

Operculo-insular pain (parasyylvian pain): a distinct central pain syndrome

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Central pain with dissociated thermoalgesic sensory loss is common in spinal and brainstem syndromes but not in cortical lesions. Out of a series of 270 patients investigated because of somatosensory abnormalities, we identified five subjects presenting with central pain and pure thermoalgesic sensory loss contralateral to cortical stroke. All of the patients had involvement of the posterior insula and inner parietal operculum. Lemniscal sensory modalities (position sense, graphaesthesia, stereognosis) and somatosensory evoked potentials to non-noxious inputs were always preserved, while thermal and pain sensations were profoundly altered, and laser-evoked potentials to thermo-nociceptive stimuli were always abnormal. Central pain resulting from posterior parasyylvian lesions appears to be a distinct entity that can be identified unambiguously on the basis of clinical, radiological and electrophysiological data. It presents with predominant or isolated deficits for pain and temperature sensations, and is paradoxically closer to pain syndromes from brainstem lesions affecting selectively the spinothalamic pathways than to those caused by focal lesions of the posterior thalamus. The term 'pseudo-thalamic' is therefore inappropriate to describe it, and we propose parasyylvian or operculo-insular pain as appropriate labels. Parasyylvian pain may be extremely difficult to treat; the magnitude of pain-temperature sensory disturbances may be prognostic for its development, hence the importance of early sensory assessment with quantitative methods.

Keywords: central pain; laser-evoked potentials; somatosensory-evoked potentials; insula

Abbreviations: LEP = laser-evoked potential; SSEP = short-latency somatosensory-evoked potential

Introduction

Central neuropathic pain arises as a direct consequence of lesions or disease affecting the central nervous system (Boivie, 2006; Treede *et al.*, 2008). After decades of presuming that central pain resulted from spinothalamic disinhibition due to a lesion of

the dorsal columns–lemniscal system (Head and Holmes, 1911; Riddoch, 1938a, b; Nathan *et al.*, 1986), it is now recognized that lesions generating central pain typically involve the spino-thalamo-cortical system for pain and temperature, while involvement of lemniscal pathways is not essential (Beric *et al.*, 1988; Boivie *et al.*, 1989; Vestergaard *et al.*, 1995; Bowsher

et al., 1996, 1998; review in Boivie, 2006). This is especially clear in spinal, brainstem and subcortical lesions, and indeed predominant thermoalgesic sensory loss is a typical feature of central pain due to syringomyelia (Ducreux *et al.*, 2006), spinal cord injury (Defrin *et al.*, 2001), multiple sclerosis (Osterberg and Boivie, 2010) or lateral medullary infarcts (Kameda *et al.*, 2004).

While it is widely accepted that focal cortical lesions may also cause pain, these are generally not considered as distinct entities *per se*, and are commonly portrayed as 'pseudothalamic' (review in Boivie, 2006). Yet, cortical lesions with the characteristic signature that combines pain and selective spinothalamic sensory loss have been described in lesions of the parasyllian cortex, in particular the region comprising the mid-posterior insula and parietal operculum. Physiological and clinical studies point to this area as an optimal candidate for a cortical pain syndrome: the parasyllian cortex is involved in the processing of pain–temperature sensations (Treede *et al.*, 2000), and is consistently activated by pain stimuli in humans (Lenz *et al.*, 1998; Frot and Mauguière, 1999; Peyron *et al.*, 2000; Garcia-Larrea *et al.*, 2003; Apkarian *et al.*, 2005). Both intracortical stimulation at operculo-insular sites and epileptic seizures originating in these areas can generate acute pain (Potagas *et al.*, 1997; Isnard *et al.*, 2004; Mazzola *et al.*, 2006; Isnard *et al.*, 2008). Not least, lesions in this region may result in specific sensory deficits for pain and temperature (Greenspan *et al.*, 1992; Bassetti *et al.*, 1993; Horiuchi *et al.*, 1996; Greenspan *et al.*, 1999) that can be associated with central pain (Biemond, 1956; Schmähmann and Leifer, 1992; Bowsher, 2006; Kim, 2007).

Surprisingly, no major effort has been devoted in the past to clarify the role of the insular-opercular region in the development of central pain, and recent reviews on neuropathic pain do not mention the possible responsibility of this area (Dworkin *et al.*, 2003; Boivie, 2006; Costigan *et al.*, 2009; Kumar *et al.*, 2009). A possible reason for this is that restricted parasyllian strokes without involvement of other areas, cortical or subcortical, are exceptional (0.08% for Cereda *et al.*, 2002), and not all of them entail painful symptoms. Recent reviews on parasyllian lesions have stressed prognostic factors and autonomic changes rather than pain alterations (Colivicchi *et al.*, 2004; Meyer *et al.*, 2004; Christensen *et al.*, 2005; Tatschl *et al.*, 2006). In patients with pain, sensory examination was most often restricted to clinical assessment, sometimes with incomplete description of sensory deficits, without objective investigation of conduction abnormalities in somatosensory pathways. The question addressed here was therefore whether central pain in subjects with insular-opercular lesions could reasonably be considered as a distinct entity, with distinguishable characteristics allowing a precise diagnosis and differentiation from other conditions.

In this study we gathered data from consecutive patients with focal cortical lesions presenting with (i) central pain; and (ii) dissociated sensory deficits. All of these patients had lesions involving the posterior insula and adjacent medial operculum, and were studied in detail with clinical, imaging, psychophysical and electrophysiological methods. On the basis of our results and previous literature, we suggest that 'parasyllian pain' should be considered as a distinct central pain syndrome, with characteristic features that make it differ from thalamic pain, and paradoxically

closer to pain syndromes related to brainstem lesions affecting selectively the spinothalamic pathways than to those caused by focal lesions of the posterior thalamus.

Patients and methods

Patients

Out of 271 patients sent to the pain unit for somatosensory clinical and physiological assessment between 2002 and 2009, 21 had pure thalamic lesions and 22 had cortico-subcortical lesions not involving the thalamus nor the brainstem. Of these, only five patients were found to present dissociated loss of thermoalgesic sensations and are reported in detail here. These five patients were all admitted due to sudden onset of focal neurological symptoms of vascular origin, and developed central pain. In three patients, neuroradiological imaging disclosed discrete lesions restricted to the posterior insular cortex with variable extension toward the inner parietal operculum. In one patient the lesion covered three fourths of the insular cortex and in one patient the insula was included in a more extended lesion involving the parietal cortex. Table 1 summarizes lesion sites and clinical pictures of the 22 patients with cortical lesions, and Table 2 details the results of radiological, somatosensory and neurophysiological testing, as well as follow-up of the five patients with pain and thermoalgesic dissociated sensory loss.

Neuroimaging investigations

Relations between the ischaemic lesions and anatomical structures were established on T₁-, T₂- and diffusion-weighted magnetic resonance images (3D mode in four patients, 2D in one). The extension of the lesions was assessed with the help of different atlases (Duvernoy, 1991; Afif *et al.*, 2009). Two blinded authors evaluated the MRIs of each patient without knowledge of their sensory status, and determined to what extent the following cerebral regions were involved in the lesion: anterior insula, middle insula, posterior insula, medial parietal operculum and lateral parietal operculum, following the procedure of Greenspan *et al.* (1999).

Sensory assessment

Each patient underwent detailed sensory examination, which integrated light touch, superficial pain, warm and heat sensation, position sense, vibration sense, stereognosis and graphesthesia. Numerical (Likert) rather than visual analogue scales were used for assessment of pain thresholds and ratings, as they have been shown to be superior to visual analogue scales in pain and stroke patients (Kremer *et al.*, 1981; Price *et al.*, 1999). Short-latency responses to electrical non-noxious stimuli were used to assess the dorsal column–lemniscal system and laser-evoked potentials (LEPs) studied the activation of cortical targets of the spinothalamic system (Plaghki and Mouraux, 2003; Garcia-Larrea, 2006; Cruccu *et al.*, 2008).

Spinothalamic pathways

Perception thresholds to contact heat and cold were tested using a Peltier-driven contact thermode in three patients (Thermotest® Medoc Inc, Israel) and water tubes in the other two patients. Perception and pain thresholds to radiant heat were assessed using focused laser stimuli in all five patients (Nd:YAP solid-state laser, wavelength 1.34 µm, surface 12.6 mm²; El-En®, Florence, Italy). Perceptive threshold was

Table 1 Summary of clinical data from 22 consecutive patients with somatosensory symptoms from cortical or cortico-subcortical lesions not including the thalamus

	Age, sex	Type	Motor deficit	Aphasia	Lemniscal deficit	Pain/temp deficit	Central pain	Lesion
1	M	Ischaemic	Transient	Transient	No	Yes	Yes	Left posterior insula and medial operculum
2	F	Ischaemic	Mild	Transient	No	Yes	Yes	Left posterior insula and medial operculum
3	M	Ischaemic	Transient	No	No	Yes	Yes	Right 4/5th insula and medial operculum
4	F	Ischaemic	Distal	No	No	Yes	Yes	Right insula + frontal operculum + parietal
5	M	Ischaemic	No	No	No	Yes	Yes	Right posterior insula and operculum
6	M	Tumour	Mild	No	No	No	No	Left precentral cortex
7	M	Haemorrhagic	Yes	No	Yes	Yes	Yes	Right temporal – insular- basal ganglia
8	M	Surgical	No	No	No	No	No	Right operculum – insula
9	M	Haemorrhagic	Yes	No	Yes	Yes	Yes	Basal ganglia extended
10	F	Haemorrhagic	Transient	No	Yes	Yes	Yes	Basal ganglia (capsulo-lenticular)
11	F	Ischaemic	Yes	No	Yes	Yes	Yes?	Parietal + frontal (extended)
12	M	Ischaemic	Yes	No	Yes	Yes	Yes	Parietal + frontal (extended)
13	F	Haemorrhagic	Yes	Yes (mild)	Yes	Yes	Yes	Fronto-temporal + operculum + insula
14	M	Ischaemic	No	No	Yes	Yes	Yes	Left and right parietal lobe
15	M	Tumour	No	No	No	No	No	Left insular tumour
16	M	Ischaemic	Yes	No	Yes	Yes	Yes	Right Parietal + fronto-insular + temporal
17	M	Ischaemic	No	No	Yes	No	No	Left internal capsula (lacunar infarction)
18	F	Haemorrhagic	Yes	No	Yes	Yes	Yes	Right internal capsula parietal + frontal
19	M	Haemorrhagic	Yes	Yes (mild)	Yes	Yes	Yes	Left parietal + frontal + basal ganglia
20	M	Surgical	No	No	Yes	Yes	Yes	Right opercular ablation
21	F	Ischaemic	Yes	No	Yes	Yes	Yes	Parietal + frontal + insula
22	F	Ischaemic	Yes	Yes (mild)	Yes	Yes	Yes	Parietal + frontal +

The five patients at the top (in bold) were the only ones to present with dissociated sensory loss (no lemniscal deficit, but altered pain and temperature sensation). Their detailed clinical and electrophysiological features, and follow-up, are described in Table 2 and in the text.

determined as the minimal energy density (in mJ/mm²) giving rise to a recognizable perception for at least four out of five stimuli. Warmth perception was assessed using a contact thermode in Patients 1, 2 and 3, and in Patients 3, 4 and 5 with selective activation of C-warmth fibres with large surface area, low-energy laser pulses (Cruccu *et al.*, 2003). Patient 3 was therefore tested with the two systems, and results were concordant. Pain threshold to A-delta stimuli was determined as the minimal laser energy producing a pricking sensation, compared to pulling a hair or receiving a boiling water drop (Cruccu and Garcia-Larrea, 2004). LEPs were obtained with a Nd:YAP solid-state laser (ELEN[®], Florence, Italy) delivering infrared laser pulses of 1.34 µm wavelength. Stimuli were applied every 10 ± 2 s to the dorsum of both hands when one of them was painful, or to the most painful cutaneous territory indicated by each patient, and its homologous contralateral area. Stimulus intensity for LEP recording was set, for both sides, at the pain threshold (+10%) obtained in the normal side (Plaghki and Mouraux, 2003; Treede *et al.*, 2003). Brain signals were averaged over 1000 ms, with 100 ms pre-stimulus baseline, using a 0.1–70 Hz bandpass and 500 Hz sampling rate. Thirty-two scalp electrodes were positioned according to the 10–20 international extended system, referenced to the nose.

Tactile and vibratory sensations

Tactile thresholds were quantified with Von Frey calibrated filaments (Somedic[®], Sweden), using both static and moving stimuli over the affected area and its contralateral homologous region. Tactile thresholds were determined as the minimal filament bending pressure giving rise to an 80% recognition rates (four out of five strokes). Vibration sense was tested comparing the subjective vibration intensity of a 100 Hz tune fork on bone points in homologous territories, beginning alternatively on the affected and non-affected sides.

Lemniscal pathways

Joint position sense was assessed by blind imitation of contralateral finger and toe movements, and blind search of the contralateral extremity. Graphesthesia by recognition of digits (0–3–5) drawn on the palm of the hands, forearms and feet, stereognosis by blind recognition of familiar objects explored by each hand. Correct performance in four out of five consecutive iterations of each test was considered normal. Two-point discrimination was assessed using two blunted needles applied at progressively decreasing distance over the painful and contralateral homologous regions. Short-latency somatosensory-evoked potentials (SSEPs) were obtained using transcutaneous, non-painful electrical stimulation of the median nerve at the wrist and/or the posterior tibial nerve at the ankle (Cruccu *et al.*, 2008). A non-cephalic reference on the shoulder contralateral to stimulus was used to record cortical and subcortical responses simultaneously (Mauguière and Desmedt, 1988; Cruccu *et al.*, 2008). Responses were averaged online, with bandpass of 10–1500 Hz (–3 dB) over a 65 ms analysis time, at 3 kHz sampling rate. SSEPs and LEPs were compared against normative data from the laboratory and from published literature (Cruccu *et al.*, 2008). Inter-side latency asymmetries were considered significant if exceeding 2.5 SD from the mean in controls. Amplitude drop >30% of normal side, reproducible over two runs, was considered significant.

Results

Tables 1 and 2 summarize clinical data from the 22 patients with focal cortical lesions and the five patients who presented with dissociated sensory loss, respectively. MRIs of these five patients

Table 2 Summary of lesion sites, clinical sensory data corresponding to the painful territory, pain characteristics and therapeutic outcome in the five patients with dissociated sensory loss from cortical lesions

Patient	Lesion (Figs 1–3)	Tactile and vibration	Lemnisal	Spinothalamic	Pain features	Follow-up	Other
1	Left posterior insula – medial operculum	Von Frey = N Vibrat = N	Joint = N Graphs = N 2-point = N SSEPs = N	Thresholds for Prick = Abn Warmth = Abn Cold = Abn Heat pain = Abn LEPs = Abn	Right side of the body and face, continuous burning, allodynia to cold and brushing	Pain refractory to pharmacological treatment. Relieved 50% with motor cortex stimulation	Flexion nociceptive reflexes (R3) attenuated and dissociated from pain sensation
2	Right posterior insula – medial operculum	Tactile = N Vibrat = N	Joint = N Graphs = N 2-point = N SSEPs = N	Thresholds for Prick = Abn Warmth = Abn Cold = Abn Heat pain = Abn LEPs = Abn	Left upper limb and trunk, continuous burning, allodynia to cold and brushing	Pain relieved 50% by pharmacological treatment with amitriptyline, pregabalin, duloxetine, escitalopram	Developed painting abilities not present before ictus
3	Right insula (4/5th)—medial operculum	Von Frey = N Vibrat = N	Joint = N Graphs = N 2-point = nd SSEPs = N	Thresholds for Prick = Abn Warmth = Abn Cold = Abn Heat pain = Abn LEPs = Abn	Left upper limb and trunk, continuous burning, allodynia to cold on left side of the face	Pain resistant to tricyclics, partial effect pregabalin, opioids and ketamine. Scheduled for transcranial magnetic stimulation	
4	Right Insula + frontal operculum + inferoparietal	Von Frey = abnormal Vibrat = N	Joint = N Graphs = N 2-point = nd SSEPs = N*	Thresholds for Prick = Abn Cold = Abn Heat pain = Abn LEPs = Absent	Left hand and trunk, continuous burning, mechanical allodynia upper limb and trunk	Pain refractory (2 years) to all pharmacological therapy. Relieved (30%) by transcranial magnetic stimulation. Relieved (80%) by surgical motor cortex stimulation	*Reduced after-sensation to noxious laser stimulation despite symmetrical heat thresholds
5	Right posterior insula + medial and lateral operculum	Von Frey = N Vibrat = N	Joint = N Graphs = N 2-point = N SSEPs = N	Thresholds for Prick = N* Warmth = N Cold = N Pain = ±* LEPs = abnormal	Dyesthesiae upper limb contralateral to lesion during acute phase only	Discharged with no analgesic treatment	

Thresholds correspond to the painful territory. Tactile thresholds (Von Frey hairs) were considered abnormal if >3 g/mm² in hands, >6 g/mm² in trunk or feet. A cotton tool instead of Von Frey hairs were used in Patient 2. Thresholds for pinprick perception and pricking pain (laser stimuli) were considered abnormal when >95% confidence limits in normal controls, i.e. >50 ml/mm² for perception and >100 ml/mm² for pain threshold, or when side-to-side asymmetry exceeded 20 ml/mm². Warm thresholds were tested with a contact thermode (Thermotest®) in Patients 1, 2 and 3 and with C-warmth laser for Patients 3, 4 and 5. Warmth thresholds were considered abnormal if no sensation of warmth was felt on the palm or the tight was obtained with stimuli as high as 40 ml/mm² using a large 15 mm spot (Cruccu *et al.*, 2003). Cold thresholds were tested with a thermode in Patients 1–3; with cold tubes and a metal fork in Patients 4–5. Vibration was tested with a 100-Hz tuning fork. N = normal; Abn = abnormal; nd = not determined.

are presented in Fig. 1. The results of clinical, quantitative sensory testing and electrophysiological exams correspond, unless otherwise stated, to periods when the condition was clinically stable.

Patient 1

A 55-year-old overweight male with sleep apnoea and atrial fibrillation developed sudden paresthesiae, aphasia and right-sided hemiparesis with sensory loss. Aphasia and motor deficits subsided in a few hours leaving an almost pure sensory syndrome with (i) right-sided multimodal hypaesthesia including the face, predominant for pain and temperature; (ii) continuous, unpleasant burning sensation over the hypaesthetic area; and (iii) allodynic sensations to touch and rubbing over the right side of the face. The 3D MRI disclosed a small ischaemic lesion restricted to the left posterior insula and innermost parietal operculum (Fig. 1, first row and Fig. 2). Nine months later, the only significant complaint was continuous right-sided burning pain predominant in right face, arm, foot and genitalia. He described allodynic phenomena in the right side of the face on shaving.

Two years after stroke, quantitative sensory testing repeatedly revealed dissociated sensory loss with altered thermal and pain sensation and preserved lemniscal modalities in the right side of the body. Thermode cooling and warming were perceived respectively at 29°C and 37°C in the left hand, and at 1°C and 48°C in the right hand. There was dynamic and static allodynia over the right side of the face. Perception and pain thresholds for thermal

laser pulses were very significantly elevated (>40%) over the right half of the body. Nocioceptive LEPs were significantly depressed and delayed after stimulation of the painful right hand (Fig. 2). Nocioceptive flexion reflexes were attenuated and dissociated from pain perception in the right lower limb, with a pattern identical to that reported in spinal lesions of the spinothalamic tract (Garcia-Larrea, 1993). In contrast, vibration sense (100 Hz) was preserved and symmetrical, and no errors were detected in joint position sense, graphesthesia, stereognosis and two-point discrimination. SSEPs were normal and symmetrical after stimulation of upper limbs, in particular early cortical components between 18 and 50 ms reflecting activation of primary sensory cortex.

After 2 years of unsuccessful pharmacological trials with tricyclic anti-depressants, anti-epileptics, tramadol and dextropropoxyfen, alone or in combination, the patient responded favourably to repetitive transcranial magnetic stimulation, thus prompting surgically-implanted motor cortex stimulation. This reduced pain from 8/10 to 2–3/10 over 1 year, then to an overall 5/10, which has remained stable (and acceptable) to this day.

Patient 2

This 36-year-old female with a history of migraine and under oral contraception developed right hemiparesis and hemianesthesia, dysarthria and partial conduction aphasia in January 2007. The outcome was favourable with rapid recovery of motor strength and dysarthria, but with residual sensory deficit for pain and

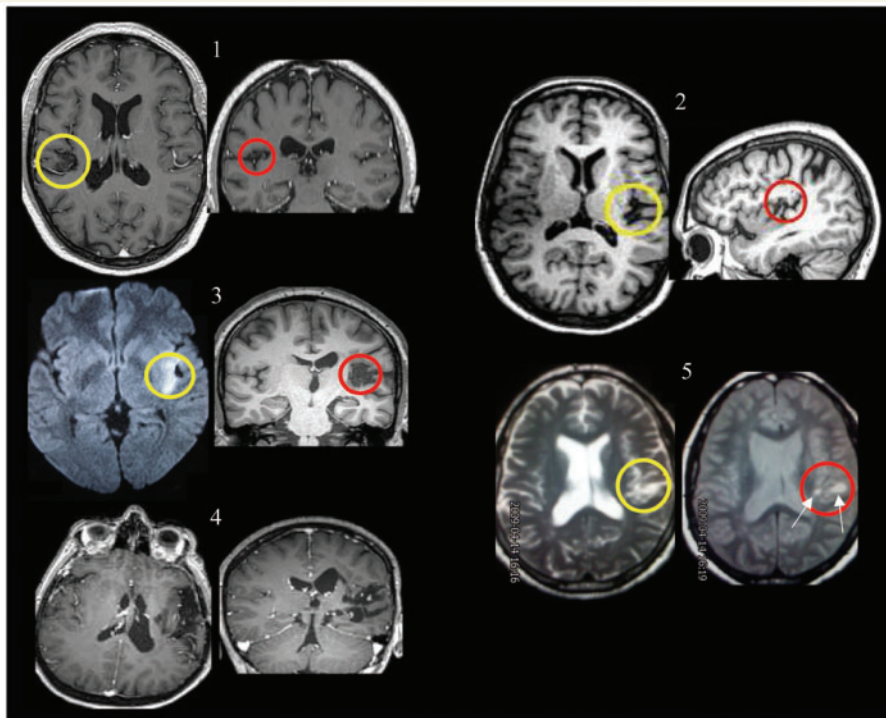


Figure 1 Magnetic resonance images of the five patients with cortical lesions and dissociated sensory loss. All patients had involvement of the posterior insular cortex and medial operculum. In Patients 1, 2 and 5, the lesion was very small and localized; it was intermediate in Patient 3, and involved the whole insula extending into the temporal lobe in Patient 4. Clinical details for each patient are given in the text and Tables.

Patient 1 – left posterior insular lesion

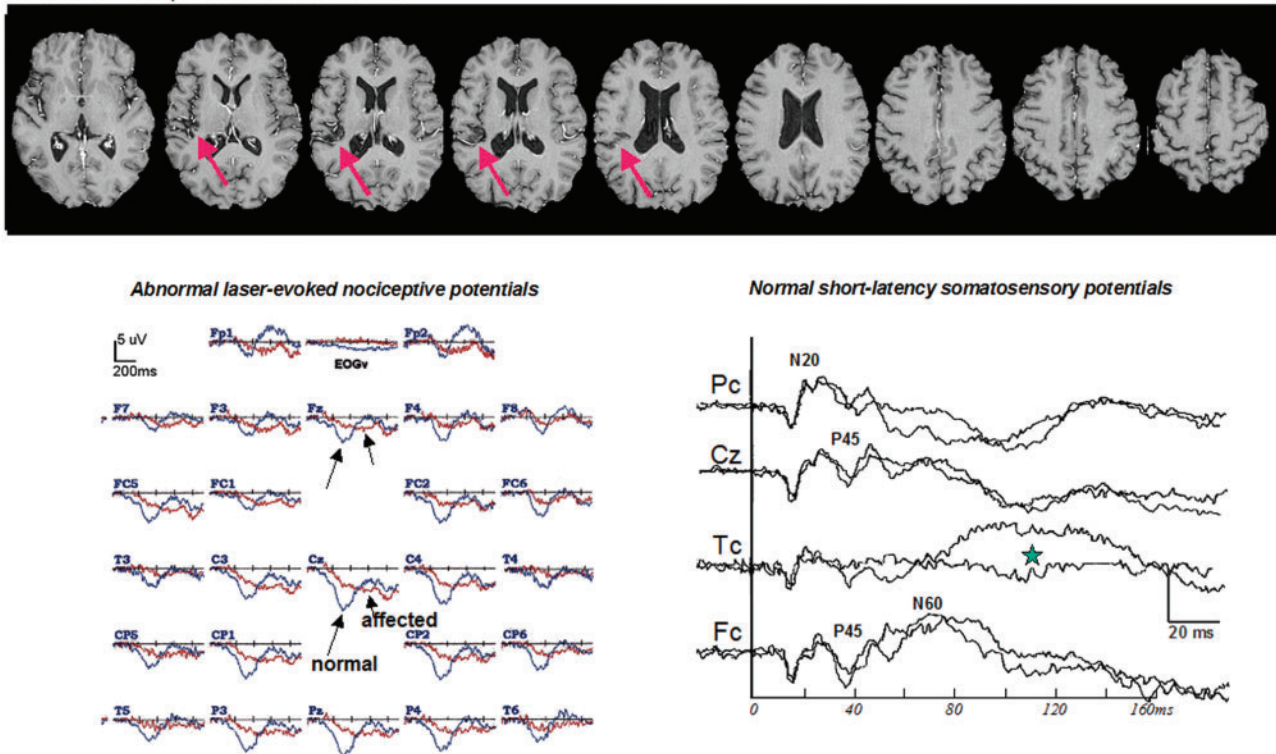


Figure 2 Anatomical lesion and electrophysiological tests in Patient 1. The ischaemic lesion (arrows) was restricted to the left posterior insula and innermost parietal operculum. Primary sensory areas as well as the lateral operculum remained intact. SSEPs were normal and symmetrical (*bottom right*) while LEPs to stimulation of the painful hand were very significantly attenuated and delayed (*bottom left*, red traces). Please note that long-latency SEPs (100–150ms) from the operculo-insular regions were also attenuated due to the lesion (*green star*).

temperature in the right side of the body. Five months later she started to complain of right-sided pain exacerbated by contact, especially cold. One year later she had severe right-sided pain with permanent burning and freezing cold sensations, and spontaneous pain paroxysms in her right upper limb. She wore a glove on her right hand to protect her from allodynia to light brushing. She also developed impairment of emotional expression, while emotional comprehension remained preserved. MRI showed two left sided cortical lesions involving a small portion of posterior insula and depth of the posterior parietal operculum (Fig. 1, upper right). Investigations for aetiological factors, including transoesophageal cardiac echography, remained negative.

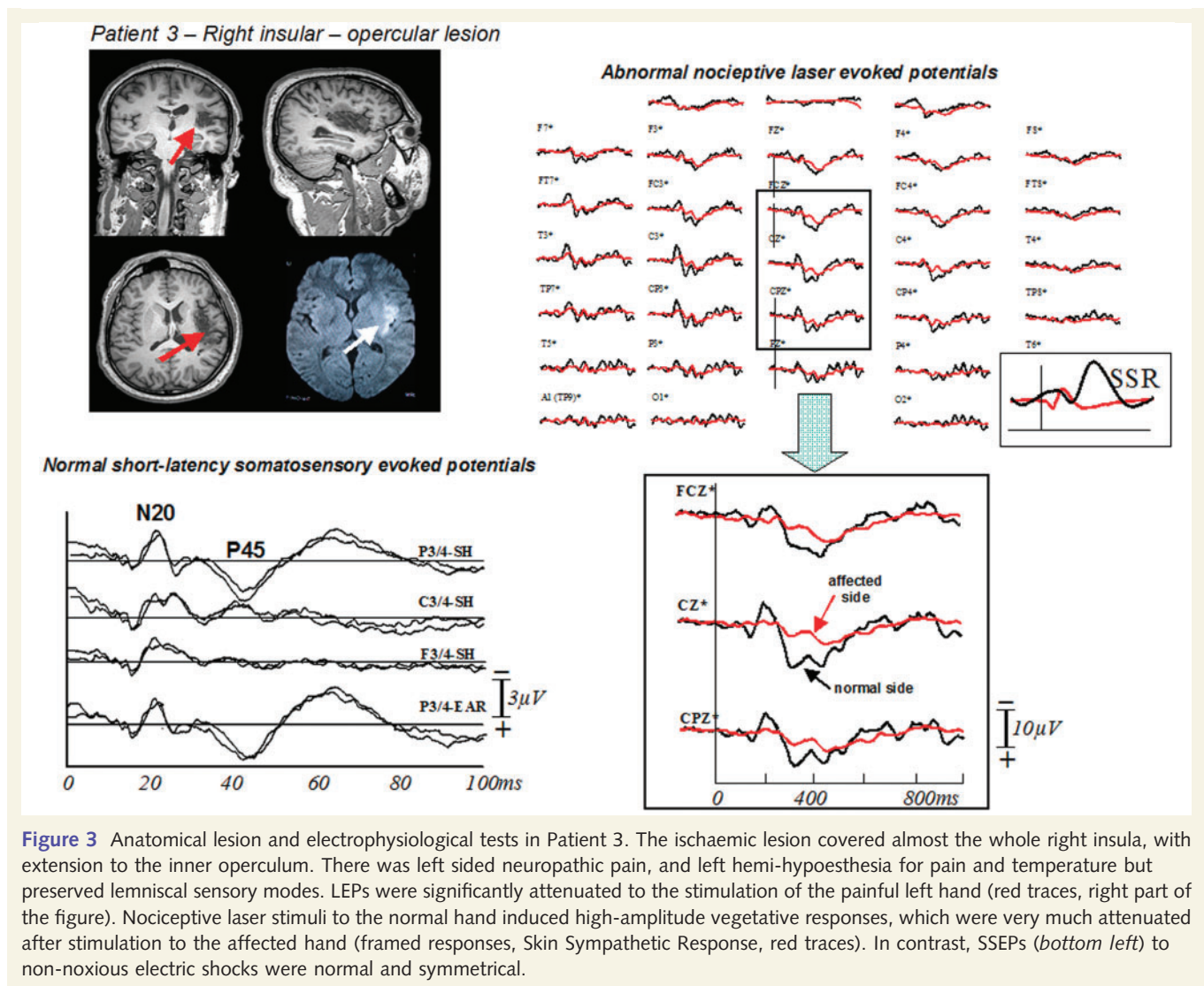
Quantitative sensory testing and evoked potentials showed evidence of selective sensory dysfunction of spinothalamic type on the right side. Thresholds for contact heat were increased in the right upper limb (pain at 48.5°C right, 44.7°C left), while cold stimuli yielded complex responses, combining hypaesthesia for 'coolness' (27°C) and severe allodynia to cold (9°C). Perception and pain thresholds to laser were severely impaired on the right body half (100% increased). LEPs were reduced (30%) and delayed (50 ms) after stimulation of the right hand. Conversely, tactile, vibration, graphesthesia, stereognosis and joint-position senses remained normal and symmetrical, as well as SSEPs to median nerve stimulation. Pharmacological treatment (tri- and tetracyclics, pregabalin, escitalopram) plus physiotherapy and psychotherapy allow 50% pain

relief to this day. She has developed painting skills, and painting with warm colours reduces her pain (Thomas-Anterion *et al.*, 2010).

Patient 3

A 35-year-old patient with a history of arterial hypertension and hypercholesterolemia developed a sudden episode of left-sided hemiplegia. On admission he was conscious and oriented, with central left facial paresis, slight motor deficit in the left upper and lower limbs, and possible motor neglect. No sensory deficit was noted at this time. Three months after discharge motor recovery was virtually complete, but the patient complained of distal deep aching pain on the left upper limb, burning pain in the left trunk and cooling sensation with summation hyperpathy and cold allodynia on the left side of the face. MRI (fluid-attenuated inversion-recovery, diffusion and T₂* sequences) revealed an ischaemic lesion involving the left posterior and mid-insula (Fig. 1 middle left and Fig. 3), with extension to the anterior-inferior parietal operculum.

Quantitative sensory testing demonstrated thermal and pain sensory loss with preserved lemniscal function in the left body side. Perception and pain thresholds for heat laser pulses were significantly elevated on the left arm, leg and face. Low-intensity/high-surface laser pulses elicited warm sensations in the right side, and no sensation at all in the left side. Laser energies producing pricking pain in the right side evoked only a blunted sensation in the left side of the



body, and did not trigger significant vegetative skin responses (Fig. 3). LEPs to stimulation of the painful territories were delayed and depressed (+44 ms, –36%, Fig. 3), with strong attenuation of the opercular-insular response over the right perisylvian region. Tactile thresholds (von Frey) were normal and symmetrical, as were vibration sense, joint position sense, graphesthesia and stereognosis. SSEPs were also normal and symmetrical, in particular the activation of primary somatosensory areas to upper or lower limb stimuli. Pregabalin up to 600 mg/day had minimal effect on pain. A trial with intravenous tricyclic antidepressants yielded some supplementary analgesia, but 18 months after stroke the main complaint of the patient was still severe pain. The patient is currently scheduled as a possible candidate for cortical stimulation of the motor cortex following therapeutic trials with high-frequency repetitive transcranial magnetic stimulation.

Patient 4

A 52-year-old female presented with sudden headache, left-sided hemiplegia, hemi-hypoesthesia and alteration of consciousness

secondary to a ruptured middle cerebral artery aneurysm. Clipping of the aneurysm resulted in rapid restoration of consciousness, and motor status improved under rehabilitation during the following months. Two years after the stroke she had a moderately spastic gait with hyper-reflexia and slight motor deficit in the left lower limb (4/5), and no clinical motor deficit in the upper extremity. Thermal sensory loss, on the contrary, persisted after operation, and the patient developed increasing pain in the left side of the body. Two years after the stroke the pain persisted, reported by the patient as a continuous burning over the left side of the trunk and the left hand, less intense over the left face and foot. There was also occasional dynamic mechanical allodynia over the trunk and left upper limb. MRI showed a lesion involving more than two-thirds of the right insula, extending posteriorly to the lower parietal lobe and subcortically to the internal capsule (Fig. 1, bottom left).

Sensory testing revealed significant dissociation between deeply altered thermal and pain sensation and preserved lemniscal sense in the left side of the body. Pain and temperature thresholds to laser pulses were significantly increased over the left upper limb

(perception +80%, laser pain threshold not obtained over the left hand). LEPs were normal to right hand stimulation, absent to stimulation of the painful left hand. Tactile thresholds were slightly elevated in hands (2.5 g/mm²) but symmetrical, and no errors were detected in joint position sense, graphesthesia or vibration sense. SSEPs to upper limb stimulation were normal and symmetrical, including the cortical components N20-P25 from primary sensory areas. Pain resisted to common analgesic and anti-neuropathic drugs at full doses, including paracetamol, tri- or tetracyclic anti-depressants, anti-epileptic drugs and baclofen, alone or in combination. High-dose intravenous clomipramine provided satisfactory but transient analgesia. Repetitive transcranial magnetic stimulation of the motor cortex was partially helpful (30% pain relief) without significant side effects. The patient was considered a suitable candidate for implanted motor cortex stimulation, performed in November 2009 with excellent results (>80% pain relief) at 6 months follow-up.

Patient 5

This 59-year-old male, heavy smoker, presented in January 2005 with left-sided sensory loss starting around the left mouth area, then progressing within 24 h to the left side of the head, left upper and lower limbs. On admission he was oriented in time and space and had pure left hypaesthesia to all modalities tested in the emergency room (pinprick, pain, joint position), with sensory ataxia but no motor signs. Twenty-four hours later, tactile, vibration and joint position senses were normal and the sensory ataxia had disappeared, while dysesthesiae and isolated deficit of pinprick and thermal sensation was persisting on left upper and lower limbs. Sensory symptoms improved in the following days and the patient was discharged on oral anti-aggregant therapy. T₂-weighted MRI confirmed an ischaemic lesion in the middle cerebral artery territory involving the right posterior insula and right parietal operculum (Fig. 1, bottom right).

On sensory examination 2 months after stroke, all subjective symptoms had resolved, the patient reported no pain, unpleasant dysesthesiae had disappeared and no allodynia or hyperalgesia were obtained. Perceptive and pain thermal thresholds to laser pulses were symmetrical and within normal limits; however, the typical after-sensation following repeated laser pulses to the right hand was absent on the left side. Nociceptive LEPs, and especially the opercular-insular responses, were significantly attenuated and delayed (50 ms, –45%) to stimulation of the left upper limb. Also, stimuli to the normal (right) hand evoked spontaneously a late component (P3) indicating attentional drive, which was absent to stimulation of the left hand. Tactile thresholds were symmetrical, and no errors were detected in vibration, joint position, graphesthesia or stereognosis.

Discussion

The insular cortex is involved in almost half of non-lacunar ischaemic middle cerebral artery strokes (Fink *et al.*, 2005), but its restricted involvement without participation of other areas is exceptional. Cereda *et al.* (2002) identified four such patients

out of 4800 consecutive strokes (0.08%), and a slightly higher frequency (0.4%) was reported for subinsular infarcts (linear lesions parallel to, but not implicating the insular cortex) (Kumral *et al.*, 2004). Although the extension of the lesion varied in our patients, the common region concerned in all (and exclusively affected in two) was the posterior insula and the innermost parietal operculum (Figs 1 and 4). In all, the common sensory deficit was dissociated sensory loss, with preservation of basic lemniscal modalities (discriminative touch, joint position sense, stereognosis and graphaesthesia) but profound alteration of thermal and pain thresholds, assessed by both quantitative sensory testing and evoked potentials. Four patients developed central pain that was highly refractory to common pharmacological treatments (but responded to motor cortex stimulation in two), and the remaining one had unpleasant dysesthesiae contralateral to the lesion, which eventually resolved. (The remaining patient declared abnormal positive sensory signs interpreted as dysesthesiae, but not clear pain. Misinterpretation of subjective signs due to poorly mastered French language cannot be excluded in this patient, who was the only one in whom the lesion extended beyond the medial part of the parietal operculum. We may speculate whether extension of the lesion toward lateral parietal networks not involved in pain processing may have ‘protected’ the patient from a full pain syndrome.)

Dissociated sensory loss with neuropathic pain is well recognized in spinal and brainstem syndromes. Central pain has been estimated to develop in 34–42% cases of spinal injury (Siddall and Finnerup, 2006), 37–67% in syringomyelia/syringobulbia (Milhorat *et al.*, 1996; Ducreux *et al.*, 2006) and 27–50% in

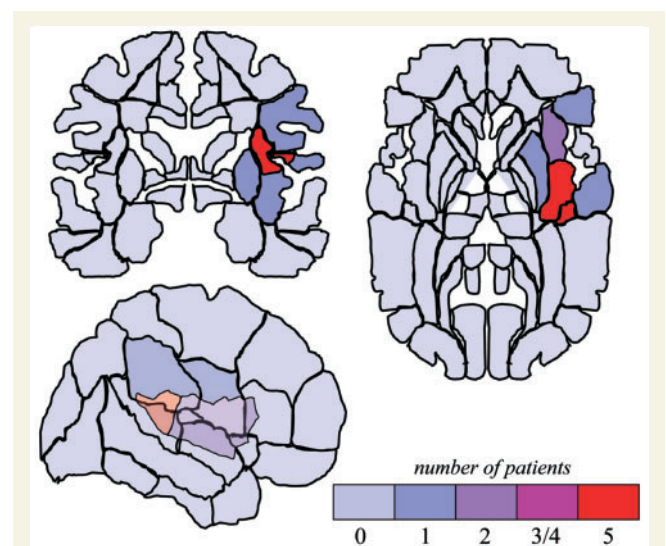


Figure 4 Schematic drawing summarizing the areas concerned by the lesions and the number of patients with lesions in each area. All lesions are displayed in the right hemisphere. Only the posterior insula and medial parietal operculum were systematically affected in all patients (indicated in red). The anterior insula was also involved in two patients (Patients 3 and 4), the lateral operculum in one (Patient 5) and the lower parietal and frontal lobes in one patient (Patient 4).

Wallenberg syndrome (Ruel *et al.*, 1992; MacGowan *et al.*, 1997), and in each case isolated or predominant spinothalamic sensory loss is the rule. Such a combination of neuropathic pain and dissociated sensory loss is rare in cortical injury (Bowsher, 1996a), and has not been recognized as a distinct neuropathic pain syndrome (e.g. reviews in Dworkin *et al.*, 2003; Boivie, 2006; Costigan *et al.*, 2009). Yet, a number of reports, the earliest of which might be traced to Dejerine and Mouzon (1915), have driven attention to the presence of isolated spinothalamic deficits, with or without pain, following focal cortical stroke. More recent studies have described patients with focal lesions inducing exclusively or predominantly pain/temperature sensory deficits (Biemond, 1956; Obrador *et al.*, 1957; Greenspan *et al.*, 1992, 1999; Schmähmann and Leifer, 1992; Bassetti *et al.*, 1993; Horiuchi *et al.*, 1996; Bowsher, 2006; Kim, 2007). All these reports concerned damage to the posterior insula and inner operculum. Conversely, lesions to the lateral parietal operculum gave rise to a cheiro-oral syndrome with preserved pain-temperature sensation or global hypesthesia (Bogousslavsky *et al.*, 1991; Bowsher *et al.*, 2004), and lesions putatively disconnecting the anterior from the posterior insula were reported to dampen emotional reactions to pain, while allowing 'adequate recognition of painful stimuli' (Berthier *et al.*, 1988). Lesions concerning exclusively the anterior insula were never associated with pain or temperature deficits in the detailed study of Greenspan *et al.* (1999), while such deficits prevailed in patients with posterior parasyllian lesions, including one individual with full recovery of tactile and nociceptive hypaesthesia after removal of a tumour compressing this region (Greenspan *et al.*, 1992). Such relative specificity of the posterior parasyllian region for pain is consistent with physiological studies showing large evoked responses to nociceptive laser stimuli in these sectors (Lenz *et al.*, 1998; Frot and Mauguière, 1999; Garcia-Larrea *et al.*, 2003), as well as with intracranial stimulation studies, in which subjective noxious responses were obtained mainly by stimulation of mid- and posterior sectors of the insula and inner operculum (Ostrowsky *et al.*, 2002; Mazzola *et al.*, 2006).

Even though the original description of the 'syndrome pseudo-thalamique' did not include painful symptoms (Foix *et al.*, 1927), the pain syndrome associated to opercular-insular lesions has commonly been termed 'pseudothalamic' (Masson *et al.*, 1991; Schmähmann and Leifer, 1992; Bassetti *et al.*, 1993; Cereda *et al.*, 2002; Takeda, 2004; Fisher, 2008; review Boivie, 2006). We do not believe the term 'pseudothalamic' is appropriate, since most patients with genuine thalamic pain do not exhibit dissociated thermoalgesic sensory loss, which both in this study and previous literature is the key feature of pain from parasyllian lesions. The original description of 'thalamic syndrome' included disturbance of both superficial and deep sensitivities (Dejerine and Roussy, 1906), and published series of thalamic pain have reported combined, rather than dissociated sensory loss in a majority of patients. Thus, retrospective analyses of thalamic lesions have identified an equal incidence of lemniscal and extra-lemniscal deficits (Nasreddine and Saver, 1997; Kim, 2001), and in patients with thalamic pain who underwent lemniscal and nociceptive evoked potentials, combined alteration of spinothalamic and lemniscal projections was the rule (Yamamoto *et al.*, 1995; Montes

et al., 2005). Large series that specifically analysed lemniscal and extralemniscal modalities in thalamic pain syndromes are not legion, but converge in reporting a majority of cases with combined sensory deficits. Schott *et al.* (1986) studied 35 patients with thalamic pain, of whom five (14%) had decreased thermal sensation with preserved proprioception. In Bogousslavsky *et al.* (1988), 5/18 cases with geniculostriate occlusion had a selective tactile and temperature deficit, and none of the patients who developed thalamic pain had dissociated symptoms (p. 843). Mauguière and Desmedt (1988) and Graff-Radford *et al.* (1985) identified 26 and 25% of thalamic lesions causing pain and dissociated sensory loss, respectively, with spared proprioception and SSEPs. In thalamic 'painful pure sensory stroke', the proportion of dissociated spinothalamic symptoms ranges from 8% (Kim, 1992) to 25% (Paciaroni and Bogousslavsky, 1998; Shintani, 1998). In our own unpublished series, only 3/23 patients with thalamic pain had dissociated spinothalamic deficits. Thus, although thalamic pain may show 'all the forms of sensory dissociation' (Garcin, 1968), most thalamic patients present with non-dissociated symptoms. This contrasts sharply with central pain resulting from opercular-insular lesions, where virtually 100% of cases reported had dissociated (isolated or clearly predominant) thermoalgesic sensory loss (Biemond, 1956; Obrador, 1957; Schmähmann and Leifer, 1992; Bowsher *et al.*, 2004; Bowsher, 2006; Kim, 2007). In his review on primates' insular functions, Augustine (1996) stated that the insula has a role in 'pseudothalamic' pain syndrome, and this was further underscored in a recent survey of cortical sensory dysfunction, where the involvement of insular and opercular areas was recognized as 'related to primitive (pain / temperature) sensory loss, and development of central pain' (Kim, 2007). The reason for the different sensory patterns in thalamic and operculo-insular syndromes is anatomical: spinothalamic and lemniscal pathways run separately in the spinal cord and brainstem up to the thalamus, where they largely converge in the ventral posterior nuclei (reviews Willis and Westlund, 1997; Jones, 2002). Although lemniscal and spinothalamic receiving neurons may remain distinct on micro-anatomical and histochemical grounds (review Steriade *et al.*, 1997), most lesions, even lacunar, within the ventral posterior complex are likely to affect both simultaneously. Thalamo-cortical afferents break up again in their respective projections to the cortex, as lemniscal axons mostly project to SI while pain-temperature afferents target predominantly the granular posterior insular areas (Dum *et al.*, 2009). It is therefore not surprising that the sensory pattern of posterior parasyllian lesions be reminiscent of subcortical lesions causing pain, such as lateral brainstem syndromes, where dissociated sensory loss is also the rule. Of notice, the abnormalities of nociceptive flexion reflexes in Patient 1 were identical to those previously described in specific lesions of the spinothalamic system such as Wallenberg syndrome or anterolateral cordotomy (Garcia-Larrea *et al.*, 1993). All these elements indicate that the term 'pseudo-thalamic' is inappropriate to describe central pain from operculo-insular lesions. Our data and previous literature suggest that the latter constitutes a recognizable syndrome that can be identified unambiguously on the basis of clinical, radiological and electrophysiological results, and which deserves the distinct label of 'parasyllian' or 'operculo-insular' pain.

The development of central pain in patients with parasyllian lesions is not constant; a survey of the literature indicates that roughly half of well-documented cases with restricted operculo-insular stroke developed central pain (Biemond, 1956; Schmahmann and Leifer 1992; Bassetti *et al.*, 1993; Horiuchi *et al.*, 1996; Greenspan *et al.*, 1999; Cereda *et al.*, 2002; Bowsher *et al.*, 2004, 2006; Kim, 2007). Also in spinal and sub-cortical lesions the development of central pain is variable and ranges from 20 to 70% (Boivie, 2006). The fact that all of our patients but one had central refractory pain, and the remaining one had transient painful dysesthesiae, probably reflects a recruitment bias of patients addressed to a neurologic pain clinic (as was the case in Schmahmann and Leifer, 1992). On the other hand, the absence of central pain in other studies may also be biased because of lack of follow-up, as central neuropathic pain does not develop immediately, but most commonly during the months following the ictus (Andersen *et al.*, 1995; reviews in Dworkin *et al.*, 2003; Boivie, 2006; Klit *et al.*, 2009). Thus, in the most comprehensive prospective study to date, 63% of patients developed pain within 1 month after stroke, and only 19% more than 6 months following the ictus (Andersen *et al.*, 1995), although central post-stroke pain may occur up to 3 years after stroke (Leijon *et al.*, 1989).

Deafferentation from thalamic input has been suggested as a putative pain mechanism since a number of the reported parasyllian strokes involved the underlying white matter (Biemond, 1956; Obrador *et al.*, 1957; Schmahmann and Leifer, 1992; see also case number 25 of Shintani, 1998). However, subinsular infarcts affecting exclusively the white matter do not typically cause pain (Wong *et al.*, 2001; Kumral *et al.*, 2004), whereas patients have been described with central pain and posterior insular lesions without white matter involvement (Cereda *et al.*, 2002; Bowsher, 2006). Bowsher *et al.* (2004, 2006) stressed that patients with opercular-insular lesions and pain had greater deficits for sharpness, temperature, mechanical pain and noxious heat sensations than those without pain. This was the case in our patients, as the patient showing only transient pain (Patient 5) also had minimal thermoalgesic deficits. The importance of thermal sensation deficits in central pain is the basis for the hypothesis that lesions of spinothalamic pathways, including their cortical projections, are necessary (although not sufficient) for central pain development (Beric *et al.*, 1988; Boivie *et al.*, 1989, 2006; Defrin *et al.*, 2001; Finnerup *et al.*, 2003; Bowsher *et al.*, 2006). In the cortex, this necessary condition appears to be present only in lesions of the posterior operculo-insular cortex, which puts patients with such lesions at higher risk of developing a painful syndrome.

Conclusion

The insula is a region known to play a role in the representation of bodily states, and the region comprising the posterior insula and medial parietal operculum constitutes a functional area containing networks devoted to pain processing. Insular pain networks, although intermingled with others subserving different functional modalities (Augustine, 1996; Isnard *et al.*, 2004), might form what can be conceived as a third somatosensory area, supporting

the particular attribute of the somatic sensation we call 'pain'. Stimulation of these networks causes acute painful symptoms, while their lesion entails dissociated sensory loss, and is associated with a higher probability of chronic central pain. This pain syndrome differs from genuine thalamic pain and is rather similar to subcortical (brainstem) central pain syndromes. The labels 'parasyllian pain' or 'operculo-insular pain' appear appropriate to define this entity. Pain from operculo-insular lesions may be extremely difficult to treat; the magnitude of sensory disturbances for pain and temperature may be prognostic for its development (Bowsher *et al.*, 2004, 2006), hence the importance of early sensory assessment with quantitative physiological methods. Early detection of patients at risk may allow early treatment, which has shown promising results in cutting down the intensity of other forms of neuropathic pain.

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