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Original article

Trigeminal responses to laser stimuli

Réponses à la stimulation trigéminale par laser

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Abstract

The majority of the studies on laser evoked potentials (LEPs) have been focused on hand and foot stimulations and only lately on the trigeminal system. Because of a high receptor density in the facial skin and the very short conduction distance, LEP recordings after trigeminal stimulation are easier and quicker than those after stimulation of the limb extremities. Laser pulses with a stimulus intensity close to perception threshold can evoke well-defined LEPs. Few trials are sufficient to yield stable and reproducible averages. Even ultralate LEPs related to the C-fibre input are comparatively easily obtained from the trigeminal territory. The brain generators of the main LEP waves are probably very close for the trigeminal and limb stimulations. Trigeminal LEPs have been found absent or delayed in patients with trigeminal neuralgia, trigeminal neuropathies, posterior fossa tumors, and brainstem infarctions or demyelinating plaques. Conversely, trigeminal LEPs appear to be enhanced in patients with migraine. High-intensity pulses directed to any trigeminal division also elicit reflex responses: a blink-like reflex in the orbicularis oculi and a single silent period in the contracting masseter muscle. The availability of a neurophysiological method of assessing function of the trigeminal nociceptive pathways reaching both the cerebral cortex and the brainstem reflex circuits, has provided new opportunities for investigating the pathophysiology of orofacial pain syndromes.

Résumé

La majorité des études portant sur les potentiels évoqués laser (PEL) se sont focalisées sur la stimulation de la main ou du pied, et seulement récemment sur la stimulation du système trigéminal. Du fait de la haute densité des récepteurs sur la peau du visage et de la très faible vitesse de conduction, les enregistrements des PEL obtenus en réponse à une stimulation trigéminale sont plus faciles à réaliser et plus rapides que ceux obtenus après une stimulation des membres supérieurs ou inférieurs. Les pulses laser délivrés avec une intensité de stimulation proche du seuil de perception donnent en général des PEL déjà bien définis. Un petit nombre d'essais est suffisant pour obtenir des réponses reproductibles et stables. Même les PEL ultra-tardifs, correspondant à une stimulation des fibres C sont obtenus plus facilement en stimulant le territoire trigéminal. Les générateurs cérébraux des principaux PEL sont probablement les mêmes pour des stimulations des membres inférieurs/supérieurs et pour des stimulations trigéminales. Les PEL obtenus en réponse à des stimulations trigéminales sont absents ou retardés chez des patients présentant une névralgie trigéminale, des neuropathies trigéminales, des tumeurs de la fosse postérieure, des infarctus du tronc cérébral ou des plaques de démyélinisation. Inversement, l'amplitude des PEL obtenus en réponse à des stimulations trigéminales est augmentée chez les patients migraineux. La délivrance de stimulations à haute intensité sur chaque division trigéminale entraîne aussi des réponses réflexes : un réflexe de clignement dans la zone orbitaire de l'œil et une période de silence au sein du muscle masséter en contraction. La possibilité d'utiliser une méthode neurophysiologique pour explorer les fonctions du système nociceptif trigéminal, et celle du cortex aux circuits réflexes du tronc cérébral, a ouvert de nouvelles perspectives dans l'étude de la pathophysiologie des syndromes de douleur orofaciale.

Keywords: Trigeminal system; Laser evoked potentials; Laser blink reflex; Laser silent; Period; Trigeminal pain

Mots clés : Système trigéminal ; Potentiels évoqués laser ; Reflex de clignement laser ; Période de silence laser ; Douleur trigéminale

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1. Introduction

Although some of the most common pains in the body affect face and mouth [42], the pathophysiology of several cranio-facial pain conditions, particularly those that are chronic, are still unknown or poorly understood, partly because of the insufficient information so far obtained with neurophysiological methods.

Because of the anatomical characteristics of the trigeminal territory, the neurophysiological investigation of trigeminal function poses far more problems than that of limb-nerve function. A standard nerve conduction study cannot be performed, and scalp potentials evoked by electrical stimuli are contaminated by almost unavoidable myogenic artifacts, due to direct excitation of facial nerve terminals or activation of trigeminal reflexes [30,31]. For these reasons, the neurophysiological assessment of trigeminal function has been mainly relying on the recording of trigeminal reflexes, i.e. the blink reflex, masseter inhibitory reflex, and jaw jerk. All these reflexes, however, are predominantly mediated by non-nociceptive, large-myelinated afferents; with high-intensity electrical stimuli, nociceptive Aδ afferents probably contribute to some of these reflex responses, but certainly they are not responsible for the latency, which is the most reliable reflex measure [12,28].

To assess the trigeminal nociceptive pathways, some studies used electrical stimulation of the dental pulp or the corneal mucosa, which are exclusively innervated by free nerve endings having a predominantly nociceptive function [35]. These methods, however, are technically difficult and confined to just one territory. Furthermore whether they provide a reliable, specific correlate of the nociceptive input is controversial [11,22].

Short-lasting radiant heat stimuli, as delivered by laser stimulators, circumvent the above difficulties, by providing selective activation of Aδ and C thermosensitive nociceptors in the hairy skin [38,48] without concomitant activation of motor nerve fibers or Aβ mechano-receptors.

2. Special characteristics of laser stimulations in the trigeminal territory

Laser stimulation techniques and evoked potentials have been refined for several facial territories, starting with intra-oral mucosa [44,45], upper lip [37], temple [6], supraorbital and mental skin [16].

Regarding laser stimulations, the trigeminal territory presents three characteristics: high receptor density, short conduction distance, and the risk/advantage of eliciting reflex responses.

2.1. Receptor density and perceptive thresholds

Although epidermal thickness varies with body site, it does not follow a regular trend. Skin thickness is similar in the forehead, upper arm and thigh, as well as cheek and trunk, and hand and ankle [53]. In contrast, skin biopsy studies have shown a higher density of epidermal free nerve endings in proximal (including face) rather than distal body sites [29,33]. Rabbits and cats show a clear concentration of thermal receptive fields around the nose, whisker pad and mouth

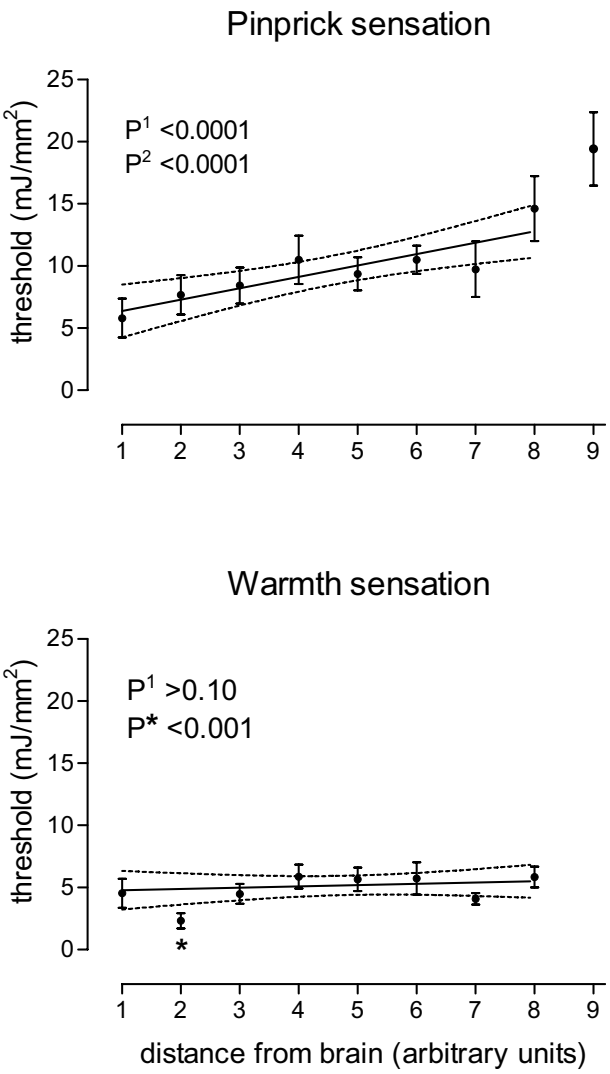

Fig. 1. Plots of the threshold values for pinprick (upper panel) and warmth (lower panel) sensations. In the *X*-axis, each stimulated body site is ranked according to its distance from the brain: (1) neck around the C5 spinal process; (2) upper lip; (3) forehead; (4) shoulder (just below the acromion); (5) dorsal trunk around the T9 spinal process; (6) T9 dermatome near the ventral midline; (7) lateral aspect of the hip; (8) hand dorsum; and (9) foot dorsum. The data for the foot have been omitted from the lower panel because we failed to evoke a warm sensation from this area. Dots are the mean ± 1 S.E. The continuous lines indicate linear regression and dashed lines the 95% confidence limits. In the upper panel, P1 indicates the level of significance of the post-test for linear trend when the data from the leg were included, P2 when they were excluded. The regression line in the upper panel is calculated after excluding from the analysis the data from the foot. In the lower panel P1 indicates the level of significance of the post-test for linear trend. *P** indicates the level of significance of the Welch's test between the data from the upper lip and those from all the other regions pooled (from [2]).

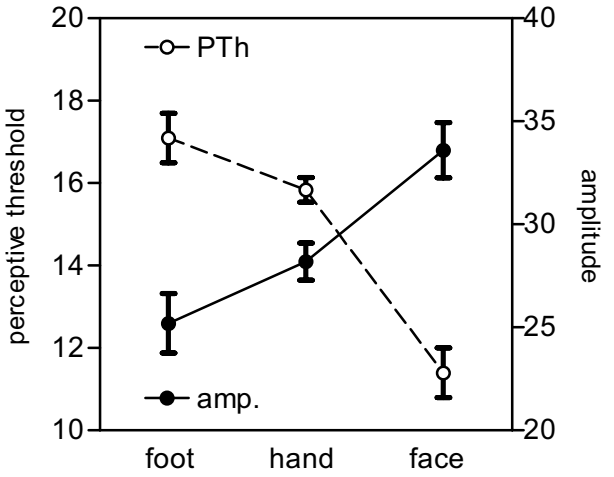

Fig. 2. Differences in threshold (mJ/mm^2) and amplitude (μV) of LEPs evoked by perioral, hand, and foot stimulations. Means ± S.E. in 30 normal subjects (from [16]).

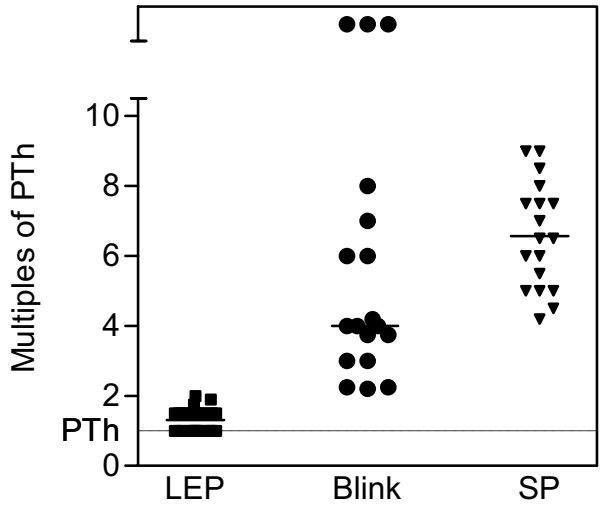

Fig. 3. Scatterplot and medians of the threshold for the scalp evoked potential (LEP), the blink response in the orbicularis oculi muscle (Blink), and the masseter SP, after laser stimulation, in the same 18 subjects. The three circles out of range represent three subjects with no blink response even at maximum stimulus intensity (from [16]).

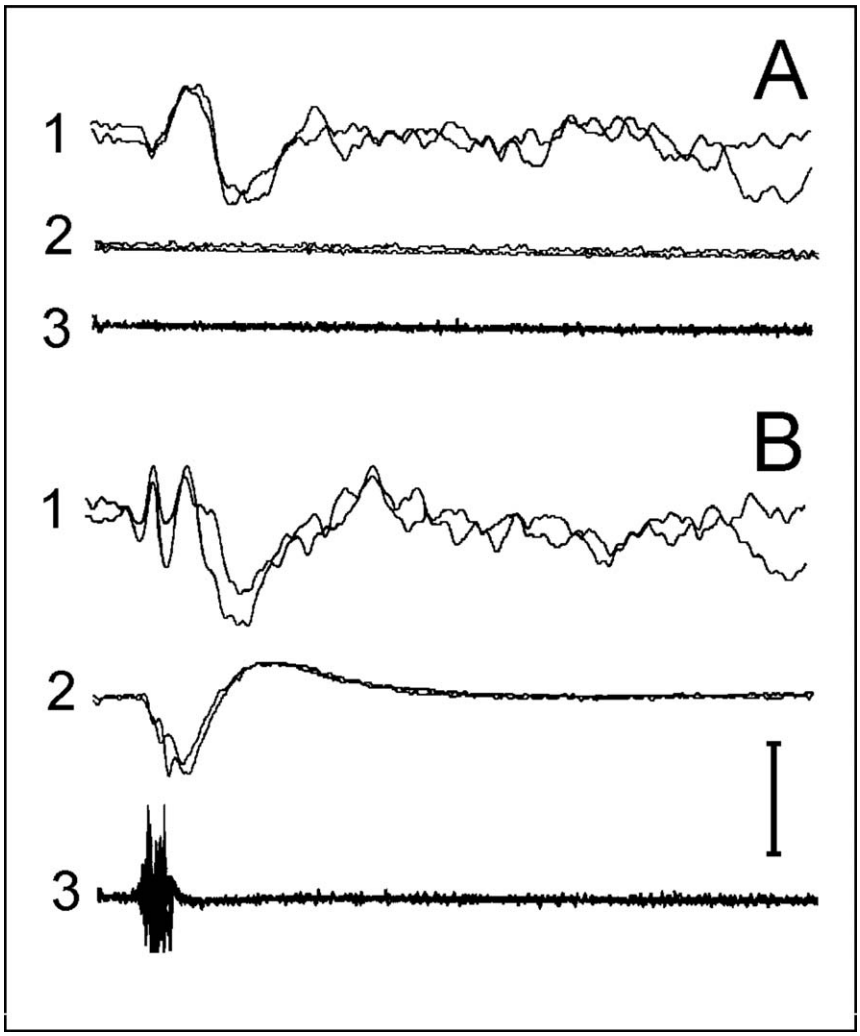

Fig. 4. Possible contamination of LEPs by laser-evoked blink responses. Recordings from Cz [1], EOG [2], and the left orbicularis oculi muscle [3] after laser stimulation of the left lower lip in a representative subject. Stimulus intensity increases from A (2× PTh) to B (4× PTh). Sweep duration 1 s. Vertical calibration 20 μV for the scalp, 50 μV for the EOG, and 200 μV for the muscle recordings (from [16]).

Table 1
LEPs after stimulation of the three trigeminal divisions in 30 normal subjects aged 22–69 years

Trigeminal division	Perceptive threshold (mJ/mm^2)	N wave latency (ms)	R-L difference (ms)	P wave latency (ms)	R-L difference (ms)	Peak-to-peak amplitude (μV)	R-L difference (μV)
V1	12.9 ± 4.2 (4.6–23)	179 ± 18 (130–211)	0.4 ± 9.8 (0–21)	269 ± 34 (183–304)	4.2 ± 24 (3–47)	29 ± 6.3 (18–40)	1.4 ± 8.4 (2–15)
V2	11.2 ± 3.6 (3.1–18)	166 ± 16 (118–198)	0.5 ± 9 (1–20)	255 ± 30 (192–306)	2.4 ± 16 (0–40)	33 ± 7 (16–50)	1.1 ± 5.6 (2–17)
V3	11.4 ± 3.3 (3.1–18)	168 ± 16 (120–200)	0.5 ± 8.5 (1–22)	252 ± 29 (190–300)	3.2 ± 15 (2–40)	34 ± 6.2 (12–60)	0.8 ± 4.6 (1–15)

[19], indicating a localized high thermal receptor density in these regions.

A high receptor density may explain why the perioral region provides the lowest laser perception thresholds, both for pinprick and warmth sensations [2–4,14,16]. In a study on topographical distribution of pinprick and warmth thresholds to CO_2-laser stimuli, Agostino et al. [2] found a significant positive correlation between distance from brain and the threshold for pinprick sensation: in Fig. 1A, note the difference between upper lip and hand dorsum (numbers 2 and 8 on the *X*-axis). Conversely, the warmth threshold did not show any distance-related trend; but the warmth threshold was significantly lower in the upper lip than any other site (Fig. 1B).

In a study on CO_2-laser evoked potentials (LEPs) in normal subjects, the investigators [16] found a significantly different perceptive threshold (PTh) to laser stimuli directed to the perioral region (11 mJ/mm^2), hand (15 mJ/mm^2), and foot (17 mJ/mm^2) (Fig. 2).

2.2. Conduction distance and LEP values

Because the short conduction distance minimizes the problem of signal dispersion along slow-conducting afferents, the trigeminal territory is advantageous for studying Aδ- and C-related LEPs. Fig. 2 shows the mean amplitude of the vertex Aδ-LEPs after foot, hand, and face stimulations (at a stimulus intensity corresponding to twice PTh) in 30 normal subjects: the amplitude progressively increased. Probably the lower signal-dispersion along a shorter distance yields a highly synchronized volley that exerts a strong spatial–temporal summation at central synapses and thus provides higher-amplitude scalp responses. No study has yet been performed to assess the correlation between LEP values and pain perception at trigeminal level [25].

Both the high receptor density and the short conduction distance concur to make the recording of trigeminal LEPs easy, quick, and safe. Few trials at a low stimulus-intensity (1.2–2× PTh) are sufficient to obtain reproducible brain signals and no damage at all is caused to the skin. Under fibreoptic guidance, or with an articulated arm, the laser beam can be directed to any facial region.

2.3. Reflex responses

Because of the high receptor density and the high number of trigeminal reflexes, laser stimuli may elicit reflex responses. Luckily, the stimulus intensity used in LEP recording is lower than the one necessary to elicit reflex responses. In a study of reflex responses possibly evoked in regional muscles, even maximum-intensity laser pulses failed to evoke reflex activity in relaxed masticatory muscles (masseter and temporal) or neck muscles (splenius capitis and sternocleidomastoid) [16]. But during voluntary contraction, high-intensity pulses induced a period of EMG suppression, between 60 and 120 ms. In masticatory muscles, a rather stable and reproducible silent period (SP) was obtained in all subjects. The mean threshold was 6.5 PTh, and stimulus intensity was never less than four times PTh, i.e. at least double the intensity used for LEP recordings (Fig. 3).

Unlike masticatory and neck muscles, the orbicularis oculi muscle showed, even in the fully relaxed condition, a bilateral (blink-like) excitatory response, with a latency of about 70 ms. This blink response varied widely among subjects. In some subjects it was absent, whereas in others it appeared easily, after relatively low-intensity pulses. The scatterplot in Fig. 3 shows a comparison of thresholds for LEPs, blink-like response, and masseter SP in the same 18 subjects, in the same session. The individual LEP thresholds were closely grouped near PTh, those for the SP were far higher, and those for the blink response were scattered throughout the whole range of intensities, overlapping in a few cases with the intensity used for LEP recordings.

Simultaneous scalp, EOG, and orbicularis oculi muscle recordings in subjects with low-threshold blink responses showed that the contaminating effect depended on the size of the blink. With large blink responses, the morphology of the main vertex negative wave (N2) changed (the rising phase steepened, the latency shortened, and the amplitude increased) or the N2-wave split into two steep peaks (Fig. 4). The P2 wave remained apparently unchanged. With small blink responses, which might, however, contaminate the LEPs, no obvious difference could be discerned between recordings with and without the blink.

This makes it mandatory to control a possible blink-reflex activity during LEP recordings: it is sufficient to place on the lower belly of the orbicularis oculi muscle one of the surface electrodes used for the EOG (one-side recording is sufficient because the blink responses are always bilateral and symmetrical); EOG is anyway indispensable in all LEP recordings, regardless of the site of stimulation.

3. Aδ-related trigeminal LEPs

Gas (Argon, CO_2) or solid-state (Tm:YAG, Nd:YAG, Nd:YAP) laser stimuli of low intensity, applied to the trigeminal territory, yield large-amplitude scalp potentials from each of the three trigeminal divisions, including the oral mucosa [16,37,44,45].

3.1. Normal Aδ-LEPs

As for limb-LEPs, the main signal consists of an N2–P2 complex with maximum amplitude at the vertex, though the latency is obviously shorter: N2 peaks at 160–180 ms and P2 at 240–270 ms. Using a CO_2-laser stimulator with a small spot (irradiated area ~5 mm^2) and low-intensity laser pulses (2× PTh) in the same subjects, Cruccu et al. [16] found that upper lip (V2) stimulation yielded LEP data similar to those for the lower lip (V3), whereas supraorbital (V1) stimulation, possibly because of a comparatively lower receptor density, evoked responses at a slightly longer latency and lower amplitude (Table 1).

An Nd:YAP laser yielded similar mean results: N2: 162 ms, P2: 242 ms, N2/P2: 21 μV after perioral stimuli; N2: 166 ms, P2: 246 ms, N2/P2: 18 μV [14].

Using a Tm:YAG laser and a program for brain electrical source analysis, Bromm and Chen [6] identified a first dipole at 106 ms after stimulation of the temple, localized in SII bilaterally, though significantly stronger contralaterally. In the study by Cruccu et al. [16], who delivered CO_2-laser pulses to the perioral region, the bilateral negativity peaked around 100–110 ms, but was more intense on the ipsilateral (left) hemisphere (Fig. 5). The maximum activities recorded at 165 and 250 ms around the vertex may reflect a major cortical generator located in deep midline brain structures, possibly the cingulate cortex, as suggested by Bromm and Chen [6]. The brain generators for trigeminal and limb Aδ-LEPs, with the exception of the primary somatosensory cortex, are probably close [23,24,46,52].

3.2. Clinical applications

Trigeminal LEPs represent a useful diagnostic tool for assessing facial sensory disturbances. Favored by the high

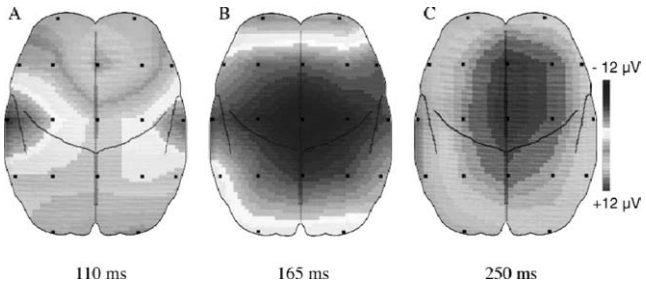

Fig. 5. Scalp topography of the grand average LEPs in five subjects (180 trials) after stimulation of the left lower lip. (A) Small-amplitude positivity in the mid-frontal region and bilateral negativity in the temporal areas (T3–T4) at 110 ms. (B) Widespread, maximum-amplitude negativity in the central regions (Cz) at 165 ms. (C) Widespread, maximum-amplitude positivity in the central regions at 250 ms (from [16]).

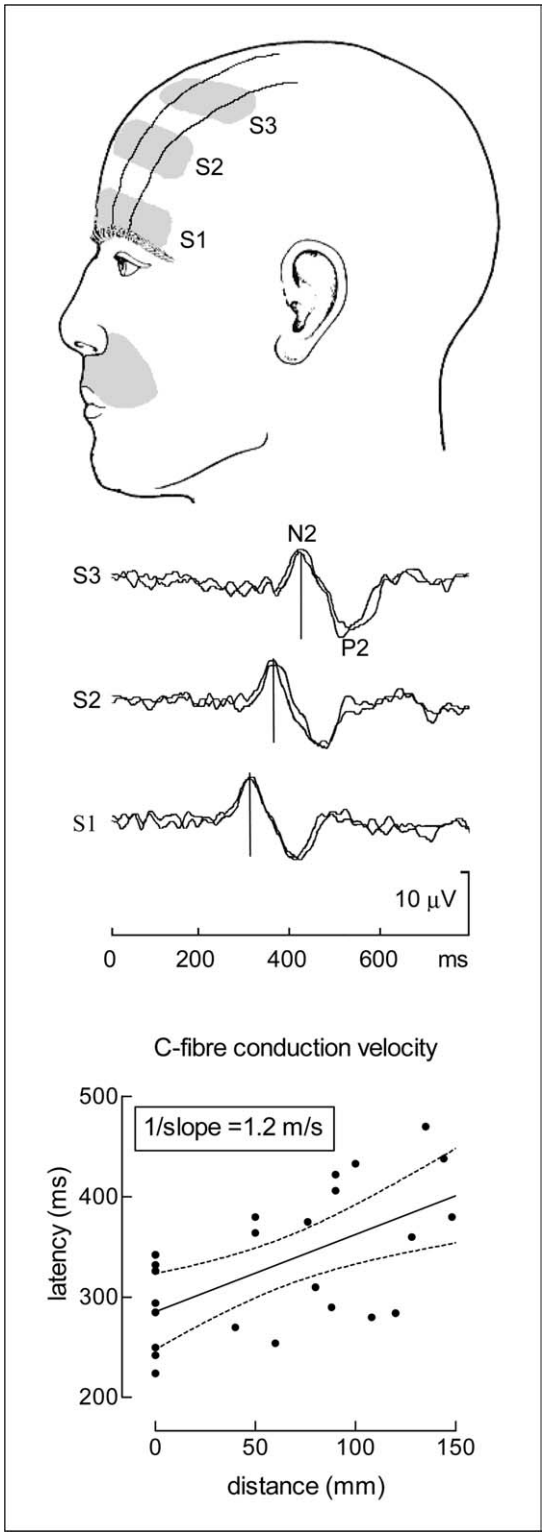

Fig. 6. Conduction velocity of unmyelinated afferents. Upper panel: schematic drawing of the three areas of stimulation (S1, S2, and S3) along the course of the supraorbital nerve branches (the grey area below the nose depicts the territory of highest sensitivity). Mid panel: C-fibre related LEPs after stimulation of the forehead skin at S1, S2, and S3 in a representative subject. Two superimposed averages of 20 trials each. Lower panel: scatterplot of the LEP latencies (taken at the N2 peak) at all stimulation sites in all subjects. Regression line ($P < 0.005$) indicated by continuous line, 95% confidence intervals by dashed lines (from [14]).

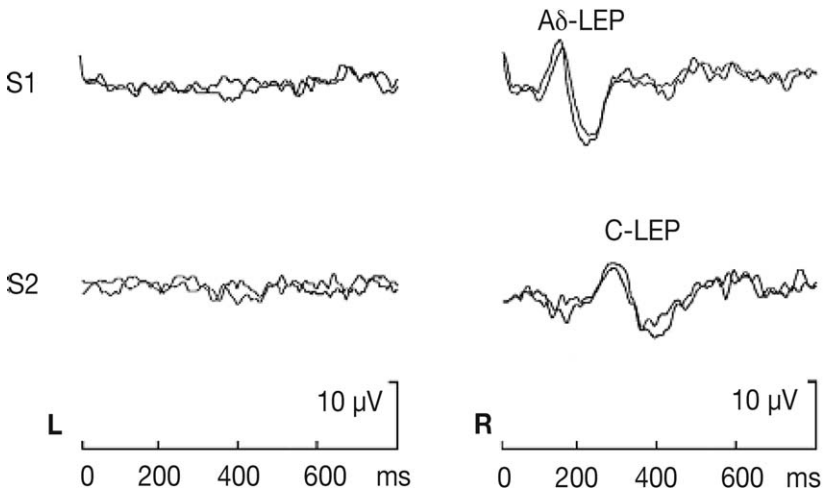

Fig. 7. Trigeminal LEPs in a patient with left Wallenberg syndrome. Laser stimuli whether set for Aδ-fibre or C-fibre activation when directed to the ipsilateral face failed to evoke LEPs, whereas those directed to the contralateral face evoked normal Aδ- and C-related LEPs (from [14]).

receptor density and short conduction distance, trigeminal-LEPs are low-threshold and high-amplitude.

Agostino et al. [1] studied trigeminal Aδ-LEPs after perioral stimulation in 52 diabetic patients, whom they classified into three groups according to severity of the distal neuropathy, as assessed by nerve conduction studies. Trigeminal LEPs had a longer mean latency and lower amplitude in diabetic patients than in normal subjects and the LEP abnormality frequency was higher in the patient-groups with a more severe polyneuropathy. Conversely, Cruccu et al. [16] demonstrated selective sparing of small myelinated fibers in patients with chronic inflammatory demyelinating polyneuropathy by finding abnormal trigeminal reflexes and normal trigeminal LEPs.

Trigeminal LEPs were abnormal in about 50% of 40 patients with idiopathic trigeminal neuralgia, suggesting that the Aδ-fibre dysfunction may play an important role in the pathophysiology of neuralgic pain, and resulting more sensitive than trigeminal reflexes [13]. In 27 patients with symptomatic trigeminal pains secondary to post-herpetic neuralgia, cerebello-pontine-angle tumors, or multiple sclerosis, LEPs were always abnormal [13,50]. In a study in patients with pain due to temporo-mandibular dysfunction, the trigeminal LEPs had a normal latency, but the mean amplitude was slightly reduced with respect to control values [40].

The latency of trigeminal LEPs is normal in patients with headache, whether tension-type or migraine. In migraine patients, however, conditions that normally dampen the vertex potentials, such as attentional tasks (e.g. distraction by arithmetic calculations), or the habituation to rhythmic stimulations, in the inter-ictal phase do not dampen trigeminal LEPs (or affect them far less than in control subjects or tension-type headache patients) [18,51]. Furthermore, the trigeminal LEP threshold has been found decreased in migraine patients during attacks [17]. This enhancement of LEPs, as well as pain, in patients with migraine is thought to be due to a deficit of the central inhibitory controls over the trigeminal circuits.

In general, trigeminal LEPs appear more sensitive than trigeminal reflexes and help to differentiate neuropathic from nociceptive pains.

4. C-related trigeminal LEPs

LEPs mediated by unmyelinated afferents (C fibers) are not easily obtained in healthy humans despite evidence that C fibers are readily excited by brief laser heat pulses in animals and humans [8,9]. The difficulty arises from the co-activation of Aδ afferents: the Aδ volley probably inhibits C-fibre transmission at central synapses; furthermore this weakened C-fibre input probably reaches the same brain areas that have been engaged by the preceding Aδ input; all this makes it difficult to identify any C-related activity after the Aδ-related scalp potentials. This is more true in the trigeminal territory, where the latency difference between Aδ- and C-LEPs is minimized by the short conduction distance. But, if the stimulus selectively excites C receptors, the short distance becomes an advantage and the C-LEPs appear more easily and are more stable and high-amplitude than those after limb stimulations.

Various techniques have been used to provide a selective activation of C fibers: experimental block of group A fibers [7]; spectral analysis of expected time window [3,5]; selection of single trials devoid of Aδ-LEPs [47]: “microspot” stimulation [5,36]; or stimulus intensities below the Aδ activation threshold [27,32,49].

Recently, Cruccu et al. [14] assessed the trigeminal C-fiber function by means of laser pulses directed to the facial skin and recorded the related brain potentials in healthy humans and in patients with impairment of the trigeminal thermal-pain pathways. Because the heat-responsive C receptors (mechano-thermal C nociceptors and C warmth receptors) have a laser threshold markedly lower than Aδ receptors, and because C warmth receptors have a very low density, these investigators used laser pulses with a very low

stimulus intensity and a very large irradiated area (~180 mm^2), raising the temperature of the facial skin to 39 °C (as measured with a thermocouple [27]). Using a CO_2-laser, these pulses elicited warmth sensations and vertex potentials with a latency compatible with C-fiber conduction (negative wave 280 ms; positive wave 380 ms) if directed to the upper lip region, close to the *sulcus nasus-genius* and *ala nasi*. This region is, in lower mammals, particularly dense with warmth receptors [19]. Using an Nd:YAP laser the same results were obtained from other trigeminal territories, such as the supraorbital region and the lower lip.

An estimate of the peripheral conduction velocity in the supraorbital territory yielded a mean value of 1.2 m/s (Fig. 6), which is consistent with microneurographic findings in unmyelinated fibers. According to dipole source analysis, the main waves of the scalp potentials originated from the anterior cingulate gyrus, but they were preceded by activity in the opercular region and followed by activity in the insular region. As for the trigeminal Aδ-LEPs, the brain generators were close to those described for limb stimulations [24].

Two patients with idiopathic trigeminal neuralgia [43] had a severe degeneration of all myelinated fibre groups, with sparing of unmyelinated fibers. In these patients, laser stimuli elicited warmth sensations or burning sensations, according to the stimulus intensity; in either case the scalp potentials fell in the C-LEP latency range, with no Aδ-related activity. In contrast, two patients with Wallenberg syndrome had absent both Aδ-LEPs and C-LEPs after stimulation of the affected side (Fig. 7). These findings demonstrated that trigeminal C-LEPs are mediated by unmyelinated fibers and the spinal trigeminal nucleus in the medulla [14].

5. Laser blink

Relatively high-intensity laser pulses delivered to the facial skin elicit a blink-like response in the orbicularis oculi muscle (laser blink reflex, LBR) with a latency of about 70 ms [21,41]. Because laser pulses selectively excite the free nerve endings in the superficial layers of the skin and activate mechano-thermal nociceptive afferents [8,32,48], the LBR is considered the nociceptive counterpart of the R2 component of the blink reflex.

Whereas in other regional muscles laser pulses fail to elicit excitatory reflex responses even at maximum stimulus intensity, in the orbicularis oculi relatively low-intensity pulses may—in some individuals—give rise to a LBR (regardless of the trigeminal division stimulated). The brainstem inter-neurons that mediate the spontaneous and reflex eye blinking seem extremely sensitive to different sensory inputs. Indeed, the orbicularis oculi muscle behaves differently from all other muscles in response to startle [10]. Ellrich [21], with a YAG-laser stimulator, first described the blink reflex response after stimulation of the three trigeminal divisions. LBR was obtained with pulses (600 mJ) above pain threshold and never with pulses at lower intensity.

In our experience [16], a few subjects (we call them "blinkers") even blinked at the same intensity used for LEP recording, whereas a few did not blink even at maximum intensity. Experimental studies in healthy volunteers, however, suggested that rather than being part of a startle reaction, the human LBR is a purely nociceptive reflex under all respects: LBR was never abolished by announcing the stimulus to the subject [21], LBR withstood relatively high-frequency rhythmic stimulations, and unexpected laser pulses failed to evoke larger responses [41]. Like other nociceptive reflexes, the LBR is mediated by Aδ afferents and is completely and quickly suppressed by anesthetic block of peripheral afferents and by opiates (Fig. 8). Data on reflex interactions and recovery curves showed that LBR is relayed

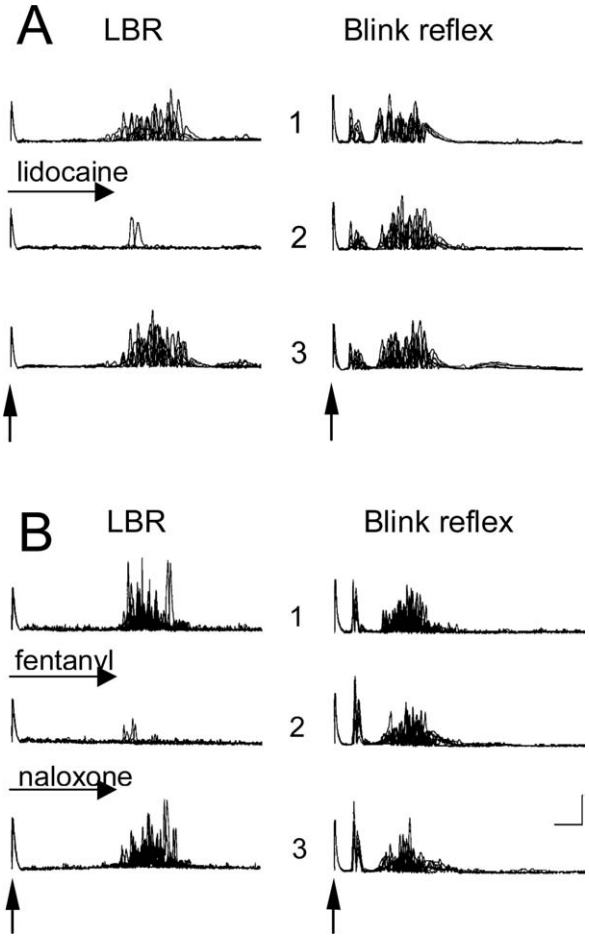

Fig. 8. In A, modulation of the LBR and the electrically elicited blink reflex induced by the lidocaine-induced supraorbital nerve block in one subject. About 5 min after the lidocaine injection, as soon as the participant no longer reported perceiving the laser stimuli, the control LBR [1] was abolished [2] whereas the R2 of the blink reflex was practically unchanged. Both responses recovered within 30 min [3]. In B, modulation of the LBR and the electrically elicited blink reflex induced by i.m. opiate injection in one subject. Twenty minutes after the fentanyl injection the control LBR [1] was suppressed [2] and the fentanyl induced-effect was reversed by the naloxone injection [3]. The electrically induced blink reflex remained appreciably unchanged. In A and B, 10 trials for each block are superimposed and full-wave rectified. Calibration: 20 ms; 200 μV. Arrow indicates the stimulus onset (from [41]).

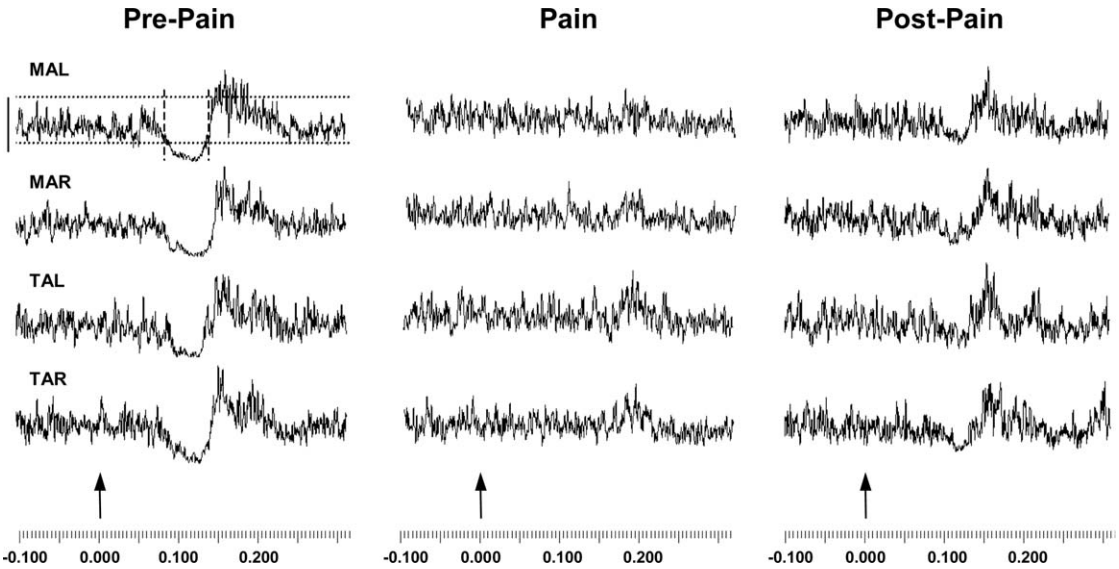

Fig. 9. Example of LSP recordings in one subject. Sixteen sweeps from the four muscles (MAL, MAR, TAL, TAR) are rectified and averaged during the three conditions (pre-pain, pain and post-pain). During tonic skin pain LSP were almost completely abolished and the responses only partially recovered in the post-pain recordings. Arrow shows the laser stimulus delivered at $t = 0$ ms. Horizontal stippled lines indicate ±50% of pre-stimulus RMS. Vertical dashed lines indicated onset and offset latencies. Time analysis: 100 ms pre-stimulus; 300 ms post-stimulus. Vertical calibration: 200 μV (from [39]).

through a polysynaptic circuit and shares part of the interneurons with the non-nociceptive R2 blink reflex [41].

For these reasons, the LBR may prove a useful tool for studying the pathophysiology of orofacial pain syndromes and for the topodiagnosis of small brainstem lesions involving the nociceptive trigeminal pathways. For clinical applications, the LBR has major advantages over the nociceptive corneal reflex evoked by mechanical or electrical stimulation of the corneal mucosa [35]. Most of all, the LBR can be elicited by laser stimuli to the skin of all the three trigeminal divisions and does not require the active collaboration of the subject.

6. Laser silent period

The only jaw reflexes (or trigemino-trigeminal reflexes) amenable to clinical investigation are the mandibular tendon jerk and the "cutaneous" inhibitory periods. Electrical or mechanical stimuli delivered to the oral region evoke a reflex inhibition of the jaw-closing muscles, the masseter (or temporalis) inhibitory reflex. In the EMG recordings from contracted jaw-closers, this reflex inhibition appears as an early and a late phase of suppression, also called ES1 and ES2 exteroceptive suppression [26], or SP1 and SP2 silent periods [35]. Probably because electrical stimuli yield a mixed—nociceptive and non-nociceptive—input, some investigators believe that the first or the second, or both components are nociceptive reflexes [21,34]. Innocuous mechanical stimuli will elicit both components, however, and indirect evidence supports the view that the afferents belong to the large-myelinated Aβ group [35].

Recent reports show that noxious laser stimuli directed to the perioral region induce a powerful inhibition in the human jaw-closers [15,20,21]. High-intensity (50 mJ/mm^2) laser pulses, fivefold the perceptive threshold, evoke a single inhibitory phase in the masseter and tremporalis muscles (laser silent period, LSP), at 50–80-ms latency [15,20,21].

The LSP circuit is still unclear. Experiments studying the interaction with heterotopic stimuli and non-nociceptive responses and the recovery curves to paired laser stimuli showed that the LSP response is mediated by a multisynaptic chain of inter-neurons and shares with the masseter SP2 part of the central circuit in the ponto-medullary region [15].

The LSP response is a useful tool for assessing the brainstem nociceptive reflex pathways in experimental and clinical pain conditions. The LSP was recently investigated in an experimental pain study where experimental muscle and skin pain had an inhibitory effect on the brainstem reflex pathways which mediate the LSP, suggesting the involvement of the antinociceptive control systems [39] (Fig. 9). A clinical study in patients with painful temporo-mandibular dysfunction matched the result yielded by the experimental study: the LSP was strongly suppressed or absent in patients with painful temporo-mandibular dysfunction compared to control subjects [40].

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