SCIENTIFIC PAPER – ABSTRACT

Trigeminal small-fibre function assessed with contact heat evoked potentials in humans


Contact heat stimuli have been reported to excite mechano-thermal nociceptors and to evoke brain potentials (CHEPs) from the limbs. We investigated whether contact heat evokes reproducible CHEPs from the trigeminal territory and may prove a reliable diagnostic tool in facial neuropathic pain. We applied contact heat stimuli to the perioral and supraorbital regions; CHEPs were recorded from the vertex in 20 controls and 2 patients with facial neuropathic pains, and reflex responses from the orbicularis oculi and masticatory muscles in 5 controls. We studied the correlation between CHEP data and perceptive ratings, site of stimulation, and age. Finally, we compared CHEPs with laser evoked potentials (LEPs). Contact heat stimuli at 51°C evoked vertex potentials consisting of an N2 complex similar to that elicited by laser pulses, though with a latency some 100-ms longer. Perioral stimulation yielded higher pain intensity ratings, shorter latency and larger amplitude CHEPs than supraorbital stimulation. CHEP data correlated significantly with age. Contact heat stimuli at 53 °C evoked a blink-like response in the relaxed orbicularis oculi muscle and a silent period in the contracted masseter muscle. In patients with facial neuropathic pain the CHEP abnormalities paralleled those seen with LEPs. We were unable to achieve reproducible signals related to C-receptor stimulation by contact heat stimuli at 41°C in the ten subjects in whom they were tested. Contact heat stimulation, as well as laser stimulation, easily yields large-amplitude brain potentials and nociceptive reflexes, both related to the Aδ input. However CHEPs are not suitable for C-fibres potentials recording.

Automated single-trial measurement of amplitude and latency of laser-evoked potentials (LEPs) using multiple linear regression.


Objective. Laser stimulation of Ad-fibre nociceptors in the skin evokes nociceptive-specific brain responses (laser-evoked potentials, LEPs). The largest vertex complex (N2–P2) is widely used to assess nociceptive pathways in physiological and clinical studies. The aim of this study was to develop an automated method to measure amplitudes and latencies of the N2 and P2 peaks on a single-trial basis.

Methods. LEPs were recorded after Nd:YAP laser stimulation of the left hand dorsum in 7 normal volunteers. For each subject, a basis set of 4 regressors (the N2 and P2 waveforms and their respective temporal derivatives) was derived from the time-averaged data and regressed against every single-trial LEP response. This provided a separate quantitative estimate of amplitude and latency for the N2 and P2 components of each trial.

Results. All estimates of LEP parameters correlated significantly with the corresponding measurements performed by a human expert (N2 amplitude: R²=0.70; P2 amplitude: R²=0.70; N2 latency: R²=0.81; P2
latency: $R^2=0.59$. All $P<0.0001$). Furthermore, regression analysis was able to extract an LEP response from a subset of the trials that had been classified by the human expert as without response.

Conclusions. This method provides a simple, fast and unbiased measurement of different components of single-trial LEP responses.

Significance. This method is particularly desirable in several experimental conditions (e.g. drug studies, correlations with experimental variables, simultaneous EEG/fMRI and low signal-to-noise ratio data) and in clinical practice. The described multiple linear regression approach can be easily implemented for measuring evoked potentials in other sensory modalities.

*Similar nociceptive afferents mediate psychophysical and electrophysiological responses to heat stimulation of glabrous and hairy skin in humans*


The ability to perceive and withdraw rapidly from noxious environmental stimuli is crucial for survival. When heat stimuli are applied to primate hairy skin, first pain sensation is mediated by type-II A-fibre nociceptors (II-AMHs). In contrast, the reported absence of first pain and II-AMH microneurographical responses when heat stimuli are applied to the hand palm has led to the notion that II-AMHs are lacking in this primate glabrous skin. The aim of this study was to assess the effect of hairy and glabrous skin stimulation on neural transmission of nociceptive inputs elicited by different kinds of thermal heating. We recorded psychophysical and EEG brain responses to radiant (laser-evoked potentials, LEPs) and contact heat stimuli (contact heat-evoked potentials, CHEPs) delivered to the dorsum and the palm of the hand in normal volunteers. Brain responses were analysed at a single-trial level, using an automated approach based on multiple linear regression. Laser stimulation of hairy and glabrous skin at the same energy elicited remarkably similar psychophysical ratings and LEPs. This finding provides strong evidence that first pain to heat does exist in glabrous skin, and suggests that similar nociceptive afferents, with the physiological properties of II-AMHs, mediate first pain to heat stimulation of glabrous and hairy skin in humans. In contrast, when contact heat stimuli were employed, a significantly higher nominal temperature had to be applied to glabrous skin in order to achieve psychophysical ratings similar to those obtained following hairy skin stimulation, and CHEPs following glabrous skin stimulation had significantly longer latencies (N2 wave, +25%; P2 wave, +24%) and smaller amplitudes (N2 wave, −40%; P2 wave, −44%) than CHEPs following hairy skin stimulation. Irrespective of the stimulated territory, CHEPs always had significantly longer latencies (hairy skin N2 wave, +75%; P2 wave, +56%) and smaller amplitudes (hairy skin N2 wave, −42%; P2 wave, −19%) than LEPs. These findings are consistent with the thickness-dependent delay and attenuation of the temperature wave format nociceptor depth when conductive heating is applied, and suggest that the previously reported lack of first pain and microneurographical II-AMH responses following glabrous skin stimulation could have been the result of a search bias consequent to the use of long-wavelength radiant heating (i.e. CO₂ laser) as stimulation procedure.

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Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans


Converging evidence from different functional imaging studies indicates that the intensity of activation of different nociceptive areas (including the operculoinsular cortex, the primary somatosensory cortex, and the anterior cingulate gyrus) correlates with perceived pain intensity in the human brain. Brief radiant laser pulses excite selectively A and C nociceptors in the superficial skin layers, provide a purely nociceptive input, and evoke brain potentials (laser-evoked potentials, LEPs) that are commonly used to assess nociceptive pathways in physiological and clinical studies. A-related LEPs are constituted of different components. The earliest is a lateralised, small negative component (N1) which could be generated by the operculoinsular cortex. The major negative component (N2) seems to be mainly the result of activation in the bilateral operculoinsular cortices and contralateral primary somatosensory cortex, and it is followed by a positive component (P2) probably generated by the cingulated gyrus. Currently, early and late LEP components are considered to be differentially sensitive to the subjective variability of pain perception: the late N2–P2 complex strongly correlates with perceived pain, whereas the early N1 component is thought to be a pre-perceptual sensory response. To obtain physiological information on the roles of the pain-related brain areas in healthy humans, we examined the relationship between perceived pain intensity and latency and amplitude of the early (N1) and late (N2, P2) LEP components. We found that the amplitude of the N1 component correlated significantly with the subjective pain ratings, both within and between subjects. Furthermore, we showed that the N2 and P2 late LEP components are differentially sensitive to the perceived sensation, and demonstrated that the N2 component mainly explains the previously described correlation between perceived pain and the amplitude of the N2–P2 vertex complex of LEPs. Our findings confirm the notion that pain intensity processing is distributed over several brain areas, and suggest that the intensity coding of a noxious stimulus occurs already at the earliest stage of perception processing, in the operculoinsular region and, possibly, the primary somatosensory area.

Simultaneous recording of laser-evoked brain potentials and continuous, high-field functional magnetic resonance imaging in humans.


Simultaneous recording of event-related electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) responses has the potential to provide information on how the human brain reacts to an external stimulus with unique spatial and temporal resolution. However, in most studies combining the two techniques, the acquisition of functional MR images has been interleaved with the recording of evoked potentials. In this study we investigated the feasibility of recording pain-related evoked potentials during continuous and simultaneous collection of blood oxygen level-dependent (BOLD) functional MR images at 3 T. Brain potentials were elicited by selective stimulation of cutaneous Aγ and C nociceptors using brief radiant laser pulses (laser-evoked potentials, LEPs). MR-induced artifacts on EEG data were removed using a novel algorithm. Latencies, amplitudes, and scalp distribution of LEPs recorded during fMRI were not significantly different from those recorded in a control session outside of the MR scanner using the same
equipment and experimental design. Stability tests confirmed that MR-image quality was not impaired by the evoked potential recording, beyond signal loss related to magnetic susceptibility differences local to the electrodes. fMRI results were consistent with our previous studies of brain activity in response to nociceptive stimulation. These results demonstrate the feasibility of recording reliable pain-related LEPs and fMRI responses simultaneously. Because LEPs collected during fMRI and those collected in a control session show remarkable similarity, for many experimental designs the integration of LEP and fMRI data collected in separate, single-modality acquisitions may be appropriate. Truly simultaneous recording of LEPs and fMRI is still desirable in specific experimental conditions, such as single-trial, learning, and pharmacological studies.

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EFNS guidelines on neuropathic pain assessment


In September 2001, a Task Force was set up under the auspices of the European Federation of Neurological Societies with the aim of evaluating the existing evidence about the methods of assessing neuropathic pain and its treatments. This review led to the development of guidelines to be used in the management of patients with neuropathic pain. In the clinical setting a neurological examination that includes an accurate sensory examination is often sufficient to reach a diagnosis. Nerve conduction studies and somatosensory-evoked potentials, which do not assess small fibre function, may demonstrate and localize a peripheral or central nervous lesion. A quantitative assessment of the nociceptive pathways is provided by quantitative sensory testing and laser-evoked potentials. To evaluate treatment efficacy in a patient and in controlled trials, the simplest psychometric scales and quality of life measures are probably the best methods. A laboratory measure of pain that by-passes the subjective report, and thus cognitive influences, is a hopeful aim for the future.

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Ad nociceptor response to laser stimuli: selective effect of stimulus duration on skin temperature, brain potentials and pain perception.


Objective. To disclose a possible effect of duration of pulsed laser heat stimuli on Ad nociceptor responses, skin temperature profiles, brain evoked potentials and pain perception.

Methods. We used a laser stimulator which works in the millisecond range and allows us to change the duration of the pulse while keeping the total energy of the stimulus constant. In 10 healthy volunteers, we measured the intensity of perceived pain with a 0–10 scale and the latency and amplitude of the early N1 and late N2 components of the scalp potentials evoked by laser pulses of equal energy and three different stimulus durations (2, 10, and 20 ms). Using a specifically developed pyrometer with a temporal resolution lower than 1 ms we also measured stimulus-induced changes of skin temperature.
**Results.** Stimulus duration significantly influenced temperature rise times, pain perception, and brain potentials. Shorter stimulus durations yielded steeper slopes in the skin temperature profiles and higher pain ratings, shortened the latency of the N1 and N2 components, and increased the amplitude of N1.

**Conclusions and significance.** The shorter stimulus duration shortens receptor activation times and yields a more synchronous afferent volley, thus providing a stronger spatial–temporal summation at central synapses that enhances intensity of first pain and brain potentials. This may prove useful in clinical applications.

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*Unmyelinated trigeminal pathways as assessed by laser stimuli in humans*


Laser pulses excite superficial free nerve endings innervated by small-myelinated (Aδ) and unmyelinated C-fibres. Whereas laser-evoked scalp potentials (LEPs) are now reliably used to assess function of the Aδ-C-fibre nociceptive pathways in patients with peripheral or central lesions, the selective activation of C-fibre receptors and recording of the related brain potentials remain difficult. To investigate trigeminal C-fibre function, we directed laser pulses to the facial skin and studied sensory perception and scalp evoked potentials related to Aδ- or C-fibre activation in healthy humans and patients. Done having a bilateral facial palsy, two a trigeminal neuropathy, and two a Wallenberg syndrome. We also measured afferent conduction velocity and, with source analysis, studied the brain generators. Whereas laser pulses of low intensity and small irradiated area elicited pinprick sensations and standard Aδ-LEPs, laser pulses of very-low intensity and large irradiated area elicited warmth sensations and scalp potentials with a latency compatible with C-fibre conduction (negative wave 280 ms, positive wave 380 ms); the estimated conduction velocity was 1.2 m/s. The main waves of the scalp potentials originated from the anterior cingulate gyrus; they were preceded by activity in the opercular region and followed by activity in the insular region. The patient with bilateral facial palsy, who had absent trigeminal-facial reflexes, had normal Aδ- and C-related scalp potentials; the patients with trigeminal neuropathy, characterized by loss of myelinated and sparing of unmyelinated C-fibres, had absent Aδ- but normal C-related potentials; and the patients with Wallenberg syndrome had absent Aδ- and C-related potentials. We conclude that laser pulses with appropriate characteristics evoke brain potentials related to the selective activation of trigeminal nociceptive Ad or thermal C-fibres. The trigeminal territory yields rewarding LEP findings owing to the high density of thermal receptors and, because the short conduction distance, minimizes the problem of signal dispersion along slowconducting unmyelinated afferents. The opercular-insular region and the cingulate gyrus are involved in the processing of C-fibre trigeminal inputs. The method we describe may prove useful in patients with lesions affecting the trigeminal thermal pain pathways.
Nociceptive Quality of the Laser-Evoked Blink Reflex in Humans


Laser radiant-heat pulses selectively excite the free nerve endings in the superficial layers of the skin and activate mechano-thermal nociceptive afferents; when directed to the perioral or supraorbital skin, high-intensity laser pulses evoke a blink-like response in the orbicularis oculi muscle (the laser blink reflex, LBR). We investigated the functional properties (startle or nociceptive origin) of the LBR and sought to characterize its central pathways. Using high-intensity CO2-laser stimulation of the perioral or supraorbital regions and electromyographic (EMG) recordings from the orbicularis oculi muscles, we did five experiments in 20 healthy volunteers. First, to investigate whether the LBR is a startle response, we studied its habituation to expected rhythmic stimuli and to unexpected arrhythmic stimuli. To assess its possible nociceptive quality, we studied changes in the LBR and the R2 component of the electrical blink reflex after a lidocaine-induced supraorbital nerve block and after intramuscular injection of the opiate fentanyl and the opiate-antagonist naloxone. To characterize the central pathways for the LBR, we investigated the interaction between the LBR and the three components of the blink reflex (R1, R2, and R3) by delivering laser pulses to the perioral or supraorbital regions before or after electrical stimulation of the supraorbital nerve at various interstimulus intervals. Finally, to gain further information on the central LBR pathways, using two identical CO2-laser stimulators, we studied the LBR recovery curves with paired laser pulses delivered to adjacent forehead points at interstimulus intervals from 250 ms to 1.5 s. The LBR withstood relatively high-frequency rhythmic stimulations, and unexpected laser pulses failed to evoke larger responses. When lidocaine began to induce hypoalgesia (about 5 min after the injection), the LBR was abolished, whereas R2 was only partly suppressed 10 min after the injection. Fentanyl injection induced strong, naloxone-reversible, LBR suppression (the response decreased to 25.3% of predrug values at 10 min and to 4% at 20 min), whereas R2 remained appreciably unchanged. Whether directed to the perioral or supraorbital regions, preceding laser pulses strongly suppressed R2 and R3 though not R1. Conversely, preceding electrical stimuli to the supraorbital nerve suppressed the LBR. In response to paired stimuli, the LBR recovered significantly faster than R2. These findings indicate that the LBR is a nociceptive reflex, which shares part of the interneuron chain mediating the non nociceptive R2 blink reflex, probably in the medullary reticular formation. The LBR may prove useful for studying the pathophysiology of orofacial pain syndromes.

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


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 signifficantly 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 allostynia. In central pain patients with exclusively spontaneous pain, LEP attenuation was more pronounced than that observed in those with allostynia and hyperalgesia. Patients with allostynia 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.

Usefulness of dorsal laser evoked potentials in patients with spinal cord damage: report of two cases


Stimulation of the dorsal skin with brief laser impulses easily evokes brain potentials (laser evoked potentials, LEPs). Dorsal LEPs were first used to study the conduction velocity in the human spinothalamic tract. In this study the diagnostic usefulness of this technique was assessed by recording dorsal LEPs in two patients with focal spinal cord lesions (one intrinsic and the other extrinsic) and spared lemniscal sensitivities. In both cases, the brain evoked potentials were normal after stimulation of the metamers above the lesion but absent after stimulation of those below. Dorsal LEP recordings may prove a useful tool in localizing lesions and in the neurophysiological assessment of focal spinal cord lesions involving the anterolateral quadrants of the spinal cord.

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