PAIN® 155 (2014) 635–642

www.elsevier.com/locate/pain

# Pain relief by touch: A quantitative approach

Flavia Mancini [a,b,*], Thomas Nash [c], Gian Domenico Iannetti [b], Patrick Haggard [a]

[a] Institute of Cognitive Neuroscience, University College London, London, UK
[b] Department of Neuroscience, Physiology and Pharmacology, University College London, London, UK
[c] Division of Medicine, University College London, London, UK

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

ARTICLE INFO

*Article history:*
Received 24 June 2013
Received in revised form 10 December 2013
Accepted 13 December 2013

*Keywords:*
Pain
Touch
Relief
Analgesia
Space
Signal detection theory

ABSTRACT

Pain relief by touch has been studied for decades in pain neuroscience. Human perceptual studies revealed analgesic effects of segmental tactile stimulation, as compared to extrasegmental touch. However, the spatial organisation of touch–pain interactions within a single human dermatome has not been investigated yet. In 2 experiments we tested *whether*, *how*, and *where* within a dermatome touch modulates the perception of laser-evoked pain. We measured pain perception using intensity ratings, qualitative descriptors, and signal detection measures of sensitivity and response bias. Touch concurrent with laser pulses produced a significant analgesia, and reduced the *sensitivity* in detecting the energy of laser stimulation, implying a functional loss of information within the ascending Aδ pathway. Touch also produced a bias to judge laser stimuli as less painful. This bias decreased linearly when the distance between the laser and tactile stimuli increased. Thus, our study provides evidence for a spatial organisation of intrasegmental touch–pain interactions.



## 1. Introduction

Pain relief by touch has been central to the study of pain mechanisms [19,28]. Neurophysiological investigations in animals indicate a class of wide dynamic range (WDR) neurons in the dorsal horn as a likely substrate of the analgesia induced by touch [14]. These neurons are multimodal, in that they respond to both nociceptive and tactile inputs. The structure of their receptive field (RF) is characterised by an excitatory centre and an inhibitory surround. Studies of WDR neurons in animals have shown a spatial gradient of inhibition: an intense tactile stimulus in the periphery of the inhibitory field could reduce the response to a nociceptive stimulus as much as a less intense tactile stimulus farther from the periphery [8,25,26].

However, RFs and firing rates of spinal neurons cannot be readily measured in humans. Instead, the spatial pattern of interactions between large and small fibres has been considered categorically, using a binary RF model. Many human studies contrasted the effect of segmental vs extrasegmental stimulation on pain thresholds or perceived pain levels [7,13,22,23,29,30]. These studies found that tactile inputs inhibited pain perception segmentally, but not when tactile and nociceptive inputs were delivered to different dermatomes.

The spatial field of multisensory interactions between cutaneous inputs can also be considered in a continuous way, by varying the distance between tactile and nociceptive stimulation within a single dermatome, and investigating the spatial dependency of touch–pain interactions. To our knowledge, the segmental spatial organisation of tactile influence on pain perception has not been systematically studied in humans.

In 2 experiments, we tested *whether*, *how*, and *where* spatiotemporally defined tactile input modulates the perception of laser-evoked pain in healthy volunteers. Our study aimed to go beyond previous investigations of these questions on humans, by combining for the first time nociceptive-selective stimulation with signal detection theory (SDT) [15] to study the spatial dependency of touch–pain interactions within a single dermatome.

## 2. Experiment 1

In Experiment 1, we investigated which aspects of pain perception are modulated by non-nociceptive somatosensory stimulation using von Frey filaments: intensity level, quality of percept, latency of detection. We also investigated tactile effects of sensitivity and response bias in judging pain levels, using SDT. Although SDT has been used previously in pain research [24], the majority of studies

* Corresponding author at: Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. Tel.: +44 0 2076791151.
*E-mail address:* f.mancini@ucl.ac.uk (F. Mancini).

http://dx.doi.org/10.1016/j.pain.2013.12.024
0304-3959/

tested pain detection ("Does the stimulus cause pricking pain, yes or no?"), rather than level detection within the pain range ("Is the pain level high or less high?" [17]). The first approach focuses on whether the Aδ pathway is activated or not. The second approach focuses instead on information *within* the ascending Aδ pathway, and may be more relevant to perception of pain *level*.

### 2.1. Method

#### 2.1.1. Participants

Eight healthy volunteers (5 females) aged 19-32 years (mean ± SD, 22 ± 4.0 years) participated for payment. Four participants were right-handed, and four were left-handed. All participants were recruited through a departmental subject pool, and gave written informed consent to take part in the experiment. Experimental procedures were approved by the University College London ethics committee (approval number: 3167/001). Eligibility criteria included: 1) no history of neurological disorders; 2) not having taken any analgesic medications nor recreational drugs in the 24 hours preceding the experiment; 3) not having participated in a brain stimulation study in the 24 hours preceding the experiment; 4) white skin, because at the wavelength of the neodymium:yttrium-aluminium-perovskite (Nd:YAP) laser we used, the radiation absorption of dark skin is larger [1].

#### 2.1.2. Laser stimuli

We delivered pulses of radiant heat generated by an infrared Nd:YAP laser with a wavelength of 1.34 μm (EIEn, Florence, Italy). This method was used to selectively activate nociceptive Aδ and C-fibre endings located in the superficial layers of the hairy skin [1]. The laser pulse was transmitted via an optic fibre, and focused by lenses to a spot diameter of approximately 3.5 mm. A visible He-Ne laser spot was used to point the Nd:YAP laser to the target location. The duration of each laser pulse was 4 ms.

For each participant, we identified the pinprick detection threshold using ascending staircases (mean ± SE, 0.39 ± 0.002 J). The threshold was identified as the first stimulus energy that elicited reports of pinprick sensation for 3 consecutive repetitions. We then set 2 suprathreshold laser energies for the main experiment ("medium" and "high"; Fig. 1). The "medium" energy was set as 0.1 J above individual detection threshold (mean ± SE, 0.49 ± 0.002 J). The "high" energy was initially set as 0.2 J above individual detection threshold. Next, we verified that participants could distinguish between these levels by asking participants to respond whether 20 stimuli presented at random were medium or high. If the discrimination accuracy was >60% and <95%, the experiment started with these levels. If the discrimination accuracy was <60%, the energy of the "high" stimulus was increased in steps of 0.1 J until the minimum accuracy of 60% was reached. If the discrimination accuracy was >95%, the energy of the "high" stimulus was decreased in steps of 0.1 J until the maximum accuracy of 95% was reached (Fig. 1; mean energy of high stimulus ± SE, 0.62 ± 0.004 J). The mean accuracy of discriminating the stimuli presented in the experiment was 77.3% (SE ± 2.86%). Four additional participants were unable to discriminate the 2 energy levels according to this procedure, and therefore were not tested in any session.

In order to avoid receptor fatigue or sensitisation, the stimulation was alternated across 4 different skin locations along the radial–ulnar axis of the left ventral forearm, approximately halfway between the elbow and the wrist (Fig. 2a). Since the output energy depends on the skin temperature, we monitored the temperature of the stimulated surface with an infrared thermometer every 16 trials. Average skin temperature was 32.6°C (SE ± 0.12°C).

#### 2.1.3. Tactile stimuli

Tactile stimuli consisted of a pair of calibrated nylon filaments (von Frey hair, 1 g, diameter 0.4 mm) mounted 2 cm apart. The tactile stimuli were applied to the skin for 1.5 seconds by a computer-controlled 3-axis robot (Arrick Robotics, Tyler, TX, USA). Robotic positioning ensured that the tactile stimuli bracketed the site of laser stimulation, so that the distance between laser stimulation and each of the pair of tactile inputs was exactly 1 cm (Fig. 2a). Note that the tactile stimulation includes both a dynamic and a static component, and is likely to stimulate both fast- and slow-adapting somatosensory afferents [11].

#### 2.1.4. Experimental procedure

Participants sat comfortably with their left forearm lying outstretched. They were blindfolded, and wore headphones. Every participant took part in 2 separate sessions in counterbalanced order. The same experimental conditions were given in the 2 sessions: 2 laser energies were used ("medium" and "high"). Importantly, both energies were above the pinprick pain threshold (see above). On each trial, the laser pulse could either be applied alone (Laser condition, L), or together with a pair of von Frey hair filaments (Laser + Touch, L+T; Fig. 2a-b).

We collected different measures in the 2 sessions. In session A, the pain level evoked by each laser pulse was reported as "high" or "not high" in a forced-choice paradigm. SDT was used to obtain independent estimates of perceptual sensitivity and response bias. In session B, the same participants provided reaction times, ratings of subjective pain intensity, and verbal descriptors of the quality of the percept.

In both sessions (Fig. 2b), white noise was played on every trial, from 1.5 seconds before the onset of the laser stimulation to 1.5 seconds after. This provided an auditory cue for the following stimulation, controlling for any possible cueing effect introduced by the tactile stimulation. It also masked the noise made by the robot movement. In the Laser + Touch condition, touch was applied 0.75 second before the laser onset, and lasted 1.5 seconds. The experimental condition (Modality: L, L+T; Energy: medium, high) was randomised. The experimenter (T.N.) was blinded to both the tactile and the laser stimulation settings. The experiment lasted around 90 minutes. In session "A" (forced-choice paradigm), 10 blocks consisting of 4 trials each were presented. In session "B,"

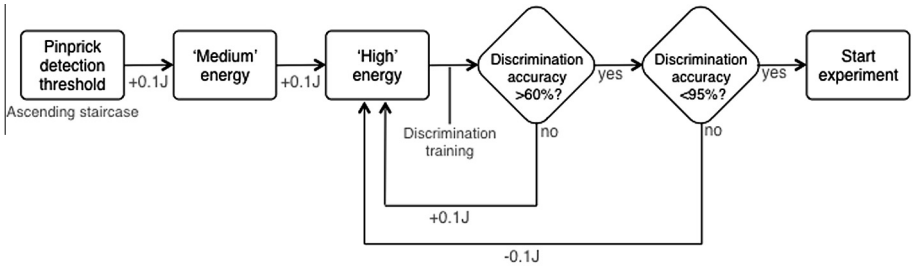


**Fig. 1.** Selection of experimental laser energies. The pinprick detection threshold was determined for each subject, and the "medium" energy level was set as +0.1 J above this level. The energy of the "high" stimulus was then adjusted in 2 ways: 1) Increasing steps of +0.1 J, until the accuracy of discriminating between the 2 levels was >60%; 2) decreasing steps of −0.1 J, until the accuracy of discriminating between the 2 levels was <95%.