A better touch: C-tactile fibres related activity is associated to pain reduction during temporal summation of second pain

Fabrizia Fidanza, Elisa Polimeni, Valentina Pierangeli, Matteo Martini

Department of Psychology, University of East London, Water Lane, London E15 4LZ, UK

Keywords: affective touch, pain modulation, chronic pain, temporal summation of second pain, sensitization, wind up

Disclosures

This research has been supported by UEL Research Capital Fund.

All authors declared no potential conflict of interest with respect, authorship, and\or publication of this article.

Corresponding author:

Matteo Martini

University of East London

Water lane E15 4LZ, London, UK

E-mail: m.martini@uel.ac.uk

Tel: +44 20 8223 4433

Abstract

C tactile (CT) fibres, responsible for the so-called "affective" touch (AT), have drawn a fair amount of attention within the scientific community for their marked social dimension. However, while the pain-relieving potential of discriminative touch (DT) has been documented, proofs of the analgesic properties of AT are still scarce. Additionally, no study has so far tested its possible pain-relieving effect on a clinically-relevant model. Temporal summation of second pain (TSSP), otherwise referred to as 'wind-up', relies on repetitive stimulation of C-nociceptors and it is thought to reflect central sensitization, a process linked to many chronic pain conditions. In the present experimental, within participants, design we induced TSSP trough trains of ascending and descending repetitive heat stimulation. Forty-two healthy participants' pain was measured during two different tactile stimulations (stroking velocities AT: 10 cm/s; DT: 0.3 cm/s) or without concomitant tactile input. Since measures of pleasantness of the tactile stimulation have been found to strongly correlate with C-tactile fibres' firing rate, these, together with participants' body awareness, were also taken into account.

Our results show that AT brought about a decrease of our participants' pain as opposed to both DT and no touch, while DT did not produce any significant pain reduction. Thus, only AT successfully modulated wind-up. As expected, AT was perceived more pleasant than DT, while a clear relationship between body awareness and pain was found only during DT.

Targeting CT fibres could pave the way to new treatments for chronic pain conditions whose aetiology depend on abnormal C-nociceptors' physiology.

Perspective

This study extends previous findings on the analgesic potential of affective touch, documenting a clear pain reduction during temporal summation of second pain (TSSP). Since TSSP is thought to reflect central sensitization, the psychophysiological mechanisms of affective touch could be exploited for new chronic pain treatments.

Introduction

Probably one of the most significant recent breakthroughs in the field of somatosensation is the discovery of a second tactile system in humans. It was in 1990 when Nordin clearly identifies a group of afferents with unmyelinated (type-C) axons, in the supraorbital area of man, which predominantly discharge in response to slow stroking of the skin [60]. These type-C unmyelinated low threshold mechanoreceptive afferents (C-LTMRs), or C-tactile (CT) fibres, are solely localised in hairy skin and have been linked to the affective facet of touch [50]. They preferentially respond to caress-like gentle stroking, at a speed of ~1-10 cm/s [39,82–84], and their firing rate positively correlates with ratings of touch pleasantness [37]. For such reason the sensation arising from this tactile system is often referred to as "sensual", "pleasant", "social" or "affective" touch (AT). Indeed, while Aβ myelinated mechano-afferents sub-serve the spatial-temporal features of discriminative touch (DT) [49], CT-mediated touch operates an affective-motivational function [92].

Noteworthily, AT plays a role in pain modulation as well. For instance, we know that CT fibres mediate allodynic processes [36,56,57] which take place when CT-mediated hedonic touch processing is reduced [35]. The neuroanatomy of CT and C-fibres, both projecting to the same layers of the dorsal horn of the spinal cord (laminae I/II) [79] and ascending in the spinothalamic tract [50], further suggests a possible interaction between AT and pain. However, while the pain-reducing effect of Aβ-mediated touch have been extensively studied [17,28,52,81,93,94] much less is known about the analgesic properties of CT fibres. Previous studies show that AT is sufficient to modulate the sharp first heat pain causing analgesia in healthy subjects [27,38]. Yet, their potential to improve chronic pain conditions is unknown. It has been shown how a particular stimulation protocol, which envisages repetitive heat pulses at a frequency of 0.33Hz, could function as a model of chronic pain in humans [75]. Such stimulation paradigm has been used for decades [64,65,89] and it primarily activates C-nociceptors, promoting a rapidly increasing sensation of "second" (burning) pain. This process, referred to as "Temporal Summation of Second Pain" (TSSP), or 'wind-up', is thought to reflect central neuronal sensitization [34] which is deemed to be at the basis of several chronic pain conditions [4]. Indeed, the clinical relevance

of paradigms based on TSSP derives from the fact that such mechanism appears to be abnormal in chronic pain patients [18,31,77].

In the present study, we used such paradigm to investigate the potential effects of AT, hypothesizing that it could produce analgesia during 'wind-up'. To do this, we measured our participants' pain in different conditions, namely in concomitance to AT, DT or no tactile stimulation.

Materials and Methods

Participants

This study involved 42 healthy volunteers, 18 males and 24 females, aged between 19 and 53 years (mean ± SD = 28.07 ± 8.8). Different and sometimes mixed ethnic groups formed our sample, with a majority of Europeans (26 European, 4 Bangladeshi, 3 Indian, 2 Black Caribbean, 2 Central Asian, 1 Non-European White, 1 White and Black Caribbean, 1 White and Black African, 1 Chinese, 1 Black African). All participants were right-handed (mean ±SD = 96.13 ± 9.36, range 62 -100) according to the Edinburgh Handedness Inventory [87].

Subjects under 18 and over 55 years, with a prior history of neurological or psychiatric disorders or with on-going chronic pain condition were excluded from the experiment. Drugs intake, skin problems (especially if related to the stimulated body part) and any other health condition that could alter pain or tactile perception were also considered as exclusion criteria.

Before commencing the experiment, all volunteers gave their written informed consent. The experimental procedures were approved by the local ethics committee and they were in accordance with the Declaration of Helsinki.

Questionnaires

Participants' anamnestic clinical data were collected through a case report form; in addition, each subject was requested to fill in the Very Short Form of the Body Perception Questionnaire (BPQ [11]). This questionnaire measures the ability of the subject to detect internal bodily states. Such ability,

referred to as “body awareness”, has been linked to pain and therapies based on body awareness have been suggested as effective interventions for chronic pain [24].

To rule out any possible order effects, half of the participants filled in the questionnaire before the start of the experiment, while the other half completed the BPQ at the end of it.

Touch Pleasantness

To be pleasant is one of the primary characteristics of AT. Thus, right after each condition we asked our participants to rate the perceived pleasantness relative to the tactile stimulations (both during AT and DT). Specifically, they were asked to tell how pleasant the tactile stimulation had been spelling out a number on a 0-10 scale, where “0” corresponded to “not pleasant” and “10” to “maximally pleasant”. To ensure that the answers were representative of the actual experience of the participants, they were told that there were no “right” or “wrong” responses and that their answers had to be based only on their true feelings.

Tactile Stimulation

Two different tactile stimulations were considered in this experiment: a ‘*normal’* tactile stimulation (“DT”) purportedly mediated by the activation of Aβ fibres, and a particularly pleasant tactile stimulation, deemed to trigger the CT-fibres response (“AT”). The stroking velocities used in this study were 0.3 cm/s for DT and 10 cm/s for AT. The former is considered to be sub-optimal to elicit the CT-fibres response and therefore it was used as a control tactile stimulation. Optimal stroking velocities are indeed considered to be within 1 and 10 cm/s, while sub-optimal velocities are 0.1, 0.3 and 30 cm/s (for ex. see [39]). During a small pilot (n = 6) we tested all the above-mentioned velocities (in randomized order) and we recorded the highest average pleasantness rating during the 10 cm/s stimulation. Thus, this velocity was chosen to be the one to represent the AT condition. Our pilot also showed us that the least pleasant tactile stimulation was the one with a speed of 0.1 cm/s. Nevertheless, a tactile stimulation with this velocity was considered to be almost imperceptible by

some of our participants, so we finally chose 0.3 cm/s to represent the DT condition. This velocity was rated as the second least pleasant.

Both DT and AT were manually delivered by a trained experimenter who wore a latex glove and stroked the participants' arms according to a proximal-distal fashion (upper arm to wrist). To keep the tactile stimulations consistent across participants the experimenter wore an earplug, whereby a pre-recorded sound was played to mark the pace of the tactile stimulations (0.3 and 10 cm/s). All participants were stimulated by the same female experimenter.

Thermal Stimulation

To elicit TSSP a TSA-II Neuro Sensory Analyzer (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) was used. Trains of six heat pulses, with a stimulation frequency of 0.33Hz, were delivered through a 30x30 mm thermode which was placed on the dorsal side of the participant's right wrist. The stimulation paradigm was adopted from Staud and colleagues [71,73]. By using a continuous-contact heat thermode, with a stimulation frequency of 0.33hz is possible to induce a robust TSSP, similar to that observed with intermittent-contact paradigms [75]. Each pulse consisted of an ascending and descending heat stimulation, with the temperature of the thermode increasing and decreasing by 8°C/sec. The duration of a whole stimulation cycle was 3 sec. (see Fig.1). Prior to the start of the experiment, the individual's target temperature was adjusted to each individual's heat pain sensitivity and it was regulated to achieve maximal thermal TSSP ratings of 45 ± 10 after six heat pulses at 0.33 Hz [72]. Pain ratings were collected via a Computerized Visual Analogic Scale (CoVAS, 0-100 scale; Medoc Ltd.) at the end of each train of stimuli.

Procedure

The experiment was carried out in the pain lab at the Stratford Campus of the University of East London (London, UK). The recruitment of participants was carried out through opportunity sampling and the subsequent data collection covered a period between February and June 2019. Upon their

arrival the participants were asked to sit comfortably on a chair and read and sign the informed consent. Half of the participants were also asked to fill in the BPQ before the beginning of the experiment while the other half did it at the end of it. Once the paperwork was finished participants were asked to place their arms on the experimental table, where a metal frame prevented them from seeing their right (stimulated) arm. In correspondence of the right wrist, on the dorsal side, the thermode was secured with an elastic Velcro strap. The left arm was placed near the CoVAS, whereby the participants could rate their pain. Headphones with a pink noise with a constant volume set at 70 dB were used to ensure noise isolation. Participants were then asked to look at a fixation cross placed on the table in correspondence of their body midline, at a distance of about 30 cm.

Before starting the three experimental conditions, the individual's target temperature was set through 3 trains of 6 heat stimuli each. The target was set when the maximal temperature of the thermode would have elicited a pain rating of 45 ± 10 at the end of each train of stimuli [72].

In each experimental condition, 5 trains of 6 heat stimuli were delivered with an intertrial interval (ITI) of 30 seconds and the duration of each heat pulse was set to 3 seconds (1.5 sec for the rise time and 1.5 sec for the return time). So, every subject overall got 15 trains of heat stimuli plus 3 delivered during the pre-experimental condition. After each train of pulses, at about 2 seconds from the last stimulus, a beep sound was played on top of the pink noise, marking the point in time where participants had to rate their pain using the CoVAS. Participants were instructed to look at a fixation cross and to pay attention to all stimuli which they had to rate after each train of thermal stimuli (pain), or at the end of each condition (touch pleasantness).

Three experimental conditions were considered: a 'No Touch' (NoT), a 'Discriminative Touch' (DT) and an 'Affective Touch' (AT) condition. During the NoT condition participants received the heat pulses with no concomitant tactile stimulation. During the other two (tactile) conditions participants received the painful heat together with that tactile stimulation. Throughout the DT condition the experimenter stroked the dorsal side of their arm with her fingertips at a speed of 0.3 cm/s. A similar procedure was used in AT condition, with the only difference that the stroke speed was set to 10 cm/s.

An experimental, within-subjects design was considered, so all the volunteers underwent the same three experimental conditions. Throughout DT and AT conditions the experimenter wore a latex glove and the direction of the tactile stimulation was proximal to distal (upper arm to wrist), starting approximately 30 cm above the position of the thermode. The use of a latex glove was adopted for hygienic reasons (both for the experimenter and participant). In particular, this precaution allowed avoiding any possible hand sweat, which could have been perceived as unpleasant by the participants. Right after both the DT and the AT conditions, the participant was requested to rate the pleasantness of the touch with a score on a numerical rating scale spanning from 0 (not pleasant) to 10 (maximally pleasant).

The dependent variables of the present experiment were then the pain and pleasantness ratings and the scores at the BPQ. The independent variable was the type of condition, with three levels: NoT, DT, AT. The order of the three conditions was perfectly counter-balanced across participants, so that every condition was presented the same amount of times as first, second and third. All the stimulations, both tactile and thermal, involved the cervical dermatomes C6, C7 and C8.

Results

All results were calculated with the statistical software JASP [30]. Mean and standard deviations (SD) of pain and pleasantness ratings are summarized in table 1.

Pain ratings

Ratings recorded after each train of stimuli were averaged together for each condition and participant. Data from the Sphericity was checked with Mauchly's test (W=0.94, p=0.31) and all data were

normally distributed according to the Shapiro-Wilk test (all W_s>0.9, p>0.05). The one-way repeated-measures ANOVA on the pain thresholds disclosed an effect of the factor "Condition" ($F_{2,82}$=12.25, p=0.00003, η^2p =0.22), meaning that the different type of stimulation did affect the participant's pain. Bonferroni-corrected post-hoc tests showed that only during the "AT" condition participants felt much less pain as compared to both the "NoT" (p<0.001) and the "DT" condition (p<0.001). During the "DT" condition there was no significant reduction of pain sensation compared to no touch (p>0.05). Therefore, only "AT" was capable of decreasing the participants wind-up pain (see Fig. 2).

Pleasantness ratings

A Shapiro-Wilk test was run to check for the assumption of normality on the pleasantness ratings. The test showed no significance, so the assumption of normality was maintained (all W_s>0.9, p>0.05). A paired T-Test was used to ascertain the actual difference in the subjective ratings of pleasantness of the two different tactile stimulations. As expected, the test revealed that a significant difference in terms of pleasantness was attributed to the "DT" compared to the "AT", showing the latter as being much more pleasant (t_{41}=-4.25, p<0.001; see Fig. 3).

Correlational analysis

To reveal any possible connection between the pain ratings and the other variables, a correlational analysis was run. A Spearman's rho was computed to check any possible correlation between the pain ratings obtained during each condition and the scores of the Likert scale of the BPQ (see Fig. 4). A significant positive correlation was reported between the pain ratings collected during the "DT" condition and the BPQ score (ρ=0.33, p=0.028), meaning that at higher body perception scores corresponded higher pain ratings during a 'normal' tactile condition. No other significant correlations

were found between BPQ scores and the other two conditions, even splitting the sample in two following the questionnaire administration order (all p_s>0.05; see Fig.4a).

A Pearson's r was computed to check for any possible significant correlations between the pain delta scores obtained during the two tactile conditions (AT pain – NoT pain and DT pain – NoT pain) and the respective pleasantness ratings. No significant correlations were found between the pleasantness scores and any of the tactile conditions (all ps>0.05).

Ratings of Attention

In a second experiment, which was identical to the current one apart from the introduction of a measure of attention (unpublished data), we asked our participants (n=21) to rate their attentional level during the thermal and tactile stimulations. The ratings were measured on a 7-point Likert scale, where '1' indicated 'my attention was not at all on the thermal stimulus but on other things, for instance the tactile stimulus' and '7' meant that 'my attention was fully on the thermal stimulus'. So, the higher the rating the greater the attention allocated to the thermal/painful stimulus.

The means (and SD) obtained from this measurement were the following: NoT = 5.12 (1.83), DT = 4.59 (2.14), AT = 4.95 (1.80). As expected, it is during the NoT ('no touch') condition that the participants' attention was more focussed on the incoming painful stimulation but, importantly, it was during the AT condition, and not during the DT condition, that the second highest score was found. So, the touch delivered in the DT condition was more attention-grabbing than the one in the AT condition. In any case, none of these slight differences seems to be statistically relevant, as confirmed by a repeated measures ANOVA on the attention scores for the three conditions: ($F_{2,40}$=0.84, p=0.43).

The data collection of the second experiment had to be interrupted due to the Covid-19 pandemic (still ongoing at the time we write), so these data have not been added in the present manuscript. However, given the role that attention plays in modulating pain [90], we thought it was important to show the above results, to provide an estimate of what the attentional levels could have been like during each condition.

Discussion

While a second tactile system in humans has been identified three decades ago, with clinical, anatomical and experimental evidences suggesting an involvement of this system in pain perception, very little has been done to unravel such relationship. In particular, it is not known if the activation of the CT-fibres can determine a decrease of TSSP. The clinical relevance of such type of pain derives from the fact that it has been deemed at the basis of some forms of chronic pain like, for example, fibromyalgia [15,70,76,77]. By making use of an experimental model which could, at least partly, mimic the psychophysical mechanisms at the basis of some chronic pain conditions, the current study shows that AT can effectively lower TSSP. According to our findings, the pain reported by the participant during the pleasant tactile stimulation is not only lower compared to when there is no concomitant tactile input, but it is also smaller compared to the pain felt during a non-hedonic tactile stimulation (DT). The stimulation of low-threshold unmyelinated mechano-afferents, which make a critical contribution to the perception of AT [37], has been shown to decrease heat pain in healthy adults [27,38], and in reducing noxious-evoked brain activity in infants [26]. However, it is also important to note that in a laser evoked potentials (LEPs) study, no clear pain-reducing effect was recorded following either slow (pleasant) or fast (non-pleasant) stroking [33]. Therefore, the role of AT as an effective pain modulator is not well established. Here we report for the first time a clear pain-reducing effect operated by AT on the pain generated by repetitive heat stimulation. Previous research has revealed that TSSP, otherwise referred to as 'wind-up', may reflect central sensitization, a process believed to contribute to the development and maintenance of many chronic pain conditions [3–5,12,22,31,88,95,96]. Hence, investigating what are the mechanisms that modulate this type of pain can bring about useful insights into how central sensitization and chronic pain operate. In contrast to the so-called 'first pain', mediated by Aδ nociceptive afferents, 'second pain', mediated by C-nociceptors, does not decreases with repetitive heat noxious stimulation [65]. The characteristics of the unmyelinated C-

nociceptive afferents, with a long latency response to input, account for the psychophysical properties of windup of second pain [65,77]. At a bio-chemical level, the mechanisms of wind-up pain rely on N-methyl-D-aspartate (NMDA) receptors and substance P synaptic processes which are localized in the dorsal horn of the spinal cord [66,96]. These transmitters are also present in the substantia gelatinosa (SG), one of the densest neuronal areas of the central nervous system and a crucial hub for the transmission and modulation of nociceptive signals [19]. A previous electrophysiological study in rats, revealed that the SG contains neural circuitry associated with modulation of C-nociceptors activity by input from other C-fibres (low-threshold mechanoreceptors, or C-LTMR) [41], supporting the hypothesis of an inhibitory action of CT-fibres on C-nociceptive-related activity. Also, the modulatory activity operated by the SG could be expressed through the excitatory and inhibitory cells of this area of the spinal cord, which are connected to the cells in laminae I and V that transmit nociceptive input to the brain [10]. Although we did not test it with the present study, and therefore we acknowledge that is it highly speculative, the decrease in windup pain seen in our experiment could be explained by the activation of inhibitory interneurons, in the SG, operated by CT-fibres, which would suppress the activity of C-nociceptors. The suppression of C-nociceptors' activity would lead to a weaker summation process, which is at the basis of the wind-up phenomenon, and therefore to less pain. The analgesic effect operated by AT could also be partly due to the fact that this type of stimulation is linked to the release of oxytocin and dopamine [91], although the anti-nociceptive properties of these two hormones in humans are still not completely clear [6,8].

It is worth noting that in our study we did not find any clear analgesic effect of the 'discriminative' tactile stimulation. Such finding seems to be in opposition to the notorious "Gate Control Theory" (GCT) [52], and in contrast with many studies pointing at a gating effect of the tactile stimulation, both at a spinal [2,9,20,68,69] and supraspinal level [29,42,44]. One explanation may reside in the type of pain considered in the current experiment. The GCT establishes that both nociceptors and tactile fibres can all carry information from the injury site to two different cell types in the dorsal horn of the spinal cord, transmission cells, and inhibitory neurons. Both the nociceptive and non-nociceptive fibres can

activate the transmission cells, opening the gate of signals sent to the brain. However, only the non-nociceptive fibres can activate the inhibitory cells, therefore closing the gate [53]. The non-nociceptive fibres considered by the theory are large myelinated tactile fibres, i.e. the Aβ fibres. As a matter of fact, current stimulation protocols in clinical settings focus on stimulation parameters that activate Aβ fibres [85]. However, the biochemical mechanisms that lead to the efficacy of treatments like the transcutaneous electrical nerve stimulation TENS have not been fully understood yet. After all, the analgesic power of popular interventions like TENS on wind-up/central sensitization-derived pain states [59] is still scarce and such protocols also rely on the activation of a complex neural network [86]. Also, to our knowledge, there are no studies that have reported a decrement on TSSP following Aβ fibres stimulation. Particular attention should be given to the fact that the tactile stimulation adopted in the current study is not similar to other studies that have shown to produce analgesia by non-pleasant tactile stimulation, so, it is not possible to ascertain whether our DT stimulation has the right physical characteristics to produce an analgesic effect. It may be that, with other stimulation's characteristics (e.g. intensity, duration, stimulation type), DT could lead to a clear analgesia even during TSSP. For instance, it has been shown how the pain inhibitory effect operated by non-painful cutaneous stimulation, may take place only during specific inter-stimulus intervals (ISI) which separates the Aβ from the Aδ inputs [78]. In addition, other studies failed to find an analgesic effect operated by touch when administering touch and pain within the same dermatome [97], when using low intensity stimuli [58] or when providing a short tactile stimulation [55]. Thus, future studies might reveal whether the stimulus' characteristics can affect the analgesic potential of DT during TSSP.

Our study has also shed some light on the link between the participants' body awareness and their pain. The strong relationship between body representation and pain modulation has been thoroughly investigated in the recent past and it points at a by-directional influence. For instance it is known that chronic pain conditions can alter normal body representations [13,23,25,40,54,80] but also that an altered perception of the body can modulates acute and chronic pain states [16,43,45–48,63]. Also, the ability to

perceive the internal bodily sensations, or interoceptive awareness, has been shown to relate to pain. For instance, healthy participants with high interoceptive sensitivity show an increased sensitivity and decreased tolerance to pain [62]. Conversely, improving body awareness has been suggested as an approach for treating chronic pain patients [51] and body awareness interventions may also improve anxiety and depression in these patients [14]. Under our particular experimental setting, we did find a small but significant correlation which reveals that those with a higher ability to perceive the internal states of their body are also those who tend to perceive a stronger pain during the DT condition. However, this relationship between the interoceptive ability and the perceived pain seems to be lost when the participants do not get concomitant tactile stimulations or when they receive pleasant strokes. These results are partly in line with those by Pollatos et al. [62], in the sense that we also found an increased sensitivity to pain in individuals with higher body awareness and autonomic reactivity, yet this relationship was only clear during DT. Why this was is not easy to say on the basis of our results and of the existing literature. DT could function as a switch which generates interoceptive awareness by activating the primary and the secondary somatosensory cortices [32], and therefore amplifying pain in individuals with high body awareness. This amplification could be hampered by the affective touch, which should also activate the Aβ fibres, but it has a completely different functional role (motivational-affective rather than sensory-discriminative) [7]. Future studies may want to address this relationship between DT, pain and body awareness further, to better understand what is the role of the two types of touch on pain perception, taking into account the different interoceptive sensitiveness of the participants.

It is right to say that the present study has also some major caveats. For instance, it should be considered that in the current experiment the manual tactile delivery could have influenced the participants' ratings. We believe that, for the intrinsic social nature of AT, this type of tactile stimulation should be delivered by a person and not by a machine. However, we acknowledge that a limitation of the manual stimulation resides in the difficulty to determine the intensity of the tactile stimulation and its precise speed. Using always the same trained experimenter can help to maintain

the intensity of the stimulation under a certain restricted range, but the exact intensity is not measurable and it cannot be kept completely constant across trials. The same applies to the stroking speed, which was regulated by an audio input but it is reasonable to think that it could have slightly varied across trials. So, the stimulation method should be acknowledged as one of the limitations of this study. Also, the fact that the tactile stimulation was provided by an experimenter could have produced a bias in the participants responses. We did our best to minimize any possible predisposition, for instance by making clear to the participants that there were no 'right' or 'wrong' responses, but we cannot entirely exclude demand characteristics. Furthermore, although the attentional data relative to a posthumous experiment would point at similar levels of attention across conditions, we did not control for this cognitive factor during the current study, so we cannot rule out a role of attention in driving the analgesic effect we found during the AT condition.

Another limitation of the present study could be found in the thermal stimulation protocol: while using unique stimulus temperature for each subject should lower the TSSP variability across participants [74], and result in a more pronounced temporal summation compared to a fixed design [1], some studies have reported a variable proportion of subjects showing no temporal summation, even during individualized protocols [61,67]. Thus, measuring only the last pain sensation in a train of stimuli, may have concealed the absence of TSSP in some of our subjects. At last, it should also be pointed out that the exact level of activation, for ex. measured in firing rate, of both Aβ and CT-fibres during the two tactile conditions is not known, and it is sensible to think that both types of tactile fibres are activated, yet to a different extent, by both types of stimulation. Thus, an electrophysiological study should identify the exact activation of each type of fibre, especially during the 10 cm/sec (AT) condition, to have a clearer picture of what is their relative contribution to the analgesic process.

To conclude, the present experiment showed that affective but not discriminative touch can be considered as an effective intervention to reduce wind up pain caused by repetitive heat stimulation. CT-fibres-related activity can contrast TSSP-related processes, while a 'normal' tactile stimulation, supposedly involving Aβ fibres activation, produces no benefit.

Given the popularity of stimulation protocols like TENS, and considering the relationship between wind up phenomena and chronic pain conditions [21], future interventions could contemplate the stimulation of CT-fibres as a possible target for their treatments.

References

1. Anderson RJ, Craggs JG, Bialosky JE, Bishop MD, George SZ, Staud R, Robinson ME: Temporal summation of second pain: Variability in responses to a fixed protocol. Eur J Pain (United Kingdom) [Internet] Eur J Pain; 17:67–74, 2013 [cited 2020 Dec 12]. Available from: https://pubmed.ncbi.nlm.nih.gov/22899549/
2. Arcourt A, Gorham L, Dhandapani R, Prato V, Taberner FJ, Wende H, Gangadharan V, Birchmeier C, Heppenstall PA, Lechner SG: Touch Receptor-Derived Sensory Information Alleviates Acute Pain Signaling and Fine-Tunes Nociceptive Reflex Coordination. Neuron Cell Press; 93:179–93, 2017.
3. Arendt-Nielsen L: Pain sensitisation in osteoarthritis. Clin Exp Rheumatol Clinical and Experimental Rheumatology S.A.S.; 35:S68–74, 2017.
4. Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A: Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain [Internet] John Wiley & Sons, Ltd; 22:216–41, 2018 [cited 2019 Nov 7]. Available from: http://doi.wiley.com/10.1002/ejp.1140
5. Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK: Altered Central Sensitization and Pain Modulation in the CNS in Chronic Joint Pain. Curr Osteoporos Rep [Internet] Current Medicine Group LLC 1; 13:225–34, 2015 [cited 2020 Jun 9]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26026770
6. Becker S, Ceko M, Louis-Foster M, Elfassy NM, Leyton M, Shir Y, Schweinhardt P: Dopamine and pain sensitivity: Neither sulpiride nor acute phenylalanine and tyrosine depletion have effects on thermal pain sensations in healthy volunteers. PLoS One [Internet] PLoS One; 8:, 2013 [cited 2020 Jun 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/24236199/
7. Björnsdotter M, Morrison I, Olausson H: Feeling good: On the role of C fiber mediated touch in interoception [Internet]. Exp. Brain Res. Exp Brain Res; page 149–552010 [cited 2020 Oct 29]. Available from: https://pubmed.ncbi.nlm.nih.gov/20963582/
8. Boll S, Almeida de Minas AC, Raftogianni A, Herpertz SC, Grinevich V: Oxytocin and Pain Perception: From Animal Models to Human Research [Internet]. Neuroscience. Elsevier Ltd; page 149–612018 [cited 2020 Jun 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/28965836/

9. Braz J, Solorzano C, Wang X, Basbaum AI: Transmitting Pain and Itch Messages: A Contemporary View of the Spinal Cord Circuits that Generate Gate Control. Neuron. Cell Press; page 522–362014.

10. BRITTON NF, CHAPLAIN MAJ, SKEVINGTON SM: The role of N-methyl-D-aspartate (NMDA) receptors in wind-up: A mathematical model. Math Med Biol A J IMA Oxford Academic; 13:193–205, 1996.

11. Cabrera A, Kolacz J, Pailhez G, Bulbena-Cabre A, Bulbena A, Porges SW: Assessing body awareness and autonomic reactivity: Factor structure and psychometric properties of the Body Perception Questionnaire-Short Form (BPQ-SF). Int J Methods Psychiatr Res [Internet] John Wiley and Sons Ltd; 27:e1596, 2018 [cited 2020 Jun 23]. Available from: http://doi.wiley.com/10.1002/mpr.1596

12. Campbell JN, Meyer RA: Mechanisms of Neuropathic Pain. Neuron. Neuron; page 77–922006.

13. Catley MJ, O'Connell NE, Berryman C, Ayhan FF, Moseley GL: Is Tactile Acuity Altered in People With Chronic Pain? A Systematic Review and Meta-analysis. J Pain [Internet] 15:985–1000, 2014 [cited 2019 Jun 15]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24983492

14. Courtois I, Cools F, Calsius J: Effectiveness of body awareness interventions in fibromyalgia and chronic fatigue syndrome: A systematic review and meta-analysis. J Bodyw Mov Ther [Internet] Churchill Livingstone; 19:35–56, 2015 [cited 2020 Jun 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/25603742/

15. Craggs JG, Staud R, Robinson ME, Perlstein WM, Price DD: Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls. J Pain 13:390–400, 2012.

16. Daniel A, Barker L, Martini M: Pain modulation by illusory body rotation: A new way to disclose the interaction between the vestibular system and pain processing. Eur J Pain (United Kingdom) :1119–29, 2020.

17. Daniele CA, MacDermott AB: Low-Threshold Primary Afferent Drive onto GABAergic Interneurons in the Superficial Dorsal Horn of the Mouse. J Neurosci [Internet] 29:686–95, 2009 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19158295

18. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL: Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum

48:1420–9, 2003.

19. Dickenson AH: Spinal Cord Pharmacology of Pain. BJA Br J Anaesth Elsevier BV; , 1995.

20. Duan B, Cheng L, Bourane S, Britz O, Padilla C, Garcia-Campmany L, Krashes M, Knowlton W, Velasquez T, Ren X, Ross SE, Lowell BB, Wang Y, Goulding M, Ma Q: Identification of spinal circuits transmitting and gating mechanical pain. Cell Cell Press; 159:1417–32, 2014.

21. Dydyk AM, Givler A: Central Pain Syndrome [Internet]. StatPearls. 2020 [cited 2020 Jun 19]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31971703

22. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C: Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis. Osteoarthr. Cartil. W.B. Saunders Ltd; page 1043–562015.

23. Galer BS, Jensen M: Neglect-like symptoms in complex regional pain syndrome: Results of a self-administered survey. J Pain Symptom Manage Elsevier; 18:213–7, 1999.

24. Gard G: Body awareness therapy for patients with fibromyalgia and chronic pain. Disabil Rehabil [Internet] Disabil Rehabil; 27:725–8, 2005 [cited 2020 Jun 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/16012065/

25. Gilpin HR, Moseley GL, Stanton TR, Newport R: Evidence for distorted mental representation of the hand in osteoarthritis. Rheumatology [Internet] 54:678–82, 2015 [cited 2017 Mar 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25246638

26. Gursul D, Goksan S, Hartley C, Mellado GS, Moultrie F, Hoskin A, Adams E, Hathway G, Walker S, McGlone F, Slater R: Stroking modulates noxious-evoked brain activity in human infants. Curr. Biol. Cell Press; page R1380–12018.

27. Habig K, Schänzer A, Schirner W, Lautenschläger G, Dassinger B, Olausson H, Birklein F, Gizewski ER, Krämer HH: Low threshold unmyelinated mechanoafferents can modulate pain. BMC Neurol [Internet] BioMed Central; 17:184, 2017 [cited 2018 Jul 20]. Available from: http://bmcneurol.biomedcentral.com/articles/10.1186/s12883-017-0963-6

28. Hayamizu M, Hagiwara K, Hironaga N, Ogata K, Hoka S, Tobimatsu S: A spatiotemporal signature of cortical pain relief by tactile stimulation: An MEG study. Neuroimage [Internet] 130:175–83, 2016 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26854558

29. Inui K, Takeshi T, Kakigi R: Temporal Analysis of Cortical Mechanisms for Pain Relief by Tactile Stimuli in Humans [Internet]. Cereb. Cortex. 2006 [cited 2020 Jun 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/15901650/

30. JASP Team: JASP (Version 0.12.2)[Computer software]. , 2020. Available from: https://jasp-stats.org

31. Julien N, Goffaux P, Arsenault P, Marchand S: Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295–302, 2005.

32. Khalsa SS, Rudrauf D, Feinstein JS, Tranel D: The pathways of interoceptive awareness. Nat Neurosci [Internet] NIH Public Access; 12:1494–6, 2009 [cited 2020 Oct 29]. Available from: /pmc/articles/PMC2787640/?report=abstract

33. Krahé C, Drabek MM, Paloyelis Y, Fotopoulou A: Affective touch and attachment style modulate pain: a laser-evoked potentials study. Philos Trans R Soc Lond B Biol Sci [Internet] 371:20160009, 2016 [cited 2018 Jul 20]. Available from: http://rstb.royalsocietypublishing.org/lookup/doi/10.1098/rstb.2016.0009

34. Latremoliere A, Woolf CJ: Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. J Pain 10:895–926, 2009.

35. Liljencrantz J, Björnsdotter M, Morrison I, Bergstrand S, Ceko M, Seminowicz DA, Cole J, Bushnell MC, Olausson H: Altered C-tactile processing in human dynamic tactile allodynia. Pain [Internet] 154:227–34, 2013 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23290550

36. Liljencrantz J, Marshall A, Ackerley R, Olausson H: Discriminative and affective touch in human experimental tactile allodynia. Neurosci Lett [Internet] 563:75–9, 2014 [cited 2018 Jul 20]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24486839

37. Liljencrantz J, Olausson H: Tactile C fibers and their contributions to pleasant sensations and to tactile allodynia. Front Behav Neurosci [Internet] Frontiers Media SA; 8:37, 2014 [cited 2018 Dec 26]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24639633

38. Liljencrantz J, Strigo I, Ellingsen DM, Krämer HH, Lundblad LC, Nagi SS, Leknes S, Olausson H: Slow brushing reduces heat pain in humans. Eur J Pain 21:1173–85, 2017.

39. Löken LS, Wessberg J, Morrison I, McGlone F, Olausson H: Coding of pleasant touch by unmyelinated

afferents in humans. Nat Neurosci 12:547–8, 2009.

40. Lotze M, Moseley GL: Role of distorted body image in pain. Curr Rheumatol Rep [Internet] 9:488–96, 2007 [cited 2016 Jan 18]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18177603

41. Lu Y, Perl ER: A specific inhibitory pathway between substantia gelatinosa neurons receiving direct C-fiber input. J Neurosci [Internet] 23:8752–8, 2003 [cited 2019 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14507975

42. Mancini F, Beaumont A-L, Hu L, Haggard P, Iannetti GDD: Touch inhibits subcortical and cortical nociceptive responses. Pain [Internet] Lippincott Williams and Wilkins; 156:1936–44, 2015 [cited 2020 Jun 8]. Available from: http://journals.lww.com/00006396-201510000-00013

43. Mancini F, Longo MR, Kammers MPM, Haggard P: Visual distortion of body size modulates pain perception. Psychol Sci [Internet] 22:325–30, 2011 [cited 2014 Apr 30]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21303990

44. Mancini F, Nash T, Iannetti GD, Haggard P: Pain relief by touch: A quantitative approach. Pain [Internet] 155:635–42, 2014 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24361816

45. Martini M: Real, rubber or virtual: The vision of "one's own" body as a means for pain modulation. A narrative review [Internet]. Conscious. Cogn. Academic Press Inc.; page 143–512016 [cited 2020 Jun 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/27295559/

46. Martini M, Kilteni K, Maselli A, Sanchez-Vives M V: The body fades away: investigating the effects of transparency of an embodied virtual body on pain threshold and body ownership. Sci Rep [Internet] 5:13948, 2015 [cited 2016 Jan 16]. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4586459&tool=pmcentrez&rendertype=abstract

47. Martini M, Perez-Marcos D, Sanchez-Vives M V: What Color is My Arm? Changes in Skin Color of an Embodied Virtual Arm Modulates Pain Threshold. Front Hum Neurosci [Internet] 7:438, 2013 [cited 2014 May 15]. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3728482&tool=pmcentrez&rendertype=abstract

48. Matamala-Gomez M, Diaz Gonzalez AM, Slater M, Sanchez-Vives M V.: Decreasing Pain Ratings in Chronic Arm Pain Through Changing a Virtual Body: Different Strategies for Different Pain Types. J Pain [Internet] 20:685–97, 2019 [cited 2019 Aug 30]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30562584

49. McGlone F, Vallbo AB, Olausson H, Loken L, Wessberg J: Discriminative touch and emotional touch. Can J Exp Psychol 61:173–83, 2007.

50. McGlone F, Wessberg J, Olausson H: Discriminative and affective touch: sensing and feeling. Neuron [Internet] Elsevier; 82:737–55, 2014 [cited 2018 Jul 21]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24853935

51. Mehling WE, Gopisetty V, Daubenmier J, Price CJ, Hecht FM, Stewart A: Body awareness: Construct and self-report measures. PLoS One [Internet] PLoS One; 4:, 2009 [cited 2020 Jun 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/19440300/

52. Melzack R, Wall PD: Pain Mechanisms: A New Theory. Science (80-) 150:971–8, 1965.

53. Moayedi M, Davis KD: Theories of pain: from specificity to gate control. J Neurophysiol [Internet] 109:5–12, 2013 [cited 2016 Jan 3]. Available from: http://jn.physiology.org/content/109/1/5.long

54. Moseley GL: Distorted body image in complex regional pain syndrome. Neurology [Internet] 65:773–773, 2005 [cited 2017 Mar 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16157921

55. Mouraux A, Plaghki L: Cortical interactions and integration of nociceptive and non-nociceptive somatosensory inputs in humans. Neuroscience [Internet] Neuroscience; 150:72–81, 2007 [cited 2020 Oct 29]. Available from: https://pubmed.ncbi.nlm.nih.gov/17976921/

56. Nagi SS, Mahns DA: Mechanical allodynia in human glabrous skin mediated by low-threshold cutaneous mechanoreceptors with unmyelinated fibres. Exp Brain Res [Internet] 231:139–51, 2013 [cited 2019 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23955107

57. Nagi SS, Rubin TK, Chelvanayagam DK, Macefield VG, Mahns DA: Allodynia mediated by C-tactile afferents in human hairy skin. J Physiol [Internet] 589:4065–75, 2011 [cited 2019 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21727219

58. Nahra H, Plaghki L: Modulation of perception and neurophysiological correlates of brief CO2 laser stimuli in humans using concurrent large fiber stimulation. Somatosens Mot Res [Internet] Somatosens

Mot Res; 20:139–47, 2003 [cited 2020 Oct 29]. Available from: https://pubmed.ncbi.nlm.nih.gov/12850823/

59. Nijs J, Meeus M, Van Oosterwijck J, Roussel N, De Kooning M, Ickmans K, Matic M: Treatment of central sensitization in patients with "unexplained" chronic pain: What options do we have? [Internet]. Expert Opin. Pharmacother. Taylor & Francis; page 1087–982011 [cited 2020 Jun 19]. Available from: https://www.tandfonline.com/doi/abs/10.1517/14656566.2011.547475

60. Nordin M: Low-threshold mechanoreceptive and nociceptive units with unmyelinated (C) fibres in the human supraorbital nerve. J Physiol [Internet] 426:229–40, 1990 [cited 2019 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2231398

61. Pedersen JL, Andersen OK, Arendt-Nielsen L, Kehlet H: Hyperalgesia and temporal summation of pain after heat injury in man. Pain [Internet] Pain; 74:189–97, 1998 [cited 2020 Dec 13]. Available from: https://pubmed.ncbi.nlm.nih.gov/9520233/

62. Pollatos O, Füstös J, Critchley HD: On the generalised embodiment of pain: How interoceptive sensitivity modulates cutaneous pain perception. Pain [Internet] Pain; 153:1680–6, 2012 [cited 2020 Jun 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/22658270/

63. Preston C, Newport R: Analgesic effects of multisensory illusions in osteoarthritis. Rheumatology (Oxford) [Internet] 50:2314–5, 2011 [cited 2015 Nov 14]. Available from: http://rheumatology.oxfordjournals.org/content/early/2011/03/28/rheumatology.ker104.full

64. Price DD: Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol [Internet] Academic Press; 37:371–87, 1972 [cited 2019 Nov 21]. Available from: https://www.sciencedirect.com/science/article/abs/pii/0014488672900817?via%3Dihub

65. Price DD, Hu JW, Dubner R, Gracely RH: Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain [Internet] 3:57–68, 1977 [cited 2019 Nov 21]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/876667

66. Price DD, Mao J, Frenk H, Mayer DJ: The N-methyl-d-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. Pain Pain; 59:165–74, 1994.

67. Raphael KG, Janal MN, Ananthan S, Cook DB, Staud R: Temporal summation of heat pain in temporomandibular disorder patients. J Oral Facial Pain Headache [Internet] NIH Public Access;

23:54–64, 2009 [cited 2020 Dec 13]. Available from: /pmc/articles/PMC2652673/?report=abstract

68. Salter MW, Henry JL: Differential responses of nociceptive vs. non-nociceptive spinal dorsal horn neurones to cutaneously applied vibration in the cat. Pain [Internet] 40:311–22, 1990 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2326096

69. Salter MW, Henry JL: Physiological characteristics of responses of wide dynamic range spinal neurones to cutaneously applied vibration in the cat. Brain Res Elsevier; 507:69–84, 1990.

70. Staud R, Bovee CE, Robinson ME, Price DD: Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. Pain Pain; 139:315–23, 2008.

71. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD: Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. Eur J Pain [Internet] NIH Public Access; 12:1078–89, 2008 [cited 2018 Dec 26]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18367419

72. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD: Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. Eur J Pain 12:1078–89, 2008.

73. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD: Brain activity related to temporal summation of C-fiber evoked pain. Pain NIH Public Access; 129:130–42, 2007.

74. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD: Brain Activity Related to Temporal Summation of C-fiber Evoked Pain.

75. Staud R, Price DD, Fillingim RB: Advanced continuous-contact heat pulse design for efficient temporal summation of second pain (windup). J Pain [Internet] 7:575–82, 2006 [cited 2019 Nov 21]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526590006005669

76. Staud R, Robinson ME, Price DD: Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. J Pain [Internet] 8:893–901, 2007 [cited 2019 Oct 28]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526590007007341

77. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD: Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 91:165–75, 2001.

78. Testani E, Le Pera D, Del Percio C, Miliucci R, Brancucci A, Pazzaglia C, De Armas L, Babiloni C, Rossini PM, Valeriani M: Cortical inhibition of laser pain and laser-evoked potentials by non-nociceptive somatosensory input. Acsády L, editor. Eur J Neurosci [Internet] Blackwell Publishing Ltd; 42:2407–14, 2015 [cited 2020 Oct 29]. Available from: http://doi.wiley.com/10.1111/ejn.13035

79. Todd AJ: Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci Europe PMC Funders; 11:823–36, 2010.

80. Tsay A, Allen TJ, Proske U, Giummarra MJ: Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. Neurosci Biobehav Rev [Internet] 52:221–32, 2015 [cited 2016 Jan 19]. Available from: http://www.sciencedirect.com/science/article/pii/S0149763415000780

81. Valeriani M, Pazzaglia C, Rizzo V, Quartarone A, Vollono C: Laser evoked potential amplitude and laser-pain rating reduction during high-frequency non-noxious somatosensory stimulation. Clin Neurophysiol [Internet] 129:920–5, 2018 [cited 2019 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29550652

82. Vallbo A, Olausson H, Wessberg J, Norrsell U: A system of unmyelinated afferents for innocuous mechanoreception in the human skin. Brain Res 628:301–4, 1993.

83. Vallbo AB, Olausson H, Wessberg J: Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. J Neurophysiol [Internet] 81:2753–63, 1999 [cited 2018 Jul 20]. Available from: http://www.physiology.org/doi/10.1152/jn.1999.81.6.2753

84. Vallbo AB, Olausson H, Wessberg J, Kakuda N: Receptive field characteristics of tactile units with myelinated afferents in hairy skin of human subjects. J Physiol 483 (Pt 3:783–95, 1995.

85. Vallejo R, Bradley K, Kapural L: Spinal Cord Stimulation in Chronic Pain. Spine (Phila Pa 1976) [Internet] Lippincott Williams and Wilkins; 42:S53–60, 2017 [cited 2020 Jun 18]. Available from: http://journals.lww.com/00007632-201707151-00004

86. Vance CGT, Dailey DL, Rakel BA, Sluka KA: Using TENS for pain control: the state of the evidence [Internet]. Pain Manag. Pain Manag; page 197–2092014 [cited 2020 Jun 18]. Available from: https://pubmed.ncbi.nlm.nih.gov/24953072/

87. Veale JF: Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory

factor analysis. Laterality [Internet] 19:164–77, 2014 [cited 2016 Jul 19]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23659650

88. Veves A, Backonja M, Malik RA: Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. Pain Med. Pain Med; page 660–742008.

89. Vierck CJ, Cannon RL, Fry G, Maixner W, Whitsel BL: Characteristics of Temporal Summation of Second Pain Sensations Elicited by Brief Contact of Glabrous Skin by a Preheated Thermode. J Neurophysiol [Internet] 78:992–1002, 1997 [cited 2019 Nov 21]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9307129

90. Villemure C, Bushnell MC: Cognitive modulation of pain: How do attention and emotion influence pain processing? Pain 95:195–9, 2002.

91. Walker SC, Trotter PD, Swaney WT, Marshall A, Mcglone FP: C-tactile afferents: Cutaneous mediators of oxytocin release during affiliative tactile interactions? [Internet]. Neuropeptides. Churchill Livingstone; page 27–382017 [cited 2020 Jun 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/28162847/

92. Weiss T, Straube T, Boettcher J, Hecht H, Spohn D, Miltner WHR: Brain activation upon selective stimulation of cutaneous C- and Aδ-fibers. Neuroimage [Internet] 41:1372–81, 2008 [cited 2019 Oct 18]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S105381190800284X

93. Willis WD: The pain system. The neural basis of nociceptive transmission in the mammalian nervous system. Pain Headache [Internet] 8:1–346, 1985 [cited 2019 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2983301

94. Willis WD, Coggeshall RE: Sensory Mechanisms of the Spinal Cord : Volume 1 Primary Afferent Neurons and the Spinal Dorsal Horn. Springer US; 2004.

95. Woolf CJ: Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011.

96. Woolf CJ, Thompson SWN: The induction and maintenance of central sensitization is dependent on N-methyl-d-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain Pain; 44:293–9, 1991.

97. Yarnitsky D, Kunin M, Brik R, Sprecher E: Vibration reduces thermal pain in adjacent dermatomes. Pain [Internet] Pain; 69:75–7, 1997 [cited 2020 Oct 29]. Available from:

https://pubmed.ncbi.nlm.nih.gov/9060015/

Figure captions

Fig. 1. Schematic representation of the experiment: during each condition [no touch ("Not"), discriminative touch ("DT") and affective touch ("AT")] 5 trains (in red and yellow) of 6 heat stimuli were delivered through a thermode attached to the dorsal side of the participants' right wrist. Each heat stimulus lasted for 3 seconds (1.5 ascending, 1.5. descending). Individuals' target temperatures were set for each participant, so that the maximal temperature of the thermode would elicit a pain rating of 45 ± 10 at the end of each train of stimuli. After about 2 seconds from the last stimulus of each train, a pain rating was recorded via a Computerized Visual Analogic Scale (CoVAS, in green). At the end of both tactile conditions (DT and AT) a pleasantness rating (in purple) was recorded via a numerical rating scale. During the tactile conditions an experimenter stroked the participants arm continuously at different velocities (0.3 cm/s for DT; 10 cm/s for AT). No tactile stimulation was provided during the NoT condition.

Fig. 2. Grand averages (histograms) and standard errors (error bars) of the pain reported by the participants in each condition [no touch ("Not") in black, discriminative touch ("DT") in grey and affective touch ("AT") in light grey]. Asterisks indicate significant differences among conditions (***$p < 0.001$).

Fig. 3. Grand averages (histograms) and standard errors (error bars) of the pleasantness scores recorded after each tactile condition [discriminative touch ("DT") in grey and affective touch ("AT") in light grey]. Asterisks indicate a significant difference between conditions (***$p < 0.001$).

Fig. 4. Correlations between the average pain recorded during each condition [no touch ("Not"), discriminative touch ("DT") and affective touch ("AT")] by each participant and their individual

Body Perception Questionnaire (BPQ) score. Only during the DT condition a positive significant correlation was found ($p<0.05$).