Greenspan and Winfield 1992, Greenspan et al. 1999) has observed reversible loss or decrease of pain and tactile sensation in patients with focal lesions involving the posterior and parietal operculum, confirming the role of these cortices in normal pain and tactile perception. Moreover, recent studies from our department reported painful somatic sensations during direct electrical stimulations of the posterior insular cortex in epileptic patients with intra-cerebral electrodes. Pain evoked by insular stimulation was lateralized to the opposite half of the body performed in epileptic patients with intracerebral electrodes (Ostrowsky et al. 2000, 2002). In most cases these painful sensations were elicited by stimulating the non-dominant hemisphere for language. During the past 20 years, many functional imaging studies were in accordance with all these anatomical and clinical data and converged to the conclusion that the operculo-insular cortex is involved in the processing of pain in humans. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies showed a bilateral pain-related activation in a broad region comprising the depth of the sylvian fissure and the parieto-frontal opercular cortex (for a review see Peyron et al., 2000). These studies highlighted two distinct sites of activations in this region : *i*) an antero-inferior activation, in the vicinity of the anterior insular

cortex and *ii*) a posterior activation, at the boundary between the second somatosensory (SII) cortex and the posterior insula (Casey et al. 1994, Xu et al. 1997, Svensson et al. 1997, Paulson et al. 1998, Davis et al. 1998, Becerra et al. 1999, Baron et al. 1999, Sawamoto et al. 2000). Moreover, some electrophysiological studies in humans have localized in the SII/insular cortex the sources of activities peaking on the scalp between 160 and 200 ms after a painful CO<sub>2</sub> laser skin stimulus (Tarkka and Treede 1993, Bromm and Chen 1995, Kakigi et al. 1995, 1996, Valeriani et al. 1996, Valeriani et al. 2000). These studies combined the scalp recordings of electrical or magnetic fields evoked by a painful stimulation and the estimation, by dipole source modeling, of the localization of the dipolar intracerebral sources of these activities. Lenz et al. (1998) have recorded by means of a sub-dural grid of electrodes CO<sub>2</sub> laser evoked potentials (LEPs) peaking between 162 and 340 ms. The spatial distribution of this response over the cortical surface of the peri-sylvian cortex was considered as compatible with generators located in the parietal operculum and/or in the insular cortices. Using depth intra-cerebral recordings in humans we have been able to demonstrate the existence of sources of pain evoked potentials in the SII cortex (Frot et al. 1997, 1999, 2001). It remains, however, that the anatomical boundary between SII and insular cortex is not easy to draw in functional neuro-imaging studies, especially along the depth axis from lateral to medial cortical structures (x axis in the Talairach's system of stereotactic coordinates). Moreover, functional neuro-imaging lacks the temporal resolution required to separate in time the activities of the suprasylvian opercular (SII) and insular cortex, respectively. Such a separation could allow to differentiate these two cortices by their response characteristics and to know how these areas, which are intimately interconnected (Friedman et al 1986), act in the processing of nociceptive inputs.

In this study, we report on response properties of the electrical potentials evoked in the supra-sylvian opercular and insular cortices by a painful skin stimulation delivered by a CO<sub>2</sub>

laser. These potentials were recorded by depth intracerebral multi-contact electrodes with a separation of 1.5 mm between two adjacent contacts (2 mm each) along the lateral medial axis (depth axis), and a millisecond resolution in time. By this way, we were able to separate in time and space the supra-sylvian opercular and insular responses to pain.

## **2. Patients and methods**

### ***2.1 Patients***

We recorded CO<sub>2</sub> laser evoked potentials (LEPs) in 13 patients (24-47 years, mean age 35 years, 9 females, 4 males). All patients included in this study presented with refractory temporal lobe epilepsy and were investigated using stereotactically implanted intracerebral electrodes before functional surgery. Among other sites (see Table 1) these patients had electrodes chronically implanted in the operculo-insular cortex for the recording of their seizures and cortical functional mapping using electric stimulation and evoked potentials recordings (see Ostrowsky et al. 2002 for a description of the stimulation procedure). The decision to explore this area resulted from the observation during scalp video-EEG recordings of ictal manifestations suggesting the possibility of a supra-sylvian and/or insular spreading of seizures such as: lip and face paresthesiae or tonic-clonic movements, laryngeal contraction, gustatory illusions, hypersalivation, (see Isnard et al. 2000 for a complete description of the rationale of electrode implantation). This procedure, as well as the recording of somatosensory evoked potentials, is part of the functional mapping of eloquent cortical areas performed routinely before epilepsy surgery in patients implanted with depth electrodes. According to the French regulations concerning invasive investigations with a direct individual benefit, patients were fully informed of the electrode implantation, stereotactic EEG and EPs recordings (SEEG), and cortical stimulation procedures used to localize the

epileptogenic and eloquent brain areas and gave their consent. The CO<sub>2</sub> laser stimulation paradigm has been approved by local ethics committee.

At the time of LEP recordings, patients were under monotherapy with one of the following major anti-epileptic drugs (carbamazepine, phenytoin, valproate, lamotrigine or topiramate). LEPs recordings were performed at the end of the SEEG monitoring, once pertinent seizures had been recorded, so that anti-epileptic drugs daily dosages were at, or slightly under, the minimum of their therapeutic range. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield 1971), ten patients were right-handed, three were left-handed. The hemisphere dominant for speech was determined using intra-carotid amobarbital test in eleven patients and by cortical stimulation in two. In the ten right-handed patients the left hemisphere was dominant for language, two left-handed patients had a bilateral hemispheric representation of language, in the third left-handed patient language was found to be represented in the right hemisphere.

A complete description of cortical structures explored by depth electrodes, and of the cortical areas found to be involved in seizures propagation is given in Table 1. In all patients but one (case 12) several spontaneous seizures could be recorded, all of which originated in the mesial structures of the temporal lobe. In these 12 patients ictal discharges were propagating outside the mesio-temporal cortex. The areas most frequently involved in seizure propagation were the temporal pole, the temporal neo-cortex, the cingulate gyrus, and the orbito-frontal cortex. In patient 12 (Table 1) no spontaneous seizure occurred during the SEEG monitoring; however seizures could be triggered by stimulating the left hippocampus which spread to the orbito-frontal cortex and spared the suprasylvian operculo-insular cortex.

(Table 1 near here)

In seven patients the supra-sylvian operculum showed a rhythmic spike-wave activity during the spread of the discharges; in four of these patients this type of activity was also observed in the insular cortex. The possibility remains that, in these seven patients, the supra-sylvian opercular and insular cortices could show some degree of interictal hyper-excitability which might modify their responsiveness to somatosensory or pain inputs. However this possibility seems unlikely for the following reasons; i) none of the patients included in this study showed ictal discharges onset in the operculo-insular cortex and no low voltage fast activity was recorded in this cortex during spontaneous seizures; ii) no sustained after discharge was elicited by electrical stimulation of the operculo-insular cortex in any of our patients; iii) in terms of latency and amplitude somatosensory and pain EPs recorded in the operculo-insular cortex of the patients showing ictal spike-wave activity were not different from those recorded in patients whose seizures were not propagating to these cortical areas.

## ***2.2. Electrode implantation***

Intracerebral electrodes were orthogonally implanted using Talairach's stereotactic frame (Talairach and Tournoux 1988). The cortical targets were identified on the patient's magnetic resonance (MR) image, previously enlarged at scale one, before the surgery. The implanted procedure has been described elsewhere in details (Frot and Mauguière 1999, Frot et al. 1999, 2001). Each electrode had a diameter of 0.8 mm and 10-15 contacts, each 2 mm long, separated by 1.5 mm; they could be left in place chronically up to 15 days. Each of the contacts could be localized in the Talairach space using its stereotactic coordinates:  $x$  for the lateral medial axis, with  $x=0$  being the coordinate of the sagittal inter-hemispheric plane;  $y$  for the rostro-caudal axis,  $y=0$  being the coordinate of VAC (Vertical Anterior Commissure) plane and  $z$  for the inferior-superior axis,  $z=0$  being the coordinate of the horizontal AC-PC (Anterior Commissure-Posterior Commissure) plane.

In the opercular region, electrodes were implanted caudal and rostral to the VAC plane ( $y=0$ ). The deepest contacts of the electrodes implanted in the supra-sylvian opercular cortex explored the insula proper. As shown in Table 1 five patients were implanted by a single opercular electrode exploring either the pre- (1 case) or the post-rolandic (4 cases) supra-sylvian cortex. In the eight other patients both the frontal operculum and the parietal operculum were each implanted by one electrode exploring the insular cortex. Thus our data were collected using a total number of 21 electrodes. Forty-two contacts explored the insular cortex, distributed along the rostro-caudal axis, 14 mm rostral and 25 mm caudal to the VAC plane ( $y$  coordinates).

Apart from the operculo-insular cortex, intra-cerebral LEPs from other regions were recorded in these patients, like the hippocampus, the amygdala, the anterior cingulate gyrus, the temporal pole, the orbito-frontal cortex and in a few cases, the supplementary motor area (see Frot et al. 1999).

### ***2.3 CO<sub>2</sub> laser stimulations***

The LEPs recordings were performed about 10 days after electrodes implantation. During the recordings, the patients lay relaxed on a bed in a semidarkened room. Cutaneous heat stimuli were delivered by a CO<sub>2</sub> laser (10.6  $\mu\text{m}$  wavelength, 10 W output power). The power output being fixed, the amount of thermal energy delivered depended on the duration of the pulse. Thresholds for innocuous and painful sensations were first determined in each patient. The intensity of pain perception (pinprick) was rated by the patients between 4 and 7 on a 0-10 Visual Analog Scale (VAS). The energy density of the Laser beam varied between 6.3 and 10.9  $\text{mJ}/\text{mm}^2$  delivered on a skin surface of 16  $\text{mm}^2$ . The stimuli were applied to the dorsum of the hand, in the radial nerve territory. A red helium-neon (He-Ne) laser was combined with the CO<sub>2</sub> laser to visualize the stimulated skin area. Two runs of 30 stimuli

were performed. For each run of stimuli, the continuous EEG was cut in 30 epochs (each epoch of EEG began 12 ms before the stimulus and ended 500 ms after). All these epochs were averaged to remove the noise and to bring out the evoked potentials. Then, the two runs were averaged after having checked that the averaged waveforms were reproducible. The interstimulus interval varied randomly between 4500 and 5500 ms. The laser beam was slightly moved between two successive stimuli to avoid habituation and especially to avoid peripheral nociceptor fatigue (Schwarz et al. 2000). The analysis time was 512 ms; the signal was bandpass filtered between 1 and 250 Hz and sampled at 500 Hz. The reference electrode was at the earlobe ipsilateral to the stimulated hand and the ground was a circular wrapped electrode at forearm ipsilateral to stimulation.

Responses were labeled according to the polarity-latency nomenclature in which the letters N and P, referring to the polarity of the potential in the contacts close to scalp surface, is followed by the mean latency in milliseconds. In all figures, negative potentials at the intracortical recording site are represented upward. In text and tables mean voltages, latencies and time intervals are given  $\pm 1$  standard deviation (SD).

### **3. Results**

#### ***3.1. Polarity, latency and voltage of operculo-insular responses.***

##### *3.1.a. Responses from the supra-sylvian opercular cortex.*

The CO<sub>2</sub> laser stimulus consistently evoked in the supra-sylvian cortex a N140 negative response followed by a P170 positivity (Figure 1). Latencies and voltages of these potentials are given in table 2. These responses, which have been described elsewhere in details (Frot et al. 1999, 2001), were picked up by all of the 21 electrodes implanted in the

supra-sylvian opercular cortex and were not recorded in the other explored areas including amygdala, hippocampus, anterior cingulate gyrus, temporal pole, orbito-frontal cortex and supplementary motor area (see Frot et al. 1999). Similar responses were equally recorded on the electrodes implanted in the homologous cortex, ipsilateral to the painful stimulus peaking  $17 \pm 7.5$  ms ( $p= 0.003$ ) and  $16 \pm 12.9$  ms ( $p= 0.03$ ) later than contralateral N140 and P170 respectively (Table 2). This latency difference between ipsi- and contralateral responses was not different for N140 and P170 potentials ( $p=0,75$ ).

(Figure 1 near here)

### *3.1.b. Responses from the insular cortex.*

Two potentials contralateral to stimulation were recorded in the insular cortex, consisting in a N180 negative response followed by a P230 positivity (Figure 1). The N180 and P230 responses, of which latencies and voltages are given in table 2, were recorded  $49.5 \pm 16.3$  and  $55.5 \pm 13.5$  ms later than the opercular N140 and P170 potentials respectively. The figure 2 illustrates these opercular and insular responses on several recordings of different patients.

(Figure 2 near here)

Negative-positive LEPs were also recorded ipsilateral to stimulus by all of the contacts located in the insular cortex, they had a similar waveform as those recorded contralateral to stimulation but peaked  $15 \pm 6.6$  ms and  $17 \pm 9.5$  ms later than contralateral N180 and P230 respectively. This difference between contra- and ipsilateral responses was statistically

significant for each of the two components ( $p = 0,02$  for N180 and  $p = 0,03$  for P230, Student's t test) but there was no difference in this inter-hemispheric transit times between N180 and P230 potentials ( $p = 0,78$ ).

(Table 2 near here)

### ***3.2. Stereotactic localization of the operculo-insular responses.***

The maximal amplitude of the N/P deflection was taken to determine the contact likely to be the closer to the source.

#### *3.2.a. Responses from the supra-sylvian opercular cortex.*

The N140-P170 responses were recorded along the trajectory of all electrodes penetrating the suprasylvian opercular cortex between vertical planes at 14 mm rostral and 20 mm caudal (y coordinates) to the anterior commissure vertical plane (VAC), and between horizontal planes at 3 mm and 21 mm above (z coordinates) the horizontal anterior commissure - posterior commissure plane (AC-PC). These responses were picked up by the majority of these electrodes contacts, between 38 and 63.5 mm from the mid-sagittal vertical plane (x coordinates) (Table 3).

The cortical volume where opercular LEPs were distributed was assessed using the mean and SD values of x, y and z coordinates of the N140-P170. This volume was of 0.25 cm<sup>3</sup> using a confidence interval of  $\pm 1$  SD and of 1.98 cm<sup>3</sup> with a confidence interval of  $\pm 2$  SD (Figure 3).

(Table 3 near here)

*3.2.b. Responses from the insular cortex.*

The N180-P230 responses were picked up by the depth contacts of the electrodes penetrating the opercular cortex between vertical planes at 14 mm rostral and 25 mm caudal (y coordinates) to the anterior commissure vertical plane (VAC), and between horizontal planes at 1 mm below and 21 mm above (z coordinates) the horizontal anterior commissure - posterior commissure plane (AC-PC). The contacts recording these responses were distributed between 29 and 45 mm from the median line (x coordinates). The average coordinates of these contacts are given in table 3. The cortical volume where insular LEPs were distributed was of 0.35 cm<sup>3</sup> using a confidence interval of  $\pm 1$  SD and of 2.8 cm<sup>3</sup> with a confidence interval of  $\pm 2$  SD (Figure 3).

(Figure 3 near here)

In the seven patients where the insular cortex was explored by several electrodes (two or three) along the rostro-caudal axis (y) we did not observe any intra-individual differences of the N180-P230 responses between contacts in terms of latency and amplitude. No significant correlation was observed between the localization of the implanted electrodes along the rostro-caudal axis (y) and the latencies of the N180 ( $r = 0.17$ ,  $p = 0.5$ ) and P230 ( $r = 0.003$ ,  $p = 0.99$ ) responses (Figure 4). Moreover there was no significant correlation between the localization of the electrodes along the rostro-caudal axis (y) and the amplitudes of the N180 ( $r = 0.22$ ,  $p = 0.39$ ) and P230 ( $r = 0.22$ ,  $p = 0.39$ ) responses (Figure 4). Thus, we could

not define distinct populations of nociceptive neurons along this axis only on the basis of the responses recorded in this cortex.

(Figure 4 near here)

As illustrated in figures 1 and 2 the first insular negativity peaked clearly later than the SII P170 potential ( $p=0,03$ , Student's t test). However in two cases (patients C and D in figure 2) this first insular negativity was preceded by a positive potential, the latency of which was the same as that of the SII N140 potential. In these two patients the polarity reversal was observed at the contact located at the border between the insular contact and the deepest SII contact so that it was difficult to decide on which side of the circular sulcus the N140 source was located. This difficulty had already been encountered in our previous studies (Frot et Mauguière 1999, Frot et al. 1999, 2001). Moreover, in one patient (patient E in figure 2) the insular N180 was preceded by a positivity peaking later than the SII N140 and a few milliseconds earlier than the SII P170 (7 ms for the frontal operculum and 14 ms for the parietal operculum). Due to the low spatial electrode sampling in the insular cortex we cannot formulate any firm hypothesis concerning this individual variation of insular responses. However neither the N180 nor the P230 insular potentials showed any polarity reversal at more superficial contacts located in the SII area. Moreover, when the N180 was spreading to the SII contacts, such as in patient E (figure 2), its amplitude was regularly decreasing from the deepest insular contact to the more superficial SII sites. Therefore we considered that these two potentials were the only consistent components that could be considered as originating in the insula proper.

#### **4. Discussion**

In this study, we were able to separate two cortical areas in the operculo-insular cortex responsive to a painful laser stimulation (Figure 3): a supra-sylvian opercular area where we recorded a response peaking at 140-170 ms after a painful stimulation and a deeper insular area where we recorded a response with a similar pattern but peaking 180-230 ms after the stimulus. The latency range of the operculo-insular responses recorded directly in the cortex is coherent with that of the earliest CO<sub>2</sub> laser potentials recorded on the scalp. Several studies of scalp or subdural LEPs converged on the conclusion that the earliest cortical response consists of a negativity peaking between 150 and 170 ms and maximal in the scalp centro-temporal region contralateral to stimulation, compatible with a generator located in SII/insular areas (Treede et al. 1988; Tarkka and Treede 1993; Miyazaki et al. 1994; Xu et al. 1995; Valeriani et al. 1996, Lenz et al. 1998). This negativity was found to be associated with a mid-frontal positivity peaking around 200 ms in mapping studies (Treede et al. 1988; Tarkka and Treede 1993; Valeriani et al. 1996), suggesting a dipolar source close to the sylvian fissure and tangent to the scalp surface. According to these studies, this dipolar source remains active at the latency of a later response recorded on the scalp at 250 ms after the painful stimulus, which is in the range of our insular positivity latency.

#### ***4.1 Is the N180-P230 actually generated in the insular cortex?***

The question whether the insular responses might reflect the diffusion of the supra-sylvian LEPs with a polarity reversal across the sylvian fissure deserved our attention.

Several arguments support the interpretation that the N140-P170 and the N180-P230 are independent responses. In most cases (8 patients) the suprasylvian P170 potential was clearly peaking before the first insular N180 negativity and its latency was significantly shorter by 27 ms ( $p=0.0002$ ) ( $26.8 \pm 11.1$  ms in average for these patients). In one patient we

even recorded a polarity reversal of the supra-sylvian opercular P170 peaking at 162 ms into a negativity peaking with the same latency at the deepest insular contact, where the first insular negativity was peaking at 214 ms (Figure 2: Patient D). Moreover, the insular N180 negativity often spread to the supra-sylvian contacts (Figure 2: Patients B and E), and was then superimposed to the P170 potential (see Results section).

Since only a few contacts per electrode track were exploring the insula proper we were not in a position to show a polarity reversal of the N180-P230 between the surface and the depth of the insular cortex. However, when at least 2 contacts explored the insular cortex, we always recorded on these contacts the N180-P230 responses with a gradient of amplitude along the x axis (Figures 1 and 2). Thus, in spite of inter-individual variations in waveforms, the suprasylvian and insular responses are unlikely to be generated by a single source in the upper bank of the suprasylvian fissure.

#### ***4.2 Location of LEPs activities in the operculo-insular cortex.***

Our results are coherent with data of numerous imaging studies showing a double representation of pain in the operculo-insular cortex (Coghill et al. 1994, Casey et al. 1996, Craig et al. 1996, Andersson et al. 1997, Rainville et al. 1997, Svensson et al. 1997, Xu et al. 1997, Svensson et al. 1998, Gelnar et al. 1999). As shown in table 4 the mean coordinates of the N140-P170 responses contralateral to stimulation are very similar those of the maximal blood-flow responses observed during different painful stimulations, even if our localization is often more anterior.

(Table 4 near here)

The restricted spatial sampling along the rostro-caudal (y) and vertical (z) axis, as determined by the number of SEEG electrodes in each patient, could explain this discrepancy. Nevertheless, the N140-P170 responses were distributed along the y axis between 14 mm rostral and 20 mm caudal to the anterior commissure vertical plane (VAC), thus including the majority of the sites with maximal blood-flow responses (see table 4). In the same way, the mean coordinates of the N180-P230 responses recorded in the insular cortex were very similar to those of the maximal blood-flow responses observed in PET and fMRI studies (see table 4). Moreover, the depth (x) coordinates of operculum and insula reported in PET studies are often on the wrong side of the circular sulcus (Table 4), whereas in this study great care was taken to have precise knowledge of which contacts were in the insula and which ones were in the operculum.

We could not define distinct functional regions in the insula along the y axis on the basis of latencies and amplitudes of pain EPs recorded in this cortex (see results). This observation is in line with data from two PET studies, using a CO<sub>2</sub> laser stimulation, showing a maximal blood-flow response either in the anterior (Svensson et al. 1997) or in the posterior insula (Xu et al. 1997) (See table 4). This suggests that a stimulus like CO<sub>2</sub> laser, which does not evoke any emotional or affective reaction, is able to activate a largely distributed functional region of the insular cortex.

#### ***4.3 Transcallosal inputs transmission***

This study showed that a painful stimulation elicits responses in the contra and ipsilateral supra-sylvian and insular cortices separated by a delay of 11-18 ms. This delay is compatible with callosal transmission times estimated by numerous studies (e.g. 15 ms between primary visual areas (Swanson et al. 1978)); it is in the same range as that measured

between ipsi- and contralateral SII magnetic fields evoked by electrical stimulation of the median nerve (20 ms in Hari et al. 1993, 10 ms in Mauguière et al. 1997), the shortest callosal transmission time between the two SI areas being estimated at 6-7 ms (Noachtar et al. 1997).

However, a callosal transfer from contralateral to ipsilateral supra-sylvian and insular cortices cannot be concluded only on the basis of this time difference. The possibility remains that responses ipsilateral to the stimulus could be triggered via ipsilateral thalamic fibers with slower conduction velocity. Only intracortical recordings of supra-sylvian or insular cortices evoked potentials to ipsilateral stimuli in patients with a lesion of the homologous areas in the opposite hemisphere could address directly this question.

#### ***4.4 Activation timing of the LEPs supra-sylvian and insular sources***

If we consider that the N140-P170 and the N180-P230 are independent responses generated by different cortices, it remains to explain the delay of ~ 50 ms observed between supra-sylvian and insular responses. This delay could reflect the transmission time from the SII area to the insula, a hypothesis which is supported by the observation in monkeys that most of inputs reaching the insular cortex come from the SII area (Friedman and Murray 1986). However, this delay of 50 ms seems quite long for a monosynaptic transmission time between two close cortical areas known to be interconnected by direct projections (Friedman et al. 1986). Alternatively, knowing that both SII and the insula receive direct projections from the thalamus (Friedman et al., 1980, Friedman and Murray 1986, see also for a review Augustine 1985, 1996), the explanation for the delay between supra-sylvian and insular responses could be that the latter are triggered via thalamo-cortical fibers with a slower conduction than that of thalamic projections to the SII area. To our knowledge, however, no electrophysiological demonstration of this hypothesis is hitherto available. A third hypothesis could be that the supra-sylvian cortex and the insula are activated by inputs conveyed by

peripheral fibers with different conduction velocities. The CO<sub>2</sub> laser beam used in this study is known to stimulate the endings of small diameters fibers and mostly those of A $\delta$  fibers (Bromm and Treede, 1981, 1984, 1991). Some studies have estimated the A $\delta$  conduction velocity in a large range of 7 to 20 m/s (Adriaensen et al. 1983, Naka and Kakigi 1998) suggesting the existence of different A $\delta$  fibers sub-populations, with different conduction velocities. One can hypothesize that these different sub-populations of A $\delta$  fibers have selective connections with the spino-thalamic neurons in layers I, II and V of the spinal cord dorsal horn (for a review see Wolf 1994). If such an organization was maintained along the spinothalamic and thalamo-cortical tracts, one could assume that these different sub-populations of peripheral fibers could project in distinct cortical regions. However, to our knowledge, no electrophysiological study has been devoted to the identification of separate sub-populations of fibers with different conduction velocities in the spinothalamic tract or thalamocortical projections. It remains that, in spite of conjectures about their parallel or sequential activation by pain inputs, the SII and insular areas are those showing the earliest responses to pain and are both receiving projections from the posterior thalamus.

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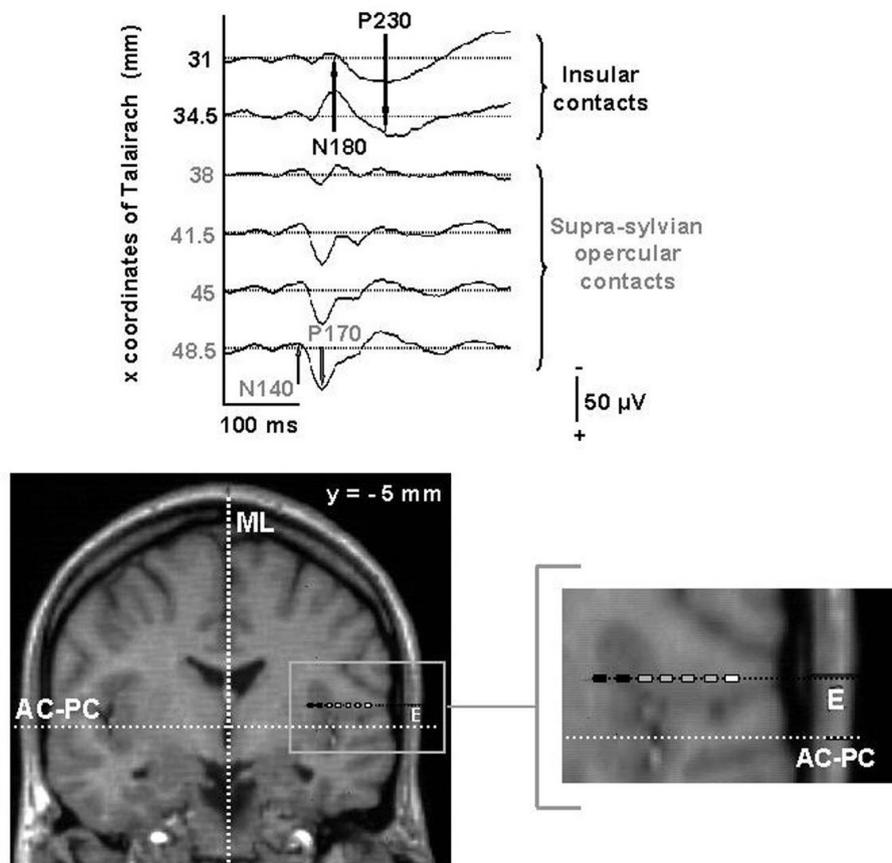
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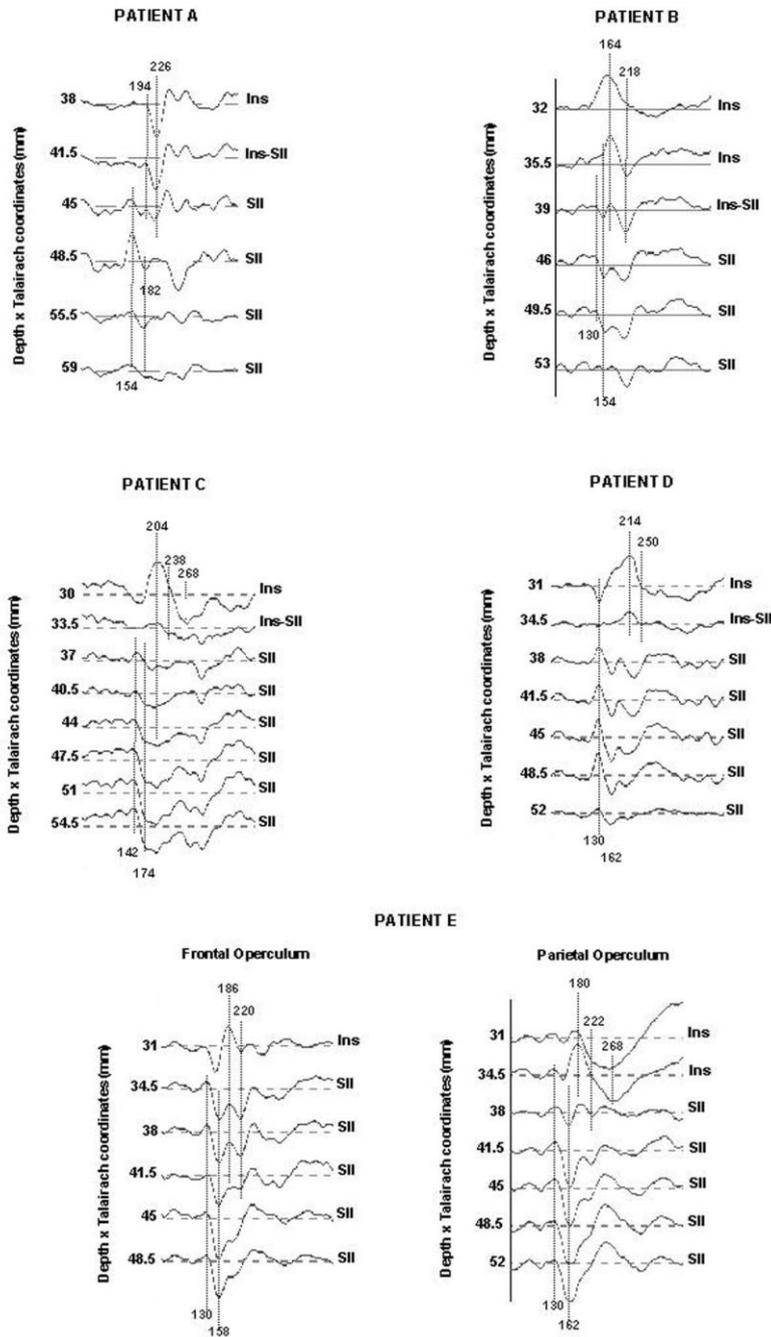
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**Figures:**



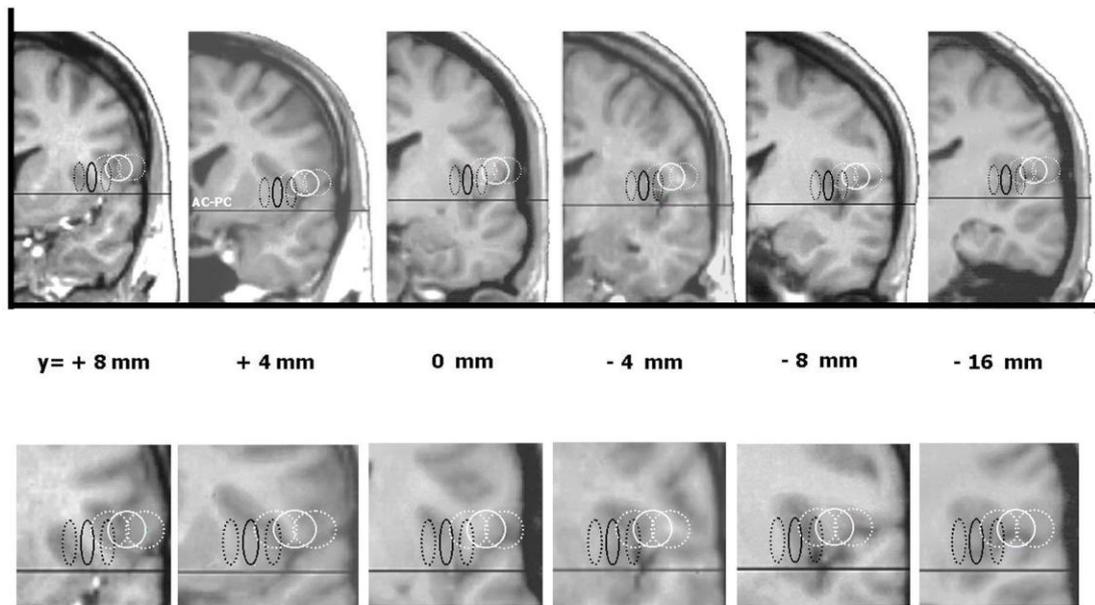
**Figure 1:** Contralateral LEPs recorded in the post-rolandic operculo-insular cortex of one patient (earlobe reference recording). The operculo-insular electrode (E) is represented on the patient's MRI slice, at -5 mm caudal to the VAC plane (y coordinate) and 8 mm above the AC-PC plane (z coordinate). The black and gray contacts are those represented above at 31, 34.5, 38, 41.5, 45 and 48.5 mm from the midline. The contacts in black are those located in the insular cortex and those in gray are located in the supra-sylvian cortex.

ML: Median Line, AC-PC: Horizontal Anterior Commissure-Posterior Commissure plane.



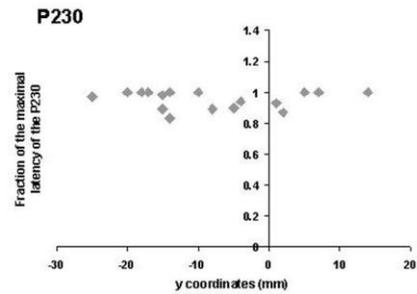
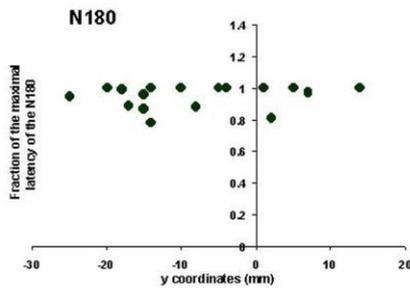
**Figure 2:** Contralateral LEPs recorded in the operculo-insular cortex of five patients (earlobe reference recording). The peaks of the supra-sylvian and insular responses are enlightened by dotted lines and characterized by their latencies.

Ins: contacts located in the insula proper; Ins-SII: contacts located at the boundary between insula and supra-sylvian cortex (SII are); SII: contacts located in the supra-sylvian cortex (SII area).

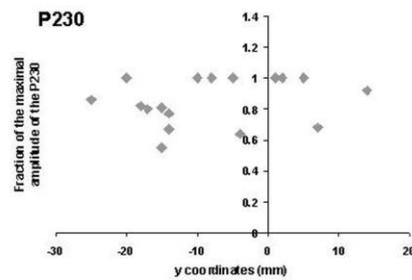
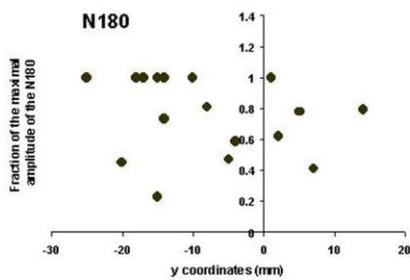


**Figure 3:** Mean distribution of the contralateral N140-P170 and N180-P230 responses, recorded in the supra-sylvian operculum (plain white circles) and in the insular cortex (plain black circles) respectively. The circles in dotted lines represent the distribution range ( $\pm 1$  SD) for the x coordinates of the supra sylvian (in white) and the insular (in black) responses. The MRI slices have been chosen in the pool of the patients, according to the corresponding Talairach slices. The second row show a zoom for each slice, focused on the operculo-insular region.

### a) Latencies



### b) Amplitudes



**Figure 4:** Correlation between the localization of the implanted electrodes along the rostro-caudal axis (y coordinates) and the latencies (a) or amplitudes (b) of the contralateral insular responses. The data have been normalized according to the maximal latency or amplitude of each component recorded in each patient. For example, the patient A had three electrodes implanted in the insular cortex (each of them with a different y coordinate, i.e. -6 mm, 2 mm and 6 mm), on which different latencies of the N180 response were recorded; i.e. 177 ms, 183 ms and 180 ms respectively. For this patient, we normalized the data according to the maximal amplitude of the response, which is 183 ms. Thus we had a latency of ‘0.96’ for y= -6mm, a latency of ‘1’ for y=2mm and a latency of ‘0.98’ for y=6mm.