

Laser evoked potential amplitude and laser-pain rating reduction during high-frequency non-noxious somatosensory stimulation

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HIGHLIGHTS

- Non-painful somatosensory stimulation has an analgesic effect.
- The analgesia induced by non-painful somatosensory stimulation is not a general phenomenon.
- High-frequency non-painful stimuli dampen the nociceptive input at the spinal cord level.

ABSTRACT

Objective: To investigate the mechanism subtending the analgesic effect of high frequency non-painful somatosensory stimulation.

Methods: Laser evoked potentials (LEPs) and laser-pain rating were obtained from healthy subjects to stimulation of different parts of the body. LEPs were recorded at baseline and during non-painful electrical stimulation of the superficial branch of the right radial nerve (RRES).

Results: RRES reduced N2/P2 LEP amplitude to right radial ($F_{(8,10)} = 82.4$, $p < 0.001$), left radial ($F_{(8,10)} = 22.2$, $p < 0.001$), and right ulnar ($F_{(8,10)} = 7.2$, $p = 0.008$) stimulation, while the N2/P2 amplitude to left ulnar territory stimulation remained unchanged ($F_{(8,10)} = 3.6$, $p = 0.07$). The laser-pain rating was reduced by RRES to bilateral radial territory stimulation ($p < 0.05$). In a control experiment, laser-pain rating and LEPs to left foot stimulation were not modified by RRES ($p > 0.05$).

Conclusions: Our study confirms that the non-nociceptive afferents dampen the nociceptive input. The spatial pattern of this interaction suggests that, when conditioning higher frequency non-painful stimulation is used, the inhibition takes place at the spinal cord.

Significance: Our experimental design reproduces what happens when non-painful somatosensory stimuli are used to reduce pain, such as rubbing a wound or during transcutaneous electrical nerve stimulation. Therefore, in these situations the analgesia is likely to occur at the spinal cord level.

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1. Introduction

The inhibition of pain by non-nociceptive cutaneous stimulation represents a well known phenomenon. Daily experience tea-

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ches us that rubbing a painful area can reduce pain. The underlying mechanism of the analgesia induced by non-painful somatosensory stimuli has been hypothesized by [Melzack and Wall \(1965\)](#). According to the “gate control theory of pain”, it is the balance between the small diameter (C and Aδ) and large diameter (Aβ) fibres at their entrance to the spinal cord to control pain. In particular, the large sensory fibres can inhibit the nociceptive input to the small fibres at the first synapse ([Melzack and Wall, 1965](#)). In case of intense painful stimulation, such as that occurring

during tissue damage, the “gate” is opened. The “gate control theory of pain” has been object of several criticisms (Mendell, 2014; Nathan, 1976), but it is still considered to explain the analgesic effect of non-painful electrical stimulation of the sensory afferents (transcutaneous electrical nerve stimulation – TENS) and dorsal column stimulation.

In humans, laser evoked potential (LEP) studies have been addressed to demonstrate the analgesic effect of the non-painful somatosensory stimulation. LEPs have the advantage to assess the nociceptive pathway selectively (Bromm and Treede, 1984) and the responses evoked from the brain to laser stimulation of the skin are generated by A δ inputs (Valeriani et al., 2012). Early studies showed that the LEP amplitude could be dampened by the concurrent activation of the large myelinated A β -fibres by vibration, active movement, or non-painful electrical stimulation of the skin (Ellrich and Lamp, 2005; Kakigi and Shibasaki, 1992).

However, no information about the site of LEP inhibition can be issued from these studies. Inui et al. (2006) used the intraepidermal electrical stimulation of the nociceptive fibres and demonstrated that the inhibitory effect of the cutaneous input on pain pathways takes place mainly at cortical level. A similar conclusion was reached by our group in a study in which the presumed site of LEP inhibition by non-painful electrical stimuli was investigated by using coupled painful laser pulses and non-painful electrical stimuli at different interstimulus intervals (Testani et al., 2015). We found that LEP amplitudes were reduced when the interaction between the nociceptive and the non-nociceptive input occurred at supraspinal level (thalamus or cerebral cortex). Both studies (Inui et al., 2006; Testani et al., 2015) explored the inhibition of a single nociceptive input by a single non-painful stimulus. However, this situation is scarcely representative of the real world where high-frequency non-painful stimuli are used to inhibit pain, such as in TENS or by rubbing a wounded part of the body.

The aim of the present study was to estimate the site of inhibition of the nociceptive input by high-frequency non-painful somatosensory stimuli, thus reproducing a more ecological situation than that investigated previously (Inui et al., 2006; Testani et al., 2015).

2. Methods

2.1. Subjects

Ten healthy right-handed subjects (5 males, 5 females, mean age 29.5 ± 3.3 years), who gave their informed consent, took part in the main experiment, while 7 right-handed subjects (3 males, 4 females, mean age 41 ± 7.3 years) were recruited for the control experiment. All subjects were free of neurological, psychiatric or pain disorders and were not receiving any medication. The study conformed to the standards set by the Declaration of Helsinki.

2.2. Stimulation and recording methods

During the recordings, the subjects lay on a bed in a comfortable room. In the main experiment, LEPs were recorded after painful CO₂ laser (Neurolas, ELEN, Florence, Italy) stimulation of four sites: (1) the radial territory of the right hand dorsum (rRadial), (2) the radial territory of the left hand dorsum (lRadial), (3) the ulnar territory of the right hand dorsum (rUlnar), and (4) the ulnar territory of the left hand dorsum (lUlnar). In the control experiment, LEPs were recorded after painful stimulation of the left foot dorsum (lFoot). A He-Ne laser beam was used to identify the skin area where the CO₂ laser pulse was delivered. The laser beam was slightly moved after each pulse, to avoid nociceptor fatigue and peripheral habituation. First, the sensory threshold (STh), defined

as the lowest stimulus intensity able to elicit a distinct sensation, was determined by the method of limits in three series of increasing and decreasing stimulus intensities. Then, the stimulus intensity was fixed at $2.5 \times$ STh. This intensity, felt as a painful pinprick by all subjects, was used to record LEPs. For LEP recording, laser pulses were delivered with an interstimulus interval variable from 9 to 11 s.

For A β fibre activation, electrical 0.3 ms square pulses were delivered over the superficial branch of the right radial nerve at the wrist by means of skin electrodes (cathode proximal). The stimulus intensity was fixed at three times the sensory threshold and was judged as non-painful by all subjects. The stimulation rate was fixed at 5.1 Hz (Fig. 1).

In the main experiment, electroencephalogram (EEG) was recorded by a cap with 31 electrodes disposed according to an extended 10–20 International System and referred to the nose. In the control experiment, EEG was obtained from 3 scalp electrodes located at Cz, T4, and Fz scalp locations and referred to the nose. An electroculogram (EOG) electrode on the supero-lateral right canthus was used to record ocular movements. Ground was placed at the Fpz location. All EEG trials including signals overtaking the amplitude of $\pm 80 \mu$ V at any recording channel, including EOG, were excluded from the average. Each average was calculated from 30 EEG trials. The filter bandpass was 0.3–70 Hz and the analysis time was 1000 ms (500 Hz of sampling rate). We ensured us that the attention of our subjects did not vary during LEP recording by asking them to count the number of received laser pulses silently.

3. Experimental procedure

The study included 2 experiments: (1) a main experiment, in which we tested whether the non-painful somatosensory stimulation of the right radial nerve could modify LEP amplitude and laser-pain rating when laser pulses were delivered to homotopic ipsi-/contra-lateral regions (rRadial and lRadial, respectively) or close heterotopic ipsi-/contra-lateral areas (rUlnar and lUlnar, respectively), and (2) a control experiment, in which we checked whether the non-painful somatosensory stimulation of the right radial nerve had any effect on LEP amplitude and laser-pain rating after stimulation of a far heterotopic region (lFoot). The main experiment was addressed to detail the spatial pattern of LEP modification during non-painful somatosensory stimulation, while the control experiment was added in order to exclude a general effect.

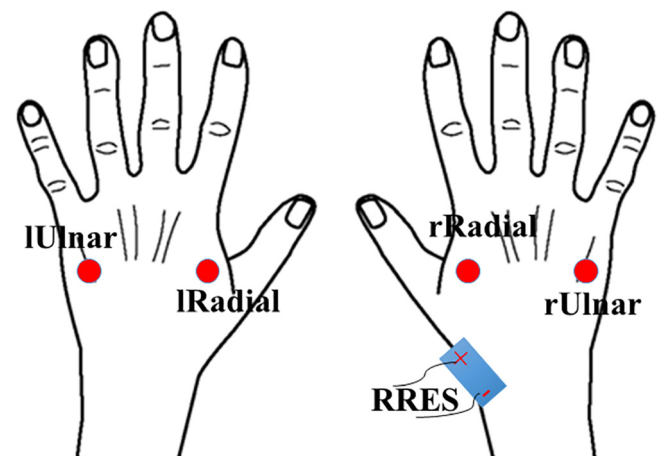


Fig. 1. The figure shows the different sites (red bulls) stimulated by laser for LEP recording in the main experiment and the non-painful electrical stimulation for RRES. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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