# Chapter 10
# Pain-Related Evoked Potentials


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**Laser-Evoked Potentials** Laser-evoked potentials were introduced more than 40 years ago [1] and now represent the most validated neurophysiological technique for the functional assessment of the nociceptive pathway. Whether galvanic stimuli at painful intensity are used to activate nerve fibers or nervous receptors, both nociceptive and non-nociceptive afferents are stimulated. Since this simultaneous activation raises inhibitory mechanisms at both cortical [2] and spinal [3, 4] level, galvanic stimuli are not suitable to evoke brain responses specifically related to the nociceptive input. As demonstrated by an early microneurographic study, laser pulses applied on the hairy skin stimulate the thin myelinated (Aδ) and the unmyelinated (C) fibers selectively, without a concurrent activation of the non-nociceptive Aβ fibers [5]. The main LEP component is represented by a negative/positive complex (N2/P2), widely distributed over the scalp and reaching its maximal amplitude at the vertex. While the negative component has a mean latency of 200 ms, the positive response peaks at around 350 ms after hand stimulation. The N2/P2 component is preceded by a negative potential (N1) distributed in the temporal region contralateral to the stimulation and a simultaneous positive response (P1) recorded in the frontal region at around 150 ms to hand stimulation [6]. While several cerebral regions contribute to the N2/P2 complex generation, including the middle cingulate gyrus and the bilateral insular cortex, the N1 and P1 components are probably generated by a dipole source in the opercular region [7].

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LEPs are suitable for the study of attentional mechanisms of pain, as the vertex component N2P2 changes in amplitude with relation to distraction [8]. They were thus employed in the study of the complex relationship between motor cortex activation and pain [9, 10]. Different factors of potential attention deviation from painful stimuli seemed to provoke an inhibitory action on the vertex complex [11, 12], indicating an interference effect between contexts of cognitive attraction, arousal, and pain.

Both in PNS and CNS disorders, studies have demonstrated a reduced LEP habituation as a result of an abnormal central pain processing [13, 14]: the loss of habituation likely represents the neurophysiological correlate of the central sensitization, a complex phenomenon comprising spinal and brain maladaptive changes, including phenotypic switch in the expression of spinal neuropeptides, thalamocortical dysrhythmia, and functional reorganization of cortical maps, thus progressively leading to the chronization of pain [15].

In the last years, LEP studies lead to new theory about the pain matrix, largely superimposed to the "salience matrix." In fact, stimuli of the same relevance as the painful ones could recruit the same cortical areas comprised in the LEP generator networks [16]. Reduced habituation seems an important aspect in amplification of pain at central level, as the loss of progressive reduction of painful stimuli relevance and novelty could be a signature of people predisposed to chronic syndromes, whatever being the initial cause of sufferance [17].

## 10.1 Laser-Evoked Potentials in Migraine

LEP amplitude was normal or even increased in migraine patients, contributing to confirm the anatomical and functional integrity of somatosensory nociceptive pathways [18]. In accord with reduced habituation to multimodal stimuli would be the main neurophysiological pattern in migraine [19]. The dishabituation pattern characterized all LEP components in migraine across different series of stimulation [20] and single responses [21]. Interestingly, this pattern would be intrinsic to migraine, as it was not associated to migraine duration and severity, and it was present just in childhood [13]. Few studies denied the presence of reduced habituation pattern in migraineurs [22], but this apparent contradictory result could be explained by the different mode of habituation phenomenon analysis, or different genetic characteristic of the studied populations [23]. Reduced habituation is present in the inter-critical phase, starts to normalize in the prodromal phase, and resolves during the attack, designing a fluctuating biobehavioral model, where the over-action of the cortical-subcortical circuits goes into restore during the attack phase, according to a homeostatic mechanism [24]. The LEP dishabituation pattern was not reversible in acute phase, its persistence probably subtending the LEP amplitude increase observed during the acute phase [25–27].

More recent studies provided for a new neurophysiological interpretation of LEP habituation phenomena in terms of progressive synchronization and reduction of information flow within the neuronal networks activated by repetitive stimuli [28]. Following painful laser stimulation delivered to the right hand, EEG rhythms exhibited lively information flow, as measured by Granger causality, in migraine patients compared with controls, who went into a progressive synchronization. The rate of information flow was inversely correlated with habituation of averaged laser-evoked responses. This correlation suggested that the phenomenon of progressive adaptation to external conditions could reduce the need for cortical connections between distant regions and create synchronized networks with reduction of stress and energy demand.

Recent studies outlined the role of stimulus-related EEG dynamic in high-frequency—gamma—range to explain complex aspects of migraine. Porcaro et al. [29] observed abnormal thalamic HFO activation under somatosensory stimulation in migraine without aura patients, which correlated with migraine age of onset. The gamma band oscillations (GBOs) evoked by noxious stimuli could be a correlate of subjective feeling of pain [45]. In migraine patients, GBOs evoked by trigeminal and somatic laser stimulation seemed the neurophysiological correlate of pain catastrophizing, anxiety, and depression suggesting a possible utility of the study of high-frequency oscillations to explain clinical characteristics of migraine and possible response to treatments [30].

## 10.2 Effects of Treatments on LEP Features

LEP amplitude and habituation changed in relation to acute and preventive treatments effects. During migraine attack, the LEP amplitude enhancement concurred with hyperalgesia to painful stimuli. Almotriptan and lysine acetylsalicylate reverted later LEP amplitude increase, in parallel with the effect on migraine intensity [31]. The study confirmed that the resolution of migraine corresponded to the inhibition of the cortical areas generating the P2 wave and subtending the emotive and cognitive compound of pain [26].

Di Clemente et al. [32] described a reversion of reduced habituation pattern of N1 wave after topiramate treatment in migraine without aura. Another study, conducted on patients affected by medication overuse headache [33], reported a normalization of LEP dishabituation after detoxification [34].

In chronic migraine, the therapeutic effect of botulinum toxin on central sensitization is associated with the reversion of reduced habituation of trigeminal evoked responses [35].

The effects of non-invasive neurostimulation on trigeminal nociceptive system were also studied by LEPs. High-frequency TMS of motor cortex reduced LEP amplitude in migraine patients and controls. Migraine patients displayed an evident real and sham effect on hand and trigeminal responses, thus

suggesting the potential utility of this therapeutic approach in the prevention of migraine [36].

Transcutaneous electrical stimulation (TENS), produced with the Cefaly device [37], modulated later LEP originating from the cingulate cortex [38]. Trigeminal TENS could thus act on the cortical regions exerting a pivotal role in pain modulation [17].

Similar results emerged by the use of non-invasive vagal nerve stimulation [39], which reduced later trigeminal LEPs more than the sham device, probably activating the vagal nerve connections with the cortical regions included in the pain/salience matrix [40].

## 10.3 Pain-Related Evoked Potentials

The recording of pain-related evoked potentials (PREPs) is an objective method for the evaluation of the nociceptive system. It has been developed almost 15 years ago [41] and has proven itself in various clinical and scientific experiments. It is simple, cheap, and non-invasive in its application.

## 10.4 Electrophysiological Setting

The skin afferents are transcutaneously excited by a concentric electrode (CE). Due to its concentric design and the narrow anode-cathode distance, the CE produces a high current density at low current intensities. Therefore, the depolarization of nociceptive fibers is limited to the superficial layer of the dermis and does not reach the deeper layers that predominantly excite Aβ fibers [41, 42].

The CE, which consists of a metal cathode (D: 0.5 mm) and an anode ring (D: 6 mm), leads to an irritation of nociceptive skin afferents (Fig. 10.1) [41]. The trigeminal stimulation for the elicitation of trigeminal PREPs occurs in the area of the first trigeminal branch with two electrodes placed 10 mm above the supraorbital nerve. The extracranial (somatic) PREPs are caused by nociceptive irritation of the second and third fingers or forefoot of the two phalanges of the second and third toes. The pain threshold is determined by increasing and decreasing stimulus series in 0.01 mA steps. Fifteen to twenty blocks of electrical triples [43] or double pulses [41] are applied (monopolar rectangular pulses; intensity, 1.5 times the individual pain threshold; duration, 0.5 ms; pulse interval, 5 ms; interstimulus interval, 12–18 s) [41, 44]. The PREPs are recorded with a needle electrode placed over Cz and connected to ear electrodes according to the international 10–20 EEG system, which analyzes the negative peak (N1), positive peak (P1), latencies, and N1P1 peak-to-peak amplitudes (PPA) of the PREPs (Fig. 10.1). A strong linear correlation between the PPA of the PREPs and the intensity of pain perception

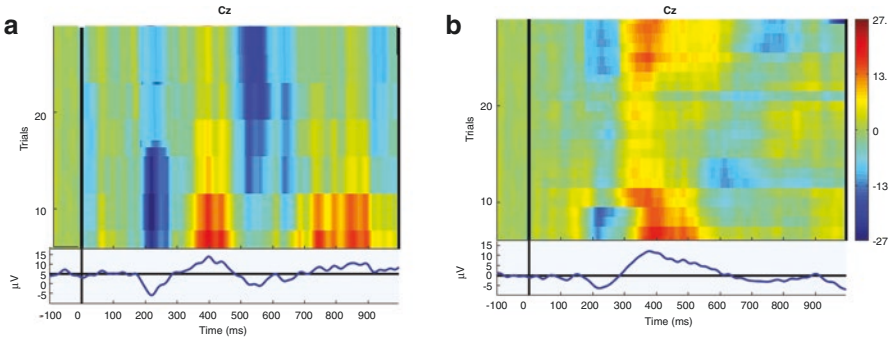


**Fig. 10.1** Time course representation of LEP amplitudes by right hand (grand average) across 30 consecutive trials obtained in (**a**) ten normal subjects and (**b**) ten migraine without aura patients. While in normal subjects the N2 and P2 showed a progressive amplitude decrease, migraine patients showed stable or even increased amplitude in the latest trials

(numeric rating scale [NRS]) showed that the PREPs represent a quantitative measure of pain processing [43].

## 10.5 Activation of Aδ Fibers

After a local treatment with the local anesthetic lidocaine, which led to a loss of the thermoesthesia and pain perception, but not the touch sensation, the PREPs were no longer triggerable up to a certain stimulus intensity [43]. This finding suggests that mainly activated Aδ and C fibers are responsible for the PREPs. In addition, local anesthesia resulted in inhibition of the nociceptive blink reflex response to the extent of 90%. This suggests that only 10% of Aβ fibers contribute to the response after electrical stimulation with CE [43]. The conduction velocity (16–18 m/s) [23] determined after stimulation with the CE and derivation of the PREPs [43] agrees with the conduction velocity of Aδ fibers [44].

## 10.6 Generators of the PREP

So far, there are no dipole source analyses on the PREPs as in the LEPs, which show that painful electrical stimuli, similar to the painful heat stimuli, activate the operculo-insular cortex in the vicinity of the secondary somatosensory cortex (SII) [45, 46]. Probably the cingulate gyrus is to be regarded as the main generator of the PREPs [45]. The PREPs are vertex potentials. The vertex potentials and thus also the PREPs can be affected by cognitive factors. In one study, Rossi et al. [47] demonstrated by LEPs in diabetic patients that the vertex potential is prolonged in

parallel with the lateralized median latency component (N1), which is likely to be generated by the SII. There is evidence that the sensory-discriminative component of pain is represented by the SII. Since N1 is not severely altered by pain experience or attention and thus provides a reliable indicator of pain transmission [48], the parallel shift of N1 and vertex potentials suggests that pain dysfunction is most likely to be sensory dysfunction in diabetic patients rather than secondary influenced by cognitive factors [49].

## 10.7 Clinical Applications of PREPs in Headache and Facial Pain

The PREPs may be used in a drug-induced history-making headache to test the efficacy of drug therapies, because it could be shown that the PPA of the PREPs were significantly reduced after the withdrawal treatment for analgesic- and triptan-induced migraine [50]. With additional deduction of the nociceptive blink reflex, the PREPs may also serve to demonstrate central sensitization in headache patients [50]. In addition, the PREPs can also serve the functional diagnosis of symptomatic side dysfunction in trigeminal neuralgia. In combination with the nociceptive blinking reflex, the lesion near the root entry zone of the brainstem could be localized in trigeminal neuralgia [51]. In the future, the PREPs could serve as proof of the effectiveness of therapeutic interventions. An example of this is the fact that the PPA of the PREPs were significantly reduced after cathodal transcranial direct current stimulation (tDCS) and significantly increased after anodal tDCS as an indication for both inhibited and facilitated pain processing [52].

## 10.8 Comparison of Different Methods of Peripheral Electrical Stimulation

There are numerous methods of peripheral electrical stimulation that cause excitation of Aδ and C fibers and after their excitation can be derived as pain-evoked potentials (Fig. 10.2). Evoked potentials after painful stimuli can be regarded as a special form of somatosensory evoked potentials (SSEP). Inui's needle electrode [53] was able to excite Aδ fibers, while Nilsson's electrode texture and the applied stimulus intensity of the electrode caused predominantly C fibers [54]. A disadvantage of the Inui electrode is its invasiveness. Another electrode design (ten electrodes with a diameter of 200 μm) enabled a spatial summation within the receptive fields of the spinal cord neurons and a high current density at low stimulus intensities in order to promote the activation of Aδ and C fibers [55]. These advantages are also found in the irritation with the CE. Clinical applications of the derivation of

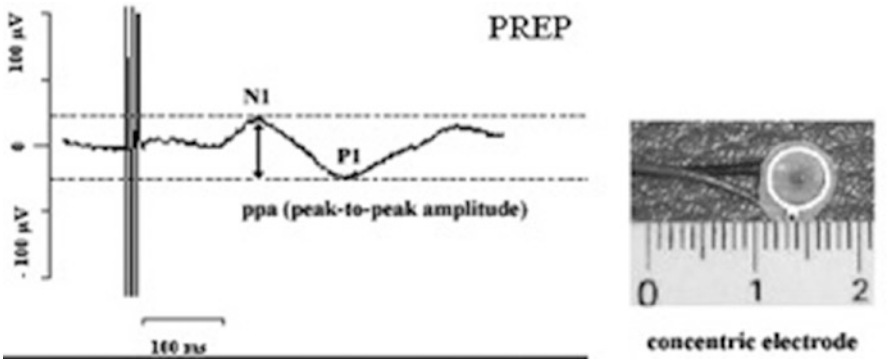


**Fig. 10.2** Pain-related evoked potentials obtained by concentric electrode in a healthy subject. The diameter of concentric electrode is reported

pain-evoked potentials are absent in these electrical stimulation electrodes in contrast to the PREPs with the CE.

The skin afferents are transcutaneously excited by a concentric electrode (CE). Due to its concentric design and the narrow anode-cathode distance, the CE produces a high current density at low current intensities. Therefore, the depolarization of nociceptive fibers is limited to the superficial layer of the dermis and does not reach the deeper layers that predominantly excite Aβ fibers [41, 42].

## 10.9 Conclusion

The PREPs are a simple, inexpensive, and non-invasive diagnostic tool to detect SFN or involvement of small fibers in MFN in routine clinical practice. They can also be used for follow-up diagnostics after therapeutic intervention or proof of central sensitization in headache patients. In addition, they serve to objectify a lesion of the nociceptive pathways. Exact localization diagnostics is so far only incompletely possible with the PREPs. The PREPs probably represent Aδ fiber activity and their generator is located in the cingulate gyrus.

## 10.10 General Remarks

Both LEPs and PREPs could provide for the study of nociceptive system in headaches and facial pain. They seem reliable in excluding the possible neuropathic origin of the symptoms and in displaying complex mechanisms of altered pain processing, such as reduced habituation or abnormal response to descending modulation, or mechanisms of treatments. While laser-evoked responses are quite expensive and invasive (especially for skin damage by CO2 laser stimulator), they are highly

selective for Aδ and C fibers. The PREPs by concentric electrode could be easily used in clinical setting, but special care should be devoted to the modality of stimulation in order to ensure elective properties for nociceptive afferents [55].

Other methods of nociceptive afferents recording are presently available, so the scenario about the mechanism of pain processing could go into enlargement in primary headaches, thus supporting the physiopathological support of inflammatory peptides such as CGRP and the mode of drug action and disease improving.

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