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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.

1. Introduction

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

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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 Aδ inputs (Valeriani et al., 2012). Early studies showed that the LEP amplitude could be dampened by the concurrent activation of the large myelinated Aβ-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 confortable room. In the main experiment, LEPs were recorded after painful CO_2 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 CO_2 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 × 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 Aβ 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 ±80 μV 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.

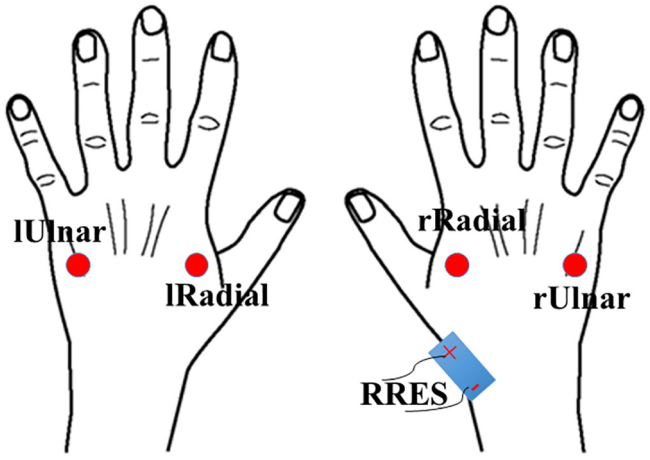

Fig. 1. The figure shows the different sites (red bulls) stimulated by laser for LEP recording in the main experiment and the non-painful electrical stimulation for RRES. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

LEPs were recorded from all stimulation sites at the baseline and during right radial electrical stimulation (RRES). In the main experiment, the order of the stimulation sites at the baseline was randomized. During RRES, the same order of the stimulation sites as at the baseline was followed, in order to reduce a possible effect of LEP habituation on the results (Valeriani et al., 2003).

At the end of each LEP recording, the laser-pain rating was obtained by using a 101-points visual analogical scale (VAS), in which 0 corresponded to "no pain" and 100 to the most "unbearable pain".

3.1. LEP components and statistical analysis

The latencies of the N1, N2, and P2 LEP components were measured at their peak. We referred the contralateral temporal (T3/T4) electrode to the Fz lead off-line in order to calculate the N1 amplitude (Kunde and Treede, 1993). In the main experiment the peak-to-peak N2/P2 amplitude was measured on the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 traces, while in the control experiment it was measured at Cz.

3.1.1. Statistical analysis in the main experiment

VAS values obtained at baseline and during RRES were compared by two-way ANOVA, considering the stimulation site (rRadial, lRadial, rUlnar, rUlnar) and the time (baseline, RRES) as the variables. Paired t-test with Bonferroni's correction for multiple comparisons was used for post hoc analysis ($p < 0.05$).

For LEP latencies, paired Student's t-test was used to compare the values at the baseline and during RRES for each stimulation site.

N1 amplitudes underwent two-way ANOVA with the stimulation site (rRadial, lRadial, rUlnar, rUlnar) and the time (baseline, RRES) as variables.

For the N2/P2 amplitude recorded at each stimulation site, two-way ANOVAs were performed with the time (baseline, RRES) and the recording electrode as the factors. Paired t-test with Bonferroni's correction for multiple comparisons was used for post hoc analysis ($p < 0.05$).

3.1.2. Statistical analysis in the control experiment

All the considered values (VAS, N1, N2 and P2 latencies, and N2/P2 amplitude) were compared between the baseline and the RRES times by paired Student's t-test ($p < 0.05$).

4. Results

4.1. Main experiment

4.1.1. Psychophysics

Laser pain ratings changed significantly between baseline and RRES ($F_{(3,10)} = 9.01$; $p = 0.004$) (Fig. 2). Post-hoc analysis showed that RRES reduced pain ratings to both rRadial and lRadial site stimulation ($p < 0.05$).

4.1.2. LEP results

The N1 and P1 potentials were recorded consistently in the temporal region contralateral to the stimulation and in the frontal region, respectively. A biphasic negative (N2) – positive (P2) component showed the highest amplitude at Cz electrode (vertex). The mean amplitudes and latencies of the LEP components at baseline and during RRES are shown in Table 1.

As compared to the baseline, the N2/P2 amplitude was clearly reduced after stimulation of the bilateral radial territories (rRadial and lRadial) and of the right ulnar site (rUlnar) (Fig. 3).

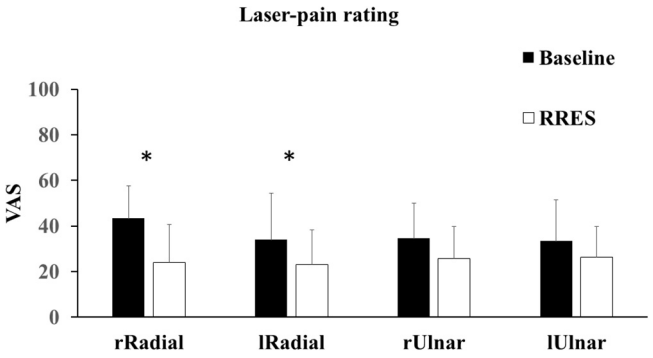

Fig. 2. The histogram shows the laser-pain rating (VAS) at baseline (black columns) and during RRES (white columns). Asterisks indicate statistical significance ($p < 0.05$).

Since RRES did not modify all LEP latencies ($p > 0.05$), no confounding effect of the peak latency prevented a correct comparison of the N1 and N2/P2 amplitudes across the experimental conditions.

The RRES effect on N1 amplitude was not significant ($F_{(3,10)} = 1.18$, $p = 0.28$), although an average reduction of the mean N1 amplitude during RRES was found after stimulation of the bilateral radial territories (Fig. 4). On the contrary, a main effect of RRES was found on of the N2/P2 amplitude to rRadial ($F_{(8,10)} = 82.4$, $p < 0.00 1$), lRadial ($F_{(8,10)} = 22.2$, $p < 0.001$), and rUlnar ($F_{(8,10)} = 7.2$, $p = 0.008$) stimulation (Fig. 4). RRES did not change the N2/P2 amplitude to lUlnar stimulation ($F_{(8,10)} = 3.6$, $p = 0.07$). In no stimulation site, a significant interaction time X electrode was found ($p > 0.05$), suggesting that the topography of the N2/P2 component was not modified by RRES. Post-hoc analysis showed that for the rRadial stimulation the N2/P2 amplitude was lower during RRES than at the baseline at all considered electrode ($p < 0.05$), while for lRadial stimulation the N2/P2 amplitude reduction during RRES was significant only at Cz ($p = 0.03$). Post-hoc analysis did not reach the statistical significance for rUlnar stimulation ($p > 0.05$).

4.2. Control experiment

The laser-pain rating to lFoot stimulation was not modified by RRES ($p = 0.11$). N1 ($p = 0.28$), N2 ($p = 0.2$) and P2 ($p = 0.73$) latencies recorded at the baseline were not different from those measured after RRES. Lastly, also both the N1 ($p = 0.13$) and N2/P2 ($p = 0.94$) amplitudes did not significantly change after RRES (Fig. 5).

5. Discussion

In the present study, we investigated the effect of high-frequency non-painful somatosensory stimuli on LEP amplitudes and laser-pain rating. Our results confirmed that the electrical stimulation of the cutaneous non-nociceptive Aβ fibres dampens the Aδ fibres input generated by laser pulses delivered over the skin. Moreover, we originally showed that this inhibition is not a general phenomenon, but it depends on the anatomical relationship between the stimulated parts of the body. In particular, the non-painful stimulation of the sensory branch of the radial nerve at the wrist dampened the nociceptive input coming from the bilateral homotopic cutaneous territory (rRadial and lRadial). Our finding of a bilateral effect of the RRES confirms previous results by Ristić et al. (2008). In this study, non-painful stimulation of both left and right surperficial radial nerve trunk at 100 Hz reduced the LEP amplitude evoked by stimulation of the left hand dorsum.

In our study, RRES exerted a weaker inhibition also on the nociceptive afferents from ipsilateral heterotopic skin (rUlnar), while it

Table 1
LEP values (main experiment).

		N1		[a]N2	[a]P2	[a]N2/P2
		Latency (ms)	Amplitude (μV)	Latency (ms)	Latency (ms)	Amplitude (μV)
rRadial	Baseline	123 ± 35.2	4.2 ± 2.2	172.8 ± 37	312.4 ± 26.3	30.5 ± 10.9
	RRES	139.9 ± 31.7	2.6 ± 1.9	185.7 ± 40.1	330 ± 36.2	15 ± 5.8
lRadial	Baseline	133.1 ± 34	5.4 ± 3.8	183.1 ± 41.3	297 ± 35.3	28.3 ± 9.4
	RRES	143 ± 37.1	3.8 ± 1.9	202.3 ± 46	306.7 ± 36.6	19.1 ± 6.7
rUlnar	Baseline	140.6 ± 33.8	2.5 ± 2.6	203.3 ± 31.3	313.3 ± 40.7	19.5 ± 6.9
	RRES	141.1 ± 33.2	2.7 ± 2.2	231.7 ± 48.8	317.4 ± 36.2	12.7 ± 2.7
lUlnar	Baseline	124.4 ± 31.5	2.6 ± 1.9	182.9 ± 32.8	325 ± 28.6	21 ± 10.6
	RRES	135.4 ± 41.3	2.9 ± 1.9	201.2 ± 35	306.9 ± 24.4	17.8 ± 8.8

[a] N2 and P2 latencies, and N2/P2 amplitudes are calculated at Cz.

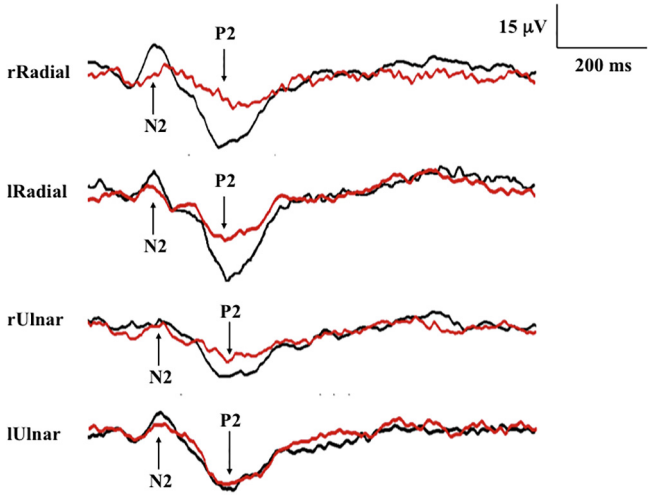

Fig. 3. Grand-average Cz traces to stimulation of the different sites at baseline (black) and during RRES (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

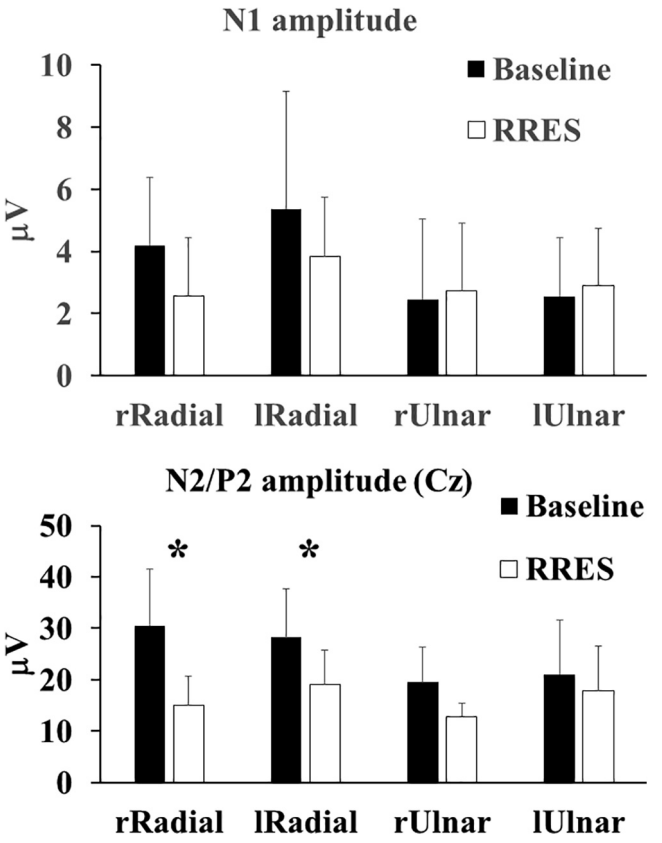

Fig. 4. The histograms show the N1 (upper) and the N2/P2 (lower) amplitudes at baseline (black columns) and during RRES (white columns). Asterisks show significant differences ($p < 0.05$).

did not modify the brain signal due to painful stimulation of the contralateral heterotopic territory (lUlnar). The control experiment demonstrated that RRES did not have any effect on laser-pain rating and LEPs to stimulation of a far region of the body (lFoot). The spatial distribution of the interaction between non-painful and painful stimuli suggests that the inhibition of the nociceptive input by higher frequency non-painful stimuli may take place at the spinal cord level. We suggest that the spinal neurons activated by the non-painful electrical stimuli exert an inhibitory effect on the nociceptive neurons through a segmental mechanism. This mechanism can explain why the LEP amplitude to stimulation of the rRadial area, which is innervated by the C6 spinal root, is reduced by the non-painful electrical stimulation of the superficial radial nerve trunk, whose fibres enter the spinal cord trough both C5 and C6 roots (Kimura, 2001). In this case, the inhibition can occur at pre-synaptic level, as expected from the gate control theory (Melzack and Wall, 1965). The segmental mechanism of inhibition can also explain the LEP amplitude reduction after stimulation of an ipsilateral close heterotopic territory (rUlnar). Cutaneous nociceptors, activated by laser pulses, project to laminas I and II, also known as Substantia Gelatinosa (Willis and Cogheshall, 1991). Nociceptive cells in lamina I are second-order pain projection neurons that send ascending axons to the brain, while cells in lamina II are generally interneurons which project at most two to three close spinal segments (Todd, 2017). This means that there is a strict connection between spinal nociceptive neurons of close dermatomes, possibly explaining the inhibitory effect of the non-painful right radial nerve stimulation on the LEP amplitudes generated by input reaching the ipsilateral C8 spinal segment (rUlnar). It is interesting that the earlier Wall's observations underlined the main role of Substantia Gelatinosa in determining the pre-synaptic inhibition (Wall, 1978). As for the LEP amplitude reduction after stimulation of the homotopic area contralateral to non-painful stimulation (lRadial), it is possible that the spinothalamic neurons in the same spinal segment of the contralateral side are inhibited by non-painful electrical stimuli. Indeed, Gjerstad et al. (2000) showed that intra muscolar-injected capsaicin could inhibit the contralateral dorsal horn neurons. Although in our experiment it is the non-nociceptive input to inhibit the contralateral nociceptive neurons, Gjerstad's data demonstrate a connection between bilateral spino-thalamic neurons of the same spinal segment.

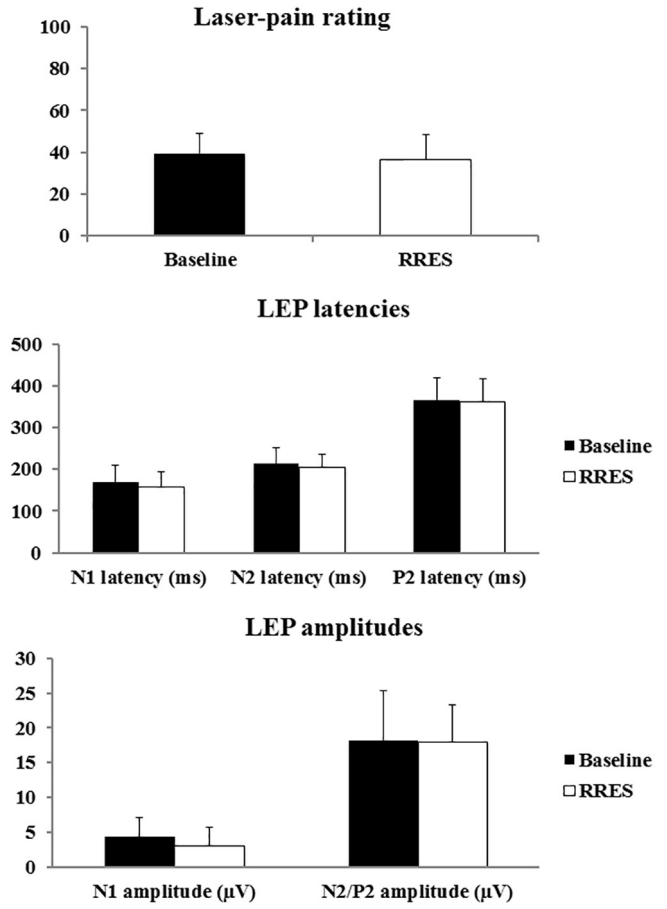

Fig. 5. The histograms show VAS values (upper), LEP latencies (middle), and LEP amplitudes (lower) at baseline and during RRES in the control experiment.

In our subjects, other possible mechanisms of interaction between non-nociceptive and nociceptive input are less likely. First, the effect of the non-painful electrical stimulation on the LEP components to stimulation of the contralateral homotopic skin area (lRadial) and of the ipsilateral heterotopic territory (rUlnar) could be hardly explained whether the interaction occurred only at the peripheral nerve level. Second, a bilateral effect of the RRES could not be surprising in case of a cortical site of inhibition, since it is known that non-painful somatosensory stimuli have a bilateral representation, at least at level of the second somatosensory area (Barba et al., 2002; Coghill et al., 1994). Moreover, a lateral inhibition mechanism at cerebral cortex level could explain also the RRES effect on an ipsilateral heterotopic, but close, site (rUlnar) (Friedman et al., 2008). However, if this were the case, the absence of LEP amplitude inhibition to stimulation of the contralateral heterotopic area (lUlnar) would remain unexplained. Third, if the RRES had activated the descending inhibitory systems, mediating the conditioned pain modulation, the effect should have been more general, involving both homotopic and heterotopic areas, including both lUlnar and lFoot sites. Lastly, LEP amplitude reduction during RRES could be due to an effect of distraction from the painful stimulus. However, this possibility is unlikely for 2 main reasons. First, the attention level of our subjects was kept constant during the whole experiment by asking them to count the number of the received laser stimuli. The averages in which the mistakes had overtaken 10% would have been excluded. Second, RRES did not reduce the N2/P2 amplitude to stimulation of both lUlnar and lFoot sites.

In the present study, we could not demonstrate any effect of the RRES on the N1 amplitude. Two main hypotheses can be proposed to explain this negative result. (1) It is possible that spinal pathway generating the N1 LEP component is minimally or not affected by non-painful electrical stimuli. Our previous study suggested that the vertex LEP component (N2/P2) and the lateralized N1 potential are generated by parallel spino-thalamic pathways with different conduction velocities (Valeriani et al., 2007). Thus, it is possible that the Aβ fibres inhibit the spinal fibres mediating the N2/P2 component, but not those generating the N1 response. (2) We cannot exclude that RRES could have a slight effect also on the N1 amplitude, whose detection is prevented by technical problems in N1 recordings (low N1 amplitude and possible muscular artefacts in the temporal region). Indeed, during RRES the average N1 amplitude was dampened to stimulation of both rRadial and lRadial sites, although statistical significance was not reached.

It is interesting to underline that in the present study the psychophysical findings paralleled those of the LEP amplitudes. Indeed, RRES reduced the subjective laser pain rating to stimulation of the bilateral Radial site.

6. Conclusions

The present results are in agreement with the "gate control theory" (Melzack and Wall, 1965), showing that high-frequency non-painful stimuli can dampen the nociceptive input at spinal level. This is different from what found by our group (Testani et al., 2015) and Inui et al. (2006), who showed that the inhibitory influence of the non-nociceptive input on the nociceptive one takes place at supra-spinal level. However, the main difference between the previous studies and our present experiment relies on the frequency of the conditioning non-painful stimulation. Indeed, while both Testani and Inui used single non-painful stimuli to condition single painful stimuli with a 1:1 ratio, in the present study we investigated the effect of high frequency non-painful stimulation, in order to better represent what happens when non-painful stimuli are used to reduce pain, e.g., rubbing a wound or during TENS. Although in our study the frequency of the non-painful electrical stimuli was far lower than that used in TENS, our experimental design probably approximates the aforementioned situations.

In conclusion, while single non-painful stimuli dampen the nociceptive input at supra-spinal level, the analgesic effect of high frequency non-painful stimulation takes place, at least in part, at the spinal cord level.

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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