The focus of spatial attention during the induction of central sensitization can modulate the subsequent development of secondary hyperalgesia

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Abstract

Intense or sustained activation of peripheral nociceptors can induce central sensitization. This enhanced responsiveness to nociceptive input of the central nervous system primarily manifests as an increased sensitivity to painful mechanical pinprick stimuli extending beyond the site of injury (secondary mechanical hyperalgesia) and is thought to be a key mechanism in the development of chronic pain, such as persistent post-operative pain. It is increasingly recognized that emotional and cognitive factors can strongly influence the pain experience. Furthermore, through their potential effects on pain modulation circuits including descending pathways to the spinal cord, it has been hypothesized that these emotional and cognitive factors could constitute risk factors for the susceptibility to develop chronic pain. Here, we tested whether, in healthy volunteers, the experimental induction of central sensitization by peripheral nociceptive input can be modulated by selective spatial attention. While participants performed a somatosensory detection task that required focusing attention towards one of the forearms, secondary hyperalgesia was induced at both forearms using bilateral and simultaneous high-frequency electrical stimulation (HFS) of the skin. HFS induced an increased sensitivity to mechanical pinprick stimuli at both forearms, directly (T1) and 20 minutes (T2) after HFS, confirming the successful induction of secondary hyperalgesia at both forearms. Most importantly, at T2, the HFS-induced increase in pinprick sensitivity as well as the area of secondary hyperalgesia was greater at the attended arm as compared to the non-attended arm. This indicates that top-down attentional factors can modulate the development of central sensitization by peripheral nociceptive input, and that the focus of spatial attention, besides its modulatory effects on perception, can affect activity-dependent neuroplasticity.

Keywords: spatial attention, nociception, central sensitization, secondary hyperalgesia, cognitive modulation

Abbreviations:

HFS: high frequency stimulation

1. Introduction

Pain is an unpleasant sensation usually evoked by the activation of nociceptors, a specific class of sensory receptors that respond to high intensity stimuli that are potentially harmful for the body tissue. What distinguishes the nociceptive system from other perceptual systems is the way its responsiveness changes when exposed to repeated stimuli. In the case of innocuous stimuli, repetition typically results in reduced responding, a phenomenon referred to as *habituation* (Thompson & Spencer, 1966). In contrast, repetition of a noxious or nociceptive stimulus can induce a progressive amplification of the usual response to the stimulus, i.e. *sensitization*. Indeed, from peripheral nociceptors to the central nervous system, the nociceptive system tends to increase its responsiveness when exposed to repeated stimulation (Latremoliere & Woolf, 2009). Habituation and sensitization are two basic but non-trivial forms of non-associative learning: whereas habituation would generally allow to filter out irrelevant sensory input about the environment, sensitization, in the context of nociception, would increase the ability to respond to stimuli potentially compromising the integrity of the organism and survival, thus fulfilling a protective role (Latremoliere & Woolf, 2009).

After tissue injury, increased sensitivity to painful stimuli is not only observed within the injured area, but also in the surrounding non-injured tissue. While the former is referred to as primary hyperalgesia, the latter is referred to as secondary hyperalgesia. Secondary hyperalgesia is thought to result from central sensitization, i.e. an enhanced responsiveness of nociceptive neurons in the central nervous system induced by intense or sustained peripheral nociceptive input (Klede, Handwerker, & Schmelz, 2003; LaMotte, Shain, Simone, & Tsai, 1991; Loeser & Treede, 2008; Raja, Campbell, & Meyer, 1984; Torebjörk, Lundberg, & LaMotte, 1992; Woolf, Thompson, & King, 1988) and considered as a key mechanism in the development and maintenance of many chronic pain disorders, such as sustained post-operative pain (Latremoliere & Woolf, 2009; Woolf, 2011; Woolf & Salter, 2000). In humans, this phenomenon can be studied experimentally using methods producing experimental lesions or generating strong peripheral nociceptive input (Fißmer et al., 2011; Klein, Magerl, Rolke, & Treede,

2005). One method, high frequency electrical stimulation (HFS) of the skin during a few seconds using an electrode designed to preferentially activate nociceptive afferents, has been shown to reliably induce a long-lasting increase in sensitivity to mechanical pinprick stimuli in the surrounding unconditioned skin site (e.g. Klein, Magerl, Hopf, Sandkühler, & Treede, 2004; Klein, Stahn, Magerl, & Treede, 2008; Pfau et al., 2011; van den Broeke et al., 2010).

While the underlying mechanisms of central sensitization and its behavioral and electrophysiological correlates have been studied extensively (e.g. Henrich, Magerl, Klein, Greffrath, & Treede, 2015; Klein et al., 2004; Pfau et al., 2011; van den Broeke, Lambert, Huang, & Mouraux, 2016; van den Broeke & Mouraux, 2014b; van den Broeke, van Heck, van Rijn, & Wilder-Smith, 2011; Woolf, 2011), not much is known about cognitive factors that might modulate its development. However, it is increasingly acknowledged that psychological factors, such as anxiety, mood, expectations, and cognitive biases towards pain, can modulate the experience of both experimental and pathological pain (Bingel & Tracey, 2008; Tracey & Mantyh, 2007; Van Damme, Legrain, Vogt, & Crombez, 2010; Wiech, 2016). Research has suggested that this could, at least in part, be explained by an activation of pain modulation circuits, including the descending pain modulatory system, a network enabling higher brain centers to regulate early nociceptive transmission and processing in the spinal cord (e.g. Eippert et al., 2009; Kucyi, Salomons, & Davis, 2013; Sprenger et al., 2012; Tinnermann, Geuter, Sprenger, Finsterbusch, & Büchel, 2017; Tracey & Mantyh, 2007). Furthermore, the state of these top-down modulatory circuits could potentially explain how affective and cognitive factors may influence the susceptibility to develop chronic pain (Bingel & Tracey, 2008).

Some studies have already suggested a potential influence of cognitive factors on secondary hyperalgesia (Matre, Casey, & Knardahl, 2006; Salomons, Moayedi, Erpelding, & Davis, 2014; van den Broeke, Geene, Rijn, Wilder-Smith, & Oosterman, 2014). Matre et al. (2006) demonstrated that the induction of placebo analgesia can reduce the area of mechanical secondary hyperalgesia induced by intense heating of the skin. Salomons et al. (2014) obtained similar results using a brief cognitive

behavioral therapy aimed to cope with painful experimental stimuli. van den Broeke et al. (2014) showed that inducing negative expectations about the after-effects of HFS can increase secondary hyperalgesia after HFS.

Selective spatial attention is the ability to process, perceive, and react to stimuli occurring in a restricted part of space, to the detriment of stimuli occurring elsewhere (Driver, 2001). On one hand, pain has been shown to attract attention towards the part of the body onto which nociceptive stimuli occur. On the other hand, explicitly directing attention towards a specific part of the body can affect the cortical responses to nociceptive stimuli and modulate the perception of pain (see Legrain et al., 2012; Van Damme et al., 2010). Here we investigated the effects of selective spatial attention on the development of secondary hyperalgesia. HFS was applied simultaneously on the left and right forearms while participants performed a task requiring to selectively focus attention on stimuli applied on one of the two forearms. Mechanical pinprick sensitivity of the two forearms was assessed before, directly after and 20 minutes after HFS. We hypothesized that HFS would induce secondary hyperalgesia at both forearms, but that the strength and extent of this secondary hyperalgesia could be significantly different between the attended and non-attended arms, suggesting that the sensitizing effect of repeated nociceptive input can be selectively modulated by the focus of attention *during* the sensitization procedure.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures or analyses was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

2.1 Participants

Twenty-five participants (mean age 23.1 years, SD= 2.29, range=18-29 years; 16 women) took part in the experiment. Sample size selection was based on a compromise between the tested samples in related studies (Matre et al., 2006; Salomons et al., 2014; van den Broeke et al., 2014), the within-subject design of our study and on the likelihood that the data of some participants would be excluded because they failed to perform the attention task correctly.

General exclusion criteria were past experience with experiments including HFS, the presence of any known psychiatric, neurological, cardiac or chronic pain condition, regular use of psychotropic or analgesic drugs, as well as any traumatic injury of the upper limbs within the 6 months preceding the experiment. Participants reported having slept at least 6h the night before the experiment and not having used any analgesic medication in the 12h preceding the experiment. According to the Flinders Handedness Survey (Flanders) (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), 21 participants were right-handed, three were left-handed and one was ambidextrous. The experimental procedure was approved by the local ethics committee (Commission d'Ethique Biomédicale Hospitalo-Facultaire de l'UCLouvain) in agreement with the Declaration of Helsinki. All participants signed an informed consent prior to the experimental session and received financial compensation for their participation.

2.2 Stimuli and apparatus

HFS was delivered to the skin of both volar forearms (approximately 10 cm distal from the cubital fossa) using two custom-built electrodes following a design proposed by the Centre for Sensory-Motor Interaction (Aalborg University, Denmark). The electrode design aims to preferentially activate cutaneous nociceptive afferents (Klein et al., 2004). It consists of 16 blunt stainless-steel pins with a diameter of 0.2 mm protruding 1 mm from the base. The pins are placed in a 10 mm diameter circle and serve as cathode. A stainless-steel circular electrode is concentrically located around the pins (inner diameter of 22 mm, outer diameter of 40 mm) and serves as anode (Figure 1A). Electrical pulses were generated by two constant current electrical stimulators (Digitimer DS7A; Digitimer Ltd, Welwyn Garden City, UK). The stimulation consisted of five trains of electrical pulses (pulse width: 2 ms)

delivered at a 100-Hz rate, lasting 1 s each, with an inter-train interval of 10 s. The intensity of the stimulation was individually adjusted for each arm to 10 times the detection threshold to a single pulse (Klein et al., 2004; Klein et al., 2008; van den Broeke et al., 2016). The detection threshold, assessed using the method of limits (using steps of approximately 0.01 mA), was 0.18 ± 0.07 mA on the left arm and 0.2 ± 0.07 mA on the right arm (mean ± sd). After having determined detection thresholds, participants were asked to report whether the sensation and intensity of a single pulse at 10 times the detection threshold were perceived as similar for both forearms. If the percept differed between the two forearms, the intensity of the stimulation was adjusted by slightly increasing or decreasing the intensity of the electrical pulses on the left and/or right forearm (steps of approximately 0.01 mA), until the perceived sensation/intensity was matched between both forearms. If the sensations/intensities could not be matched using stimulation intensities differing by less than 0.1 mA, the electrodes were displaced at both forearms and the entire procedure was restarted. After adjustments, mean stimulation intensity for HFS was 1.8 ± 0.7 mA for the left arm and 2 ± 0.7 mA for the right arm (mean ± sd). Both the electrodes and the electrical stimulators used to stimulate each of the two forearms were counterbalanced across participants.

To confirm the successful induction of secondary hyperalgesia by HFS, mechanical pinprick stimuli were applied to the skin on both forearms at different time points, in the skin area surrounding the HFS electrode (in a delimited area located 5-25 mm away from the ring of cathode pins, distally and proximally). A calibrated punctuate probe with an exerting force of 128 mN was used to test mechanical pinprick sensitivity (The Pin Prick, MRC Systems, Heidelberg, Germany). Such punctuate probes elicit a pinprick sensation related to the preferential activation of mechanosensitive nociceptors in the skin (Garell, McGillis, & Greenspan, 1996; Slugg, Campbell, & Meyer, 2004; Slugg, Meyer, & Campbell, 2000). Numerous studies have shown that HFS induces a long-lasting increase in the sensitivity to these stimuli (e.g. Klein et al., 2004; Pfau et al., 2011; van den Broeke et al., 2016; van den Broeke & Mouraux, 2014a, 2014b). Even though the sensation elicited by 128 mN pinprick stimuli is not always reported as being painful, this increase in pinprick sensitivity can be related to the

secondary mechanical hyperalgesia resulting from a central sensitization of mechanical nociceptive pathways (see van den Broeke et al., 2016 for a discussion).

For the spatial attention task, vibrotactile stimuli were generated by two vibrotactile transducers driven by standard audio amplifiers (TL-002-14R Haptuator Redesign, Tactile Labs, Inc., Montreal, Canada). One vibrotactile transducer was fixed with gauze approximately 2 cm distally from the HFS electrode on each forearm. The vibrotactile stimuli were 20-ms vibrations at 250 Hz (Figure 1A).

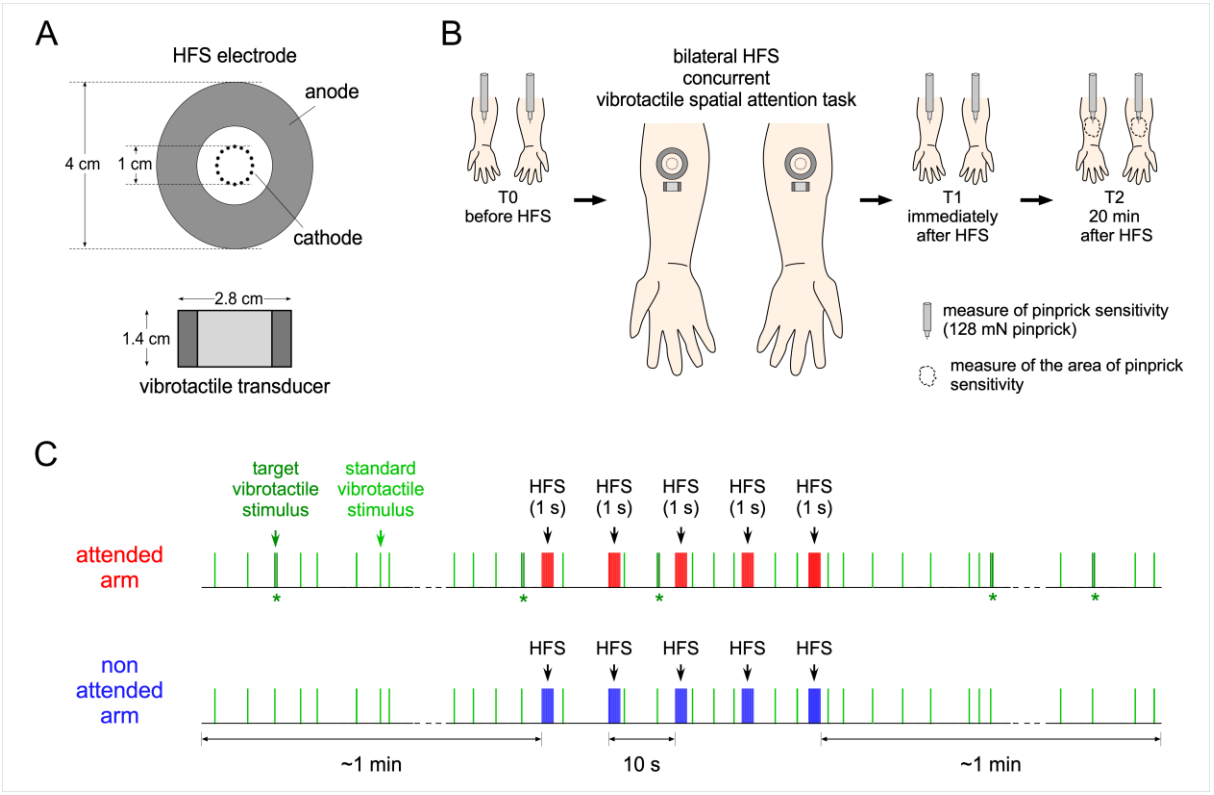

Figure 1. Material and methods. (A) The electrode used to deliver high frequency stimulation (HFS) on both forearms consisted in sixteen pins placed in a 1-cm diameter circle, serving as cathode, concentrically surrounded by a large-surface circular electrode serving as anode. View of the surface in contact with the skin. At both forearms, a vibrotactile transducer was placed against the skin, approximately 2 cm distally from each HFS electrode. **(B)** Experimental procedure. Pinprick sensitivity was measured on both forearms before the start of the vibrotactile spatial attention task and the application of bilateral and simultaneous HFS (T0). Pinprick sensitivity was measured again at both forearms immediately after the end of HFS and the spatial attention task (T1), as well as 20 min after the end of the procedure (T2). Additionally, at T2, the spatial extent of the area of increased pinprick sensitivity was measured along the distal-proximal and medial-lateral axes on both forearms. **(C)** Bilateral HFS & concurrent vibrotactile attention task. Short-lasting vibrotactile stimuli were presented

simultaneously on both arms, with a random time interval. Standard stimuli consisted in a single 20-ms vibration. On 8 occasions, on the attended arm, the standard vibrotactile stimulus was replaced by a target stimulus, consisting in two succeeding vibrations separated by 50 ms. The participant was instructed to report each occurrence of a target stimulus at the attended arm, and to ignore stimuli applied on the non-attended forearm. Approximately one minute after the start of the task, five HFS trains were applied simultaneously on both the attended and on the non-attended arm. Vibrotactile stimuli were also applied between the HFS trains, and the task continued during approximately one minute after the end of the last HFS train.

2.3 Procedure

The experimental procedure is illustrated in Figure 1B. Participants were seated comfortably with the arms placed palms up on a table in front of them, with a distance of approximately 20 cm between the arms. The experiment started with a first measurement of pinprick sensitivity (T0, before HFS). For each arm, participants rated the mean intensity of 3 consecutive pinprick stimuli applied perpendicular to the skin at different locations surrounding the area onto which HFS would be applied later (see stimuli and apparatus section 2.2). Ratings were provided on a numerical rating scale (NRS) ranging from 0 (no detection) to 100 (maximum pain), with 50 marking the transition between a non-painful and a painful sensation. Participants did not receive any specific instruction on whether they should observe the application of pinprick stimuli or not. The order in which the arms were tested was counterbalanced across participants and was retained for subsequent pinprick sensitivity measurements. Afterwards, the HFS electrodes and vibrotactile transducers were attached to both forearms and detection thresholds to single electrical pulses were measured and adapted if necessary, as described above. Participants were familiarized with the vibrotactile stimuli and, if necessary, vibration amplitude was adapted in order to match the perceived sensation and intensity between the left and right vibrotactile transducers. After these first measurements, the attentional task was immediately introduced (Figure 1C). Participants fixated a cross placed between their arms, while 138 single vibrotactile stimuli (standard stimuli) were presented on both arms simultaneously (i.e. 69 stimuli on each arm) at random time intervals (every 1-8 s). On only one of the forearms, eight of the 69 standard vibrotactile stimuli were replaced at predefined time points by a double vibrotactile

stimulus, i.e. two succeeding vibrations separated by 60 ms (target stimuli). Target stimuli were never presented directly one after another. To mask any sound produced by the vibrotactile stimulators, white noise was presented continuously through headphones. The participants were instructed to only attend the forearm on which the occasional target stimuli were applied (the *attended* arm), such as to be able to detect these target stimuli, and to verbally report each perceived occurrence of a target stimulus on-line (by stating the word "double"). They were further told that there would be no target vibrotactile stimuli delivered to the other, *non-attended*, arm. The attended arm was either the arm with the lower detection threshold to a single electrical pulse or the arm with the higher detection threshold to a single electrical pulse, counterbalanced across participants. Depending on the participant, this could be either the dominant (N= 11) or the non-dominant arm (N= 13). One minute into the task, the five HFS trains were applied on both arms simultaneously. During each stimulation train, the experimenter held both arms of the participant in a steady position, to avoid that abrupt movements of the arms would remove the electrode and/or the vibrotactile stimulator. Participants were thus warned of each upcoming train of HFS. Vibrotactile stimuli (standard and target stimuli) were also presented between the HFS trains and the task continued after the end of HFS, during approximately 60 s. In total, the duration of the task was 170 s. At the end of the task, HFS electrodes and vibrotactile transducers were removed and pinprick sensitivity on both forearms was measured again (T1, directly after HFS), as well as 20 minutes after the procedure (T2, 20 min after HFS). This 20 minutes delay was chosen based on the results of previous studies showing a consistent increase in pinprick sensitivity at that time point (van den Broeke et al., 2016; van den Broeke & Mouraux, 2014a, 2014b). Additionally, at T2, the spatial extent of the area of increased pinprick sensitivity was measured on both forearms. The pinprick stimuli were applied every 1 cm along the proximal-distal and the medial-lateral axis, approaching the area onto which HFS was applied. Participants did not look at their arms and verbally indicated the point at which the percept elicited by the pinprick stimulus changed ("now the perception changed"). The location of that stimulus was marked on the skin. During the 20

minutes pause between T1 and T2, participants waited in the testing room while having a conversation with the experimenter. They were instructed to move their arms as little as possible.

2.4 Measures and analysis

To minimize the risk of including participants that did not perform the selective attention task correctly and, hence, might not have focused spatial attention onto the attended arm, the data of participants that reported less than 4 vibrotactile target stimuli (out of the eight targets) or more than 8 false alarms (i.e. wrongly identified targets) were excluded from further data analyses. Since target stimuli were presented at predefined time points, it was possible to assess whether participants reported actual targets, or whether they wrongly identified standard stimuli as target stimuli. Based on these criteria three participants were excluded: one reported <4 target stimuli (0 correct target detections), two reported >8 false alarms (16 and 25 reported targets, including 16 and 23 false alarms, respectively). One participant explicitly reported having paid attention to both arms and was therefore also excluded.

Increased pinprick sensitivity was assessed at each forearm by comparing the pinprick ratings at T1 and at T2 to the ratings at T0, using a Wilcoxon signed-rank test. A Wilcoxon signed-rank test was also used to compare pinprick ratings between T1 and T2 for each arm, to assess the potential effect of time on the development of secondary hyperalgesia. A non-parametric test was chosen because the self-reported perception of pinprick intensity can be considered as an ordinal variable (Decruynaere, Thonnard, & Plaghki, 2007). To test the difference in increased pinprick sensitivity after HFS between the attended and the non-attended arm, we computed, for both arms, the percentage of change with regard to T0, for T1 and T2. To assess whether attention modulated pinprick sensitivity immediately after the delivery of HFS and performance of the spatial attention task, the percentage of change in pinprick sensitivity was compared between the attended and the non-attended arm at T1. Furthermore, to assess whether attention modulated the long-lasting HFS-induced enhancement of pinprick sensitivity, the percentage of change in pinprick sensitivity was compared between both arms

at T2, i.e. 20 minutes after HFS. The comparisons were performed using paired-sample t-tests. The comparisons were conducted using percentage of change in pinprick ratings to take into account potential differences in pinprick sensitivity between the two arms that could already be present before applying HFS. For this analysis, another participant was excluded, because he did not use the rating scale consistently, with an extreme difference in ratings between T0 and T2 that lead to an extremely increased difference between the attended and the non-attended arm.

To assess the proximal, distal, medial and lateral extent of the area of increased pinprick sensitivity, we measured the distance (in mm) from the skin mark that indicated the change in pinprick sensitivity to the center of the HFS electrode, for every skin mark that was outside the edge of the 40-mm diameter electrode. For every skin mark that was inside the 10-mm diameter of the circle of pins, the distance was coded 0 mm, and for every mark that was between the circle of pins and the edge of the electrode, the distance was coded 12.5 mm, corresponding to the midpoint between the circle of pins and the edge of the electrode. The sum of the proximal and distal measurements was used as an estimate of the proximal-distal extent of the area of increased pinprick sensitivity. The sum of the medial and lateral measurements was used as an estimate of the medial-lateral extent of the area of increased pinprick sensitivity. These were then compared between the attended and the non-attended arm using paired-sample t-tests. Data was missing from one participant for this measurement. Analyses regarding the extent of the area of increased pinprick sensitivity were thus performed on 20 participants.

Finally, to assess the relationship between the different measurements of the after-effects of HFS on pinprick sensitivity, we computed, at T2, the difference in percentage of change (T2 with regard to T0) in pinprick ratings at the attended arm minus the non-attended arm, as well as the difference in the extent of the area of increased pinprick sensitivity between the attended and the non-attended arm along the proximal-distal and the medial-lateral axes. Positive values indicated that the percentage of change in pinprick sensitivity, or the extent of the area of secondary hyperalgesia, was greater at the

attended arm as compared to the non-attended arm. The relationships between the different variables were assessed using the Pearson correlation coefficient.

For the Wilcoxon signed-rank tests, the T statistic corresponds to the smaller of the two sums of ranks of given sign. Effect sizes were measured using Cohen's d or Pearson's r (for non-parametric tests, based on the *z* statistic) and significance level was set at p ≤0.05. No corrections for multiple comparisons were performed.

3. Results

Behavioral performance on the vibrotactile detection task. The 21 participants kept for the data analysis detected, on average, 6.9 out of the 8 vibrotactile targets (SD= 1.37, range= 4-8, mode= 8) and committed on average 1.05 false alarms (SD= 1.6, range= 0-5, mode= 0).

HFS-induced increase in pinprick sensitivity (Figure 2). HFS induced an increase in pinprick sensitivity at both forearms, which was present directly after HFS (T1-T0 attended arm: T= 20, *z*= -3.02, *p*= .003, r= - .46; T1-T0 non-attended arm: T= 28, *z*= -2.89, *p*= .004, r= -.44) and 20 minutes after HFS (T2-T0 attended arm: T= 0, *z*= -3.83, *p*≤ .001, r= - .59; T2-T0 non-attended arm: T=1, *z*= -3.79, *p*≤ .001, r= - .58). Indeed, for both the attended and the non-attended arm, pinprick sensitivity was rated higher at T1 (attended arm *Mdn* = 30, *range*= 5-80; non-attended arm *Mdn* = 30, range= 4-70) and T2 (attended arm *Mdn* = 50, *range*= 6-85; non-attended arm *Mdn* = 45, range= 5-75) as compared to T0 (attended arm *Mdn* = 20, *range*= 2-50; non-attended arm *Mdn* = 20, range= 2-45). For both arms, this increase was greater at T2 than at T1 (attended arm: T= 25, *z*= -2.82, *p*= .005, r= -.43; unattended arm: T= 22.5 *z*= -2.92, *p*= .003, r= -.45) (Figure 2A). These results confirm that HFS succeeded in inducing secondary mechanical hyperalgesia, which continued to increase from the end of the sensitization procedure to at least 20 minutes after the induction of sensitization.

At T1, there was no significant difference in increased pinprick sensitivity between the attended arm and the non-attended arm (*t*(19)= 1.43, *p*= .17, d= .32). In contrast, at T2, the increased pinprick

sensitivity at the attended arm was significantly greater than the increased pinprick sensitivity at the non-attended arm ($t(19)= 3.35$, $p= .003$, d= .75). This indicates that, 20 minutes after HFS, the secondary hyperalgesia induced at the attended arm was significantly stronger than the secondary hyperalgesia induced at the non-attended arm (Figure 2B).

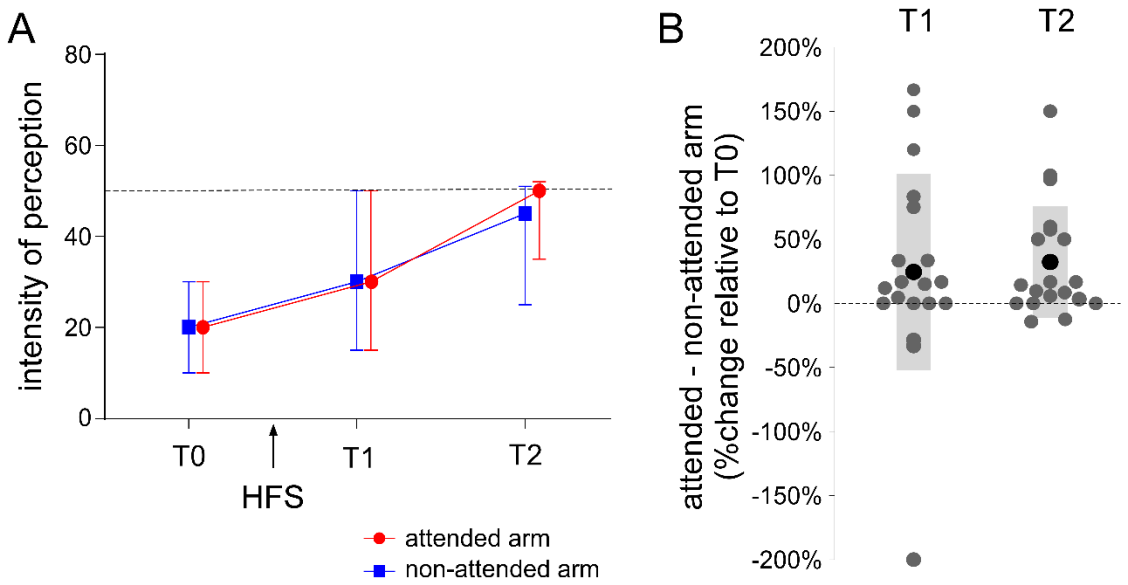

Figure 2. Increase in pinprick sensitivity induced by high frequency stimulation (HFS) at the attended arm and the non-attended arm. (A) Intensity of the percept elicited by pinprick stimulation before (TO), directly after applying HFS (T1) and 20 minutes after applying HFS (T2) at the attended and non-attended arms (group-level median and interquartile range). As compared to T0, pinprick sensitivity was significantly increased at T1 and at T2, at both forearms. For both the attended and the non-attended arm, this increase was significantly greater at T2 than at T1. This confirms the successful induction of secondary hyperalgesia by HFS at both forearms. Participants rated the intensity of perception on a numerical rating scale ranging from 0 (no perception) to 100 (maximum pain). The rating of 50, represented by the dotted line, marked the transition between painful and non-painful sensations. **(B)** Difference in increased pinprick sensitivity between the attended and the non-attended arm, at T1 and at T2, expressed as the difference in the percentage of change with regard to T0. Positive percentage values indicate that the percentage of change with regard to T0 was greater at the attended arm as compared to the non-attended arm. Individual values are shown as grey dots. The group-level average is shown as a black dot and the standard deviation as grey rectangle. At T2 (20 min after HFS), the increased pinprick sensitivity was significantly greater at the attended arm as compared to the non-attended arm.

Spatial extent of the HFS-induced increase in pinprick sensitivity (Figure 3). Along the medial-lateral axis, the extent of the area of increased pinprick sensitivity was significantly greater at the attended arm as compared to the non-attended arm ($t(19)= 3.99$, $p \leq .001$, d= .89) (Figure 3B). There was no significant difference between the attended arm and the non-attended arm for the proximal-distal axis ($t(19)= 1.31$, $p= .206$, d= .29) (Figure 3A).

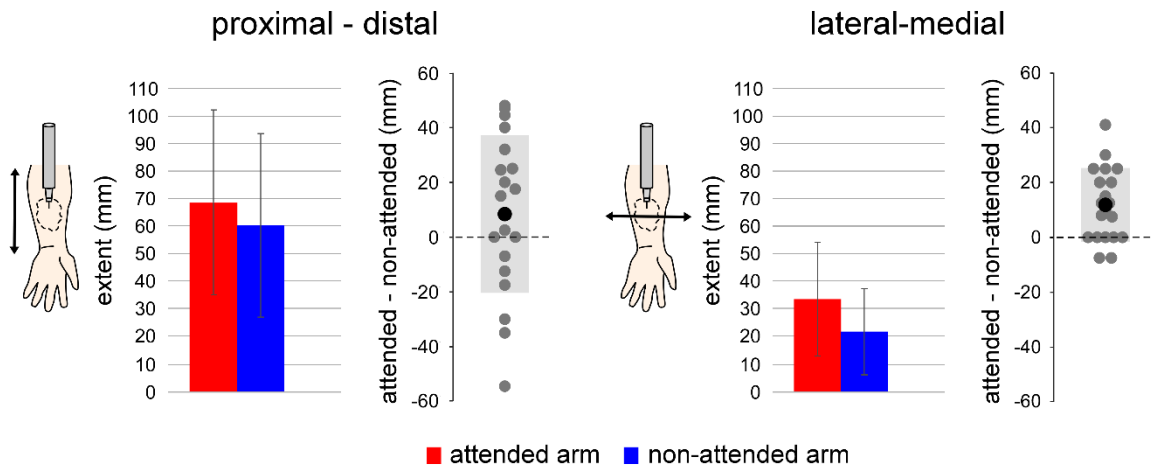

Figure 3. Spatial extent of the increase in pinprick sensitivity induced by high frequency stimulation (HFS) at the attended and the non-attended arm, 20 min after HFS (T2). (A) Proximal-distal axis. **(B)** Medial-lateral axis. The bar graphs show the group-level average extent (in mm) of the area of increased pinprick sensitivity at the attended arm and the non-attended arm. Error bars correspond to the standard deviation. The right graphs show the difference in extent between the attended and the non-attended arms (in mm). Positive values indicate that the extent of the area was greater at the attended arm as compared to the non-attended arm. Individual values are shown as grey dots. The group-level average difference is shown as a black dot and the standard deviation as grey rectangle. There was no significant difference between the attended and the non-attended arm along the proximal-distal axis. In contrast, the spatial extent of the increase in pinprick sensitivity along the medial-lateral axis was significantly greater at the attended arm as compared to the non-attended arm.

The correlation analysis revealed that the percentage of change in pinprick sensitivity at T2 was not significantly correlated with the extent of the area of secondary hyperalgesia on the proximal-distal axis ($r= -0.1$, $p= .693$). There was also no significant correlation of the percentage of change in pinprick sensitivity with the extent of the area of secondary hyperalgesia on the medial-lateral axis, but the

analysis still showed a medium effect (r= 0.38, p= .105). In contrast, there was a positive relationship between the extent of the area of increased pinprick sensitivity along the proximal-distal axis and the medial-lateral axis (r= .51, p= .025).

4. **Discussion**

In the present study we tested the influence of selective spatial attention on the experimental induction of secondary hyperalgesia by intense peripheral nociceptive input. Secondary hyperalgesia is believed to be a key outcome of activity-dependent central sensitization at spinal level, which is considered an important mechanism in the chronification of pain (Woolf, 2011). Showing that cognitive factors can actually modulate the behavioral correlates of central sensitization makes these factors an interesting target for the treatment of chronic pain conditions that are at least in part due to such neuroplastic changes, and could even contribute substantially to our knowledge on how to prevent such chronification in the first place. By introducing a vibrotactile detection task that forces participants to focus attention towards one arm while inducing the sensitization process at both arms using bilateral and concomitant HFS, we show that the focus of spatial attention can modulate the strength of the induced secondary hyperalgesia, here evidenced by a larger increase in mechanical pinprick sensitivity at the attended arm as compared to the non-attended arm, 20 minutes after having applied HFS. Additionally, the extent of the area of secondary hyperalgesia along the medial-lateral axis was larger on the attended arm as compared to the non-attended arm.

Critically, the somatosensory stimuli delivered to the attended and non-attended arms were identical: both arms were exposed to intense nociceptive stimulation (HFS), and both arms were exposed to innocuous vibrotactile stimuli (with only a very small difference in the number of applied vibrotactile stimuli between the two arms). Therefore, the only factor that was manipulated during the induction of central sensitization at the two forearms was the focus of spatial attention, directed towards one of the two arms. In some participants, a stronger increase in pinprick sensitivity at the attended arm vs. the non-attended arm was already observed immediately after HFS (T1). However, a significant group-

level difference was observed only 20 minutes after the end of the sensitization procedure. This is in line with the results of previous studies having shown that the increase in pinprick sensitivity tends to build up after HFS, being maximal 20-40 minutes post-HFS (Klein et al., 2004; Pfau et al., 2011; van den Broeke et al., 2014; van den Broeke et al., 2016; van den Broeke & Mouraux, 2014a, 2014b).

That attention can modulate the perception of pain has been proposed by numerous studies (for a review see Van Damme et al., 2010). For example, pain can be perceived as less intense when participants perform a task that focuses attention away from the nociceptive stimulus (Honoré, Hénon, & Naveteur, 1995; Miron, Duncan, & Bushnell, 1989; Van Ryckeghem et al., 2011), especially if the distracting task is cognitively demanding (e.g. Buhle & Wager, 2010; Romero, Straube, Nitsch, Miltner, & Weiss, 2013, for a discussion see Legrain et al., 2009; Van Damme et al., 2010). Conversely, increases in perceived pain intensity can be observed when attention is directed towards pain (Miron et al., 1989; Quevedo & Coghill, 2007). Electrophysiological studies have shown that focusing attention towards nociceptive stimuli can selectively enhance the cortical activity elicited by these stimuli (Legrain et al., 2012), compatible with the "sensory gain control" hypothesis of selective attention (Hillyard, Vogel, & Luck, 1998; Legrain, Guérit, Bruyer, & Plaghki, 2002). These effects of attention on nociceptive processing have been interpreted as reflecting mechanisms that filter the activity of the cortical areas involved in the perceptual analysis of the nociceptive inputs (Legrain et al., 2012). In addition, neuroimaging studies (Torta, Legrain, Mouraux, & Valentini, 2017) have highlighted that some of the cortical and subcortical structures whose activity can be modulated by attention, are structures that are thought to participate in the descending pain modulation systems that can inhibit or facilitate nociceptive processing at the spinal level, such as the prefrontal cortex, the rostral anterior cingulate cortex and the periaqueductal gray (Bingel & Tracey, 2008; Tracey & Mantyh, 2007). That selective attention could modulate spinal nociceptive processing is further supported by the results of studies on the influence of attention on the nociceptive flexion reflex (RIII), a correlate of spinal nociceptive activity. Willer, Boureau, and Albe-Fessard (1979) demonstrated an inhibition of the nociceptive flexion reflex measured in the biceps femoris muscle and elicited by electrical stimulation

of the sural nerve when participants were engaged in mental subtraction. More recently, Ruscheweyh, Kreusch, Albers, Sommer, and Marziniak (2011) tested the effects of different distraction strategies on the RIII reflex and showed that the RIII reflex was reduced when participants were engaged in a distraction task involving innocuous tactile stimuli, whereas it was enhanced when participants focused their attention towards the painful RIII-eliciting stimulus (see also Bjerre et al., 2011, demonstrating a modulation of the area of the reflex receptive fields by attentional state). Sprenger et al. (2012) corroborated these findings using functional magnetic resonance imaging of the spinal cord. Specifically, they showed that a distraction task involving high cognitive load, as compared to a distraction task involving low cognitive load, leads to a greater reduction in the dorsal horn response to task-irrelevant thermal nociceptive stimuli, which furthermore was related to a reduction in pain ratings at individual level. These latter findings suggest that at least part of the effects of attention on the perception of pain could result from a top-down modulation of nociceptive processing at the spinal level.

Since the spinal dorsal horn has also been shown to be an important site for the development of central sensitization (Latremoliere & Woolf, 2009), we specifically tested whether selective spatial attention could affect the *induction* of central sensitization, and its after-effect, the development of a sustained secondary hyperalgesia. We demonstrate that selectively focusing attention on one of the arms *during* a 50 seconds procedure to induce sensitization at both forearms can induce significant differences in the development of secondary hyperalgesia between the attended and the non-attended arm, i.e. the strength and the extent of increased pinprick sensitivity in the area surrounding the conditioned skin. In this sense, our results suggest that, besides the well-known top-down effects of attention on perception, attentional processes can also affect other outcomes of sensory processing, such as the *induction* of activity-dependent central sensitization of the nociceptive system and, consequently, the development of secondary hyperalgesia. Whether this is due to a top-down effect of spatial attention on the induction of central sensitization at the level of the spinal cord, or whether it results from other interactions between attention and central sensitization at supraspinal level remains an open

question. It should however be noted that it is difficult to disentangle whether the focus of selective attention induced more secondary hyperalgesia on the attended arm, less secondary hyperalgesia on the non-attended arm, or both, as we did not include any control condition without attentional modulation.

Previous studies have already shown that experimentally-induced secondary hyperalgesia can be modulated by cognitive contextual factors (Matre et al., 2006; Salomons et al., 2014; van den Broeke et al., 2014). However, these studies manipulated expectations or beliefs about the painfulness of the conditioning stimulus and/or the change in sensitivity that would be induced by the sensitization procedure. van den Broeke et al. (2014), for example, instructed the participants that, after HFS, the skin would become more sensitive to pinprick stimulation. Even though expectations about the effects of HFS were manipulated before it was applied, we cannot fully exclude the possibility that similar results might be observed if the manipulation of expectations had been performed immediately after having applied HFS. Indeed, at least part of the increase in pinprick sensitivity induced by this manipulation of expectations could be due to an influence of cognition on the subjective evaluation of the pinprick test stimuli, rather than a direct influence on the mechanisms responsible for the induction of central sensitization. However, an argument against this interpretation is that the effect of expectations on pinprick sensitivity was significant 20 minutes after HFS, but not immediately after HFS, i.e. only once secondary hyperalgesia had fully developed.

In the present study we aimed to minimize this interpretational challenge, by assessing the effect of an attentional task that was completely pain-unrelated and, most importantly, did not deliberately create any expectations about the after-effects of the painful conditioning stimulation at the attended arm vs. the non-attended arm. While the task was expected to manipulate the focus of attention *during* the induction of secondary hyperalgesia, it is very unlikely that it would also lead to a spatial attention bias when the assessment of pinprick sensitivity was performed, especially at the second time point 20 minutes after the end of the attentional manipulation and HFS procedure, and

considering that participants were then asked to focus alternatively on the two forearms to perform the pinprick rating task. Nevertheless, and such as in van den Broeke et al. (2014), it was at this second time point that the difference in pinprick sensitivity between the two arms was significantly pronounced, whereas there was no significant difference between the two arms at the first time point. It seems highly improbable that spatial attention could bias the assessment of pinprick sensitivity 20 minutes after the end of the attentional manipulation, without modulating perception immediately after the attentional manipulation. Taken together, our results thus indicate that the focus of spatial attention can modulate the strength and extent of central sensitization *during* its induction.

One possible limitation of our study is that we had limited control on whether the participants performed the attention task correctly, i.e. whether they focused their attention exclusively on the attended arm. Although we applied exclusion criteria based on the performance of the vibrotactile detection task, and debriefed with the participants their behavior during the task, we cannot be entirely certain that the focus of attention was systematically directed towards the designated arm. Notably, although there was a significant group-level difference between the attended and the non-attended arm at T2, there was also some amount of interindividual variability, with some participants manifesting a strong difference between the attended and the non-attended arm and others showing little or no difference between the two arms. Furthermore, although intensities of stimulation for the HFS procedure were adapted to match the perceived intensities between both forearms, five participants reported a stronger experience of HFS on one of the two forearms. Since this was the non-attended arm in four of these five participants, this should not have contributed to the group-level finding of a stronger increase in pinprick sensitivity at the attended arm. Indeed, regardless of attention, one might expect a greater increase in pinprick sensitivity at the arm where HFS was perceived as more intense.

In conclusion, our results indicate that higher order brain processes such as those underlying selective spatial attention can shape the experimentally-induced development of secondary hyperalgesia

following exposure to intense peripheral nociceptive input. This suggests that the focus of attention can impact activity-dependent neuroplasticity, thus going beyond its modulatory effects on perception. In future studies it will be important to clarify whether this finding relies on a top-down effect on spinal sensitization, possibly through descending pain modulatory pathways, or on an interaction between attention and supraspinal mechanisms contributing to the increased pinprick sensitivity.

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Open practices

Materials and data for the study are available at https://osf.io/hnpfv/?view_only=f09f008565704ac99baa8aafff4dbd74

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