Starting from Scratch

Exploring Attentional Bias Towards Itch

Jennifer Mareen Becker

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CHAPTER 1

General Introduction

Itch

Itch is a common somatosensory experience that initiates the urge to scratch. Evolutionarily, the purpose of the scratching response is twofold. On the one hand, scratching removes the itching object from the skin, e.g., an insect, to relieve an acute itch and on the other hand it starts an immune response to fight pathogens (Mack & Kim, 2018). This means itch serves a nocifensive function, i.e., it induces behaviours to react to a threat and protect bodily integrity (Paus et al., 2006). Opposite to these acute situations, several conditions are accompanied by prolonged itch, being defined as chronic itch if it lasts longer than six weeks (Matterne et al., 2013; Mollanazar et al., 2015; Silverberg et al., 2018). The lifetime prevalence of chronic itch is estimated to be about 22-25% (Matterne et al., 2011, 2013), and the incidence of common skin conditions in Europe, often accompanied by itching, is up to 30% (Richard et al., 2022). In chronic itch, the scratch response elicited by itch might no longer be adaptive. It does not relieve the itch in the long term and is even assumed to worsen many conditions by disrupting the skin barrier which causes an exaggerated immune response and (further) skin inflammation (Mack & Kim, 2018). As a consequence, chronic itch induces high emotional distress, amplifying the burden of chronic itch and significantly decreasing patients' quality of life (Dalgard et al., 2020; Reich et al., 2016; Silverberg et al., 2018).

Biopsychological models of itch recognise the multifaceted nature of the experience of itch. It has become clear that on top of the physiological characteristics of the itch and the underlying condition, there are also psychological determinants of itch which have a significant effect on the experience of itch (Verhoeven et al., 2008). These factors play an important role in the maintenance of itch symptoms and need to be taken into account during the treatment of itch (Evers et al., 2019; van Laarhoven et al., 2020). Hence, knowledge about the psychological factors and their working mechanisms is needed to develop comprehensive interventions. For instance, it has been shown that patients become especially vigilant to symptom-related information, which in turn might increase symptom perception (Andersen et al., 2018; van Laarhoven et al., 2013, 2020). This suggests that attention could be an important determinant of the sensation of itch.

Itch and Attention

Attracting attention is necessary for individuals to identify a threat in the environment, such as a potential source of itch, and only then can it serve its nocifensive function to induce adaptive behaviours accordingly (Mack & Kim, 2018; Paus et al., 2006). The phenomenon of contagious itch further supports the role of attention in itch (Evers et al., 2019; Schut et al., 2015; van Laarhoven et al., 2020). Contagious itch means that someone can feel itchy and the urge to scratch while for example, seeing someone else scratch or hearing someone talk about itch (Schut et al., 2015; Swithenbank et al., 2016). This phenomenon of contagious itch suggests that our attention is automatically drawn towards itch-related stimuli in our environment. This means conceptually that from all incoming information, this sound or view is selected by attentional processes to be further investigated and maybe even to elicit a behavioural response by starting to scratch ourselves. This would again serve the nocifensive function of itch. Therefore, it can be assumed that selective attention is highly relevant in itch because potentially threatening stimuli are preferentially attended to.

A prominent model of selective attention was formed by Michael Posner, who originally assumed that three components constitute selective attention: alerting, orienting and executive control (Petersen & Posner, 2012; Posner, 1980, 2016; Posner & Petersen, 1990). Alerting means that there is some form of arousal to be able to eventually engage with the world around us, i.e., someone is in an alert state. Thereafter, orienting occurs to select a certain stimulus which means that from all incoming sensory input, something is prioritised above all other possible input. This process starts preconsciously but to proceed to the next step, will reach conscious awareness to become available for further investigation and cognitive engagement, which is called executive control (Petersen & Posner, 2012). Lastly, our attention must be disengaged from any stimulus again, to free the capacity to eventually engage with the next stimulus. Integrating this model with the nocifensive function of itch, one could argue that itch attracts attention at an orienting stage, preconsciously and consciously, by prioritising itch-related stimuli above other stimuli in the environment. Likewise, it could be that attention is not easily disengaged from the itch-related stimuli, because of its relevance to protecting bodily integrity but due to that not freeing the capacity to engage with something else. Altogether, it can be assumed that itch-related information in our environment, which indicates a threat to our body, is selectively attended to. This is also called an attentional bias towards itch-related information.

Attentional bias

Research on this topic first focussed mainly on attentional bias towards general threat-related stimuli, specifically in anxiety disorders (Bar-Haim et al., 2007). It was proposed that while selectively attending to threat-related stimuli is generally adaptive, this might be facilitating the aetiology of anxiety disorders. Even though within the field, methodological concerns of attentional bias measurements were discussed (McNally, 2019), a recent meta-analysis focussing on eye-movement data still supports the relationship between attentional bias towards threat and anxiety (Clauss et al., 2022). While these studies used all different kinds of negatively valenced, potentially threatening stimuli, the question arose whether a similar process might be involved in somatosensory sensations. Somatosensory sensations, like itch or pain, serving their nocifensive function, might be processed as potentially threatening.

While in the field of pain, meta-analytical evidence emerged that individuals might show an attentional bias towards pain-related information (Crombez et al., 2013; Todd et al., 2018), research on attentional bias towards itch-related stimuli is very scarce so far. In a study that investigated the attentional processing of different types of stimuli, there were some indications of an attentional bias towards itch-related pictures (van Laarhoven et al., 2018). Results of attentional processing during somatosensory stimuli however did not support an attentional bias towards somatosensory itch (van Laarhoven et al., 2017, 2018). All in all, the evidence for or against an attentional bias towards itch remains too limited to draw conclusions yet. Nevertheless, pain shares its nocifensive function with itch, which makes it likely that attentional processing could be similar for both somatosensory sensations which warrant further investigation (Carstens, 2016; Schmelz, 2010; Ständer & Schmelz, 2006a).

Attentional Bias Modification

In addition to understanding how an attentional bias towards itch occurs in the first place, research is needed on the possible modifiability of attention towards itch. On the one hand, this opens up possibilities to modify attention towards itch in patient populations and relieve disease burden. As discussed so far, even though attentional bias research in itch is limited, we do see from patient-reported outcomes that attention plays a role (e.g., Silverberg et al., 2016) which should be further investigated. On the other hand, modifying the attentional processing of itch can add to our understanding of the mechanisms that are involved in attention to itch which in turn might also inform interventions in the future. The most commonly used paradigm to modify attentional biases is Attentional Bias Modification (ABM) training.

ABM training has so far been employed in the field of attentional bias towards threat and also specifically in pain (Bar-Haim, 2010; Mogg et al., 2017; Schoth et al., 2013; Todd et al., 2016). Early findings in the field of threat-related bias, had promising results for the effectiveness of ABM training in individuals with anxiety disorders, as well as in healthy individuals (Bar-Haim, 2010), but more recently also showed mixed results and is mostly focussed on patients with anxiety-related psychopathology (e.g., Hang et al., 2021; Mogg & Bradley, 2018; Rooney et al., 2024). Nevertheless, the original approach to ABM training was readily adopted in the field of pain but with less consistent findings. Most recent studies in patients with chronic pain showed inconsistent small effects (e.g., Carleton et al., 2020; Hasegawa et al., 2021). In healthy individuals, some studies showed an effect of ABM training, but this was also mostly not directly visible in attentional bias measurements, but instead in experimentally induced pain outcomes like pain threshold or intensity (e.g., Sharpe et al., 2012, 2015; Todd et al., 2016). ABM training has not yet been employed for itch but the abovementioned mixed evidence nevertheless calls upon more research. Even though, itch and pain share their nocifensive function, mechanisms might be similar and therefore, ABM training for itch still calls for further investigations.

Methodological considerations

Even though there are different assessment methods used to assess attentional processing, the most commonly used paradigm to assess selective attention towards a specific stimulus, i.e., attentional bias, is a dot-probe paradigm (Bar-Haim et al., 2007; Crombez et al., 2013). In such a computerised task, a stimulus pair containing a neutral stimulus and a stimulus of interest, i.e., threat-related stimulus, are presented simultaneously on the screen. Subsequently, the stimuli disappear and a target appears in one of the previously occupied locations. It is assumed that a faster reaction to targets in the same location as the threat-related stimulus (i.e., a congruent trial) compared to targets in the location of the neutral stimulus (i.e., incongruent trial) would indicate an attentional bias towards the threat-related stimulus. If attention is selectively directed towards this stimulus in the first place, re-directing towards the target in another location would need a longer reaction time.

An attentional dimension that can be manipulated in this task, is the stimulus display time which probably corresponds to different stages of attentional processing. While most often conscious orienting towards the stimuli is investigated with display times around 500ms, very short display times could also be employed to investigate preconscious processing. While this has not been researched a lot so far in attentional bias research towards pain (Asmundson et al., 2005; Keogh et al., 2003; Snider et al., 2000), different processing times show different effects, suggesting that differences in attentional bias occur based on display time (Crombez et al., 2013). Especially in itch, it seems reasonable that attention is captured extremely fast to ensure an adaptive behavioural response, such as scratching to remove an irritant (Sanders et al., 2019). Hence, preconscious processing of itch-related information should be studied in addition to conscious processing to shed light on the full attentional spectrum.

While most often, either words or pictures are used as stimulus materials, recently also a somatosensory variant of this task has been developed, the somatosensory attention task (van Laarhoven et al., 2017, 2018). In this task, a tonic somatosensory stimulus is applied by electrical stimulation, either on the left- or right arm while target lights are presented either congruent or incongruent to the stimulation side. Within the same line of reasoning as in the dot-probe paradigm, an attentional bias is assumed if responses to itch-congruent targets are faster compared to itch-incongruent targets. This holds the possibility of capturing the attentional processing of actual somatosensory stimuli in addition to the visual representations used in the dot-probe paradigm.

The current dissertation

Taken together, the involvement of attentional processing in itch is likely, due to its nocifensive function, but research on that topic is very scarce. Therefore the current dissertation aimed to investigate an attentional bias towards itch, either somatosensory itch or visual representations, at conscious and preconscious attentional processing stages. In the next step, ABM training, again conscious and preconscious, was studied in healthy individuals to further explore the mechanisms of attention to itch and the possibility of using such training as a treatment option in patients with chronic itch. The first study (*Chapter 2*) investigated an attentional bias towards visual representations of itch, pain and general negativity, e.g., rotten oranges, to elucidate possible differences in attentional bias towards itch specifically compared to another somatosensory-related stimulus (i.e., pain) or general negative stimuli. The second study (*Chapter 3*) followed up on these results by including electrical somatosensory itch and pain stimulation in addition to visual representations of itch and pain, i.e., the somatosensory attention task was used. While these studies, in line with earlier research, focused on conscious processing only, the next study (*Chapter 4*) adapted the visual paradigm to investigate the preconscious attentional processing of itch-related pictures. The remaining two studies then used an attentional bias modification training, based on the dot-probe task. This was again studied at a conscious processing stage (*Chapter 5*) and a preconscious processing stage (*Chapter 6*). Altogether, these studies add to our knowledge about the mechanisms underlying attention to itch and form a basis towards studying attentional processing in patients with chronic itch in the future.

CHAPTER 2

Attentional bias towards visual itch and pain stimuli in itch- and pain-free individuals?

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Abstract

Itch and pain are important attention-demanding sensations that allow adaptive responses to potential bodily harm. An attentional bias towards itch and pain stimuli, i.e. preferential attention allocation towards itch- and pain-related information, has been found in healthy, as well as patient groups. However, it remains unclear if attentional bias for itch and pain differs from a general bias towards negative information. Therefore, this study investigated attentional bias towards itch and pain in 70 itch- and pain-free individuals. In an attention task, itch- and pain-related stimuli, as well as negative stimuli were presented alongside neutral stimuli. Results did not indicate an attentional bias towards itch-, pain-, and negative visual information. This finding suggests that people without itch and pain symptoms do not prioritize itch- and pain-related information above neutral information. Future research should investigate whether attention towards itch- and pain-related information might be biased in patients with chronic itch and pain.

Introduction

People allocate their attention preferentially to negative stimuli (e.g. an angry face or a picture of a snake) to protect themselves from potential harm: an attentional bias (AB) towards these stimuli can occur (Bar-Haim et al., 2007). Accordingly, acute itch and pain have a nocifensive function (Paus et al., 2006), i.e. they signal possible negative consequences (e.g. disease or injuries) and enable us to adapt our behaviour to prevent bodily harm. The assumption that itch demands attention is supported by studies on contagious itch which show that people scratch themselves after seeing or hearing someone else scratching (Schut et al., 2015). Moreover, recent studies showed that healthy people show an AB towards itch (van Laarhoven et al., 2016a, 2018). In pain research, studies have also supported that people show a small AB for pain, especially people who are suffering from chronic pain, but not all studies could support that (Crombez et al., 2013; Todd et al., 2018; Van Ryckeghem & Crombez, 2018). Still, the similarities in psychophysiology between itch and pain may imply similar exaggeration of an AB in chronic itch (Evers et al., 2019; Ständer & Schmelz, 2006).

Concerning the underlying mechanism of an AB towards itch and pain, it is unclear whether itch and pain demand attention only because of their negative valence or because there is a distinct AB specifically towards itch- and pain-related information on top of a general bias towards negativity. Moreover, it is unknown which aspect of attentional processing might be biased in relation to itch and pain. A possible candidate might be inhibition of irrelevant information (Fan et al., 2002a; Petersen & Posner, 2012), because acute itch and pain can interrupt ongoing goal-directed behavior that is unrelated to itch and pain. Therefore, higher general ability of attentional inhibition might be related to less AB towards itch and pain, which is indeed suggested by some earlier studies (Basanovic et al., 2017; Mazidi et al., 2019). Besides, there are other characteristics that may explain individual differences in AB towards itch and pain, like neuroticism and catastrophization that showed associations with itch and pain respectively, in some studies (Crombez et al., 2013; Mazidi et al., 2019; Schut et al., 2015; Van Damme, Crombez, & Eccleston, 2004).

Experimental methods to assess AB towards itch and pain, have made use of different stimulus materials, but to our knowledge, there is no consensus yet about which material works best (Crombez et al., 2013; van Laarhoven et al., 2018). From an evolutionary perspective, visual itch and pain cues can enable protective behavior by signalling threat. Therefore, visual materials, like words or pictures, are a representative choice that have been most frequently applied and seem to be most ecologically valid, except for the somatosensory perception itself (Crombez et al., 2013; van Laarhoven et al., 2018).

All in all, to the best of our knowledge, AB towards itch, pain and negative information has not yet been investigated within one healthy sample despite many similarities in psychophysiology and protective function (Ständer & Schmelz, 2006). Therefore, the current study investigated AB towards itch- and pain- related printed words and pictures in itch- and pain-free individuals. Specifically, it was hypothesized that itch- and pain-related stimuli draw more attention as opposed to concurrently presented neutral stimuli. We also hypothesized a stronger AB towards itch and pain than towards solely negative stimuli. Furthermore, it was explored if more attention towards itch- and pain-related stimuli is related to general attentional inhibition and self-reported individual characteristics, e.g. pain catastrophizing and attention towards bodily sensations.

Materials and Methods

Participants

The sample consisted of 70 itch- and pain-free volunteers. Power calculations using a power of 0.90 and an alpha of 0.05 yielded a targeted sample size of 63 plus 10% possible data loss, based on a previous study using a similar behavioral attention task (i.e. dot-probe task) for itch that found a Cohen's d of 0.45 (van Laarhoven et al., 2018).

Participants had to be between 18 and 30 years old and fluent in the Dutch language. Exclusion criteria for participants were: current itch or pain levels > 3 on a scale from 0 ('no itch/pain') to 10 ('worst imaginable itch/pain'), diagnosis of any chronic pain condition (e.g. rheumatoid arthritis), chronic itch condition (e.g. eczema) or psychiatric disorder (e.g. major depression, AD(H)D). Participants were recruited through the Leiden University Research Participation system (SONA Systems Ltd., Tallinn, Estonia) and social media (e.g. Facebook), and all participants provided written informed consent. The local ethical review committee of the institute of Psychology of Leiden University approved the study (CEP16-1223/390).

Procedure

Written information about the study was sent to potential participants in which participants were informed that the aim of the study was to investigate people's responses to visual itch- and pain-stimuli. Potential participants were screened via the online system Qualtrics (Provo, Utah, USA). Screening consisted of questions about demographics, psychiatric diagnoses and chronic itch and pain, as well as visual analogue scales on itch, pain and fatigue. A battery of self-report questionnaires was also included. Eligible participants were invited to the lab at the Faculty of Social and Behavioral Sciences at Leiden University for a testing session of approximately 50 minutes. Participants were instructed neither to take medication and drugs, nor more than 4 glasses of alcohol <24 hours before the test session, nor to consume any foods or drinks containing caffeine <1 hour before the test session. After a brief explanation of the procedures and check of in- and exclusion criteria, informed consent forms were signed. Participants indicated current levels of itch, pain and fatigue and thereafter a questionnaire on psychological distress was filled in. During all tasks, participants were positioned in front of the computer monitor with their heads in a chin rest throughout testing (distance ca. 50cm). Participants then started with an attentional inhibition task, followed by two tasks that assessed attentional bias towards itch, pain and negative stimuli. The order of the two attentional bias tasks was randomized, stratified by gender (www.randomization.com). Instructions were presented on the screen before the start of each task and summarized orally by the experimenter. After performance of all tasks, participants rated the applicability to itch and pain of a selection of the stimuli. Lastly, participants were debriefed and received monetary reimbursement or instead received research participations credits (as part of Leiden University's undergraduate program).

Attention Tasks

All tasks were designed and administered using E-Prime 2.0 with Microsoft Windows 7 and a Philips Brilliance 220B TFT screen (Resolution 1280 x 1024, 60 Hertz). Custom-made finger buttons (Pushbutton Switch, SPDT, Off-(On)) were connected to a Serial Response Box at a fixed position on the table to collect participants' responses (Psychology Software Tools, Inc., Sharpsburg, PA, USA).

Dot-Probe Tasks

Two dot-probe tasks were administered to measure attentional bias for itch- and pain-related words and pictures (Crombez et al., 2013; van Laarhoven et al., 2017). In these tasks, participants were instructed to respond to the orientation of two small dots appearing after the presentation of a word pair (i.e. dot-probe task with words) or after the presentation of a picture pair (i.e. dot-probe task with pictures).

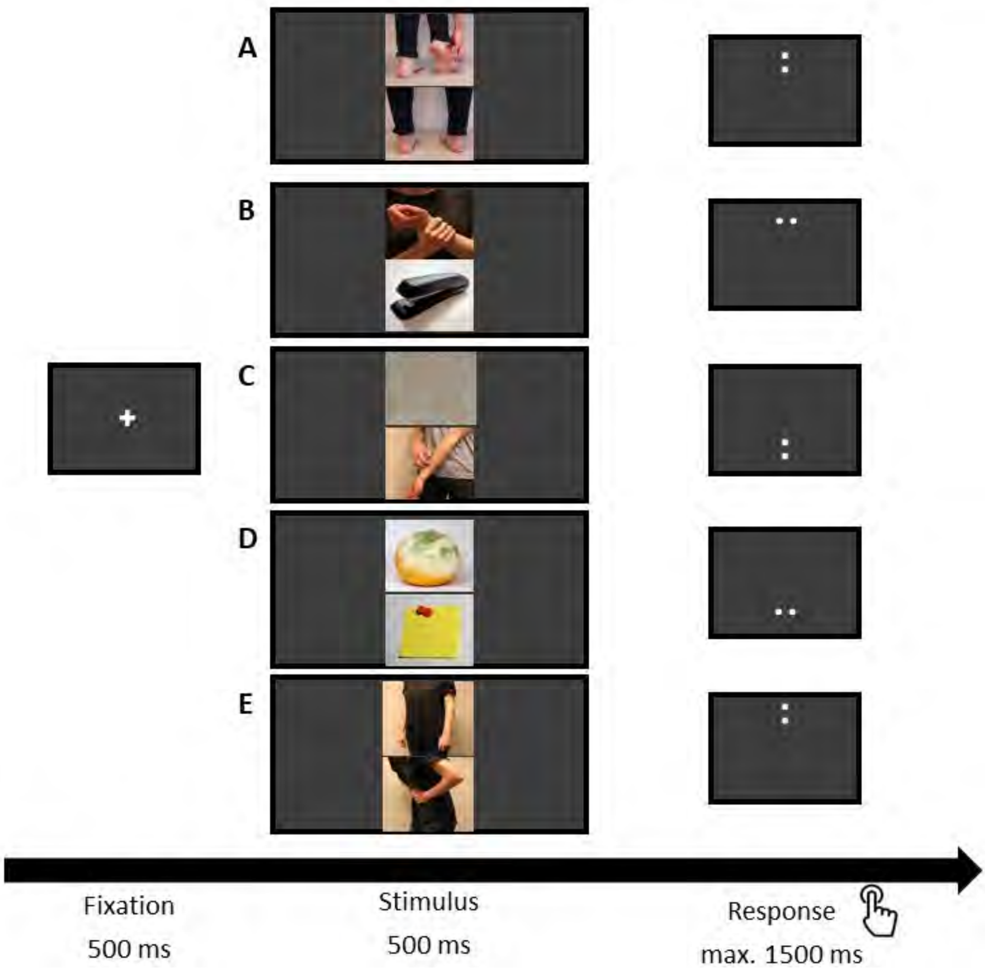
Attentional bias is defined as faster reaction times on trials when the dots appear at the location of the nocifensive (itch, pain or negative) stimuli (i.e. congruent trial) than at the location of the neutral stimuli (i.e. incongruent trial).

For the dot-probe task with pictures, 20 itch- and 20 pain-picture pairs consisted of respectively one itch- and pain-related image paired with one neutral image, half of these depicting either skin or objects (e.g. coffee mug). Itch-related images showed hands scratching the skin of various body parts (e.g. neck, back, legs). Pain-related images depicted hands putting pressure on the skin of various body parts or supporting joints. Neutral skin images featured the same body parts without any hands. In all these images, it was made sure that the skin was free of marks that could be related to pain or itch (e.g. red spots, bruises, cuts). The hands in the images were positioned on top of bare skin or on clothes without bright colors or patterns. Ten negative picture pairs consisted of a negative image (e.g. garbage, skull) and a neutral object image. Pictures were matched in color and brightness as much as possible. All pictures were 256px by 256px and displayed on a black background.

For the dot-probe task with words, 20 itch-, 19 pain- (one pair was used twice by accident), and 10 negative (i.e. affective) words were paired with neutral words. The affective words were somatosensory pain words (e.g. throbbing), associative pain words (e.g. infection), somatosensory itch words (e.g. itching), associative itch words (e.g. eczema), and negative words (e.g. bomb). Neutral words (e.g. clock, pillow) were matched in length and syllabi to the nocifensive words, as well as on word type (adjectives or nouns). Stimulus words were presented in bold white lowercase letters (Courier New font, size of 26pt) on a black background.

Each trial started with the appearance of a central fixation cross for 500ms, followed by a stimulus pair presented above each other at the 20% and 80% (height) position on the screen with the fixation cross in between at 50%, all centered in the

Figure 1. One trial of the dot-probe task with pictures.



Note. Examples of each picture pair (A = itch – neutral skin; B = pain – neutral object; C = itch – neutral object; D = negative – neutral object; E = pain – neutral skin) and each of the 4 response windows are shown. Proportions of pictures to the screen were adjusted to enhance the visibility of the pictures.

middle of the screen (50% width). Stimulus pairs were displayed for 500ms, where after two dots appeared at the upper or lower stimulus location for a duration of max. 1500ms as response targets. These dots were either horizontally or vertically oriented and were equally likely to appear at the location of the neutral stimulus or the nocifensive stimulus. Hand side and dots orientation mapping was counterbalanced across participants. The stimulus pairs were presented in random order and each pair appeared four times, twice with the nocifensive stimulus on the top (bottom) of the screen and twice with the dots oriented horizontally (vertically). ***Figure 1*** displays one trial of the dot-probe task with pictures and shows examples of each picture pair. In order to reduce potential habituation effects to the itch-, pain- and negative stimuli, additional filler trials were included showing pairs of only neutral pictures (20 trials of neutral object pairs and 20 trials of neutral skin pairs) or neutral words (20 trials in total) (Van Ryckeghem, Crombez, Van Hulle et al., 2012). Both dot-probe tasks started with a practice phase of 16 trials including feedback on performance, followed by two first trials containing two neutral stimuli. The test phase consisted of 240 trials in the dot-probe task with pictures and 220 in the dot-probe task with words. Blocks of 40 trials were separated by breaks of 30 seconds. Each task took approximately 6 minutes to complete. Accuracy and reaction times (RTs) to respond to the orientation of the dots were recorded for each trial.

Validation of the Dot-Probe Stimulus Material

Based on a consensus on face-validity by four researchers, 50 pain-related images, 54 itch-related images, 118 neutral images of skin, 120 neutral images of objects, 36 negative images, 75 pain-related words, 66 itch-related words, 215 neutral words, and 55 negative words were preselected for validation.

These preselected words and pictures were subsequently rated in random order in an online questionnaire via Qualtrics by a sample of 28 individuals (9 males, 19 females, age range 25-67). The sample consisted of 6 health care professionals, 19 patients with chronic itch/pain and 3 people from the general population without chronic itch or pain. Participants were reimbursed by taking part in a lottery for a gift voucher (4x €25,-).

Based on these ratings, the whole validated set includes 40 itch-related images and 46 itch-related words, as well as 38 pain-related images and 45 pain-related words. Additionally, 108 neutral images of objects, 108 neutral images of human skin, and 110 neutral words were selected for the overall validated set. Lastly, 10 negative images and 11 negative words were included. A subset of this validated set was used in the current study. Ratings for the selected stimuli in the different stimulus categories, as well as more details on the validation ratings can be found in the Supplementary Material (***Table S1***).

Flanker task

The Flanker task was used to measure attentional inhibition of task-irrelevant information (Moore et al., 2012). Each trial started with the appearance of a fixation cross for a duration of 500ms after which a set of five numbers was shown. The number in the center was flanked either by the same stimuli in congruent trials (‘44444’ or ‘22222’) or by different stimuli in incongruent trials (‘44244’ or’ 22422’). The complete task consisted of eight practice trials and two blocks of 60 experimental trials with a self-determined break in between. Congruent and incongruent trials were presented randomly, but equally distributed across the two blocks. Participants were instructed to indicate as quickly as possible whether the number in the center was the number two or the number four. The task lasted approximately 5 minutes and accuracy and RTs to respond to the stimulus in the center were measured.

Questionnaires

All questionnaires were presented via the online system Qualtrics (Provo, Utah, USA).

Psychological distress was measured to confirm that all participants were healthy as was intended. This was measured with the Depression, Anxiety, and Stress Scale- short form (DASS-21; De Beurs et al., 2001). Cronbach α for the subscales depression, anxiety, and stress were respectively 0.78, 0.63, and 0.79. To assess individual characteristics that are possibly related to attentional bias the following questionnaires were used: Attentional disengagement from bodily sensation, i.e. itch, pain, and fatigue was assessed with three Likert scales ranging from 1 (not at all) to 5 (always). Attentional focus on bodily sensations was measured with the Body Vigilance Scale (BVS; Schmidt et al., 1997), Cronbach α = 0.71. Attentional focus on pain and itch was assessed with respectively the Pain Vigilance and Awareness Scale (PVAQ; McCracken et al., 1992), Cronbach α = 0.91, and the PVAQ adjusted for itch (PVAQ-I; van Laarhoven et al., 2018), Cronbach α = 0.89. Catastrophizing was assessed with the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995), Cronbach α = 0.92, and PCS-adjusted for itch (PCS-I; van Laarhoven et al., 2018), Cronbach α = 0.88. Cognitive intrusion was measured with the Experience of Cognitive Intrusion of Pain (ECIP;Attridge, Crombez et al., 2015) and the ECIP-adjusted for itch (ECIP-I; van Laarhoven et al., 2018), both Cronbach α = 0.96. Neuroticism was measured with the subscale Neuroticism of the Eysenck Personality Questionnaire – revised short form (Eysenck, 1991), Cronbach α = 0.77.

Lastly, a subset of stimuli (20 neutral skin-, 20 itch-, 20 pain- pictures and 20 itch- and 20 pain-words) was rated on a Likert scale ranging from –4 (applicable to intense pain) to 4 (applicable to intense itch) with 0 labeled as neutral. ***Table S2*** displays the minimum and maximum obtainable scores for each questionnaire.

Statistical analyses

Data of the attention tasks were extracted with E-DataAid (Psychology Software Tools, Inc., Sharpsburg, USA). For the dot-probe tasks, RTs > 150 were extracted and for the Flanker task RTs between 150ms and 1500ms. As accuracy rates of all participants were high and above 70%, all cases were included in the analyses (van Laarhoven et al., 2017; van Laarhoven et al., 2018). Statistical analyses were performed using SPSS 23 (IBM SPSS Statistics, Armonk, NY, USA). Data on RTs were normally distributed. One participant showed outlying RTs for the Flanker task, as well as for negative trials of the dot-probe task with words (step of 1,5 x Interquartile Range). Therefore, analyses were performed both including and excluding data of this participant. For the dot-probe task for words and the dot-probe task for pictures separately, differences in RTs on congruent and incongruent trials per stimulus type were investigated by means of a 3 (stimulus type: itch, pain, negative) x 2 (congruency: congruent vs. incongruent) repeated measures analysis of variance (RM-ANOVA) with both factors as within-subjects factors. Of interest was the main effect of congruency as well as the stimulus type by congruency interaction. For stimulus type, planned contrasts were defined to specifically assess responses on itch and pain vs. negative trials, as well as responses on itch vs. pain trials. For the Flanker task, RTs between congruent and incongruent trials were compared in a RM ANOVA with congruency (congruent vs. incongruent) as within-subjects factor.

Additional exploratory analyses were performed on the dot-probe task data by exploring whether RTs on the itch-neutral and pain-neutral stimulus pairs in the dot-probe task with pictures differed when the neutral image depicted skin or objects. A 2 (neutral picture type: skin vs. object) x 2 (congruency: congruent vs. incongruent) RM ANOVA was performed separately for itch- and pain- trials. Second, for the dot-probe task with words, differences in RTs between trials with associative and somatosensory words were explored by means of a 2 (word type: associative vs. sensory) x 2 (congruency: congruent vs. incongruent) RM ANOVA for the itch and pain trials separately.

Attentional bias (AB) indices were calculated using the following formula: $RT_{incongruent} - RT_{congruent}$ for each stimulus type for both dot-probe tasks (Todd et al., 2018; van Laarhoven et al., 2018). In the same way, a Flanker congruency index was calculated. A higher and positive AB index represents more attentional bias towards itch, pain or negative stimuli and a higher Flanker congruency index represents stronger attentional inhibition. Correlations between AB indices and the Flanker congruency index, as well as outcomes of self-report questionnaires were explored, to investigate whether attentional bias towards itch or pain is associated with attentional inhibition and individual characteristics (e.g. neuroticism, catastrophizing). An alpha of 0.05 was considered statistically significant for all statistical tests and for the results of the RM ANVOA generalized eta-squared was calculated as a measure of effect size (Lakens, 2013).

Results

The final sample of 70 participants consisted of 47 females/23 males and had a mean age of 21.9 years (standard deviation (*SD*) = 2.1), see ***Table S2*** for descriptive statistics of individual characteristics. As intended, the DASS-21 confirmed that participants were not substantially depressed, anxious or stressed before testing. In ***Table S3***, the itch and pain intensity ratings for the stimulus material of both dot-probe tasks are presented.

Dot-Probe Tasks

Similar average accuracy scores were obtained for the congruent and incongruent trials in both dot-probe tasks; 93% (*range* = 83% - 98%) for the dot-probe task with pictures and 92% (*range* = 78% - 99%) for the dot-probe task with words. Mean RTs per trial type of both dot-probe tasks are presented in ***Figure 2*** and in ***Table 1***.

Dot-Probe Task with Pictures

The main hypothesis of an attentional bias towards itch and pain could not be confirmed, as the stimulus type by congruency interaction was not significant, $F(2,138) = .306$, $p = .737$, $\eta_G^2 = .002$. Planned contrast showed no significant differences in RTs on congruent and incongruent trials between itch and pain trials in comparison to negative trials ($p > .05$). In addition, there were no differences in RTs on congruent and incongruent trials between itch and pain trials ($p > .05$). A tendency

Figure 2. Mean reaction times in milliseconds per trial type of the dot-probe tasks with pictures (A) and words (B). Error bars represent standard error of the mean (n = 70).

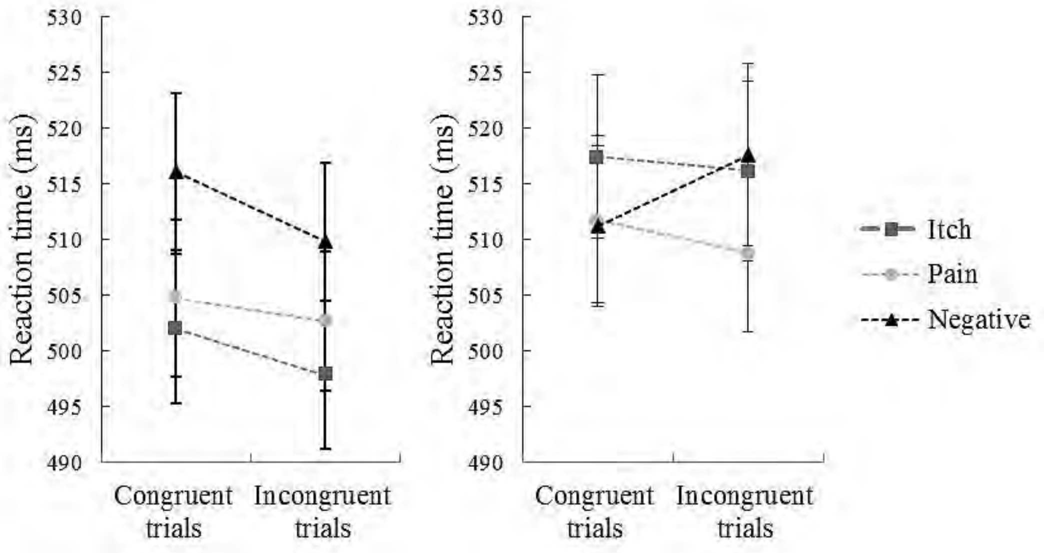


Table 1. Means and standard deviations of reaction times (RT) in milliseconds per trial type of the dot-probe tasks with pictures and words (n = 70).

	Dot-probe pictures		***Dot-probe words***	
	RT congruent	RT incongruent	RT congruent	RT incongruent
Itch trials	502.01 ± 56.15	497.83 ± 55.80	517.44 ± 61.09	516.13 ± 67.61
Pain trials	504.74 ± 58.95	502.68 ± 52.20	511.78 ± 62.94	508.76 ± 58.92
Negative trials	516.09 ± 58.84	509.83 ± 58.84	511.21 ± 60.50	517.59 ± 68.50

towards significance was observed for the main effect of congruency, $F(1,69)$ = 3.77, p = .056, η_G^2 = .011, with incongruent trials being faster than congruent trials. Furthermore, results showed a significant main effect of stimulus type, $F(2,138)$ = 12.94, $p < .001$, η_G^2 = .068. Planned contrasts indicated that participants responded overall significantly faster on itch and pain trials compared to negative trials ($p < .001$) but there was no significant difference in RTs between itch and pain trials ($p > .05$). Exclusion of the outlier did not change the significance levels of the results.

Dot-Probe Task with Words

There was no AB towards itch and pain words found; the interaction of stimulus type and congruency was not significant, $F(2,138) = 1.87$, $p = .158$, $\eta_G^2 = .011$. Planned contrast showed no significant results ($p > .05$). No significant difference was found between the congruent and incongruent trials, $F(1,69) = .13$, $p = .718$, $\eta_G^2 = .0003$. However, a significant main effect of stimulus type was found, $F(2,138) = 3.08$, $p = .049$, $\eta_G^2 = .019$. Planned contrasts showed faster overall RTs on pain trials compared to itch trials ($p < .05$) but no significant differences in responses on itch and pain trials compared to negative trials ($p > .05$). After exclusion of the outlier, the main effect of stimulus type was no longer significant, but a tendency towards significance remained $F(2,68) = 2.91$, $p = .058$, $\eta_G^2 = .019$.

Attentional Bias Indices

For the dot probe task with pictures, AB indices for itch, pain and negative pictures were on average -4.2 (*SD* = 24.2), -2.1 (*SD* = 27.6), and -6.3 (*SD* = 40.6), respectively. For the dot probe task with words, AB indices for itch, pain and negative words were on average respectively -1.3 (*SD* = 24.0), -3.0 (*SD* = 27.3), and 6.4 (*SD* = 36.1).

Exploration of Effect of Neutral Picture Types

For itch trials, no significant differences were found in RTs between trials with itch-skin and itch-object picture pairs, $F(1,69) = 2.21$, $p = .142$, $\eta_G^2 = .008$. Similarly, in pain trials no significant differences were found in RTs between trials with pain-skin and pain-object picture pairs, $F(1,69) = 0.46$, $p = .502$, $\eta_G^2 = .002$. Moreover, the interaction between neutral picture type (skin vs. object) and congruency (congruent vs. incongruent) was neither significant for itch trials, $F(1,69) = 0.91$, $p = .341$, $\eta_G^2 = .005$, nor for pain trials, $F(1,69) = 0.01$, $p = .943$, $\eta_G^2 = .00003$. Means and standard deviations for RTs on trials with skin versus object pictures can be found in Supplementary ***Table S4***.

Exploration of Effect of Word Types

Results neither indicated significant differences in RTs between trials with associative and sensory itch words, *F*(1,69) = 0.22, *p* = .640, η_G^2 = .0009, nor between trials with associative and sensory pain words, *F*(1,69) = 0.82, *p* = .370, η_G^2 = .006 Also, no significant interaction between congruency and word type was found in itch trials, *F*(1,69) = 1.21, *p* = .274, η_G^2 = .006, and in pain trials, *F*(1,69) = 0.54, *p* = .466, η_G^2 =.007. Supplementary ***Table S4*** presents means and standard deviations for RTs on trials with associative and sensory itch and pain words.

Flanker Task

On average, participants responded correct on 95.5% (*range* = 82% - 100%) of all trials of the Flanker task. Results showed a significant main effect of congruency, *F*(1,69) = 265.845, *p* < .001, η_G^2 = .111, indicating faster RTs on congruent (*M* = 411.76ms, *SD* = 59.79ms) compared to incongruent trials (*M* = 452.34ms, *SD* = 55.56ms). Exclusion of the outlier did not change significance of the results. The congruency index was on average 40.59 (*SD* = 20.83, *range* = -31.35 – 80.40).

Correlation between Attentional Bias Indices with Individual Characteristics

No significant correlations were observed between AB indices for itch and pain in the dot-probe tasks and outcomes of self-report questionnaires on individual characteristics. With regards to the correlation between AB indices and attentional inhibition there were also no significant correlations. See ***Table S5*** for the correlation matrix.

Discussion

The current study did not provide evidence for the presence of an attentional bias (AB) towards itch, pain and negative pictures and words in healthy participants. However, responses on trials with itch- and pain pictures were overall faster than on trials with negative pictures, suggesting that particularly general negative information, unrelated to itch or pain, slowed down attentional processing in the current sample. The results of the current study are in contrast with earlier findings demonstrating an AB towards visual itch cues in healthy individuals (van Laarhoven et al., 2016, 2018), and add to the evidence that there is no AB towards pain cues in healthy individuals as meta-analyses already suggested (Crombez et al., 2013; Todd et al., 2018).

Van Ryckeghem and Crombez (2018) suggest to approach AB from a motivational account of attention towards pain, which states that attention is only biased towards pain if pain is related to someone's current goals (Van Ryckeghem et al., 2019). Within their proposed framework, it seems reasonable that itch- and pain-free individuals show no AB towards stimuli that are unrelated to the task goal, i.e. the visual stimuli in the current design were not essential to focus on for good task performance. This does however not explain previous findings of AB to itch in healthy individuals using a similar design (van Laarhoven et al., 2018). Moreover, from a dysfunctional information processing account, it is suggested that visual material does not sufficiently activate pain schemas in healthy individuals, because seeing someone in pain usually does not induce pain in the viewer (although research has shown that pain can be vicarious i.e. people empathize with someone in pain (Fitzgibbon et al., 2010)), which could be an additional reason that people whose current goal is unrelated to pain, i.e. healthy individuals, show no AB towards pain (Van Ryckeghem & Crombez, 2018). However, this explanation does not apply to itch, because itch can elicit itch in the observer, i.e. itch is contagious (Schut et al., 2015; Swithenbank et al., 2016).

The absence of an AB towards itch-related, pain-related, and negative pictures in the current study might be related to the neutral skin and neutral object pictures. First of all, the neutral *skin* pictures depicted the same person in the same posture as in the itch- and pain pictures, but without a scratching or painful gesture (see ***Figure 1*** for examples of these picture pairs). It is possible that more effort is required to process and interpret a picture of a gesture, but this is not in line with findings showing that attention is more easily drawn to action-related vs static (i.e. a gesture vs. no gesture) pictures (Pratt et al., 2010). Furthermore, it might also be that object pictures draw more attention because they are easier to process and interpret than the more complex itch- and pain pictures. Altogether, these concerns cannot exclusively explain the current findings, because earlier studies on itch used comparable itch-related and neutral pictures and did show an AB towards itch in healthy volunteers (van Laarhoven et al., 2016, 2018). Moreover, the itch and pain stimuli (words and pictures) were rated rather low on itchiness and painfulness in the current study. Notably, using *intense itch* and *intense pain* as anchor points likely explains lower ratings than during the validation process (with anchors "How applicable is this stimulus to itch and pain").

Our results demonstrate no AB towards itch-related and pain-related words, and also not towards negative words. Words were often used in earlier research in AB towards itch and pain and these words were rather similar to our stimuli. Moreover, the neutral words were not different in aspects other than the relatedness to itch or pain (e.g., matched on length, word type). Because we know that itch is contagious when people talk about itch (Schut et al., 2015), we would assume that these kinds of words would draw attention towards their location. However, for pain, a previous meta-analysis has shown that only sensory pain words elicit an AB towards pain in healthy people, compared to affective and associative pain words, although there were only a few studies that included associative words (Crombez et al., 2013). This is in contrast to our results that could not support such a difference in AB towards sensory or associative words, neither for itch nor for pain. Nevertheless, the existing evidence at this point is too limited to draw definitive conclusions about potential differences in AB towards sensory or associative itch- and pain-words.

We generally found no associations between the measured individual characteristics, including attentional inhibition, and AB for itch, pain and negativity. This finding is mostly in line with earlier studies on itch and pain (Crombez et al., 2013; van Laarhoven et al., 2017; 2018), except for previous studies reporting significant associations between AB for pain and attentional inhibition and/or attentional control (Basanovic et al.,2017; Heathcote et al., 2015; Oosterman et al., 2010). Though, as healthy individuals in our study did not show an AB towards itch and pain in the first place, it is difficult to draw firm conclusions about their possible association with other characteristics.

Studies on AB towards itch and pain were so far not able to specify at which time point in attentional processing an AB might occur. Still, in recent meta-analyses, results suggest that different display times (e.g. 500-1000ms vs. >1000s) elicit an AB towards pain stimuli or not (Crombez et al., 2013; Todd et al., 2018). This suggest that display time of stimulus material is a key parameter to investigate in AB research. More research is needed to investigate early orienting of attention (e.g. presentations of 20ms) or later disengagement of attention (e.g. presentations of >1000ms).

In line with a motivational account (Van Ryckeghem & Crombez, 2018) as described above, it is important to note that people who are suffering from itch or pain for a prolonged time probably react differently to itch- and pain-related stimuli in their environment. This has indeed been shown in pain research (Crombez et al., 2013; Van Ryckeghem & Crombez, 2018), as well as in itch research (van Laarhoven et al., 2016). In patients, dealing with their itch- and pain-symptoms might become a goal on its own which can lead patients to focus even more on itch and pain. It appears reasonable then to assume that itch- and pain-related information is more relevant and more salient for patients who are daily confronted with and disrupted by these symptoms. Future research could, for instance, include priming for itch and pain to increase saliency and relevance in a healthy sample, although, research in patients is still desirable as well.

For further research, we propose that different stimulus material should be continued to be investigated. Also, other presentation times should be included (e.g. 20ms or >1000ms) and besides behavioral measurements, physiological measurements like eye-tracking and electro-encephalography (EEG) may be more sensitive to investigate the time course of attention allocation towards itch and pain, assuming that attention is indeed fluctuation during the presentation of a stimulus (Kappenman et al., 2014; Waechter et al., 2014). Although this study could not find any self-reported predictors of AB, future studies could examine other components of attention for example attentional control (Basanovic et al., 2017) to potentially shed more light on the mixed results of the different studies on AB done so far. Lastly, a more heterogeneous sample concerning gender, age and education level is desirable to enhance generalizability to the broader population.

In conclusion, the current study could not support the presence of an AB towards representations of itch and pain in itch- and pain-free individuals. Nonetheless, this study leads to future directions to further elucidate the different components of attention allocation towards itch- and pain-related visual cues in healthy individuals and, most importantly, recommends future research on AB in patient groups.

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Detailed Information on Validation of Dot-Probe Task Material

For the dot-probe task with pictures, hundreds of pain-related photos, itch-related photos and neutral skin photos were taken by the research team. In addition, neutral images and negative copyright free images were taken from the internet with the International Affective Picture System (IAPS) as reference in mind (Lang et al., 1997). The authors decided to not use the IAPS pictures as the negative pictures of this set are moderately to highly aversive and rather old-fashioned in their content and quality (e.g. blurry). Furthermore pictures are from a limited range of categories (e.g. wild and dangerous animals) which did not fit our purposes well. Therefore, new mildly aversive pictures were selected that healthy people could easily relate to (e.g. dirty trash bin) to match the itch- and pain-related material that was used best.

Itch- and pain- related and neutral words were derived from different questionnaires (e.g. McGill Pain Questionnaire (van der Kloot et al., 1995), Eppendorf Itch Questionnaire (Darsow et al., 1997)), previous attention tasks (Asmundson et al., 2005; Keogh et al., 2001), and by brainstorming. Only somatosensory (e.g. itching, stiff) and associative (e.g. lice, migraine) itch and pain words were included in the selection. Words that had an affective component (e.g. unbearable, tiring) were excluded, because they were often ambiguous in their applicability to itch and pain. The valence of each word and picture was rated on a scale ranging from -5 (very negative) to +5 (very positive), and on applicability to itch and pain, both scales ranging from 1 (not applicable) to 5 (very applicable).

The resulting set of itch- and pain-related words and pictures has been rated moderately on valence and high on applicability to itch (pain) for the itch (pain) stimuli. The resulting set of neutral pictures and words on the other hand, has been rated close to 0 on the valence scale and had a low rating on applicability to both itch and pain. The resulting set of negative words and pictures has been rated low on applicability to itch and pain and moderately on negativity.

Table S1. Means ± standard deviations of the ratings for applicability to itch and pain and affectivity for the used stimulus material per category as validated in a separate sample ($n = 28$).

	# Stimuli	**Applicability to itch**	**Applicability to pain**	**Affectivity**
Neutral skin pictures	19	1.1 ± 0.1	1.1 ± 0.1	0.0 ± 0.2
Neutral object pictures	30	1.1 ± 0.1	1.0 ± 0.1	0.2 ± 0.2
Itch pictures	20	**2.8 ± 0.1**	1.4 ± 0.1	-1.2 ± 0.1
Pain pictures	19	1.2 ± 0.1	**2.7 ± 0.3**	-1.5 ± 0.3
Negative pictures	10	1.1 ± 0.1	1.3 ± 0.2	**-1.8 ± 0.4**
Neutral words	50	1.0 ± 0.0	1.0 ± 0.1	0.2 ± 0.2
Sensory itch words	10	**2.8 ± 0.6**	1.4 ± 0.1	-0.9 ± 0.6
Associative itch words	10	**2.9 ± 0.3**	1.5 ± 0.1	-1.9 ± 0.4
Sensory pain words	10	1.1 ± 0.1	**2.5 ± 0.5**	-1.6 ± 0.3
Associative pain words	10	1.2 ± 0.3	**3.1 ± 0.4**	-2.1 ± 0.4
Negative words	10	1.1 ± 0.1	1.3 ± 0.2	**-1.7 ± 0.4**

Note. All stimuli rated on Likert-scales. Affectivity rated from -5 (very negative) to +5 (very positive). Applicability to itch and pain both rated from 1 (not applicable) to 5 (very applicable). Corresponding variable of interest for each stimulus category is printed in bold type.

Table S2. Self-report measures of individual characteristics (n = 70).

	Mean ± SD	***Median***	***IQR***	***Range (theoretical range)***
Age	21.9 ± 2.1	22.0	10.0	18-28 (18-30)
Attentional disengagement from				
Itch	3.8 ± 0.9	4.0	1.0	1-5 (1-5)
Pain	3.8 ± 0.9	4.0	1.0	1-5 (1-5)
Fatigue	4.2 ± 0.9	4.0	1.0	1-5 (1-5)
Attentional focus on bodily sensations				
Body vigilance (BVS)	3.3 ± 1.5	3.2	2.1	0.6-7.7 (0-10)
Itch vigilance and awareness [a] (PVAQ-I)	22.4 ± 11.6	21.0	16.8	0-50 (0-80)
Pain vigilance and awareness (PVAQ)	30.2 ± 12.6	31.0	21.0	6-59 (0-80)
Catastrophizing				
Itch catastrophizing (PCS-I)	8.4 ± 6.7	7.0	8.3	0-30 (0-52)
Pain catastrophizing (PCS)	13.1 ± 8.8	12.5	15.3	0-38 (0-52)
Cognitive intrusion				
Cognitive intrusion of Itch (ECIP-I)	6.4 ± 7.7	2.0	9.0	0-27 (0-60)
Cognitive intrusion of Pain (ECIP)	10.1 ± 9.6	8.0	16.3	0-32 (0-60)
Neuroticism (EPQ-RSS)	3.9 ± 2.8	4.0	4.3	0-10 (0-12)
Psychological distress (DASS-21)				
Depression	2.0 ± 0.3	1.0	2.3	0-12 (0-21)
Anxiety	1.8 ± 0.2	1.0	3.0	0-9 (0-21)
Stress	4.3 ± 0.8	3.0	4.3	0-13 (0-21)

Note. [a] n = 68. BVS= Body Vigilance Scale; PVAQ(-I) = Pain Vigilance and Awareness Questionnaire (-adjusted for itch); PCS(-I) = Pain Catastrophizing Scale (-adjusted for itch); ECIP(-I) = Experience of Cognitive Intrusions of Pain Scale (-adjusted for itch); EPQ-RSS-neuroticism = Neuroticism Scale of Eysenck Personality Questionnaire – revised short form; Measured on a scale from 1-6 instead of 0-6; DASS-21 = Depression, Anxiety, and Stress Scale- short form

Table S3. Mean ± *SD* for the stimulus material of the dot-probe tasks on a scale from –4 (intense pain) to 4 (intense itch) with 0 labelled as neutral as rated by the current sample (*n* = 70).

	Mean ± SD	***Range***
Neutral skin pictures	0.0 ± 0.1	-0. 3- 0.2
Itch pictures	1.4 ± 0.6	0.2 - 3.5
Pain pictures	-1.6 ± 0.8	-3.0 - 1.20
Itch words	1.6 ± 0.6	0.0-2.9
Pain words	-2.2 ± 0.7	-3.7 - 0.0

SD = Standard deviation

Table S4. Means and standard deviations of reaction times (RT) in milliseconds for Itch and Pain trials separately for the different stimulus categories. (*n* = 70).

	Itch trials		***Pain trials***	
	RT congruent trials	***RT incongruent trials***	***RT congruent trials***	***RT incongruent trials***
Sensory words	519.38 ± 514.57	514.57 ± 71.33	512.30 ± 60.37	511.81 ± 65.79
Associative words	515.67 ± 61.93	517.81 ± 69.85	511.18 ± 70.84	505.78 ± 56.87
Skin pictures	503.01 ± 56.39	501.91 ± 65.40	502.79 ± 60.68	499.71 ± 59.32
Object pictures	501.21 ± 62.03	493.69 ± 54.49	507.43 ± 63.29	505.46 ± 52.08

Table S5. Spearman Rho's correlations between attentional bias (AB) indices for itch and pain during the dot-probe tasks, the congruency index of the Flanker task, applicability to itch and pain ratings of the dot-probe stimuli, and outcomes of self-report questionnaires within the study sample (*n* = 70).

See table on next page.

	Dot-probe pictures		Dot-probe words	
	AB index itch	AB index pain	AB index itch	AB index pain
Dot probe pictures				
AB index itch	-	-	-	-
AB index pain	.072	-	-	-
AB index negative	.156	-.041	-.041	.007
Dot probe words				
AB index itch	.013	-.134	-	-
AB index pain	.084	-.106	-.024	-
AB index negative	.037	.038	-.164	-.026
Flanker index	.150	.002	-.158	.066
Applicability to itch and pain [a]				
Neutral skin pictures	.083	-.216	.170	-.017
Itch pictures	-.008	.111	-.046	-.227
Pain pictures	.085	-.109	.064	.281*
Itch words	-.050	-.035	.074	.132
Pain words	.003	-.070	-118	.006
Attentional disengagement from				
Itch	.074	.122	-.118	.025
Pain	.001	.043	-.111	.029
Fatigue	-.103	.032	.018	.030
Attentional focus on bodily sensations				
Body vigilance (BVS)	.096	.127	-.081	-.060
Itch vigilance and awareness (PVAQ-I)	.095	-.052	-.047	.102
Pain vigilance and awareness (PVAQ)	-.062	.075	.011	-.036
Catastrophizing				
Itch catastrophizing (PCS-I)	.043	.004	.022	-.179
Pain catastrophizing (PCS)	.050	.110	-.032	-.125
Cognitive intrusion				
Cognitive intrusion of Itch (ECIP-I)	.097	-.121	.087	.180
Cognitive intrusion of Pain (ECIP)	.051	-.040	.139	.218
Neuroticism (EPQ-RSS)	.130	.049	-.026	-.165

Note. BVS= Body Vigilance Scale; PVAQ(-I) = Pain Vigilance and Awareness Questionnaire; PCS(-I) = Pain Catastrophizing Scale; ECIP(-I) = Experience of Cognitive Intrusions of Pain Scale; EPQ-RSS = Neuroticism Scale of Eysenck Personality Questionnaire – revised short form; [a] Measured on a scale from –4 (intense pain) to 4 (intense itch) with 0 labelled as neutral $^{*}p < .05$.

CHAPTER 3

Attentional interference, but no attentional bias, by tonic itch and pain stimulation

Published as

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Abstract

Introduction: Attentional processes are involved in the experience of itch and pain. They interrupt task performance (i.e., attentional interference) or bias allocation of attention towards the somatosensory stimulation, i.e., attentional bias (AB). Research on AB towards pain is mostly focused on stimuli with short durations; hampering generalisation to tonic pain sensations. Evidence for AB towards itch is lacking so far. This study investigated attentional interference by and AB towards experimentally induced tonic itch and pain.

Methods: Fifty healthy volunteers performed a somatosensory attention task (SAT), that measured attentional interference and AB during tonic (35s duration) pain, itch and vibrotactile stimuli. In addition, a dot-probe task measured AB towards visual representations of itch and pain, a Flanker task was used to assess attentional inhibition and self-reported characteristics were measured.

Results: Attentional interference during itch and pain stimuli compared to vibrotactile stimuli was found during the SAT. Exploration of shorter time segments within one tonic stimulus showed slowed responses for all three stimulus types during the first 5s of stimulation. However, no prolonged interference in the following time segments was found. There was no AB towards somatosensory and visual stimuli. Furthermore, there was no association between any of the attentional measures and self-reported characteristics.

Discussion: These findings suggest that the beginning of any somatosensory stimulus is interfering with cognitive performance, but the results for prolonged interference by itch and pain are equivocal. There was no indication for biased attention allocation. Whether this pattern is different in patients remains to be investigated in the future.

Introduction

Itch and pain signal potential threats to the body. In most situations, this is an adaptive mechanism that leads to behavioural adjustment. It has been suggested that itch and pain interrupt ongoing behaviour, and that attention is drawn towards the location of these stimuli, i.e., an attentional bias (AB) towards itch and pain occurs (Eccleston & Crombez, 1999; Legrain et al., 2009; Van Damme et al., 2010; Van Ryckeghem & Crombez, 2018). This is in accordance with the functional attentional system as described by (Allport, 1989), which states that the attentional system makes a difference between stimuli that are irrelevant to the ongoing behaviour (e.g., distracting noises in the office) and relevant stimuli that adaptively interrupt behaviour (e.g., a fire alarm) drawing attention.

Studies using somatosensory stimuli have shown that pain interferes with the performance of a concurrent task. These studies mostly used short (phasic) stimuli (Moore et al., 2012; Roa Romero et al., 2013; Van Damme, Crombez, Eccleston, Goubert, 2004; Van Ryckeghem, Crombez, Eccleston et al., 2012) but support also comes from studies with longer (tonic) stimuli (Keogh et al., 2013; van Laarhoven et al., 2017; Van Ryckeghem, Van Damme, Crombez, et al., 2011) and from studies that used naturalistic pain (Attridge, Noonan, et al., 2015; Keogh et al., 2014; Van Ryckeghem, Rost, et al., 2018; Veldhuijzen et al., 2006). Evidence for itch is lacking; the only two studies on interference by tonic itch on a cognitive task yielded conflicting results (van Laarhoven et al., 2017; van Laarhoven et al., 2018). However, similarities in the physiology of itch and pain, and their shared protective function (Ikoma et al., 2006; Ständer & Schmelz, 2006), suggest that itch also causes attentional interference.

Besides overall interference of itch and pain on task performance, people might show an AB towards itchy or painful somatosensory stimuli. Findings regarding AB towards painful stimuli are mixed for experimental pain in healthy participants and AB towards itchy stimuli has not yet been demonstrated (Van Damme et al., 2007; van Laarhoven et al., 2017; van Laarhoven et al., 2018; Vanden Bulcke et al., 2014). With regard to differences between phasic and tonic stimuli, an AB towards phasic pain has been shown (Van Damme, Crombez, & Eccleston, 2004; Van Damme et al., 2007), whereas an AB towards tonic pain is not yet supported (van Laarhoven et al., 2017). Studies suggest that during tonic stimuli attention may fluctuate, which calls for a more fine-grained analysis of the time course of attention effects (van Laarhoven et al., 2017). There is some evidence of an AB towards visual representations of itch and pain (Crombez et al., 2013; Schoth et al., 2012; Todd et al., 2018; van Laarhoven et al., 2016, 2018; van Ryckeghem & Crombez, 2018) but visual stimuli are inherently different from the somatosensory sensation of itch and pain, which promotes more research on actual somatosensory stimuli. In addition, inconclusive evidence has emerged from explaining the mixed findings by individual differences (e.g., neuroticism or catastrophizing, Crombez et al., 2013; Schut et al., 2015; Van Damme, Crombez, & Eccleston, 2004; van Laarhoven et al., 2017; van Laarhoven et al., 2018). Lastly, investigations of attentional inhibition, i.e., inhibit irrelevant information and attending to the relevant information (Diamond, 2013) may predict how well people can adjust their task performance when experiencing pain or itch (Basanovic et al., 2017; Mazidi et al., 2019; Ranjbar et al., 2020).

Therefore, the current study aimed to examine attentional interference by tonic itch and pain stimuli (i.e., representing acute itch and pain) and an AB towards these stimuli in a healthy sample. It was hypothesised that responses on a concurrent task would be slowed down by somatosensory itch and pain compared to vibrotactile control stimulation. Secondly, it was hypothesised that people show an AB towards the itch and pain stimulation. In addition, it was explored whether fluctuations in attention occur during the stimulus and whether there is an AB towards visual representations of itch and pain.

Methods

Participants

Fifty healthy volunteers (10 males, 40 females) aged between 18 and 31 years (Mean (M) = 21.9, Standard deviation (SD) = 2.78) participated in this study. The minimum required sample size was 42, based on power calculations using a power of 0.80, an alpha of 0.05, and an effect size of d = 0.45, i.e. the smallest interference effect of itch on attention observed in a previous study with a similar SAT set-up with healthy participants (van Laarhoven et al., 2018). Additional participants were included to account for potential data loss, e.g., due to technical issues. Inclusion criteria were being aged between 18 and 30 years old (one participant turned 31 between sign-up and the testing session) and being fluent in the Dutch language. Exclusion criteria were: severe or long-term morbidity (e.g., diabetes mellitus, atopic eczema, rheumatoid arthritis), psychiatric disorders (e.g., depression), use of a pacemaker or pregnancy as a safety precaution of the electrical stimulation, chronic pain or itch complaints (> 2 on a numeric rating scale (NRS) from 0-10; no pain/itch – worst imaginable pain/itch), and current medication use (e.g., analgesics or antihistamines).

Participants were recruited via advertisements at the faculty of Social and Behavioural Sciences of Leiden University, the Leiden University Research Participation system (SONA systems Ltd., Tallinn, Estonia), and on a national website for the recruitment of research participants (www.proefpersonen.nl). All participants provided written informed consent. Research complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the METC Leiden-Den Haag- Delft, local Medical Ethical Committee (NL54237.058.15).

Design

This is an experimental study with a within-subjects design, in which attentional processing of somatosensory itch and pain stimuli was investigated on a behavioural level with computerized attention tasks, combined with electroencephalography (EEG) measurements to investigate underlying neurophysiology (for which data will be presented in another paper).

Procedure

Potential participants received written information about the study procedures in which the study was described as an investigation of the perception of itch and pain. They were screened online via Qualtrics (Provo, Utah, USA) to obtain information on demographics, psychiatric and medical history, and current itch and pain levels. Moreover, participants filled in a battery of self-report questionnaires. Participants were instructed to refrain from medication, alcohol, and drugs 24h before the testing session and not to smoke or consume caffeine 1 hour prior to the testing session.

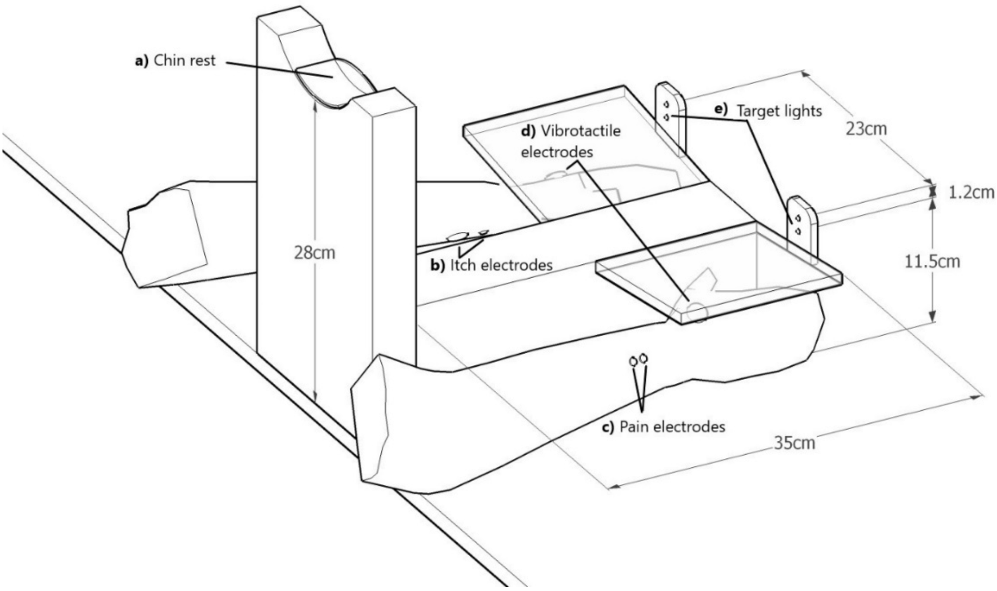
Testing sessions took place at the faculty of Social and Behavioural Sciences of Leiden University. The session started with a brief explanation of the procedures and a check of in- and exclusion criteria, after which participants signed the informed consent. Participants reported experience of current itch and pain (yes/no), rated their current levels of fatigue from 0 (no fatigue) to 10 (worst fatigue ever experienced) on a NRS and filled in a questionnaire on depression-, anxiety- and stress-levels via Qualtrics. Thereafter, participants performed a computerized task on attentional inhibition. Next, participants were prepared for EEG measures. Brain activity was recorded during rest, during somatosensory stimulation and during all attention tasks.

Thereafter, a comparable hand temperature between participants was induced with a warm water bath immersion and then the somatosensory electrodes were attached. During the whole procedure, participants were asked neither to touch the electrodes, nor to scratch the surrounding area to prevent displacement of the electrodes and invalidating the stimulation. Next, a step-up procedure was employed to determine an individually-tailored intensity of the somatosensory stimuli followed by a five-minute break in which participants engaged in filler tasks (i.e. finding differences between two pictures, Bartels et al., 2017) irrelevant to the experiment. Participants then received stimulation-only baseline somatosensory pain, itch and vibrotactile stimuli, and subsequently the somatosensory attention task (SAT) was administered. During the step-up, the baseline and the SAT, participants received standardized instructions via headphones. After the SAT, the somatosensory electrodes were removed and participants performed a computerized visual attentional bias task. Thereafter, the EEG electrodes were removed. Lastly, participants answered an Exit questionnaire on paper, were debriefed, and obtained a monetary reimbursement. The complete procedure took about 3 hours.

Somatosensory stimuli and step-up procedures

Itch and pain stimuli were delivered in accordance with earlier studies (Andersen, van Laarhoven, et al., 2017; van Laarhoven et al., 2017; van Laarhoven et al., 2018), by an Isolated Bipolar Constant Current Stimulator DS5 (Digitimer, United Kingdom) to induce comparable itch and pain in the same modality. Vibrotactile (control) stimuli were delivered through two C-2 tactors (Engineering Acoustics, Inc., Florida (Vanden Bulcke et al., 2015). As preparation of the somatosensory induction, participants held both hands and wrists for a duration of 3 minutes in a warm water bath of about 34 °C to induce comparable baseline hand temperature (Bartels et al., 2014). ***Figure 1*** shows the experimental set-up. Electrodes for pain (c) and itch (b) stimuli were attached to the wrists, placement of itch and pain on the right or left hand was counterbalanced across participants, and vibrotactile (pulsating) stimuli (d) were attached on both hands. Participants were positioned with their head in a chin rest (a), their arms symmetrically on a platform, and their left and right foot on a left and right foot pedal, respectively.

Figure 1. Experimental set-up showing the electrode locations (b: itch, c: pain, d: control) and the locations of the participant (a, chin rest) in relation to the target lights (e).



Individual stimulus intensities of the somatosensory stimuli were determined through step-up procedures aiming at inducing perceived pain, itch and vibrotactile sensations of at least 5 on a slider box with NRS ranging from 0 (not at all) to 10 (worst imaginable) (***Table 1***). During stimulation, participants continuously rated their perception of the stimuli on this slider box on painful, itchy, intensity and unpleasantness. Each step-up procedure was finished as soon as the targeted NRS ≥ 5 on the scale of interest for the specific stimulus type (e.g., $NRS_{pain} > 5$ after a pain stimulus) was reached or the maximum stimulus strength (mA) was delivered, see ***Table 1***. Whenever NRS ≥ 7, the intensity of the previous step of the procedure was taken as target intensity, e.g., rating suddenly increased from NRS = 4.7 to NRS = 7.5. For the pain stimulus painful was the scale of interest (NRSpain), for the itch stimulus itchy (NRSitch) was the scale of interest and for the vibrotactile stimulus intensity (NRSintensity) was the scale of interest. Intensity was defined as an increasing/ stronger sensation that is not specifically painful or itchy. Participants who did not exceed an NRS ≥ 2 for both, itch and pain stimuli during the step-up

Table 1. Specifications of somatosensory stimuli and the employed step-up procedures to determine individual stimulus intensities.

	Electrodes	***Frequency, pulse duration***	***Step-up procedure***	***Maximum intensity***	***Targeted NRS***
Pain	Two disk electrodes of ø 1cm attached to the dorsal side of the wrist.	50Hz, 0.4ms	20s stimuli starting at 1mA, building up in steps of 1mA	6mA	≥ 5 NRS_{pain}
Itch	One disk electrode of ø 1cm and a reference electrode of ø 2cm attached to the ventral side of the wrist	50Hz, 0.1ms	120s stimuli with continuous ramping of 0.05mA, starting at 0mA	6mA	≥ 5 NRS_{itch} `
Control	One C-2 tactor of ø 3.05cm attached on the dorsal side of each hand (between thumb and index finger)	220Hz, sine wave	20s stimuli, increasing in six steps (arbitrary unit)	Step 6	≥ 5 $NRS_{intensity}$

Note. Technical set-up and procedures adapted from Vanden Bulcke et al. (2015) and van Laarhoven et al. (2017).

procedure were excluded from the study right after the step-up procedure and were replaced by another participant. After the step-up procedure, two blocks of 35s per stimulus type at the individual determined target intensities were subsequently applied as baseline stimuli. During these baseline stimuli, no tasks were administered to the participants. After every stimulus during baseline and during the SAT, participants rated their mean experience of the whole stimulus on the same slider box once. Thereafter, participants rated their current sensation again, at 30s and again at 60s after the stimulation has ended. In between blocks of different stimulus types, i.e. pain, itch or control, current sensations were rated every 30s until a total of 180s, i.e. at 30s, 60s, 90s etc. If participants scored NRS > 2 at 60s after a stimulus or at 180s after a block, they were asked to rate their current sensations again every 30s until scores were NRS < 2, that means the ratings were continued until the NRS of interest (e.g., NRSpain after a pain stimulus) were sufficiently low to continue with the task to minimize the risk of carry over effects of previous stimuli.

Attentional tasks

All computerized tasks were designed and administered using E-prime software version 2.0 (Psychology Software Tools, Inc., Sharpsburg, USA). Responses were collected with a regular keyboard or with foot pedals (Marquardt GmbH, Rietheim-Weilheim, Germany) that were connected with E-Prime via a Chronos box (Psychology Software Tools, Inc., Sharpsburg, USA). Also, the audio output and the self-made slider box for NRS ratings were connected to the computer via the Chronos box.

Somatosensory Attention Task

Interference by and AB towards induced somatosensory stimuli were measured with a SAT (van Laarhoven et al., 2017; van Laarhoven et al., 2018). The 12 blocks of the SAT consisted of four consecutive blocks of one of the three somatosensory stimuli type (i.e. pain block, itch block, control block). The order of stimulus type was randomized across participants to minimize possible interactions of stimuli. Stimulation side of itch and pain stimuli were randomized across participants, but stayed constant within each participant. The first and third block of the vibrotactile stimuli were delivered on the right hand and during the second and fourth block on the left hand or vice versa (randomized).

Whilst delivering the somatosensory stimuli for a duration of 35s each, each block contained 15 trials in which 1 or 2 visual targets (green LED lights) were turned on at once on either the left or right side for 200ms with a maximum response window of 1500ms (***Figure 1e***). Randomized inter-trial intervals of 300, 500 and 1100ms were used. Participants were asked to focus on the visual targets and indicate whether 1 or 2 lights lighted up via foot pedals (correct response mapping was randomized across the sample).

Congruent trials were trials in which the visual target(s) appeared ipsilateral to the side of the somatosensory stimuli and incongruent trials were trials in which the visual target(s) appeared contralateral to the side of the somatosensory stimuli. Semi-randomization of visual targets was used for each block so that no more than two incongruent or two congruent trials would be presented sequentially. Two practice blocks of 15 trials with the visual targets, but without any somatosensory stimulation, preceded the actual SAT. The total task took approximately 30 minutes to administer. Reaction times (RT) and accuracy to respond to the visual targets were measured.

Dot probe task for itch and pain

A previously used pictorial dot-probe task was used as a measure of attentional bias for pain- and itch-related information (Becker et al., 2020). Validated pain, itch, and negative (e.g., garbage) pictures of comparable valence were paired with neutral pictures of skin or objects (e.g., pencil), matched in colour and brightness as much as possible (Becker et al., 2020). Neutral skin pictures depicted body parts (e.g., knee, head, back) of non-identifiable individuals (male and female). The itch and pain pictures showed either scratching (itch pictures) or supporting/holding (pain pictures) these same body parts. One trial consisted of the presentation of a central fixation cross for 500ms, after which two pictures were simultaneously presented for 500ms on the screen followed by the appearance of two horizontal or two vertical dots (target stimulus; maximum response window 1500ms). Participants were instructed to respond to the orientation of the target stimulus by pressing foot pedals (e.g., left pedal for horizontal dots and right pedal for vertical dots, counterbalanced across the sample). First, 16 practice trials and two first trials were administered containing only neutral-neutral pairs that were not used for analyses, followed by 240 experimental trials in which a pain-, itch- or negative picture was always shown with a neutral picture. A 30s break was included after every 40 trials and in total the task took 10-15 minutes. RTs and accuracy to respond to target stimuli were measured.

Attentional Inhibition

The Flanker task was used to measure inhibitory control, which is part of selective attentional processing, in the following called general attentional inhibition unrelated to pain or itch (Moore et al., 2012). After presentation of a central fixation cross of 500ms, participants were presented with a target stimulus ‘2’ or ‘4’. The target stimulus was flanked by two non-target stimuli on each side, which were either congruent (i.e. same as target stimulus) or incongruent (i.e. different from target stimulus). Participants were instructed to indicate which target stimulus had appeared on the screen. Participants responded by pressing the correct button on a standard keyboard with their index finger (left arrow key if the target was ‘2’ and right arrow key if the target was ‘4’). Participants first completed 8 practice trials, followed by a total of 120 trials (randomized 50% congruent, 50% incongruent) with a break halfway. The entire task lasted approximately 5 minutes. RT and accuracy to respond to target stimuli were measured.

Self-report questionnaires

Self-reported attentional disengagement from pain, itch and fatigue was assessed with three Likert scales ranging from 1 (not at all) to 5 (always) (e.g., If you feel pain, to what extent are you able to continue with your daily routine as if you did not feel pain?’; van Laarhoven et al., 2017). Attentional focus on bodily sensations was assessed with the Body Vigilance Scale (BVS; 4 items; Schmidt et al., 1997) The fourth item of the BVS is originally divided into 15 sub-items, each measuring attentional focus on a specific anxiety-related bodily sensation. Only sub-items about bodily sensations were included and therefore two sub-items about dissociation were omitted and replaced with two items to measure attentional focus on itch and pain (van Laarhoven et al., 2017). Attentional focus on itch and pain was measured with the Pain Vigilance and Awareness Questionnaire (PVAQ; 16 items; McCracken et al., 1992), and the PVAQ adjusted for itch (PVAQ-I, 16 items; Becker et al., 2020). Catastrophizing was assessed with the Pain Catastrophizing Scale (PCS; 13 items; Sullivan et al., 1995) and PCS-adjusted for itch (PCS-I, 13 items; Andersen, van Laarhoven et al., 2017). Cognitive intrusion was measured with the scale Experience of Cognitive Intrusion of Pain (ECIP; 10 items; Attridge, Crombez, et al., 2015) and ECIP-adjusted for itch (ECIP-I; 10 items; van Laarhoven et al., 2018). Neuroticism was measured with the subscale neuroticism of the Eysenck Personality Questionnaire – revised short form (EPQ-RSS; 12 items; Eysenck, 1991). Psychological distress was measured with the Depression Anxiety Stress Scale short version (DASS-21; 21 items; De Beurs et al., 2001). For all questionnaires, total scores were used for analyses with higher scores indicating higher levels of the specific trait measured with the questionnaire, e.g., higher total PCS score indicates more pain catastrophizing and higher total BVS score indicates more body vigilance. Due to a technical error, both versions of the ECIP were recorded on a 6-point Likert-scale instead of a 7-point Likert-scale and the DASS-21 could not be used. All other questionnaires were recorded properly. A short set of questions was given as Exit questionnaire after the experiment concerning how much they were able to ignore the stimulation during the concurrent task on Likert scales from 0 (never) to 6 (always), as well as whether other factors (i.e. itch, pain, vibration, environment, experimenter, temperature, own thoughts, fatigue and hunger/thirst) influenced their concentration during the task on a scale from 1 (not at all) to 5 (very much), and how threatening the stimuli were experienced on an NRS from 0 (not threatening) to 10 (very much threatening).

Statistical Analyses

Mean RT and accuracy for each participant on the attention tasks were extracted from E-prime. From the SAT data, trials with RTs >150ms and only correct responses were included. From the dot-probe task and the Flanker task, only trials with 150< RT< 1500ms and correct responses were included.17 Additionally, data from participants making >30% mistakes in the Flanker task, SAT or the dot-probe task were excluded from the statistical analyses of the corresponding task (*N* = 2 for the SAT, *N* = 2 for the dot-probe task; van Laarhoven et al., 2017; van Laarhoven et al., 2018). Due to time constraints caused by technical issues, data of the itch blocks during the SAT and the dot-probe task could not be collected for one participant. Statistical tests were carried out using SPSS version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). For all analyses, if not stated otherwise, a significance level of $\alpha < .05$ was considered significant. As a measure of effect size for each Repeated- measures Analysis of Variance (RM ANOVA), partial eta-squared was used. All values are represented as mean ± standard deviation (*M* ± *SD*) unless stated otherwise.

Manipulation check of somatosensory induction

The manipulation was checked by verifying that the somatosensory induction of itch and pain were indeed perceived as painful and itchy, respectively. Inspection of the distribution of the different NRS variables showed that the assumption of normality was not met and log transformation could not solve this issue. Therefore, non-parametric tests were employed. Separate Friedman tests were used to compare the ratings on pain, itch and intensity for each stimulus type separately, e.g., the mean *pain*, *itch* and *intensity* ratings of the *pain* stimuli were compared. In addition, Wilcoxon Signed Ranked tests were done as planned comparisons to compare the different ratings separately with each other, i.e. comparing *pain-* and *itch-* ratings, *pain-* and *intensity-* ratings and i*tch-* and *intensity-* ratings. A Bonferroni correction was applied due to multiple testing with the Wilcoxon Signed Rank test (i.e. $\alpha = 0.05$ divided by three tests, resulting in an $\alpha_{corrected} = 0.017$). These analyses were done for the baseline stimuli and the SAT stimuli separately. Furthermore, a Friedman test was employed to compare unpleasantness ratings of the three different stimulus types during baseline and the SAT, again followed by Wilcoxon

Signed Ranked tests with Bonferroni correction for planned comparisons. Similarly, the experienced threat value for each stimulus type was compared with a Friedman test and post hoc Wilcoxon Signed Rank tests, again with a Bonferroni correction.

Attentional interference and attentional bias

One outlier (step of 1,5 x IQR) in mean RT of incongruent trials during the SAT pain blocks was identified and all SAT analyses were therefore performed including and excluding data of this participant. RTs for visual targets during the SAT were compared between itch and pain stimulation and vibrotactile stimulation by means of planned simple contrasts of pain/itch blocks to control blocks within a 3 (stimulus type: pain, itch, control) x 2 (congruency: congruent, incongruent) within –subjects RM ANOVA. The primary research question of attentional interference by itch and pain compared to control stimuli was examined with the main effect of stimulus type and corresponding contrasts. The secondary research question that itch and pain draw attention to their location was examined with the stimulus type x congruency interaction effect and its corresponding contrasts. Sensitivity analyses without participants that had very low sensations and people that had contaminating sensations (e.g., felt itch during pain stimulus) were done. Details of these analyses and their results are described in the supplementary material methods S1.

Time course of attentional interference and attentional bias

In order to meet the assumptions of normality, analyses on the time segments of the SAT data were conducted after log10-transforming RTs. To examine the time course of attention over the different stimulus types, each 35s SAT block was divided into seven equal and consecutive segments of 5s of which the mean RTs per segment for correct incongruent and correct congruent trials of each stimulus type were calculated using MATLAB (Mathworks, 2011). A 2 (congruency: congruent, incongruent) x 3 (stimulus type: itch, pain, control) x 7 (time segment: 1-7) RM ANOVA was performed, with all factors as within-subject factors. The interaction effect of congruency x segment number was of interest, as this shows whether and when attention allocation towards the stimulus location occur, i.e. AB. Planned contrasts were specified to compare RTs in the first segment with the RTs of all subsequent segments. In addition, post hoc tests with a Sidak correction (Lakens, 2013) further explored possible significant changes of attention between segments. Also, the interaction of stimulus type x segment number, as well as the three-way interaction between stimulus type x congruency x segment number was explored to investigate possible differences in interference between stimuli types over time and differences in AB between stimulus types over time.

Attentional bias and attentional inhibition

For the dot-probe task, a 3 (trial type: itch, pain, negative) x 2 (congruent vs incongruent) RM ANOVA was performed with both factors as within-subject factors. Post hoc tests with a Sidak correction (Lakens, 2013) were specified to explore significant main effects. Data of the Flanker task was analysed by conducting a RM ANOVA with congruency (congruent vs. incongruent) as within-subjects factor and RT as outcome variable.

Attentional bias and interference indices and associations with other measurements

Attentional bias indices for itch and pain were calculated using the formula $RT_{incongruent\ –}\ RT_{congruent}$ for the itch and pain blocks of the SAT separately. A higher index is indicative of a stronger attentional bias towards pain or itch, respectively. For the Flanker and dot-probe task, a congruency index was calculated by the same formula: higher indices on the dot-probe task indicating more AB and higher indices on the Flanker task indicating less attentional inhibition. In addition, post hoc analyses were done with an interference index for itch and pain, calculated by $RT_{pain\ or\ itch}$ - $RT_{control}$, with a higher index suggesting more interference. All indices were subsequently correlated with data from self-report questionnaires to explore associations between individual characteristics and AB, as well as interference for somatosensory itch and pain. Additionally, associations between the three behavioural tasks were explored by correlating the itch and pain indices of the SAT and the congruency indices of the dot-probe task and the Flanker task.

Results

Manipulation check of somatosensory induction

Descriptive statistics for the NRS ratings and significant differences in ratings per stimulus type during the stimulation-only baseline stimuli and during the SAT can be found in ***Table 2***.

Table 2. Median (25%; 75% percentile) Numeric rating scale score for pain, itch, and intensity ratings per stimulus during baseline and during the SAT (*n* = 50).

	NRS_{pain}	NRS_{itch}	$NRS_{intensity}$	*Significant Comparisons*
Baseline				
Pain*	**2.9 (1.8; 4.6)**	0.0 (0.0; 0.5)	3.8 (1.9; 5,1)	painful > itchy
Itch*	0.0 (0.0; 0.8)	**1.5 (0.9; 2.5)**	1.0 (0.3; 2.0)	itchy > painful
Control*	0.0 (0.0; 0.0)	0.0 (0.0; 0.4)	**2.8 (1.7; 3.5)**	intense > painful; intense > itchy
SAT				
Pain*	**2.0 (1.3; 3.9)**	0.0 (0.0; 0.0)	2.2 (1.2; 3.5)	painful > itchy
Itch* [a]	0.0 (0.0; 0.0)	**1.0 (0.5; 1.7)**	0.5 (0.1; 1.1)	itchy > painful; itchy > intense
Control*	0.0 (0.0; 0.0)	0.0 (0.0; 0.2)	**1.8 (1.3; 2,4)**	intense > painful; intense > itchy

Note: Friedman test showed significant difference between NRS_{pain}, NRS_{itch}, and $NRS_{intensity}$, $p < .001$. [a] $n = 49$ due to a missing itch block for one participant. The NRS of interest per stimulus type is underlined.

Concerning the unpleasantness ratings during the stimulation-only baseline, significant differences appeared, χ^2 (2, N = 48) = 38.83, $p < .001$. With pain (M = 3.6) and itch (M = 1.1) stimuli being significantly more unpleasant than control (M = 0.6) stimuli, Z = -5.41, p = .006 and Z = -2.75, $p < .001$, respectively. Unpleasantness ratings for the three stimulus types during the SAT also significantly differed from each other, χ^2 (2, N = 47) = 44.73, $p < .001$. Planned comparisons showed that pain (M = 2.4) and itch (M = 0.8) stimuli were significantly more unpleasant than vibrotactile control (M = 0.4) stimuli, Z = -5.46, $p < .001$ and Z = -3.13, $p < .001$ respectively.

Low and contaminating sensations

Although, all participants had sufficiently high itch and pain ratings during the step-up procedure, sixteen participants reported $NRS_{pain} < 1$ during the pain blocks *and/or* reported $NRS_{itch} < 1$ during the itch blocks of the baseline stimuli. Seven participants reported $NRS_{pain} < 1$ during the pain blocks *and* $NRS_{itch} < 1$ during the itch blocks of the SAT. In addition, five participants experienced $NRS_{itch} > 1$ during the pain blocks of the SAT in addition to painful, pointing towards no pure pain sensation in these participants. No participants did report $NRS_{pain} > 1$ during the itch blocks of the SAT. ***Figure S1*** shows itch and pain ratings for each participant for each stimulation type during the SAT and further details on sensitivity analyses without these participants can be found in the supplementary material results S1.

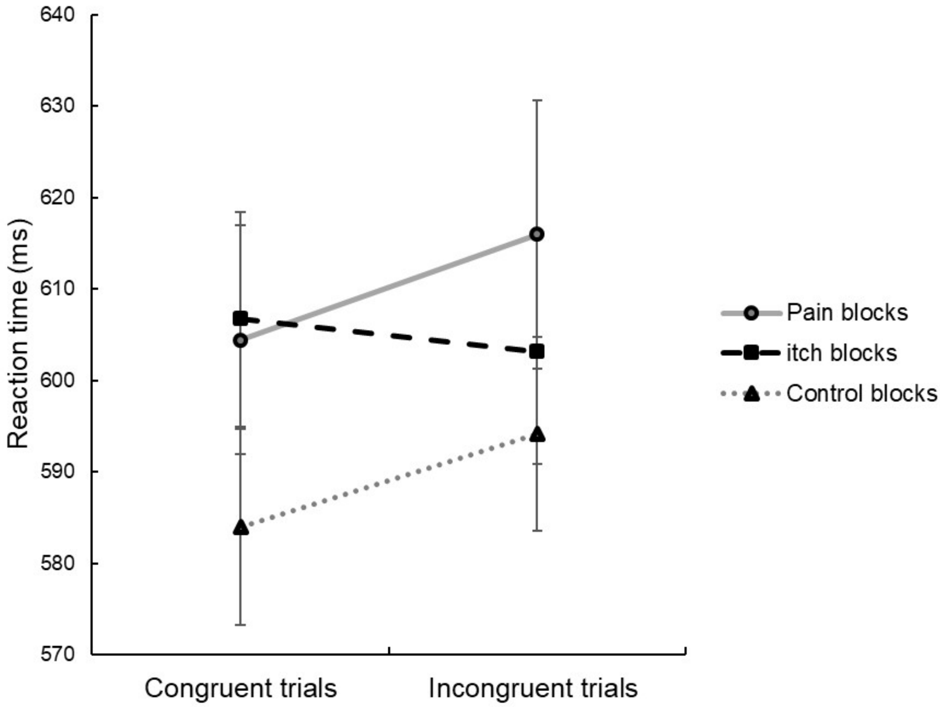
Somatosensory Attention Task

The average accuracy score was 94% for all trials of the SAT, ranging from 80% to 100% correct. Analyses without the one outlier in RT on incongruent trials during the pain blocks (n = 47) did not change the results.

Attentional Interference

As hypothesized, participants responded slower during the itch and pain blocks compared to the control blocks (***Figure 2***), indicated by a significant simple contrast for pain vs. control stimuli, $F(1,47) = 6.78$, $p = .012$, $\eta_p^2 = .126$, and itch vs. control stimuli, $F(1,47) = 6.37$, $p = .015$, $\eta_p^2 = .119$ (main effect of stimulus type, $F(2, 94) = 4.29$, $p = .016$, $\eta_p^2 = .084$). However, there was no significant difference between itch and pain blocks, $F(1,47) = .437$, $p = .512$, $\eta_p^2 = .009$.

Figure 2. Mean reaction times (ms) of congruent and incongruent trials for the pain, itch and control blocks in the somatosensory attention task (N = 48). Error bars represent ± 1 standard error of the mean.



Attentional bias

The hypothesis that participants respond faster if the location of the visual target was congruent with the side of itch and pain stimulation compared to the incongruent location could not be confirmed, as the stimulus type x congruency effect was not significant, $F(2,94) = 1.50$, $p = .229$, $\eta_p^2 = .031$. All corresponding contrasts were also not significant ($p > .05$). The main effect of congruency was not significant either, $F(1,47) = 2.67$, $p = .109$, $\eta_p^2 = .054$.

Time course of attentional bias and interference during the SAT

Medians and Interquartile ranges of RTs per time segment can be found in ***Table S1***, as well as mean RTs for the time segments per stimulus type in ***Figure S2***. In contrast with the hypothesis, results indicated no shifts in attention allocation towards the location of the somatosensory stimulation, i.e. no attentional bias; the congruency x segment number effect was not significant, $F(6, 252) = 1.60$, $p = .147$, $\eta_p^2 = .037$. The main effect of time segment was significant, $F(6, 252) = 22.68$, $p < .001$, $\eta_p^2 = .351$. Simple contrast analysis revealed that RTs were significantly slower in the first segment than in all subsequent segments ($p < .01$), suggesting a larger interference effect in the beginning of stimulation for all stimulus types. In a further exploration of this main effect, post hoc comparisons of RTs in the last time segment with each of the previous time segments showed that RTs were significantly faster in the last segment than in the second and third segments (both $p < .001$), whereas RTs in the last segment did not significantly differ from RTs in the fourth, fifth and sixth segment (all $p > .05$). All other main effects and interaction effects appeared to be non-significant.

Attentional bias towards visual representations of pain- and itch during the dot-probe task

The average accuracy score was 95% (range 83%-100%) for the dot-probe task. Mean reaction times and standard deviations can be found in ***Table 3***. Results showed a significant main effect of trial type, indicating significant differences in RTs between trials with itch, pain, and negative pictures, $F(2,92) = 9.14$, $p < .001$, $\eta_p^2 = .16$. Post hoc pairwise comparisons revealed significantly longer RTs for negative trials compared to pain trials ($p = .002$) and compared to itch trials ($p = .004$) and no significant difference between itch and pain trials ($p = 1.0$). No significant main effect was found for congruency, $F(1,47) = .086$, $p = .771$, $\eta_p^2 = .002$ and also the congruency x trial type interaction was not significant, $F(2,94) = .938$, $p = .395$, $\eta_p^2 = .020$.

Table 3. Reaction times (RT, in ms) for trials of the dot-probe task per trial type (pain, itch, negative) (N = 47), Mean ± Standard deviation.

	RT congruent trials	***RT incongruent trials***
Pain trials	631.83 ± 71.59	626.76 ± 80.68
Itch trials	624.27 ± 78.75	633.01 ± 86.47
Negative trials	645.44 ± 88.92	644.21 ± 87.11

General attentional inhibition during the Flanker task

The average accuracy score was 96% (range 88%-100%) for the Flanker task. RTs were significantly longer for incongruent (496.55ms ± 68.57) than for congruent trials (451.48ms ± 69.72), $F(1,49) = 240.03$, $p < .001$, $\eta_p^2 = .83$.

Relations between individual characteristics and congruency indices

No significant correlations (all $p > .05$) were found between the SAT attentional bias (AB) indices for itch and pain and outcomes of the Flanker task, dot-probe task and self-report questionnaires. For the SAT interference indices, some significant correlations were found, namely between the itch interference index and the pain trials of the dot-probe task, and between the pain interference index and the itch trials of the dot-probe task and disengagement from itch and pain (all $p < 0.05$). Descriptive statistics for the questionnaires can be found in ***Table S2*** and all correlations can be found in ***Table S3***.

Discussion

The findings of the current study demonstrate attentional interference with task performance by itch and pain in comparison to a vibrotactile control stimulus in healthy individuals. Participants responded generally slower during itch and pain stimuli than during control stimuli. Contrary to our expectations, attention was not systematically allocated towards the location of the itch and pain stimuli: i.e., there was no AB towards somatosensory stimuli. Exploratory analyses of the time course of attention suggest that overall responses were slower during the first 5s after stimulus onset, but that this was also true for vibrotactile stimuli and that attention was not allocated towards the stimulus locations. Our results therefore point towards attentional interference by itch and pain, but could not support an AB towards itch and pain.

The finding that both itch and pain, rather than vibrotactile stimulation, can interfere with a concurrent task replicates the results of one previous study showing interference by tonic itch and pain stimuli on attention (van Laarhoven et al., 2017), although no attentional interference was found for itch alone in another study (van Laarhoven et al., 2018). Possible explanations for this discrepancy might be a smaller sample size in the latter study (van Laarhoven et al., 2018b), as well as lower itch ratings compared to the current study and the earlier study on itch and pain (van Laarhoven et al., 2017). In any case, the current findings add to the evidence that experimental pain interferes with the execution of a cognitive task (e.g., Attridge, Noonan, et al., 2015; Boselie et al., 2016), but also of simulated everyday tasks such as making breakfast, or of actual driving skills (Keogh et al., 2013; Veldhuijzen et al., 2006). These results are in line with the assumption that acute itch and pain disrupt attention to adjust our behaviour to protect our body. Our results of higher threat and unpleasantness ratings for the itch and pain stimuli than for vibrotactile control stimuli support the idea that the attentional interference of itch and pain is probably driven by their threatening and aversive nature (Van Damme et al., 2007).

The hypothesis that there is an AB towards somatosensory itch and pain could not be supported. In all, our findings replicate previous studies using tonic pain and/or itch stimuli that found interference but no AB (van Laarhoven et al., 2017; van Laarhoven et al., 2018). In contrast to our results, some studies using phasic pain stimuli did indeed find an AB towards pain (Durnez & Van Damme, 2017; Van Damme, Crombez, & Eccleston, 2004; Van Damme et al., 2007). Phasic pain cannot readily be compared with a tonic stimulus, because such a short stimulus might attract attention primarily during its beginning (Posner, 1980, 2016); this is in line with our finding that all somatosensory stimuli interfere with attention during the first 5s of stimulation. Moreover, it has been proposed that for tonic stimuli previous tasks may have failed to capture an AB because of potential shifts in attention over the time course of such stimuli (van Laarhoven et al., 2017; Zvielli et al., 2015). Despite the stronger focus on attention fluctuations over time than earlier studies (van Laarhoven et al., 2017; van Laarhoven et al., 2018), the current study found no indications for attentional shifts towards the location of these stimuli during a tonic stimulus. It could be speculated though that attention is drawn to the spatial location only in the very beginning of the stimulation, even before a response was required in the current set-up. This would suggest a general orienting response towards itch and pain (Crombez et al., 1997) similar to attention captured with a phasic stimulus. Because the time interval between the stimulus onset and the first target light is too long to capture these responses with the SAT, more specific measures are needed to experimentally investigate different phases in spatial attention allocation towards itch and pain, for instance, eye-tracking-measures.

With regard to attentional fluctuations during itch and pain, an alternative interpretation for slower reaction times immediately after the onset of the stimulation than later on during stimulation is that our attention is easily distracted by anything that is starting new (Petersen & Posner, 2012; Posner, 1980; Posner & Petersen, 1990). However, slower responses in the first time segment were not only observed during itch and pain but also during control stimulation. This suggests that itch and pain have no distinctive quality that governs their interfering effect on attention at the beginning of a sensation. Sustained interference might only be present with an aversive somatosensory stimulus, like itch and pain, which was shown by a significant interference effect of itch and pain in the main analyses. However, as these effects could not be replicated within the current more fine-grained time segment analyses this effects needs replication in the future. Cognitive-motivational models of pain, which can be translated to itch (van Laarhoven et al., 2020), state that pain overrules competing attentional demands, such as daily activities, in order to alarm the individual of potential bodily harm and activate related behavioural strategies, e.g., avoidance, which makes sense for itch and pain, and could explain why the interference of a vibrotactile stimulus vanishes after a few seconds (Eccleston & Crombez, 1999; Evers et al., 2019; Moore et al., 2012; Van Damme et al., 2010; Van Ryckeghem & Crombez, 2018; Van Ryckeghem et al., 2019).

Explorative findings neither indicated that individual characteristics such as attentional focus on bodily sensations and catastrophizing about itch and pain were associated with AB towards or interference by itch and pain, nor that there is an association with attentional inhibition. However, as there was no significant AB found in this study no firm conclusions can be drawn. Still, these results are in line with several previous studies on attentional interference and AB in healthy participants that did not find associations between AB and for example catastrophizing (Roa Romero et al., 2013; van Laarhoven et al., 2017; van Laarhoven et al., 2018). There were some associations between attentional interference indices and the dot-probe task and disengagement, however, these findings are unexpected and difficult to interpret.

Several improvements should be noted compared to earlier research that employed the SAT (van Laarhoven et al., 2017; van Laarhoven et al., 2018). First, an improved control condition with a non-itchy and non-painful somatosensory sensation was added instead of no stimulation at all. Second, stimulations were grouped in blocks to minimize interactions between evoked sensations. Third, interference by hand movements with sensations was minimized by using foot pedals to measure responses. Fourth, as attentional fluctuations over time were assumed, the order of target lights was semi-randomized and time-analyses were more fine-grained to trace fluctuations within a few seconds.

Several limitations of the current study should be noted as well. First, targeted levels of induced itch and pain during the SAT were not reached in a substantial proportion of participants and a number of participants unintendedly rated pain stimuli as painful *and* itchy. As studies have shown that ratings of painful sensations become lower when a concurrent neutral task distracts someone from the sensation (Roa Romero et al., 2013), lower ratings during the SAT were expected. In addition, it might be possible that habituation towards the stimuli and the task makes it difficult to repetitively induce a strong sensation, which can be seen in higher ratings during baseline than during the SAT (Bartels et al., 2017), see ***Table 2***. However, manipulation checks confirmed that stimuli led to the perception of interest (e.g., pain stimulus more painful than itchy) and sensitivity analyses without these participants led to the same results as the overall analyses. Nonetheless, it remains to be determined whether stronger sensations would elicit different effects on interference and AB. Second, the relatively long duration of the current experiment and repetitive nature of the somatosensory attentional tasks, in addition to repetitive step-up and baseline stimulations, may have induced fatigue and lowered participants' motivation to engage in the tasks. Future research should take this potential confounder into account. Moreover, repetitive stimulation might be associated with decreases in evoked itch over time (Bartels et al., 2014, 2017) but there is also evidence against a decrease in itch (Andersen, van Laarhoven, et al., 2017). Development of other itch induction methods to evoke prolonged and/or repetitive itch needs investigation. Third, although to our knowledge, this study is the first that used a somatosensory control stimulus, research is needed on different neutral somatosensory stimuli. While we used a vibrotactile, hence mechanical, stimulation here, neutral electrical stimuli need investigation if compared to electrically induced pain or itch. Fourth, a restricted variance in the self-report characteristics in healthy people could explain the lack of significant correlations with attentional indices. Fifth, the sample was rather homogeneous in terms of gender, age, and education which may limit generalizability of the findings to other groups. Lastly, the current methodology was developed to induce a sensation that is a proxy for acute itch and pain. However, the onset of the itch and pain stimuli was highly predictable, which hampers its generalizability to the real world emergence of acute itch and pain which is usually unpredictable. However, this might be the opposite for the emergence of itch and pain in patients with chronic symptoms. In these cases, individuals are already used to the symptoms and might be able to predict their occurrence. In line with predictive coding theory (Büchel et al., 2014; Kaptchuk et al., 2020), this means that unexpected and hence unpredicted symptoms (acute itch and pain) would demand attention to take action, while regular symptoms (chronic itch and pain) are expected and do not need particular attention. Therefore, future studies are recommended to apply a similar design with acute itch and pain in individuals with chronic symptoms to further investigate these hypotheses.

In conclusion, results of the current study show that in healthy individuals, itch and pain interfere with attention. Considering that relatively low levels of induced itch and pain were sufficient to demand attention and slow down task performance in healthy individuals, attentional interference of clinical levels of itch and pain in patients may be even stronger. Moreover, we could speculate that in experimental settings participants are convinced that stimuli will be non-harmful and transient, whereas patients associate itch and pain with bodily threat and are uncertain about its progression. Tonic itch and pain might be more realistic in representing somatic symptoms and this needs further investigation. Furthermore, we found no AB towards the stimulated location. This might imply that regular attentional bias modification trainings based on attention allocation with the SAT cannot be used to train attention away from itch and pain. Still, as itch and pain distract attention away from other tasks, it might warrant further exploration whether focusing attention on a task despite experiencing pain or itch is possible (Van Ryckeghem, Van Damme, Eccleston et al., 2018), e.g., during meditation based trainings (e.g., mindfulness). Altogether, research is needed that examines how attentional interference and attentional bias play a role in symptom perception and symptom maintenance in patients suffering from chronic pain or itch.

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Figure S1. Mean NRS itch and pain ratings per stimulus type during the SAT (n = 50). Pain represented by blue circles, itch by red triangles and control by green squares. Ideally, all data points for pain would lay over the y-axis to call it a pure pain sensation and all data points for itch would lay on the x-axis to call it a pure itch sensation. The data points for control stimulation instead should ideally gather around zero for both NRS_{pain} and NRS_{itch}.

See figure on next page.

Methods S1

As an additional manipulation check, a priori planned sensitivity analyses on the main analyses were conducted without data from participants that indicated an NRS < 1 on the sensations of interest during the baseline stimuli and separately during the SAT (e.g. NRS_{itch} < 1 for itch stimulus and NRS_{pain} < 1 for pain stimulus). A similar sensitivity analysis was conducted to examine influence of "contaminating sensations" during the SAT only, defined as NRS_{pain} > 1 for an itch stimulus or NRS_{itch} > 1 for a pain stimulus.

Results S1

Results of the sensitivity analyses excluding data of participants with unsuccessful inductions during baseline showed no significant main and interaction effects, meaning that the interference effect by pain and itch disappeared, $F(2, 29) = 1.57$, $p = .225$, $\eta_p^2 = .098$. Analysis with only the data of participants with a pure pain sensation during the SAT (pain stimulation with NRS_{itch} >1, $n = 43$) and without participants with unsuccessful inductions ($n = 41$) gave the same results as the main analysis.

Figure S1

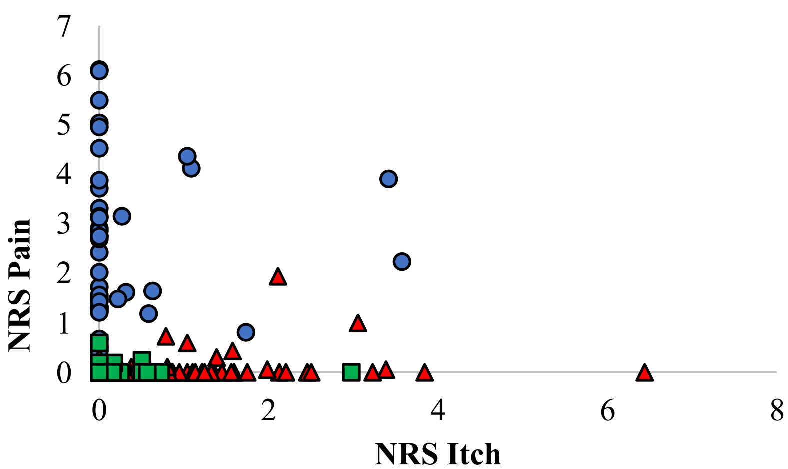

Figure S2. Mean reaction times for congruent and incongruent trials per time segment in the pain (A), itch (B) and control blocks (C) of the SAT ($n = 43$). Error bars represent ± 1 standard error of the mean.

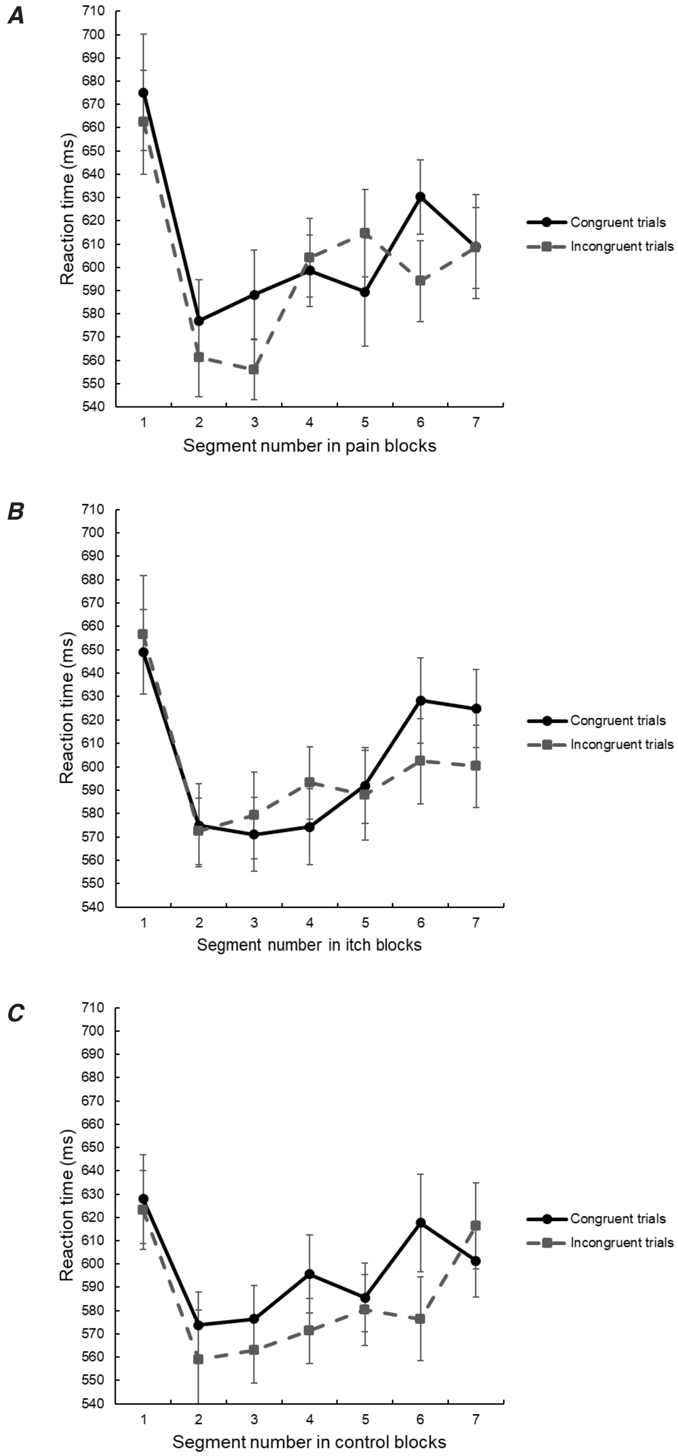

Table S1. Reaction times (RT) in milliseconds for the congruent and incongruent trials of the somatosensory attention task (SAT) per 5s time segment during the pain, itch, and control blocks (total duration each stimulus 35s, averaged across 4 stimuli per block) (*n* = 44).

	RT congruent trials Median (IQR)	***RT incongruent trials Median (IQR)***
Pain blocks		
Segment 1	645.00 (188.10)	634.63 (205.25)
Segment 2	551.00 (124.06)	532.08 (136.35)
Segment 3	577.60 (118.08)	526.30 (131.83)
Segment 4	584.46 (152.80)	588.33 (131.83)
Segment 5	575.95 (123.64)	576.13 (136.41)
Segment 6	588.44 (160.23)	572.10 (153.46)
Segment 7	593.17 (125.11)	580.55 (126.31)
Itch blocks		
Segment 1	654.50 (210.68)	629.87 (129.23)
Segment 2	549.98 (123.23)	573.25 (112.44)
Segment 3	561.75 (144.60)	580.88 (143.48)
Segment 4	555.43 (132.10)	565.20 (148.65)
Segment 5	569.25 (125.08)	559.67 (152.71)
Segment 6	605.29 (178.86)	582.17 (154.88)
Segment 7	598.58 (161.92)	589.30 (140.27)
Control blocks		
Segment 1	617.90 (164.40)	617.23 (162.51)
Segment 2	562.50 (113.04)	548.57 (104.35)
Segment 3	558.67 (162.58)	537.13 (136.59)
Segment 4	584.55 (117.88)	556.00 (103.22)
Segment 5	566.75 (120.05)	580.42 (143.16)
Segment 6	577.38 (132.66)	548.70 (88.30)
Segment 7	577.92 (132.53)	591.83 (134.69)

Note. Because of missing data in some time segments (i.e. no correct responses given) cases had to be excluded resulting in *n* = 44 for the separate segments. IQR = Interquartile range

Table S2. Outcomes of the self-report-questionnaires on psychological characteristics and baseline measures ($n = 50$).

	Mean ± SD	***Actual range***	***Median (IQR)***
Attentional disengagement			
Pain	3.5 ± 1.1	1.0 - 5.0	4.0 (1.0)
Itch	4.0 ± 1.0	1.0 - 5.0	4.0 (1.0)
Fatigue	3.9 ± 0.8	2.0 - 5.0	4.0 (1.0)
Attentional focus on bodily sensations			
Body vigilance general	3.3 ± 1.2	1.1 - 5.9	3.5 (1.6)
Body vigilance pain	1.8 ± 2.0	0.0 -7.1	1.1 (2.0)
Body vigilance itch	1.5 ± 1.7	0.0 - 6.7	0.9 (1.9)
Pain vigilance and awareness	29.9 ± 12.3	5.0 - 56.0	28.0 (19.0)
Itch vigilance and awareness[a]	1.4 ± 0.8	0.3 - 3.9	23.0 (20.0)
Catastrophizing			
Pain catastrophizing	13.0 ± 7.5	0.0 - 26.0	13.0 (12.5)
Itch catastrophizing	8.6 ± 7.3	0.0 - 35.0	8.0 (10.0)
Cognitive intrusion			
Cognitive intrusion of pain	9.6 ± 7.3	0.0 - 29.0	10.0 (10.0)
Cognitive intrusion of itch	6.8 ± 7.2	0.0 - 30.0	5.0 (10.5)
Neuroticism	3.2 ± 2.6	0.0 - 10.0	2.0 (3.0)
Baseline			
Pain	0.0 ± 0.1	0.0 - 1.0	0.0 (0.0)
Itch	0.0 ± 0.0	0.0 - 0.0	0.0 (0.0)
Fatigue	2.2 ± 1.5	0.0 - 6.0	0.0 (2.0)

Note. [a]$n = 49$; IQR = Interquartile range

Table S3. Spearman rho correlations between attentional bias (AB) and interference indices for pain and itch during the SAT and congruency indices of the Flanker and Dot-probe task, as well as outcomes of self-report questionnaires (*n* =50).

	AB Pain	***AB Itch***	***Interference Pain***	***Interference Itch***
Attentional indices				
Pain (SAT) [a]	-	-	0.223	-.006
Itch (SAT) [a]	-0.105	-	-0.118	0.021
Flanker task	0.058	-0.222	0.011	0.196
Dot-probe pain trials [b]	0.055	0.115	-0.282	-0.296*
Dot-probe itch trials [b]	0.036	-0.096	0.316*	0.123
Dot-probe negative trials [b]	-0.304	-0.069	0.123	0.155
Attentional disengagement				
Pain	0.161	-0.107	0.442*	0.156
Itch	0.246	-0.165	0.302*	0.000
Fatigue	0.202	0.012	0.163	-0.177
Attentional focus on bodily sensations				
Body vigilance	0.054	0.117	0.166	0.124
Pain vigilance and awareness	0.087	-0.062	0.154	0.048
Itch vigilance and awareness	0.060	-0.020	0.157	0.020
Catastrophizing				
Pain catastrophizing	-0.063	0.133	0.032	-0.036
Itch catastrophizing	0.114	0.147	0.109	-0.052
Cognitive intrusion				
Cognitive intrusion of pain	-0.071	0.119	0.077	0.015
Cognitive intrusion of itch	0.102	0.029	0.146	0.008
Neuroticism	0.042	-0.174	0.052	-0.014

Note. [a] $n = 48$, [b] $n = 47$; * $p < 0.05$

CHAPTER 4

No preconscious attentional bias towards itch in healthy individuals

Published as

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Abstract

Rapidly attending towards potentially harmful stimuli to prevent possible damage to the body is a critical component of adaptive behavior. Research suggests that individuals display an attentional bias, i.e., preferential allocation of attention, for consciously perceived bodily sensations that signal potential threat, like itch or pain. Evidence is not yet clear whether an attentional bias also exists for stimuli that have been presented for such a short duration that they do not enter the stream of consciousness. This study investigated whether a preconscious attentional bias towards itch-related pictures exists in 127 healthy participants and whether this can be influenced by priming with mild itch-related stimuli compared to control stimuli. Mild itch was induced with von Frey monofilaments and scratching sounds, while control stimuli were of matched modalities but neutral. Attentional bias was measured with a subliminal pictorial dot-probe task. Moreover, we investigated how attentional inhibition of irrelevant information and the ability to switch between different tasks, i.e., cognitive flexibility, contribute to the emergence of an attentional bias. Attentional inhibition was measured with a Flanker paradigm and cognitive flexibility was measured with a cued-switching paradigm. Contrary to our expectations, results showed that participants' attention was not biased towards the itch-related pictures, in fact, attention was significantly drawn towards the neutral pictures. In addition, no effect of the itch-related priming was observed. Finally, this effect was not influenced by participants' attentional inhibition and cognitive flexibility. Therefore, we have no evidence for a preconscious attentional bias *towards* itch stimuli. The role of preconscious attentional bias in patients with chronic itch should be investigated in future studies.

Introduction

Somatosensory stimuli, such as itch or pain, are common experiences in everyday life, signaling potential danger in the environment that may be harmful to the body. These perceptions may lead to behavioral adaptation in attempting to avoid further contact with the source of itch and pain to protect bodily integrity. This is an adaptive process, called attentional bias (AB), that is defined as preferential attention allocation towards threat-related stimuli compared to neutral stimuli (Crombez et al., 2013; Van Ryckeghem & Crombez, 2018).

AB can occur at different stages in time of the attentional processing. Posner suggested the existence of an initial *alerting* response, elicited by an external stimulus, i.e., perceiving something in the environment, which then leads to *orienting* of attention towards this stimulus, and lastly *executive control* which determines how we engage with the stimulus (Posner, 2016; Posner & Petersen, 1990). Meta-analyses on AB in the context of pain, which shares many similarities with itch (Ikoma et al., 2006; Schmelz, 2010; Ständer & Schmelz, 2006), confirmed that different presentation times of pain-related information lead to different findings, suggesting that the allocation of attention may differ over time (Crombez et al., 2013; Todd et al., 2018). These analyses showed significant attentional bias towards pain for conscious processing between 500-1000ms, while there is limited evidence for shorter(<500ms) or longer presentation times (>1000ms) (Crombez et al., 2013; Todd et al., 2018). However, this might also be due to a very limited amount of studies, especially in the preconscious processing range (Asmundson et al., 2005; Keogh et al., 2003; Schoth et al., 2015; Snider et al., 2000).

Regarding itch-related stimuli, research on how attention fluctuates over time is absent. Research so far has focused on conscious (500ms presentation) processing (Becker et al., 2020; Todd et al., 2018; van Laarhoven et al., 2018), showing an AB towards itch-related pictures in healthy individuals (van Laarhoven et al., 2018). This finding was however not replicated in a later study performed in a healthy sample using itch-related pictures and words (Becker et al., 2020). As available studies only tapped into late orienting towards- and engaging with itch-related stimuli, it remains unclear whether attention is preconsciously and automatically drawn towards itch. It is important to gain more insight in this early phase of alerting and early orienting as fast and automatic processing is found to be important for the protective function of itch (Ikoma et al., 2006; Schmelz, 2010; Ständer & Schmelz, 2006).

Furthermore, there are indications that people who are dealing with itch on a regular basis, i.e., patients with chronic itch, process itch-stimuli differently (Fortune et al., 2003; van Laarhoven et al., 2016) - a parallel process was already suggested for pain (Crombez et al., 2013; Todd et al., 2018). However, reacting to itch-stimuli in our environment is evolutionarily useful for everyone alike, i.e. we all want to avoid potential harm. In addition, it seems reasonable that dealing with itch on a daily basis might enhance the stimuli's relevance and saliency (Kini et al., 2011), which might in turn enhance an AB towards (representations of) itch. This raises the question whether an enhanced relevance and saliency of itch is required before individuals show an AB towards itch.

Overall, there is a mixed pattern of results regarding a conscious AB towards itch. One possible explanation for mixed findings could be the influence of individual characteristics which modulate attention to itch. In addition to self-reported characteristics (e.g., catastrophizing about itch) (Becker et al., 2020; Crombez et al., 2013; van Laarhoven et al., 2016; van Laarhoven et al., 2018), it might be that executive functions can influence an AB towards potentially harmful sensations (Diamond, 2013; Fan et al., 2002; Miyake et al., 2000; Posner, 2016). For instance, attentional inhibition of irrelevant stimuli is a necessary component of AB, e.g., there are more things in our environment than only the itch-related stimulus which compete for attention. Furthermore, after perceiving the itch-related stimulus, switching between different demands (i.e., cognitive flexibility) is necessary to adapt our behaviour: from the external stimulus towards the actual itch-unrelated behaviour. Studies on these characteristics are scarce, with some findings indicating that attentional control (related to cognitive flexibility) is negatively associated with AB towards pain (Basanovic et al., 2017; Mazidi et al., 2019; Ranjbar et al., 2020) In the context of itch, one study is performed showing no association between AB towards itch and attentional inhibition (Becker et al., 2020). However, this study did also not find evidence for an association between AB towards pain and attentional inhibition

The aim of the current study was to investigate the existence of an AB towards subliminally presented itch-related pictures in a healthy sample using a dot-probe task, which measures attention towards an itch-related- compared to a neutral stimulus. Implicit priming was used in half of the sample to investigate the possible enhancement of the relevance and saliency of itch in the healthy sample before AB towards itch was measured. We hypothesized that the participants would show an AB towards the itch-related pictures, compared to neutral pictures. Second, we assumed that AB towards itch would be greater after itch-priming compared to control-priming. Lastly, we explored whether individuals' attentional inhibition and cognitive flexibility, as assessed by flanker- and task-switching paradigms, respectively, as well as, several self-reported itch-related cognitions, could predict an AB towards itch.

Materials and Methods

Participants

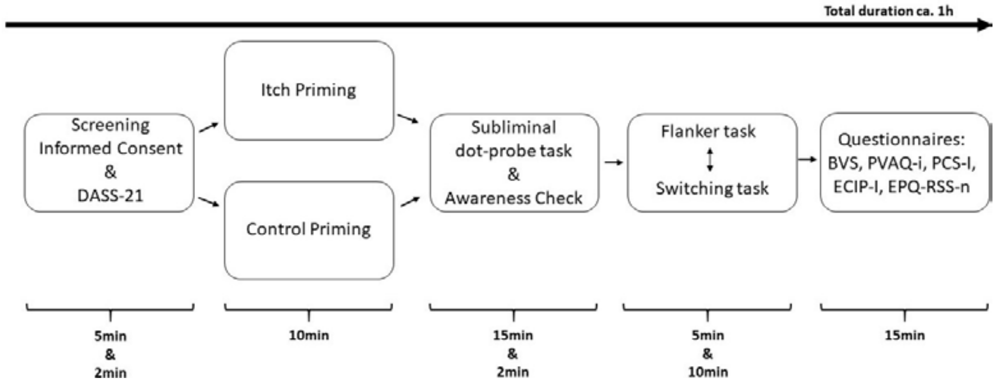
Altogether, 128 healthy volunteers were included, an due to a lack of earlier research in this area this was based on an estimated medium effect size (Cohen's d = 0.5) in a between-subjects design, an alpha of 0.05, and a power of 0.80. One participant had to be excluded because testing appeared to be done twice with the same person, resulting in a sample of 127. Participants needed to be aged between

18 and 35 years and needed to have normal vision (if applicable, corrected with contact lenses, but not with glasses due to eye-tracking measurements). Participants were excluded if they had any (history of) psychological (e.g., ADHD) or medical (e.g., epilepsy, eczema or rheumatoid arthritis) diagnosis; if participants had dyslexia or were color blind, or if they were regular illicit drug users. Recruitment took place within Leiden University, i.e., posters at the faculty and on the university research participation system (SONA Systems Ltd., Tallinn, Estonia) and via social media. All participants gave written informed consent and data was processed in a pseudonymized manner. The Psychology Research Ethics Committee (Leiden University, the Netherlands) approved the study (CEP18-0514/254).

Procedure

Information about the procedure was provided digitally and after online registration. Communication went either in Dutch or in English. The experimental lab session took place at the Faculty of Social and Behavioural Sciences, Leiden University and took approximately one hour, see ***Figure 1*** for an overview. Information about all procedures were repeated verbally upon arrival in the lab. However, to warrant the subliminal design of the study, participants were told that the sensitivity of different senses would be assessed without mentioning itch specifically. Furthermore, in- and exclusion criteria were checked, whereafter informed consents were signed and participants filled in a short questionnaire on current depression-, anxiety- and stress-levels. Thereafter, participants were randomly allocated to either an itch-priming or control-priming group, based on random number generation (Microsoft Excel, Redmond, Washingtion, United States), stratified by gender and handedness. After the itch- or control-priming procedure, participants completed a subliminal dot-probe task to measure preconscious attentional bias towards itch pictures, followed by a stimulus-awareness check task. Afterwards, a Flanker task to measure attentional inhibition and a cued-switching task to measure cognitive flexibility were completed; the order was counterbalanced across the sample. Responses were given with

Figure 1. Study design. Overview of the procedure during the lab session.



Note. DASS-21 = Depression, Anxiety, and Stress Scale- short form; BVS = Body Vigilance Scale; PVAQ = Pain Vigilance and Awareness Questionnaire -adjusted for itch; PCS = Pain Catastrophizing Scale -adjusted for itch; ECIP = Experience of Cognitive Intrusions of Pain Scale -adjusted for itch; EPQ-RSS = Neuroticism Scale of Eysenck Personality Questionnaire – revised short form

the index fingers of both hands. Subsequently, several self-report questionnaires related to the experience of itch were filled in on a computer. Lastly, participants were debriefed about the aim of the study and received monetary reimbursement (€7.50) or course credits for participation.

Technical Set-up

Tasks were presented on an Iiyama HM703UT A Vision Master Pro 413 CRT monitor (17 inch) with a refresh rate of 100Hz and a resolution of 1024x768px. All attention tasks, i.e., dot-probe task, Flanker task, switching task and the awareness check, were administered in E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, USA) and responses were collected with custom-made response buttons on the right and left side of the table, attached to a Serial Response Box (Psychology Software Tools, Inc., Sharpsburg, USA). Questionnaires were presented with Qualtrics (Provo, Utah, USA) on the computer. Eye movements were measured during the Dot-Probe task by means of a Tobii Pro X3-120 Eye Tracker (Tobii AB, Danderyd, Sweden). The eye tracker was attached to the table in front of the screen.

Participants were asked to put their heads in a chin rest in front of the computer screen during all tasks to guarantee a constant distance towards the screen and the eye-tracker (78cm and 71cm, respectively).

Priming

The sample was split into an itch-priming and a control-priming group. The priming consisted of three mechanical and three auditory stimuli for both, the itch group and the control group (see specifications below). The stimuli for the itch-group were selected to induce itchiness and therefore may trigger attention to itch, whereas the control stimuli were assumed not to induce any itchiness or attention to itch.

Participants described the experience of each stimulus on six adjectives adapted from the McGill Pain Questionnaire (Part 2) (Melzack, 1975). These descriptors were *itchy* as the variable of main interest and five other descriptors, namely *bothersome, painful, light, pleasant*, and *unpleasant.* All adjectives appeared in random order after each stimulus, embedded in the question "*Please rate how [adjective] you perceived the stimulus on a scale from 0 (does not describe my experience at all) to 4 (describes exactly my experience)*".

Mechanical stimuli

During the itch-priming, three Touch Test Evaluators (filaments of 4.08, 4.17 and 4.31 mN, consistently in this order; Stoelting, North Coast Medical, Gilroy, California, USA) were pressed on the skin three consecutive times for one second each (Andersen, van Laarhoven, et al., 2017). During the control-priming, one steady stroke for about 1s was applied with a Somedic brush (MRS, Heidelberg, Germany) over a length of 1-2cm on the forearm of the participant (Rolke et al., 2006). This was repeated three times to match the Touch Test Evaluators procedure in the itch-priming group.

Auditory stimuli

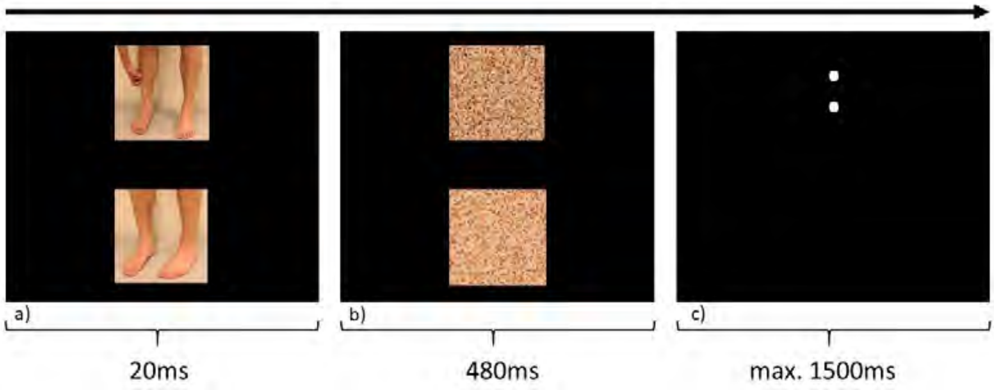
Three scratching sounds (Swithenbank et al., 2016), with a duration of 20s, were presented as itch-priming. The itch sounds comprised the sound of scratching different body parts (i.e., arm, arm pit and beard), used in an earlier study on itch contagiousness (Swithenbank et al., 2016). Three itch-unrelated control sounds matched in pitch and length were presented as control-priming. The control sounds were recorded for the purpose of this study and consisted of everyday life noises that would not be recognized too easily (rolling a plastic ball over a table, squishing a plastic bag and rummaging about a box of foam stickers). Face validity of these new control stimuli was assessed by the research team. Overall loudness of each audio clip was normalized using PRAAT (https://www.fon.hum.uva.nl/praat/). The auditory stimuli were presented in random order within one group (itch vs. control).

Subliminal Dot-probe task

A subliminal Dot-probe paradigm with a validated set of 40 picture pairs was used (Becker et al., 2020), with 40 itch-related pictures showing someone scratching (itch-pictures). Half were paired with neutral pictures depicting human skin without scratching gestures (skin-pictures) and half being paired with neutral objects (object-pictures). The pairs stayed constant across the task. In total, the task consisted of 320 trials, preceded by 24 practice trials with only skin-picture - object-picture pairs not used during the actual task.

The trial sequence consisted of three displays, as can be seen in ***Figure 2***. First, two pictures appeared, one in the lower and one in the upper part of the screen, followed by two masks at the same location as the original pictures to further inhibit conscious processing of the pictures, i.e., backward masking was employed (Mogg & Bradley, 2002), and lastly a target. The target consisted of two dots to which a response by button press was needed. Orientation of the dots (horizontally vs. vertically) and button side (left vs. right) was counterbalanced

***Figure 2.* Dot-probe task.** One trial of the subliminal Dot-Probe task showing a trial with an itch-picture and a skin-picture as control (a) with their corresponding masks (b). The target (c) is presented in the same location as the itch-picture (until button press), making this trial a congruent trial. Additionally, in the middle of the screen, a fixation cross is shown in-between trials (500ms).



across participants, i.e., press right for horizontal dots and left for vertical dots or vice versa. If the dots appeared at the same location as the itch-picture this constituted a congruent trial, whereas if the dots appeared at the same location as the neutral-picture this constituted an incongruent trial. Across the whole task, the itch-pictures appeared in both locations, with both dot orientations and as an incongruent and as a congruent trial. Breaks of 20s were inserted after every 40 trials. Reaction times and accuracy to respond to the orientation of the targets were measured. This task took approximately 15 minutes to complete.

Stimuli and display configurations

The pictures and the masks were 192x192px which was 25% of the height of the screen (1024x768px screen resolution). The masks were made by dividing the pictures into 4x4px cubes and shuffling them randomly into a new 192x192px picture (MATLAB Release 2017b, The MathWorks, Inc., Natick, Massachusetts, United States). In this way, each picture had its own mask, identical in color and brightness. The pictures and masks appeared at the 20% and 80% height position on the screen and the fixation point at 50% height; all stimuli were in the middle of the screen (50%

width). Pictures were presented for 20ms, masks for 480ms and the target dots with a maximum response window of 1500ms (see ***Figure 2***).

Awareness Check

As an objective awareness check, a forced-choice paradigm was employed (Mogg & Bradley, 2002). On each trial, participants were presented with one new picture and one picture that was subliminally shown during the dot-probe task. Twenty-five percent of the itch-pictures (10), skin-pictures (5) and object-pictures (5) that were shown during the dot-probe task were used for all participants, resulting in 20 trials. The new pictures came from the same validated set and pairs were matched in color and brightness (Becker et al., 2020). Participants indicated which one of the two pictures they thought they had seen earlier. If the previously shown pictures were selected at chance level, it was assumed that the pictures were not consciously processed during the dot-probe task. There was no time limit and only accuracy to select the previously shown pictures was measured. Therefore, an accuracy level around 0.5 would indicate that the previously shown pictures were detected at chance level. In addition, as a subjective awareness check, participants were asked orally if they noticed something special during the dot-probe task and this was tracked with 'yes' or 'no' as the outcome. If this was answered with 'yes', participants were asked what they noticed and if they mentioned pictures (Did you see any pictures?), this was recorded as 'yes', as well ('no', if answer did not contain pictures). The total awareness check took approximately two minutes to complete.

Attentional Switching Task

A cued attentional switching task was used to assess cognitive flexibility (Moore et al., 2012). In this task, participants followed two different instructions. On each trial, first a cue appeared to indicate which of two instructions needed to be followed during this trial. One instruction indicated that participants had to identify if a target number shown in the middle of the screen (i.e., 1, 2, 3, 4, 6, 7, 8, 9) was above (right button) or below (left button) five and the other instruction indicated that they had to identify if the number was odd (left button) or even (right button). Two different trial types can be distinguished, depending on whether the trial before had the same instruction (repeat-trials) or the other instruction than the trial before (change-trial). In total, the task consisted of 200 trials (100 trials per instruction type, randomly presented) plus 16 practice trials, with a break halfway. Reaction times and accuracy to respond to the target number were measured. The task took approximately 10 minutes to complete.

Flanker Task

A Flanker task was used to measure attentional inhibition (Eriksen & Eriksen, 1974; Moore et al., 2012). During this task, a string of five numbers appeared on the screen, consisting of '4' and '2', with the middle number being the target. Participants were asked to identify the target as being a two (left button) or a four (right button). The flanking numbers on both sides of the target were either the same as the target (i.e., congruent) or not (i.e., incongruent). The task consisted of 120 trials (50% congruent, 50% incongruent) plus 8 practice trials at the beginning, with a break halfway through the task. Reaction times and accuracy to respond to targets were measured. The task took approximately 5 minutes to complete.

Eye-Tracking measurements

Eye movements were measured during the dot-probe task only. During the task, it was measured whether the participant's eyes were positioned at the Area-of-Interest (AoI) with a sampling rate of 120Hz. AoI's were specified as the area of both pictures that were shown during the task (see *Stimuli and display configurations*). Data was pre-processed with the PhysioDataToolbox AiO Hit Analyzer (Sjak-Shie, 2019). Data was extracted for each trial of the task, with one variable for hit count on the itch-picture and one variable for hit count on the neutral-picture. A hit was counted whenever the participant looked at the AoI.

Self-report questionnaires

Next to questions about current itch, pain, and fatigue (Numeric rating scales from 0 (not at all) to 10 (worst imaginable)), the following concepts were measured: attention to bodily sensations by the Body Vigilance Scale (BVS) (Schmidt et al., 1997) adapted to the current purpose by replacing two items on derealization with itch and pain which were used individually during analyzes; neuroticism by the EPQ-RSS (Eysenck Personality Questionnaire- revised short form): Subscale neuroticism (and subscale extraversion as filler items; Sanderman et al., 1991); Vigilance towards itch by the Pain Vigilance and Awareness Questionnaire (Roelofs et al., 2003) adjusted for itch (PVAQ-I; Becker et al., 2020); catastrophizing about itch by the Pain Catastrophizing Scale (Sullivan et al., 1995), adjusted for itch (PCS-I; van Laarhoven et al., 2017); and how much itch intrudes one's thoughts by the Experience of Cognitive Intrusion of Pain scale (Attridge, Crombez, et al., 2015), adjusted for itch (ECIP-I; Becker et al., 2020). Lastly, depression, anxiety and stress were measured with the short version of the Depression, Anxiety and Stress Scale (DASS-21; De Beurs et al., 2001). Completion of all questionnaires took approximately 15min, the DASS-21 (2min) before testing and the remaining questionnaires thereafter (13min; see ***Figure 1***).

Statistical Analyses

E-prime data were extracted with E-Prime E-DataAid 3.0 (Psychology Software Tools, Inc., Sharpsburg, USA). For the Dot-Probe task, reaction times (RT, in ms), accuracy, congruency (congruent vs. incongruent), group (priming vs. control), trial number (1 to 320) and trial type (neutral skin vs. neutral object picture) for all individual experimental trials (i.e., without practice trials) were extracted. For the Flanker task, mean RT for congruent and incongruent trials were extracted separately, only including correct trials of the experimental trials with RT > 150ms. In the same way, mean RT for change- and repeat-trials of the Attentional Switching task were extracted. A Flanker index was calculated to use as a predictor describing general attentional inhibition ($RT_{incongruent}$ – $RT_{congruent}$), with positive values indicating greater ability to suppress goal-unrelated responses (Fan et al., 2002b). Switch costs were calculated to use as a predictor interpreted as general cognitive flexibility (RT_{change} – RT_{repeat}), where positive values indicate a greater ability to shift attention from one task to another (Verhoeven et al., 2011).

Furthermore, mean accuracy was extracted from E-Prime for the objective Awareness check, as well as the individual answers to the subjective awareness questions (i.e., yes or no). Concerning the ratings of the priming material (itch and control), mean ratings for all six adjectives per category (mechanical and auditory) were extracted. Questionnaire data was extracted from Qualtrics and total scores and reliability for the different questionnaires were calculated with SPSS version 23 (IBM Statistics for Windows, Armonk, NY, USA). Missing items of the PVAQ-I (10 participants, one item each) were imputed using the mean of all other items of the corresponding participant. Subsequent statistical analyses were done with R version 4.0.3 (R Core Team, 2019). All tests were done with $\alpha \leq 0.05$ and descriptive results were given as mean and standard deviation, if not indicated otherwise.

Reliability of the Dot-Probe task was assessed with the R package 'splithalfr' (Pronk, 2020). First, mean RT for congruent and incongruent trials were calculated for every participant. Second, Monte Carlo splitting was used to get 5000 split-half's of the sample of mean congruent RT and mean incongruent RT, separately. Lastly, these samples were used to estimate Spearman-Brown coefficients as an estimate of reliability. The mean coefficient and the range of all coefficients were reported. Reliability of an AB index (mean incongruent RT – mean congruent RT) was calculated in the same way. For the reliability analyses, only participants with an accuracy level above 0.70 were included (Becker et al., 2020; van Laarhoven et al., 2018).

Manipulation checks

Concerning the priming manipulation, a one-way Analysis of Variance (ANOVA) was done for each outcome rating (i.e., itchy, painful, bothersome, light, unpleasant, pleasant), separately for the mechanical and the auditory stimuli, to check for group differences (priming vs. control group). Due to violations of normality, the ANOVA was done with bootstrap (1000 samples) of the residuals (R package “lmboot”) (Heyman, 2019). For the objective awareness measure, single proportion tests were used to assess whether picture selection deviated from chance level (50%) by the overall sample. For the subjective awareness questions, frequencies for answering ‘yes’ and ‘no’ to the questions were calculated. Lastly, paired sample t-tests were employed to assess whether congruent and incongruent trials differed significantly during the Flanker task and whether change and repeat trials differed significantly during the Attentional Switching task, both for the sample as a whole.

Preprocessing

In line with previous work on AB using a dot-probe task, trials with RT <150ms were excluded from the main analyses (Becker et al., 2020; van Laarhoven et al., 2018). Additionally, one participant had to be excluded due to an excessive amount of missing data due to technical issues during data collection. Lastly, inspection of the raw data showed one outlier on the Flanker index and to eliminate any possible bias within this participant’s responses, this participant was excluded from the main analyses of AB. Altogether 0.02% of the data was excluded from the main analyses.

Inspection of the raw eye -tracking data showed that most of the eye-tracking data points were zero (69,7%) which means that during these trials participants did not fixate on one of the two pictures at all. Likewise, total fixation duration was zero or very close to zero during most trials. Due to this, we decided to omit analyses of the eye-tracking data.

Multilevel Model of AB

Due to the repeated measures design of the Dot-Probe task with trials (level 1) nested within subjects (level 2), multilevel models were estimated with the mixed models R packages 'lme4' and 'lmerTest' (Bates et al., 2015; Kuznetsova et al., 2017). RT data typically do not follow a normal distribution and therefore initially a generalized linear model was used with an inverse Gaussian link function (Lo & Andrews, 2015). Inspection of its results, a visual check of the empirical RT distribution in the current sample, as well as results from a linear multilevel model using a normal distribution showed that results of the linear multilevel model did not substantially differ from the results using an inverse Gaussian link function. As the linear model with a non-inverse Gaussian link function is simpler to compute and to interpret (e.g., estimates on original scale), we decided to use a linear multilevel model with a Gaussian link function for the analyses.

Our hypotheses were tested with a multilevel model with Dot-Probe task RT data as outcome and random intercepts for subject to account for the repeated measures design and random intercepts for trial number to account for an expected learning curve during the task (i.e., participants are getting better at the task over time). Models were built according to the hypothesis of the study and in case of convergence issues, choices were based on the priority of the research questions. As of main interest, the fixed effect of accuracy, congruency and priming group were added to the model (Model 1). Accuracy was included to control for its effect on RT, i.e., it might be assumed that participants did not attend well to the task at all whenever they gave a wrong response. The hypothesis of whether the participants display an AB towards itch was tested with the effect of congruency. The hypotheses that AB would be greater after itch priming compared to control priming was investigated with the congruency by group interaction effect. In a next step, the Flanker index and switch cost were added as predictors (fixed effects) to the model to investigate their effect on an AB towards itch (Model 2) and their interaction with congruency was explored to investigate their specific effect on AB (Model 2a and 2b). Lastly, participants' scores on the self-report questionnaires (i.e., body vigilance, neuroticism, itch vigilance and awareness, itch catastrophizing and cognitive intrusions by itch) were added as covariates to the model to control for their possible effect on the outcome and more precise estimates of the effects of interest (Model 3). QQ-plots of the residuals of the final model were inspected for possible bias in the estimation.

Results

Participants

The sample consisted of 127 participants, 107 females and 20 males with a mean (*M*) age of 21.9 years (standard deviation (*SD)* = 2.5). Participants were mostly right-handed (113 right vs. 14 left). Descriptive statistics for the self-report questionnaires can be found in ***Table S1*** and correlations with the AB-index can be found in ***Table S2***. The priming group and the control group did not differ significantly on any of the demographic and self-report variables (e.g., age, gender, Flanker Index, itch vigilance), all $p > 0.05$.

Manipulation checks

Priming

Descriptive statistics and test results of the priming manipulation can be found in ***Table 1***. Concerning the descriptor of main interest – 'itchy', the priming group rated both, the mechanical and the auditory stimuli as significantly more itchy than the control group, see ***Table 1***.

Table 1. *M (SD)* for the ratings of the mechanical and auditory stimuli for the priming group (n = 63) and the control group (n = 64). *P*-values with bootstrapped residuals are reported to indicate significant group differences due to skewed distributions. Parametric effect sizes (η^2) are reported. 'Itchy' as the descriptor of main interest is printed in bold.

	Mechanical priming stimuli				***Auditory priming stimuli***			
	Priming	Control	p	η^2	Priming	Control	p	η^2
Itchy	***1.13 (1.13)***	***0.71 (0.91)***	***0.025***	***0.04***	***1.21 (1.21)***	***0.77 (0.92)***	***0.018***	***0.04***
Painful	0.35 (0.52)	0.24 (0.51)	0.246	0.01	0.55 (0.79)	0.32 (0.56)	0.071	0.03
Light	2.58 (1.11)	3.02 (0.90)	0.020	0.05	1.13 (0.92)	1.40 (0.92)	0.101	0.02
Bothersome	0.81 (0.84)	0.50 (0.77)	0.033	0.04	1.98 (1.04)	1.66 (0.94	0.075	0.02
Pleasant	1.49 (1.30)	2.21 (1.25)	0.003	0.08	0.75 (0.78)	1.11 (0.88)	0.019	0.05
Unpleasant	0.86 (0.89)	0.51 (0.80)	0.029	0.04	1.98 (1.05)	1.45 (1.02)	0.006	0.06

Awareness

Overall, the whole sample selected the picture that was shown during the subliminal Dot-Probe task compared to a new, unused picture, with a mean accuracy of 0.49 (*SD* = 0.13) and the single proportion test showed that this did not significantly differ from 50%, p = 0.592. Furthermore, for the subjective awareness questions, 50 participants indicated that they noticed something during the Dot-Probe task and 45 of these participants also indicated that they saw some other pictures besides the scrambled masks that were used during the task, but none reported anything related to itch or scratching.

General attention tasks

During the Flanker task, participants were, conform expectations, significantly faster during congruent trials (*M* = 393.39ms, *SD* = 71.44ms) than incongruent trials (*M* = 439.14ms, *SD* = 81.81ms), indicating significant interference by incongruent flanking numbers that needed to be inhibited, t = -4.73, $p > 0.001$, mean difference (*MD*) = 45.62. During the Attentional Switching task, participants were significantly faster during repeat trials (*M* = 643.51ms, *SD* = 187.03ms) than change trials (*M* = 729.48ms, *SD* = 234.30ms), indicating that there was a significant switch cost due to switching between sub-task instructions, $t = -3.23$, $p = 0.0014$, $MD = 85.97$.

Analyses of AB

Reliability of the congruent and incongruent trials of the dot-probe task was high, with a mean Spearman-Brown coefficient of 0.98 (IQR = 0.96; 0.98) for congruent trials and 0.98 (IQR = 0.97; 0.99) for incongruent trials. The mean Spearman-Brown coefficient for the AB index was 0.51 (IQR = 0.45; 0.59). Descriptive statistics for the RT data can be found in ***Table 2***. Model fit can be inspected in ***Figure S1***.

Table 2. Mean (*SD*) for the reaction time data (ms) of the subliminal Dot-Probe task for itch per group (priming vs. control) and congruency (congruent vs. incongruent) ($n = 127$).

	Priming Group	***Control Group***
Congruent	468.05 (129.27)	480.22 (137.93)
Incongruent	466.46 (128.07)	476.88 (134.58)
AB index	*1.77 (13.83)*	*2.99 (13.62)*

Note. AB index = reaction $\text{times}_{\text{incongruent}}$ – reaction $\text{times}_{\text{congruent}}$

Model 1 (***Table 3***) of the multilevel analyses shows that that there was a significant effect of congruency on the outcome RT, indicating that congruent trials are 3.23ms slower than incongruent trials, $t\,(39528.57) = -1.998$, $p = 0.046$. Thus, participants were slower to make orientation judgments to targets appearing in a location previously occupied by an itch picture, as compared to a neutral picture, showing a preconscious tendency to avoid itch pictures. Furthermore, there was no significant main effect or interactions involving the factor group, indicating that priming does not change the difference in reaction times between congruent and incongruent trials.

Table 3. Multilevel analyses with RT as outcome variable for the subliminal dot-probe task for itch: estimates (*ES*) with standard errors (*SE*), significance level (*p-value*) and 95% Confidence Intervals (95% *CI*) (*n* = 125)

		ES	***SE***	***p-value***	***95% CI***
Model 1	(Intercept)	462.53	8.83	< 0.001	[445.24, 179.83]
	Accuracy	19.76	2.24	< 0.001	[15.37, 24.15]
	Congruency	-3.23	1.62	0.046	[-6.40, -0.06]
	Group	-11.88	11.99	0.324	[-35.38, 11.62]
	Congruency * Group	1.52	2.28	0.505	[-2.95, 5.98]
Model 2	(Intercept)	471.40	15.14	< 0.001	[442.00, 500.87]
	Accuracy	19.75	2.24	< 0.001	[15.36, 24.14]
	Congruency	-3.23	1.62	0.046	[-6.40, -0.06]
	Group	-11.75	11.95	0.328	[-34.98, 11.49]
	Congruency * Group	1.52	2.28	0.505	[-2.95, 5.98]
	Flanker Index	-0.33	0.24	0.176	[-0.80, 0.14]
	Switch Cost	0.07	0.07	0.327	[-0.07, 0.21]
Model 3	(Intercept)	473.90	24.38	< 0.001	[428.28, 519.50]
	Accuracy	19.80	2.24	< 0.001	[15.42, 24.20]
	Congruency	-3.23	1.62	0.046	[-6.40, -0.06]
	Group	-11.30	12.16	0.355	[-34.04, 11.46]
	Congruency * Group	1.52	2.28	0.505	[-2.95, 5.98]
	Flanker Index	-0.35	0.25	0.163	[-0.82, 0.12]
	Switch Cost	0.04	0.07	0.570	[-0.10, 0.18]
	Disengagement Itch	-1.64	3.75	0.663	[-8.65, 5.32]
	Disengagement Pain	-0.57	3.10	0.854	[-5.23, 6.37]
	Body Vigilance total	-3.66	4.21	0.386	[-11.52, 4.20]
	Body Vigilance Itch	2.64	4.16	0.527	[-5.13, 10.41]
	Body Vigilance Pain	3.38	3.20	0.293	[-2.60, 9.36]
	Itch Vigilance & Awareness	-0.61	0.62	0.326	[-1.77, 0.55]
	Itch Catastrophizing	-0.14	1.24	0.907	[-2.17, 2.46]
	Cognitive Intrusions by Itch	0.52	1.07	0.629	[-2.52, 1.48]
	Neuroticism	3.44	2.12	0.108	[-0.52, 7.40]

Note. Model fit statistics; Model 1: AIC = 491202.2; Model 2: AIC = 491207.8; Model 3: AIC = 491190.1

Model 2 (***Table 3***) confirmed the significant effect for congruency found in Model 1, $t(3953) = -1.998$, $p = 0.046$, controlling for Flanker Index and Switch Cost. Both variables were not significantly related to the outcome. However, when Flanker Index and Switch Cost were both added as an interaction term with congruency (Model 2a, see ***Table S3***), the significant main effect of congruency disappeared $t(3953) = -1.076$, $p = 0.282$, while also the Flanker Index by congruency interaction, $t(3953) = -0.128$, $p = 0.898$, and the Switch Cost by congruency interaction remained not significant, $t(3953) = 0.098$, $p = 0.922$. Although, the original hypothesis was to include the Flanker Index and Switch Cost as predictors, including them as covariates was explored to further investigate the abovementioned findings. When the Flanker Index by congruency interaction is removed and it is only controlled for the main effect of Flanker index (i.e., it is included as a covariate only) (Model 2b, see S3 Table), a trend towards a significant main effect of congruency returns, $t(3952) = -1.702$, $p = 0.089$. This means that the non-significant Flanker Index by congruency interaction is collinear to the main effect of congruency, showing that the interaction does not add any new information to the model in addition to the main effect of congruency.

Lastly, Model 3 (***Table 3***) which included several self-report characteristics as covariates, again showed a significant association of congruency with the outcome, $t(3953) = -1.998$, $p = 0.046$.

Discussion

Because it is assumed that potentially threatening stimuli, including itch, draw attention, the current study investigated whether attentional bias (AB) towards visual itch stimuli already shows up when stimuli are subliminally presented. In contrast to the hypothesis, healthy participants avoided the preconsciously presented itch-pictures and this effect was not influenced by priming participants with a mild itch stimulus and scratching sounds. Moreover, there was no significant association between preconscious AB towards itch and attentional inhibition or cognitive flexibility. But preliminary findings showed that attentional inhibition might be related to the emergence of an AB. Altogether, this study did not support preconscious orienting of attention towards itch-related stimuli, but rather suggests that healthy individuals orient away from these stimuli.

The finding that peoples' attention is not preconsciously biased towards itch-related pictures, but is actually oriented away, is in contrast with our hypothesis. However, very fast and automatic avoidance of itch-related stimuli can still be explained by its protective function, because the ultimate goal is to avoid the source of the potential threat (Ikoma et al., 2006; Schmelz, 2010; Ständer & Schmelz, 2006). In addition, scratching is stigmatized (Silverberg et al., 2018; van Beugen et al., 2016, 2017, 2021) which could explain why people avoid the itch-related stimuli. Actually, this could be adaptive as long as someone is not directly in contact with someone who is scratching: infection through a picture is not possible. Consequently, orienting away from someone who is scratching is adaptive to avoid direct contact. In addition, seeing someone else scratching could induce disgust in the viewer which would also support avoidance of these stimuli. However, to our knowledge, it has not been studied yet how disgust specifically relates to attention to itch and related stimuli. Yet, research has shown that skin-related disgust plays a role for patients with chronic skin diseases, so a relationship between attention to itch and disgust seems plausible (Lahousen et al., 2016)

Nevertheless, the cumulative evidence for a preconscious AB towards- or avoidance of threat-related stimuli like itch or pain is limited. It has to be taken into account, that the handful of studies on subliminal processing of pain-related stimuli used different stimuli and some also different paradigms which makes drawing conclusions difficult (Asmundson et al., 2005; Keogh et al., 2003; Schoth et al., 2015; Snider et al., 2000). Beyond the fact that these studies had contradictory findings, two studies measured attentional interference (using a Stroop task) instead of attention towards a location, i.e., orienting towards a stimulus (Asmundson et al., 2005; Snider et al., 2000) which is a different aspect of attention, although related to AB (Posner, 1980, 2016). Lastly, none of these earlier studies used pictorial stimuli but used word stimuli, and research on AB towards pain and threat has shown that results might differ for picture- and word stimuli (Bar-Haim et al., 2007; Crombez et al., 2013; Todd et al., 2018). Therefore, it is unclear how this might influence preconscious attention. Moreover, the saliency of the aversive content probably differs between itch- or pain-related content, as well as for pictorial representations compared to semantic processing, i.e., words.

In contrast to our expectations, priming with a mild itchy stimulus and scratching sounds did not seem to enhance relevance and herewith attention to itch in the current study. This was in spite of the fact that the itch-priming stimuli were, as intended, rated as significantly more itchy than the control stimuli. Possible explanations why the itch-priming did not result in more attention to itch might be that the stimulus was not itchy enough and that more pronounced itch stimuli, like cowhage (Andersen, Elberling, et al., 2017), are needed to heighten the relevance and saliency sufficiently in healthy participants. Hence, participants presumably were not consciously focused on itch which may have hampered the priming's effectiveness to change AB towards itch. Not mentioning the context of itch to participants in the present study is in contrast to most studies that used audiovisual stimuli for the investigation of contagious itch, which as far as we know, explicitly mentioned the relation to itchiness to the participants (Marzell et al., 2019; Swithenbank et al., 2016). Furthermore, the actual task that needed to be executed (identification of dot orientation) was not related to itch and therefore not directly related to the priming, which could also decrease its effectiveness. Lastly, in the current study, the priming and the actual task were in different modalities (feeling and hearing during priming and visual processing during the task) (van Laarhoven & Holle, 2019).

Investigating cognitive flexibility in relation to AB, which has not been done before, did not yield any significant associations. In line with this, there was also no significant association between AB and attentional inhibition, although exploratory analyses showed, that AB and inhibition share a common factor as their effects overlapped in the current models. This could mean that someone who can generally better inhibit/ignore irrelevant information, is also better in ignoring a task-irrelevant itch-related cue in the environment. This would support the avoidant pattern observed in the current study and underline the fact that itch-related pictures are no direct danger of infection and can be ignored (see above). Nevertheless, as these finding is exploratory and preliminary, future research is needed. There is one other study so far that investigated an association between AB towards itch and attentional inhibition, but this study did not find a significant overall AB (nor avoidance), which makes interpretation difficult (Becker et al., 2020). Nevertheless, attention is a complex phenomenon that is interrelated with other executive functions (Diamond, 2013; Fan et al., 2002; Petersen & Posner, 2012), and accordingly, it is recommended not to study AB in isolation. There are indications that attentional control, as a part of executive functions, is compromised in patient groups (Henrich & Martin, 2018), although not always confirmed (Godfrey et al., 2020; Pidal-Miranda et al., 2019) which could suggest that executive functions play a bigger role in AB in patient groups than in healthy controls. Regarding the exploratory investigation of possible associations between itch-related cognition and AB towards itch, it is interesting to note that specifically awareness of bodily sensations is negatively related to a lower AB towards itch (see ***Table S2***). As a low (i.e. negative) index of AB actually indicates avoidance, this could mean that individuals who are more aware of bodily sensations might also be more avoidant of potential bodily harm. But this remains speculation at this point.

The current study has several limitations. First, the sample was very homogeneous with mostly female university students. Second, in the current study, the between-group difference in induced itch by using only a mild itch-stimulus was of limited size. Third, due to the subliminal design, there was no baseline itch measurement and also no proof that participants were completely itch-free before participation (e.g., no mosquito bites). Fourth, the current subliminal design appeared to be inappropriate to make good use of the eye-tracking data. Future research could aspire to circumvent these limitations by using a more pronounced itch stimulus and additionally also mention the fact that the stimulus is expected to induce itch. In this way, participants would be also consciously primed for itch which could enhance its effects on attentional processing. However, this would be difficult to combine with a preconscious design with deception as used in the present study. A possible solution might be to use longer presentation times, which make the itch-related content visible to the participant and to combine this with a very time-sensitive measurement like eye-tracking and/or electroencephalograms to differentiate between the different stages of attentional processing, e.g., early orienting towards the stimulus compared to late disengagement.

All in all, the current study found preconscious avoidance of itch-related visual stimuli in healthy individuals. Such avoidance might be different from attentional processing of actual somatosensory itch stimuli, but as somatosensory itch is difficult to study preconsciously, our study is a good approximation for a preconscious study. Furthermore, patients with chronic itch need to be investigated in the future because it can be assumed that patient’s attention towards itch-related stimuli differs compared to healthy controls which has already been shown for contagious itch which involves attentional processing (Schut et al., 2015).

Acknowledgements

We would like to thank Fabiënne van den Ende, Rose van Oostveen, Annie Nguyen, Klara Bokelmann and Diana Czepiel for their support with data collection and Rosanne van den Berg for recording the control priming sounds with us.

Figure S1. QQ-plot of the residuals of Model 1 for the reaction times outcome of the subliminal dot-probe task for itch. Inspection of the residual distribution of this QQ-plot to assess model fit and potential bias shows that the fitted models were more accurate for lower values, while being slightly biased upwards for higher values. However, inspecting the QQ-plot of Model 3 (not shown here, but similar to the QQ-plot of Model 1) with more sources of information, even after adding scores of the awareness check and control neutral picture type (skin vs. object), could not reduce the observed small bias for higher values. Note. Because all QQ-plots for all the different models are similar, this one is shown as an example for all described models in this study.

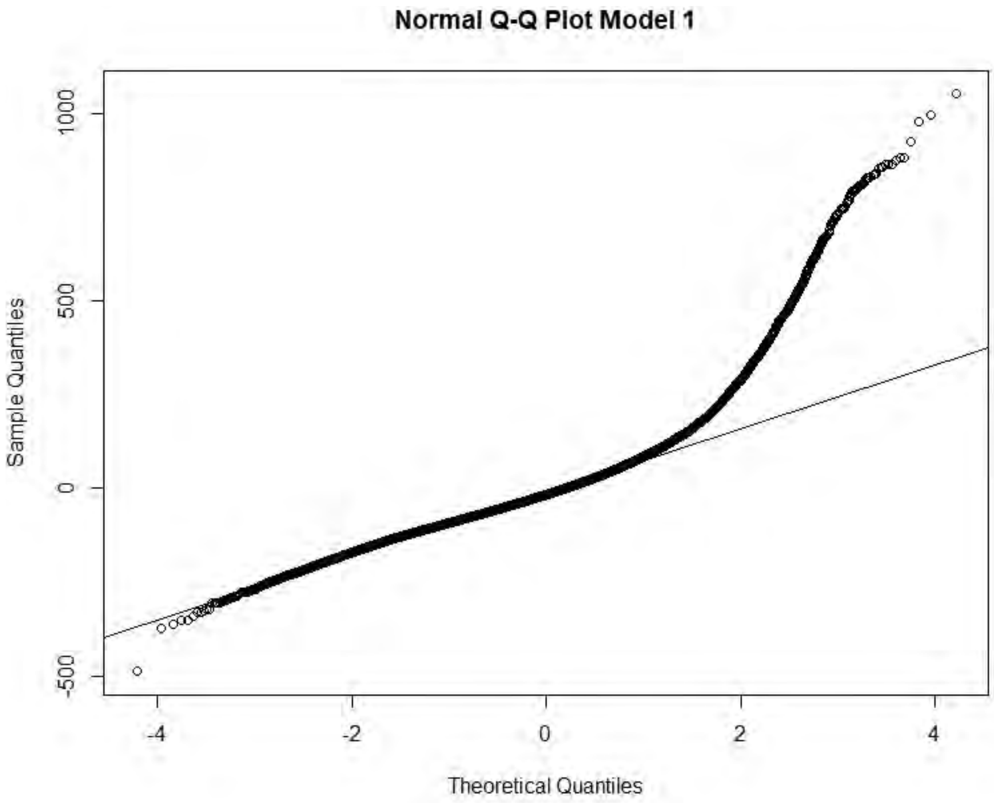


Table S1. Self-report questionnaires of individual characteristics (n = 127).

	Mean (SD)	***Range***	***Cronbach Alpha***
Item on attentional disengagement from-			
Itch	3.6 (1.0)	1 - 5	-
Pain	2.7 (1.0)	1 – 5	-
Fatigue	3.0 (0.8)	1 – 5	-
Body vigilance (BVS)	3.7 (1.6)	0.3 – 8.1	0.79
Body Vigilance – item on Itch	2.2 (2.2)	0 – 8.2	-
Body Vigilance – item on Pain	3.3 (2.5)	0 – 8.8	-
Itch vigilance and awareness (PVAQ-I)	26.0 (13.9)	2 – 75	0.91
Itch catastrophizing (PCS-I)	8.6 (8.0)	0 – 37	0.91
Cognitive intrusion of Itch (ECIP-I)	7.8 (8.7)	10 – 41	0.95
Neuroticism (EPQ-RSS-n)	7.3 (4.3)	0 – 12	0.78
Psychological distress (DASS-21)			
Depression	0.9 (1,6)	0 – 7	0.75
Anxiety	0.9 (1.5)	0 – 9	0.67
Stress	1.6 (2.5)	0 - 11	0.88

BVS = Body Vigilance Scale (theoretical range 1 – 10);
PVAQ-I = Pain Vigilance and Awareness Questionnaire -adjusted for itch (0 – 80);
PCS-I = Pain Catastrophizing Scale -adjusted for itch (0 – 52);
ECIP-I = Experience of Cognitive Intrusions of Pain Scale -adjusted for itch (10 – 60);
Note. Measured on a scale from 1-6 instead of 0-6 like in the original ECIP
EPQ-RSS-n = Neuroticism Scale of Eysenck Personality Questionnaire – revised short form (0 – 12)
DASS-21= Depression, Anxiety, and Stress Scale- short form (0 – 10 for each subscale)

Table S2. Spearman rho (ρ) correlations between individual characteristics and the Attentional Bias (AB) Index for itch (n = 127).

	AB Itch
Item on attentional disengagement from -	
Itch	-0.16
Pain	0.05
Fatigue	-0.02
Body vigilance (BVS)	-0.06
Body Vigilance – item on Itch	-0.34 *
Body Vigilance – item on Pain	-0.23 *
Itch vigilance and awareness (PVAQ-I)	-0.20 *
Itch catastrophizing (PCS-I)	0.02
Cognitive intrusion of Itch (ECIP-I)	0.01
Neuroticism (EPQ-RSS-n)	-0.03
Flanker Index	0.07
Switch Cost	0.02

* $p < 0.05$
BVS = Body Vigilance Scale (theoretical range 1 – 10);
PVAQ-I = Pain Vigilance and Awareness Questionnaire -adjusted for itch (0 – 80);
PCS-I = Pain Catastrophizing Scale -adjusted for itch (0 – 52);
ECIP-I = Experience of Cognitive Intrusions of Pain Scale -adjusted for itch (10 – 60);
Note. Measured on a scale from 1-6 instead of 0-6 like in the original ECIP
EPQ-RSS-n = Neuroticism Scale of Eysenck Personality Questionnaire – revised short form (0 – 12)

Table S3. Exploratory analyses of the effect of the Flanker Index and Switch Cost on attentional bias during the subliminal dot-probe task for itch: estimates (ES) with standard errors (SE), significance level (p-value) and 95% Confidence Intervals (95% CI) (n = 125)

		ES	*SE*	*p-value*	*95% CI*
Model 2a	(Intercept)	471.4	15.19	< 0.001	[441.84, 500.88]
	Accuracy	19.75	1.24	< 0.001	[15.36, 24.14]
	Congruency	-3.08	2.86	0.282	[-8.68, 2.53]
	Group	-11.75	11.95	0.328	[-34.98; 11.49]
	Flanker Index	-0.33	0.24	0.182	[-0.80, 0.15]
	Switch Cost	0.07	0.07	0.333	[-0.07, 0.21]
	Congruency * Group	1.52	2.28	0.505	[-2.95, 5.98]
	Flanker Index * Congruency	-0.01	0.05	0.898	[-0.10, 0.09]
	Switch Cost * Congruency	0.001	0.01	0.922	[-0.03; 0.03]
Model 2b	(Intercept)	471.5	15.15	< 0.001	[442.04, 500.94]
	Accuracy	19.75	2.24	< 0.001	[15.36, 24.14]
	Congruency	-3.34	1.96	0.088	[-7.19, 0.51]
	Group	-11.74	11.95	0.328	[-34.98, 11.49]
	Flanker Index	-0.33	0.24	0.176	[-0.80, 0.14]
	Switch Cost	0.07	0.07	0.334	[-0.07, 0.21]
	Congruency * Group	1.52	2.28	0.506	[-2.95, 5.98]
	Switch Cost * Congruency	0.001	0.01	0.920	[-0.03, 0.03]

Note. Model 2a: AIC = 491222.8; Model 2b: AIC = 491216.5

CHAPTER 5

Attentional bias modification training for itch: a proof-of-principle study in healthy individuals

Published as

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Abstract

Itch draws our attention to allow imposing action against bodily harm (e.g., remove insects). At the same time, itch is found to interfere with ongoing tasks and daily life goals. Despite the key role of attention in itch processing, interventions that train individuals to automatically disengage attention from itch cues are lacking.

The present proof-of-principle attention bias modification (ABM) training study was aimed at investigating whether attention to itch as well as sensitivity to mild itch can be changed. Healthy volunteers were randomized over three ABM-training conditions. Training was done via a modified pictorial dot-probe task. In particular, participants were trained to look away from itch stimuli (n = 38), towards itch stimuli (n = 40) or not trained towards or away from itch at all (sham training, n = 38). The effects of the ABM-training were tested primarily on attention to itch pictures. Secondarily, it was investigated whether training effects generalized to alterations in attention to itch words and mechanical itch sensitivity. The ABM-training did not alter attention towards the itch pictures, and there was no moderation by baseline levels of attention bias for itch. Also, attention bias to the itch words and itch sensitivity were not affected by the ABM-training.

This study was a first step towards trainings to change attention towards itch. Further research is warranted to optimize ABM-training methodology, for example increasing motivation of participants. Eventually, an optimized training could be used in patient populations who suffer most from distraction by their symptoms of itch.

Introduction

Itch, and particularly chronic itch interferes with one's behavior and psychosocial functioning (Jensen et al., 2018; Matterne et al., 2011; Strom et al., 2016). In turn, reduced psychosocial well-being can intensify itch, resulting in a vicious cycle (Mochizuki et al., 2019; van Laarhoven et al., 2012). Unique for itch compared to pain is that it can be further amplified or even induced audiovisually (e.g., by hearing scratch sounds or looking at pictures of scratching people); i.e. itch is contagious and this is amplified in itch patients (Schut et al., 2015). A key mechanism of contagious itch is attention (Holle et al., 2012; A. van Laarhoven & Holle, 2019). Focusing attention on potential threats is essential to sort its nocifensive function and protect skin integrity (Paus et al., 2006; Ross, 2011). Since attention may play a central role in the vicious circle of itch amplification (van Laarhoven et al., 2010) and psychological burden (Becker et al., 2022; Evers et al., 2019; van Laarhoven et al., 2017; van Laarhoven et al., 2018, 2020), interventions targeting attention to itch seem promising.

Research indicates that patients with chronic itch may have increased attention (AB; attention bias) towards words related to itch compared to neutral words (van Laarhoven et al., 2016), and compared with healthy controls (Fortune et al., 2003). Similarly, healthy individuals display an AB towards itch words and pictures (van Laarhoven et al., 2017, 2018), although evidence is equivocal (Becker et al., 2022). Some techniques have been investigated to reduce itch temporarily (Leibovici et al., 2009; Stumpf et al., 2017) , but no strategies exist that reduce AB to itch; hence attention strategies effectuating longer-term itch relief are lacking. Attention bias modification (ABM) training for itch may offer a solution, as such training has been shown effective in other fields (Jones & Sharpe, 2017).

In the domain of pain, closely related to itch (Ikoma et al., 2006; Ross, 2011), ABM-trainings have been developed to alter AB for pain. Such ABM-trainings aim to train individuals to automatically focus attention on neutral stimuli while concurrently displaying pain stimuli (pain-related words and/or painful faces). Initial studies in patients with chronic pain indicated that single- as well as multi-session ABM-trainings could reduce pain sensitivity (Carleton et al., 2011; Schoth et al., 2013; Sharpe et al., 2012). In healthy individuals, ABM-trainings affected pain thresholds, pain tolerance, or experienced pain (Bowler et al., 2017; McGowan et al., 2009; Sharpe et al., 2015; Todd et al., 2016), and some studies demonstrated altered AB for pain (McGowan et al., 2009; Sharpe et al., 2015). In addition, a study has shown that the effects of an ABM-training with words generalized to effects on AB for painful faces after the training (Sharpe et al., 2015). Furthermore, individual characteristics, like catastrophizing or the ability to inhibit attention to irrelevant information (as feature of executive control), may play a role in (the retraining of) AB for pain (Goubert et al., 2004; Heathcote et al., 2015; Van Ryckeghem et al., 2019). All in all, evidence on ABM-training effectiveness in pain as well as the role of individual characteristics is equivocal (Bowler et al., 2017; Crombez et al., 2013; Heathcote et al., 2017; Van Ryckeghem, Van Damme, Vervoort, 2018; Todd et al., 2016). Overall, based on theory and promising evidence in pain, it seems worthwhile to investigate whether an ABM-training for itch would be effective to reduce itch sensitivity and/or AB towards itch. However, to our knowledge, an ABM-training for itch has not yet been developed. As a first step of intervention-development, it should be verified whether AB towards itch can be trained – in either direction (i.e. in a proof-of-principle study; Wiers et al., 2018).

In this proof-of-principle study, we aimed to investigate whether AB to itch pictures can be altered by an ABM-training away from and towards pictorial itch stimuli. Furthermore, we investigated whether these effects would generalize to altered AB to itch words and actual itch sensitivity. It was hypothesized that, when compared to sham training, an ABM-training away from itch pictures would result in AB away from itch pictures and words as well as a lowered itch sensitivity, whereas an ABM-training towards itch would effectuate the opposite. Additionally, the possible role of individual characteristics, including general attentional inhibition, neuroticism, and itch catastrophizing, in the ABM-training effects was explored. Moreover, given some recent evidence (Fox et al., 2015), we explored post-hoc whether the training effects were moderated by the baseline AB for itch.

Materials and Methods

Design

This study comprises a 2 (pre-training, post-training) x 3 (ABM-training away from itch, ABM-training towards itch, sham training: equal allocation ratio) mixed research design with AB to itch pictures, AB to itch words and sensitivity to mechanically induced itch as dependent variables. This study was preregistered in the Netherlands Trial Registry under number: NL6134 (/NTR6273). The protocol was approved by the Psychology Research Ethics Committee of Leiden University (CEP17-0228/116).

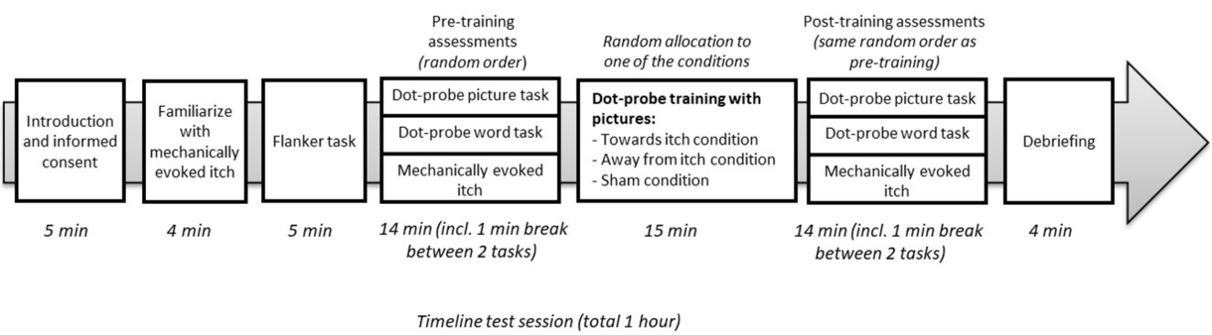
Participants

Participants were recruited through advertisements on social media, at Leiden University, and via the Leiden University Research Participation system SONA systems Ltd (Tallinn, Estonia). Recruitment and testing took place between March and May 2017. Inclusion criteria for participation were being aged between 18 and 30 years and being proficient in the Dutch language. Exclusion criteria were current itch or pain ≥ 3 on a numeric rating scale (NRS) from 0 (no itch/pain) to 10 (worst imaginable itch/pain), diagnosis of a chronic itch or pain condition (e.g., eczema or rheumatoid arthritis), psychiatric diagnosis (e.g., major depression or ADHD), color blindness, dyslexia, and impairment in visual acuity that is not corrected with glasses or contact lenses. All participants provided written informed consent for their participation in the study.

Procedure

Potential participants were informed about the study via written information and, when interested in participation, they were asked to fill out (online) self-report questionnaires, which also included questions regarding the in- and exclusion criteria (see *Self-report questionnaires*). When found eligible for participation, participants were instructed to refrain from intake of alcohol and drugs 24 hours before the test session and of caffeinated drinks within one hour before the session started. Adherence to this guideline was checked in the lab (n = 1 missing), resulting in 15 participants who had taken alcohol the preceding 24 hours (11 of them drank ≤ 2 units), 5 participants who had taken caffeinated drinks in the preceding hour (all ≤ 2 units), and none had used drugs. During each session, two experimenters were present, one conducting the practical tasks (e.g., starting computer tasks and itch stimulus application) and the other one guiding participants through the procedures, mainly by providing instructions. Upon arrival at the Leiden University lab (see ***Figure 1*** for a timeline), participants were verbally informed about the study procedures and told that they were free to terminate the experiment at any time. Next, participants signed the informed consent and rated their current levels of spontaneous itch and pain on the NRSs. Participants were familiarized with the mechanical itch induction by applying Touch test evaluators as described in the paragraph *Mechanical itch sensitivity* (ca. 4 min). Thereafter, the Flanker task (ca. 5 min) was conducted measuring general response inhibition (*Flanker task*). Consecutively, participants

Figure 1. Timeline of the experimental session (total ca. 1 hour)



performed the pre-training AB assessments using the dot-probe task with pictures (ca. 5 min), the dot-probe task with words (*Dot-probe tasks;* ca. 5 min), and the mechanical itch induction (ca 2 min). These tasks were provided in random order, i.e. an independent person had put the randomization information in opaque envelopes stratified by participant's sex and handedness. After these pre-training assessments, participants were randomized to one of the three ABM-training (ca. 15 min) conditions (participants were blind for receiving any intervention). Post-training assessments were carried out in the same order as the pre-training assessments of that specific participant. Upon completion of the tasks, participants were debriefed about the purposes of the study and reimbursed for their participation.

Measures

All computer tasks were run on a desktop computer with Microsoft Windows 7 attached to a Philips Brilliance 220B TFT screen (Resolution 1280px x 1024px, 60Hz). Both the Dot-probe task and the Flanker task were programmed and run in E-prime 2.0 (Psychology Software Tools Inc., Sharpsburg, PA, USA). Randomization to one of the ABM-training conditions was also done in E-prime based on participant number (this was unknown to the experimenters), with separate lists for males and females. E-prime automatically started the correct condition the participant was randomized to, so the participant was blinded. Responses were given using finger response buttons, one for each hand (Pushbutton Switch, SPDT, Off-(On)) connected to a serial response box model 200A (Psychology Software Tools Inc. Sharpsburg, PA, USA). During the tasks, participants kept their head in a chin rest to keep the distance to the screen at 54 cm.

Dot-probe tasks

A dot-probe paradigm was used to measure AB towards itch pictures and words. The dot-probe paradigm assumes that being attentive to a stimulus speeds up responding to targets at the focused location (congruent trials) when compared to the opposite location (incongruent trials). There were in total 60 stimulus pairs of an itch-related and a neutral stimulus (40 picture-pairs and 20 word-pairs with Dutch words). Itch stimuli depicted a hand scratching him-/herself on e.g., the head, limb and back. Neutral stimuli depicted objects, e.g., light bulb, doorbell, and spoon. The itch stimuli had been validated earlier (Becker et al., 2020) on the basis of their applicability to itch (average itch scores per task ranged from 2.7 to 2.8 for the dot-probe tasks assessing AB and the ABM-training task rated on a Likert scale from 1 (not applicable to itch) to 5 (very applicable to itch), non-applicability to pain (average pain scores ranged from 1.0 to 1.4 on a 1 to 5 Likert scale for pain) and slightly negative valence (ranging from -1.2 to -1.1 on a Likert scale ranging from -5 (very negative) to 5 (very positive)), whereas the neutral stimuli were characterized as neither itchy nor painful (average itch and pain scores were 1.1 at maximum), and were of neutral valence (average score ranging from 0.1 to 0.2) (Becker et al., 2020). Based on the validation scores, the picture-pairs were randomized in advance over three pictorial dot-probe tasks, i.e., two regular dot-probe tasks (10 stimulus-pairs each) and one training dot-probe task (20 stimulus-pairs). The word-pairs were randomized in advance, across two regular dot-probe tasks. Randomization of the stimulus-pairs occurred on basis of the previously acquired validation ratings on itch in order to make sure that the itch ratings would overall be comparable across the dot-probe tasks used. For each participant, the order of the two dot-probe tasks was randomized (i.e. one was administered pre-training and the other post-training). The regular dot-probe tasks contained 40 trials each (van Laarhoven et al., 2018). Half of the trials were congruent (itch stimulus and target at same location) and half of the trials were incongruent (itch stimulus and target at opposite location). The proportion of itch stimuli displayed in the upper and lower half of the screen was equal over all trials. Right before the experimental trials in the pre-training dot-probe tasks only, there were 16 practice trials with neutral-neutral stimulus pairs. Feedback on the accuracy of responses to the targets was included. A trial was constructed as follows: First, a fixation point was shown in the middle of the screen for 500ms. Upon disappearance, a stimulus pair was presented on the screen for 500ms (Bowler et al., 2017; Crombez et al., 2013; Sharpe et al., 2015). One stimulus of each pair was presented centrally at the lower half of the screen (20% height), and the other was presented centrally at the upper half of the screen (80% height). The stimulus-pair was followed by a target stimulus that consisted of two dots aligned either horizontally or vertically. The target stimulus was presented at either one of the stimulus locations until the participant pressed a response button, with a maximum response window of 1500ms. Correct response-mapping was counterbalanced across participants, i.e. right button for horizontally oriented target stimuli and left button for vertically oriented target stimuli or vice versa (e.g., a participant responded with the right button to horizontally oriented targets in all dot-probe tasks). Reaction times and accuracy in responding to the targets were measured.

The ABM-training exclusively contained pictorial stimuli. The training task was comparable to the regular dot-probe tasks, but contained 320 trials (Sharpe et al., 2012) and the locations of the targets as opposed to the itch pictures were manipulated in the ABM-training conditions that were trained towards and away from itch. Specifically, in the training condition towards itch, 100% of the trials were congruent (i.e. at the itch picture location), whereas, in the ABM-training away from itch condition, 100% of the trials were incongruent (i.e. at the neutral picture location). In the sham training condition, 50% of the targets were displayed congruently and 50% were shown incongruently to the itch picture location, akin to the regular dot-probe tasks. One-minute breaks were built-in after every 40 trials.

Mechanical itch sensitivity

Sensitivity to touch evoked itch (STI) was assessed, using three von Frey monofilaments (4.08 mN, 4.17 mN, and 4.31 mN; Stoelting, North Coast Medical, Gilroy, CA) as described in previous research (Andersen, van Laarhoven, et al., 2017). The monofilaments were applied to the non-dominant inner forearm. Each filament was applied for 1s in triplicate after which the participants rated the evoked itch per filament on the NRS for itch.

Flanker task

This task (Eriksen & Eriksen, 1974; Moore et al., 2012) was used to measure general attentional inhibition. In each trial, 5 numbers were shown. The middle number was the target stimulus, which was flanked by non-target stimuli. The flankers could be congruent to the target stimulus, e.g., 44444, or incongruent, e.g., 44244. Half of the trials were congruent and half were incongruent and the use of 2's and 4's was balanced across the task. The task contained 120 experimental trials and 8 practice trials without feedback at the beginning of the task. The left response button was used to indicate '2' as target and the right button was used to indicate '4'. A short break was included half-way the task if desired. The average reaction time to the congruent versus the incongruent target stimuli is the outcome measure.

Self-report questionnaires

Questions assessing demographic information (e.g., age) and information required to screen for in- and exclusion criteria (e.g., having medical or psychiatric conditions, experiencing spontaneous itch or pain) were included. In addition, *attentional focus on bodily sensations* was measured using both the Body Vigilance Scale (BVS with Cronbach alpha 0.70) as previously described (i.e. only including the sub items of question 4 that concern bodily sensations) (van Laarhoven et al., 2010) with two additional items assessing one's attention directed towards itch and pain and the Pain Vigilance and Awareness Questionnaire adjusted for itch (PVAQ-I with Cronbach alpha 0.88). Adjustments for itch were made by substituting the word "pain" by "itch" for all concerning items. This procedure was also applied to the following questionnaires originating from the pain field. *Catastrophizing* about itch was measured using the Pain Catastrophizing Scale adjusted for itch (PCS-I with Cronbach alpha 0.91) (Andersen, van Laarhoven, et al., 2017). *Experience of*

Cognitive Intrusion of itch was assessed using the Experience of Cognitive Intrusion of pain scale adjusted for itch and, accidentally, with scales ranging from 1 to 6 for each item instead of 0 to 6 like the original version (ECIP-I with Cronbach alpha 0.96). *Attentional disengagement from itch and pain* was assessed using two Likert scales ranging from 1 (not at all able to disengage attention) to 5 (always able to disengage attention) (van Laarhoven et al., 2017). Finally, *Neuroticism* was measured with the Eysenck Personality Questionnaire revised short scale (EPQ-RSS with Cronbach alpha=0.72) (Eysenck, 1991). All self-report questionnaires were administered in Dutch using the online system Qualtrics (Provo, Utah, USA).

Statistical analyses

All statistical analyses were conducted using SPSS 25.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA) if not specified otherwise. All values displayed are means ± standard deviation (SD), if not stated otherwise. Effect sizes were reported as partial eta squared (η_p^2). A $p < 0.05$ was considered statistically significant.

For the dot-probe tasks, reaction times (RT) were extracted from E-prime for trials with RT ≥ 150ms (0.2% and 0.08% of the RT were excluded for the picture and word tasks respectively) and trials with correct responses (7.2% and 8.5% of the RT were excluded from the picture and word tasks, respectively). Cases for which no responses were recorded due to a programming error (see paragraph *Sample*) were excluded from the respective analysis. Participants' data that had accuracy levels below 70% were excluded from the respective analyses; in the case that < 70% of the trials in the training were incorrect, this participant was not included in any of the analyses. For the pre- and post-training dot-probe tasks, AB-indices were calculated by subtracting the RT of the congruent trials from the RT of the incongruent trials ($RT_{incongruent} - RT_{congruent}$). A positive AB-index indicates an AB towards itch, whilst a negative AB-index indicates an AB away from itch. All variables to be included in the statistical analyses were checked for normality.

First, baseline between-group differences in demographics, current spontaneous itch and pain, total scores of the questionnaires, AB towards itch pictures and words, mechanically evoked itch, and general attentional inhibition (i.e. Flanker task) were assessed using Kruskal-Wallis tests for interval variables (due to a violation of normality for most variables) and a Chi-square test for the dichotomous variable sex. Second, the presence of ABs towards itch pictures and words at baseline was tested using one-sample t-tests checking whether the AB-index significantly differed from 0. Additionally, the effectiveness of participants' attentional inhibition (entire group) was checked by comparing the RT on the congruent and incongruent trials of the Flanker task as a within-subjects factor in a repeated measures analysis of variance (RM-ANOVA).

For the primary aim to assess whether ABM-training resulted in altered attention to itch pictures, a 2 x 2 x 3 RM-ANOVA was conducted with the within-factors *itch congruency* (congruent vs incongruent trials) and *time* (pre- vs post-training assessments) and the between-factor *condition* (ABM-training away, ABM-training towards, sham training). Additionally, post hoc moderation analyses were carried out using the Process Macro v3.3 (Hayes, 2018) (model 1) in SPSS to investigate whether the effects of the training were different depending on the baseline level of AB towards the main outcome of itch pictures. Here, *condition* was the independent variable (X), the training effect on itch pictures (AB-index $_{post\text{-}training}$ – AB-index $_{pre\text{-}training}$) was the dependent variable (Y; centered) and the pre-training AB towards itch pictures was the moderator variable. Another post-hoc RM-ANOVA tested the change in AB-index for the itch pictures before vs. after the training in the entire sample.

For the secondary aim to assess the effect of the ABM-training on itch words, a RM-ANOVA akin the one with pictures was conducted with the RT of the word dot-probe tasks. For the mechanical itch sensitivity outcome, pre- and post-training levels of evoked itch, as subjectively rated on NRS, were compared using a RM-ANOVA with the within-factor *time* (mechanically evoked itch pre- vs post-training) and the between-factor *condition* (ABM-training away, ABM-training towards, sham training). Finally, to test associations between the main study outcomes and the individual characteristics, Spearman correlation coefficients (ρ) were calculated for each condition separately. Specifically, the ABM-training effects on the AB towards itch pictures and AB towards itch words (both AB-index post-training – AB-index pre-training) as well as itch sensitivity (pre – post assessment) were correlated with both the Flanker index ($RT_{incongruent}$- $RT_{congruent}$) and the total scores of the self-report questionnaires. The Sidak-Holm correction was applied for all RM-ANOVAs when performing post-hoc tests.

Reliability of the dot-probe tasks was assessed with split-half reliabilities. These were calculated with R (R version 4.0.3);(R Core Team, 2019) with the ‘splithalfr’ package (Pronk, 2020). The reliability of the AB index was calculated for all four versions of the dot-probe task (version 1 and version 2 with pictures as well as version 1 and version 2 with words) of all participants that were included in the analyses. The function used a Monte-Carlo splitting technique to estimate 5000 split-half samples that were used to estimate Spearman-Brown correlations for all 5000 samples. The resulting mean and median coefficients of all 5000 samples accompanied by the minimum, maximum, and interquartile range were calculated per task.

Results

Sample

We aimed to include 40 participants per condition as this would be sufficient to detect a small effect (in GPower 3.1.6, effect size f of 0.10; with an alpha of 0.05, power of 0.80 and an estimated correlation between the pre- and post- measurements between 0.75 and 0.80). On top, 5% of participants extra were tested in order to be able to overcome potential data loss. Therefore, 126 participants had been included in the study. For the following reasons, data of several participants could not be used in data analyses: Seven participants responded differently to the orientation of the dots during the training task as opposed to the pre- and post-training dot-probe tasks due to incorrectly provided instructions (e.g., they were instructed to respond to horizontal oriented targets with the right button during the pre- and post-training dot-probe tasks and with the left button during training). Due to a programming error, data of the dot-probe picture and word tasks had not been recorded /could not be retrieved for two participants and for similar reasons data of another 12 participants was unavailable for the word tasks (amongst them, there was one participant of whom data of the mechanically evoked itch were missing, too). Moreover, one participant was excluded from the main analysis because of exceeding the predetermined 30% error rate (specifically 33% errors) for the post-training dot-probe picture task. None of the participants had to be excluded based on their number of errors during the ABM-training; at maximum 18% of the trials were incorrect (n = 1). Finally, 116 participants could be included in the main analysis with the pictorial stimuli, 105 in the secondary analyses with the word stimuli, and 116 in the analyses for the mechanically evoked itch. The sample of 116 participants was mostly female (74%), right-handed (89%) and most participants were following or had finished tertiary education (85%). Participants' baseline characteristics did not differ across training conditions (***Table 1***). Median levels of spontaneous itch and pain at baseline were 0.0.

Dot-probe tasks

Reliability was good for all versions of the task with a mean Spearman-Brown coefficient between 0.61 and 0.71, based on 5000 split-half samples, see ***Table 2***. For the dot-probe task with pictures and the itch sensitivity analyses, one outlier (> 3 interquartile range) was excluded (final $n = 115$ for both outcomes). Variables for the dot-probe task with pictures were log-transformed to obtain normal distribution.

Pre-training AB towards itch pictures and words

The one-sample t-test with the pre-training AB-index differed significantly from zero ($t(114) = -2.26$, $p= 0.026$), indicating that participants overall were focused away from the itch pictures at baseline (see ***Table 3*** for descriptive values). There was no pre-training AB for itch words ($t(104) = 0.248$, $p = 0.805$) (***Table 4***). The RM-ANOVA demonstrated that ABM-training conditions did not significantly differ in their pre-training AB-index for itch pictures ($F(2,113) = 0.09$, $p = 0.911$, $\eta_p^2 = 0.002$) or words ($F(2,102) = 0.559$, $p = 0.574$, $\eta_p^2 = 0.011$).

Training AB towards itch pictures

The 2 (time: pre- vs post- training) x 2 (itch congruency: itch-congruent vs itch-incongruent) x 3 (training condition) RM-ANOVA, testing the main hypothesis whether training attention away and towards pictorial itch stimuli altered attention towards itch pictures (***Figure 2***, ***Tables 3A*** and ***B***) showed no significant time x itch congruency x condition effect ($F(2,112) = 0.41$, $p = 0.663$, $\eta_p^2 = 0.007$). There was a significant main effect of time ($F(1,112) = 199.87$, $p < 0.001$, $\eta_p^2 = 0.641$), showing that RT were shorter after the training than before (***Tables 3A*** and ***B***). There was

Table 1. Baseline individual characteristics per attention bias modification (ABM) training condition. Values displayed are medians (interquartile range: IQR) and absolute numbers for the variable sex

See table on next page.

	Total sample	ABM-training away from itch (n=38)	ABM training towards itch (n=40)	Sham training (n=38)	Statistic for condition difference
Prior to session					
Sex (*n* M/F)	30 / 86	11 /27	10 /30	9 /29	χ^2 (2) = 0.298, *p* = 0.861
Age	22 (21;23)	22 (21; 23)	22 (21;23)	21 (21; 23)	*H*(2) = 0.021, *p* = 0.990
Body vigilance (BVS)	3.0 (1.8; 3.9)	3.2 (1.6; 4.0)	2.9 (1.8; 3.8)	3.1 (1.9; 3.9)	*H*(2) = 0.044, *p* = 0.978
Single item for attentional focus on itch / pain (0-10)	1.6 (0.3; 3.8) / 2.3 (0.7; 5.0)	1.3 (0.2; 3.9) / 2.2 (1.5; 5.0)	1.6 (0.7; 3.2) / 2.9 (0.8; 5.0)	1.7 (0.1; 3.8) / 1.8 (0.5; 5.0)	*H*(2) = 0.418, *p* = 0.811 / *H*(2) = 0.910, *p* = 0.635
Itch vigilance and awareness (PVAQ-I)	25.0 (17.0; 32.0)	24.5 (17.8; 31.0)	22.5 (15.3; 32.0)	28.0 (16.8; 32.8)	*H*(2) = 1.067, *p* = 0.587
Single item for attentional disengagement from itch/pain	4.0 (3.0; 5.0) / 4.0 (3.0; 4.0)	4.0 (3.0; 5.0) / 4.0 (3.0; 4.0)	4.0 (3.0; 5.0) / 4.0 (3.0; 4.0)	5.0 (3.8; 5.0) / 4.0 (3.0; 5.0)	*H*(2) = 3.883, *p* = 0.143 / *H*(2) = 2.770, *p* = 0.250
Itch catastrophizing (PCS-I)	6.0 (2.0; 12.0)	7.5 (3.5; 12.0)	6.0 (2.0; 12.8)	5.5 (2.0; 12.3)	*H*(2) = 0.454, *p* = 0.797
Cognitive intrusions of itch (ECIP-I)	14.0 (11.0; 22.0)	14.0 (11.0; 22.0)	15.0 (11.0; 22.3)	13.0 (11.0; 22.3)	*H*(2) = 0.372, *p* = 0.830
Neuroticism (EPQ-RSS)	3.0 (2.0; 5.0)	3.0 (2.0; 5.0)	3.5 (2.0; 6.0)	3.0 (1.0; 6.0)	*H*(2) = 1.806, *p* = 0.405
During session					
General response inhibition (Flanker index)	51.1 (37.3; 64.1)	52.9 (40.8; 66.0)	54.7 (39.4; 64.1)	47.2 (31.8; 60.8)	*H*(2) = 1.820, *p* = 0.403

Abbreviations: EPQ-RSS: Eysenck Personality Questionnaire revised short scale (theoretical range 0-12 neuroticism subscale); Single items assessing attentional focusing on itch and pain (theoretical range 0-10); BVS: Body Vigilance Scale (theoretical range 0-10); PVAQ-I: Pain Vigilance and Awareness Scale, adjusted for itch (theoretical range 0-80); PCS-I: Pain Catastrophizing Scale, adjusted for itch (theoretical range 0-52); ECIP-I: Experience of Cognitive Intrusions of Pain, adjusted for itch (theoretical range original version 0-60 – in the current study 10-60); Single items about attentional disengagement (theoretical range 1-5). The flanker index was calculated by subtracting the RT for congruent trials from the RT from incongruent trials. Because most questionnaires were not-normally distributed, the conditions were compared using non-parametric Kruskal-Wallis tests (H) on most outcomes, except for sex, which was compared in a Chi-square test.

Table 2. Reliability coefficients for the different versions of the dot-probe tasks. Mean and the range of the Spearman-Brown coefficient of 5000 split-half samples are reported, as well as the median and interquartile range (IQR)

Dot-probe tasks with pictures	Version 1	0.68 (0.34 – 0.84)	0.68 (0.64; 0.72)
	Version 2	0.71 (0.41 – 0.70)	0.72 (0.68; 0.75)
Dot-probe tasks with words	Version 1	0.67 (0.23 – 0.86)	0.68 (0.62; 0.72)
	Version 2	0.60 (0.20 – 0.84)	0.61 (0.55; 0.66)

Table 3A. Mean ± standard deviation of reaction times for the trials congruent and incongruent to the itch pictures of the dot-probe tasks administered pre- and post-attention bias modification (ABM)-training, displayed for the total sample and per training condition.

		Total sample (n = 115)	***ABM-training away from itch (n = 38)***	***ABM-training towards itch (n = 40)***	***Sham training (n = 37)***
Pre-training	Congruent trials	545.4 ± 77.5	544.7 ± 67.8	537.1 ± 75.2	555.0 ± 89.5
	Incongruent trials	536.2 ± 77.8	532.1 ± 65.8	528.7 ± 83.8	548.5 ± 83.0
	AB-index	-9.1 ± 43.4	-12.6 ± 38.0	-8.4 ± 41.5	-6.5 ± 51.0
Post-training	Congruent trials	474.0 ± 63.3	475.1 ± 62.0	462.7 ± 50.2	485.0 ± 75.8
	Incongruent trials	475.1 ± 68.9	473.4 ± 65.4	467.8 ± 58.7	484.9 ± 82.1
	AB-index	1.2 ± 31.5	-1.7 ± 30.0	5.1 ± 31.8	-0.1 ± 33.2

neither a significant main effect of congruency ($F(1,112) = 2.46$, $p = 0.120$, $\eta_p^2 = 0.022$) nor of condition ($F(2,112) = 0.753$, $p = 0.473$, $\eta_p^2 = 0.013$).

Training AB towards itch words

The 2 x 2 x 3 RM-ANOVA testing the secondary hypothesis of whether ABM-training away and towards pictorial itch stimuli would generalize to changes in AB towards itch words showed no significant time x itch congruency x condition effect ($F(2,102) = 0.091$, $p = 0.913$, $\eta_p^2 = 0.002$). The significant main effect of time ($F(1,102) = 118.29$, $p < 0.0001$, $\eta_p^2 = 0.537$) showed RT to be shorter after the training than

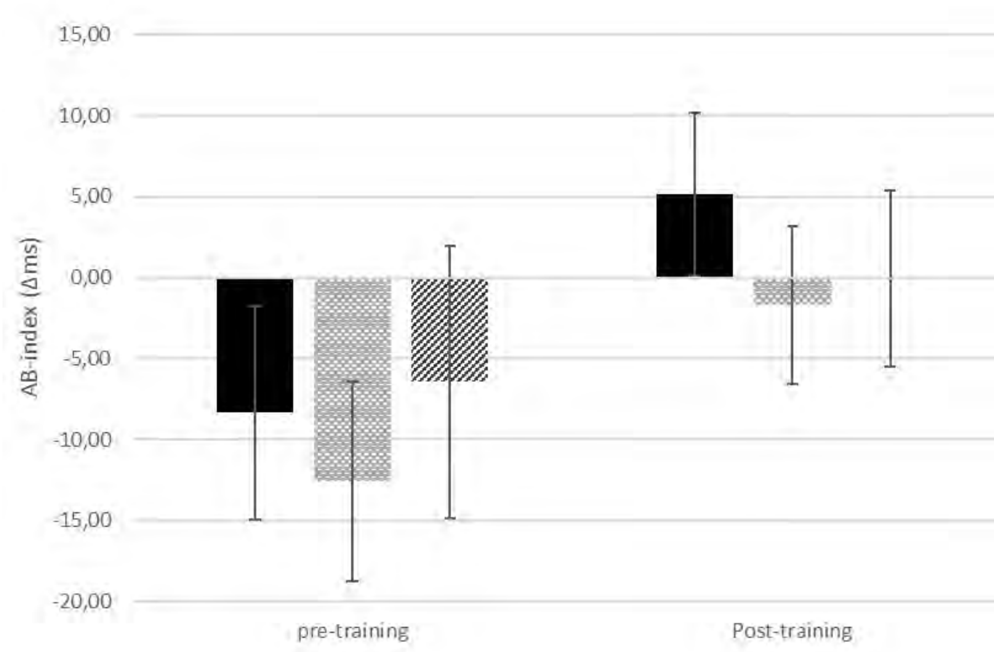
Table 3B. Median (and interquartile range; IQR) of reaction times for the trials congruent and incongruent to the itch pictures of the dot-probe tasks administered pre- and post-attention bias modification (ABM)-training, displayed for the total sample and per training condition.

	Trial Type	*Total sample (n = 115)*	*ABM-training away from itch (n = 38)*	*ABM-training towards itch (n = 40)*	*Sham training (n = 37)*
Pre-training	Congruent trials	534.2 (488.9; 580.7)	535.0 (492.7; 579.7)	529.3 (485.5; 567.1)	537.4 (491.3; 605.4)
	Incongruent trials	521.3 (473.0; 579.8)	515.6 (480.2; 574.2)	511.1 (468.6; 566.5)	531.6 (476.0; 613.0)
Post-training	Congruent trials	464.3 (429.0; 507.5)	453.7 (430.2; 510.5)	458.8 (426.9; 501.8)	480.2 (424.5; 536.1)
	Incongruent trials	463.2 (426.4; 516.6)	460.6 (423.2; 513.6)	462.6 (424.4; 503.6)	480.9 (430.3; 533.6)

Table 4. Mean ± standard deviation of reaction times for the trials congruent and incongruent to the itch words of the dot-probe tasks administered pre- and post-training, displayed for the total sample and per attention bias modification (ABM)-training condition.

	Trial Type	*Total sample (n = 115)*	*ABM-training away from itch (n = 38)*	*ABM-training towards itch (n = 40)*	*Sham training (n = 37)*
Pre-training	Congruent trials	557.6 ± 84.9	544.6 ± 87.9	535.9 ± 67.4	591.1 ± 89.4
	Incongruent trials	558.5 ± 85.0	550.2 ± 90.7	537.9 ± 69.5	586.8 ± 88.2
	AB-index	0.9 ± 39.2	5.5 ± 35.9	2.0 ± 32.0	-4.3 ± 48.1
Post-training	Congruent trials	497.6 ± 62.9	483.1 ± 47.6	481.6 ± 62.4	527.0 ± 66.5
	Incongruent trials	494.1 ± 61.3	487.3 ± 55.4	476.7 ± 55.3	517.8 ± 66.2
	AB-index	-3.5 ± 36	4.2 ± 34.9	-4.9 ± 38.1	-9.2 ± 34.7

Figure 2. Attentional Bias (AB)-index for the itch pictures pre- and post-ABM-training. Results are displayed for the ABM-training away from itch (black; *n* = 38), ABM-training towards itch (light grey dots; *n* = 40), and the sham training (intermediate grey stripes; *n* = 37). Positive values indicate an AB towards itch. Error bars represent standard errors of the mean.



before (***Table 4***). No significant main effect of itch congruency ($F(1,102) = 0.194$, $p = 0.661$, $\eta_p^2 = 0.002$), but a significant main effect of condition was found ($F(2,102) = 5.842$, $p = 0.004$, $\eta_p^2 = 0.103$) with contrasts showing that RT for targets was faster in both, the condition trained away and towards itch, than in the sham training condition (mean difference (*MD*)= -39.4, standard error(*SE*)=15.2, $p = 0.032$ and *MD* = -47.7, *SE* = 14.9, $p = 0.005$, respectively).

Itch sensitivity

On the pre-training assessment of mechanically evoked itch (log-transformed), training conditions did not significantly differ ($F(2,112) = 0.458$, $p = 0.634$, $\eta_p^2 = 0.008$). The 2 x 3 RM-ANOVA testing the secondary hypothesis whether

ABM-training attention away and towards pictorial itch stimuli would generalize to changes in itch sensitivity (residuals were normally distributed after excluding the outlier, so variables were not transformed) obtained no significant time x condition effect ($F(2,112) = 0.259$, $p = 0.772$, $\eta_p^2 = 0.005$). There was neither a significant main effect of time ($F(1,112) = 0.294$, $p = 0.588$, $\eta_p^2 = 0.003$) nor of condition ($F(2,112) = 0.625$, $p = 0.537$, $\eta_p^2 = 0.011$). See ***Table 5*** for descriptive values.

Post-hoc analyses

Post-hoc moderation analysis showed that the effect of the ABM-training on AB for itch pictures was not moderated by the pre-training level of AB for itch pictures (***Table 6***). Additionally, over the entire sample, AB for itch pictures increased significantly ($F(1,114) = 5.16$, $p = 0.025$, $\eta_p^2 = 0.043$).

Flanker effect

A significant Flanker effect ($F(1,115) = 419.76$, $p < 0.001$, $\eta_p^2 = 0.785$), with faster RT for congruent (423.8 ± 78.7) than incongruent trials (472.2 ± 69.6) indicated attentional inhibition across the sample.

Associations with individual characteristics

Of all Spearman correlation coefficients between the individual characteristics and the ABM-training effect on the different outcomes, only a significant correlation was found between high levels of neuroticism and larger increases in mechanically induced itch in the ABM-training condition towards itch ($\rho_S = 0.35$, $p = 0.03$). Another significant correlation emerged in the sham training condition, which was between a better disengagement ability from itch and a larger decrease in mechanically induced itch ($\rho_S = 0.46$, $p = 0.004$).

Table 5. Mean ± standard deviation of mechanically evoked itch measured on a numeric rating scale from 0 (no itch) to 10 (worst itch imaginable) displayed for the total sample and per attention bias modification (ABM) training condition.

	Total sample (n = 115)	***ABM-training away from itch (n = 37)***	***ABM-training towards itch (n = 39)***	***Sham training (n = 39)***
Pre-training itch[a]	1.8 ± 1.5	2.0 ± 1.5	1.7 ± 1.4	1.8 ± 1.5
Post-training itch	1.8 ± 1.5	2.0 ± 1.8	1.6 ± 1.4	1.9 ± 1.5

Abbreviations: [a] For the pre-training analysis, the variables were not-normally distributed, hence the medians and interquartile ranges are reported here. Median (IQR) was for the total sample 1.5 (0.7; 2.7), for the ABM-training away from itch 1.7 (0.9; 2.8), for the ABM-training towards itch 1.3 (0.5; 2.8), and for the sham training 1.7 (0.5; 2.7)

Table 6. Linear model of pre-training attention bias (AB)-index for itch pictures as predictor (moderator) of the attention bias modification (ABM) training effect (*n* = 115; 95% confidence intervals (CI) and standard errors based on 1000 bootstrap samples).

	B [CI]	***SE B***	***t***	***p***
Constant	-10.40 [-16.21, -4.60]	2.93	-3.551	0.001
Condition	2.56 [-4.88, 10.01]	3.76	0.683	0.496
Pre-training AB-index for itch pictures (Centered)	0.85 [0.71, 0.98]	0.07	12.516	<0.001
Pre-training AB-index for itch pictures X Condition effect	0.12 [-0.04, 0.28]	0.08	1.478	0.142

Note: R^2 = 0.61. The training effect is defined by the change in AB-index before minus after the training (a positive value indicates a decreased AB after training)

Discussion

We assessed the effects of attention bias modification (ABM)-training on healthy individuals' attentional bias (AB) towards itch pictures and itch words as well as on sensitivity to mild itch. This is the first proof-of-principle ABM-training study in the field of itch. Specifically, we also included a condition in which attention was trained towards itch, besides the training away from itch and a sham condition. In contrast to expectations, ABM-training did not alter attention to itch pictures. Furthermore, ABM-training using itch pictures did not affect AB towards itch words or itch sensitivity. Additionally, of the individual characteristics, only neuroticism was associated with a larger training effect, specifically with an increase in mechanically evoked itch in the condition trained towards itch. In sum, although we expected ABM-training to be promising for itch, given the contagiousness and attention-capturing characteristics of itch (Evers et al., 2019; Schut et al., 2015; van Laarhoven et al., 2020), we can conclude that the hypotheses could not be confirmed.

Given the novelty of an ABM-training for itch, comparing current findings with findings of previous ABM-trainings for pain may provide some further insight. Largely inspired upon previous ABM research on pain (Bowler et al., 2017; Crombez et al., 2013; Sharpe et al., 2015), we opted for a 500-ms stimulus display time, the use of pictures, and a target discrimination instead of a localization task. Yet, we can conclude that although results are not in line with our hypotheses, current findings are also not completely unexpected when inspecting the ABM-training literature. Indeed, although initial results of ABM for pain-related information showed promising results (McGowan et al., 2009; Sharpe et al., 2015), more recent studies indicate that ABM-trainings for pain are ineffective in changing AB towards pain in healthy participants (Bowler et al., 2017; Van Ryckeghem, Damme, Vervoort, 2018; Todd et al., 2016). For both, potential moderation of ABM-training effects by baseline levels of AB for itch and generalization to another type of AB (i.e. from pictures to words), only preliminary evidence from the pain literature is available (Fox et al., 2015). Moreover, generalization occurred only from words to pictures and not vice versa (Sharpe et al., 2015). That itch sensitivity was unaffected by the ABM-training is also partly in line with previous pain studies. Specifically, some studies favored effectiveness of ABM-training on experienced pain or pain thresholds (Bowler et al., 2017; McGowan et al., 2009; Sharpe et al., 2015), while others did not find effects on pain outcomes or only for some pain outcomes (Bowler et al., 2017; Van Ryckeghem, Damme, Vervoort, 2018; Todd et al., 2016). Furthermore, in multiple studies changes in somatosensory pain outcomes were not accompanied by changes in AB for pain (Bowler et al., 2017; Sharpe et al., 2015). Comparable mixed results emerged in other fields, such as anxiety for which ABM-trainings were originally developed (Jones & Sharpe, 2017; Mogg et al., 2017). Overall, previous findings of the effects of ABM-training are mixed or preliminary.

Various explanations of current findings in relation to the inconsistent evidence for ABM-training studies for pain (see also Van Ryckeghem, Damme, Vervoort, 2018) can be considered. First, the present study included a sham training to inform about potential distinct effects of each training condition. Nonetheless, previous pain research often compared an ABM-training towards pain with an ABM-training away from pain, which likely obtains larger effects due to comparison of the most 'extreme' conditions. Noteworthy, post-hoc analyses comparing our extreme conditions does not change the conclusions. Second, lack of effectiveness on AB for pictures and words may relate to the fact that after the active training conditions (including either congruent or incongruent trials), both congruent and incongruent trials were offered in the dot-probe tasks to assess AB for itch. This may have diluted potential training effects. Moreover, given the null-findings of an AB towards itch pictures, the lack of a generalization towards the itch words and sensitivity is not surprising. Third, participants did not have a baseline AB for itch stimuli, as would be expected (van Laarhoven et al., 2016, 2018). This generally hampers the possibility to train attention away, although also no moderation by the baseline AB levels was found. Moreover, this does not explain the lack of training effects for those trained towards itch, particularly because at baseline average RT pointed in the opposite direction, which could be interpreted as attentional avoidance of itch pictures. Nevertheless, previous ABM-trainings away from pain have shown to be effective in reducing pain outcomes despite the absence of a baseline AB towards pain (Bowler et al., 2017; McGowan et al., 2009; Todd et al., 2016). However, the current study did not find effects on itch sensitivity either. This does not seem to be due to the levels of itch induced, which were comparably moderate in previous studies (Andersen et al., 2016; Andersen, van Laarhoven, et al., 2017), in which itch reduction was effectuated (by heterotopic stimulation; Andersen, van Laarhoven, et al., 2017). Fourth, as elaborated on by Wiers and colleagues (Wiers et al., 2018), a proof-of-principle study in healthy individuals entails that participants are not aware of receiving an intervention and have no motivation to change their responses. Motivation to pursue certain goals, e.g., getting rid of the itch, as well as having positive expectations about an intervention play an important role in the experience and treatment of various symptoms (Evers et al., 2019; Field et al., 2016; Van Ryckeghem et al., 2013, 2019; Wiers et al., 2020). Therefore, the possible effects to be obtained are probably smaller in healthy individuals than in patients.

Interestingly, at baseline, participants were faster on itch incongruent than congruent trials for the itch pictures (also seen in Becker et al., 2020; this may be related to the picture content, e.g., the itch pictures are of weak emotional valence (Field et al., 2016) to the healthy individuals), which could be indicative of attentional avoidance of itch. This "avoidance bias" hampered the ability to train attention away, and simultaneously increased the opportunity to train attention towards itch. In fact, the "avoidance bias" was abolished, as demonstrated by the lack of a significant itch-congruency effect after the training irrespective of the condition participants were in (though seemingly mostly in the training towards itch; ***Figure 2***). This unexpected finding of increased attention to itch in the entire sample is in the direction opposite to what is desirable. This may have been caused by participants becoming generally more familiar with the picture content over time. Additionally, particularly in the pre-training assessment, the stimuli were new to the participants and the neutral pictures apparently drew more attention than the itch pictures. This may be related to the more heterogeneous content of the neutral (various objects) than the itch pictures (scratching hand), making the neutral pictures more novel (Ernst et al., 2020). It may be worthwhile to explore if the attention increase to the itch pictures would still occur when presenting stimuli subliminally. Noteworthy, participants' responses were significantly faster after the training than before, which can be attributed to a task learning effect.

Several limitations and directions for future research should be mentioned. First, although reliability of the dot-probe tasks in the current study was adequate, generally the use of dot-probe tasks to measure AB (not so much to train attention) has recently been questioned because attention may vary highly across trials which is not reflected by the calculated average reaction times (Dear et al., 2011; Field et al., 2016). However, the majority of, if not all, ABM-trainings used the dot-probe paradigm with comparable analyses, and some were successful. Nevertheless, future studies may benefit from using other tasks, e.g., the dual probe task variant (Macleod et al., 2019), as well as eye-tracking methodology to fully capture the fluctuating process of attention over time (Field et al., 2016; Jiang & Vartanian, 2018). Second, training effects could be assessed on more intense itch stimuli, e.g., cowhage (Andersen et al., 2015). Third, including somatosensory itch stimuli as opposed to visual stimuli in the task would enhance ecological validity. However, because of the lack of spatial attention allocation effects towards somatosensory itch (Becker et al., 2022; van Laarhoven et al., 2017, 2018), translating the ABM-training paradigm into a somatosensory variant remains challenging. Fourth, current ABM-trainings may be improved by incorporating motivational components, e.g., by implementing reward, gamification, or creating a more representable context

(Ryckeghem, Damme, Vervoort, 2018; Van Ryckeghem et al., 2019). It is also worthwhile to explore how to extend and personalize cognitive bias trainings for itch in line with the innovative, promising, theory-driven ABC-training for addiction (Wiers et al., 2020). Actually, the itch-scratch cycle behavior and addiction share common neurobiological mechanisms (Ishiuji, 2019). Finally, when ABM-training for itch would eventually be successful, future studies should also include patients with chronic itch, who are generally motivated to diminish the itch, hence have a baseline AB towards itch that can be targeted (e.g., Field et al., 2016; Todd et al., 2018; Van Ryckeghem & Crombez, 2018 for results in related fields).

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CHAPTER 6

Subliminal attentional bias modification training for itch

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Abstract

Itch is unpleasant and induces the urge to scratch. This is adaptive to remove the itch-inducing stimulus from the skin. Accordingly, itch draws attention to protect our bodily integrity. Recent studies investigated whether attention is preferentially drawn towards its location, i.e., attentional bias, and also whether this bias could be changed in healthy individuals. So far, results are mixed concerning the existance of an attentional bias towards itch stimuli in healthy individuals as well as the impact of modifications. However, available studies have typically focused on conscious processing and might miss preconscious aspects of attention and potential biases at these stages.

This study included 117 healthy individuals who underwent a subliminal Attentional Bias Modification (ABM)- training for itch based on a dot-probe paradigm with itch- related pictures. Participants were randomly assigned to a training towards itch group, a training away from itch group and a control group. This was done by manipulating the itch-target congruency of the dot-probe task during a training block. Pre- and post-training assessments were regular dot-probe tasks. Exploratorily, also attentional inhibition, cognitive flexibility and itch-related cognitions were assessed. Lastly, participants received an itchy stimulus on the inner forearm before and after the ABM-training to assess potential effects on itch sensitivity.

Results showed no AB towards itch across groups at baseline, i.e., pre-training, but an AB away from itch, hence, avoidance of itch, post-training. Further analyses showed that this effect was driven by an attentional bias away from itch in the control group, while there were no significant effects in the experimental groups. There was no effect on itch sensitivity.

These findings are in line with recent studies on conscious ABM-training for itch and pain that also did not find significant training effects. Therefore, it is suggested that the field of AB might need to reconsider the current assessment of

AB. Moreover, AB is probably a dynamic process that is highly dependent on current itch-related goals and relevance of itch in a specific situation. This suggests that processes probably differ in patients with chronic itch and that also ABM-training might work differently in these populations.

Introduction

Itch is an unpleasant sensation which induces the urge to scratch and can lower individual's quality of life if it is present for a prolonged time (Kini et al., 2011; Matterne et al., 2011, 2013; Roh et al., 2022). Recent studies have highlighted the importance of psychological mechanisms in the experience of itch, such as attention (Evers et al., 2019; van Beugen et al., 2021; van Laarhoven et al., 2020). Specifically, it has been suggested that the experience of itch is impacted by attentional processing (Becker et al., 2020; van Laarhoven et al., 2010; van Laarhoven et al., 2018). Although attention allocation towards itch-related stimuli may be helpful in adapting our behavior to protect bodily integrity, it can also interfere with the execution of other tasks in daily life. This is especially true if itch can no longer be adaptively controlled, e.g., chronic itch; no concrete action allows to alleviate the itch.

Overall, research on attention to itch showed that, in healthy individuals, itch interferes with the execution of other tasks, i.e., itch is distracting (Becker, Vreijling et al., 2022; van Laarhoven et al., 2017, 2018). Furthermore, it has been researched whether visual itch-related stimuli draw attention towards their location, i.e., an attentional bias towards itch, which resulted in mixed findings so far (Becker et al., 2020; Becker, Vreijling, et al., 2022; van Laarhoven et al., 2018). These studies have shown that attention for itch might differ between conscious and preconscious processing stages: while some studies found heightened conscious attention towards itch (van Laarhoven et al., 2018), others could not replicate this finding (Becker et al., 2020; Becker, Vreijling, et al., 2022) and a recent finding suggests preconscious avoidance of itch-related stimuli (Becker, Holle, et al., 2022). The importance of fast processing of itch is also supported by contagious itch which suggests very fast and maybe unconscious processing of itch-related gestures, e.g., scratching, which then induces itchiness in the observer (Holle et al., 2012; Schut et al., 2015).

A possible intervention for biases for itch-related information is Attentional Bias Modification (ABM) training for itch. These kind of trainings use itch-related stimuli, like words or pictures to manipulate individuals' attention away from (or towards) these stimuli. As yet, only one study employed an ABM-training for itch in healthy individuals which investigated conscious processing of itch-related visual stimuli (van Laarhoven et al., 2021). This study investigated whether attention could be either trained towards visual itch stimuli or away from these stimuli. Results of this study could, however, not support the effectiveness of an ABM-training, neither by affecting attention directly, nor by influencing individuals' sensitivity to a light cutaneous itch stimulus on the skin (van Laarhoven et al., 2021).

Nevertheless, there is some evidence that ABM-training for other somatic complaints such as pain can be effective (Schoth et al., 2013; Sharpe et al., 2012, 2015; Todd et al., 2016), although this could not be supported by all studies (Heathcote et al., 2017; van Ryckeghem, Van Damme, Vervoort, 2018). Interesting to note here is that in most cases there was no direct effect on attentional bias towards pain stimuli after the training but effects on for example pain intensity or tolerance (Sharpe et al., 2012, 2015; Todd et al., 2016). This suggests that ABM-training might show effects on symptom perception, for instance itch tolerance or sensitivity, which could be especially valuable for clinical practice. After all, the lack of significant effects on attentional bias measures themselves leaves open questions about the working mechanism of ABM-training.

Because attention is a continuum, including first orienting towards a stimulus, actual selective attention to a stimulus and eventual disengagement (Petersen & Posner, 2012; Posner, 2016, Posner & Petersen, 1990), attention can be biased at different stages of attentional processing (Fashler & Katz, 2016) which is suggested by the inconsistent findings on attentional bias towards itch so far at different processing stages, e.g., conscious engagement and disengagement vs. preconscious orienting (Becker et al., 2020; Becker, Holle, et al., 2022; Becker, Vreijling, et al., 2022; van

Laarhoven et al., 2018). However, preconscious ABM-trainings are scarce and actually lacking in itch. To our knowledge, there is only one study which investigated preconscious ABM training. This study used an ABM training for threat-related stimuli in socially anxious individuals (Maoz et al., 2013) which, while not finding an effect on attentional bias, did find a positive effect on anxiety during a stressful task. This finding indicates that training attention away from itch-related information very early in the attention process may prove helpful in reducing negative outcomes.

With the very limited knowledge on preconscious ABM-training and attention towards itch in general, the current study investigated the effect of preconscious ABM-training for itch in healthy individuals in a proof-of-principle approach. More specifically, the effects on attentional measures and on sensitivity to a somatosensory itch stimulus were investigated. Participants were either trained towards or away from visual itch stimuli or received a sham (control) training by means of computerized, single-session ABM-training. We expected an effect on attentional bias post-training compared to pre-training in both training groups, i.e., more attention towards itch in the towards group vs. less attention towards itch in the away group, compared to the control group. In line with this, we expect higher itch sensitivity after the training in the towards group, and lower itch sensitivity in the away group, compared to the control group. In addition, a possible role of general attentional abilities, namely attentional inhibition and cognitive flexibility, as well as on self-reported itch-related cognitions was explored to shed more light on individual differences that might be related to the effectiveness of the ABM-training and could potentially explain mixed-findings in this field.

Materials and Methods

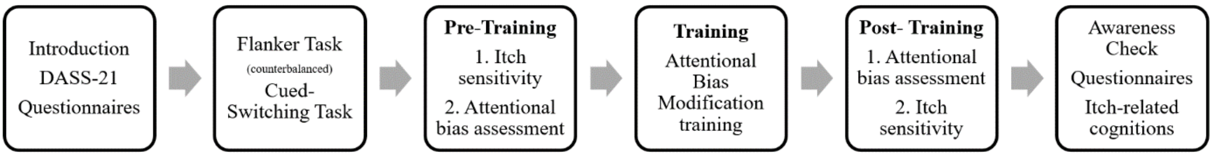
Participants

The study sample consisted of 117 healthy individuals. This sample size was calculated in line with an earlier study with a comparable design (van Laarhoven et al., 2021). Participants were included if aged between 18 and 35 years, fluent in either Dutch or English, and with normal vision (corrected with contact lenses if needed). Participants were excluded if they had a (history) of psychological disorder (e.g., depression or anxiety), had a medical diagnosis (e.g., atopic dermatitis or heart disease), used recreative drugs on a regular basis (e.g., MDMA or cannabis) or suffered from color blindness or dyslexia. All participants gave written informed consent before the experiment. Data collection took place between October 2018 and July 2019. The study was approved by the Psychology Research Ethics Committee of Leiden University (CEP19-0703/376) and registered in the Nederlands Trial Register (Dutch Trial Register; NTR7561).

General Procedure

Participants were recruited via the Online Research Participation system of the university (SONA Systems Ltd., Tallinn, Estonia) and via advertisement at the faculty. The experiment took place at the Faculty of Social and Behavioral Science of Leiden University and took about 1.5h. See ***Figure 1*** for an overview. Information about the study was given upon sign-up and repeated at the start of the study, after which participants signed the informed consent form. The procedure started with a short questionnaire about current levels of depression, anxiety and stress and demographic information. Thereafter, two general attention tasks (order counterbalanced) were completed measuring attentional inhibition and cognitive flexibility. Next, an itchy stimulus was applied to the forearm of the participant to assess their itch sensitivity at baseline (randomized either the dominant or non-dominant arm). The actual subliminal attention bias modification (ABM) training was completely automatized with a pre-training, i.e., baseline- attentional bias block, and a post-training block and the training block in between. Group allocation was based on participant number and the experimenter and the participants were unaware of the corresponding group, i.e., a blinded design. A second itch sensitivity assessment followed by applying the same itch stimulus on the other forearm of the participant (e.g., dominant arm if first application was on the non-dominant arm). Lastly, participants filled out several questionnaires, assessing itch-related cognitions, e.g., catastrophizing and body vigilance. All participants were debriefed and received either monetary reimbursement or course credits for their time investment.

Figure 1. Overview of the general procedure.



Technical set-up

All computer tasks, including the ABM-training, were programmed with E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, USA) and self-report questionnaires were presented with Qualtrics (Provo, Utah, USA) on an Iiyama HM703UT A Vision Master Pro 413 CRT monitor (17 inch; refresh rate 100Hz; resolution 1024x768px). Participants used a chin rest to keep a constant distance of 78cm to the screen. Responses were collected with a Serial Response Box (Psychology Software Tools, Inc., Sharpsburg, USA) with two custom-made buttons for the left and right index fingers. A Tobii Pro X3-120 Eye Tracker (Tobii AB, Danderyd, Sweden) was also installed to measure eye-movements during the ABM-training. Unfortunately, data quality of eye-movement data appeared to be insufficient for further analyses.

Attention tasks

Subliminal Attentional Bias assessment and training

Attentional bias towards itch was measured with a dot-probe paradigm (Becker et al., 2020; Becker, Vreijling, et al., 2022; van Laarhoven et al., 2018b). Forty pairs of two pictures were used, one being itch-related and one being neutral (i.e., twenty stimuli presenting neutral skin and twenty presenting a neutral object), validated and used in earlier studies (Becker et al., 2020; J. M. Becker, Holle, et al., 2022). An itch-related picture showed someone scratching their own body. Neutral skin pictures displayed the same body parts, but without a scratching gesture.

Each trial began with a fixation cross (500ms) followed by a picture pair (20ms). The picture pair was thereafter masked with corresponding scrambled versions of the same pictures (480ms). The pictures were presented at the 80% and 20% height position of the screen. Lastly, a target appeared which consisted of two dots, either horizontally or vertically oriented. If the target appeared in the same location as the itch-picture, this was a congruent trial, while if the target appeared in the opposite location, this was an incongruent trial. Participants had to respond to the orientation of the dots by pressing a left button with their left index finger to indicate vertical dots or a right button with their right index finger to indicate horizontal dots or vice versa (counterbalanced). Accuracy and reaction times were assessed as outcome measures. Attentional bias towards itch is inferred if congruent trials have a shorter reaction time (RT) than incongruent trials, while attentional bias away from itch (i.e., avoidance) is inferred if incongruent trials have a shorter RT than congruent trials. The resulting difference score is called the AB-index. The whole ABM-training, including pre- and post-training assessment, took about 30min to complete.

In line with an earlier study for itch (van Laarhoven et al., 2021), participants were distributed across three groups: one trained towards itch (towards-group), one trained away from itch (away-group) and one control-group (sham training). For each participant, the picture pairs were randomly distributed to the pre-training, training and post-training block.

Pre- and post-training attentional bias. For the pre-training, i.e., baseline, assessment of attentional bias towards itch, and the post-training attentional bias towards itch assessment, ten picture pairs (different picture pairs for baseline and post-training assessment) were used. All pairs appeared two times with the itch picture in the upper and lower part of the screen, as a congruent and incongruent trial, and with horizontal and vertical dots, resulting in 160 trials. A break of 10s was inserted after every 40 trials.

Training. For the training, twenty picture pairs (different from baseline and post-training assessment) were presented two times in both locations and with both targets types. The task was manipulated for the towards-group by only consisting of itch-congruent trials and for the away-group by only consisting of itch-incongruent trials. The control-group received evenly distributed congruent and incongruent trials, alike the pre- and the post-training. The whole training block consisted of 320 trials, also interrupted with 10s breaks after every 40 trials.

Awareness check. Awareness of the subliminally presented pictures during the ABM-training, was checked by two subjective awareness questions and an objective awareness check in line with an earlier study(Becker, Holle, et al., 2022). Subjective awareness was assessed by directly asking whether participants noticed something special during the task (question 1) and if this was answered with yes, whether they noticed any pictures (question 2). For the objective awareness check, a forced-choice paradigm was used. Furthermore, participants were presented with twenty picture pairs that consisted of one picture shown during the ABM-training and one new picture from the same validated stimulus set (Becker et al., 2020). For each pair, they had to indicate which of the two pictures they had seen earlier during the ABM-training. There was no time pressure, but participants were asked to answer as intuitively as possible. Accuracy was measured and if this was at chance level (ca. 50%), the subliminal design was assumed to be successful.

Flanker task

General attentional inhibition, unrelated to itch, was measured with a Flanker paradigm (Eriksen & Eriksen, 1974; Moore et al., 2012) to assess any individual differences in attentional inhibition that might influence an AB towards itch. During each trial within this task, a target number appeared in the middle of the screen, flanked by either two target-identical flanking numbers on each side (i.e., congruent trial) or two different flanking numbers on each side (i.e., incongruent trial). Stimuli were twos and fours, e.g., '22222' or '22422'. Numbers were shown until a response was given, with a maximum of 1500ms. After eight practice trials, 120 trials were presented (50% congruent and 50% incongruent) with a short break in the middle. Accuracy and reaction times to respond to the target (middle) number were measured. Attentional inhibition is inferred if incongruent trials have a longer RTthan congruent trials, that is, more time is needed to inhibit the incongruent flanking numbers. This is called a Flanker effect (Flanker Index = $RT_{incongruent} – RT_{congruent}$). The Flanker task took about 5 minutes to complete.

Cued-Switching task

General attentional switching, unrelated to itch, was measured with a cued-switching paradigm (Moore et al., 2012). On each trial of the cued-switching paradigm, a target number between one and nine appeared on the screen. Before the target number appeared, one of two instructions were given for 500ms: either to indicate by button press whether the target is odd or even ("odd/even") or whether the target is above or below five ("high/low"). Target numbers were shown until a response was given, with a maximum of 1500ms. After sixteen practice trials, 200 experimental trials were administered (50% odd/even, 50% high/low) with a short break after 100 trials. Trials could be either repeat-trials (same instruction as preceding trial, 50% of trials) or change-trials (other instruction than preceding trial, 50% of trials). A switching cost is inferred if change trials have longer response latencies than repeat trials, that is, switching from one instructions to another instructions costs time. This is called switching cost (RT_{change} – RT_{repeat}). Accuracy and reaction times to respond to the targets was assessed as outcome measure. The cued-switching paradigm took about 10 minutes to complete.

Itch sensitivity

General itch sensitivity was assessed by applying cowhage spicules (hairs of the tropical mucuna pruriens plant) on the inner forearm of the participants. Forty to forty-five spicules were taken with negative grip tweezers (Dumont Tweezers Negative Action Style NS, Electron Microscopy Sciences, Switzerland), counted with the aid of a Bresser microscope Advance ICD 10x-160x (Meade Instruments Europe GmbH & Co. KG, Rhede, Westfalen, Germany). The spicules were applied to a 1.5cm by 1.5cm area on the inner forearm, 1cm above the wrist. The area was demarcated with 1.25cm surgical tape (3M Transpore White, St. Paul, MN, USA). The experimenter gently rubbed the spicules, with the index finger, onto the skin for 45s. Thereafter, participants rated their itch level continuously for three minutes on a digital Visual Analogue Scale (VAS) ranging from zero ('not at all') to ten ('worst imaginable itch') on a Lenovo Tab 4 10 Plus (Lenovo Group Limited, Beijing, China). The VAS was displayed with the APK Pure VAS App 1.3 (Shellie Boudreau Christensen, 2017). After three minutes, the spicules were removed by rapidly attaching and removing a 2.5cm surgical tape (3M Transpore White, St. Paul, MN, USA) to the demarcated area for five times. After another three minutes, participants rated their current itch once orally on a numeric rating scale from zero to ten. If the answer was above one, participants indicated their current level of itch again after another two minutes to make sure that the itch had passed before continuing the session.

Self-report questionnaires

Besides general demographic information and information about in- and exclusion criteria, several questionnaires were administered. The Depression, Anxiety and Stress Scale- short version (DASS-21; De Beurs et al., 2001; Lovibond & Lovibond, 1995); the Pain Vigilance and Awareness Questionnaire- adjusted for itch (Becker et al., 2020; McCracken et al., 1992; Roelofs et al., 2003); the Experience of Cognitive Intrusion of Pain scale- adjusted for itch to assess cognitive intrusions about itch (Attridge, Crombez, et al., 2015c; Becker et al., 2020); and the Pain Catastrophizing Scale- adjusted for itch (Becker et al., 2020; Sullivan et al., 1995). These questionnaires were used to assess emotional distress, vigilance to itch, intrusive cognitions about itch and catastrophizing about itch, respectively. Lastly, one item about disengagement from itch (van Laarhoven et al., 2017) was measured, as well as the current level of itch and fatigue with two VAS scales ranging from zero ("not at all") to ten ("worst imaginable"). These questionnaires were administered to explore the effect of itch-related cognitions on an AB towards itch.

Statistical analyses

Data of the computer tasks was extracted with E-Prime Data Aid 3.0 (Psychology Software Tools, Inc., Sharpsburg, USA). For the dot-probe pre-training and post-training task the following data was extracted for all experimental trials: reaction times (RT, ms), accuracy, congruency, group and trial number. In addition, mean accuracy levels per participant were extracted for the training itself. For the Flanker task, mean RT, separately for congruent and incongruent trials, and accuracy were extracted for each participant. Likewise, for the cued-switching task mean RT for the change-trials and for the repeat- trials were extracted, as well as mean accuracy. In both tasks, only trials that were responded to correctly and with RT > 150ms were included for the mean calculations. As explained in paragraph 'Flanker task' and 'Cued-Switching Task', respectively, a Flanker index (attentional inhibition) and switching costs (cognitive flexibility) were calculated to use as predictors during statistical analyses. For the questionnaires, data was extracted from Qualtrics (Provo, Utah, USA) and total scores and reliability scores were calculated with SPSS (IBM Statistics for Windows, Armonk, NY, USA). Itch sensitivity data was operationalized as Area Under the Curve (AUC) during the 180s that were rated on the digital Visual Analogue Scale. AUC was calculated for each participant's pre- and post-training itch induction.

All subsequent analyses, as described below, were done with R Version 4.0.4 (R Core Team, 2019) with a significance level of 0.05. Descriptive statistics are given as mean (*M*) and standard deviation (*SD*) if not stated otherwise. Reliability of the dot-probe pre- and post- training was calculated with the package 'splithalfr' (Pronk, 2020) in line with earlier studies (Becker, Holle, et al., 2022; van Laarhoven et al., 2021).

Manipulation and baseline checks

The objective awareness measure was analyzed with a single proportion test to check if accuracy to detect the picture that was shown during the subliminal pre-training dot-probe task was at chance level (0.5). Subjective awareness (i.e., aware of something and aware of pictures) was investigated with frequency tables.

Baseline between-group differences were checked with bootstrapped (1000 samples) analyses of variance (ANOVA) with group (control vs. towards vs. away group) as between-subjects effect. This was done for age, the Flanker index, switching costs, self-report questionnaire scores and the pre-training itch-sensitivity AUC score. Gender distribution across groups was assessed with a chi-square test.

Attentional bias pre- and post-training

For the pre- and post-training analyses, only trials with RTs > 150ms were included. Furthermore, all variables were checked visually for extreme values. For the post-training, only participants who had an accuracy level of at least 0.70 during the training were included (van Laarhoven et al., 2021).

Pre-training attentional bias was analyzed with a mixed-model analysis with RT as dependent variable and random effects for participant and trial number. Model 1 included fixed effects for accuracy, congruency (congruent vs. incongruent) and group (away vs. towards vs. control) as well as the interaction between congruency and group. In Model 2, the Flanker index (and its interaction with congruency), switching costs (and its interaction with congruency) and self-report scores were added as covariates. Post-training attentional bias was analyzed with the same mixed- models (Model 3 and 4, respectively) but added pre-training AB index ($RT_{congruent}$ - $RT_{incongruent}$) as a covariate to control for baseline attentional bias effects. A negative AB index indicates that attention is biased towards itch.

Itch sensitivity pre- and post-training

Itch sensitivity was analyzed with bootstrapped (1000 samples) ANOVA on cowhage evoked itch scores (AUC) with group as between-subject effect. Again, pre-training itch scores (AUC) was added as a covariate in the post-training analysis to control for any baseline effects.

Results

Participants and baseline characteristics

The final sample of 117 participants was mostly female (86% female and 14% mal) with a mean age of 21.0 years (SD = 2.3). ***Table 1*** shows descriptive statistics for all self-report questionnaires and the flanker and cued-switching paradigm. As expected, participants showed a significant Flanker index, $t(231.98) = -4.99$, $p < 0.001$, and a significant switching cost, $t(223.33) = -3.55$, $p < 0.001$. Overall, scores on self-reported itch-related cognitions were low to moderate in the current sample

Table 1. Descriptive statistics (mean (*M)* and standard deviation (*SD*)) for all background variables. *P*-values with bootstrapped residuals are reported to indicate significant group differences due to skewed distributions.

	Total sample		***Control group***		***Towards group***		***Away group***		
	N = 117		***N = 42***		***N = 38***		***N = 37***		
	M(SD)	Range	M(SD)	Range	M(SD)	Range	M(SD)	Range	*p*-value
Age [a]	21.0 (2.3)	18–29	21.0 (2.3)	18–26	21.2 (2.6)	18–29	20.8 (2.1)	18–25	0.807
PVAQ-I	41.3 (14.7)	5–74	40.0 (12.4)	9–67	42.7 (15.2)	5–74	41.3 (16.4)	10–74	0.650
PCS-I	23.0 (9.0)	0–45	21.8 (9.0)	0–45	24.0 (8.9)	0–43	23.3 (9.0)	2–43	0.412
ECIP-I	11.1 (9.0)	0–48	10.7 (10.1)	0–48	13.2 (11.4)	0–39	9.9 (11.6)	0–45	0.758
DASS-Depression [b]	7.2 (4.6)	0–19	7.4 (4.2)	0–16	7.3 (4.9)	0–17	6.8 (4.9)	0–19	0.592
DASS-Anxiety [b]	7.1 (4.1)	0–17	7.1 (3.9)	0–17	7.4 (4.3)	0–14	6.7 (4.1)	0–14	0.748
DASS-Stress [b]	9.5 (4.8)	0–18	9.4 (4.0)	0–17	9.7 (5.0)	0–18	9.2 (5.4)	0–17	0.889
Diseng-I	3.7 (1.0)	1–5	3.9 (1.0)	2–5	3.4 (0.9)	1–5	3.7 (1.1)	1–5	0.297
Flanker Index (ms)	46.7 (27.3)	-25.5–141.2	44.0 (25.0)	-0.1–123.7	50.5 (27.2)	6.49–133.0	44.7 (29.5)	-25.7–141.2	0.991
Switching cost (ms)	133.7 (118.4)	-41.5–551.9	153.9 (130.6)	-21.1–551.9	112.6 (90.0)	-6.9–319.1	132.5 (125.5)	-41.5–481.8	0.422

[a] Total sample n = 116; Control group n = 41, due to one missing value
[b] Total sample n = 113; Control group n = 38, due to four missing values
PVAQ-I = Pain Vigilance and Awareness Questionnaire -adjusted for itch (0 – 80); Cronbach's alpha = 0.91
PCS-I = Pain Catastrophizing Scale -adjusted for itch (0 – 52); Cronbach's alpha = 0.91
ECIP-I = Experience of Cognitive Intrusions of Pain Scale -adjusted for itch (0 – 60); Cronbach's alpha = 0.97
DASS = Depression, Anxiety, and Stress Scale- short form (0 – 21 for each subscale);

Cronbach's alpha $_{Depression}$ = 0.94; Cronbach's alpha $_{Anxiety}$ = 0.88; Cronbach's alpha $_{Stress}$ = 0.91

Diseng-I = One item on ability to disengagement from itch (1 – 5)

Table 2. Mixed-model analyses of the pre-training attentional bias measurement: estimates of the effect of the predictors in the outcome (*ES, in ms*) with standard errors (*SE*), significance level (*p-value*) and 95% Confidence Intervals of the estimates (95% *CI*) ($n = 114$)

		ES	***SE***	***p-value***	***95% CI***
Model 1	(Intercept)	478.60	18.62	< 0.001	[442.14; 515.07]
	Accuracy	21.69	3.40	< 0.001	[14.26; 29.12]
	Congruency	-4.15	4.68	0.375	[-13.33; 5.02]
	Group	0.11	8.62	0.990	[-16.78; 17.00]
	Group x Congruency	0.22	2.22	0.922	[-4.13; 4.57]
Model 2	(Intercept)	513.10	42.77	< 0.001	[431.55; 594.66]
	Accuracy	21.71	3.79	< 0.001	[14.30; 29.16]
	Congruency	-11.34	6.22	0.069	[-23.53; 0.86]
	Group	0.07	8.32	0.993	[-15.79; 15.94]
	Flanker index	-0.73	0.25	0.005	[-1.210; -0.25]
	Switch Cost	0.14	6.88	0.028	[0.020; 0.27]
	Diseng-I	-11.14	6.88	0.108	[-24.24; 1.97]
	PVAQ-I	0.001	0.97	0.999	[-1.14; 1.14]
	PCS-I	1.75	1.19	0.146	[-0.52; 4.02]
	ECIP-I	-1.58	0.96	0.104	[-3.41; 0.26]
	Group x Congruency	0.10	1.23	0.966	[-4.28; 4.47]
	Flanker index x Congruency	0.15	0.07	0.032	[0.01; 0.28]
	Switching costs x Congruency	0.01	0.02	0.768	[-0.03; 0.04]

Note: Model fit statistics; Model 1: AIC = 226245; Model 2: AIC = 226233

with a high dispersion of individual scores. There were no significant differences between all three groups on any background variables (all $p > 0.05$).

Pre-Training

During the pre-training attentional bias measurement, 3% of the data had to be excluded due to trials with RT < 150ms, data due to an extreme value of two participants' switching costs, and data due to one participant's low accuracy during the task. Reliability analyses showed high reliability for congruent trials, with a mean Spearman-Brown coefficient of 0.97 (Interquartile Range (IQR) = 0.96; 0.97). Likewise, for incongruent trials, the mean Spearman-Brown coefficient was 0.96 (IQR = 0.96; 0.97). AB index reliability has a mean Spearman-Brown coefficient of 0.43 (IQR = 0.36; 0.52).

Mixed model analyses of the pre-training attentional bias measurement showed no significant effect of congruency, group or congruency by group interaction, see Model 1 in ***Table 2*** and ***Figure 2*** for visualisation of the data. Therefore, there was no significant attentional bias towards itch in the three groups. After adding the Flanker index, switching costs and self-report questionnaires as covariates (Model 2), results show a significant effect of Flanker index and switching costs on RT during the pre-training block, as well as a significant interaction between Flanker index and congruency. This means that overall RT during the attentional bias measurement was influenced by participants' attentional inhibition (Flanker index) and their cognitive flexibility (switching costs). More attentional inhibition led to overall faster RT and more switching costs led to overall slower RT. Moreover, the effect of congruency (congruent vs. incongruent) interacted with someone's ability to inhibit irrelevant information (Flanker index). Specifically, participants with a higher Flanker index showed slower RT during incongruent trials compared to congruent trials during the attentional bias measurement, see ***Table 2***. Pre-training itch sensitivity AUC scores did not differ significantly between groups before the training, $p_{boot} = 0.609$.

Post-training

Post-training attentional bias measurement data was filtered based on trials with RT < 150ms, extreme values for the switching costs (*n* = 2), and due to very low accuracy (<0.70) during the training block (*n* = 1). This resulted in a data loss of 16.9%. Again, reliability analyses showed a high mean Spearman-Brown coefficient for congruent trials (0.94; IQR = 0.93; 0.95) and incongruent trials (0.92; IQR = 0.91; 0.93), but the mean Spearman-Brown coefficient for the AB index was lower (0.70; IQR = 0.65; 0.75), indicating lower reliability.

For the post-training measurement of attentional bias, mixed model analyses revealed a significant main effect of the difference between congruency, in which RT on incongruent trials was lower compared to congruent trials. This could be interpreted as an attentional bias away from itch stimuli. The analyses also revealed a significant difference between groups. Pairwise comparisons for the main effect of group showed no significant results (all $p > 0.05$). Even though this seems counterintuitive based on the main effect, this can happen because the main effect takes into account all possible comparisons. However, only the pairwise comparisons relevant to the hypotheses were inspected and appeared to be not significant.

Figure 2. Estimated marginal means per trial type (congruent vs. incongruent) and group (away- vs. towards- vs. control-group) during the pre-training (A) attentional bias measurement and the post-training (B) attentional bias measurement.

Figure 2A. Pre-training attentinal bias assesment (RT)

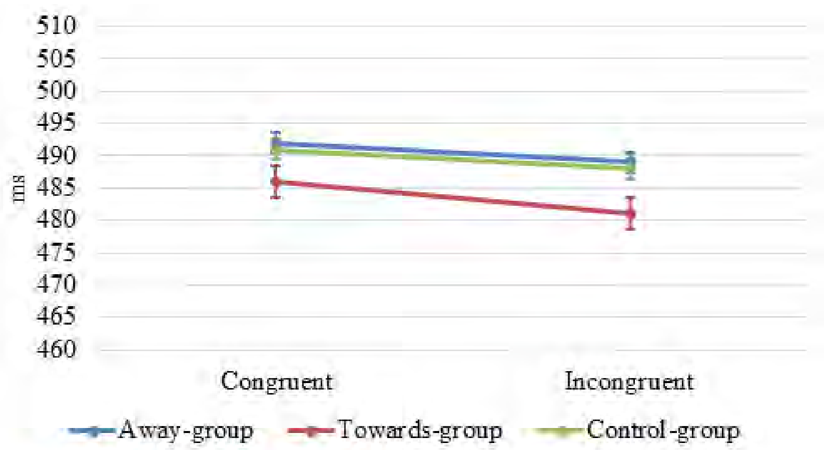
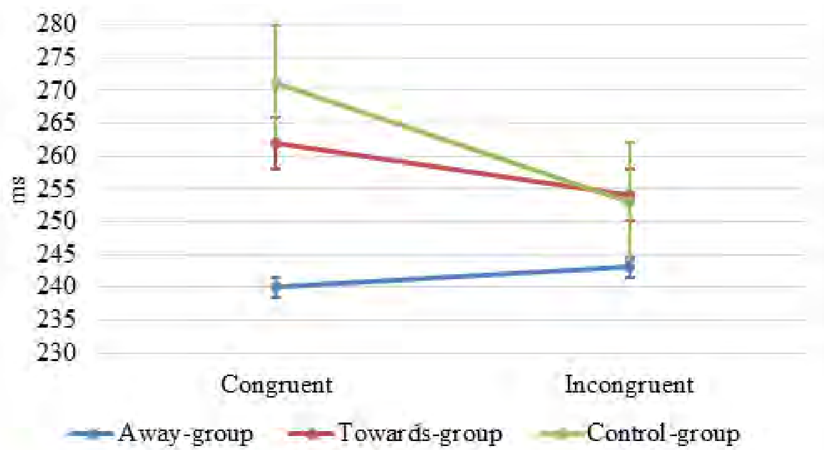


Figure 2B. Post-training attentinal bias assesment (RT)



Furthermore, we found a significant association between pre-training AB-index and RT. This means that a higher AB-index during the pre-training is associated with slightly higher RT during the overall RT during the post-training. Lastly, there was a significant group by congruency interaction effect, see Model 3 in ***Table 3*** and ***Figure 2B*** for visualisation of the data. Pairwise comparisons showed a significant effect for congruency in the control group only ($p = 0.028$), with faster RTs for incongruent trials (Estimated Marginal Mean (*EMM*) = 253.0) compared to congruent trials (*EMM* = 271.0). Therefore, it can be concluded that the interaction effect between congruency and group is driven by this single comparison within the control group.

Table 3. Mixed-model analyses of the post-training attentional bias measurement: estimates of the effects of the predictors on the outcome (*ES in ms*) with standard errors (*SE*), significance level (*p-value*) and 95% Confidence Intervals of the estimates (95% *CI*) ($n = 114$)

		ES	***SE***	***p-value***	***95% CI***
Model 3	(Intercept)	226.68	14.99	< 0.001	[197.44; 256.01]
	Accuracy	120.87	6.42	< 0.001	[108.09; 133.51
	Congruency	-28.97	8.86	0.001	[-46.24; -11.51]
	Group	-15.60	5.90	0.009	[-27.13; -4.08]
	Pre – AB index	0.52	0.24	0.032	[0.05; 0.99]
	Group x Congruency	10.73	2.07	< 0.001	[6.67; 14.79]
Model 4	(Intercept)	205.60	32.17	< 0.001	[144.50; 266.82]
	Accuracy	120.90	6.42	< 0.001	[108.16; 133.57]
	Congruency	-36.38	9.70	< 0.001	[-55.38; -17.37]
	Group	-14.78	6.03	0.016	[-26.22; -3.33]
	Pre – AB index	0.42	0.24	0.089	[-0.04; 0.87]
	Flanker index	-0.23	0.18	0.212	[-0.58; 0.12]
	Switch Cost	0.04	0.05	0.383	[-0.05; 0.13]
	Diseng-I	0.45	4.94	0.927	[-8.92; 9.83]
	PVAQ-I	-0.09	0.42	0.919	[-0.89; 0.70]
	PCS-I	1.29	0.86	0.137	[-0.34; 2.91]
	ECIP-I	-0.23	0.69	0.738	[-1.54; 1.08]
	Group x Congruency	11.98	2.11	< 0.001	[7.85; 16.10]
	Flanker index x Congruency	-0.04	0.06	0.559	[-0.16; 0.09]
	Switching costs x Congruency	0.05	0.02	0.001	[0.02; 0.09]

Note: Model fit statistics; Model 3: AIC = 195003; Model 4: AIC = 194996

Model 4, with Flanker index, switching costs and self-report questionnaires as covariates (see ***Table 3***), shows significant main effects for congruency and group, as well as significant interaction effect for group by congruency and a significant interaction effect for congruency by switching costs. This means that after controlling for all these covariates, it can be seen that congruent trials are significantly slower than incongruent trials, which is interpreted as an attentional bias away from itch for all participants. Pairwise comparisons to investigate the main effect of group did not yield significant differences (all $p > 0.05$), but pairwise comparisons of the interaction effect of congruency by group, showed a significant congruency effect for the control group ($p = 0.017$). Lastly, the significant interaction effect between switching costs and congruency showed that higher switching costs, which means less cognitive flexibility, are related to slightly slower RT on incongruent trials. However, the estimate is too low to be interpreted as a meaningful effect ($ES = 0.05$ms).

Lastly, itch sensitivity AUC scores post-training did not differ significantly between groups, while controlling for pre-training AUC scores, $p_{boot} = 0.412$.

Discussion

Results of this study indicated that healthy individuals did not show an attentional bias (AB) towards visual itch-related stimuli. Next, it was found that a single-session attentional bias modification training (ABM) could influence attention towards visual itch-related stimuli in healthy individuals. Across all training groups, participants showed an AB away from itch after the training, i.e., avoidance of itch. However, when looking into the AB effect for specific groups, i.e., the interaction between group and AB, only the sham- training (control) group showed avoidance of visual itch-related stimuli after the training while there was no effect in the experimental groups. Finally, and in contrast with our hypotheses, the ABM-training did not impact upon itch-sensitivity.

While we indeed found an effect of ABM-training on attention to itch, this effect was not as intended, because the experimental groups that were either trained towards or away from itch showed no significant effect. Therefore, we cannot conclude that the ABM-training worked as we assumed. This is in line with the most recent findings on ABM-training for itch (van Laarhoven et al., 2021) and also pain (Hasegawa et al., 2021; Van Ryckeghem, Damme, Vervoort, 2018), as well as the limited findings on preconscious ABM-training for threat (Maoz et al., 2013). In addition to the fact that the current ABM-training did not have the expected effect on the AB assessment measures, it also did not show effects on itch sensitivity, although this appeared to be more promising according to earlier findings in pain (Sharpe et al., 2012, 2015; Todd et al., 2016). Lastly, the current findings also add to the mixed findings on baseline AB towards visual itch-related stimuli in healthy individuals (Becker et al., 2020; Becker, Holle, et al., 2022; Becker, Vreijling, et al., 2022; van Laarhoven et al., 2018). The absence of an AB towards itch at baseline might therefore explain why we did not find specific effects of the current training. Patients with chronic itch, in line with previous research showing a small AB towards pain in patients with chronic pain (Crombez et al., 2013; Todd et al., 2018), are expected to display a baseline attentional bias. For patients with chronic itch, the experience of itch is highly relevant and acting upon this experience is probably a relevant goal for patients. However, current ABM-training in patients with chronic pain are thus far also not very successful (Sharpe et al., 2012, 2015; Todd et al., 2016), so it remains unknown how patients with chronic itch would respond to ABM-training for itch.

Recent developments in the field of pain have suggested that AB might be more dynamic, i.e., changes from moment to moment, than current AB assessment paradigms can capture and this might explain why attention bias modification training effects are often not found (Van Ryckeghem & Crombez, 2018). In light of this, we might miss other, probably interrelated, aspects of cognitive bias, such as interpretation and memory biases towards itch (Van Ryckeghem et al., 2019). Especially interpretation of stimuli might be highly important, because, at this moment, we are unaware of the specific interpretation that individuals give to used stimulus materials. To our knowledge, only one study asked participants to rate the stimulus material that was used during AB assessment which actually showed that the material was not rated very high on its intended dimension (i.e., itchiness or painful in this study) and the results indeed showed no AB towards itch or pain in healthy individuals (Becker et al., 2020). Because the same stimulus material was used in the current study, this might also be true for the current study. In addition, especially for healthy individuals like in the current study, the ABM paradigm lacks personal significance because it is not related to an individual's goal to relieve an itch. Although participants received an itchy stimulus before the ABM-training, the actual experience of itch had already vanished during ABM, as intended in our case. It is assumed that AB in its original evolutionary function informs us about potential harm to our bodies and to induce adaptive behaviours, but this was not the case in the current study. The idea that individuals only show AB towards itch while experiencing itch is supported by the recent finding that only participants who received a histamine-induced itch stimulus on their skin, showed avoidance of itch-representing stimuli (Etty et al., 2022). Although the itch-stimulus was not even goal-related in this study, it might at least set a context that was related to itch and hence, increase personal relevance.

The finding that the control-group in the current study actually showed avoidance after the sham-training is surprising. For this group, the training did not differ to the pre-training and post-training assessment, which would not suggest any changes during the post-training. There are no clear explanations for this, but one could speculate about an effect of prolonged exposure and learning which might enhance attentional control, and therefore distraction by the pictures from the actual task. Still, these same effects would have been true for the experimental groups. Interestingly, the current result in the control group is in line with a recent study on preconscious AB towards itch which also showed avoidance in healthy individuals

(Becker, Holle, et al., 2022). This would suggest that this effect is not yet visible with less exposure and an extensive number of trials is needed to evoke avoidance of itch-related stimuli. In the current study, the control-group actually did one long AB assessment without any manipulations which in this sense is comparable to regular AB assessments, in line with earlier findings of preconscious avoidance (Becker, Holle, et al., 2022).

In conclusion, the current study suggests that common ABM-training paradigms for itch are not working for healthy individuals as we assume. Development of theories on how cognitive biases in itch, and more specifically attentional biases, work are needed and these should guide the development of new paradigms and research designs. In a second step, the possibility to modify these biases can be investigated, because as long as we do not know how these biases operate we do not know where, when and how we should intervene. This is of course even more important if we consider bias modification training in the clinical context where patients with chronic itch are included. All in all, assessment of AB and application of ABM-training in the clinical setting needs to be investigated in more detail, e.g., by taking the dynamics and context relevant to the individual into account, in the future before any conclusions can be drawn.

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CHAPTER 7

Summary and General Discussion

Summary of Main Findings

The current dissertation investigated attentional mechanisms concerning itch with a special focus on selective attention towards itch, that is, an attentional bias towards itch in healthy individuals. Itch is a somatosensory experience, eliciting the urge to scratch. Itch can be seen as a signal of potential threat to the body. Based on Posner's model of selective attention, it is proposed that from all incoming stimuli, itch-related information will be selected preferentially because of its threatening nature that induces nocifensive behaviours. This means that potentially threatening information, such as itch- or pain-related information will be attended to more quickly than neutral information to protect bodily integrity. *Chapter 1* introduced preliminary findings on attention and itch. First evidence emerged that itch is distracting, interfering with a concurrent task, and one study also showed that healthy individuals might display an attentional bias towards visual representations of itch. However, based on these few studies so far, it is unclear at which processing stage attention is captured, either consciously or preconsciously, and also whether attention towards itch could be modified in healthy individuals. Therefore, the current dissertation investigated an attentional bias towards itch, at conscious and preconscious processing stages, in healthy individuals, as well as the modifiability of selective attention to itch in this population.

In *Chapter 2*, attentional bias was investigated with itch-related, pain-related and general negative stimuli, once with pictures and once with words, in an itch- and pain-free sample. It was expected that these individuals would show an attentional bias towards each of these three stimulus types but this was not supported by the results. However, we found that participants were overall slower during trials that involved negative pictures compared to itch- and pain pictures. This could be interpreted as attentional interference by these negative stimuli. Descriptive statistics, however, suggested an attentional bias away from itch-related pictures, but this effect was not significant.

Chapter 3 used an adaptation of the visual attentional bias paradigm by using electrically induced itch and pain stimuli, hence, making it possible to investigate an attentional bias towards somatosensory stimuli. Contrary to expectations, results showed no attentional bias towards the somatosensory stimuli. Yet, overall responses were slower during itch and pain stimulation compared to vibrotactile control stimulation. Therefore, it can be concluded that itch and pain specifically interfered with the execution of another, unrelated task which resembles the distracting nature of actual itch and pain. In addition, the findings of the visual paradigm used in *Chapter 2* were replicated, showing slowed responses to visual negative stimuli, but no significant effect for visual itch and pain stimuli.

Chapter 4 adapted the visual attentional bias paradigm into a preconscious design. In addition, an implicit priming procedure was employed that induced a mild itch stimulus versus a neutral control stimulus on the participants' skin before the attentional bias assessment. The question was whether healthy individuals would show an attentional bias towards itch at a preconscious processing stage. In addition, it was expected that the perception of itch would enhance an attentional bias towards visual itch. Results did not show a preconscious attentional bias towards itch, but away from itch. This would be interpreted as avoiding the itch-related pictures compared to neutral pictures, i.e., attentional avoidance. No difference in attentional bias was found between the group primed with an itchy stimulus compared to the control group which received a neutral stimulus assessment.

In the next chapter, *Chapter 5*, a conscious Attentional Bias Modification (ABM) training for itch was developed to modify attention towards itch. As proof of principle, healthy individuals were trained towards itch-related pictures, away from itch-related pictures or underwent sham-control training. In addition, it was investigated whether this training with pictorial stimuli would generalise to itch-related words and whether it would influence sensitivity to a mild itch stimulus on the skin. Contrary to expectations, no training effect was found, neither for an attentional bias towards itch-related pictures nor for itch-related words or on itch sensitivity. Notably, there was an attentional bias away from itch pictures found, i.e., attentional avoidance, before the training, within the whole sample which replicates the findings of *Chapter 4* but this time in a conscious design.

The last study in *Chapter 6*, adapted the design of the ABM training of *Chapter 5* into a preconscious design, alike *Chapter 4*. Participants were either preconsciously trained towards or away from itch pictures or underwent a sham-control condition, and sensitivity to a mild itch stimulus on the skin was assessed pre- and post-training. Again, against expectations, no training effects were found for either of the training groups. During baseline, no attentional bias was seen. Surprisingly, the sham-control group showed an attentional bias away, i.e., attentional avoidance, from itch after the training. This might show that an attentional bias away from itch only emerges after a specific number of presentations, i.e., trials, which would resemble the findings from *Chapter 4*. None of the groups showed a significant effect on sensitivity to itch after the training.

Taken together, the hypothesis that healthy individuals show an attentional bias towards visual representations of itch or somatosensory itch stimuli could not be supported by the current studies. While some studies revealed no significant effect of visual representations of itch on attentional processing (*Chapters 2 and 3*), some studies pointed towards an attentional bias away from itch (i.e., attentional avoidance; *Chapters 4, 5 and 6*). Notably, attentional avoidance was found in both preconscious studies, while the results of the conscious studies are mixed. The ABM- training that was employed in two studies did not lead to modification of attention to itch, neither towards or away from it (*Chapters 5 and 6*). In the *General Discussion*, these findings will be further examined in light of the current literature. Moreover, implications for future research and clinical practice will be discussed.

General Discussion

Attentional Bias towards Itch

Based on the current studies, healthy individuals did not show an attentional bias towards somatosensory itch or visual representations of itch, neither consciously, nor preconsciously. From a theoretical perspective, it was assumed that itch-related stimuli in the environment would draw attention to induce an adaptive behavioural response to protect bodily integrity (Paus et al., 2006). This would correspond to the orienting stage of attentional processing in which a stimulus from the environment is selected to pay attention to (Posner, 2016). Despite the current findings, we assume that itch induces nocifensive behaviours because a scratching response is usually elicited by somatosensory itch (Paus et al., 2006; Petersen & Posner, 2012), but this might not be reflected in the attentional processing of visual representations of itch. The current findings in somatosensory itch did also not support an attentional bias towards itch, but overall, the evidence for somatosensory stimuli is very limited and therefore inconclusive (Chapter 3; van Laarhoven et al., 2017, 2018). The finding that healthy individuals do not show an attentional bias is, however, in line with meta-analyses in the field of pain pointing towards an attentional bias in patient populations only (Abudoush et al., 2023; Broadbent et al., 2021; Crombez et al., 2013; Todd et al., 2018).

In line with these findings, also the attentional bias modification (ABM) training towards or away from visual representations of itch in healthy individuals was unsuccessful in the current dissertation (*Chapters 5 and 6*). Yet, this is in line with the very limited evidence, including meta-analyses, for attentional bias modification training for pain, either in healthy individuals or in patient populations (Abudoush et al., 2023; Hasegawa et al., 2021; Todd et al., 2015; Van Ryckeghem, Van Damme, Vervoort et al., 2018). Interestingly though, attentional bias away from itch was found in both studies. In *Chapter 5* healthy individuals showed a conscious attentional bias away from itch even before the training and in *Chapter 6* the same happened preconsciously in the sham-control group after the training. A possible explanation was that an attentional bias away from itch would only become apparent after a sufficient amount of exposure, i.e., after many itch-related pictures were presented. This remains speculative though. Moreover, this would need further investigation with somatosensory stimuli because the current dissertation first, did not find an effect on attentional bias, and second a somatosensory training task has not yet been designed (*Chapter 3*). Nevertheless, altogether, this dissertation's findings seem to support an attentional bias away from, i.e., attentional avoidance of, visual itch-related stimuli (*Chapters 4, 5 and 6*).

Even though avoidance of itch-related stimuli contrasts with our hypotheses, it is still in line with the nocifensive function of itch (Paus et al., 2006). While we assumed beforehand that attention might be drawn towards itch to adapt behaviour, it makes equally sense that eventually, the goal is to avoid these stimuli in our environment. Indeed, one recent study showed attentional avoidance of itch-related stimuli after inducing acute itch compared to a control condition in healthy individuals (Etty et al., 2022). However, it is unclear yet, how attentional avoidance, i.e., not paying attention to something, will serve the goal to escape a potential threat. Usually, avoidance is seen as a behavioural process, meaning someone avoids certain behaviours or situations to prevent further (hypothetical) damage (Meulders, 2019; Nadinda et al., 2024; Vlaeyen et al., 2016; Vlaeyen & Linton, 2012). Research into attentional avoidance specifically is very scarce so far (Etty et al., 2022; Lautenbacher et al., 2011). However, our results would suggest that attentional avoidance is a very fast process, due to our preconscious findings, hence, someone is screening the environment for potential danger and setting in behavioural avoidance to fulfil the nocifensive function.

The concept of avoidance of itch is in line with the concept of a behavioural immune system. This states that someone protects their body from potential pathogens even before these might enter the body (Schaller & Park, 2011). This might be a highly relevant concept in itch as the skin, where the itch is commonly experienced, forms a physical barrier to repel infectious agents such as parasites or other agents that infiltrate the skin. Within this model, it is indeed assumed that even stimuli that are only superficially related to a potential threat might activate the system (Schaller & Park, 2011). Therefore, seeing someone scratching might activate a response, even though an actual infectious transmission is unlikely. At this point, only one study investigated avoidance in the context of itch (i.e. using itch-related pictures). This study did not provide evidence for behavioural avoidance tendencies, neither in patients with psoriasis, their significant others, nor in controls (Nadinda et al., 2023). Additionally, even when focussing on attentional avoidance, visual representations used in the current studies might not fully elicit the adaptive process; somatosensory itch might be needed for further investigation of these processes. Altogether, avoidance of itch and related stimuli and potential differences in attentional and behavioural avoidance patterns need further investigation.

Therefore, the exact mechanisms of attentional processing of itch, its relation to behavioural avoidance and potential differences in attentional bias towards itch in patient groups compared to healthy individuals need to be investigated in the future. Additionally, recent developments in the broader field of attentional bias towards (or away from) potentially threatening or negative information suggest that the current conceptualisation of attentional bias needs adjustments (Todd et al., 2015; Van Ryckeghem & Crombez, 2018). Overarching topics that emerged within the different fields, such as pain and anxiety or depression research are that attentional bias might be a rather dynamic process instead of a static trait. Therefore the current context, flexible adjustment of attention and arousal should be included in attentional bias conceptualisations (Godara et al., 2023; Van Ryckeghem et al., 2019; Zsidó, 2024).

Attentional bias as a dynamic process

A functional-contextual framework has been proposed in the field of pain that highlights the dynamic nature of attentional bias that should be goal-dependent and related to the current context of the individual (Van Ryckeghem & Crombez, 2018; Van Ryckeghem et al., 2019). It is suggested that selective attention towards or away from pain changes within different situations and whether the individual is currently engaged in something related to the painful experience or not. The currently most used dot-probe paradigm, as used in the current dissertation, does not fulfil these criteria as it assumes that attentional bias is a rather static trait someone possesses or not. It does not take into account that attentional processing might be different in different moments of time or situations. With a simple example, being attentive to something buzzing around your head is more important at night than during the day because the chances it is a mosquito and not a fly are higher at night. During the night it is adaptive to attend to this buzzing sound because someone wants to adapt their behaviour accordingly. In the tasks of the current studies, the itch-related stimuli that we used were not related to the goal of the given tasks and the overall goal of the task was not to prevent an itchy reaction itself. Therefore, if an attentional bias is reliant on a specific context, tasks that can account for this are needed.

The more flexible nature of attentional biases has also been discussed in the broader field of attention to potentially threatening information (Godara et al., 2023). In this so-called contextual goal-dependent attentional flexibility framework, it is supposed that attention needs to be *flexibly* directed towards emotional information in our environment. It again, depends on the situation whether attending to either positive or negative stimuli is more adaptive. While in the field of anxiety and depression, as well as pain and itch, so far the prevailing assumption was that attentional bias towards negatively valenced stimuli is always dysfunctional, they propose that this is highly dependent on the current context and which behavioural adaptation, i.e., which goal within this situation, is appropriate. This would align with our findings that attentional avoidance of itch might be adaptive in healthy individuals in a situation that does not pose a threat. The itch-related pictures were not related to, or even interfering with, the current goal of completing the task at hand. In addition, for someone with no history of frequent itching, the stimuli were probably neither very important nor relevant within the neutral laboratory context, hence, their nocifensive function is not valid in this situation. Moreover, very recently, studies in pain showed that patients with chronic pain, but not healthy individuals, are prone to change their attentional focus, called attentional malleability (Mac Goris et al., 2024; Todd et al., 2023). In one study, patients with chronic pain who changed their selective attention towards or away from pain more flexibly showed higher levels of pain and disability (Mac Goris et al., 2024). Another recent study showed that being more flexible in the attentional processing of pain buffered against pain interference in daily life (Todd et al., 2023). Therefore, the flexible adjustment of selective attention towards potentially threatening information might be promising also in itch and needs investigation.

Another aspect mostly neglected in research so far that might be important in attentional processing is arousal. Most research on visual attention towards emotionally charged stimuli is only concerned with valence, either positive or negative (Zsidó, 2023). Yet, initial arousal is an important force in visual attention which is most often not specifically included in studies. Based on the theoretical framework utilised in this dissertation (Petersen & Posner, 2012; Posner, 2016), arousal is a necessary factor in attentional processing before the orienting of attention takes place. Someone needs to be alert to attend to their environment. Arousal might also be highly related to how someone appraises a stimulus because this might either lead to higher arousal or not. If it leads to heightened arousal this could lead to increased selective attention, towards the more negative or positive (neutral) stimulus site (van Steenbergen et al., 2011). Furthermore, since the typical stress response includes heightened arousal, individuals tend to interpret physiological arousal as fear, i.e., a threat, which would also suggest that arousal might play a crucial role in the assessment of attention towards potentially harmful stimuli. It might mean that higher arousal could lead to a more threatening interpretation which in turn could guide selective attention into a specific direction. The notion that the appraisal of a stimulus as a threat plays a crucial role in attentional bias was also put forward to explain how attentional processing might exaggerate and maintain symptoms in pain (Todd et al., 2015). However, current paradigms do not assess how arousing their stimulus materials are, also not in the studies of the current dissertation when attentional bias towards itch was examined. Therefore, it seems important for further understanding to include arousal levels when investigating attentional bias towards a potential threat such as itch.

Strengths and limitations

The overall strength of this dissertation is that studies were executed with a strong focus on experimental rigour. All studies were well-controlled and *Chapters 4 and 6* switched from traditional ANOVA models to multilevel models to control for the variation in trial-based reaction time data. *Chapters 4 and 6* were also the first to use preconscious designs to assess attentional bias for itch and by this, a first attempt was made to investigate different stages of attentional processing. In addition, all studies used the same validated stimulus material (*Chapter 2*) to represent itch and used the same dot-probe paradigm which makes them highly comparable. Moreover, a somatosensory variant of the dot-probe paradigm, the somatosensory attention task, was used to increase comparability to the real-life phenomenon of itch. The use of rather homogeneous samples could on the one hand be seen as a strength concerning the comparability of the studies but at the same time of course hamper generalisations to the broader population.

There are also learning points from the current studies that future research should consider to improve study designs. While the comparability of the current studies is an advantage, it also means that the paradigm and materials are a common confounding factor. Even though the stimulus material was validated in an independent sample (see *Chapter 2*), the other studies did not include any ratings of itch-relatedness of the material. Hence, there is a possibility that participants in subsequent studies did not interpret the material as such. Furthermore, the dot-probe paradigm on which all studies were based, is not without criticism (Chapman et al., 2019; Dear et al., 2011; Evans & Britton, 2018; Kappenman et al., 2014). Recent studies on attentional bias towards itch used a spatial-cueing paradigm instead (Etty et al., 2022, 2023). It needs to be investigated whether one of the two might be superior to measure attentional bias. Still, as already discussed above, both would probably need adaptation to capture attentional bias as a dynamic construct that serves goal-directed, functional behaviours. For instance, future studies could try to incorporate an itch-related stimulus, visually or somatosensory, that is inherent to the goal of completing the task instead of a neutral target stimulus. In addition, we are not sure yet whether different tasks measure the same stage of attentional processing while their results are often directly compared. For instance, it could be argued that a Stroop paradigm measures interference and not preferential allocation of attention such as a dot-probe paradigm. So far, these are used both to infer an attentional bias while other cognitive processes might be also at stake which also poses difficulties for meta-analytical evidence (Abudoush et al., 2023; Crombez et al., 2013). It is possible that one measures earlier or later processing stages only and attentional bias might occur only at one of these stages, hence results could differ between the different tasks. This was nicely illustrated in recent work that used a spatial-cueing paradigm to measure attention towards itch that indeed showed differences in early versus late processing (Etty et al., 2023). Studies using different paradigms and various display times, i.e., processing stages, are needed to research the full attentional spectrum and to elucidate differences between the paradigms.

Implications for future research and clinical practice

The results of the current dissertation should be used to guide future research in the field of attention and itch. Based on the current findings, one would assume that attentional avoidance plays a critical role in the attentional processing of itch in healthy individuals. Hence, attentional avoidance of itch should be investigated more specifically and extended with studies on behavioural avoidance as is already done in pain (Meulders, 2019). While attentional avoidance might be interesting in itself, the translation to avoidance behaviour might be important for new treatment directions in patients, such as exposure therapy. Especially considering that scratching, a behaviour, is intrinsically linked to itch (Ikoma et al., 2006; Ishiuji, 2019; Paus et al., 2006; Ständer et al., 2007). In addition, the discussed developments in pain and depression research suggest new avenues on how to conceptualise and measure attentional bias towards itch. For instance, a paradigm was developed to assess attentional flexibility towards negative or positive faces that included contextual cues and manipulated current goals during the task (Godara et al., 2021). This could be a starting point for including contextual factors and goals into these types of measurements and adapting them for itch as the stimulus of interest. As an example, this could be done by using a medical consultation room picture in the background of the computer task as the context. In addition, the completion of the task could be linked to a decrease in actual itch stimulation on a participant's skin. Only if we get more insight into how attention interacts with contextual factors and current goals, we can disentangle its specific role in symptom perception and eventually in patient's daily life.

A direct translation into clinical practice based on the current knowledge of attention and itch in healthy subjects is rather preliminary. Yet, it should be acknowledged that attention is one of the psychological processes that probably plays a role in the experience of itch in patients with chronic itch (Silverberg et al., 2018; van Laarhoven et al., 2020). Hence, it is suggested on the one hand to compare the attentional processing of itch-related stimuli in patients and healthy controls, and on the other hand to investigate the role of context, flexible adjustment and arousal in the clinical context. This means that the perception of itch and associated scratching behaviour likely is, or at least initially feels adaptive to patients, serving the goal of relieving the itch and a clinical setting might be a relevant context. It needs further investigation into how cues in a patient's environment might trigger the itch and a scratch response, and how this might amplify the symptoms. This would call for more research into a potential attentional bias towards itch-related stimuli in patient populations to see whether attention is indeed preferentially drawn towards these cues. We need to understand how attention and itch interact in patients with chronic itch first and how attentional processes affect the overall quality of life. Only after that, suitable attention re-training paradigms for patients with chronic itch can be developed.

Conclusions

In conclusion, the current dissertation contributes to the so far limited research on attentional processing of itch-related stimuli and specifically attentional bias. The current findings are mixed but it seems like attentional avoidance of itch-related stimuli and an interfering effect of itch is the most evident in healthy individuals at this point. This dissertation acknowledges, though, that the field of attentional bias research, as can be seen in pain or depression, needs improvements in terms of ecologically valid measurements. Hence, with the lessons learned from the current dissertation, it is recommended that future studies critically evaluate attention paradigms, test them in different populations of both healthy participants and patient groups, and only then move forward to use these insights to develop interventions to re-train attention in patient populations with chronic itch. Eventually, we hope to be able to relieve symptoms, as well as improve the overall quality of life of patients who suffer from chronic itch.

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APPENDIX

NEDERLANDSE SAMENVATTING

In dit proefschrift zijn aandachtsmechanismen met betrekking tot jeuk onderzocht bij gezonde individuen, met specifieke focus op selectieve aandacht voor jeuk, oftewel een aandachtsbias voor jeuk. Jeuk is een somatosensorische ervaring, die de drang tot krabben oproept. Jeuk kan gezien worden als een signaal van potentiële bedreiging voor het lichaam. Gebaseerd op Posner's model van selectieve aandacht wordt verondersteld dat van alle inkomende sensorische stimuli, jeuk-gerelateerde informatie bij voorkeur wordt geselecteerd vanwege de mogelijk bedreigende aard ervan die nocifensief gedrag uitlokt. Dit betekent dat potentieel bedreigende informatie, zoals jeuk- of pijn-gerelateerde informatie, sneller aandacht zal krijgen dan neutrale informatie om daarmee de lichamelijke integriteit te beschermen. *Hoofdstuk 1* introduceerde voorlopige bevindingen over aandacht en jeuk. Eerst werd aangetoond dat jeuk afleidt en interfereert met een gelijktijdige ongerelateerde taak, en één studie toonde ook aan dat gezonde individuen mogelijk een aandachtsbias hebben voor visuele representaties van jeuk, zoals bijvoorbeeld plaatjes van hoe iemand zichzelf krabt. Op basis van deze weinige studies tot dan toe was het echter onduidelijk in welke verwerkingsfase aandacht wordt getrokken, bewust of onbewust, en ook of aandacht voor jeuk kan worden veranderd bij gezonde individuen. Daarom werd in dit proefschrift een aandachtsbias voor jeuk, in bewuste en onbewuste verwerkingsstadia onderzocht bij gezonde individuen, evenals de modificeerbaarheid van selectieve aandacht voor jeuk in dezelfde populatie.

In ***hoofdstuk 2*** werd aandachtsbias onderzocht met jeuk-gerelateerde, pijn-gerelateerde en algemene negatieve stimuli, één keer met plaatjes en één keer met woorden, in een jeuk- en pijnvrije steekproef. Er werd verwacht dat deze mensen een aandachtsbias zouden hebben voor elk van deze drie stimulustypen, maar dit werd niet ondersteund door de resultaten. Wel vonden we dat deelnemers over het algemeen langzamer waren tijdens presentaties van negatieve plaatjes in vergelijking met jeuk- en pijnplaatjes. Dit zou geïnterpreteerd kunnen worden als aandachtsinterferentie door deze negatieve stimuli, dat wil zeggen mensen rakten afgeleid. Beschrijvende statistieken suggereerden echter wel een aandachtsbias bij jeuk-gerelateerde plaatjes, maar dit effect was niet statistisch significant.

Hoofdstuk 3 gebruikte een aanpassing van het visuele aandachtsbias paradigma door gebruik te maken van elektrisch geïnduceerde jeuk- en pijnstimuli, waardoor het mogelijk werd om een aandachtsbias ten opzichte van somatosensorische stimuli te onderzoeken. Tegen de verwachting in, toonden de resultaten geen aandachtsbias voor de somatosensorische stimuli. Toch waren de algehele reacties langzamer tijdens jeuk- en pijnstimulatie in vergelijking met vibrotactiele controlestimulatie. Daarom kan geconcludeerd worden dat jeuk en pijn specifiek interfereerden met de uitvoering van een andere, niet-gerelateerde taak. Dit lijkt op de afleidende aard van daadwerkelijke jeuk en pijn. Daarnaast werden de bevindingen van het visuele paradigma uit *hoofdstuk 2* gerepliceerd, waarbij vertraagde reacties op visuele negatieve stimuli werden gevonden, maar geen significant effect voor jeuk- en pijnstimuli.

Hoofdstuk 4 paste het visuele aandachtsbias paradigma toe in een onbewust verwerkingsstadium. Dit betekent dat mensen de stimuli niet bewust waarnamen. Daarnaast werd een impliciete priming procedure gebruikt die een milde jeukstimulus versus een neutrale controlestimulus op de huid van de deelnemers toepaste voordat de aandachtsbias werd gemeten. Men werd hierbij niet vooraf ingelicht dat deze studie over jeuk gaat en er jeuk opgewekt zou worden om een bewuste beïnvloeding te voorkomen. De vraag was of gezonde mensen een aandachtsbias voor jeuk zouden vertonen in een fase van onbewuste verwerking. Daarnaast werd verwacht dat de milde jeukstimulus een aandachtsbias voor visuele jeuk zou versterken. De resultaten toonden geen onbewuste aandachtsbias voor jeuk, maar wel weg van jeuk. Dit zou geïnterpreteerd kunnen worden als het vermijden van jeuk-gerelateerde plaatjes in vergelijking met neutrale plaatjes, d.w.z. vermijding van aandacht voor jeuk-gerelateerde plaatjes. Er werd geen verschil in aandachtsbias gevonden tussen de groep die vooraf een jeukstimulus ervoer, vergeleken met de controlegroep die een neutrale stimulus kreeg.

In het volgende hoofdstuk, ***hoofdstuk 5***, werd een Attentional Bias Modification (ABM) training voor jeuk ontwikkeld om de aandacht voor jeuk te veranderen in een bewust verwerkingsstadium. Om het onderliggende principe te onderzoeken, werden gezonde individuen getraind naar jeuk-gerelateerde plaatjes toe, weg van jeuk-gerelateerde plaatjes of ondergingen ze een actieve controletraining. Daarnaast werd onderzocht of deze training met jeuk-gerelateerde plaatjes zou generaliseren naar jeuk-gerelateerde woorden en of het de gevoeligheid voor een milde jeukprikkel op de huid zou beïnvloeden. Tegen de verwachting in, werd er geen trainingseffect gevonden, noch voor een aandachtsbias naar jeuk-gerelateerde plaatjes, noch voor jeuk-gerelateerde woorden of op jeukgevoeligheid. Er werd met name een aandachtsbias weg van jeuk-gerelateerde plaatjes gevonden, d.w.z. vermijding van aandacht voor jeuk, vóór de training, binnen de gehele steekproef. Dit repliceert de bevindingen uit *hoofdstuk 4*, maar dit keer in een bewust verwerkingsstadium.

Het laatste onderzoek in ***hoofdstuk 6*** paste het ontwerp van de ABM-training van hoofdstuk 5 aan naar een onbewust verwerkingsstadium, net als in *hoofdstuk 4*. Deelnemers werden onbewust getraind naar jeukplaatjes toe, ervan weg, ofwel ondergingen ze een actieve controletraining. Ook de gevoeligheid voor een milde jeukstimulus op de huid werd voor en na de training beoordeeld. Ook hier werden, tegen de verwachting in, geen trainingseffecten gevonden voor de trainingsgroepen. Tijdens de baseline werd geen aandachtsbias gevonden. Verrassend genoeg vertoonde de actieve controlegroep na de training een aandachtsbias weg van jeuk, d.w.z. vermijding van aandacht voor jeuk-gerelateerde plaatjes. Dit zou kunnen aantonen dat een aandachtsbias voor jeuk pas na een bepaald aantal presentaties ontstaat, wat zou kunnen lijken op de bevindingen uit *hoofdstuk 4*. Geen van de groepen vertoonde een significant effect op de gevoeligheid voor jeuk na de training.

Alles bij elkaar genomen kon de hypothese dat gezonde individuen een aandachtsbias vertonen voor visuele representaties van jeuk of somatosensorische jeukstimuli niet worden ondersteund door de huidige onderzoeken.

Terwijl sommige studies geen significant effect van visuele representaties van jeuk op de aandachtsverwerking lieten zien (*hoofdstukken 2 en 3*), wezen sommige studies op een aandachtsbias weg van jeuk (d.w.z. vermijden van aandacht voor jeuk-gerelateerde stimuli; *hoofdstukken 4, 5 en 6*). Aandachtsvermijding werd met name gevonden in de studies naar onbewuste verwerkingstadia, terwijl de resultaten van studies in bewuste verwerkingsstadia gemengd zijn. De ABM-training die in twee studies werd gebruikt, leidde niet tot aanpassing van de aandacht voor jeuk-gerelateerde stimuli, noch naar jeuk toe, noch ervan weg (*hoofdstukken 5 en 6*). Dit proefschrift erkent echter dat het onderzoeksgbied naar aandachtbias, zoals te zien is bij pijn of depressie, verbeteringen behoeft in termen van ecologisch valide metingen. Met de lessen uit dit proefschrift wordt daarom aanbevolen dat toekomstige studies aandachtsparadigma's kritisch evalueren, deze testen in verschillende populaties van zowel gezonde deelnemers als patiëntengroepen, en daarna deze inzichten gebruiken om interventies te ontwikkelen om aandacht te hertrainen in patiëntenpopulaties met chronische jeuk. Uiteindelijk hopen we de symptomen te kunnen verlichten en de algehele kwaliteit van leven van patiënten met chronische jeuk te kunnen verbeteren.

CURRICULUM VITAE

Jennifer Mareen Becker was born on June 14th, 1991 in Essen, Germany. In 2010, she finished her high school education (Abitur) at Mädchengymnasium Borbeck in Essen, Germany. After working as an au-pair in a Dutch family with two children in The Hague, she started her ***Bachelor in Psychology at Leiden University*** in 2011. In addition to her studies, she was actively involved in several committees of study association Labyrint and was a member of the 68th board in the academic year of 2014-2015. After graduating in 2015, Jennifer continued her academic education with the ***Research Master in Psychology, Cognitive Neuroscience track, at Leiden University***, for which she graduated in 2018. During her studies, she participated in several research projects as a research assistant, including different departments and research methods including behavioural and neuroimaging data.

Following upon her experience as a research assistant, Jennifer started her PhD-project in 2018 under the supervision of prof. dr. Andrea Evers and dr. Antoinette van Laarhoven at the Health, Medical and Neuropsychology Unit of Leiden University. Her PhD- research included behavioural and psychophysiological methods concerning the attentional processing of itch and pain in healthy individuals. Next to her research activities, Jennifer gained ample experience in teaching, including workgroups, lectures and thesis supervision at the Bachelor and Master level, resulting in obtaining a University Teaching Qualification. Currently, she works as a postdoctoral researcher on multidisciplinary projects concerning pandemic preparedness at Leiden University.

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waar deuren altijd open staan en je met vragen altijd terecht kan. Ook al lopen korte vragen geregeld uit in een gezellig kletspraatje over de wetenschap, de wereld en de zin van het leven in zijn geheel. En mijn erg gewaardeerde write meet, de laatste loodjes wegen het zwaarst en dat was echt zo, maar dank jullie steun, waren ze in ieder geval een stuk gezelliger.

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