Clinical usefulness of laser-evoked potentials

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Abstract

In contrast to the function of the visual or auditory pathways which are electrophysiologically accessible by visual or auditory evoked potentials, the somatosensory pathway cannot be investigated as a whole by conventional somatosensory evoked potentials (SEP), because these only reflect function of large fibers, dorsal columns, medial lemniscus and their thalamo-cortical projections mediating sensations like touch and vibration. The other half of the somatosensory system, signaling temperature and pain perception, uses a different set of afferents and different central pathways, the function of which is accessible by laser-evoked potentials (LEPs). LEP can document lesions of the spinothalamic tract and (lateral) brainstem and of thalamo-cortical projections conveying thermo-nociceptive signals. In the peripheral nerve, LEP can help distinguish between large and small fiber neuropathies. The rapid heating of the skin by infrared laser pulses can easily be applied to non-glabrous skin in any dermatome. In recent years, many clinical studies have demonstrated that LEP can supply evidence for establishing clinical diagnoses when deficits of the nociceptive system are present. This review outlines principles and recording techniques for LEP in patients and compiles typical LEP findings in patients with lesions due to different diseases at various levels of the nociceptive pathways. Limitations for the use of LEP are pointed out, too, like the uncertainty of lesion location along these pathways and the fact that LEP can reliably show correlates of reduced nociceptive function but only rarely of enhanced transmission (like in hyperalgesia).

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Résumé

Contrairement aux fonctions visuelles ou auditives, facilement accessibles sur le plan électrophysiologique via les potentiels évoqués correspondants, les voies somesthésiques ne peuvent pas être explorées complètement avec les potentiels évoqués somesthésiques (PES), car ceux-ci ne reflètent que la fonction des fibres de plus gros calibre, les cordons postérieurs, le lemniscus médian et les projections thalamo-corticales sous-tendant des sensations comme le toucher et la vibration. L’autre moitié du système somesthésique, qui a la charge de signaler les sensations de douleur et de température, utilise des groupes différents de fibres afférentes aussi bien dans la périphérie qu’au niveau central, dont la fonction est accessible par les potentiels évoqués par pulsation laser (PEL). Les PEL détectent les lésions du système spinothalamique dans la moelle et le tronc cérébral latéral, ainsi que celles des projections thalamo-corticales conduisant les signaux thermo-nociceptifs. Dans le système périphérique, les PEL aident à distinguer les neuropathies concernant les fibres de gros ou de petit calibre. La stimulation laser entraîne un réchauffement cutané très rapide, qui peut être appliqué à la peau poilue sur pratiquement tous les dermatomes. Des nombreuses études cliniques ont montré l’importance des PEL comme aide au diagnostic clinique en cas de déficit patent ou suspecté du système nociceptif. Cette revue s’intéresse d’abord aux principes et techniques de l’enregistrement des PEL chez le patient, et compile des résultats typiques chez des patients porteurs de lésions à différents niveaux des voies thermo-nociceptives. Nous signalons également certaines limites de ce type d’examen, comme les incertitudes quant à la localisation topographique des lésions détectées, ainsi que le fait que les PEL montrent de façon fiable des signes de diminution des fonctions nociceptives, mais témoignent rarement des augmentations de la transmission douloureuse (comme l’hyperalgesie).

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Keywords: Laser-evoked potentials; Somatosensory system; Pain; Temperature; Sensory testing

Mots clés : Douleur ; Potentiels évoqués par laser ; PEL ; Nociception ; Spinothalamique ; Thalamus

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1. General considerations

The visual and auditory pathways are projecting one modality only, and can thus be easily tested using visual and auditory evoked potentials (VEP, AEP). Pain pathways are a part of the somatosensory system. Therefore, neurological studies of pain pathways may be expected to be related to the recording of somatosensory evoked potentials (SEP). However, the somatosensory system includes more than one modality and cannot electrophysiologically be tested by only one type of evoked potential. The pathways by which information on painful stimuli is transmitted, differ in many important aspects from those pathways that are assessed by standard SEP:

- Aδ- and C-fibers instead of Aβ-fibers in the peripheral nerve,
- first synaptic relay in the spinal cord instead of the brainstem,
- rostral projection in the contralateral spinothalamic tract instead of the ipsilateral dorsal column,
- different representation in somatosensory and limbic cortex.

Because of these differences, evoked potentials following painful stimuli may provide important additional information beyond standard SEP for topological diagnostics in neurology, particularly in peripheral nerve, plexus, root, spinal and brainstem disorders. At the thalamo-cortical level, pain pathways partly converge with other somatosensory pathways. Therefore, the diagnostic value of pain related evoked potentials are less evident for supratentorial lesions. As differences between the cortical representation of touch and pain become more and more apparent, a clinical role for laser-evoked potentials (LEP) testing in thalamo-cortical lesions may develop in the near future, e.g. for characterization of insular lesions. For documentation of supratentorial lesions, MRI is still regarded as gold standard. However, despite the increasing spatial resolution of MRI, electrophysiological testing using evoked potentials is still most important as functional test for the peripheral nervous system and tracts of the central nervous system. In this context, LEP are the tool for functional testing of the integrity of the nociceptive pathway. They can help differentiate between neurogenic and psychogenic hypoalgesia and, in patients with spontaneous neuropathic pain, may allow conclusions upon the underlying mechanisms (i.e. deafferentation vs. central sensitization).

2. Stimulation and recording techniques

2.1. Stimulation

In normal skin, the sensation evoked by laser stimuli near pain threshold is comparable to a weak pinprick or pulling a single hair follicle. In order to obtain reproducible evoked potentials, it is necessary to use suprathreshold stimuli, which are usually perceived as slightly stinging and/or burn-

Laser evoked potentials: methods

Stimuli:
painful heat pulses generated by an infrared laser (wavelength 1060 nm),
3 ms duration, 5 mm diameter,
2 runs of 20 stimuli (540 mJ energy)

Recording:
0.2-70 Hz bandpass,
200 Hz sampling rate,
Fz, Cz, Pz vs. earlobes, T3, T4 vs. Fz

Fig. 1. LEP recording montage. Recording montage for late (Fz, Cz, Pz vs. earlobes) and early LEPs (T3-Fz, T4-Fz). Modified from Ref. [73].

As an untoward effect, the skin may transiently turn red as a sign of a first degree burn. This harmless discoloration disappears within a few days. However, in patients prone to skin ulcerations, such as in diabetic neuropathy or in Behçet’s disease, there may be a relative contraindication for LEP. Superficial burns are less likely to occur with thulium lasers (2.03 µm wavelength) than with carbon dioxide lasers (10.6 µm wavelength), due to the different temperature distribution in the skin [69] (see Plaghki and Mouraux, this volume). In order to minimize nociceptor fatigue which leads to amplitude reduction, stimuli should not be applied to the same spot all the time, but slightly vary across the stimulation area. Variation of interstimulus intervals between e.g. 8 and 12 s is advisable to reduce habituation. Additionally, attention has a strong impact on LEP amplitudes (for review see Lorenz, this volume) and thus should be controlled by the investigator by using a standard task. As an example, it is convenient to have the patient give pain ratings following each stimulus to keep the same level of attention.

2.2. Recording techniques for late LEP components

In clinical studies, only the late LEP components are routinely evaluated (Fig. 2). These components are maximal
between the vertex Cz and the midline parietal lead Pz vs. linked earlobes or nose (for sources see García-Larrea, this volume). It is a negative–positive complex comprising the so-called N2 and P2, measured individually from baseline (or both together peak-to-peak). The recording bandpass should be not narrower than 0.2–70 Hz with a digitization rate of at least 200 Hz (Fig. 1). In order to detect and eliminate ocular artefacts, the EOG should be recorded in parallel. Most investigators record the LEP while patients have their eyes closed, however in individual patients with large alpha-waves it may improve the signal when the eyes are left open and patients fixate a point. Averaging across 20–40 trials in 2–3 runs (for reproducibility) is sufficient to measure these LEP components. Their latency depends on stimulus duration, since the peak skin temperature is reached at the end of the laser pulse [80], and their amplitude depends on interstimulus interval and the task performed by the subject. Therefore, each laboratory needs to determine their own normative values. Roughly, hand stimulation using a Tm-laser yields N2 latencies of about 210 ms and P2 latencies of 330 ms. Amplitudes vary between 12 and 67 µV; see Table 1 [68]. Using a carbon dioxide laser, the LEP N2 occurs at about 240 ms and the P2 at about 380 ms [41,76]. There is little effect of age on LEP amplitudes or latencies up to 60 years. Beyond that, LEP amplitudes decrease and latencies increase with age [32].

Under the conditions mentioned above, the absence of late LEP can be considered abnormal. In addition, intraindividual differences in amplitude and latency between a clinically affected and a healthy control site may be evaluated, too [7,12,69].

### 2.3. P300-like components

The P300 is usually evoked in an oddball paradigm that alternates between tones of different frequency, and in general terms appears following rare task-relevant stimuli [70]. As the LEP P2 has peak latency near 300 ms, it has been suggested that it may be functionally equivalent to the auditory P300 [92]. This proposal ignores the differences in afferent conduction times in auditory and nociceptive pathways. Studies with appropriate tasks have indeed shown that the LEP P3 appears at longer peak latency near 600 ms with an amplitude maximum further posterior compared to the P2 [46,52,67,72]. Because of its endogenous character not specific for nociception, the LEP P3 is usually not being evaluated in clinical settings, but may be useful in disorders with attention deficits.

### 2.4. Ultralate LEP components

Although heating the skin by laser pulses activates C-fiber nociceptors [13] (see Plaghki and Mouraux, this volume), corresponding LEP components were difficult to isolate, possibly due to a central inhibitory interaction with the preceding afferent volley carried by Aß-fibers. To make ultralate LEP components visible in healthy subjects, it is necessary to "unmask" these components through one of the following techniques: (1) controlled temperature steps to 40 °C or low intensity stimulation of a large surface, leading to activation of C-nociceptors and C-warm receptors only [25,57], (2) tiny beams (Ø = 0.5 mm), taking advantage of the more dense distribution of C-nociceptors in the skin [10], (3) ischemic nerve block that reversibly knocks out conduction of myeli-
nated fibers but sparing unmyelinated C-fiber conduction [15]. Based on the same principle, it is possible to retrieve C-fiber responses from patients suffering from demyelinating neuropathy (for details see Plaghki and Mouraux, this volume). Only then these ultrade components appear as a vertex positivity (same recording setup as for late compo-
ents) at a latency of about 1000 ms. Since ultrade LEPs are not reliably present in all healthy subjects, they have not been used to test for intactness of nociceptive C-fiber afferents in patients. Axon reflex measurements may be more useful for that purpose [5,59]. However, if ultrade LEP components are directly visible in patients while Aδ-LEP is absent, this is a sign for selective loss of myelinated nociceptive fibers (see below).

2.5. Early LEP components

Early subcortical LEP components have not been described, in contrast to the well known subcortical SEP components following electrical nerve stimulation. This is probably due to latency jitter in the afferent volley elicited by laser heat pulses [13]. The earliest cortical LEP component is negativity N1 (Fig. 2) with a peak latency of about 170 ms [76], and maximum amplitude bilaterally at the temporal leads [50]. The N1 is best recorded in a bipolar montage with Fz as reference electrode, because there is a nearly simulta-
neous positivity in the frontal midline region. The underlying generator is located in the parasylvian cortex (c.f. García-Larrea, this volume). Because of their small amplitude, the early LEP components have not yet been used clinically.

2.6. Dermatomal LEP

Because type II Aδ-fiber nociceptors are missing in the glabrous skin of hands and feet [13,81], late LEPs are not useful to assess the innervation of the palm of the hand or the sole of the foot. In contrast to electrical nerve stimulation, laser stimuli can easily be applied to all other dermatomes includ-
ing the innervation territory of the trigeminal nerve [26,55,79]. As a shorter conduction distance is associated with lower latency jitter, the signal-to-noise ratio for LEP is even better for proximal dermatome stimulation than for distal limb stimulation [57]. A major advantage for the use of LEP in the trigeminal system is the absence of a stimulus artefact, which often interferes with the recording when an electrical stimulus is employed. These properties make LEP an attractive tool in documenting the segmental level of a lesion and assessing fiber function in radiculopathies. The clinical utility of dermatomal SEP is compromised by the fact that their signal-to-noise ratio depends on the size of the nerve stimulated and its cortical representation in the sensory homunculus, whereas late LEP components are not depend-
ent on these factors. An elegant application of LEP for estimating conduction velocity of the spinothalamic tract is to stimulate at different dermatomal levels at the back and use the latency differences for calculation [38]. Dermatomal LEP are also useful in single spinal root lesions, because pain dermatomes are smaller than tactile dermatomes [55].

3. Pathological LEP changes

The anatomical specificity of the peripheral and central thermoreceptive and nociceptive pathways represents the major rationale of a clinical use of the LEP method. Many groups documented disturbances of pain and temperature sensitivity by abnormal LEP that are typically missed by the standard SEP method in a variety of pathologies (Table 2). Evidence strongly indicates, and will be reviewed below, that LEP usefully supplement standard electrical SEP when minus-signs of the pain and temperature sense dissociate from the touch and joint position sense, which occur for certain lesions of the peripheral, radicular, spinal, midbrain and supraspinal neuraxis. A second group of studies explored the use of the LEP method to monitor the plus-signs of the pain sense, thus described LEP changes in pathologies charac-
terized by the presence of pain or enhanced pain sensitivity such as hyperalgesia and allodynia. However, the review of results in this approach indicates that LEP reflect only particular aspects of nociceptive function being more strongly activated in some, but suppressed in the majority of other conditions substantiating the diversity of pathophysiological mechanisms underlying these phenomena.

3.1. LEP in patients with peripheral, plexus or root lesions

Peripheral neuropathies (PNP) comprise a heterogeneous group of pathologies among which the “small fiber disease” exhibits a characteristic predominance of loss in temperature and pain sensitivity and autonomous peripheral nerve func-
tion. In such conditions (Fig. 3, lesion site 1 and Fig. 4), the late LEPs may be absent, attenuated in amplitude or delayed in latency [1,2,42]. The severity of latency and amplitude changes were found to correlate with the loss of thin myeli-

tinated nerve fibers in sural nerve biopsy and with the degree of hypoalgesia [45]. Although a study of 45 patients with diabetic PNP showed more frequent impairment of vibratory than pinprick sensation, LEP yielded similar abnormalities like the electrical sensory nerve action potentials pointing to higher diagnostic sensitivity of LEP compared to clinical examination in detecting small-afferent dysfunction [1]. A complete loss of all LEP components in PNP probably indicates impaired function of both Aδ- and C-fibers. However, in some cases of PNP and in a reported case of tabes dorsalis late LEP components were abnormal and ultralate LEP compo-

nents became unmasked indicating loss of Aδ-fiber at the presence of intact C-fiber function [51,60,79]. In contrast to nerve biopsies that do not yield quantitative information on C-fibers, unless electron microscopic studies are performed, LEP may thus provide some indirect evidence on C-fiber function. Yet, the inverse constellation of an isolated C-fiber
pathology with normal Aδ-function is difficult to evaluate by LEP because ultralate LEP typically fail to occur in normal subjects unless the Aδ-responses are experimentally abolished by a selective A-fiber block, a procedure that cannot be applied in patients. Single rare cases of selective large-fiber neuropathies exhibited loss of electrical SEP and preservation of late LEP indicating the remaining function of small myelinated afferents [21,75,91].

Monosegmental dorsal root affections represent another condition in which LEP exhibit greater diagnostic sensitivity compared to SEP because small fibers of the nociceptive system do not overlap between adjacent spinal segments to the same extent as large fibers of the tactile system. Therefore, LEP components may provide objective evidence for the border between intact and affected dermatomes [55]. In patients with carpal tunnel syndrome, LEP amplitude was reduced for stimulation of the third finger that is innervated by the median nerve, but not the fifth finger that is innervated by the ulnar nerve [4]. Therefore, even when both small and large fibers are similarly affected dermatomal LEPs may be indicated in segmental dorsal root or single nerve lesions because laser unlike electrical stimuli recruit significantly less intact neighboring afferents and, therefore, more likely yield abnormal EP.

3.2. LEP in patients with spinal lesions

Whereas localized structural damage to neural tissue in the periphery most often results in uniform sensory deficits due to the close anatomical association of small and large diameter fibers within the mixed nerve, the extent of an intramedullary spinal damage critically determines the degree of dissociation of sensory symptoms. This is because the ascending spinal pathways separate into the ipsilateral dorsal column and the contralateral spinothalamic tract mediating respective mechanoreceptive and thermoreceptive/nociceptive functions. Spinal lesions are, therefore, among the most important indications for LEP testing (Fig. 3, lesion sites 2 and 3). Studies indicate that LEPs provide a sensitive and specific clinical neurophysiological correlate for dissociated sensory loss in patients with a variety of spinal lesions due to syringomyelia, arteriovenous malformations, and inflammatory myelopathies, though the latter apparently yield more variable LEP findings with less consistent relationship to sensory symptoms [12,43,77]. LEP have also been used to document the dermatomal level of focal spinal cord lesions [37]. Most patients with syringomyelia present with a total loss of LEPs for stimulation of affected skin areas, in some patients only the...
amplitudes are reduced or the latencies increased [43,77].

Often, sensory loss and impairment of the LEP are unilateral, in spite of symmetric appearance of the lesion on MRI.

Surgical treatment by a shunt between syrinx and subarachnoid space reduced the LEP abnormalities [43]. Normal LEP was only reported in two patients with syringomyelia: one patient had completely normal sensory testing [61], the other patient had thermal hypoaesthesia but normal pain sensitivity [77].

In a series of patients with clinically definite multiple sclerosis [68], LEPs were more sensitive both to document an objective correlate of sensory deficits (86% vs. 50%) and in discovering clinically silent lesions (seven vs. five cases). Subclinical lesions have also been documented in HTLV-I-associated myelopathy (tropical spastic paraparesis), where LEP latencies were prolonged for foot stimulation in spite of normal sensory testing [40]. These findings may indicate slowed conduction velocity in the spinothalamic tract by demyelinating lesions [23].

3.3. LEP in patients with brainstem lesions

In the lower brainstem, the spinothalamic tract is situated laterally near the descending autonomic pathways, whereas the tactile pathways are located in the medial lemniscus near the midline. For that reason, similar to a lesion at spinal cord level, lesions of the lower lateral brainstem (Fig. 3, lesion site 4) can lead to a dissociated sensory loss. Pain and temperature sensation may be disturbed while tactile sensitivity remains intact, yielding LEP that are abolished or reduced in amplitude, but normal SEP [36,47,64]. A typical clinical picture reflecting these changes is that of Wallenberg’s syndrome. In cases like these, LEP can also reflect the time course of improved function due to treatment or spontaneous remission of brainstem lesions (Fig. 5). If the descending
trigeminal spinal tract is included in the lesion, an abolished blink reflex is a further clinical neurophysiological test that allows objective documentation of the functional nociceptive deficit when the afferent limb of the reflex is affected. This type of deficit may be a predictive factor for the development of neuropathic facial pain [29]. In patients with lacunar infarctions in the ventrolateral medullary tegmentum that spare the spinal trigeminal tract and nucleus, impaired LEP sometimes are the only objective functional sign for the lesion of the spinothalamic tract [83].

3.4. LEP in patients with thalamo-cortical lesions

It is still controversial, whether the converging tactile and nociceptive afferents form separate clusters in the ventrobasal relay nucleus of the thalamus or not [53]. Thalamic infarctions often exhibit non-selective sensory deficits that correlate well with early SEP abnormalities [87], but may sometimes cause a dissociated loss of pain sensation with intact touch sensation. In those cases, standard SEP are normal [58]. LEP were found to be abnormal in two patients with thalamic infarctions that led to altered pain sensitivity, and the LEP of one patient with normal pain sensation in spite of a thalamic infarction was normal [89]. LEP studies may thus also be useful in patients with thalamic lesions, but this potential indication has not been investigated well enough.

Although the primary somatosensory cortex (SI) contains some nociceptive neurons [48], cortical lesions most often do not change pain sensitivity, and it is yet still controversial, whether SI substantially contributes to the generation of LEP (c.f. Garcia-Larrea et al., this volume). There is some evidence that lesions in the fronto-parietal operculum may be associated with a reduced pain sensitivity [35]. In a few cases, late LEPs were found to be reduced in patients with lesions that included this area [8,88]. Since the early LEP component N1 is generated in the fronto-parietal operculum, it may provide a more specific sign for lesions in that area than the late N2–P2, but the small amplitude has so far impeded clinical use.

3.5. LEP in patients with psychiatric disorders

Psychiatric conditions rarely yield specific abnormalities of pain perception or sensitivity nor would one expect a pain test to significantly contribute to the differentiation of psychiatric diagnoses. Yet, a few studies of LEP in psychiatric patients, such as conversion disorder with circumscribed sensory deficit [56] and borderline personality disorder with self-destructive behaviors [6] found normal LEP and substantiated the diagnostic validity of this method to verify an organic cause of thermo-nociceptive symptoms as outlined in the previous sections. Severe cases of dementia yield abnormal or absent LEP [90]. Notably, Lorenz et al. [56] and Yamamoto et al. [90] observed abnormalities of the cognitive P3 potential following auditory oddball stimuli that allowed delineating cognitive rather than perceptual abnormalities in respective conversion disorder and dementia patients, whereas Baumgärtner et al. [6], who elicited a laser-P3 in a specific laser task found it to be normal in borderline personality disorder patients.
3.6. LEP in patients with chronic pain, headaches and enhanced pain sensitivity

LEPs were investigated in patients with chronic or recurrent episodes of pain or different types of hyperalgesia and allodynia due to fibromyalgia [32,34,55], trigeminal neuralgia [24], headache [27,62,85] and peripheral or central neuropathic pain [18,30,82,88]. So far, fibromyalgia is the only disease, for which an increase in LEP amplitude has been documented at a group level by comparisons with healthy subjects [33,54]. The abnormal amplitude increase was present for early (N1) and late (P2) LEP components, and it was associated with reduced heat pain thresholds and greater suprathreshold laser intensity ratings. These findings may indicate a primary hyperalgesia to heat due to peripheral sensitization, but alternative mechanisms include central sensitization, deficient descending inhibition, or enhanced attentional modulation. The latter, sometimes misleadingly referred to as hypervigilance, regards a general liability of patients with fibromyalgia to process threatening and aversive stimuli with heightened attentional engagement.

Patients suffering from migraine headache exhibit abnormally high LEP amplitudes, involving the N1 and N2–P2 components, exclusively over repeated blocks, thus reflecting a lack of normal time-dependent habituation [85]. This phenomenon, as tested in non-nociceptive paradigms to elicit the contingent negative variation (CNV = a slow negative ERP preceding an expected and task-relevant stimulus), appears to indicate the impending migraine attack in the pain-free period, but not shortly after it [49]. This points to a migraine-specific pathophysiological mechanism of abnormal (exteroceptive) excitability. It would be interesting to study whether reduced habituation of LEP amplitudes also shows a systematic relationship to the changes in CNV and the episodic variability of migraine. Notably, attentional enhancement of LEP due to presentation of pain descriptor vs. neutral words (semantic priming) is not different in migraine patients compared to healthy controls [86].

Late LEP in patients with neuropathic pain of peripheral and central origins were in most cases found to be decreased in amplitude rather than increased [18,31,82,88], and hence reflected the sensory deficit rather than the ongoing pain and hyperalgesia. In some patients LEP were absent or reduced although the laser stimulus was perceived more intense than in a non-affected control dermatome [18,30,88]. This paradox suggests that pathways required for the normal elicitation of LEP are disturbed whereas alternative pathways may project the laser-induced hyperalgesic response. Rousseaux et al. [64] observed residual ill-defined pain perception when touching very hot objects in patients suffering lateral brainstem infarction (Wallenberg’s syndrome) even though LEP were completely abolished. Due to the main projection of laser evoked nociceptive activity via the spinothalamic tract into lateral thalamic nuclei and the somatosensory cortex LEP appear to primarily represent a correlate of the “lateral” pain pathway that subserves a patient’s ability to adequately discriminate the location, duration and intensity of the laser pulse as a discrete exteroceptive pain event. Neuropathic pain may involve an increased recruitment of the “medial” pain system represented by multi-synaptic spinal pathways to brainstem homeostatic centers and medial thalamic nuclei that relay nociceptive input to the limbic forebrain [22]. In accordance with this view, it was reported that neuropathic pain patients with hyperalgesic phenomena to laser could exhibit ultralate LEP after stimulation of the affected side [31,88]. On practical grounds, chronic pain associated with circumscribed hypoalgesia or hyperalgesia to laser stimuli and reduced late LEP substantiates the neuropathic nature of the condition [31].

In patients with familiar progressive myoclonus epilepsy the amplitude of both early and late components of standard SEP is markedly enhanced [66]. In a small group of patients with this disease, late LEP amplitudes were found to be normal [44]. Facilitation of the somatosensory system in this disease thus appears to be specific to the tactile or proprioceptive pathways, sparing the nociceptive pathways.

4. Clinical use and misuse of LEP

4.1. Topodiagnosis of lesions using LEP

As shown in the previous section, LEP can document lesions anywhere along the nociceptive pathway (Fig. 3). Although all dermatomes are accessible, the absence of an LEP in a patient cannot necessarily provide the exact level of the lesion without additional clinical, electrophysiological or imaging data. The absence of an LEP may be due to a lesion anywhere between the cortex and the dermatomal level of the spinal cord where the stimulation is done, or even in the periphery. It is important to keep in mind, that even unilateral stimulation on two different levels with normal LEP from a higher level and absent LEP from the lower level does not necessarily mean that the lesion is between those two levels in the spinal cord: for instance, a clinical deficit of pain and temperature perception of the left leg with reduced or absent LEP from the foot and normal LEP from the hand could well be due to a spinal lesion at lumbar level affecting the STT. However, at brainstem level (medulla oblongata), the STT is somatotopically organized with afferent fibers from lower body parts on the lateral part and afferents from the upper body in medial parts of the STT [11]. Thus, a right sided lateral medullary infarction (Wallenberg’s syndrome) sparing the medial part of the STT would lead to the same symptoms and LEP abnormality, as described by Urban et al. [83]. However, together with the result of a thoroughly done neurological examination (and MRI), the picture becomes clear.

4.2. LEP as a measure for subjective pain?

One of the most fascinating findings in the early days of LEP was that amplitudes correlate better with subjective pain...
ratings than with stimulus intensity [17]. Similar findings were reported for tooth pulp evoked potentials [20], which led to the hypothesis, that LEP reflected neural processing of pain perception rather than stimulus encoding. Further evidence supporting this hypothesis came from studies, where attention was modulated which led to changes in LEP amplitudes and perceived pain without changes of stimulus intensity [31,52,65]. When interstimulus intervals become shorter, however, amplitudes decrease while subjective pain ratings remain unchanged. This is shown in Fig. 6 (lower part) where double pulses were given on the hand dorsum. It demonstrates, that despite a normally close relationship, LEP and subjective pain perception can be dissociated. Similar results were obtained in tooth pulp stimulation, where evoked potentials became reduced in amplitude while pain ratings were unchanged, and, in the same study, the same dissociation was shown for AEP amplitudes and ratings of perceived loudness [19]. Overall, evoked potentials obviously rather reflect the state of the sensory pathway and not subjective perception [6,56].

### 4.3. LEP in hyperalgesia and chronic pain

LEP are useful to demonstrate lesions along the pain pathway. As a lesion in combination with a sensory deficit like hypoalgesia usually results in prolonged latency and/or decreased amplitude, one could expect that in hyperalgesia with increased pain transmission amplitudes might be enhanced. Apart from tension type headache with higher amplitudes from pericranial stimulation sites [27], only fibromyalgia has been shown to yield generally higher LEP amplitudes compared to healthy subjects [33,54]. It is still questionable, whether the basis of this disease is directly related to increased pain perception (or reduced inhibition), or to a higher level of attention. Usually, in a more or less intact pain pathway, LEP amplitudes are not enhanced [18,30,88]. In a human surrogate model for hyperalgesia (topical capsaicin), amplitudes were normal or decreased [84]. The LEP is no direct measure for spontaneous pain; it may, however, give hints on the underlying mechanism: spontaneous pain in combination with reduced LEP amplitudes may derive from deafferentation, whereas spontaneous pain with normal LEP may be due to central sensitization (or may be psychogenic).

For the evaluation of hyperalgesia and related pain mechanisms, quantitative sensory testing (QST) is the better tool.

### 4.4. LEP for screening?

In clinical practice it would be useful to improve assessment of hyperalgesia. Although LEP are sensitive and suitable for application in any dermatome, they cannot serve as a screening tool. The recording (and evaluation) of LEP takes 1–2 h rather than minutes, the device is expensive, and reimbursement is usually not adequately implemented in the clinic’s billing system (LEP testing may be charged as standard SEP which of course does not cover the effort). Therefore, in the clinical setting, there has to be a clear indication: objectify/clarify an STT lesion or involvement of the nociceptive pathway. Additionally, LEP can be an objective measure for follow-up examinations and allow a differentiation between neurogenic and psychogenic origin of disturbed pain perception.

### 5. Conclusions

Standard SEP are of limited value in patients, who present with a dissociated sensory loss of pain and temperature sensitivity and preserved tactile and proprioceptive sensitivity. The technique of LEP recording allows the assessment of the functional status of the nociceptive pathways within the somatosensory system. According to the anatomy of the nociceptive pathways, this type of a sensory deficit occurs predominantly with peripheral, spinal, or brainstem lesions. LEP abnormalities consist of complete absence, amplitude reductions and/or latency increases. Objective neurophysiological documentation of clinically relevant sensory deficits, detection of subclinical lesions, differentiation of axonal and demyelinating lesions and differential diagnosis of organic vs. psychogenic deficit in pain perception are potential clinical uses of this technique.

Care should be taken to use a defined task for the patients, because the LEP components that are evaluated clinically are late components (similar to VEP), and are more sensitive to attention and other task-related variables than the early components of the standard SEP. Small generalized changes in pain sensitivity are not detectable with LEPs, except when...
using statistical comparisons between groups of subjects. In psychiatric patients with altered pain perception, LEP can be normal, because the pathways are intact. If the dissociated sensory deficit is localized, however, the within-subject comparison of an affected and a healthy control site allows to judge the integrity of the nociceptive pathways on a single-case basis as well as follow-up studies to document treatment efficacy.

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