

## Clinical note

# Thalamic thermo-algesic transmission: ventral posterior (VP) complex versus VMpo in the light of a thalamic infarct with central pain

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## Abstract

The respective roles of the ventral posterior complex (VP) and of the more recently described VMpo (posterior part of the ventral medial nucleus) as thalamic relays for pain and temperature pathways have recently been the subject of controversy. Data we obtained in one patient after a limited left thalamic infarct bring some new insights into this debate. This patient presented sudden right-sided hypesthesia for both lemniscal (touch, vibration, joint position) and spinothalamic (pain and temperature) modalities. He subsequently developed right-sided central pain with allodynia. Projection of 3D magnetic resonance images onto a human thalamic atlas revealed a lesion involving the anterior two thirds of the ventral posterior lateral nucleus (VPL) and, to a lesser extent, the ventral posterior medial (VPM) and inferior (VPI) nuclei. Conversely, the lesion did not extend posterior and ventral enough to concern the putative location of the spinothalamic-afferented nucleus VMpo. Neurophysiological studies showed a marked reduction (67%) of cortical responses depending on dorsal column-lemniscal transmission, while spinothalamic-specific, CO<sub>2</sub>-laser induced cortical responses were only moderately attenuated (33%). Our results show that the VP is definitely involved in thermo-algesic transmission in man, and that its selective lesion can lead to central pain. However, results also suggest that much of the spino-thalamo-cortical volley elicited by painful heat stimuli does not transit through VP, supporting the hypothesis that a non-VP locus lying more posteriorly in the human thalamus is important for thermo-algesic transmission.

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## 1. Introduction

Neural lesions causing pain primarily involve the nociceptive and temperature pathways (Boivie, 2003; Boivie et al., 1989; Bowsher, 1996). It is therefore logical to consider that thalamic lesions entailing painful symptoms should concern, at least partially, the thalamic relays of nociceptive pathways. In humans, thalamic nociceptive regions were first characterised on the basis of symptoms

associated with clinical lesions, notably loss of pain and temperature sensation (Dejerine and Roussy, 1906; Garcin and Lapresle, 1954; Head and Holmes, 1911; Schuster, 1937), and later by neuroanatomical studies following spinothalamic tract (STT) transection (Mehler, 1962, 1966). In animals, characterisation of thalamic nuclei involved in nociceptive processing has been derived from numerous anatomical and electrophysiological studies (see Lenz and Dougherty, 1997; Willis and Westlund, 1997). Both lateral and medial thalamic regions have been identified in monkeys and humans as receiving STT terminations, the most important direct projections ending up in the ventral posterior complex (VP) (Apkarian and Hodge, 1989; Boivie, 1979; Jones, 1985; Mehler, 1962, 1966; Ralston

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and Ralston, 1992; Willis, 1985; Willis et al., 2001). Microstimulation and recording experiments too have supported a role of VP in pain and temperature sensation, both in monkeys (Apkarian and Shi, 1994; Bushnell et al., 1993; Casey and Morrow, 1983; Kenshalo et al., 1980) and in humans (Lee et al., 1999; Lenz et al., 1993a,b; Ohara and Lenz, 2003). On the basis of such evidences, the VP has been widely considered as the critical thalamic region for the sensory-discriminative processing of pain (Jones, 1985, 2002; Willis and Westlund, 1997).

In contrast with this view, Craig et al. (1994) have suggested a different region, clearly outside the VP limits, as a specific relay for pain and temperature. After injections of tracers in layer I of the monkey dorsal horn, these authors described labelled terminals in a region lying posterior and inferior to VP, which they named 'posterior portion of the ventral medial nucleus' (VMpo). Anatomical and electrophysiological considerations incited them to definitively consider the VMpo as the dedicated spinothalamic relay for pain and temperature sensation in humans (Blomqvist et al., 1996, 2000; Craig, 2000, 2002, 2003a,b; Craig and Blomqvist, 2002; Craig et al., 2002), and to propose that lesions to the VMpo would be the neural substrate for thalamic pain syndromes (Craig, 2003a). Such diverging views have originated a vivid controversy as to the respective contribution of VMpo and VP to the transmission of nociceptive inputs (Craig and Blomqvist, 2002; Graziano and Jones, 2004; Jones, 2002; Jones et al., 2001; Price and Verne, 2002; Ralston, 2003; Treede, 2002; Willis, 1995; Willis et al., 2001, 2002a,b).

Data obtained in one patient with pain following a discrete thalamic lesion bring new insights to this debate. Combined clinical, neuroanatomical and neurophysiological results show that VP is undoubtedly relevant for pain and temperature transmission in man, and that its lesion can lead to typical thalamic pain. However, results also demonstrate that, contrary to the lemniscal system, much of the nociceptive information conveyed by the STT may not transit through VP, supporting the presence of an extra-VP locus involved in thermo-algesic transduction.

## 2. Patient and methods

### 2.1. Case report

In January 2001, a 51 year-old man developed sudden right-sided paresthesiae with upper limb predominance, weakness of right lower limb and multiple modal sensory loss, including marked thermalgesic hypesthesia, due to a left thalamic infarct. He had a previous history of diabetes, hypertension, hypercholesterolemia and smoking, in addition to a familiar history of stroke. Over the next months, he developed a severe thalamic syndrome, the dominant feature of which was pain over the right side of the body, including the face. After several months of inefficacious pharmacological therapy (see details below), he was referred to the multidisciplinary pain unit in Lyon.

During the months that followed stroke, the patient developed neuropathic pain in the right side of the body. One year after the stroke, pain had a continuous burning component with 'stab' paroxysms, was exacerbated by warm temperatures, and provoked frequent awakenings from night sleep. Pain was rated 8/10 on a visual analogue scale (VAS).

Bedside sensory examination included assessment of (a) thresholds for cotton brush, pinprick and blunt pressure; (b) joint position sense (blind imitation of contralateral finger and toe movements, and blind search of the contralateral extremity); (c) graphaesthesia, (recognition of figures drawn on the hand palm and the forearm); (d) vibration sense (100 Hz tune fork); (e) stereognosis (blind recognition of familiar objects put into the hand), and (f) heat and cold sensory and pain thresholds (30 × 30 mm<sup>2</sup> thermode Medoc® and graded laser stimuli). Examination revealed multi-modal hypaesthesia in the right side of the body, including elevated thresholds for perception of tactile stimuli, deficits in joint position sense with some degree of sensory ataxia, loss of graphaesthesia, deficits in stereognosis, and altered two-point discrimination. Pain and temperature sensations were also decreased, with right-sided severe hypaesthesia for cold (threshold lower than 15 °C) and hot stimuli (pain sensation not obtained with stimuli up to 50 °C on upper and lower limbs). There were many errors when trying to distinguish pinprick from blunt touch, and significantly increased pain thresholds for electrical and thermal (laser and thermode) stimuli (see also Results). There was mechanical static and dynamic allodynia over the right lower limb (light brush, and Von Frey hair, calibre 6.65), but no summation hyperpathia. Contact with cold objects was often felt as unpleasant burning. The patient also described some loss of smell and taste (partial ageusia), which he considered being maximal on the right side, but this latter symptom had partially subsided by the time of the electrophysiological testing. There was no muscle weakness and no muscle atrophy; motor symptoms consisted in some difficulty for fine fingers movements and intentional tremor of the right hand.

Background pain, and notably paroxysms, were initially controlled with carbamazepine, but reappeared rapidly. Gabapentine, lamotrigine, clomipramine, paracetamol-codeine, bromazepam, amitriptyline and oxcarbazepine were subsequently used in various combinations, without success. Intravenous tests with morphine, ketamine or placebo were negative. In particular, i.v. ketamine at 0.20 mg/kg provoked somnolence and increased the burning background sensations. After multidisciplinary discussion and failure of pharmacological trials, the patient was scheduled for inclusion in a motor cortex stimulation (MCS) program.

### 2.2. Neuroimaging investigations

MRI showed a well localised left thalamic infarct with no evidence of other focal brain lesions, notably in the brainstem. In order to superimpose the T1-weighted magnetic resonance (MR) images obtained in 3D mode and the corresponding stereotactic atlas planes of the human thalamus (Morel et al., 1997), MR coronal images (slice thickness: 1 mm) were cut orthogonal to the anteroposterior commissure (AC-PC) horizontal plane using MRIcro software (Rorden and Brett, 2000). The slice passing through PC was taken as the reference to calculate the anteroposterior coordinates of the other slices. Scales of MR images and atlas sections were then adjusted, and MR images

superimposed to their corresponding atlas sections. The best fit between the two was ensured in the posteroanterior dimension by superimposing the PC levels and in the mediolateral axis aligning the medial borders of the thalamus. Thus, anatomical relations between the ischaemic lesion and the different thalamic nuclei

could be established. A similar procedure was done in the horizontal plane to countercheck the results obtained in the coronal plane.

As the VMpo nucleus is not featured in the Morel et al. (1997) atlas, its stereotactic location was obtained from the very detailed

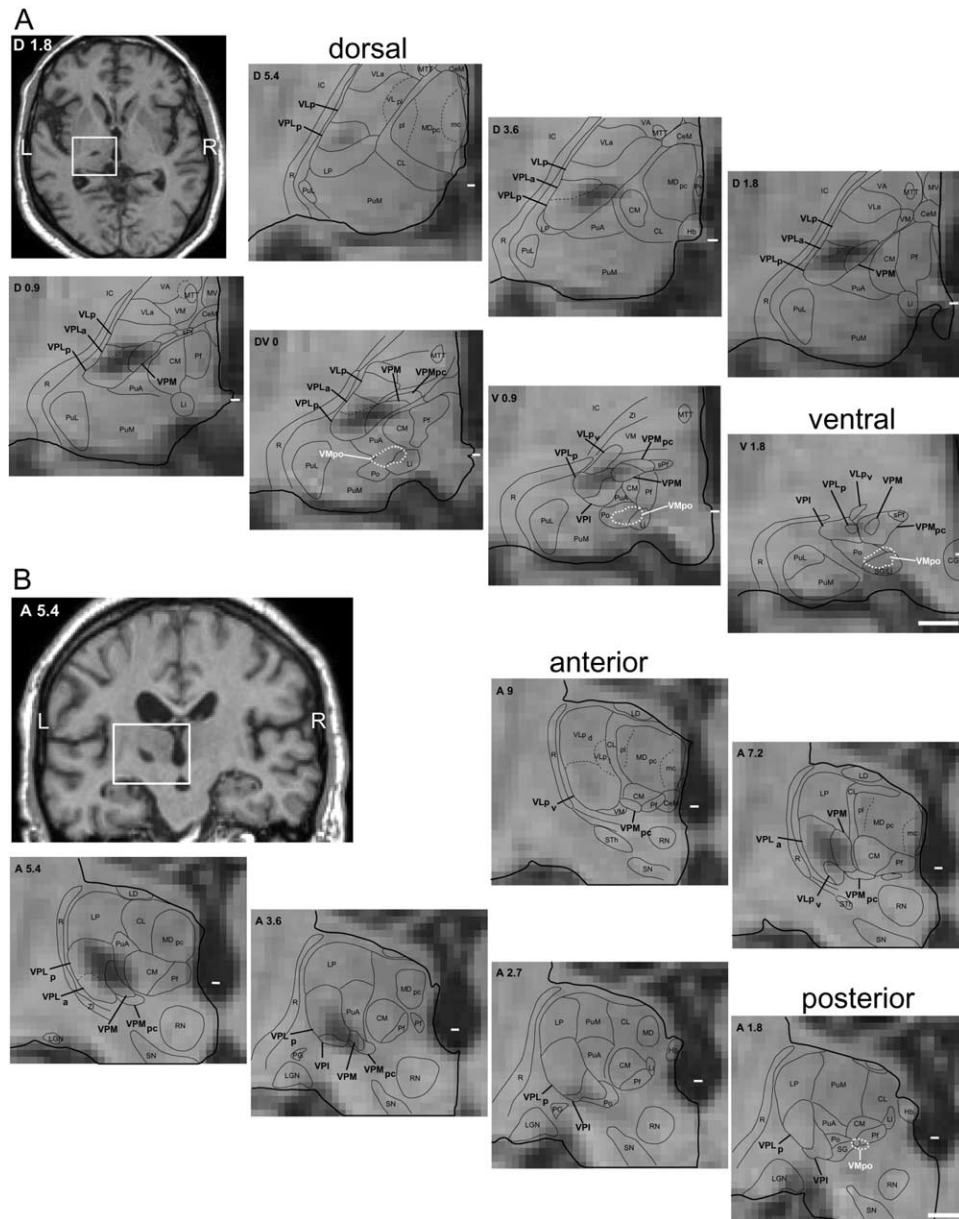


Fig. 1. MRI-to-atlas projections allowing the localization of the thalamic lesion on horizontal (A) and coronal (B) planes. This lesion involves the two anterior thirds of the VP (including VPL, VPM and VPI) and the entire ventrodorsal extent of this complex. Additional but very limited damage involves the VPMpc (horizontal plate V 1.8; coronal plate A 3.6) and the most posterior extent of the VLP explaining the partial ageusia and the motor symptoms. No lesions were found elsewhere in the brain of this patient. VMpo location and limits which are not featured in the Morel et al. (1997) atlas are extrapolated from figures 2 and 4 in Blomqvist et al. (2000). Stereotactic coronal plane A 2.7: unpublished material, by courtesy of A. Morel. White bar in each panel indicates the level of the vertical or horizontal plane passing through the posterior commissure. L and R: left and right hemispheres, respectively. Scale bar, 5 mm. CeM, central medial nucleus; CG, central gray; CL, central lateral nucleus; CM, centre median nucleus; Hb, habenula; IC, internal capsule; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; Li, limitans nucleus; LP, lateral posterior nucleus; MD, mediodorsal nucleus (pl, paralamellar; pc, parvocellular; mc, magnocellular divisions); MTT, mamillothalamic tract; MV, medioventral nucleus; Pf, parafascicular nucleus; PG, pregeniculate nucleus; Po, posterior nucleus; Pu, pulvinar (A, anterior; L, lateral; M, medial divisions); R, reticular thalamic nucleus; RN, red nucleus; SG, supragenicular nucleus; SN, substantia nigra; sPf, subparafascicular nucleus; STh, subthalamic nucleus; VA, ventral anterior nucleus; VLA, ventral lateral anterior nucleus; VLP, ventral lateral posterior nucleus (d, dorsal; l, paralamellar; v, ventral divisions); VM, ventral medial nucleus (po, posterior division); VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus (p, posterior; a, anterior divisions); VPM, ventral posterior medial nucleus (pc, parvocellular division); ZI, zona incerta.

description and illustrations available in Blomqvist et al. (2000). Based on horizontal sections in their Fig. 4, drawings A and B exhibiting the PC appeared to be located 300  $\mu\text{m}$  dorsal and ventral to the stereotactic plane DV 0 of the Morel et al. (1997) atlas, respectively. In the coronal plane, drawing B of Fig. 2 in Blomqvist et al. (2000) corresponded to plane AP 0 of the Morel et al. (1997) atlas. Considering these relationships, VMpo was featured on Morel et al. (1997) atlas stereotactic planes taking into account the tridimensional coordinates of its limits measured on Blomqvist et al. (2000). The final anatomical location of the VMpo with respect to neighbouring nuclei was identical in Blomqvist et al. (2000) drawings and corresponding Morel et al. (1997) stereotactic atlas planes. Thus, the VMpo was posteromedial to the VPL and VPM nuclei, posteroventral to the centre médian and parafascicular nuclei and dorsal to the medial geniculate nucleus. It overlapped more or less with the posterior, the supragenicular and the limitans nuclei as classically defined.

### 2.3. Somatosensory electrical and laser-evoked potentials

Since responses to electrical non-noxious stimuli reflect the activation of the dorsal column-lemniscal system (Mauguière et al., 1995), while those to infrared laser stimulation reflect activation of the spinothalamic system (Plaghki and Mouraux, 2003; Treede et al., 2003), both types of stimuli were used in this patient to record, respectively somatosensory evoked potentials (SEPs) and laser-evoked potentials (LEPs).

SEPs were obtained using transcutaneous electrical stimulation of the median nerve at the wrist. Stimulus intensity was set at motor threshold for abductor pollicis brevis, plus perception threshold. This intensity yielded a clearly perceived but non-noxious

sensation distributed over the median sensory territory of the hand (Mauguière et al., 1995). Recordings were obtained from Erb's point (peripheral response), C6 spinous process (segmental spinal potential), and parietal and frontal scalp sites (brainstem and cortical potentials). A non-cephalic (shoulder) reference was used to record cortical and subcortical responses simultaneously (Mauguière and Desmedt, 1988; Mauguière et al., 1995). Responses were averaged *on line*, over a 65 ms analysis time, which included 5 ms pre-stimulus delay for baseline computation (Bio-Logic® EP system, Chicago, Illinois).

Laser-evoked potentials (LEPs) were obtained with a CO<sub>2</sub>-laser stimulator (Optilas® France) delivering infrared laser pulses of 10.6  $\mu\text{m}$  wavelength, beam diameter 3.5 mm and output power 10 W. Laser stimuli were applied to the dorsum of the hand (superficial branch of the radial nerve territory). The power output of the stimulator being fixed at 10 W, the amount of thermal energy delivered (in mJ) depended on the duration of the pulse (in ms). Thus, for a spot surface of about 10 mm<sup>2</sup>, 1 ms increase in pulse duration roughly equalled 1 mJ/mm<sup>2</sup> energy density. Pulses were delivered every  $8 \pm 3$  s. Thresholds for innocuous and painful sensations were first determined by the method of limits before recording LEPs. After estimation of psychophysical thresholds, the stimulus intensity used for LEP recording was set, for both sides, at 80 mJ/mm<sup>2</sup>, i.e. about 20% above the pain threshold in the normal side (see Plaghki and Mouraux, 2003; Treede et al., 2003). The mean subjective intensity perceived after each series of laser stimuli was rated on a scale going from 0 (no sensation) to 3–4 = pain threshold, 'pulling a hair', to 10 (worst imaginable pain). Thirty-two scalp electrodes positioned according to the 10–20 international extended system (Jasper, 1958; Klem et al., 1999), and referenced to the nose, were used for LEP recordings. The

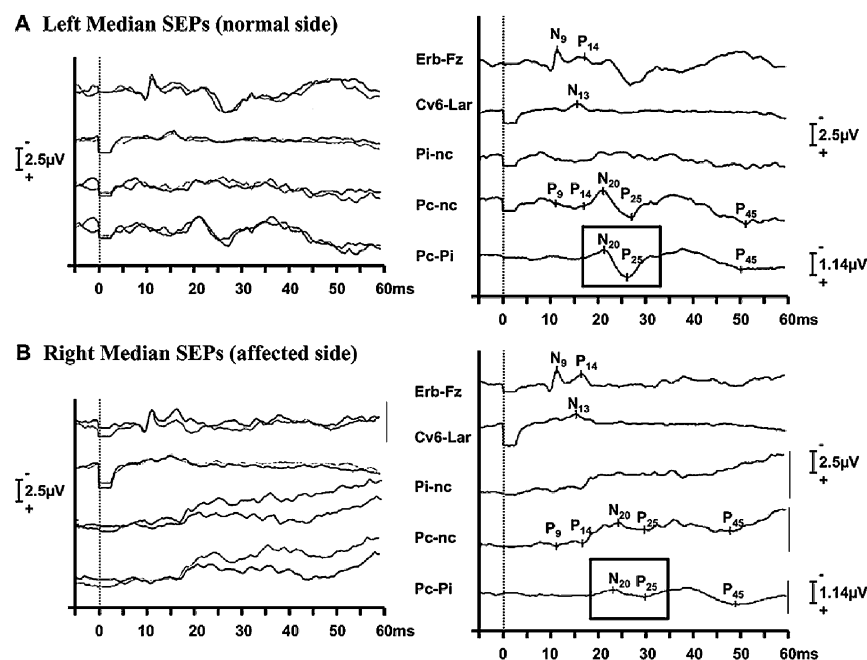


Fig. 2. Somatosensory potentials (SEPs) to activation of the dorsal columns-lemniscal system by 200  $\mu\text{s}$  electric shocks. Responses to stimulation of the normal side are shown in the upper frame; those to stimulation of the painful (right) side in the lower frame. In each case, the left column shows superimposition of two consecutive runs, and the right part their average. The cortical responses N20 and P25 were isolated from subcortical components by subtraction of ipsilateral from contralateral parietal leads (Pc–Pi), and are shown in the lowermost traces on the right (framed). Cortical responses N20–P25 (within frames) were very significantly delayed and attenuated (–67%) after stimulation of the right (painful) side, while peripheral (N9) and spinal (N13) responses were symmetrical. Note also slight attenuation of P14, probably due to retrograde degeneration of cuneate-thalamic axons.



continuous EEG (Ceegraph®; Bio-Logic Sys. Corp.) was segmented on line, averaged according to stimulation type, displayed and analysed using a BPM® System (Orgil Corp., Orgil Medical Equipment, En Ayalla, Israel). For eye movement artefact control, the electro-oculogram (EOG) was recorded from an infra-orbital electrode, also referenced to the nose. Evoked potentials were averaged *off line*, after visual inspection and segmentation of the EEG, baseline correction and artefact removal. After segmentation (epoching) of the EEG, single trials contaminated by blinks, eye movements, or any other signal exceeding  $\pm 50 \mu\text{V}$  were rejected previous to averaging, which was performed over 2 blocks of 30 stimulus repetitions each. Brain signals were averaged over 1000 ms using a band pass of 0.3–35 Hz, a gain of 30,000 and a sampling rate of 256 Hz. A 70 ms pre-stimulus delay was used for baseline computation.

LEPs were compared against normative data from the laboratory (Garcia-Larrea et al., 2002; Valeriani et al., 1996) and from published literature (Devos et al., 2000; Treede et al., 1988). Inter-side latency asymmetries were considered significant (mean + 2.5 SD) if exceeding 30 ms for N2 and 40 ms for P2. Amplitude drop of the vertex response was significant if it exceeded 30% of the normal side.

Grand-averaged LEPs from an unpublished series of 8 patients with a lateral medullary infarct (Wallenberg's syndrome) were used to illustrate differences in the LEP pattern of abnormalities as compared to the present case.

### 3. Results

#### 3.1. Anatomical localization of the lesion

Superposition of MR images and atlas planes (Morel et al., 1997) is shown in Fig. 1. The lesion was centred on the VP and involved the ventral posterior lateral (VPL), medial (VPM) and inferior (VPI) nuclei. It mostly concerned the anterior two thirds of the VPL. It also encroached, to a lesser extent, on the VPM and its parvocellular division (VPMpc). The posterior part of the ventral lateral nucleus (VLp), and the anterior part of the VPI were also somewhat involved by the most ventral anterior and posterior extent of the lesion, respectively. Conversely, the lesion spared the posterior thalamic nuclear group. In particular, the region that has been recently isolated as the VMpo nucleus (Beggs et al., 2003; Blomqvist et al., 1996, 2000; Craig, 2000, 2002, 2003a,b; Craig and Blomqvist, 2002; Craig et al., 2002) was far enough from the lesion limits to be considered as not affected by the infarct.

#### 3.2. Somatosensory evoked potentials (SEPs)

SEP results are shown in Fig. 2. Electrical stimulation of the median nerve at motor threshold was felt as a tingling, non painful sensation on either side, but much attenuated when applied to the right (affected) hand. Stimulation of the left (normal) side yielded values within normal limits at peripheral and central levels. In particular, the parietal cortical complex (N20–P25) peaked at 21.3 and 27.4 ms,

Table 1

Latencies of main components of median nerve somatosensory evoked potentials (SEPs) at peripheral (EP), spinal (N13), brain stem (P14) and cortical levels (N20, P25)

	EP	N13	P14	N20	P25
Right Median	11.4 ms	15.5 ms	16.6 ms	23.3 ms	30.0 ms (0.52 $\mu\text{V}$ )
Left Median	11.4 ms	15.5 ms	17.2 ms	21.3 ms	27.4 ms (1.59 $\mu\text{V}$ )

Amplitude in  $\mu\text{V}$  corresponds to the cortical complex N20–P25 peak-to-peak. EP, Erb's point.

respectively, (see Table 1). Stimulation of the right median nerve yielded peripheral and spinal components with latencies and amplitudes comparable to those obtained for the left side. P14 was slightly attenuated, probably due to retrograde degeneration of cuneate-thalamic projections (Restuccia et al., 1996). The cortical sensory responses N20 and P25 were significantly delayed (23.3 and 30 ms) and the N20–P25 amplitude reduced by 67% relatively to stimulation of the normal side (Table 1 and Fig. 2).

#### 3.3. Laser evoked potentials (LEPs)

The subjective pain intensity after each laser stimulus (on a verbal numerical scale) ranged from 1 to 3/10 on the left (normal) side, and 0 to 2/10 on the right (affected) side. Detection and pain thresholds to laser stimuli in the healthy side were 34 and 65 mJ, respectively, and increased significantly to 65 and 80 mJ when the affected (right) side was stimulated. The increase in both thresholds was significant according to our normative data.

Latency values of the N2/P2 cortical components of LEPs were, respectively, 260 and 410 ms after stimulation of the normal side, and were delayed to 340 and 450 ms when the affected (right) side was stimulated (Fig. 3, Table 2). The 80 ms delay of N2 was significant (see Methods), while the 40 ms delay of P2 was not. Amplitude of the N2/P2 complex was reduced from 12 to 8  $\mu\text{V}$  (33%) with respect to the normal side (Fig. 3). The early lateralised negativity of LEPs, which is the closest reflect of parietal opercular (SII) activation (Frot and Mauguière, 1999; Garcia-Larrea et al., 2003), was assessed using a bipolar montage between the midline frontal electrode (Fz) and the lateral temporal T3 and T4 electrodes (Treede et al., 2003; Valeriani et al., 1996). The results were comparable to those obtained with vertex responses, namely a significant delay of 65 ms after stimulation of the right (affected) side, with amplitude decreased by 40%. As shown in Fig. 3, the *ipsilateral* temporal negativity after stimulation of the healthy side (left) was greater than the contralateral negativity following stimulation of the affected side, which rules out the possibility that amplitude reduction of early lateralised responses are due to bad electrode contact.

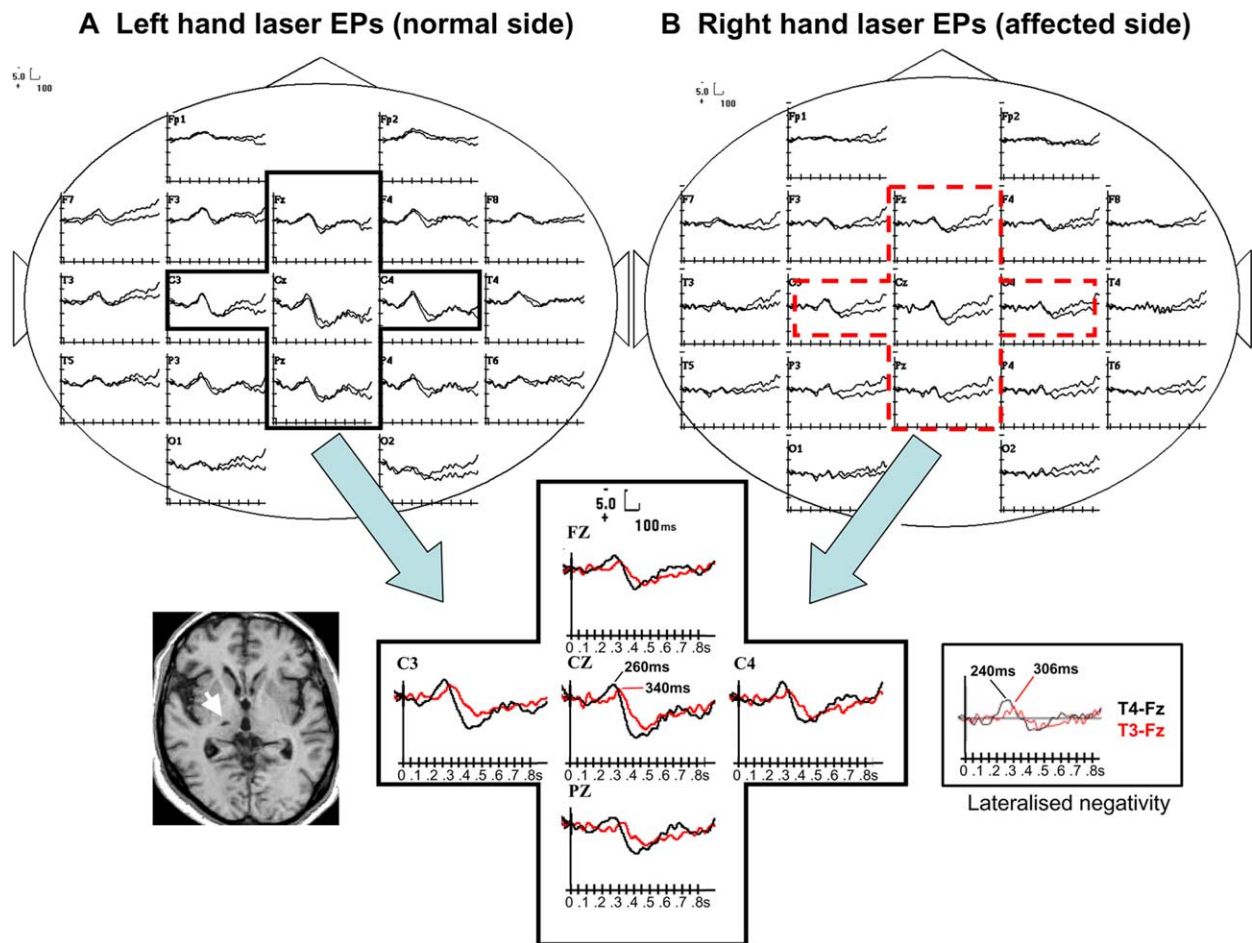


Fig. 3. Cortical responses to spinothalamic activation by CO<sub>2</sub>-laser pulses (LEPs). Upper part: LEPs recorded over 19 scalp sites, after stimulation of the left (normal) and right (painful) hands. Two consecutive recording runs of 30 stimuli each are superimposed to assess reproducibility. Measurements were performed on the average of the two (see text). Note that the *ipsilateral* temporal negativity after stimulation of the healthy side (left) was greater than the contralateral negativity following stimulation of the affected side, ruling out the possibility that amplitude reduction of early lateralised responses be due to bad electrode contact. The lower part of the figure shows superimposition of *right* vs *left* hand LEPs (averaged over 2 runs) recorded over the midline (Fz, Cz, Pz) and lateral (C3, C4) scalp sites, to illustrate latency delay (80 ms) and slight decrease of LEPs (–33%) to stimulation of the painful side. The inset at right bottom shows the lateralised early LEP negativity (‘N1’) obtained with bipolar montage (T3–Fz and T4–Fz) after stimulation of the healthy (black) and painful (red) hands. The early negativity was depressed by about 40%, and delayed by 65 ms after stimulation of the affected hand.

4. Discussion

The patient reported herein developed central pain contralateral to a focal thalamic lesion. Evoked potentials disclosed deficits in both dorsal column-medial lemniscus (SEPs) and spinothalamic (LEPs) responses. Modifications were, however, more important for non-noxious inputs than for the specific activation of noxious spinothalamic afferents.

Detailed anatomical study demonstrated a restricted infarct which included most of the VP but respected the posteromedial region of the thalamus—in particular the VMpo. The fact that thermo-algesic thresholds and nociceptive cortical responses were significantly affected by a lesion sparing this nucleus suggests that the VMpo is not the only thalamic structure that relays spinothalamic inputs to the cerebral cortex in man.

4.1. Neuroradiological localization of the thalamic infarct

Boundaries between thalamic nuclei being particularly difficult to observe on MRI images, we projected the lesion onto an outlook of such boundaries issued from a human thalamic atlas (Morel et al., 1997) (Fig. 1). The accuracy and appropriateness of this atlas to localize human thalamic regions has been acknowledged in previous works using a variety of validation procedures (Behrens et al., 2003;

Table 2  
Latencies and amplitudes of cortical laser evoked potentials (LEPs) to stimulation of the superficial radial territory

	N2	P2	N2/P2
Right Arm	340 ms	450 ms	8 μV
Left Arm	260 ms	410 ms	12 μV

Lateral medullary lesion  
(Wallenberg's syndrome)  
Averaged LEPs from 8 subjects

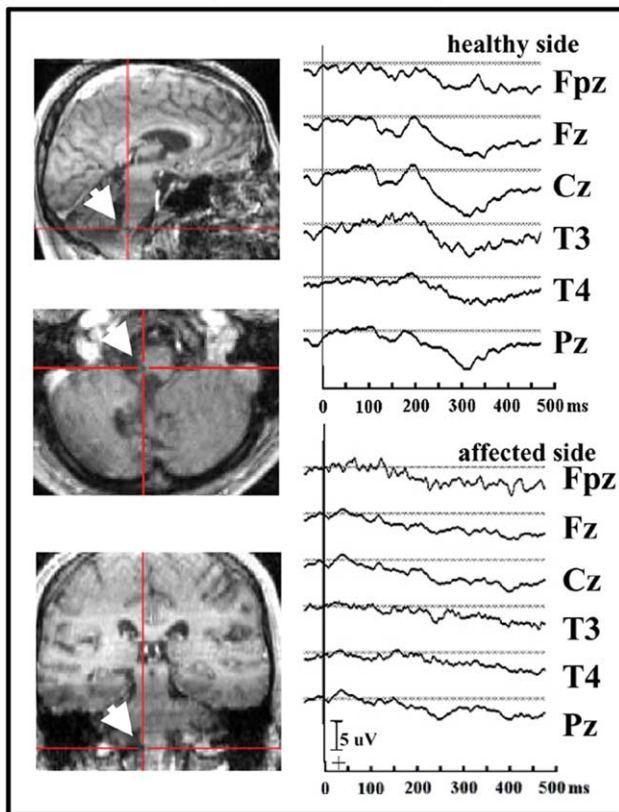


Fig. 4. LEPs in Wallenberg's syndrome. White arrows on MRI show the small lateral medullary infarct typically resulting in Wallenberg's syndrome. LEPs obtained from midline (frontal, central and parietal) and lateral temporal electrodes are shown in the upper and lower panels to stimulation of, respectively, the healthy and affected sides. In Wallenberg's syndrome, LEPs are virtually absent to stimulation of the affected side, contrasting with the results obtained in the lateral thalamic lesion.

Jeanmonod et al., 2001; Magnin et al., 2000, 2001; Niemann et al., 2000).

Correlations between the lesion localization and clinical signs also confirmed the accuracy of the thalamic projection onto this atlas. For instance, the lesion partially included the VLp (Fig. 1A, plates V0.9-D1.8; Fig. 1B, plate A7.2), a region heavily connected with both the cerebellum and motor-premotor cortices (Macchi, 1997; Rouiller et al., 1994, 1999). In accordance with this, the patient described motor difficulties for fine movements and a right hand tremor. Also, the VPMpc appeared to be partially included within the lesion (Fig. 1A, plate V0.9; Fig. 1B, plate A3.6). This small nucleus is considered to participate in gustatory and olfactory sensations (Lenz et al., 1997; Pritchard et al., 1986), and accordingly the patient described partial ageusia and anosmia.

According to the MRI-to-atlas projection, the infarct was localized in the territory of the thalamo-geniculate (infero-lateral) artery (Bogousslavsky et al., 1988; Percheron,

1973). This branch originating from the posterior cerebral artery supplies the ventral–lateral–posterior part of the thalamus, including the VLp, and, directly or through collaterals, the lateral thalamus and the VP. Conversely, the region where the VMpo has been located receives its vascular supply from the paramedian artery (originating from the basilar communicating artery), which irrigates a distinct area in the ventromedial thalamus (Macchi, 1997). Anatomical variations in small thalamic supply vessels are common, and definite correlations difficult to establish; yet, the impairment of the VP with preservation of the posterior nuclei group is consistent with the common thalamo-geniculate supply of this thalamic region.

#### 4.2. The VP as a spinothalamic relay in humans

Consistent with clinical examination of this patient, which disclosed hypesthesia to all sensory modes, neurophysiological deficits concerned inputs mediated by both the dorsal columns-medial lemniscus system (explored by electrical SEPs) and the spinothalamic tract (assessed by LEPs). The thalamic regions damaged by the infarct (mainly the VPL, VPI and VPM) appear therefore to be significantly involved in the transmission of the thermal and nociceptive inputs triggered by noxious laser pulses. This agrees with a bulk of data obtained in human and non-human primates. Indeed, terminal degeneration in VP was observed after lesions of the spinothalamic tract in humans and monkeys (Boivie, 1979; Mehler, 1962, 1966; Mehler et al., 1960). Also, injection of retrograde tracers in the VP, have demonstrated many retrogradely labelled neurons in both laminae I and V of the spinal dorsal horn, where the soma of most spinothalamic neurons is known to lie (Apkarian and Hodge, 1989; Willis et al., 1979, 2001). Finally, micro-stimulation of the VP has been able to provoke pain and thermal sensations in man (Lenz et al., 1993a; Ohara and Lenz, 2003). Some of these previous tracing and stimulation studies have been criticised because of possible spreading of the retrograde tracer or of electrical stimulus pulses outside the VP (Craig and Blomqvist, 2002). However, our results showing attenuated and delayed spinothalamic-mediated LEPs after a very restricted thalamic lesion of the VP, sparing other nuclei receiving spinal projections, indicate that selective damage to this structure can affect the spinothalamic transmission, and thus confirm the role of VP as a thermal nociceptive relay in the human thalamus.

#### 4.3. Arguments for a non-VP nociceptive relay

Evoked response changes in our patient were not of the same magnitude for LEPs and SEPs. Indeed, while responses to non-noxious stimuli were desynchronised, poorly reproducible over runs and attenuated by 67% (Fig. 2), LEPs to noxious laser pulses remained synchronised and were decreased by 33% only (Fig. 3). Although statistically significant, this moderate abnormality of LEPs



contrasts with what can be commonly seen in more caudal lesions of the spinothalamic tract. In spinal or brainstem STT lesions, LEPs after stimulation of the affected side are extremely decreased or abolished (Garcia-Larrea et al., 2002; Hansen et al., 1996; Kakigi et al., 1991; Treede et al., 1991, 2003). As shown in Fig. 4, STT lesions at the medullary level are also associated with highly altered and desynchronised LEPs which contrast sharply with the results in this thalamic lesion. The relatively moderate LEP abnormalities following noxious stimulations suggests that the VP, although involved in nociceptive transmission, is definitely not the only relay for spinothalamic inputs in the human thalamus. As estimated by the amplitude ratio of LEP between affected and non-affected sides, approximately 60% of the spinothalamic input triggered by the laser pulses was transmitted to the cortex via thalamic relays other than the damaged VP. It seems unlikely that up to 60% of the spinothalamic responses may have been relayed in the small residual VP volume spared by the lesion. In view of recent and rather convincing evidence pointing to the existence of a distinct nucleus (the VMpo) receiving spinothalamic afferents (Beggs et al., 2003; Blomqvist et al., 1996, 2000; Craig, 2000, 2002, 2003a,b; Craig and Blomqvist, 2002; Craig et al., 1994, 2002; Davis et al., 1999), it appears reasonable to assume that this locus might indeed represent the thalamic relay of the remaining spinothalamic fibres that went undamaged through our patient's thalamus.

The lesion could potentially have damaged fibre tracts, such as lemniscal afferents to VP and efferent fibres from VPL, VPM and VPI. While this agrees with the observed 67% decrease in SEPs amplitude, the very limited decrease of LEPs departs from what could be expected. Indeed, VPI concentrates STT afferents (Apkarian and Shi, 1994), and damage to its efferent fibers as they pass through VPL toward the cortex should have led to a much larger attenuation of LEPs, *unless* a separate spinothalamic-related pathway remained spared by the lesion (STT afferents to more caudal structures such as the posterior group, including VMpo). The integrity of the *efferent* fibres issued from the latter structures can in turn be questioned, but the exact course of these thalamocortical fibres has not been so far described. The SEP/LEP dissociation suggests that all or part of efferent fibres from the posterior group may reach their cortical targets without crossing the VP, perhaps through the internal medullary lamina.

#### 4.4. Thalamic lesions and central pain in humans

One prevalent view on the mechanisms of central post-stroke pain considers disinhibition of 'medial' pain channels by a lesion affecting the lateral pain pathway ending in VL (Bennett, 1994; Bowsher, 1996; Tasker, 1990), thus consistent with the present observation. It has been however recently proposed that central pain may be the consequence of lesions interrupting a specific thermosensory pathway

which transmits spinothalamic inputs from dorsal horn lamina I neurons to the VMpo thalamic nucleus (Bester et al., 2000; Blomqvist and Craig, 2000; Craig, 2000, 2002, 2003a). According to this view, it may be assumed that lesions of VMpo, its afferent fibers or cortical targets, are needed for the development of such types of central pain. The case we present herein suggests, on the contrary, that clinically typical central thalamic pain can develop in the absence of any demonstrable lesion of the VMpo. Our data rather indicate that, although the VP does not represent the exclusive sensory thalamic relay for thermal nociceptive inputs, lesions in this area sparing the VMpo are *sufficient* to produce central pain. It is likely, however, that other patients may present pain after thalamic lesions that do affect the VMpo, underscoring the proteiform mechanisms of central pain. Mauguière and Desmedt (1988) analysed patients with thalamic lesions and central pain, and distinguished different subtypes associated with different SEP alterations. In 8 patients thalamic pain coexisted with intact SEPs (and intact touch and position senses) indicating complete preservation of the VP. At least three of these eight patients had clinical loss of pain and/or temperature sensation, and may therefore have corresponded to 'pure' lesions of the posterior nuclei (VMpo?), sparing the VP. Our patient appears as the mirror image, namely a 'pure' lesion of the VP with a spared VMpo. The fact that both types of lesions may result in central pain and thermal hypesthesia supports the concept that the VP, but also more posterior thalamic nuclei, have an important role in relaying spinothalamic activity to cortex.

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