Spatial tuning in nociceptive processing is driven by attention

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Abstract

When the source of nociception expands across a body area, the experience of pain increases due to the spatial integration of nociceptive information. This well-established effect is called spatial summation of pain (SSp) and has been the subject of multiple investigations. Here, we used cold-induced SSp to investigate the effect of attention on the spatial tuning of nociceptive processing. Forty pain-free volunteers (N=40, 20 females) participated in this experiment. They took part in an SSp paradigm based on three hand immersions into cold water (5°C): Participants either immersed the ulnar segment ("a"), radial segment ("b") or both hand segments ("a+b") and provided overall pain ratings. In some trials based on "a+b" immersions, they were also asked to provide divided (i.e., first pain in "a" then in "b"; or reversed) and directed attention ratings (i.e., pain only in "a" or "b"). Results confirmed a clear SSp effect in which reported pain during immersions of "a" or "b" was less intense than pain during immersions of "a+b" ($p<0.001$). Data also confirmed that spatial tuning was altered. SSp was fully abolished when participants provided two ratings in a divided fashion ($p<0.001$). Furthermore, pain was significantly lower when attention was directed only to one segment ("a" OR "b") during "a+b" immersion ($p<0.001$). We conclude that spatial tuning is dynamically driven by attention as reflected in abolished SSp. Directed attention was sufficient to focus spatial tuning and abolish SSp. Results support the role of cognitive processes such as attention in spatial tuning.

Keywords: spatial summation, spatial tuning, pain, attentional modulation, cold pressor, receptive field, Traxler fading

1. INTRODUCTION

Pain is a complex experience that integrates spatial and temporal aspects of sensory processing. Temporal phenomena such as wind-up have been topics of intensive research. However, the spatial aspects of pain, such as localization[42], spread[41], and spatial summation[1], remain poorly understood and have important clinical meaning. For example, the spread of pain is related to disease duration[41], whereas the size of the painful area contributes to clinical pain intensity[47]. Spatial summation of pain (SSp) describes the phenomenon of increases in perceived pain while stimulating larger areas of the body and represents one of the best-established tests of spatial aspects of pain. Spatial summation occurs both within and between dermatomes[12,35], can occur over large distances (up to 7 dermatomes)[38], and is altered in chronic pain[15].

The phenomenon of SSp provides a useful tool to investigate spatial tuning of nociceptive processing – the dynamic regulation of spatial integration of nociceptive input. For instance, in the study by Quevedo & Coghill[37], participants were exposed to SSp, which used two separated thermal probes at 49°C to produce a moderate pain intensity level. Participants provided overall pain ratings, which spatially integrated nociceptive information from the two nociceptive foci or directed attention ratings, which were limited to just one of two simultaneously stimulated foci. Participants were also prompted to divide their attention by first providing a pain rating of one and to the other site. Dividing attention significantly abolished SSp[36,37]. This form of spatial tuning may result from a shrinkage and/or expansion of receptive fields (RF), such that SSp is reduced or enhanced, respectively. This hypothetical model is in line with i) observation that SSp is facilitated in chronic pain[15], ii) evidence that chronic pain is associated with RFs enlargement[3] and iii) physiological data showing that RFs are shifted under the influence of attention in awake animals[18].

To date, studies of attentionally mediated spatial tuning have only been conducted with noxious heat and in the context of discrete SSp – where spatially separated stimuli are used to evoke pain. The existence of spatial tuning across contiguous zones of pain remains unknown, but may be highly relevant to some types of clinical pain, such as complex regional pain syndrome (CRPS), where pain extends in a contiguous fashion[22]. Would contiguous pain be associated with overlapping distributions of activity in populations of nociceptive neurons and, hence, be impossible to regulate via spatial tuning? The primary aim of this experiment was to test whether spatial tuning is present even though the attention is divided between different zones of the contiguous area stimulated with noxious cold. A secondary aim was to test if attentionally-driven spatial tuning can be reproduced with noxious cold instead of heat. Lastly, we employed directed-

attention ratings to test if attention directed only at a smaller zone of the painful area leads to systematic underestimation of reported pain.

2. METHODS

The study used a within-subject repeated-measurement design. Healthy, pain-free participants underwent multiple CPT in which they immersed their hand into cold water. The study aimed to assess spatial tuning previously investigated in the context of discrete SSp[37]. Data was collected in a single session (~1.5h duration). Every participant who started the first trial completed the entire experiment. The study procedures were positively approved by the local Bioethical Committee at the Academy of Physical Education in Katowice (1-2021/02-25-2021), and the protocol of the experiment was preregistered in the Open Science Framework using the AsPredicted.org template (https://osf.io/cdwra). The experiment took place in the Laboratory of Pain Research (ISO certified 9001:2015).

2.1. Participants

Forty participants with an average age of 27.2 years (± 11.3) took part in the experiment (20 females). Only healthy participants between 19 and 65 years old were included. Participants were excluded if they suffered from chronic (pain lasting >3 months) or acute pain on the study date, took drugs or medications, were diagnosed with a disease related to cold temperature intolerance (e.g., Raynaud syndrome, cryoglobulinemia, cold urticaria, etc.), had experienced in the past a pathological reaction to cold temperature (e.g., excessive edema or redness, blisters, etc.), had a chronic cardiovascular or neurological disease. Recruitment was continued until 40 participants had completed the experiment. Six additional individuals were screened but not included because of not meeting all criteria.

2.2. Sample size

This study is considered novel as no previous data on attentionally-driven spatial tuning exists in contiguous SSp with noxious cold as a pain model. The relevant effect size from this study was extracted (Cohen's d_z = 0.62) from a previous study that used discrete SSp[37] and reflected the statistical *t* contrast between pain obtained through divided attention ratings vs. overall ratings **(Appendix 1)**. Sample size calculations were performed using the G*Power software[13] and showed that N = 23 was needed to detect the effect with 80% power ($\alpha = 0.05_{2\text{-tailed}}$). Because the trial presented here differs from the study used to calculate statistical power[37], the sample size was nearly doubled to prevent underpowering a potentially smaller effect. A sample of 40 also protects against small group effects that fail to reproduce[6].

2.3. Equipment for CPT

To induce pain, the CPT was employed[26,51]. For this task, participants immersed their dominant hand (or its part) in a circulating cold-water bath UTE-24BB (LaboPlay, Bytom, PL). A fixed temperature of 5°C was maintained by the electronic thermostat of the device as this temperature has been shown to produce moderate pain[26] in CPT and robust SSp. Pain intensity was rated using the Verbal Rating Scale used previously[46] which ranges from 0 (no pain at all) to 100 (worst pain imaginable). Participants were instructed that they could provide any number within the 0-100 interval. Skin temperature of the hand was measured before each immersion using a non-contact infrared thermometer (LX-26, ThermoFlash®, Visiomed, FR) to control for confounding effects resulting from variability in skin temperature recovery between immersions.

2.4. Experimental design

Upon arrival at the laboratory and after providing informed consent, participants were screened for a set of inclusion and exclusion criteria. They received an explanation that they would undergo multiple repetitions of 7 different trials (immersions) using CPT. Participants' hands were divided into two segments: radial (referred to as a segment "a") and ulnar (referred to as a segment "b", see **Figure 1**). To delineate sections of the hand, an ink-based black line was drawn on the subjects' hand, starting from the tip of the middle finger up to the distal crease of the wrist. The size of the hand was measured using centimeter tape (length, width, circumference). Following the preparation and anthropometric measures, participants took part in a training session, in which they familiarized themself with the water environment, and most importantly, they were trained on how to perform different types of immersions by pronating and supinating their forearm and how to provide varied form of pain ratings, i.e., divided attention, directed attention or overall pain ratings **(Figure 1)**. Cold pain threshold was measured (i.e., duration of immersion until the pain starts) as a part of the training session and after the main session. During the training session, each type of trial was presented one time (in total 7 trials/immersions), but participants were offered to practice more if needed. Immersions of 30s durations during the training session were separated by 30s breaks to reduce study time and thereby maximize the participants' attention. After training, a 10-minute break was followed by the experimental session. In the end of the sessions participants completed Pain Vigilance Awareness Questionnaire (PVAQ).

After the training session, participants took part in the main session divided into two blocks of 7 trials each. Trials were organized pseudo-randomly within each block. Each trial consisted of a 30s stimulation period (180s interval). Participants fixed their gaze on the middle point of the stimulated area and were prompted to provide pain ratings immediately before hand withdrawal. The following trials were employed **(see Figure 1)**: (1) immersion of two segments,

i.e., whole hand ("a+b") with overall pain rating, (2) immersion of segment "b" and overall rating, (3) immersion of segment "a" and overall rating, (4) immersion of both segments ("a+b") and attention directed at segment "a" and rating only from segment "a", (5) immersion of both segments ("a+b") and attention directed at segment "b" and rating only from segment "b", (6) immersion of segments "a+b" and divided attention such that first rating was provided from segment "a" then from "b", trial (7) was the same as a trial (6), but first rating from segment "b" was obtained and then from "a".

2.5. Statistical analysis

Descriptive statistics were reported as means or standard deviations (SD). The main analysis plan followed the one reported in the study protocol, i.e., first the repeated measures analysis of variance (ANOVA) was performed to test for the main effect of the factor "trial" (see above trials 1 to 7). Planned *t-test* comparisons were used to test effects related to SSp, divided attention, and directed attention **(Table 1)**. Because the skin temperature restorations can vary between individuals, and to rule out that this factor confounded our results, an additional analysis was performed using a Linear Mixed Model (LMM) with "block" (first, second) and "trial" (1 to 7) as within-subject factor and skin temperatures as a covariate. Also, Pearson product coefficients were used to perform exploratory analyses and test if the SSp effect (calculated as a ratio of pain in "a+b" to the mean of pain from smaller areas, i.e., "a" and "b") was associated with hand size, sensitivity (CPT, pain at baseline) and fear of pain. To test if baseline sensitivity drives spatial summation, SSp was correlated with mean pain ratings from trials 2 and 3. All statistical analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS Version 25, Armonk, NY, USA). Visual presentation of the data was performed using GraphPad Prism v.8.0.0 (GraphPad Software, San Diego, California, USA). The original α level was set at $p < 0.05$ and adjusted for multiple testing using Bonferroni correction. Effects sizes higher than 0.14 (η^2_p), and 0.8 (d_z) were interpreted as large[9].

3. RESULTS

Descriptive statistics for main and secondary variables are presented in **Table 2.** Forty participants (50% females) completed the experiment. As reported in **Table 2,** the average age of the sample was 27.20 years (± 11.30), body mass 71.57 kg (± 13.75), cold pain threshold 20.38 seconds (± 14.23), PVAQ 44.75 (± 7.15), and fear of pain level was 44.55 (± 21.60). Raw data supporting the results are presented in **Appendix 2**.

3.1. Primary analyses

Repeated-measures ANOVA showed a significant effect of the factor "trial", indicating that the type of trial influenced reported pain ($F_{[6,234]} = 8.52$, $p < 0.001$, $\eta^2_p = 0.18$).

Spatial summation (Contrasts 1 to 3). Paired student *t*-tests revealed that the intensity of pain was higher during the immersion of the whole hand ("a+b") compared to only immersing the radial ("a", M=9.23, 95% [CI: 6.08, 12.37], $t_{[39]} = 5.93$, $p < 0.001$, $d_z = 0.93$; Contrast 1) or ulnar ("b", M=9.18, 95% [CI: 5.74, 12.62], $t_{[39]} = 5.40$, $p < 0.001$, $d_z = 0.85$; Contrast 2) segments. No significant difference in pain intensity was found during immersion of the radial ("a") and ulnar ("b") segments individually (M=-0.05, 95% [CI: -3.21, 3.11], $t_{[39]} = 0.03$, $p = 0.98$, $d_z < 0.01$; Contrast 3). This set of comparisons confirmed that the SSp effect was able to be reproduced with noxious cold water in support of previous experiments[20,21] **(see Figure 2 and 4)**.

Divided attention (Contrasts 4 to 5). Attentional tuning was significant, as SSp was fully abolished when ratings were provided in a divided fashion. Overall pain ratings during the immersion of the whole hand ("a+b") were significantly higher compared to the same immersion but with divided ratings [i.e., "a|b" (M=7.56, 95% [CI: 5.30, 9.81], $t_{[39]} = 6.78$, $p < 0.001$, $d_z = 1.07$; *Contrast 1*) or "b|a" (M=7.74, 95% [CI: 5.15, 10.32], $t_{[39]} = 6.05$, $p < 0.001$, $d_z = 0.96$; *Contrast 2*)]. Exploratory comparison of directed versus divided attention ratings was not significant (M = 1.55, 95% [CI: -0.12, 3.23], $t_{[39]} = 1.88$, $p = 0.07$, $d_z = 0.27$). These comparisons provide support for attentionally-driven spatial tuning **(Figure 2)**.

*Directed attention (Contrasts 6 to 8). P*ain was perceived as less intense when attention was directed to only one segment ("a" or "b"). When the whole hand ("a+b") was immersed, pain ratings were less intense in trials with attention directed to only the radial ("a"; M = 5.20, 95% [CI: 2.71, 7.69], $t_{[39]} = 4.23$, $p < 0.001$, $d_z = 0.67$; Contrast 6) or ulnar ("b"; M=6.99, 95% [CI: 4.06, 9.92], $t_{[39]} = 4.82$, $p < 0.001$, $d_z = 0.76$; Contrast 7) segments compared to overall ratings of whole hand immersion ("a+b"). No significant difference in pain was found between attention directed to segment "b" or "a" (M = 1.79, 95% [CI: -2.47, 6.04], $t_{[39]} = 0.85$, $p = 0.40$, $d_z = 0.13$; Contrast 8) during whole hand immersion **(Figure 3)**. Furthermore, directed attention in full hand immersions ("a+b") led to similar pain level as in immersion involving only segment "a" (M = 4.03, 95% [CI: 1.06, 6.99], $t_{[39]} = 2.75$, $p = 0.01$, $d_z = 0.43$) or "b" (M = 2.19, 95% [CI: -1.32, 5.70], $t_{[39]} = 1.26$, $p = 0.22$, $d_z = 0.20$, see **Figure 3**).

3.2. Additional exploratory analyses

The LMM analysis with skin temperature as a covariate lead to similar results as the original ANOVA. In brief, main effect of "trial", remained statistically significant ($F_{[6,520]} = 9.42$, $p < 0.001$, $\eta^2_p = 0.10$), and neither factor "block" ($F_{[1,520]} = 1.08$, $p = 0.30$, $\eta^2_p = 0.03$) nor "trial" × "block" interaction ($F_{[6,520]} = 0.43$, $p = 0.86$, $\eta^2_p = 0.01$) was significant.

Contrasts corrected by skin temperature are reported in **Appendix 3**. Pain from each trial/immersion was tested for correlation with corresponding measurement of the skin temperature performed right prior to immersion. No significant correlation was found in any of the trials (r between 0.15 and 0.28, p between 0.08 and 0.48, see **Appendix 4**). The magnitude of spatial summation (ratio) was not correlated with cold pain threshold measured before (r = -0.02, p = 0.91) and after the study (r = 0.02, p = 0.93) and no correlation between SSp and the baseline pain sensitivity (pain in trials 2 and 3) was found (r = -0.30, p = 0.06). No significant relationship between SSp and fear of pain (r = 0.08, p = 0.64) or pain hypervigilance (PVAQ, r = 0.04, p = 0.83) was found. Anthropometric measurements of the hand such as hand width (r = 0.16, p = 0.32), length (r = 0.11, p = 0.51) and circumference (r < -0.01, p = 0.99) were not related to the magnitude of SSp. Sex differences in the magnitude of SSp (M=-0.09, 95% [CI: -0.33, 0.14], $t_{[38]}$ = -0.80, p = 0.43, d_z = 0.25) and experienced pain ratings (M=2.27, 95% [CI: -12.02, 16.57], $t_{[38]}$ = 0.32, p = 0.75, d_z = 0.10) were not found.

4. DISCUSSION

Spatial tuning in the nociceptive system has been the target of several investigations. However, the understanding of mechanisms by which nociceptive information is tuned within the neuroaxis remains incomplete. In the current study attention regulated the magnitude of contiguous SSp, which is in line with physiological data[4], previous findings observed in discrete SSp[36,37] as well as attentional RF shifts observed in the visual[10] and auditory systems[14]. The novel observations in our study were that nociceptive foci must not necessarily be spatially distinct for attention to abolish SSp, and that directed attention was sufficient to produce significant pain reductions of the same magnitude as divided attention. These observations were made with CPT, which extends previous observations from discrete SSp using noxious heat[36,37].

4.1. Spatial tuning during acute and chronic pain

At the computational level, spatial tuning reflects how afferent nociceptive information is filtered within the spatial domain. Spatial tuning can be broad and allow information to be collected from widespread body regions, or spatial tuning could be narrow to optimize extraction of information from very focal areas. The relatively broad spatial tuning can be responsible for enhanced SSp, whereas focused tuning might effectively hamper SSp such that pain summation is reduced[15], disproportionate[23], nonlinear[1], or in some circumstances, is even absent[1,39]. At a mechanistic level, tuning may be accomplished by a complex interaction between facilitatory and inhibitory processes that regulate receptive field (RF) sizes of nociceptive neurons within the central nervous system[4,8,37] leading to a determination of spatial attributes of perceived pain. For example, spatial tuning affects the perceived intensity of pain by amplifying and/or inhibiting afferent input based on how spatial information is integrated by excitatory and inhibitory filtering.

Previous studies showed that SSp, is amplified in patients with chronic osteoarthritic pain[15], and fibromyalgia[20] and that the discrimination of spatial features of pain may also reflect spatial tuning[27]. In that sense, discrimination may be poorer when spatial tuning is broad and stimulus features cannot be extracted. Although all available studies on chronic pain patients have been conducted using innocuous tactile stimuli, they provide evidence of disrupted spatial tuning[7]. For example, patients with CRPS[7], chronic low back[29] or neck pain[17] respond poorer with 2-point discrimination tasks. Moreover, more recent studies have confirmed that such a tuning disruption already occurs in the acute phase of pain[28] or even immediately following noxious stimulus application[2] and preliminary data shows that intervention directed at spatial retuning might be effective in pain reduction[30,31].

4.2. Contiguous spatial summation of pain

Contiguous SSp induced by cold stimulation was significant and robust (d_z = 0.85-0.93), comparable to reports on electrical[1], heat[23], pressure[16] as well as other studies on noxious cold stimulation[20,21,24,45,50]. Participants immersed either their ulnar or radial segment of the hand or the whole hand into cold water and provided overall pain ratings. Pain was greater when a larger area was stimulated; however, the increase in pain was disproportionate: doubling the stimulation area led to a pain increase of only 19.96%. This is in line with well-documented cases wherein pain produced by the immersion of the entire upper extremity did not double reported pain compared to stimulation of only the hand[23]. Interestingly, the individual differences in the magnitude of SSp **(Figure 4)** showed that in 12.5% of individuals, full hand immersion produced paradoxically less intense pain, which may be a manifestation of extreme spatial tuning, potentially driven by robust lateral inhibition[39].

4.3. Attentionally-driven spatial tuning

The role of attention in SSp has been examined previously with discrete SSp[4,11,36,37]. Pain intensity from two distinct nociceptive foci can be reduced when pain ratings are provided in a divided fashion[37]. In the study by Quevedo & Coghill, divided attention between 2 nociceptive foci (10 cm apart) abolished summation, which was explained by the reduction of neuronal output due to RF shrinkage. In addition, attention could disrupt the feeling of connectivity between two stimuli, previously shown to contribute to robust SSp[38]. In a study by Defrin et al.[11] two heat stimuli were applied with a separation of 30 cm. Participants directed their attention to only one stimulus, and as a result, the overall pain significantly dropped. Thus, directing attention can transform pro-nociceptive into an antinociceptive profile[11], but more importantly, such a transformation can occur when pain is limited to one body region. Indeed, in this current study, directed attention to just one segment of the hand abolished SSp, as reflected by a significant pain reduction. This

reduction can be considered large because when contrasted with pain from the immersion of only one segment, pain from directed attention was not significantly higher.

In some trials of the present study, participants were instructed to divide their attention between different zones of the same stimulated part of the body. Such a task is likely to be more complex to perform with contiguous stimuli, given the lack of non-stimulated space between nociceptive foci. Nevertheless, despite this difficulty, SSp was abolished in line with previous observations with discrete SSp[37]. An attentional switch between different zones could work as a distraction mechanism leading to pain reduction, however this is not the case as comparable pain reduction was observed in directed-attention conditions where subjects focused on either the ulnar or the radial side of the hand only.

In the previous experiment by Quevedo & Coghill, directed attention did not produce statistically significant pain reductions[37], but lower ratings in divided compared to directed attention ratings. In contrast, the current study showed that divided attention has a comparable effect on SSp abolishment as directed attention. Yet, the magnitude of the effect was slightly larger in the divided attention condition (d_z = 0.72 vs. 1.02). Thus, directing attention to a small part of the body can inhibit nociception from the surrounding tissue. Indeed, a robust lateral inhibition in the visual system leads to illusionary contrast (e.g. Mach bands) or even abolishment of perceived objects despite their reflection on retina cells[40]. Another relevant visual phenomenon is Troxler fading[48]. Here, presentation of a dot surrounded by shaded low-contrast object fades away after stable gaze fixation at a dot[25]. In the nociceptive system, focusing on the target zone of the painful area might “push” away peripheral zones and thus attenuate pain from surrounding areas.

4.4. Attentional regulation of spatial tuning

Current results provide indirect evidence for the dynamic regulation of RF sizes through attention. In the model proposed previously[37], total neuronal output was reduced in divided attention ratings because RFs were thought to shrink, in contrast to the condition of overall ratings where RFs were thought to enlarge. This is in line with experiments showing that reflex RFs are reduced when attention is directed to a stimulated site of the body compared to a distraction condition, e.g., the Stroop task[19]. The ultimate size of the RF is likely to be the result of the complex interaction between top-down and bottom-up processes starting from the activation of nociceptive neurons within the dorsal horn. Spinothalamic tract neurons were shown to be involved in a variety of spatial aspects of pain, such as its radiation[34] and summation[44]. At the supraspinal level ventral and dorsal nociceptive pathways contribute to the perception of different sensory features of pain[32]. The ventral pathway conveys information regarding the intensity of noxious stimuli from the primary (SI) and secondary sensory cortices (SII) to the insula and prefrontal cortex. In contrast, the dorsal sub-system is involved with

spatial aspects of pain and conveys information from the somatosensory cortices to the posterior parietal cortex (PPC) and right dorsolateral prefrontal cortex (DLPFC)[32]. Brain imaging studies have shown that the PPC and DLPFC are crucially involved in spatial discrimination of pain[33]. Although SSp with attentional effects has not yet been tested in terms of brain mechanisms, lesion studies confirmed that damage to the PPC can result in excessive pain, spread over large parts of the body[43], a further manifestation of spatial tuning broadening. In this context, PPC activation can contribute to the regulation of pain intensity encoding through spatial attention, within and between nociceptive foci. This regulation can have profound implications for treating chronic pain but may also be associated with confounds. The fact that directed attention to just a part of the painful region reduces its intensity implies caution when collecting pain ratings in clinical practice: A potential underestimation of pain by patients during a clinical presentation may be caused by selective attention only to the most painful zone of the whole painful region, thereby leading to under-treatment.

4.5. Decomposing pain through attention: clinical implications

One possible non-invasive treatment strategy employed to treat pain is distraction. Distraction involves shifting attention away from pain to another type of stimulation[4]. Although some evidence supports this technique in children[5], its clinical application to chronic pain populations in adults remains controversial[49]. It seems that physiologically, reflex RFs become enlarged following a distraction maneuver[19], whereas they shrink when attention is directed to painful stimulation[4]. Thus, engaging in pain-related attention, a task that can be potentially designed as a mixture of divided and directed attention ratings, may potentially reduce pain. Under this framework, the spatial distribution of pain in e.g., CRPS can be decomposed to smaller, less interconnected zones which, if carefully targeted with spatial attention, may be used to induce pain relief.

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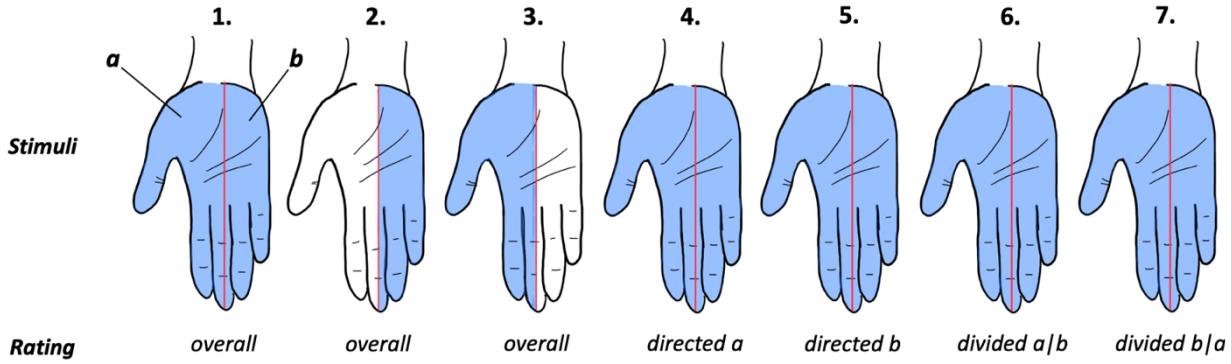

Figure 1. Spatial summation of pain paradigm. Segments of the hand exposed to noxious cold stimulation are presented in blue. The hand was divided into two equal segments (see trial 1), i.e., "a" (radial) and "b" (ulnar). The border dividing the hand into segments was marked on the skin. Participants immersed either two segments simultaneously ("a+b", trials: 1, 4-7) or just one of them ("a" or "b", trials 2-3). Overall pain ratings were obtained from both segments (1), only the ulnar (2) or radial (3) segment. Directed attention ratings were obtained from radial (4) and ulnar (5) segments. Divided attention ratings were obtained sequentially such that the first rating from "a" then "b" (trials 6) or in a reversed fashion (trial 7).

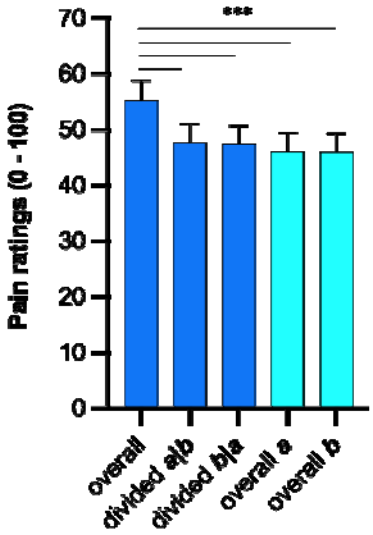

Figure 2. Spatial summation of pain was abolished in the divided attention condition. The horizontal axis includes experimental conditions and the type of stimuli is marked with colors: Cyan, immersions of segments "a" or "b" alone, blue, immersions of segments "a+b". A clear spatial summation effect was observed when contrasting pain from stimulation of 2 segments ("a+b") vs. just one segment ("a" or "b"). Note that the spatial summation was fully abolished when ratings were collected in a divided fashion, e.g., first "a" then "b" ("a|b" or reversed). Error bars refer to the standard error of the mean (SEM). $^{***}p < 0.001$.

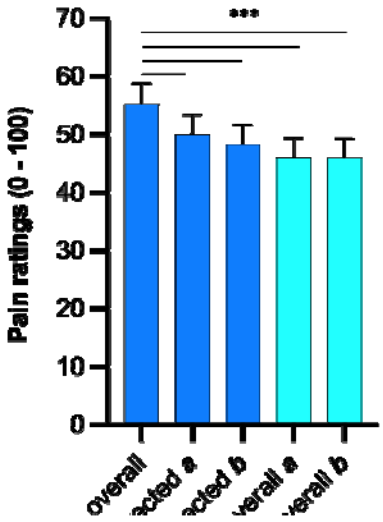

Figure 3. Directed attention diminished experienced pain intensity. The horizontal axis includes experimental conditions, and the type of stimuli is marked with colors: Cyan, immersions of segments "a" or "b" alone, blue, immersions of segments "a+b". Note that pain was significantly lowered when the two segments were immersed, and participants directed their attention only to one segment of the hand ("a" or "b"). Even though the stimulation area was doubled in these immersions, the pain did not significantly differ from ratings during immersion of only one segment. Error bars refer to the standard error of the mean (SEM). $^{***}p < 0.001$.

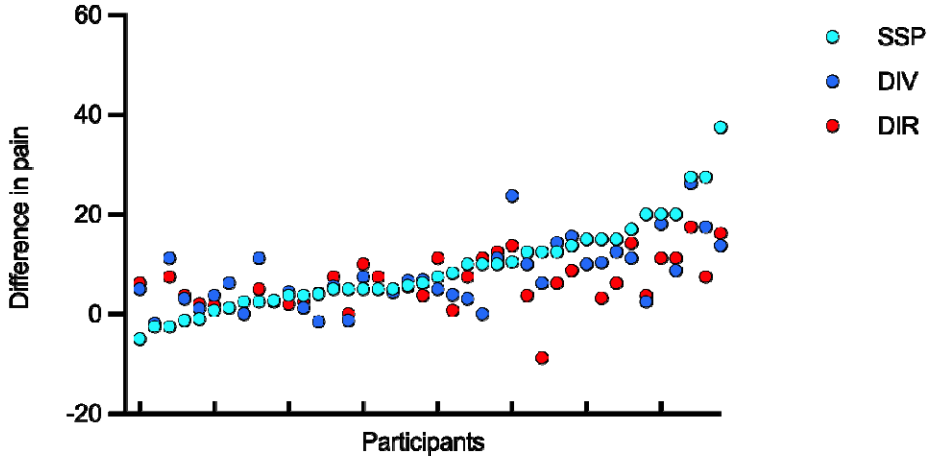

Figure 4. Individual differences of spatial summation (cyan) directed (red), and divided attention (blue) effects. Effects are presented as differences of pain in whole hand immersion (a+b) minus pain in just one segment (mean pain from the immersion of segments a and b). Note that 12.5% of participants (5/40) paradoxically reported less pain during stimulation of both segments of the hand compared to the immersion of just one segment.

Table 1. Main contrasts of interests for hypothesis testing

Hypothesis	Stimuli (immersion)	Rating	Contrast
SSp - more intense pain in stimulation if both segments	***a*** + ***b*** vs. ***a***	Overall (trial 1) vs. Overall (trial 3)	1*
	a + ***b*** vs. ***b***	Overall (trial 1) vs. Overall (trial 2)	2*
	a vs. ***b***	Overall (trial 3) vs. Overall (trial 2)	3
Divided attention - less intense pain in divided vs. overall ratings	***a*** + ***b*** vs. ***a*** + ***b***	Overall (trial 1) vs. Divided ***a*** | ***b*** (trial 6)	4*
	a + ***b*** vs. ***a*** + ***b***	Overall (trial 1) vs. Divided ***b*** | ***a*** (trial 7)	5*
Directed attention - less intense pain in directed vs. overall ratings	***a*** + ***b*** vs. ***a*** + ***b***	Overall (trial 1) vs. Directed at ***a*** (trial 4)	6*
	a + ***b*** vs. ***a*** + ***b***	Overall (trial 1) vs. Directed at ***b*** (trial 5)	7*
	a + ***b*** vs. ***a*** + ***b***	Directed at ***a*** (trial 4) vs. Directed at ***b*** (trial 5)	8
	a vs. ***a*** + ***b***	Overall (trial 3) vs. Directed at ***a*** (trial 4)	9
	b vs. ***a*** + ***b***	Overall (trial 2) vs. Directed at ***b*** (trial 5)	10

Letters in column "stimuli" refer to the immersed segments of the hand. Primary comparisons were marked with*. The remaining (unmarked) comparisons served as additional control tests.

Table 2. Descriptive statistics

Variable	Mean	SD
Participant characteristics		
Age [years]	27.20	11.30
Body mass [kg]	71.57	13.75
Height [cm]	174.05	9.16
Hand length [cm]	19.31	1.59
Hand width [cm]	8.98	0.99
Hand circumference [cm]	20.35	2.14
CPT		
Before the testing session [sec]	20.38	14.23
After the testing session [sec]	22.02	14.92
Psychological measures		
Fear of pain	44.55	21.60
PVAQ	47.75	7.15

Legend: PVAQ, Pain and Vigilance Awareness Questionnaire, CPT, Cold Pain Threshold, fear of pain was measured on 0 – 100 scale.

Appendix 1. Extracted data used for sample size calculation*

Condition	Value extracted	Extracted	SEM	Mean	N	$N^{(0.5)}$	SD
divided / distal	Mean	2.733					
divided / distal	SEM	3.317	0.583	2.733	15	3.873	2.259
overall / distal	Mean	4.200					
overall / distal	SEM	4.850	0.650	4.200	15	3.873	2.517
divided / proximal	Mean	3.033					
divided / proximal	SEM	3.600	0.567	3.033	15	3.873	2.195
overall / proximal	Mean	4.217					
overall / proximal	SEM	4.867	0.650	4.217	15	3.873	2.517
Mean overall	-	-	-	**4.208**	-	-	**2.517**
Mean divided	-	-	-	**2.883**	-	-	**2.227**

***Sample size** calculation was made using G*power for the following comparison: overall pain ratings vs. divided attention pain ratings. Relevant data were extracted from Figure 2 of the study by Quevedo & Coghill (2007). Extraction was made using WebPlotDigitizer. Standard errors were converted to SD using the formula. In red means and standard deviations used ins sample size calculation.

Appendix 3. Contrasts from Linear Mixed Model with temperature as a covariate

Trial	CONTRASTS									
	I^{***}	II^{***}	$III^{0.97}$	IV^{***}	V^{***}	$VI^{0.23}$	VII^{***}	VIII^{***}	$IX^{0.007/ns}$	$X^{0.138}$
1) a+b overall	**+1**	**+1**	0	**+1**	**+1**	0	**+1**	**+1**	0	0
2) b overall	**-1**	0	**+1**	0	0	0	0	0	**+1**	0
3) a overall	0	**-1**	**-1**	0	0	0	0	0	0	**+1**
4) a+b directed a	0	0	0	**-1**	0	**+1**	0	0	**-1**	0
5) a+b directed b	0	0	0	0	**-1**	**-1**	0	0	0	**-1**
6) a+b divided a|b	0	0	0	0	0	0	**-1**	0	0	0
7) a+b divided b|a	0	0	0	0	0	0	0	**-1**	0	0

Legend: Note that the ***p*** value has been marked in the upper index of each contrast (from I to X). *** indicate ***p*** < 0.001, ns indicates p value >0.05 after Bonferroni Correction. Letters in the first column depict the immersed area of the hand (a, b or a+b).

Appendix 4. Correlations with skin temperatures

Trial	*R* coefficient	*p*	*N*	Pain		Temperature	
				Mean	SD	Mean	SD
1) a+b overall	0.17	0.28	40	55.26	22.06	32.95	1.66
2) a overall	0.17	0.29	40	46.04	21.28	32.96	1.75
3) b overall	0.15	0.34	40	46.09	21.08	32.39	1.62
4) a+b directed a	0.28	0.08	40	50.06	21.07	32.96	1.71
5) a+b directed b	0.20	0.23	40	48.27	21.81	32.93	1.95
6) a+b divided a|b	0.12	0.48	40	47.71	21.10	32.50	1.91
7) a+b divided b|a	0.13	0.43	40	47.53	20.37	32.80	1.84

Legend: stimulated segment is marked outside parentheses, whereas rated segment(s) is inside parentheses. Pain was measured using 0-100 Verbal Ratings Scale.