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Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain

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Summary

We recorded laser-evoked cortical potentials (LEPs) in 54 consecutive patients presenting with unilateral neuropathic central pain (*n* = 42) or with lateralized pain of non-organic origin (*n* = 12). A number of cases in each group had superimposed hyperalgesia or allodynia. In patients with central pain, LEPs were significantly attenuated after stimulation over the painful territory, relative to stimulation of the homologous normal territory. LEP attenuation concerned not only patients with decreased pain/heat sensation, but also those with allodynia or hyperalgesia to laser pulses. In contrast, LEPs were never attenuated in patients with non-organic forms of pain, in whom LEPs could even be enhanced to stimulation of the painful territory. Increased responses in non-organic pain were a reminder of the cognitive modulation observed in normal subjects who direct attention to a laser stimulus. Enhanced LEPs never accompanied truly neuropathic hyperalgesia or allodynia. In central pain patients with exclusively spontaneous pain, LEP attenuation was more pronounced than that observed in those with allodynia and hyperalgesia. Patients with allodynia also presented occasionally ultra-late responses (>700 ms) to stimulation of the painful side. The hypothesis that such responses may reflect activation of a slow conducting 'medial' pain system is discussed. We conclude that, as currently recorded, LEPs essentially reflect the activity of a 'lateral' pain system subserved at the periphery by rapidly conducting A-δ fibres. They are useful to document the sensorial deficits (deafferentation) leading to neuropathic pain syndromes. Conversely, in the case of deafferentation, they fail to index adequately the affective aspects of pain sensation. On practical grounds, chronic pain coupled with reduced LEPs substantiates the diagnosis of neuropathic pain, whereas the finding of normal or enhanced LEPs to stimulation of a painful territory suggests the integrity of pain pathways, and does not support a neuropathic pathophysiology. In neuropathic cases, partial LEP preservation might increase the probability of developing provoked pain (allodynia/hyperalgesia). The possible predictive value of this phenomenon, when observed before the development of pain, remains to be demonstrated. In selected contexts (pain *sine materia*, non-organic anaesthesia), normal or enhanced LEPs may support a psychogenic participation in the syndrome.

Keywords: central pain; laser-evoked potentials; neuropathic pain; non-organic pain; pain

Abbreviations: LEP = laser-evoked potential; VAS = Visual Analogue Scale

Introduction

Patients with pain resulting from damage to the nervous system ('neuropathic' or 'deafferentation' pain) often experience both spontaneous painful sensations and abnormal pain in response to external stimuli. Abnormally provoked pain is commonly referred to by the terms 'hyperalgesia' or 'allodynia': the latter is defined as inappropriate pain in response to a normally innocuous stimulus, while hyperalgesia refers to enhanced pain sensation to a stimulus that is noxious (Merskey, 1986; Bennett, 1994). Although the conceptual difference between allodynia and hyperalgesia is clear, the two symptoms are often simultaneously present in individual patients, and are frequently difficult to dissociate in clinical practice (Bennett, 1994). This leads sometimes to their grouping under the somewhat ambiguous label of 'painful dysaesthesiae' (Finnerup *et al*., 2001). Abnormally provoked pain sensations are common in patients with neuropathic pain (Riddoch 1938*a*, *b*; Boivie *et al*., 1989; Tasker, 1990) and represent extremely disabling symptoms, hardly compatible with normal life: patients with mechanical allodynia may for instance be unable to stand the contact of their own clothes over the painful territory. In spite of the high incidence of these symptoms, and the importance of their alleviation in pain-therapy programmes, their objective evaluation remains difficult, and the clinician currently has no tools to predict whether a hyperalgesic or allodynic state will develop after injury of the nervous system. Thus, in a recent study of patients with chronic spinal cord injury, Defrin and colleagues observed that a similar degree of anatomical spinal lesion and of clinical somatosensory involvement could be followed by spontaneous pain only, spontaneous pain plus allodynia, or no pain at all (Defrin *et al*., 2001).

Allodynia and hyperalgesia are present in up to 60% of patients with central neuropathic pain (Bowsher, 1996). They are considered as the expression of plastic changes that develop in the CNS after lesions involving mainly the spinothalamic pathways (Boivie *et al*., 1989; Boivie, 1995; Vestergaard *et al*., 1995; Bowsher, 1996; Béric, 1998). For instance, recordings from the ventrolateral thalamus in patients with central pain have shown loss of receptive fields in neurones corresponding to the affected territories, while abnormally enlarged receptive fields and peculiar unitary activities develop to neurones whose receptive field lies adjacent to the affected area (Lenz *et al*., 1989; Bennett, 1994). In primates, partial transection of the spinothalamic tract alters the thalamic processing of innocuous somatosensory information, and induces both increased spontaneous activity and burst-like responses to light cutaneous stimuli in the ventroposterolateral nucleus (Weng *et al*., 2001). Changes in thalamic transduction would then result in altered cortical responses to innocuous somatic inputs, thus contributing to the generation of abnormal provoked pain such as mechanical allodynia. In support of this idea, microstimulation of ventrocaudal thalamic neurones corresponding to both the affected and adjacent territories tend to evoke painful sensations in patients with neurogenic pain, but not in patients without pain (Lenz *et al*., 1998). In addition, microstimulation of the medial thalamus, which usually does not evoke unpleasant sensation in cases without central pain (Bennett, 1994), may provoke painful sensations in central pain patients (Tasker *et al*., 1983; Gybels and Kupers, 1995). Since medial thalamic sites are mainly innervated by ascending spinoreticular fibres (Willis and Westlund, 1997), the hypothesis has been put forward that lateral spinothalamic lesions would create abnormally increased pain responsiveness (allodynia and hyperalgesia) through disinhibition of the spino-reticulo-thalamic system and its medial thalamic targets (Cesaro *et al*., 1986; Tasker, 1990).

The recording of brain responses to short laser pulses [laser-evoked potentials (LEPs)] has progressively established itself as a useful tool for evaluating the function of central nociceptive pathways. This relies on the fact that CO_2-laser stimuli applied to hairy skin excite exclusively A-δ and C mechano-thermal nociceptors, the resulting central ascending signals being mediated by spinothalamic tracts (Bromm and Treede, 1987; Bromm *et al*., 1991; Treede *et al*., 1995). LEPs have demonstrated their ability to detect lesions in peripheral and central pain pathways, including small-fibre neuropathies (Kakigi *et al*., 1991*a*; Lankers *et al*., 1991; Agostino *et al*., 2000; Lefaucheur *et al*., 2002), spinal cord lesions (Kakigi *et al*., 1991*b*; Treede *et al*., 1991) and brainstem infarcts affecting the spinothalamic system (Bromm *et al*., 1991; Kanda *et al*., 1996). Even if they are used to detect lesions in sensory pathways, LEPs reflect an integrative cortical response to the painful stimulus rather than a simple reaction of the sensory cortex to it (Carmon *et al*., 1978; Arendt-Nielsen, 1994). Thus, in healthy subjects the amplitude of cortical LEPs correlates with the subjective sensation of pain, rather than with the physical stimulus intensity. For instance, paying attention to the laser stimulus simultaneously increases the subjective pain sensation and the LEP amplitude, both of which decrease in turn when attention is diverted away from the stimulus (Garcia-Larrea *et al*., 1997). Also, hypnotically induced hyperalgesia may increase the amplitude of LEPs in parallel with the sensation, in the absence of any real change in the stimulus physical magnitude (Arendt-Nielsen *et al*., 1990). In patients with spinothalamic lesions, reduction of pain sensation is also associated with LEP decrease (Kakigi *et al*., 1991*b*; Treede *et al*., 1991; Casey *et al*., 1996), whereas enhanced cortical responses to laser have been reported in patients with increased pain sensitivity (Gibson *et al*., 1995; Treede *et al*., 1995; Lorenz *et al*., 1996). All these observations have led to the opinion that the magnitude of LEPs might, in both normal and pathological conditions, be an accurate index of the subjective pain experience, and that if heat/pain sensitivity is pathologically increased (as in allodynia and hyperalgesia) the amplitude of LEPs may also be increased (Treede *et al*., 1995). This point of view has, however, been challenged by

some reported cases showing a dissociation between decreased cortical LEPs (due to deafferentation) but enhanced pain sensation to laser stimuli in case of neuropathic pain (Casey *et al*., 1996; Wu *et al*., 1999). An alternative view has therefore developed suggesting that, while in normal subjects LEPs might accurately reflect the degree of pain sensation, in patients with neuropathic lesions they essentially reveal the degree of spinothalamic deafferentation (Casey *et al*., 1996; Wu *et al*., 1999; Garcia-Larrea *et al*., 2000).

The main objectives of the present study were to examine the value of LEPs in the evaluation of central neuropathic pain, as well as their possible significance in discriminating among patients those who are more likely to be susceptible to the development of provoked pain (allodynia and hyperalgesia). Since allodynia and hyperalgesia have never been systematically studied with the aid of LEPs, specific questions were: (i) does hyperalgesia to laser stimuli produce exaggerated LEPs; (ii) do patients with such symptoms differ in terms of their cortical responses from those with purely spontaneous pain; and (iii) can LEPs be of use in understanding the pathophysiology of spontaneous versus provoked neuropathic central pain? With these aims, we recorded LEPs from three groups of patients presenting, respectively, with (i) chronic spontaneous central pain, (ii) spontaneous central pain plus allodynia and/or hyperalgesia, and (iii) chronic pain with no proven organic cause, but presenting with symptoms reminiscent of those observed in central pain.

Patients and methods

Patients

A total of 64 patients recorded during the 1997–2000 period were selected for this study. Fifty-two patients were classed as having 'central pain', as they fulfilled the following criteria: (i) presence of pain secondary to a lesion of the CNS confirmed by clinical and neuroradiological data; (ii) causal relation between the lesion and the pain supported by clinical characteristics, notably pain regional distribution; (iii) duration of pain >6 months; and (iv) LEPs obtained to stimulation of both the affected and non-affected (usually contralateral) territories.

From these 52 central pain consecutive cases, 10 were eliminated from the study because of a low signal-to-noise ratio of LEP recordings (n = 6), lack of control LEPs from the normal side (n = 1) or absence of enough clinical data to correlate with LEPs (n = 3). The final sample of central pain patients consisted of 42 subjects, of whom 20 had thalamic or thalamo-cortical lesions, 10 had brainstem lesions (all but one with Wallenberg syndrome) and 12 had spinal lesions.

The group of 'non-organic' pain consisted of 12 patients whose pain, lasting >6 months, had also been first considered as of possible central origin, but in whom repeated clinical and radiological studies failed to demonstrate any significant CNS lesion able to explain the pain syndrome. Possible causes of chronic enhanced nociceptive input (inflammation, trauma, etc.) were also ruled out in these patients by clinical and paraclinical investigations. This group was classified as 'non-organic pain' or pain '*sine materia*' (the two terms will be used synonymously).

The whole group was therefore composed of 54 patients, the clinical data of whom are summarized in Table 1.

Clinical assessment

The clinical characteristics of sensation over the painful areas were examined in all cases before and during the recording session, with special emphasis on stimulus-induced pain. Somatosensory deficit was assessed during the LEP recording session with standard clinical methods: two-point discrimination and tactile hypoaesthesia with blunted needles and cotton balls, joint position sense using mirror movements of fingers and toes (distal), and by 'searching hand' methods (proximal). Graphaesthesia and stereognois were not assessed systematically. Thermal hypoaesthesia was searched for with hot/cold tubes, and in every case using laser pulses of ascending/descending intensity. Quantified Sensory Testing of hot/warm/cold thresholds was performed in about two-thirds of the sample, but during a different session. The presence of abnormally provoked pain was tested systematically on the day of LEP recording.

Allodynia was defined as pain arising in response to innocuous stimuli (i.e. stimuli that never caused pain in normal controls) (Merskey, 1986; Bennett, 1994). Whenever possible, mechanical allodynia was tested with touch (static) or light rubbing of the skin (dynamic). Hyperalgesia was defined as abnormally enhanced pain sensation in response to noxious stimuli (Merskey, 1986; Bennett, 1994), and was tested with pinprick and supraliminal (>35 ms) laser stimulation [see Valeriani *et al*. (1996) for threshold values and associated sensation in normals].

Hyperalgesia to laser was first determined before LEP recording, by applying series of stimuli of ascending/descending intensity (the same series used to obtain the perceptive and pain thresholds to laser). This was first performed in the normal limb, which allowed the patients to become accustomed to the sensation associated with laser pulses, and provided them with a comparison level to refer to when describing sensations in the affected limb. The results were then confirmed by Visual Analogue Scale (VAS) quotations yielded by patients during the repetitive stimulation used to obtain LEPs. Hyperalgesia to laser stimuli was considered significant when patients rated laser pulses delivered to the affected territory at least two VAS points higher than those addressed to the homologous non-affected area. Allodynia to laser was considered to exist if a painful sensation (VAS $\geqslant$4/10) was triggered by stimulation levels well below the pain threshold in the normal limb. Summation hyperpathia was defined as pain arising (or increasing disproportionately) after repeated stimulation ('temporal

Table 1 *Summary of demographic and clinical data from the 54 patients studied*

Patient	No.	Age	Group	Lesion level	Aetiology	Localization of pain	Comments
Red	1	36	CP - Spont	Brainstem	Wallenberg	Left (–f)	
Tour	2	61	CP - Spont	Brainstem	Wallenberg	Left (–f)	
Corn	3	55	CP - Spont	Brainstem	Wallenberg	Left (–f)	Abolished LEP
Fau	4	55	CP - Spont	Brainstem	Trauma	RUL	
Douh	5	61	CP - Spont	Spinal	Syringomyelia	T12-L3	
Brif	6	48	CP - Spont	Spinal	Injury (knife)	LLL>>RLL	
Verd2	7	45	CP - Spont	Spinal	Angioma	RLL + T2	Abolished LEP
Dum	8	39	CP - Spont	Spinal	Angioma	RLL	
Font	9	40	CP - Spont	Spinal	Cerv myelopath	C6 left and LLL	Abolished LEP
Guyo	10	34	CP - Spont	Spinal	MS	LLL>>RLL	Abolished LEP
Walt	11	39	CP - Spont	Spinal	MS	LUL	
Vial1	12	46	CP - Spont	Thalamo-cort	Stroke (i)	Left hemibody	Abolished LEP
Vial2	13	49	CP - Spont	Thalamo-cort	Stroke (i)	Right hemibody	
Mor	14	60	CP - Spont	Thalamo-cort	Stroke (i)	Left hemibody	
Squi	15	49	CP - Spont	Thalamo-cort	Stroke (i)	RUL	
Bern	16	71	CP - Spont	Thalamo-cort	Stroke (h)	LUL	
Wat	17	50	CP - Spont	Thalamo-cort	Trauma	RLL	
Catt	18	40	CP + allo	Brainstem	Wallenberg	RLL > RUL	Hyperalg laser
Verd1	19	44	CP + allo	Brainstem	Wallenberg	LUL	
And	20	46	CP + allo	Brainstem	Wallenberg	RUL	
Card	21	49	CP + allo	Brainstem	Wallenberg	LUL + LLL	
Pomm	22	67	CP + allo	Brainstem	Wallenberg	RLL > RLL	
Coll	23	42	CP + allo	Brainstem	Haematoma	Right (–f)	Hyperalg laser
Vign	24	52	CP + allo	Spinal	Tumour	LLL	
Bon	25	57	CP + allo	Spinal	Syringomyelia	LUL	Abolished LEP
Coq	26	39	CP + allo	Spinal	Trauma T6	LLL	
Lass	27	51	CP + allo	Spinal	Angioma	LUL	Hyperalg laser*
Bess	28	25	CP + allo	Spinal	MS	LLUL	
Plant1	29	49	CP + allo	Thalamo-cort	Stroke (h)	Right hemibody	
Ramp	30	72	CP + allo	Thalamo-cort	Stroke (i)	LUL, LLL	Hyperalg laser*
Chav	31	59	CP + allo	Thalamo-cort	Stroke (i)	RUL	Hyperalg laser
Dim	32	26	CP + allo	Thalamo-cort	Stroke (i)	LLL	
Coz	33	36	CP + allo	Thalamo-cort	Stroke (h)	RUL	
Ross	34	62	CP + allo	Thalamo-cort	Stroke (h)	LUL	
Croz	35		CP + allo	Thalamo-cort	Stroke (i)	LLL	
Vau	36	55	CP + allo	Thalamo-cort	Stroke (i)	Right hemibody	
Jon	37	64	CP + allo	Thalamo-cort	Stroke (i)	Left hemibody	
Bene	38		CP + allo	Thalamo-cort	Stroke (i)	Right hemibody	
Dea	39	62	CP + allo	Thalamo-cort	Stroke (h)	LUL	Hyperpath laser
Odi	40	55	CP + allo	Thalamo-cort	Stroke (i)	LUL, LLL	
Plant2	41	49	CP + allo	Thalamo-cort	Stroke (i)	RUL	
Lach	42	70	CP + allo	Thalamo-cort	Stroke (i)	LUL	Hyperalg laser*
Gue	43	53	Non-organic	A-Ch	No	RUL, RLL	
Plas	44	54	Non-organic	No lesion	Psychogenic	RUL, RLL	
Bust	45	31	Non-organic	No lesion	Simulation?	RUL + both LL	
Maal	46	42	Non-organic	No lesion	Psychogenic	LUL	Hyperalg laser
Ret	47	45	Non-organic	No lesion	Fibromyalgia?	Left T7 & LUL	Hyperalg laser
Sgr	48	42	Non-organic	No lesion	Myofascial + psy	Left side (–f)	Hyperalg laser
Jar	49	19	Non-organic	No lesion	Posttrauma neur	RUL	Hyperalg laser
Pas	50	53	Non-organic	No lesion	No	LUL	
Mad	51	53	Non-organic	No lesion	Psychogenic	Left hemibody	
Herv	52	48	Non-organic	No lesion	Narcolepsy	Diffuse R>>L	
Rah	53	29	Non-organic	No lesion	Psychogenic	LUL>>RUL	
Mon	54	46	Non-organic	No lesion	No	LLL	Hyperalg laser

CP = central pain; CP + allo = central pain plus allodynic or hyperalgesic symptoms; LUL = left upper limb; LLL = left lower limb; RUL = right upper limb; RLL = right lower limb; (–f) = not involving face; (i) = ischaemic; (h) = haemorrhagic; A-Ch = Arnold-Chiari; no = diagnosis not yet established; spont = spontaneous; posttrauma neur = posttraumatic neurosin; cerv myelopath = cervical myelopathy; cort = cortical. *Ultra-late LEP.

summation'; see Bennett, 1994). In addition, it was checked in every patient whether other, more natural stimuli (such as a shower, or contact with clothes) were able to trigger abnormal pain in everyday life. After each recording run, patients were asked to estimate their subjective sensation to laser stimuli on a 101 mm VAS. The bottom end of the VAS represented absence of sensation, a point corresponding to 4 cm from the bottom corresponded to pain threshold, and the top end of the scale was defined as 'unbearable pain'.

Laser stimulation and LEP recording

Laser stimuli were applied to the dorsum of the hand (radial nerve territory) and/or to a cutaneous territory corresponding to the distribution of pain. Pulses were delivered every 10 ± 2 s by a CO_2 laser stimulator (laser wave length 10.6 μm, beam diameter 3.5 mm, output power 10 W). The power output being fixed, the amount of thermal energy delivered, depended on the duration of the pulse, which typically ranged between 40 and 80 ms. Thresholds for innocuous and painful sensations were first determined in each patient. Pain thresholds in the healthy side ranged between 35 and 50 ms, while those in the affected side ranged between 15 and 110 ms. After estimation of psychophysical thresholds, the stimulus intensity used for LEP recording was set at 15–20% above the pain threshold obtained in the healthy side.

Twenty scalp electrodes positioned according to the 10–20 international system (Jasper, 1958; Klem *et al*., 1999), and referenced to the nose, were used for recordings. For eye movement artefact control, the EOG (electro-oculogram) was recorded from a supra-orbital electrode, also referenced to the nose. Trials contaminated by blinks, eye movements, or any other signal exceeding 65 μV were automatically rejected by the system. Evoked potentials were averaged over blocks of 20–30 stimulus repetitions. Brain signals were averaged over 1024 ms using a band pass of 0.3–37 Hz, a gain of ×30 000 and a sampling rate of 256 Hz. An 80 ms pre-stimulus delay was used for baseline computation. In 10 cases, a smaller window of 512 ms was used, with a 40 ms pre-analysis delay and a 256 Hz sampling rate.

Statistical analyses

Changes in LEP amplitude and latency were assessed using a two way, mixed-design ANOVA (analysis of variance), with one 'between' and one 'within' factors. The 'between' factor separated subjects in three groups: (i) patients with non-organic pain; (ii) patients with central pain and allodynia/hyperalgesia; and (iii) patients with exclusively spontaneous central pain. The repeated measures ('within') factor distinguished the painful versus non-painful sides of stimulation. The dependent variables were baseline-to-peak amplitude of the main LEP positive component (P2 amplitude), the peak-to-peak amplitude of this same LEP component from the preceding negativity (N2-P2 amplitude) and the peak latency of the P2 component.

Amplitude ratios were also calculated by dividing LEP amplitude to stimulation of the painful side by that obtained to stimulation of the healthy side; therefore, a possible enhancement of LEPs in response to stimulation of the painful side was reflected by ratios exceeding the unit. Amplitude ratios between stimulation of the painful and non-painful sides were assessed between the three groups using a one-way ANOVA. In all cases, post-hoc comparisons using *t*-tests were performed in case of significant main factors effects.

When the main LEP response was made of several subcomponents, the amplitude of the highest positive peak was taken as the 'LEP amplitude' and entered into an ANOVA. Latency measurements in cases of multiple peaks were performed using the method advised by the International Federation of Clinical Neurophysiology Societies, i.e. extrapolating the ascending and descending branches of the component and taking the latency at their point of convergence (Goodin *et al*., 1994).

Results

Spontaneous and provoked pain in central pain patients

On clinical examination, all central pain patients had decreased pain and temperature sensation over the painful territory. In the light of the clinical assessment described above, the group of central pain patients was further subdivided into two sets based on the presence or absence of painful provoked dysaesthesiae (i.e. allodynia or hyperalgesia) in addition to spontaneous pain. Seventeen patients (40.5%) did not describe abnormal painful sensations to external stimuli, either during clinical examination or in everyday life. This group was labelled 'spontaneous pain only', and was composed of four brainstem lesions, seven spinal lesions and six thalamo-cortical lesions. The 25 remaining patients (59.5%; six brainstem, five spinal, 14 thalamo-cortical lesions) had spontaneous pain of a comparable intensity to that of the former group, but with additional allodynic and/or hyperalgesic symptoms that could be reproduced the day of the recording. Allodynia was most often mechano-thermal, i.e. could be triggered by either mechanical (touch, rubbing or vibration) or thermal stimuli, the combination of both types of stimuli commonly being more painful than any of them separately (e.g. a cold shower). Allodynia and hyperalgesia could be either associated or dissociated in the same subject. Distribution, demographic and clinical data of patients are shown in Table 1.

From the 25 central pain patients with hyperalgesia, only seven patients described abnormally enhanced pain triggered by the laser pulses themselves. In five of them (one spinal injury, two Wallenberg and two thalamocortical), there was hyperalgesia to suprathreshold laser stimuli delivered to the affected side, while one further patient with a cortico-subcortical haemorrhage described genuine allodynia to laser

Table 2 *ANOVA on LEP amplitude from a mixed design with one between factor (patient group) and one within factor (stimulus side)*

Source	Degrees of freedom	Sum of squares	Mean square	*F* value	*P* value (G-G)
Group	(2,50)	10.816	5.408	0.149	0.8616
Stimulus side	(1,50)	112.080	112.080	18.009	0.0001
Side × group	(2,50)	130.655	65.328	10.497	0.0002

G-G = Greenhouse-Geisser correction of degrees of freedom.

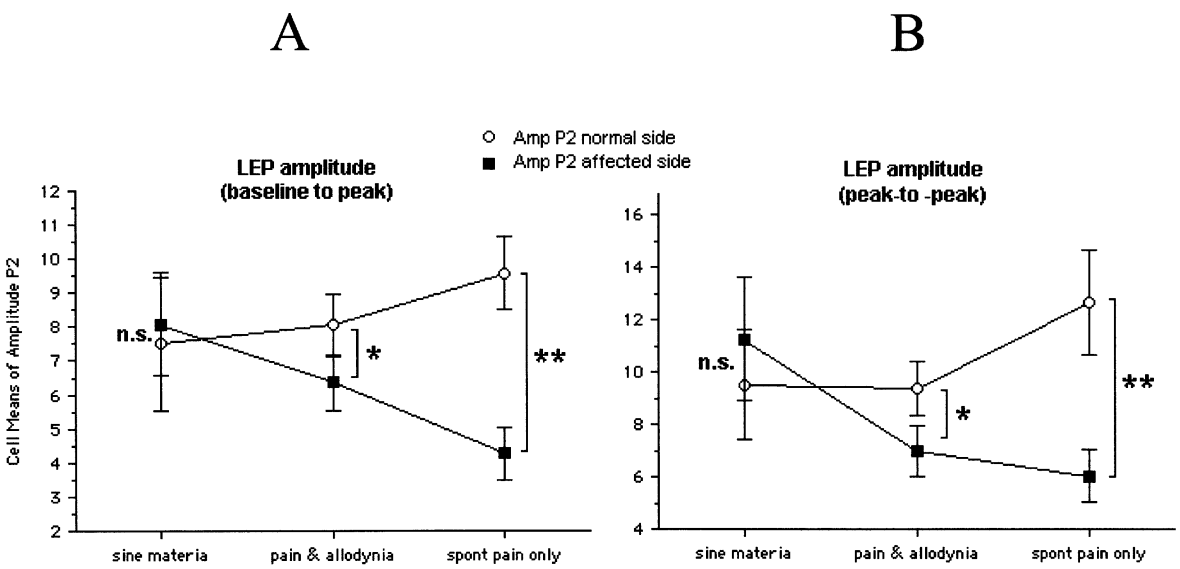

Fig. 1 ANOVA interaction plots of LEP amplitude. Amplitudes of the main positive LEP response (P2) relative to pre-stimulus baseline are shown in (**A**), and amplitudes relative to the preceding negative peak are shown in (**B**). LEP amplitudes to stimulation of the normal and the painful sides were almost identical in the group of non-organic pain (left plots in each panel). Conversely, the stimulation of the painful territory evoked significantly attenuated LEPs in both groups of central pain patients. LEP attenuation was maximal in patients with exclusively spontaneous pain, and less marked (but significant) in patients with both spontaneous pain and painful provoked dysaesthesiae (hyperalgesia and allodynia). These results explain the strong group × side interaction found on ANOVA.

stimuli delivered at very low intensities, just above the sensory threshold. In the last patient (thalamo-cortical infarct), repeated suprathreshold laser stimuli over the painful (but hypaesthetic) territory induced summation hyperpathia. Of the 12 patients with non-organic pain, six described hyperalgesic sensations to a variety of stimuli, including laser pulses in five patients. However, whereas hyperalgesia in central pain was associated with protracted, long lasting, dull and ill-localized pain, hyperalgesia observed in 'non-organic' cases (either clinical or to laser) was always very well localized in the body, entailed phasic responses and tended to disappear rapidly.

Central pain versus 'pseudocentral' non-organic pain

A side × group ANOVA on LEP amplitude (Table 2) showed a strong effect of the side of stimulation, with lower amplitudes to stimulation of the painful side [$F(1,50) = 18.01$, $P = 0.0001$]. A very significant interaction was also detected between the patients' group and the stimulation side [$F(2,50) = 10.49$, $P = 0.0002$], indicating that the degree of LEP attenuation in the affected side depended on the patients' group. This was confirmed in post-hoc tests, where side-to-side differences in LEP amplitude were highly significant for the two groups of patients with central pain [$t(16) = 5.71$, $P = 0.0001$; and $t(24) = 3$, $P = 0.006$], whereas no significant amplitude difference was apparent in the group of patients with 'pseudocentral' non-organic pain [$t(11) = –0.45$; not significant]. Thus, in central pain patients, but not in non-organic pain, LEPs to stimulation of the painful side were attenuated relative to those obtained by stimulation of the normal side. Conversely, in the non-organic group, LEP amplitude did not vary across sides. These results were virtually identical, whether the LEP P2 amplitude was measured from baseline or from the preceding negativity (Fig. 1).

Figure 2 illustrates grand averaged LEPs from the three groups of patients, as well as the corresponding maps of electrical activity at the time of maximal response amplitude. LEP amplitude to stimulation of the painful side was attenuated in both groups with central pain, but such

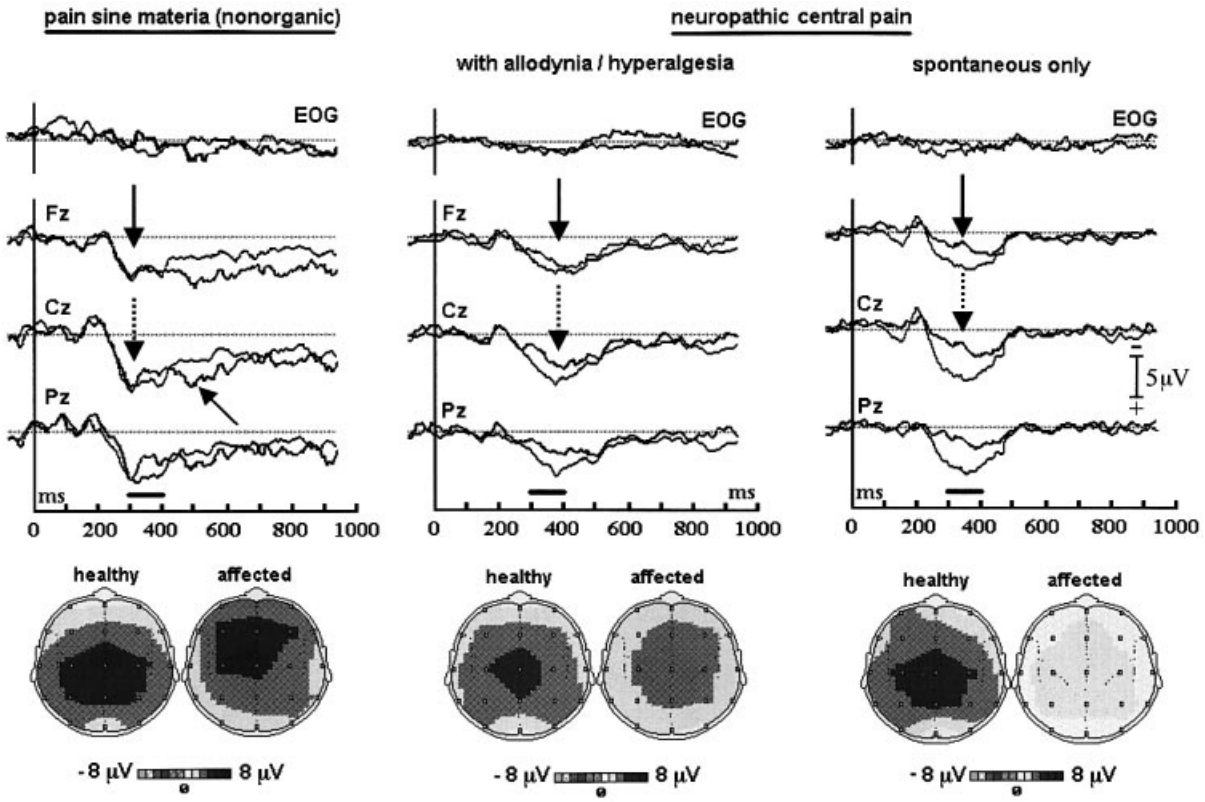

Fig. 2 Grand averaged LEPs from the three groups of patients analysed in this study. In each case, responses from the affected side (grey) are superimposed on those resulting from stimulation of the healthy side (black). Represented at the bottom of each panel are scalp maps of electrical activity, averaged across the 100 ms of maximal response amplitude. LEP amplitude appears attenuated to stimulation of the painful side in the two groups of central pain patients (middle and right panels); however, attenuation is especially marked in the group with exclusively spontaneous pain (right column). In the 'non-organic' group (left panel), P2 LEP amplitude was equivalent to stimulation of either side, and a second positive peak at ~550 ms appeared in response to the painful side only (oblique arrow). This second positivity was considered to be a 'cognitive P3', described previously in conditions of enhanced attention to the stimulus (Towell and Boyd, 1993). As shown by scalp maps in the two groups with central pain, the P2 response remained centred around the vertex whatever the side of stimulation. In the group of patients with non-organic forms of pain, the scalp distribution of the P2 response to painful side stimulation was displaced toward the frontal regions. This figure can be viewed in colour as supplementary material at Brain Online.

attenuation was much more marked in the group with exclusively spontaneous pain than in patients with pain plus hyperalgesia (Fig. 2, right and middle panels, respectively). In the 'non-organic' group, the P2 LEP amplitude was equivalent to stimulation of both sides, and a subsequent positive peak, considered as a 'cognitive P3' (Towell and Boyd, 1993), appeared in several subjects and in the grand average. Although mean LEP amplitude appeared increased in the normal side for the group with spontaneous central pain, differences were not statistically significant. Figure 2 also depicts the scalp distribution of the main LEP positive response, averaged across the 100 ms of maximal voltage. In the two groups with central pain, the response remained centred around the vertex after stimulation of either side; conversely, in the group of patients with non-organic forms of pain, the scalp topography of the LEP P2 was displaced toward frontal regions in response to the painful side stimulation.

Side × group ANOVA was also applied to latency data (except for the six patients in whom the response was abolished to stimulation of the painful side). This analysis showed a significant effect of side [$F(2,45) = 10.38$, $P = 0.002$] but not of group on P2 latencies, which were significantly delayed with stimulation of the painful limb. As illustrated in Fig. 3, latency delay after stimulation of the painful limb was evident in both groups with central pain (with and without hyperalgesia), but not in the 'non-organic' group where LEP peak latencies were comparable to stimulation of the painful and non-painful territories. There was no significant group × side interaction on ANOVA.

LEPs in patients with hyperalgesia to CO_2-laser stimuli

On the basis of previous claims in the literature, we tested on our patients the hypothesis that abnormally increased pain to laser could be reflected by abnormally enhanced LEPs. A one-way factorial ANOVA on LEP amplitude ratios was applied to results from the 12

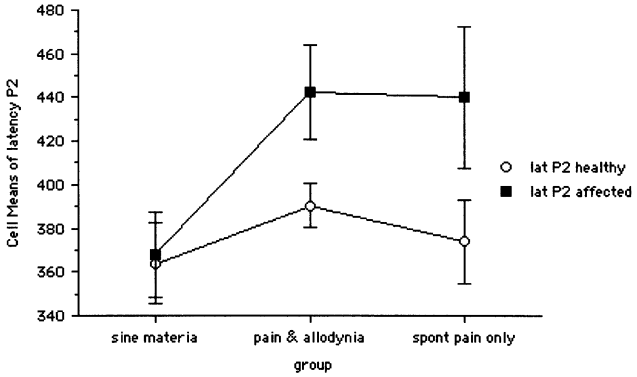

Fig. 3 Interaction plot of ANOVA on LEP latency. P2 latency to stimulation of either side remained identical in the non-organic group, while it was significantly delayed to stimulation of the painful side in both groups of central pain patients.

subjects (seven with central pain, five with pain *sine materia*) who described hyperalgesic or allodynic reactions to laser pulses (VAS difference $\geq$2 points relative to the normal side). According to the method of calculation (see Patients and methods), enhancement of LEPs in response to stimulation of the painful side was reflected by ratios exceeding the unit. ANOVA was applied both to baseline-to-peak and peak-to-peak amplitude ratios of the main LEP-positive complex.

There was a significant influence of patient group on LEP amplitude ratios between the painful and the normal sides. Mean amplitude ratios remained <1 in patients with central pain, in spite of laser hyperalgesia (0.8 $\pm$ 0.2 and 0.9 $\pm$ 0.3 for peak-to-peak and baseline amplitudes, respectively), while they exceeded the unit in non-organic pain patients with laser hyperalgesia (1.4 $\pm$ 0.5 and 1.4 $\pm$ 0.5, respectively). The difference was significant for peak-to-peak amplitude [F(1,10) = 6.2, P = 0.03]. Thus, *hyperalgesia to laser stimuli was associated with enhanced LEPs exclusively in non-organic pain*. Conversely, patients with central neuropathic pain had decreased LEPs even in the presence of hyperalgic reactions triggered by laser stimuli. This is illustrated in Fig. 4, showing LEPs recorded in four individual patients, of whom three had central neuropathic pain and one non-organic pain with 'pseudocentral' presentation. As shown in the figure, central patients describing hyperalgesic reactions to the CO_2-laser stimuli (Patients A and B) had delayed and attenuated LEPs in response to the painful side, in spite of higher VAS scores to stimulation.

A particular feature of patients with central pain and hyperalgesia to laser was the occasional presence of ultra-late LEPs to stimulation of the painful side, which was observed in four out of the seven patients. Ultra-late responses were neither recorded in central pain patients without laser hyperalgesia, nor in *sine materia* patients with hyperalgesia. One example of such ultra-late responses is shown in the uppermost panel of Fig. 4.

LEPs in central pain with or without allodynic and hyperalgesic symptoms

As shown in Fig. 2, although LEPs to stimulation of the painful side were attenuated in the two groups of patients with central pain, such attenuation appeared to be greater in patients with exclusively spontaneous pain. This point was assessed specifically by comparing LEP amplitude ratios between painful and non-painful sides in central patients with or without abnormally provoked pain. Patients who presented clinical signs of abnormally provoked central pain (allodynia and hyperalgesia) had a lower degree of LEP attenuation as compared with those who presented exclusively spontaneous pain [amplitude ratios: 0.78 $\pm$ 0.06 (SE) in patients with hyperalgesia versus 0.49 $\pm$ 0.08 (SE) in patients with spontaneous pain; $F(1,40) = 8.58$, $P = 0.006$]. Another parametric approach, considering this time a LEP attenuation >50% as a criterion, confirmed this result: attenuation >50% relative to the control side was observed in 64.7% of patients with spontaneous pain only, compared with 12.5% of patients with both spontaneous pain and hyperalgesia. The difference was significant on χ^2 analysis ($\chi^2 = 10.06$, $P = 0.01$ after correction of Yates; Fig. 5). In accordance with these results, LEPs were found to be absent with stimulation of the affected side in six patients, five of whom had exclusively spontaneous pain.

We also checked whether the smaller degree of LEP attenuation in the 'central pain + hyperalgesia' group could be due to the specific contribution of patients with laser-induced hyperalgesia (who, due to the bias of enhanced alertness, might have increased responses from the abnormal side). Thus, the side $\times$ group ANOVA was repeated after eliminating from the analysis the seven patients with specific hyperalgesia to laser stimuli. The results essentially remained the same, notably still with a very strong interaction between side and patient group [$F(2,43) = 9.18$, $P = 0.0005$]. Also, the comparison between amplitude ratios in the two central pain groups after eliminating the seven patients with laser hyperalgesia still yielded significant results [amplitude ratios 0.74 $\pm$ 0.07 versus 0.49 $\pm$ 0.08; $F(1,33) = 4.39$, $P = 0.04$]. Thus, patients with central pain and hyperalgesia consistently had a smaller degree of LEP attenuation than patients with spontaneous pain only, even after eliminating from the calculation a possible bias due to laser hypersensitivity.

No other significant differences could be established among patients as a function of the particular type of clinically provoked pain (e.g. static versus dynamic allodynia, mechanical versus thermal hyperalgesia).

Discussion

In patients with central pain, cortical responses to laser stimuli were significantly attenuated after stimulation over the painful territory. Moreover, LEP attenuation concerned even those patients with enhanced painful responses to laser. In contrast, LEPs were not attenuated in patients with non-

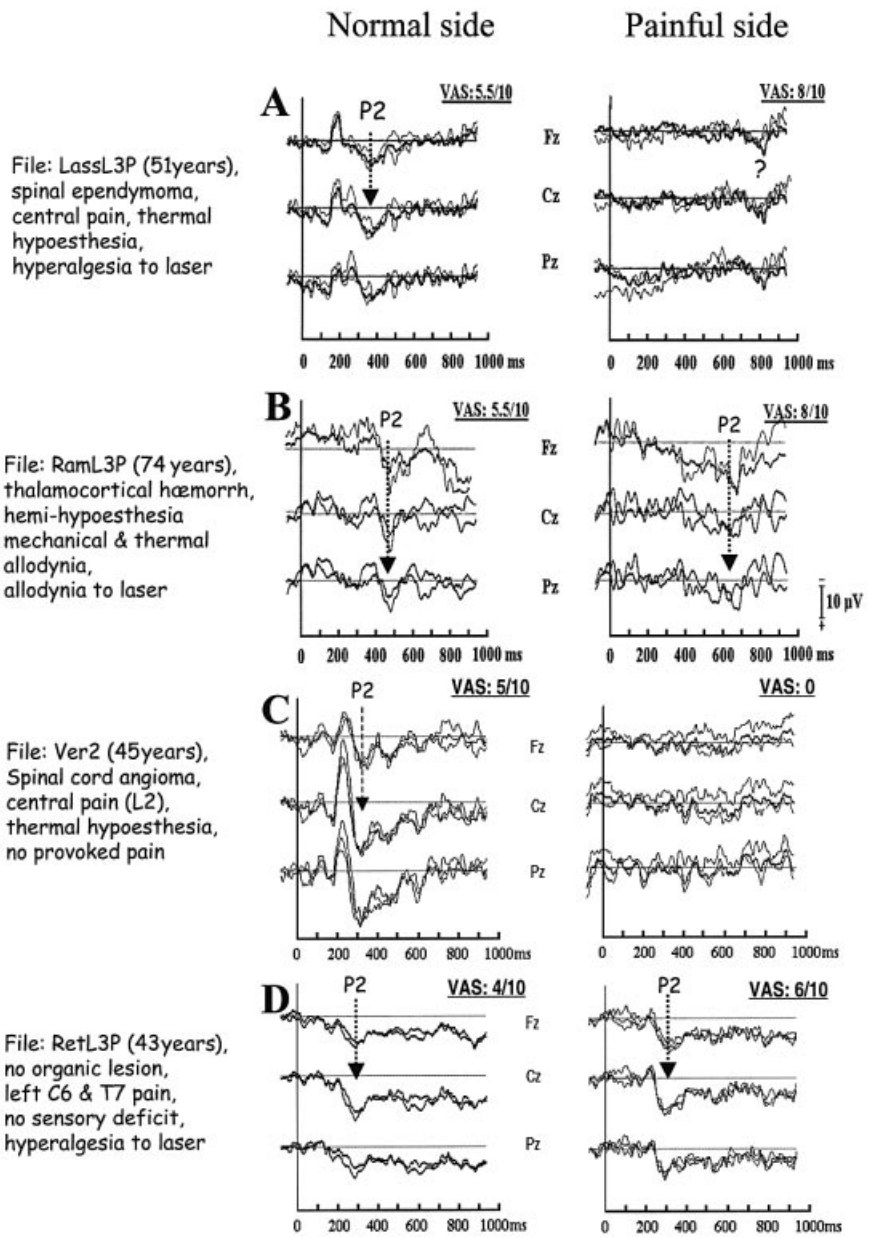

Fig. 4 Individual LEPs illustrating different types of abnormality in central pain (**A**–**C**) and non-organic pain (**D**). Responses to stimulation of the non-painful side (left traces) were within normal limits for age in each case, while those to painful side stimulation displayed various types of abnormalities. (**A**) Ultra-late responses culminating at 890 ms in a patient with central pain and hyperalgesia to laser. (**B**) Desynchronized, attenuated but partially reproducible response with multiple components in a patient with hyperalgesia and allodynia to laser, who described painful long-lasting sensations to stimulus intensities barely exceeding sensory threshold. (**C**) Absence of any reproducible response to stimulation of the painful side in a patient with central pain of exclusively spontaneous nature. (**D**) Responses of a patient with lateralized upper limb and thoracic pain, first thought to be of possible neuropathic origin, and then considered as 'non-organic' after extensive clinical and paraclinical expertise. LEPs are within normal limits on both sides, and relatively enhanced to stimulation of the painful territory.

organic (*sine materia*) forms of pain presenting with 'pseudocentral' symptoms. In the latter group of patients, LEPs could even be enhanced in response to stimulation of the painful territory—a result that was never observed in patients with neuropathic pain. We believe that these results, obtained from a relatively large cohort of patients, may be relevant for the clinical use of laser-evoked cortical responses, and may also shed light on some mechanisms of central pain syndromes. Each of the results is discussed specifically below.

LEP attenuation in central pain

Cortical responses to laser were attenuated significantly after stimulation over the painful territory in cases with central pain, including those with hyperalgesic reactions to laser.

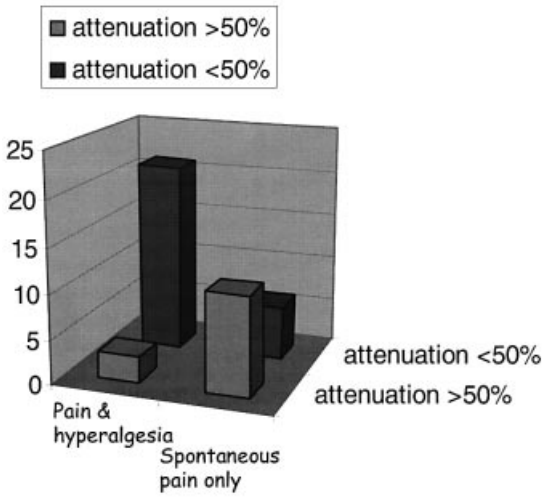

Fig. 5 Three-dimensional histogram illustrating the association between degree of LEP attenuation and the presence of painful evoked dysesthesiae (hyperalgesia or allodynia). The group of central patients with hyperalgesic symptoms had a significantly lower incidence of deeply attenuated LEPs ($\chi^2 = 10.06$, $P = 0.01$).

Attenuation of LEPs was rather independent of the actual pain sensation triggered by the stimulus, and appeared to reflect principally deafferentation in spino-thalamo-cortical pathways. In support of this conclusion stand three facts: first, all patients with decreased LEPs had clinical deficits in temperature and/or pain sensation in the stimulated territory. Secondly, reduced LEPs were observed even when the laser stimulation itself triggered abnormally increased pain. Finally, pain patients with no objective signs of neural sensory lesion and no clinical signs of pain/heat hypoaesthesia had no significant attenuation of LEPs. Therefore, changes in laser EPs in central pain patients appeared more related to sensory deficits reflecting deafferentation in spinothalamic pathways than to the actual pain sensation evoked by laser stimuli. This is in accordance with the results of Casey and colleagues, who documented the decrease or absence of LEPs in six patients with central post-stroke pain and pain/temperature sensory deficits (Casey *et al*., 1996). These authors were also, to our knowledge, the first to document one case of attenuated LEPs in spite of increased ratings of laser pulse sensation [Casey *et al*. (1996), patient E.M.]. Two singular cases of neuropathic pain were also reported by our group, in whom hyperalgesic reactions to laser stimuli coexisted with abnormal and attenuated LEPs (Wu *et al*., 1999). We concluded that in patients with pain secondary to nervous system lesions, LEP changes reflect spinothalamic transmission deficits, and not pain sensation. Our results in a much larger sample of patients substantiate these conclusions by showing a significant pre-eminence of deficitary LEP signs in central pain, including in patients with enhanced allodynic or hyperalgesic reactions to external stimuli.

In normal subjects, the amplitude of LEPs recorded at the vertex correlates positively with the subjective sensation of pain (Carmon *et al*., 1978; Chen, 1993; Treede *et al*., 1995; Beydoun *et al*., 1996). This correlation has been shown to persist even when pain perception becomes dissociated from the actual stimulus intensity by hypnotic suggestion (Arendt-Nielsen *et al*., 1990) or by attentional manoeuvres (Garcia-Larrea *et al*., 1997). In patients with non-neuropathic forms of pain, stimulation of the painful territory has been shown to trigger enhanced LEPs (Gibson *et al*., 1994; Lorenz *et al*., 1996). This has led to the suggestion that when heat/pain sensitivity is pathologically increased, the amplitude of late LEPs may also be increased (Treede *et al*., 1995). Our present results indicate that this assumption does not hold in the central neuropathic forms of pain. Therefore, contrary to what is observed in subjects with an intact nervous system, in whom the amplitude of vertex LEPs adequately reflects the laser-evoked subjective sensation, in central pain patients LEP attenuation is the rule, even in cases with increased subjective reactions to laser pulses.

Why should LEPs be a good index of pain sensation in normal subjects, but become dissociated from pain in neuropathic patients? Cortical LEPs peaking 200–400 ms after a laser stimulus reflect the activity of a nociceptive subsystem conveying the most synchronized and rapidly transmitted pain and temperature volleys (Bromm and Treede, 1987; Bragard *et al*., 1996; Casey *et al*., 1996; Wu *et al*., 1999). This system is subserved in the periphery by A-δ fibres, and in the CNS by the 'lateral' or 'neo-spinothalamic' arrangement of spinal tracts and thalamocortical projections. The lateral nociceptive system mediates elaborated and discriminative aspects of nociception, and it is therefore predictable that its lesion should result in deficits of pain and temperature sensation, as well as a concomitant alteration of LEPs (Bromm *et al*., 1991; Kakigi *et al*., 1991*a*, *b*; Treede *et al*., 1991; Lefaucheur *et al*., 2002). Conversely, such LEP responses are inappropriate to reflect the overreaction (hyperalgesic) phenomena, which are thought to be mediated by spino-reticulo-thalamic 'medial' projection systems (Tasker, 1990; Jeanmonod *et al*., 1994; MacGowan *et al*., 1997) not readily accessible using current LEP recording techniques. Therefore, while the laser stimuli can sometimes trigger hyperreaction phenomena, the LEPs recorded to such stimuli do not index the neural events directly underlying allodynia and hyperalgesia, but rather the lateral spinothalamic deafferentation leading to pain discrimination deficits. This appears to be the electrophysiological counterpart of a clinical paradox commonly observed in partial spinothalamic lesions, namely the presence of exaggerated evoked pain reactions within territories where pain discrimination is decreased or abolished (Bowsher, 1996).

The fact that LEPs mainly reflected spinothalamic deafferentation, and not pain sensation, does not imply a lack of relationship between LEP alterations and the pain syndrome. While until the 1980s emphasis was placed on lesions affecting the dorsal columns/medial lemniscus to account for central pain (e.g. Nathan *et al*., 1986; Mauguière and Desmedt, 1988), spinothalamic lesions are now regarded as

crucial, or even *sine qua non* conditions for the occurrence of this syndrome (e.g. Boivie *et al*., 1989; Vestergaard *et al*., 1995; Defrin *et al*., 2001). For a number of investigators, deafferentation in the lateral, rapidly conducting channels, together with preservation of activity in the medial spino-reticulo-thalamic system, may be a most important point underlying the pathophysiology of central pain and the development of painful positive symptoms (Cesaro *et al*., 1986; Pagni, 1989; Jeanmonod *et al*., 1994; MacGowan *et al*., 1997). Therefore, as laser-evoked potentials reflect uniquely this lateral spinothalamic component most commonly altered in central pain, the finding of abnormally decreased LEPs after stimulation of a painful territory clearly substantiates the neuropathic nature of the pain. Accordingly, LEPs deserve in our view to be added to the current armamentarium of paraclinical exams in pain patients, as the sole method to document objectively spinothalamic deafferentation within a painful territory.

LEPs and the development of hyperalgesic symptoms

LEPs differentiated well, at the group level, between central pain patients with and without hyperalgesia or allodynia. Although we also assessed various forms of provoked pain (static versus dynamic allodynia, thermal versus mechanical hyperalgesia, etc.), these phenomena did not discriminate further among patients on the basis of LEP results. In spite of very thorough clinical analyses on central pain patients (Boivie *et al*., 1989; Boivie, 1995; Vestergaard *et al*., 1995; Bowsher, 1996), there have been surprisingly few attempts to differentiate between patients with or without provoked pain (see Defrin *et al*., 2001). In our series, although both central pain groups (with and without hyperalgesia) had decreased LEPs to stimulation of the painful side, LEP attenuation in patients with just spontaneous pain was greater than in those who also experienced allodynia or hyperalgesia (see Figs 1, 2 and 4). LEP attenuation exceeded 50% in almost two-thirds of patients with exclusively spontaneous pain, compared with only 12.5% of patients with superimposed hyperalgesia (Fig. 5), and five out of six central patients with abolished LEPs had spontaneous pain exclusively. These results may suggest that profound deafferentation in heat/pain pathways to some extent 'protected' against induced pain of the allodynic or hyperalgesic type, while partial deafferentation was associated with a higher probability of provoked pain.

Since hyperalgesia makes the patient more alert to stimuli given to the affected region, higher levels of attention toward the stimulated limb may have contributed to enhance LEPs in those patients, compared with cases with spontaneous pain. Partially preserved LEPs in patients with hyperalgesia would then be in part a consequence of provoked pain, rather than a contributing factor to it. It is, however, noteworthy that only seven of the 25 hyperalgesic patients developed this symptom to LEP stimuli specifically. When these patients were excluded from the analyses, ANOVA still detected significant amplitude differences between the two central pain groups (see Results), indicating that such differences existed even in LEPs to stimuli that did not evoke abnormal pain. Although it can be argued that patients with allodynia are very much alert to their abnormal region independently of whether it is stimulated or not (because of the potential painfulness of any input), such attentional bias is also common in patients with exclusively spontaneous pain, who usually describe the abnormal region as 'continuously burning and distorted', yet LEPs clearly differentiated the two groups. Therefore, although the possibility of attention-related LEP enhancement in selected patients with allodynia should not be excluded, this effect alone can hardly explain the group differences observed in our patients' sample.

Experimental and clinical reports support the idea that partial deafferentation may give rise to abnormally provoked pain by inducing an imbalance between the different subcomponents of ascending heat/pain systems. For example, in rats submitted to traumatic spinal injury, behavioural signs suggestive of allodynia were higher in case of incomplete spinal cord lesions, and lower in groups with more extensive spinal damage (Siddall *et al*., 1995). In primates, partial section of the spinothalamic tract produces abnormal bursting activity in the sensory thalamus in response to innocuous stimuli, and these abnormalities have been proposed to support the allodynic experience (Weng *et al*., 2001). In patients undergoing anterolateral cordotomy, paradoxical painful complications may develop, notably protracted painful sensations attributed to incomplete lesions of the spinothalamic tract sparing the spinoreticular fibres (Gybels and Sweet, 1989*a*; Garcia-Larrea *et al*., 1993). Finally, imbalance between activities in heat/pain ascending subsystems has been also recently considered to underlie central pain in Wallenberg syndrome by MacGowan and colleagues (MacGowan *et al*., 1997). These authors observed that a greater degree of spinothalamic deafferentation, with inclusion of medial brainstem, was associated with a lesser incidence of central pain and allodynia, and suggested that these symptoms could result from supersensitivity of the reticulothalamic connections due to a partial and 'selective' neospinothalamic lesion.

Results from intracranial stimulation experiments also support an imbalance between spinothalamic and spino-reticulo-thalamic subsystems in central pain. Stimulation of the rostromedial midbrain and medial thalamus can be painful in patients with central pain, while they usually do not evoke any sensation in cases not suffering from pain (Tasker *et al*., 1983; Gybels and Sweet, 1989*b*; Bennett, 1994; Gybels and Kupers, 1995). Tasker and colleagues first pointed out the peculiar sensitivity of the medial thalamus in patients with deafferentation pain, in whom electrical stimulation induced contralateral ill-localized burning resembling the pain from which the patient suffered (Tasker *et al*., 1983). Since medial thalamic and midbrain sites are innervated by reticulo-thalamic ascending fibres (Fujino *et al*., 1996; Willis and

Westlund, 1997), a hypothesis was proposed that abnormally provoked pain after lesions of the CNS might be related to residual, disinhibited activity of the spino-reticulo-thalamic component of the pain pathways (Tasker, 1990). Our data lend substance to this hypothesis by suggesting that incomplete spinothalamic lesions, more than complete abolition of LEPs, are likely to become associated to allodynia and hyperalgesia. We may therefore hypothesize that: (i) functionally extended lesions affecting all spinothalamic systems are likely to induce very deeply attenuated or abolished LEPs; and (ii) at the same time, these extended lesions are less prone to create an imbalance between spinal-thalamic subsystems. Therefore, the probability of observing hyperalgesia/allodynia will be lesser in patients with profoundly attenuated LEPs than in patients with partial LEP preservation, in whom the probability of lateral/medial systems imbalance is enhanced. Total LEP deafferentation, however, does not protect against spontaneous pain, since this latter was present despite the total absence of LEPs in five patients. Coexistence of spontaneous central pain and absent LEPs has been previously reported (Casey *et al*., 1996), and it is reasonably well established that central pain may occur in association with a complete lesion of the ascending spinal-thalamic systems (Gybels and Sweet, 1989*a*, *b*).

Ultra-late LEPs in central pain

A striking feature of LEPs in four patients with central pain was the presence of 'ultra-late' components (i.e. responses with latency >800 ms), which were in one of them the only LEP to persist after stimulation of the painful side (see Fig. 4A). Although exceptional in our series, such ultra-late components were observed exclusively in patients describing allodynic symptoms to the laser stimuli (Table 1). Ultra-late components of LEPs have been described in healthy controls after selective stimulation of C-fibres, obtained either by tiny surface stimulation (Bragard *et al*., 1996; Opsommer *et al*., 1999), by stimulation at warm-temperature levels (Magerl *et al*., 1999) or by pressure-induced blocking of A-fibres (Bromm and Treede, 1987). In this latter case, ultra-late components were accompanied by a poorly localized and unpleasant sensation, reminiscent of hyperalgesic pain (Bromm and Treede, 1987).

Landau and Bishop were the first to report concomitant abolition of the pricking pain sensation and the development of burning, poorly defined pain to skin simulation after A-δ pressure block (Landau and Bishop, 1953). They proposed 'a suppression effect of the pricking pain endings on the sensation induced at C-fibre endings'. This conclusion might be expanded to suggest a general suppression effect of the lateral, rapidly conducting spinothalamic system on the sensation induced by the slowly conducting, medial ascending components. To our knowledge, the only previous description of ultra-late responses in neuropathic pain concerns two patients reported by Wu and colleagues (Wu *et al*., 1999). In the two cases, both mechanical and thermal stimulation produced intense allodynic sensations, which could also be induced by brief radiant laser pulses at non-noxious intensity ranges.

The present results provide some support, albeit indirect, for a possible association between ultra-late responses and hyperalgesic reactions to laser. We conjecture that the occasional presence of ultra-late LEP responses in patients with allodynia and hyperalgesia (but never in patients without those symptoms) might be the electrophysiological expression of cortical activity generated by a slow-conducting, multisynaptic system, consistent with a spino-reticulo-medial thalamic pathway, which in normal conditions does not evoke scalp-recordable activity. An alternative hypothesis is that ultra-late responses could be mediated through residually intact fibres of lateral pain pathways. Although this cannot be formally discarded, two points stand again this hypothesis: first, the sensation associated with ultra-late responses in our patients was a dull, painful, strongly unpleasant and poorly localized feeling, inconsistent with activation of a lateral pain system. Indeed, even the most medially projecting fibres of the lateral system (i.e. bifurcating neurones projecting simultaneously to the lateral and medial thalamus) have response properties almost identical to those of cells projecting solely to the VPL (ventro-postero-lateral nucleus), and relatively small receptive fields, inconsistent with the sensations reported by our patients. Secondly, ultra-late LEP had latencies around 800 ms, clearly separated from those of A-δ LEPs. This suggests a bimodal distribution of responses, rather than the 'continuum' that should be expected were the ultra-late responses generated by residually intact fibres of the lateral system. The time-window used for recordings precluded the systematic study of possible ultra-late responses peaking later than 1000 ms (Bromm and Treede, 1987; Bragard *et al*., 1996; Opsommer *et al*., 1999). Longer analysis windows in future studies should permit estimation of the actual incidence of such responses associated with hyperalgesia.

LEPs in pain 'sine materia'

No consistent alteration of LEPs was found in the group of patients who complained of chronic pain in the absence of clinical sensory deficit, or neuroradiological/neurophysiological signs of lesion affecting sensory pathways. According to selection criteria (see Patients and methods), these patients did not present either any indication of excessive nociceptive input, such as inflammation or trauma, and their pain was considered to be non-organic or '*sine materia*' accordingly.

Patients with chronic pain in the absence of demonstrable neural lesion are frequently encountered in algologic centres and neurology services. In most clinical series, this group is dominated by chronic low back and pelvic pain, but also includes neck pain and headache (Okasha *et al*., 1999; Sobel *et al*., 2000), abdominal and chest pain (Martina *et al*., 1997), and musculoskeletal pain (Fritz *et al*., 1981). Fibromyalgia is a particular category of musculoskeletal pain that has been

associated with vegetative and functional abnormalities, including changes in cerebral blood flow (Mountz *et al*., 1998; Lekander *et al*., 2000), but not with organic nervous system disease. Fibromyalgic patients have similar laser detection thresholds as normal controls (Lorenz *et al*., 1996), but exhibit increased sensitivity to laser pain, as well as enhanced LEP amplitude (Gibson *et al*., 1994; Lorenz *et al*., 1996). Interestingly, recent data from Granot and colleagues showed coexistence of late and ultra-late LEPs to stimulation of tender points, suggesting localized C-nociceptor (and perhaps also central) sensitization, without evidence for any lesional effect on pain pathways (Granot *et al*., 2001). A number of our '*sine materia*' patients also showed enhanced LEPs to stimulation of the painful territory, of which one example is shown in Fig. 4. Although LEP enhancement has generally been considered to reflect hyperalgesia to heat pain (Treede *et al*., 1995; Lorenz *et al*., 1996), our present results and those of others (Casey *et al*., 1996; Wu *et al*., 1999) suggest that this pattern of increased LEPs is not encountered in patients with neuropathic hyperalgesia. Exaggerated LEPs therefore appear particular to cases where pain develops in the context of an intact nervous system, including non-organic pain. The pattern of response enhancement observed in non-organic patients, as well as in previous studies (Gibson *et al*., 1994; Lorenz *et al*., 1996), is reminiscent of the LEP up-regulation described during hypnotically induced hyperaesthesia and other attentional manipulations (Arendt-Nielsen *et al*., 1990; Miyazaki *et al*., 1994). In particular, willingly directing attention to the laser stimulus increases both the subjective pain sensation and the amplitude of LEPs (Garcia-Larrea *et al*., 1997). We may therefore suggest that an attentional mechanism may be the primary contributor to LEP enhancement in non-organic pain, since sustained attentional focusing on the painful region is a known characteristic of patients with psychologically maintained pain (McGrath, 1994). Although a deficient endogenous pain modulation (deficit in inhibitory mechanisms triggered by pain) might also contribute to this effect, the fact that the LEP up-modulation was strictly unilateral rather supports the selective attention hypothesis.

Correct diagnosis of non-organic pain is important since it contributes to predict the probability of early return to work (Lancourt and Kettelhut, 1992; Karas *et al*., 1997; Gaines and Hegmann, 1999) and/or failure of surgical therapy (Dzioba and Doxey, 1984; Donceel and Du Bois, 1999). Moreover, the inclusion of patients with non-organic pain has been shown to introduce a bias in controlled therapeutic trials (Lehmann *et al*., 1983). Tests developed to facilitate detection of non-physiological pain include the 'Waddell' scale (Waddell *et al*., 1980; Main and Waddell, 1998), the search for implausible sensory symptoms (Fishbain *et al*., 1991; Kiester and Duke, 1999), and, in case of sensory complaints, the recording of normal somatosensory evoked potentials (Mauguière *et al*., 1995). Our present results suggest that normal LEPs can also, in selected cases, contribute to support the non-organic origin of chronic pain. Lorenz and colleagues described normal LEPs (but absent P300) in one patient with complete anaesthesia due to conversion disorder, and stressed the use of neurophysiological testing to distinguish between conversion and malingering (Lorenz *et al*., 1998).

Normal or enhanced LEPs to stimulation of a purportedly neuropathic painful territory may play a double role in the assessment of pain *sine materia*. First, they document the non-neuropathic nature of the pain by showing preservation of normal spino-thalamo-cortical transmission. Secondly, LEP enhancement after stimulation of the affected territory suggests an attentional bias towards the stimulated region, in the context of intact neural machinery for pain transmission, and thus increases the likelihood that psychophysiological mechanisms may contribute to maintenance of the pain. This line of reasoning is only valid, however, if all causes of somatogenic pain, such as peripheral inflammation or trauma, have been ruled out. Indeed, information emanating from peripheral nociceptors and heat receptors converge at the spinal level, enhancing pain sensation and nociceptive reflexes (Plaghki *et al*., 1998), and may consequently also enhance cortical LEPs if the laser stimulus is applied onto a territory already sensitized by inflammation.

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