EEG and laser stimulation as tools for pain research

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Current Opinion in Investigational Drugs 2005 **6**(1):
 ISSN 1472-4472

Laser heat stimulators selectively activate Aδ- and C-nociceptors in the superficial layers of the skin. Their high power output produces very steep heating ramps, which improve synchronization of afferent volleys and therefore allow the recording of time-locked events, such as laser-evoked brain potentials. Study of the electrical brain activity evoked by Aδ- and C-nociceptor afferent volleys revealed the existence of an extensive, sequentially activated, cortical network. These electrophysiological responses are modulated by stimulus-driven and, even more extensively, top-down processes. The specificity and validity of these components for pain research are currently under intense scrutiny.

Keywords Aδ-fibers, C-fibers, electroencephalogram, laser evoked potentials, pain

Introduction

Along with other electrophysiological and psychophysical techniques, cerebral evoked potentials have provided substantial knowledge with regard to sensory, perceptual and cognitive processes in the brain. Additionally, clinical investigations routinely use evoked potential techniques to assess the integrity of the nervous system. Conventional somatosensory evoked potentials (SEPs), elicited by transcutaneous electrical nerve stimulation, explore the output of the fast conducting mechanoreceptive Aβ-fibers and their contribution to the dorsal column and medial lemniscal system. However, these techniques do not allow identification of responses mediated through the antero-lateral spinothalamic thermoalgesic pathways. Therefore, when pain and temperature sensitivity are predominantly affected (eg, small fiber neuropathies, syringomyelia, and Wallenberg's syndrome) conventional SEPs do not succeed in revealing objective correlates of the underlying selective sensory deficit [for a review, see references [1••, 2••]). It was long assumed that the absence of evoked potentials (EPs) related to Aδ- or C-fiber activation resulted from temporal dispersion or desynchronization of peripheral and central afferent inputs, and from the inability to detect volume-conducted potentials originating from a small population of cortical neurons activated by a small number of Aδ- or C-fibers [3]. Up to the mid 1970s, attempts to record EPs following painful stimulation in humans and animals were restricted to electrical stimulation of the tooth pulp (assumed to be richly and selectively innervated by Aδ-fibers), and to selective blockade of different nerve fiber groups for a review see reference [4]. Nevertheless, it was hoped that if an adequate modality-specific stimulus could be developed, EPs could be used as a neurophysiological tool for exploring the thermoalgesic system in the same manner by which short latency or modality-specific exogenous EPs had provided measures for the auditory and visual modalities. The requirements were high: (i) to allow time locking of stimulus-related EEG responses, the stimulus needed to be brief (milliseconds); (ii) to improve the signal-to-noise ratio of these responses, the method should allow the presentation of a large number of consecutive stimuli; (iii) to evoke responses specifically mediated by spinothalamic pathways, the stimulus had to be selective for the small nociceptive afferents (no skin contact); and finally (iv) for ethical reasons, but also to avoid unwanted sensitization of nociceptors, the stimulus had to be non-injurious.

The laser as a heat stimulator

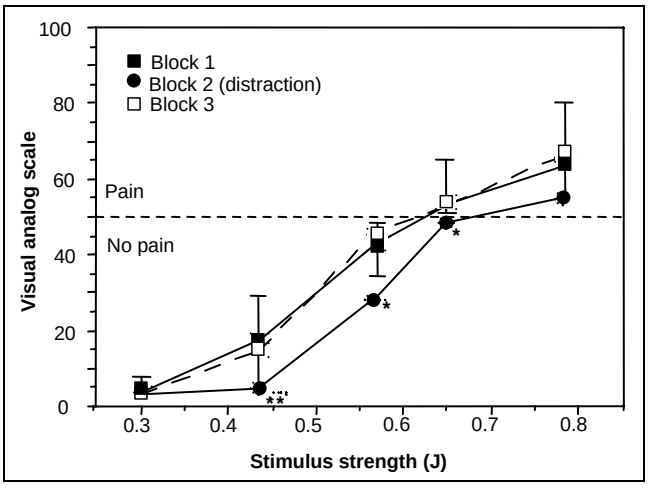
In search of an adequate nociceptive-specific stimulus, Mor and Carmon [5] designed the CO_2 laser stimulator. This instrument offers several remarkable advantages over conventional heat stimulators. It produces a collimated beam of monochromatic light in the far infrared spectrum of (wavelength 10.6 μm, invisible to the human eye) with a Gaussian irradiance profile. The stimulus is natural, meaning that unlike electrical stimuli, it does not bypass transduction processes. Its reflectance is negligible (< 0.5%), and independent of skin pigmentation. Prior blackening of the skin is therefore unnecessary. Skin transparency is low (< 60 μm). As a consequence, the calorific energy is confined to the epidermal layers, where the free nerve endings of Aδ- and C-nociceptors are located. Stimulus parameters (intensity, duration and surface area) are perfectly controlled and reproducible. Finally, as the CO_2 laser stimulator can deliver a high power output, it allows production of very steep heating ramps of thousands of degrees Celsius. This latter advantage is an essential requirement of recording of time-locked events, such as nociceptive reflexes, reaction times and evoked brain potentials. Indeed, Bromm e*t al* [6] showed that, due to the rapid rise in skin temperature, the laser stimulus allowed a much better synchronization of the afferent volley of small Aδ- and C-fibers than conventional heat stimulators. For a thorough review of the respective properties, advantages and disadvantages of other laser stimulators, references [7••, 8••] are recommended reviews.

Behavioral responses to laser stimuli

Depending on stimulus intensity, brief laser stimuli (eg, ≤ 50 ms duration, approximately 2 to 10 mm beam diameter) directed to a non-glabrous area of skin (eg, dorsum of the hand) evoke a variety of sensations, extending from the non-painful to the painful domain (Figure 1). At stimulus intensities slightly above the absolute detection threshold, perception is dominated by warmth and touch-like

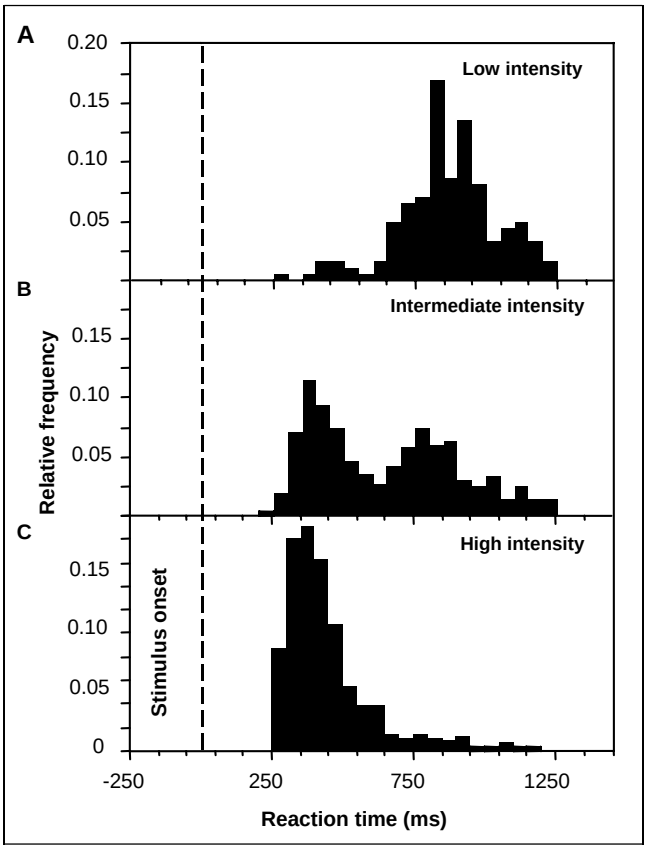
sensations. The average reaction time is above 800 ms (Figure 2A). Given their low conduction velocity, this latency is compatible with the detection of signals ascending trough C-fibers. At higher intensities, individuals report a well-localized, predominantly pricking sensation (referred to as 'first pain'). This sensation is detected with much shorter reaction times (350 ms on average), compatible with the peripheral conduction velocity of Aδ-fibers (Figure 2C). Most interestingly, individuals often spontaneously report that this first sensation is followed by a second diffuse and long lasting burning sensation, referred to as 'second pain'. When intermediate stimulus intensities are used, a bimodal frequency distribution of intensity of sensations and of reaction times is observed (Figure 2B). The dual nature of these behavioral responses may be interpreted as resulting from the activation of two distinct afferent nociceptive pathways; one with a low heat threshold (approximately 40°C) and slow conduction velocity (< 1 ms) related to non-myelinated C-fibers, and the other with a high heat threshold (typically > 46°C) and fast conduction velocity (about 10 to 20 ms), related to small myelinated Aδ-fibers. The difference between the detection latency of Aδ fiber-mediated 'first pain' and C-fiber-mediated 'second pain' is only observed when very fast heating ramps (> 1000 °C) are used. Under these conditions, and despite the fact that the heat threshold of Aδ-nociceptors is higher than that of C-nociceptors, the stimulus activates all polymodal nociceptors quasi-simultaneously. Due to the difference between Aδ- and C-fiber conduction velocities, Aδ-nociceptor input activates central projections well before C-nociceptor input (Figure 3). Depending on peripheral conduction distance, the difference in arrival time of both afferent volleys may vary between 0.2 s and more than 1 s.

Figure 1. Intensity of sensation as a function of laser intensity.



Visual analog scale (VAS) ratings (median values, 10 individuals) for five laser stimulus intensities, repeated six times in random order during each of three blocks of an experimental session. In the middle of the scale (VAS = 50), an anchor marks the borderline between the non-painful and painful domain of sensation. Block 1 is the control situation (vertical bars represent interquartile range). Block 2 examines the influence of a distracting task (arithmetic subtraction), and block 3 corresponds to the recovery situation. The effect of distraction appears as a global shift of the stimulus-response curve towards higher stimulus intensities (Wilcoxon paired rank test of Block 2 versus Block 1; * $p < 0.05$, ** $p < 0.01$).

Figure 2. Frequency distributions of reaction times.



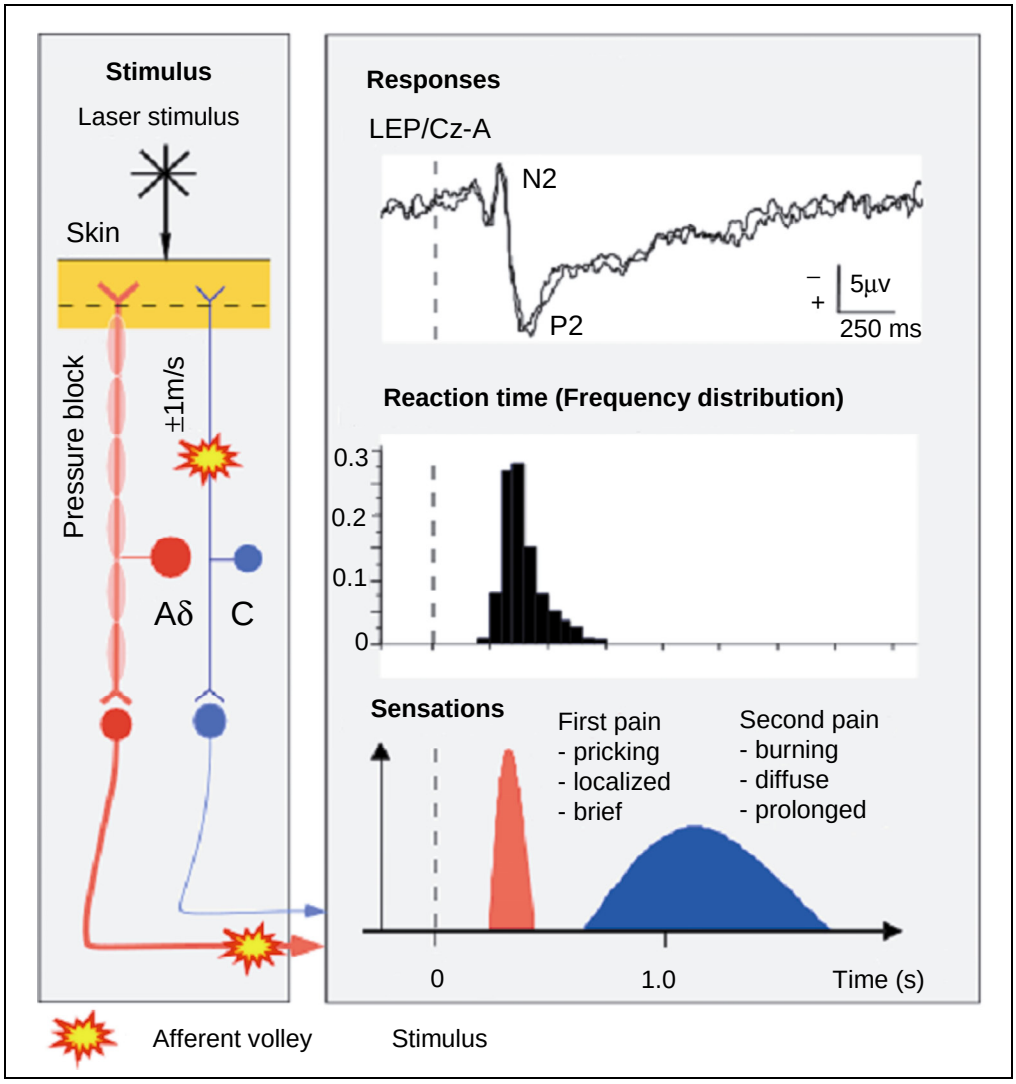
Relative frequency distribution of reaction times obtained from five individuals each exposed to 90 laser stimuli (duration of 40 ms, beam diameter of 10 mm) of three intensities (5.0, 7.5 and 10.5 mJ/mm^2) directed in random order to the dorsum of the hand.

When experimental conditions are rigorously controlled, these behavioral measures are quite stable, both within and between individuals. However, these measures are highly sensitive to variations of peripheral parameters (eg, base skin temperature and stimulus surface area) and central factors (eg, attention and distraction), as well as to drugs that may influence one or more of these factors. For example, performing a mental subtraction task during laser stimulation produces a significant and immediately reversible reduction in intensity of perception (Figure 1) [9].

LEPs mediated by Aδ-fibers

When heating the skin with a brief (eg, ≤ 50 ms), intense (≥ 8 mJ/mm^2) and relatively large (eg, beam diameter of 2 to 10 mm) laser stimulus, laser-evoked brain potentials (LEPs) recorded over the scalp reveal components whose latencies are compatible with the conduction time of Aδ-fibers. Even though most individuals report not only the perception of Aδ-nociceptor-related 'first pain', but also the perception of C-nociceptor-related 'second pain', no later components, compatible with the conduction time of C-fibers, can be identified (Figure 3). Typically, laser stimulation of the hand dorsum produces a triphasic complex (referred to as late LEP), starting with a small negativity (N1) maximum at contralateral temporal leads and peaking at 170 milliseconds. This initial component is immediately

Figure 3. Coactivation of Aδ and C-fibers by laser stimuli.

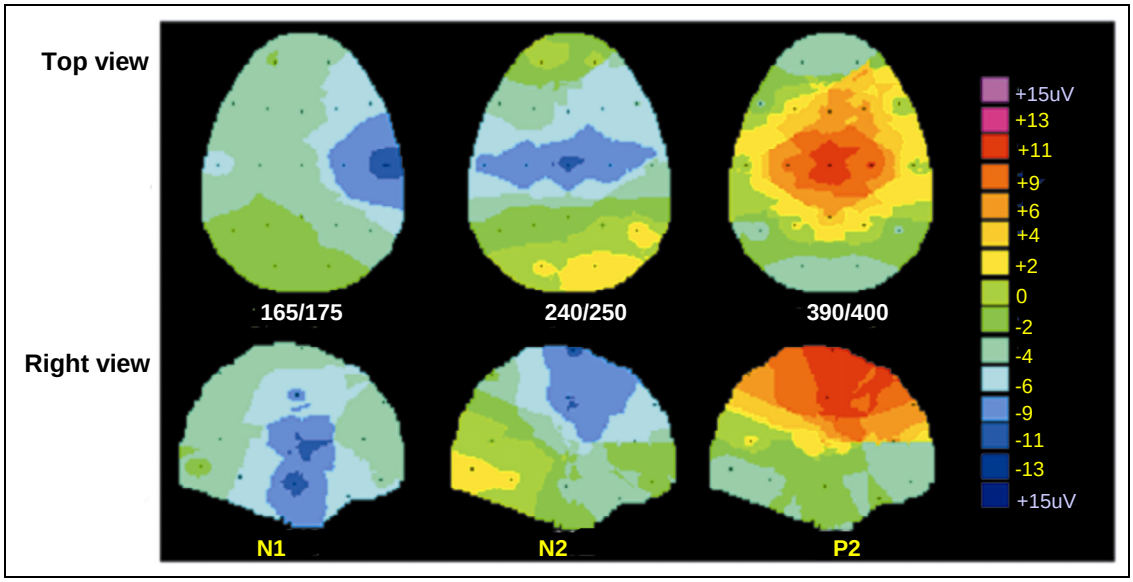


After nociceptive laser stimulation of the hand dorsum, individuals spontaneously report perception of a double-pain sensation. Reaction times and the N2-P2 complex of LEPs recorded at the vertex are evoked by the afferent volley of Aδ-nociceptors, which arrive at central projection sites with much shorter delay compared with the slower afferent volley from C-fibers. Note the absence of an electrophysiological correlate for the second pain evoked by the C-fiber afferent volley.

followed by a large negative-positive complex (N2-P2) maximum at the vertex, and peaking at 250 and 390 ms, respectively [10]. Electrical scalp topography (figure 4) and source localization by dipolar modeling of these electroencephalogram (EEG) signals [11, 12, 13••], consistently revealed the activation of an extensive bilateral cortical network, comprising the secondary somatosensory cortex (S2), the insular cortex and the anterior cingulate cortex. Ipsilateral activation of these areas appeared with a delay of approximately15 ms, compatible with transcallosal transfer times. These cortical generators have been confirmed by epidural and intracerebral recordings [14, 15], the earliest response being recorded contralateral to the stimulus, in the cortex of the superior bank of the sylvian fissure (corresponding to the localization of S2 in humans). This early response was relatively insensitive to attentional modulations and cognitively-induced manipulations of pain sensation [13••] see also reference [16•].

Both the amplitude of the vertex N2-P2 complex and the intensity of perception co-vary with the intensity of laser stimulation. As reported by Carmon *et al* [17] using single trial analysis, a significant correlation was found between the magnitude of late LEP recorded from the vertex, subjective report of pain and intensity of the stimulus. However, partial correlation coefficients demonstrated that late LEP amplitude was more strongly related to subjective intensity of perception than to intensity of stimulation. It is now generally accepted that late LEP vertex components are correlates of secondary mechanisms of sensory information processing which, in contrast to the laser stimulus, are probably not specific to the nociceptive system. These components are sensitive to numerous endogenous factors, such as the experimental surroundings of the individuals involved, general level of arousal and focus of attention. To validate pain-related changes using cerebral evoked potentials, it is therefore mandatory to keep these attentional

Figure 4. Scalp topography of late-LEPs.



[Figure Legend] Late-LEP topographic maps of components N170 (N1), N245 (N2) and P395 (P2) evoked by nociceptive laser stimulation (duration of 50 ms, beam diameter of 10 mm) of the dorsum of the left hand. The upper row represents top view maps and the lower row represents right view maps of grand means (five individuals).

variables constant across experimental conditions using, for example, a stimulus intensity rating task [2••,18]. To maintain a high and constant level of vigilance during the entire experimental session, it is often worthy to induce pain in an unpredictable manner by randomizing, for example, inter-stimulus interval and stimulus intensity. When different conditions or skin areas are tested, the experimental design must imperatively be balanced. When different stimulus properties are used within a block (eg, different intensities or surface areas), these properties should be randomized, have equal probabilities of occurrence and be equally relevant to the task.

Finally, the possible relationship between endogenous P3-like components and the LEP P2 component should be discussed. P3b components, typically elicited by infrequent task-relevant stimuli presented within two-stimuli oddball paradigms, are thought to reflect closure of sensory information processing, or 'context closure' [19,20]. Several studies have shown that laser-evoked P2 is not a P3b-like component [16•,20,21,22]. These investigations showed that approximately 600 ms after stimulus onset, infrequent task-relevant laser stimuli could elicit an additional parietal P3b-like positivity. Deviant or novel stimuli can evoke another component, labeled P3a, and are thought to reflect involuntary shifts of attention towards unexpected or potentially significant events. Compared with P3b, the P3a component has an earlier latency and a more anterior scalp topography. One study has shown that overlapping P3a-related components most probably contributed to the laser-evoked P2 component [23].

LEPs mediated by C-fibers

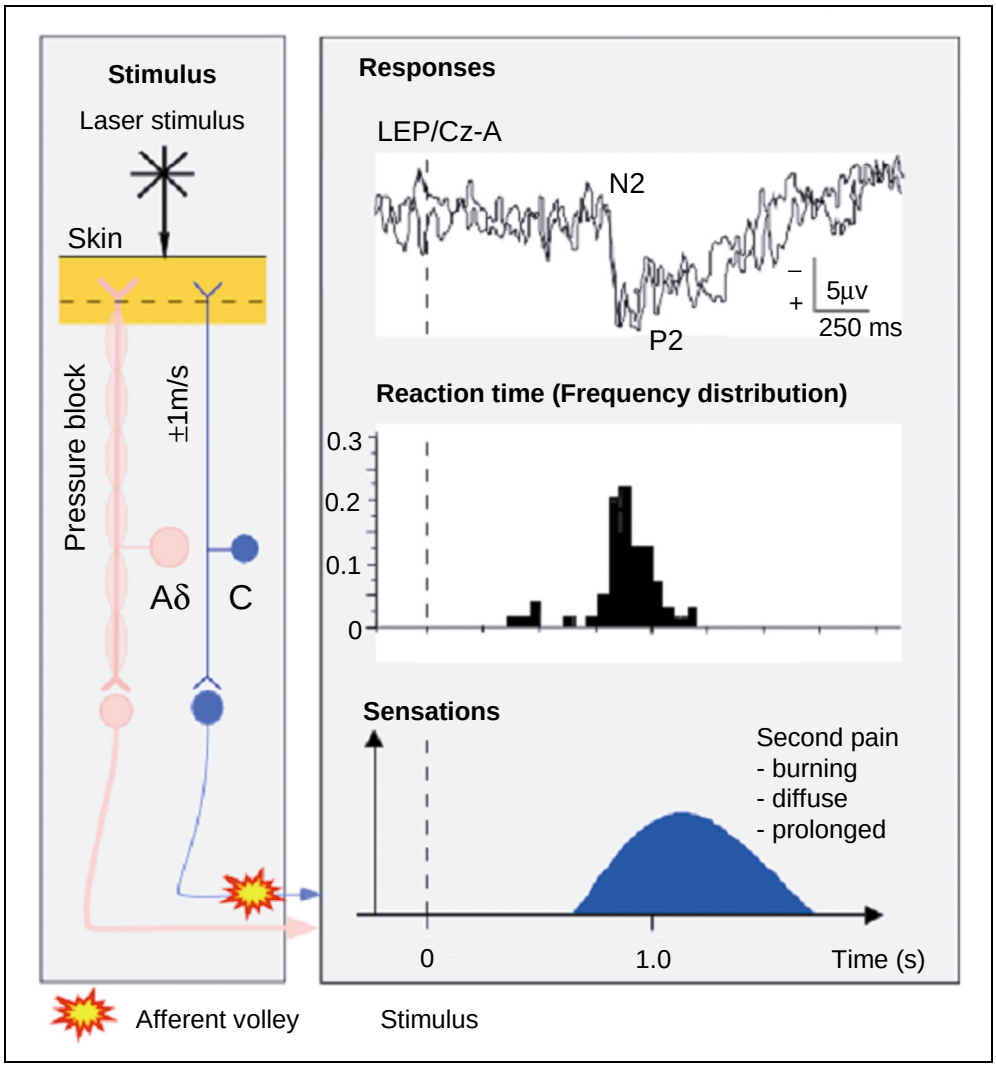
C-nociceptor afferent volleys can evoke electrical brain responses (referred to as ultra-late-LEPs) provided that the Aδ-nociceptor volley is suppressed by producing a selective ischemic pressure block [24, 25], by stimulating with tiny (< 0.5 mm^2) laser beams to lower the probability of activating Aδ-nociceptors [26], by reducing stimulus intensity to keep skin temperature below the Aδ-nociceptor threshold [27, 28], or by combining the two latter methods [29]. The latency of the ultra-late N2-P2 complex is compatible with the longer conduction time of C-fibers (Figure 5). Most interestingly, electrical brain topography [12,30] and source localization [12, 31] of these ultra-late components suggest that cortical areas activated by the C-nociceptor afferent volley are similar to those activated by Aδ-nociceptor afferents.

To account for the fact that the C-fiber-related LEP response is observed only when concomitant activation of Aδ-nociceptors is avoided, several mechanisms such as spinal inhibition, selective attention and refractoriness of cortical generators, have been proposed. It seems improbable that spinal inhibition of C-nociceptor input could account for the occlusion of ultra-late LEPs, as the C-nociceptor volley elicits a sensation (ie, second pain) even when it is preceded by an Aδ-nociceptor volley. Refractoriness of LEP generators is an equally unlikely explanation. It was recently shown that when two consecutive laser stimuli are applied, such as to produce a second Aδ-nociceptor volley arriving in the time window of the C-afferent volley of the first stimulus, the latency, amplitude and scalp topography of the LEP evoked by the second Aδ volley is unaltered by the preceding stimulus [20]. Nevertheless, the fact that concomitant activation of Aδ- and C-nociceptors induces a corresponding double sensation, but evokes only Aδ-nociceptor-related LEPs, suggests a dissociation between perception and processes reflected by LEPs.

Applications in pain research

Until recently, most investigators in the field of pain research have considered LEP components as quantitative

Figure 5. Selective activation of C-fibers by laser stimuli.



After ischemic A-fiber block of the superficial radial nerve at the wrist [25], C-fibers were activated selectively by laser stimulation. Individuals reported a delayed sensation of second pain. Due to the slow conduction velocity of C-fibers, the reaction times and the N2-P2 complex of LEPs recorded at the vertex are also considerably delayed, as compared to the situation depicted in figure 3.

neurophysiological correlates of the nociceptive barrage, and therefore as a valid technique for objective assessment of the functional integrity and modulation of the nociceptive system. Evidence for these assertions were found in the following observations:

(i) Noxious laser stimuli applied to the skin evoked brain potentials similar to those evoked by noxious electrical and mechanical cutaneous stimuli [18].

(ii) Late-LEPs contained components related to Aδ-fiber activation and perception of first pain [32,17].

(iii) Ultra-late-LEPs contained components related to C-fiber activation and perception of second pain [26,6]

(iv) A positive correlation between stimulus intensity and late-LEP components was observed in both normal and diseased individuals [1••, 9,17,18,33,34,35].

(v) Administration of analgesics and their antagonists induced changes in amplitude and spectral power density of late-LEPs, which paralleled their effect on pain sensation [18,36].

However, to consider LEPs as specific correlates of nociception and pain perception, these electrophysiological responses should satisfy the following additional criteria;

(i) LEPs should be modality specific. Pain is generally recognized as a submodality of the perceptual somatosensory repertoire. However, all components of LEPs to high intensity painful stimuli are also evoked by low intensity non-painful stimuli [9, 18, 33]. The response continuum from innocuous to noxious levels of laser stimulation does not allow the claim that LEPs are modality specific.

(ii) A positive relationship should exist between the magnitude of pain perception and the amplitude of LEP components. LEPs evoked by noxious stimulation are indeed of larger amplitude than LEPs evoked by innocuous stimulation. However, it is most probable that at least part of this increase results from co-varying endogenous factors, such as stimulus salience. At present, this aspect has not received enough

consideration, as only a few studies have explored LEPs in the non-noxious range.

Conclusions and further directions

The biological functions and neurophysiological correlates of first and second pain are still poorly understood. Further research is required to better understand the different processes reflected by LEP components, since their functional significance determines the specificity and validity of interpretations given to changes in LEP components induced by various experimental manipulations and pathological states of the nociceptive system.

Nevertheless, the possibility of selectively or sequentially activating Aδ- and C-nociceptors by manipulating laser stimulation parameters, such as intensity, duration and beam diameter, combined with the use of new tools for the analysis of EEG signals is opening exciting future opportunities for pain research. It has been reported that the use of wavelets to explore the time-frequency domain of EEG signals allowed the enhancement of previously unidentified laser-induced electrophysiological changes, such as synchronization and desynchronization of cortical rhythms [37]. Similarly, the use of new methods that increase the accuracy and spatial resolution of EEG dipole source analysis (eg, Independent Component Analysis, sLORETA) appears promising.

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