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Mini-review

Laser evoked potentials for assessing sensory neuropathy in human patients[☆]

A. Truini, A. Romaniello, F. Galeotti, G.D. Iannetti, G. Cruccu*

Department of Neurological Sciences, University 'La Sapienza', Viale Università 30, 00185 Rome, Italy

Abstract

Sensory neuropathy usually impairs tactile sensations related to large myelinated afferents (A β) as well as thermal-pain sense related to small myelinated (A δ) and unmyelinated (C) afferents. By selectively affecting large or small fibres, some sensory neuropathies may also provoke a dissociated sensory loss. Standard nerve conduction studies and somatosensory evoked potentials assess A β -fibre function only. Laser pulses selectively excite free nerve endings in the superficial skin layers and evoke A δ -related brain potentials (LEPs). From earlier studies and new cases we collected data on 270 patients with sensory neuropathy. LEPs often disclosed subclinical dysfunction of A δ fibres and proved a sensitive and reliable diagnostic tool for assessing small-fibre function in sensory neuropathy.

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Sensory neuropathy is a common neurological disorder secondary to various diseases that manifests with sensory loss, paresthesias, and pain. In most cases, sensory impairment involves tactile, vibration, and joint-position sense, related to large-myelinated (A β) afferents, as well as thermal-pain sense related to small-myelinated (A δ) and unmyelinated (C)

afferents. Some sensory neuropathies selectively affect large or small afferents thus inducing a dissociated sensory loss. The neurophysiological assessment of sensory neuropathy traditionally relies on standard nerve conduction studies and somatosensory evoked potentials. Both techniques assess A β fibres alone. Because large-size, non-nociceptive afferents have a lower electrical threshold than small-size, nociceptive afferents, electrical stimuli always generate a large A β volley that masks the nociceptive signals. Non-nociceptive and nociceptive afferents both contribute to vertex potentials from painful electrical stimuli. Studies investigating the potentials evoked by painful electrical stimulation have so far failed to identify the pain-related components of the brain signals [5].

Special techniques have been used to improve the selectivity of electrical stimuli. Zimmermann and associates have shown that experimental blocks of large fibres in peripheral nerves, induced with direct current or local nerve heating, preserve normal function in most small fibres and thus provide a selective nociceptive input [15,23,24]. These useful methods have been used to assess nociceptive pathways and in particular the effect of the C-fibre input in the central nervous system [15,16]. For clinical applications, however, these methods are unsuitable because they require nerve exposure.

Although many studies investigated reflex responses and brain potentials after electrical stimulation of special organs exclusively innervated by small fibres, such as the cornea

[☆] In honour of Professor Manfred Zimmermann's on the occasion of his 70th birthday. I am not going to comment on the scientific merits of Manfred Zimmermann and all what he did in the field of pain; these clearly emerge from his articles and books. I wish to remember a few things that I will probably never forget. The first time I met him personally was in 1985, at the world congress of Neurology in Hamburg. We had a teaching course on low-back pain. His subject was pathophysiology of muscle pain. I was the speaker immediately after him and to talk after this sacred personality made me very anxious. He was giving a beautiful lecture, when a loudspeaker began to announce that a car must be immediately removed. This announcement interrupted him several times, until he said, looking at the audience with a smile: "Well, this is more distressing than muscle pain!" All laughed and clapped their hands, and ...I was completely relieved and was able to manage my talk. I also remember him when the University of Siena gave him the *Laurea Honoris Causa*: his lecture was magnificent but even more impressive were his brilliant and humane talks at the dinner, when I really felt nostalgic of the Sacred Roman Empire and its German Emperors. Finally, one confession; I have always been fond of his illustrations; they were so intelligent, clear and graphically nice, that I still use them in my lessons to the students and try to copy their style in my papers. Very best wishes, Manfred!

* Corresponding author. Tel.: +39-6-4991-4178; fax: +39-6-4991-4758.
E-mail address: cruccu@uniroma1.it (G. Cruccu).

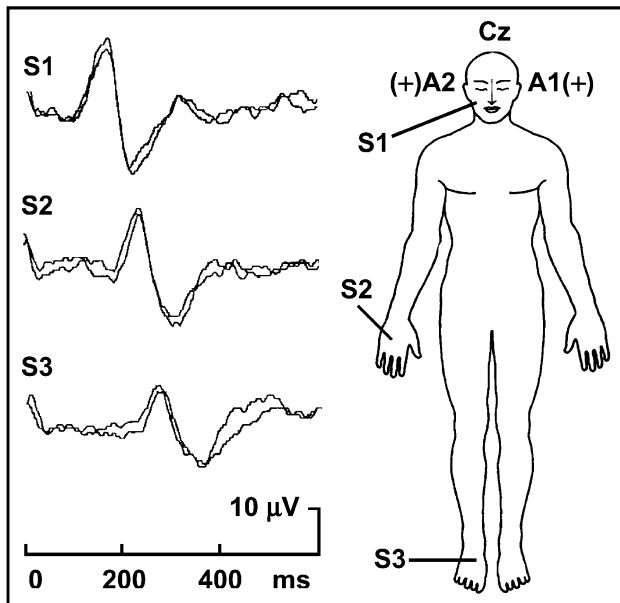


Fig. 1. Laser evoked potentials (LEPs) in a representative normal subject. Two series of ten trials collected and averaged after perioral (S1), hand (S2) and foot stimulation (S3). Recordings from the vertex (Cz) referenced to linked earlobes (A1–A2).

and tooth pulp none yielded stable correlates of the nociceptive input [9].

The currently accepted neurophysiological method of assessing nociceptive pathways relies on laser evoked potentials (LEPs) [7]. Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and activate A δ and C nociceptors. In brief, low-intensity pulses directed to the hairy skin evoke pinprick sensations and 'late' brain potentials (LEPs), both related to the activation of type II AMH mechanothermal nociceptors [6]. The afferent volley is conducted along small-myelinated (A δ) primary sensory neurons, and relayed to the spinothalamic tract and brain. The main, clinically useful LEP signal is a widespread negative-positive complex (N2–P2) that ranges from 200 to 350 ms in latency and reaches maximum amplitude at the vertex (Fig. 1) [6]. This complex is generated by the anterior cingulate gyrus, and possibly contributed to by the bilateral opercular-insular regions [6].

Although laser stimuli activate both A δ and C fibres, 'ultralate' potentials (750–1200 ms) [7], related to C-fibre activation, can be obtained only with dedicated techniques [18] that have not yet been standardised for clinical application.

Although several types of laser stimulators are now available, all the studies in patients with sensory neuropathy have used a CO₂-laser. This device has the advantage of a wavelength (10.6 μ m) that closely matches the thermophysical properties of skin.

The main current aim of clinical LEP studies in peripheral neuropathy is to provide information on A δ -fibre function and on the pathophysiology of neuropathic pain. To evaluate the clinical utility of LEPs in sensory

neuropathy, we discuss here LEP findings in 204 patients from earlier studies of ours, 56 patients reported in the literature, and ten new patients (Table 1).

In a study of patients with peripheral neuropathy, Kakigi [13,14] showed that LEPs correlate strongly with the impairment of pain sense and density of A δ fibres, as assessed by histopathological examination of the sural nerve, whereas somatosensory evoked potentials (SEPs) correlate strongly with the impairment of deep sensation and A β -fibre dysfunction. Consistently with this view, several studies verified selective large myelinated fibre dysfunction in single patients with neuropathy by finding abnormal SEPs and normal LEPs [4,8,22].

Although diabetic neuropathy is the most common polyneuropathy, few studies have explored A δ -fibre function with LEPs. Investigating LEPs in 45 diabetic patients with various degrees of peripheral nerve damage Agostino and associates [3] reported that the most frequent abnormalities were absent or decreased amplitude LEPs, as expected in axonopathies. The LEP abnormalities strongly correlated with large-fibre dysfunction as evaluated by nerve conduction studies, thus indicating that diabetes induces large and small afferent dysfunction in parallel. Conversely, Rossi and associates [19] studied LEPs in 21 diabetic patients who had neither clinically apparent neuropathy nor electrophysiological evidence of large-fibre damage. No patients had individual LEP abnormalities, but LEPs after foot stimulation had a longer mean latency and smaller mean amplitude than those in normal subjects, thus demonstrating an early, subclinical and selective damage of the peripheral nociceptive pathway.

In patients with facial sensory disturbances trigeminal LEPs are a useful diagnostic tool. Depending on the receptor density and conduction distance trigeminal-LEPs have a larger amplitude and a shorter latency than hand- and foot-LEPs [2,11]. Agostino and associates studied LEPs after perioral stimulation in 52 diabetic patients [1]. Trigeminal LEPs had a longer mean latency and lower amplitude in diabetic patients than in normal subjects and the abnormality frequency of the LEPs correlated with the severity of polyneuropathy.

In an earlier study from our group, in three patients with chronic inflammatory demyelinating polyneuropathy and no trigeminal sensory loss we found abnormal trigeminal reflexes and normal trigeminal LEPs thus documenting selective sparing of small myelinated fibres [11].

Sensory neuropathy, especially small-fibre neuropathy typically causes neuropathic pain [17]. Its pathophysiological mechanisms remain unclear. Although neuropathic pain is related to nociceptive pathway dysfunction, few studies have used LEPs to investigate peripheral neuropathic pain.

Post-herpetic neuralgia severely impairs LEPs [21], but LEP abnormalities do not correlate with pain. Hence in this chronic painful condition, pain may arise from a more complex pathophysiological mechanism also involving unmyelinated afferent dysfunction. The observation that

Table 1
Laser evoked potentials (LEPs) in sensory neuropathy

Disease	LEP abnormalities (%)			n	LEP type	References
	Normal	Delay	Absence			
Asymptomatic diabetes	100	0	0	21	H-F	¹ Rossi et al. [19]
Diabetic neuropathy	73	21	6	52	T	¹ Agostino et al. [1]
	38	2	60	45	H-F	² Agostino et al. [3]
Postherpetic neuralgia	35	0	65	40	V	² Truini et al. [21]
Small fibre neuropathy	0	30	70	10	H-F	Present study
Essential trigeminal neuralgia	49	35	16	47	T	¹ Crucchi et al. [10]
Symptomatic trigeminal neuralgia	0	64	36	20	T	¹ Crucchi et al. [10]
Various neuropathies	13	50	37	30	H-F	Kakigi et al. [13]
	60	0	40	5	H-F	³ Single case reports
Total	Abnormality frequency = 56%			270	All	

LEP type: stimulation of trigeminal (T), hand (H), or foot (F) skin. 1–2: Significant results of group statistics between patients and control subjects. 1: Longer latency and lower amplitude. 2: Lower amplitude. 3: Amantini et al. (1996), Cole et al. (1995), Lankers et al. (1991), Yamamoto et al. (1997), Wu et al. (1999).

patients with symptomatic and those with idiopathic trigeminal neuralgia both have abnormal LEPs suggests that A δ -fibre dysfunction may play an important role in the pathophysiology of neuralgic pain [10]. Further support for this conclusion came from a recent unpublished study from our group showing that ten patients with small-fibre neuropathy all of whom had neuropathic pain (burning feet) and normal nerve conduction studies had absent or delayed LEPs (Table 1).

LEPs have some drawbacks. Rather than reflecting the first arrival of the somatosensory input to the brain, the N2–P2 complex of the late LEP may reflect secondary processing of sensory information. The P2 component is influenced by arousal and attention. Hence some investigators noted that the sensitivity of LEPs to cognitive factors may hamper their use for diagnostic purposes [12]. Because P2 is only partly influenced by arousal and attention and is spared in demented patients, most investigators regard the LEP as a sensory specific response that is merely modulated by attention [6].

Studies dealing with LEPs in sensory neuropathy report that LEPs have a significantly lower mean amplitude in the patient group than in the control group. But because the normal amplitude limit has not yet been defined, no study relied on individual LEP amplitude to classify patients as normal or abnormal [3,10,21].

Unlike SEPs, LEPs lack a peripheral measure of the afferent volley, a signal that would be useful to localise a nociceptive pathway dysfunction in the peripheral or central nervous system [14].

LEPs nonetheless have important advantages in investigating A δ fibre function. Laser stimulation selectively activates A δ and C nociceptors, thus providing a specific nociceptive input. After only a few trials, laser stimulation yields clear and large-amplitude scalp potentials related to A δ afferent activation. LEPs can document sparing of small myelinated fibres in patients with damage to the large

myelinated fibres as well as disclose selective dysfunction of nociceptive pathways.

In conclusion, LEPs provide a sensitive, reliable, and easy tool for evaluating the nociceptive A δ pathways in patients with sensory neuropathy. Currently the main limit is the relatively scarce availability of laser stimulators [20].

A more complex technical problem regards the ultralate LEPs related to the C-fibre input. An easy method of recording ultralate LEPs and its clinical application in patients with neuropathic pain is a hopeful aim for the future.

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