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Short trains of intra-epidermal electrical stimulation to elicit reliable behavioral and electrophysiological responses to the selective activation of nociceptors in humans

André Mouraux[a], Emilie Marot[a], Valéry Legrain[a,b,*]

[a] Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium
[b] Department Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

HIGHLIGHTS

- Here we explored the perceptual and neurophysiological responses to intra-epidermal electrical stimulation (IES).
- The strength of the nociceptive afferent volley was increased using trains of repeated IES.
- Trains of IES increased gradually the intensity of the perception.
- Trains of IES increased the magnitude of the elicited ERPs, but their latencies were unaffected.
- Trains of IES can be used as reliable method to activate selectively nociceptors.

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ABSTRACT

Currently, the study of nociception in humans relies mainly on thermal stimulation of heat-sensitive nociceptive afferents. To circumvent some limitations of thermal stimulation, it was proposed that intra-epidermal electrical stimulation (IES) could be used as an alternative method to activate nociceptors selectively. The selectivity of IES relies on the fact that it can generate a very focal electrical current and, thereby, activate nociceptive free nerve endings located in the epidermis without concomitantly activating non-nociceptive mechanoreceptors located more deeply in the dermis. However, an important limitation of IES is that it is selective for nociceptors only when very low current intensities are used. At these intensities, the stimulus generates a very weak percept, and the signal-to-noise ratio of the elicited evoked potentials (EPs) is very low. To circumvent this limitation, it was proposed that the strength of the nociceptive afferent volley could be increased through temporal summation, using short trains of repeated IES. Here, we characterized the intensity of perception and EPs elicited by trains of 2, 3 and 4 IES delivered using a 5-ms inter-stimulus interval. We found that both the intensity of perception and the magnitude of EPs significantly increased with the number of pulses. In contrast, the latency of the elicited EPs was not affected by the number of pulses, indicating that temporal summation did not affect the type of activated fibers and, therefore, that trains of IES can be used to increase the reliability of stimulus-evoked responses while still preserving its selectivity for nociceptors.

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1. Introduction

During the last decades, investigation of the neurophysiological mechanisms underlying nociceptive processing and pain perception has relied mainly on the thermal stimulation of cutaneous Aδ- and C-fiber free nerve endings [17]. For example, thermal stimuli generated by laser stimulators have been used extensively because of their indisputable selectivity for heat-sensitive nociceptors [1]. In addition, due to their high power, lasers can generate very steep heating ramps, and thus elicit synchronous afferent discharges enabling the recording of time-locked responses such as event-related brain potentials (ERPs) or reaction times [2]. More recently, intra-epidermal electrical stimulation (IES) [10] and electrical stimulation using a small surface concentric electrode [12] have been proposed as alternative methods to activate nociceptors selectively and, thereby, explore nociception [10]. The rationale for these stimulation techniques relies on the fact that nociceptive free nerve endings are preferentially located in the epidermis, while non-nociceptive mechanoreceptors are mainly located more deeply in the dermis. Therefore, pulses of electric current spatially

* Corresponding author at: Institute of Neuroscience, Université catholique de Louvain, Avenue Mounier 53, COSY bte B1.53.04, 1200 Brussels, Belgium.
Tel.: +32 2 764 53 61.
E-mail address: valery.legrain@uclouvain.be (V. Legrain).

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restricted to the epidermis could activate nociceptors selectively. These alternative methods could circumvent some limitations of laser stimulation, such as skin overheating and lesion due to stimulus repetition, and delay or relative desynchronization of the nociceptive afferent volley due to transduction of thermal energy into a neural impulse. However, these stimulation techniques suffer from their own limitations, in particular, the need to use low stimulation current intensities to guarantee its selectivity for nociceptors. Indeed, it has been shown that if IES is delivered using a strong intensity (e.g. an intensity corresponding to the pain threshold), the stimulus is not selective for nociceptors because it also activates more deeply located low-threshold mechanoreceptors [5,18]. In particular, it was shown that selective denervation of nociceptive free nerve endings by prolonged topical application of capsaicin abolishes the behavioral and electrophysiological responses to laser stimuli and IES delivered at low current intensities (corresponding to twice the absolute detection threshold; 0.18 ± 0.25 mA) but does not affect the responses to conventional transcutaneaous electrical stimulation and IES delivered at a stronger intensity of current (2.5 mA) [15]. Thus, there is converging evidence that IES can activate nociceptors selectively, if and only if low intensities of current are used [14]. The important drawback is that at such low intensities, a single pulse of IES elicits a very weak sensation and the signal-to-noise ratio of the elicited ERPs is low, possibly because of the very small number of recruited afferents. This drawback has probably limited the use of this technique for pain research, and as a consequence, its availability. To circumvent the lack of spatial summation, some authors have proposed to deliver short trains of electrical pulses (e.g. three pulses delivered at a 5-ms inter-stimulus interval) [7,11,13,16,20,21], with the aim of increasing the strength of the nociceptive afferent volley through temporal summation. However, in these studies, the latency of the elicited ERPs was not systematically analyzed. As the latency of ERP components depends on the conduction velocity of the sensory fibers, and, therefore, on the type of fiber activated by the eliciting stimulus, it is important to ensure that temporal summation does not affect the type of fibers activated by IES. The aim of the present study was to compare the magnitude and latency of the perception and ERPs elicited by trains of 2, 3 or 4 pulses of IES delivered using a 5-ms inter-stimulus interval.

2. Methods

Eleven volunteers took part in the study (4 women, aged from 21 to 45 years) with no prior history of neurological, psychiatric or chronic pain disorder. Written informed consent was obtained and all experimental procedures were approved by the local ethics committee and conformed to the latest revision of the Declaration of Helsinki.

IES was delivered to the right hand dorsum using a stainless steel concentric bipolar electrode developed by Inui et al. [10] (Nihon Kohden, Japan). The electrode consists of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By gently pressing the device against the skin, the needle electrode was inserted in the epidermis of the hand dorsum, within the sensory territory of the superficial radial nerve. In order to guarantee the selectivity of the nociceptive stimulation, the intensity of the stimulus was individually adjusted to twice the absolute detection threshold to a single 0.5 ms constant-current square-wave pulse (DS7 Stimulator, Digitimer Ltd., UK). The detection threshold was estimated using an adaptive algorithm [3]. After positioning the electrode, single-pulse stimuli were applied using a staircase procedure, with detection vs. non detection as criterion, by increasing or decreasing the intensity of the electrical current in steps of 0.01 mA. The procedure was interrupted after the occurrence of four staircase reversals. The staircase converged toward the intensity at which the probability of detecting the stimulus was 50% [3]. The intensity was then set to twice the detection threshold, defined as the average of the intensity delivered at the four staircase reversals, with an intensity of $\leq$0.50 mA as restrictive criterion [4,6]. If this criterion was not met, the electrode was displaced and the adaptive staircase procedure was restarted.

During a first session, stimuli were applied using a single pulse or a train of 2, 3 or 4 pulses separated by a 5-ms inter-pulse interval. The different types of stimuli were repeated 5 times in random order. After each stimulus, the participants were asked to rate the perceived intensity of the stimulus using a numerical rating scale (NRS) extending from 0 to 100 (0 = not perceived; 100 = maximum pain; 50 = limit between non-painful and painful domains of sensation).

During a second session, the electroencephalogram (EEG) was recorded using 19 Ag-AgCl electrodes placed on the scalp according to the International 10–20 system and referenced to linked earlobes (A1–A2). Ocular movements and eye-blinks were recorded using two additional bipolar electrodes placed at the upper-left and lower-right sides of the left eye. The signals were amplified, digitized at a 167 Hz sampling rate (PL-EEG, Walter Graphtek, Germany). Stimuli were applied using a train of 2, 3 or 4 pulses separated by a 5-ms inter-pulse interval, delivered in a random order in three consecutive blocks of 30 trials each (one block = 10 trials $\times$ 3 stimulus types). Within a block, the inter-train interval varied randomly from 5 to 10 s (rectangular distribution). Each block was separated by a 2–5 min pause. Participants were asked to press a button held in the left hand as soon as they perceived the stimulus. The mean reaction time (RT) recorded relative to stimulus onset was used as a measure of response speed. RTs greater than 1000 ms were considered as undetected. We also examined the frequency distribution of RTs according to stimulus type. For this purpose, RTs were grouped in 100-ms bins extending from 0 to 1000 ms.

Offline analyses of the EEG data were carried out using Brain Vision Analyzer 1.05 (Brain Products GmbH, Germany) and Letswave 5 (Université catholique de Louvain, Belgium). The continuous EEG recordings were band-pass filtered (0.5–45 Hz) and segmented into 2000 ms epochs extending from −500 to +1500 ms relative to stimulus onset. Artifacts produced by eye blinks and eye movements were corrected using an Independent Component Analysis [9]. Signals were re-referenced according to a common average reference, and baseline-corrected from −500 to 0 ms. Epochs containing artifacts were identified by visual inspection and excluded from further analyses (rejected epochs constituted less than 15% of the total number of epochs). The epochs were then averaged according to the number of pulses (2, 3 or 4). Furthermore, an additional set of average waveforms was computed to test the effect of repetition. For each subject, the full set of epochs were split into four blocks according to trial order (blocks 1–4) and number of pulses (2, 3 or 4), yielding 6 average waveforms for each subject. Within each average waveform, the latency and amplitude of three distinct peaks were measured as follows. First, a negative peak (N2) was identified as the most negative peak obtained at Cz within 200–300 ms after stimulus onset. Second, a positive peak (P2) was defined as the most positive peak obtained at Cz within 300–400 ms after stimulus onset. The peak-to-peak amplitude of the N2–P2 complex was obtained by subtracting the N2 peak amplitude from the P2 peak amplitude. Third, a negative peak (N1) was identified at the contralateral electrode T3 re-referenced to Fz, within 120–170 ms after stimulus onset.

The effect of the number of stimuli was assessed using an ANOVA for repeated measures (GraphPad 5, GraphPad Software Inc., CA) with *stimulus type* as within-subject factor with four levels (1 vs. 2 vs. 3 vs. 4 pulses) for the intensity of perception, and three levels (2 vs. 3 vs. 4 pulses) for RTs and ERP amplitudes and latencies. For the

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