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Cognitive processing of itch and pain: The role of attention and expectations.

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Although itch and pain are distinct phenomena, they have a lot in common. Both phenomena are unpleasant, somatosensory sensations that warn for potential threat of bodily integrity ('nociception') and their presence is determined by intertwined biopsychosocial factors [23,61].

Formerly, pain was understood from a biomedical perspective, suggesting a clear pathophysiological cause [16]. Since the 1960s, however, this perspective has shifted to a biopsychosocial perspective, where there is involvement of psychological and social factors [1,16]. This perspective is also underscored by its widely acknowledged definition: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Taxonomy). According to this view, pain is understood as a multidimensional and dynamic interplay between physiological and psychosocial factors, including attention and expectation [1,16,21,61]. Particularly chronic pain, in which central sensitization processes that amplify pain (i.e. amplification of central excitatory signaling [3]) supposedly play a role, is associated with reduced psychological wellbeing. Often increased levels of distress and worrying, impaired sleep quality, and loss of work are noticed, resulting in substantial societal costs [1,3,21]. These psychosocial factors are, however, not only consequences of pain. They can also act as determinants. In fact, the association between biopsychosocial factors and pain is often bidirectional [1,21].

For itch, the interplay between biopsychosocial factors and itch is also recognized. Indeed, itch has been defined back in 1660 as "an unpleasant cutaneous sensation which provokes the desire to scratch" [23]. Itch captures our attention and a behavioral response of scratching is often initiated [23]. Scratching can intensify itch, potentially resulting in a vicious itch-scratch cycle [60]. Itch is also associated with a decreased quality of life, including depressive symptoms and sleep disturbances [60]. This is particularly the case for chronic itch, wherein – similar to pain-

central sensitization processes are thought to play a role [23]. Itch is, more than pain, characterized by its contagiousness. Observing others' scratching and talking about itch can result in itch and scratching responses in the observer [40]. Moreover, scratching and visible skin lesions can result in stigmatization. This also contributes to the experience of negative emotions [23,60], which in turn can amplify itch [52]. Akin pain, itch and its consequences on wellbeing likely make one focus more on bodily symptoms. Furthermore, one may start to expect itch in certain situations, for instance due to previous experiences [19,46], e.g., when wearing wool, which can further aggravate itch. This underlines a bidirectional interaction of biopsychosocial factors and itch. However, a biopsychosocial model of itch has only recently put forward [60].

A direct comparison of itch and pain may provide further information about mutual processes. This comparison may result in a general model of symptom perception, which improves current understanding and future treatment of both phenomena. A modal model of symptom perception has recently been put forward by Van den Bergh and colleagues, summarizing several existing models designed to explain patients' symptoms that do not reflect physical input (e.g., medically unexplained and chronic symptoms) [46]. This model poses that somatic input, including regularly perceived sensations derived from physiological arousal, prompts individuals to focus attention on bodily sensations. This can lead to a reduced threshold for sensation perception, and potential misinterpretation of sensations as threatening or part of their condition. This in turn increases physiological arousal, eventually resulting in a vicious cycle of symptom perception. The modal model positions cognitive processes as key mediators between the somatic input and the experienced symptoms. In this chapter, we focus on attentional and expectancy processes as frequently studied cognitive processes and important mechanisms for central sensitization and development of chronic itch and pain and propose a

cognitive model of itch and pain perception (Fig. 1.). In addition, a large number of demographic, contextual, biomedical, and psychosocial factors (e.g., social anxiety due to visible skin damage, pain-related fear, or genetic predisposition) may moderate the relationship described in the cognitive model [e.g., 1,13,30,37,46,60,61]. Given the central role of attention and expectancy in information processing, targeting these processes in the treatment of itch and pain can sort widespread effects [18,54,61].

Within the current chapter, we will focus on the role of attention and expectations in itch and pain and summarize the current knowledge on basis of the proposed cognitive model. Furthermore, directions for future research and interventions will be discussed.

Attention

Attention plays a key role in the processing of information, both internal and external, to which we are continuously exposed. Attentional processes are involved in the selection and prioritization of this information. From a functional perspective, attention ensures that one can perform the desired tasks without being distracted by irrelevant information, while being interrupted in ongoing behavior when more important information emerges [54]. The latter process is a bottom-up process that initiates a primary response of physiological arousal and orienting the attention to the source where threat is present or expected [43]. Orienting attention towards itch or pain is adaptive as it enables one to initiate protective action, such as avoiding or removing itch or pain triggering factors or their cause [23,61]. Different individual and contextual factors play a role in the degree of interference by potentially harmful input. For example, it is dependent on one's individual goals [54], which may either be symptom-irrelevant or focused on avoiding itch or pain. In the latter case, attention will more likely be

captured by itch- or pain-related information. Another factor is the degree of engagement in current tasks [54]. If a high degree of cognitive resources is required, e.g., during complex problem solving, or one is highly dedicated to attain the set goal(s), attention is less likely to be interrupted by itch- or pain-related input [54]. Thus, the attention system works appropriately when activity is interrupted by highly demanding sources of threat, while it is able to detach attention from the threat source in low threatening instances in order to continue task execution [43,54]. A balance in staying focused on goals and monitoring the background is essential to maintain health [54]. In contrast, when itch and pain remain capturing attention, it may contribute to chronification of symptoms [1,3,16,60].

Role of attention in itch and pain

For pain, heightened attention toward pain-related signals is suggested to be involved in pain sensitization and associated distress and disability [1,13,61]. This is empirically supported by higher levels of attentional focusing being associated with more pain [e.g., 8,15,49], although evidence is mixed [13]. In addition, patients with acute or chronic pain preferentially attend towards (i.e. have an attentional bias) pain-related information [for meta-analyses see 13,39,42]. Such an attentional bias is not observed in healthy people or people anticipating experimental pain [13,42]. However, by far, most studies investigating attentional bias towards pain that used behavioral tasks (required to also grasp attentional processes that occur outside conscious awareness) have typically used words, such as affective (e.g., annoying) or sensory pain words (e.g., burning); note that an overall attentional bias was exclusively found for the latter category [13,42]. Other studies have used pictures with a painful expression (e.g., a hand holding the forehead to indicate headache pain) or health-threat related images (e.g., ambulance) [13,39,42]. Some scholars have suggested that words and pictures may not sufficiently be appraised as pain-related [13]. Some researchers have tried to overcome this problem by using

(cues of) actual pain [e.g., 28,44,50,55,58]. These studies have shown that people direct attention to a location where pain is expected or briefly perceived [e.g., 44,55,58], but do not necessarily stay focused on the location of tonic pain [50]. In addition, the experience of pain can also interfere with attention while performing pain-irrelevant tasks, especially when pain is more intense, more threatening, and novel [28,50,54,61]. Noteworthy, attentional processes have a strong neurobiological basis, as for example shown in electroencephalography (EEG) and magnetic resonance imagining (MRI) research for pain [43].

For itch, processes comparable to pain likely play a role. However, evidence is limited as only a handful experimental studies focused on attentional processing of itch [20,47,50,51]. Preliminary evidence suggests that patients with chronic itch are more attentive to symbolic itch-related stimuli than to neutral stimuli [20,47]. However, in contrast to pain research [13,42], healthy controls may also preferentially attend to symbolic itch stimuli [47,51]; this is possibly related to the contagiousness of itch. Evidence for the association between increased bodily attention and an increased itch perception is currently limited to healthy people [49]. Furthermore, attention does not seem to be consistently drawn towards the location where tonic itch, alike tonic pain, is delivered [50,51]. Tonic itch can interfere with task performance [50], although this finding is not consistent [51].

It is unknown whether itch or pain is evolutionary prioritized over the other sensation. One can imagine that the consequences of pain can potentially be more life-threatening than those of itch (e.g., severe wounds versus parasites entering the skin, respectively). Contrarily, itch cues from the environment might be particularly demanding and susceptible to cognitive influences, as demonstrated by itch' contagiousness or its susceptibility to suggestion [19,40]. In a chronic state, the signals that are congruent to the patient's condition are likely to become prioritized,

as symptom-management becomes a goal in itself [43,54], whereas an attentional bias towards the symptom can enhance symptom perception and associated distress. In turn, this may lead to more attentional bias, initiating a vicious cycle (Fig. 1.). This cycle may then be amplified, or reduced, by individual and contextual factors [1,13,61]. In the end, increased attention for pain information is no longer functional. Such a situation has devastating effects for patients and exerts a large impact on their daily life.

Attention interventions

To reduce attentional bias for pain and its impact on pain outcomes, several studies have investigated the effectiveness of attention bias modification (ABM) training. For ABM training, a computerized task is utilized to train attention away from symbolic pain stimuli. Results in both pain patients and healthy subjects are currently inconsistent; some studies showed positive effects of ABM training on participants' pain sensitivity or attentional bias to pain, but these effects could not consistently be replicated [53]. Further research is warranted to investigate under which conditions ABM training is useful, e.g., ABM training may only be helpful if people are biased towards pain-related stimuli at baseline [53]. Other frequently used attention-modulating techniques are attentional distraction (i.e. directing attention away by engaging in a competing demand or goal) and sensory monitoring (i.e. focusing on the sensory features of the sensation instead of on the emotional valence of the sensation) [56]. There is evidence that both strategies are effective to reduce pain and associated distress resulting from experimental inductions or medical procedures in healthy people [56]. For chronic pain patients, however, meta-analytic findings deliver no clear evidence for an effect of distraction or sensory monitoring on clinical and experimentally induced pain [56]. There is a need for additional research of good quality, for instance with proper control conditions. Moreover, promising

additions to current attention-modulating techniques may relate to the use of individual goals to help people distract attention away from pain [56].

For itch, research on attention-based intervention techniques is scarce. An ABM training for itch did not change attentional bias for itch or itch sensitivity to low-intense mechanical stimuli in healthy participants [48]. In addition, a simple distraction task did not effectively reduce itch and scratching [41]. Effective reduction of patients' itch and scratching could however be obtained by a more complex and engaging distraction task, either with or without virtual reality [31].

All in all, although attention plays an important role in both itch and pain, current attention-based interventions are suboptimal. We therefore call for theory-driven research considering factors (e.g., goal setting) that may increase the effectiveness of attentional interventions for itch and pain [e.g., 54,56].

Expectancy

Expectancies are essential in the perception of our experiences and the world. Expectancies are particularly influential when they are precise and when they concern ambiguous sensations [46], like itch and pain commonly are. For itch and pain, predominantly expectations regarding the likelihood and intensity of future itch and pain symptom development and treatment outcomes are of importance. Also, expectations pertaining to other characteristics of the sensations (e.g., quality, location, time course, impact) and self-efficacy expectancies about the capability of coping with these sensations can influence symptom perception. As for attention, expectations of itch and pain are largely functional since they facilitate the quick interpretation

of stimuli and help us prepare by, for instance, enabling protective behavior [19,54,61]. Moreover, expectancies of itch and pain can shape the actual experiences and act as self-fulfilling prophecies [29]. Notably, expectancies, along with related psychoneurobiological mechanisms, are a core mechanism of placebo and nocebo effects (i.e. beneficial and adverse treatment outcomes, respectively that cannot be ascribed to pharmacological or physical treatment components).

Expectancies are shaped by our previous experiences and from what we hear and see from people around us [35]. First, the influence of prior experiences on expectancies and, consequently, future experiences can partially be ascribed to conditioning. During classical (or Pavlovian) conditioning, an association is formed between a stimulus that naturally elicits an experience (e.g., aspirin eliciting pain relief) and an initially neutral stimulus (e.g., appearance of the pill), so that the neutral stimulus alone comes to evoke a similar experience (e.g., pain relief upon taking placebo medication with the same appearance as the aspirin). Second, we also learn via instructional learning, i.e. from what people tell us. For example, a health professional can determine our expectations of future experiences when diagnosing, providing prognostic information about a symptom, and when prescribing a treatment. Third, psychological learning theories describe also how observation of others around us can determine expectancies via vicarious learning. We might expect a certain event (e.g., an insect bite) to be itching or painful or a treatment to be effective because we saw this to be the case for a peer or in the media. In addition, expectancies may also be formed by imagining, e.g., sensation reduction [33]. Moreover, situational factors such as one's present mood, symptom and treatment characteristics, as well as more stable individual characteristics (e.g., a person's tendency to be optimistic) may influence itch and pain expectations [30].

Role of expectancies in itch and pain

For pain, a vast body of research in both experimental and clinical settings shows that expecting that a (placebo) treatment is effective for relieving pain can substantially reduce perceived pain intensity, as well as pain unpleasantness and distress [34,59]. The mere suggestion that a placebo is an active analgesic can be sufficient [34]. Expectancies seem to elicit particularly strong effects on pain when they have been induced with verbal suggestions that are strengthened using a classical conditioning procedure [2]. Also, observational learning can induce placebo analgesic effects that can be of comparable size to the placebo effects induced via combined verbal suggestion with conditioning procedures [11]. In addition to expectations of treatment outcome, self-efficacy expectancies, i.e. expectations regarding the own capacities to, for example, be able to cope with pain, have been found to predict chronic pain intensity, distress, and impairment [25]. The induction of high self-efficacy expectancies regarding the ability to control pain may decrease perceived pain [57]. Importantly, expectancies do not only affect reported pain levels, but also the associated neurobiological responses, including altered activation of brain areas engaged in pain, expectancy, and emotion as well as involvement of endogenous opioids [6,38].

For itch, evidence is accumulating that expectations of the itch-relieving or itch-evoking properties of a (placebo) treatment, and itch expectations independent of treatment, can shape itch perception [19]. As for pain, particularly the combination of verbal suggestions and classical conditioning procedures has been found to be effective for inducing placebo and nocebo effects on itch [4]. The phenomenon of 'contagious itch' illustrates that merely observing other people who discuss itch or are scratching (even itch-related images) may evoke itch and scratching, particularly in patients with chronic itch [40]. It is, however, not yet known whether these processes are also mediated by itch expectancies. Furthermore, high general self-

efficacy expectancies have been associated with low levels of perceived itch in adolescents' daily life [14]. Verbal suggestions about itch have occasionally been found to also affect wheal and neurogenic flare responses to histamine applications [22]. As with nocebo effects on pain, nocebo effects on itch have been associated with altered brain activity illustrating top-down modulation [45].

Taken together, expectancies appear to play a comparable role in itch and pain. Direct comparisons of expectancy effects on itch and pain within studies are relatively rare. There is some preliminary evidence that expectancies can exert a larger effect on itch than on pain [19], probably because itch sensations have more ambiguous qualities than pain sensations. Other differences between itch and pain have been observed regarding the expectations people have about itch and pain relieving medication; itch and pain medication is expected to be more effective via topical application and injection, respectively [32]. There is a need for further research into the specific mechanisms underlying expectancy processes, particularly for itch and the comparison between itch and pain.

Expectancy interventions

Experimental research in both healthy and patient samples suggests that the beneficial effects of positive expectancies and the detrimental effects of negative expectancies on itch and pain can be harnessed in clinical care in multiple ways. The robust empirical evidence for the analgesic effects of providing suggestions of pain relief upon administering a (placebo) treatment indicates that the instructions a health professional provides during medical consults are essential for treatment effects [34]. For example, when providing a treatment, discussing the benefits a patient can expect from that treatment can produce positive effects. At the same time, consultation on the possible side effects and negative outcomes of a treatment needs to be

handled carefully as to prevent inducing nocebo effects, while ensuring transparency about potential risks [36]. Health professionals might ask patients about their previous experiences and expectations for future symptom development and treatment outcomes so that the information given can be tailored to the patient where possible. Notably, the effects of negative expectancies on itch can be countered by the induction of subsequent positive expectations of itch relief using a counterconditioning paradigm [5]. Additionally, ensuring patients that they will be able to cope with future symptoms and possible negative treatment outcomes might raise their self-efficacy expectancies and thereby reduce their complaints [25]. Furthermore, research indicates that health professionals who are perceived as empathic, warm, trustworthy, and competent, tend to elicit better positive expectancy effects [27]. Novel avenues for addressing expectancies using placebos in an ethical manner are the administration of open-label placebos, i.e., prescription of placebos to patients who knowingly consent [10], and using dose-extending placebos, i.e., giving placebos or subclinical doses of medication after repeated administration of active medication to utilize conditioning processes [12]. However, further research into the mechanisms for diverse treatments, medication doses, and patient groups is required. To ensure that expectancies are addressed effectively, educating patients about the influential role of expectancies and training health professionals in targeting expectancies is essential [18].

Discussion

It is evident that both itch and pain should be understood from a biopsychosocial perspective, with psychosocial factors being their consequences as well as their predictors. The model we propose here is based on a modal model of symptom perception [46]. This model centrally positions cognitive processing of the somatosensory input, specifically attentional and expectancy processes, in symptom perception. Attention and expectancies can either decrease

or increase itch and pain, depending on their specific content. Generally, increased attention for itch and pain and negative expectations of itch and pain have been found to lead to more itch and pain, respectively, and vice versa. Via this bidirectional relationship, a negative feedback loop of symptom worsening can be the result, leading to chronification of symptoms in the long run [3,16,23,46,60].

Attention and expectations are not stand-alone processes. Both have jointly been investigated in several pain studies. Expectancy and attention components are, for instance, hard to disentangle within placebo research that demonstrates, in an open-hidden design, that active medication is less effective when provided outside the patient's awareness (e.g., with an automatic pump) than when administered in full view of the patient [7]. Also, when expectations of threat were induced, patients with chronic pain showed to be more attentive to pain stimuli than when expectations of threat were low [24]. The effects of attention and expectations can also divergently affect pain [9,26]. For example, both a distraction task and a placebo treatment can sort analgesic effects in an additive manner [9]. Conversely, sensory monitoring of the body can reduce the pain amplifying effects of high-pain expectancies, suggesting that this strategy – rather than distraction - might particularly be effective when severe pain is expected [26]. Regarding potential moderators, none of the stable and contextual factors (e.g., personality characteristics, genetic predisposition, individual goals) seems to reliably predict attention or expectancy effects on itch and pain perception [1,13,16,30,37,60,61]. Instead, a complex interaction between these variables is likely at work. Together this calls for more research to unravel the specific interplay between attention, expectancies, and other biopsychosocial factors (see also van den Bergh and colleagues' comprehensive predictive processing model of perception [46]) and their impact upon acute and chronic itch and pain [46].

Given the importance of attention and expectancy in itch and pain perception, interventions targeting itch and pain should preferably have a biopsychosocial approach, as applied in multidisciplinary cognitive behavioral trainings for itch addressing both attentional and expectancy processes [16,17]. Nevertheless, future research could attempt to disentangle the specific contribution of targeting attention, expectancies, and their interaction, amongst other components of interventions, to further improve the interventions. For example, patients who attend to their positive expectations might more readily perceive the predicted outcome and hence experience more beneficial treatment outcomes. Clinicians may also target the underlying fear and itch or pain expectations using cognitive behavioral therapy to change attention bias for itch and pain [37,61]. For instance, resigning the goal to control pain (potentially by engaging in a new goal unrelated to pain) when pain is chronic may reduce the attention-capturing character of pain [61], an approach that may also work for itch. These strategies may enhance patients' quality of life despite having itch or pain.

In conclusion, within the biopsychosocial approach, it is essential to recognize the role of cognitive processes as these can partly explain the discrepancy between somatic input and perceived itch and pain. Preferably, the interaction between the cognitive processes of attention and expectancies as well as other biopsychosocial factors should be examined. Broadening our understanding of the role that cognitive processes play in itch and pain perception can eventually lead to improved interventions for both acute and chronic itch and pain.

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Figure legend

Fig. 1. Cognitive model of itch and pain perception