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Heterotopic pruritic conditioning and itch – Analogous to DNIC in pain?

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ABSTRACT

Pain can be endogenously modulated by heterotopic noxious conditioning stimulation (HNCS) through a mechanism which is known as diffuse noxious inhibitory control (DNIC). Since DNIC can be impaired in patients suffering from chronic pain, a comparable impaired itch inhibition may exist in patients suffering from chronic itch. The aim of the present study was to investigate whether heterotopic pruritic conditioning stimulation (HPCS) would display an impaired modulation of itch in patients suffering from chronic itch compared with healthy subjects. To this end, electrical stimuli were applied before and after histamine application (HPCS) to female patients with psoriasis and healthy female control subjects. Subjects reported the intensity of electrically evoked itch before and after HPCS. In order to replicate earlier findings for DNIC, electrically evoked pain was additionally investigated before and after cold stimulation (HNCS). As expected, the intensity of itch evoked by the electrical stimulus was significantly less after than before HPCS in healthy subjects, and the same was found for the intensity of electrically evoked pain after compared to before HNCS. Contrarily, in the patients levels of electrically evoked itch were significantly higher after than before HPCS, and no significant difference in pain intensity before and after HNCS was observed. In line with pain modulation, results suggest that there is a DNIC analogous mechanism for itch, i.e., diffuse pruritic inhibitory control (DPIC), which is impaired in patients with chronic itch, possibly due to a dysregulation of descending itch modulatory systems.

1. Introduction

Diffuse Noxious Inhibitory Controls (DNICs) have been proposed to play a major role in the modulation of pain, by which painful conditioning stimulation of one part of the body inhibits pain in a remote area [8,36,39]. When a spinal wide-dynamic range neuron receives conditioning afferent nociceptive input from *within* its receptive field, DNIC strongly inhibits convergent spinal afferent nociceptive input *outside* the neuron's receptive field via descending bulbo-spinal pathways. DNIC will thus reduce pain originating from any area outside the receptive field being stimulated by the conditioning stimulus [35,51,52]. However in patients suffering from chronic pain, dysregulation of the balance between descending inhibitory and facilitating pathways is supposed to play a main role in central sensitization processes. In particular, the descending control by DNIC mechanisms seems to be inefficient in these patients, as shown by the finding that heterotopic noxious conditioning stimulation (HNCS) in different patient groups suffering from chronic pain does not result in the modulation of experimentally induced pain [2,28–30,33]. For central sensitization processes in patients suffering from chronic itch, a similar dysfunction of inhibitory control mechanisms, i.e., Diffuse Pruritic Inhibitory Controls (DPICs), may play a role in the maintenance and increase of chronic itch symptoms [19,21,22,47]. However, to our knowledge, inhibitory control mechanisms for itch have not been investigated yet. In addition, cognitive-affective factors, such as attentional focus on bodily sensations or negative outcome expectancies, measured by concepts such as negative affectivity, anxiety, worrying and catastrophizing, are known to play an important role in pain processing and may influence DNIC-like mechanisms [14–16,18,26,27,48].

The aim of the present study was to investigate whether itch can be centrally modulated by the application of a pruritic stimulus to another location, i.e., by heterotopic pruritic conditioning stimulation (HPCS) in both healthy subjects and patients suffering from chronic itch. We also attempted to replicate earlier findings on pain modulation by DNIC in healthy subjects and investigated pain

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modulation in patients with chronic itch. A secondary goal was to explore the role of cognitive-affective factors, specifically attention to bodily sensations, anxiety sensitivity, worrying and neuroticism in the modulation of itch and pain by DNIC-like mechanisms.

2. Methods

2.1. Participants

Twenty-five female outpatients (mean age 47 years, range 20–75 years) of the Department of Dermatology of the Radboud University Nijmegen Medical Center diagnosed with psoriasis by a dermatologist and suffering from chronic itch due to psoriasis as well as thirty-one healthy female controls (mean age of 52 years, range 19–71 years), recruited via advertisements, were included in this study. Exclusion criteria for both groups were comorbid conditions (e.g., multiple sclerosis, diabetes mellitus, rheumatoid arthritis, and fibromyalgia), severe psychiatric disorders and pacemaker use. In addition, patients were excluded when their current levels of acute itch or pain at the start of the experiment were 1.0 or higher on a visual analogue scale (VAS) which ranged from 0 to 10 for reasons other than their skin disease. In this study, one patient was excluded because of pain due to headache on the day of testing (VAS pain 4.0). Healthy subjects were not included in the study if they suffered from chronic itch or pain complaints either currently or in the past. Healthy subjects were also excluded if they had acute itch or pain levels of 1.0 or higher (on a VAS ranging from 0 to 10) at the start of the experiment. In this study we excluded one healthy subject because of baseline pain levels of 5.0 on the day of testing. Mean disease duration of the patients was 23 years (range 2–57 years). Seventy-six percent of the patients and 65% of the healthy controls had completed secondary education, and 24% of the patients and 35% of the controls had completed tertiary education. Seventy-two percent of the patients and 48% of the healthy controls were married or lived with a partner, and 20% of the patients and 35% of the controls used oral contraceptives. There were no significant differences between patients and healthy controls in age, education level or proportion of subjects living with a partner. All participants were of Caucasian ethnicity.

The protocol was approved by the regional medical Ethics Committee and all participants gave their informed consent prior to investigation. Patients were asked not to alter their use of medication on the test day. On arrival at the test facility, participants were informed about the procedure and asked about their menstrual cycle, cigarette smoking, and intake of caffeine and alcohol over the previous 24 h. Participants had earlier been asked not to drink black tea or coffee 1 h before testing. Subjects were asked about their use of (topical) medication over the previous 24 h. Ninety-two percent of the patients used topical creams or ointments, 79% of whom used corticosteroid creams. Ten patients had taken systemic medication: 4 patients had taken medication for the treatment of psoriasis [methotrexate ($n = 3$) and ciclosporin ($n = 1$)] and 5 patients used other medication [antihypertensives ($n = 3$), benzodiazepines ($n = 1$), thyromimetics ($n = 1$), platelet aggregation inhibitors ($n = 1$), or selective serotonin reuptake inhibitors (SSRIs) ($n = 1$), alone or a combination of medication]. Of the healthy controls, 2 HC had taken systemic medication [antihypertensives ($n = 2$), or statins ($n = 1$)]. The severity and extent of the skin disease of the patients measured with the validated skin status scale of the impact of chronic skin disease on daily life (ISDL) showed that the severity of skin disease in our sample (mean = 15.8 ± 3.4) was representative of that of norm groups of psoriasis outpatients (mean = 16.9 ± 3.7) [11]. Patients also reported significantly higher levels of current baseline itch (mean = 2.7 ± 2.3) and current baseline pain (mean = 1.4 ± 2.6) than the healthy controls (mean = 0.2 ± 0.4 and mean = 0.2 ± 0.4, respectively) at the start of the experiment, as assessed with a VAS ranging from 0 to 10 ($t = 5.5$, $p < 0.001$ for itch and $t = 2.2$, $p < 0.05$ for pain). Of the patients with psoriasis, 76% and 24% suffered from itch (ranging from 1 to 8) and pain (ranging from 3 to 8), respectively, on the day of testing due to their skin disease, which is comparable to norm groups of psoriasis outpatients [44,49].

2.2. General procedure

Self-report questionnaires were sent to the participants 1 week before the experiment. On the test day, the subjects were told about the procedure and familiarized with the stimuli in a pretest trial with the electrical thresholds. Subjects were told that the stimuli could provoke any type of sensation, for example itch and pain. For each stimulus, participants were asked to rate their perceived sensation using a 10-point-VAS for both itch and pain ranging from no itch/pain (0) to the worst itch/pain imaginable (10). Sensitivity to itch and pain was measured by applying the same two single electrical test stimuli before and after both the pruritic and noxious conditioning stimuli which were applied contralaterally to the test stimuli. Stimuli were applied to unaffected body areas of the patients with psoriasis. We used iontophoretically applied histamine as pruritic conditioning stimulus and a cold pressor test as noxious conditioning stimulus. The same experimenter administered all stimuli. First, electrical thresholds were determined, and test stimulus intensities were calculated (see Section 2.3.1), and the first electrical test stimulus was applied 5 min later. After a 4-min interval, histamine (HPCS) was applied, followed by a 4-min interval after which the second electrical test stimulus was applied. After a 20-min break, the participants received again the first electrical test stimulus and 4 min later the cold pressor test was applied. After an interval of 4 min, the second electrical test stimulus was applied.

2.3. Somatosensory stimuli

2.3.1. Electrical stimulation

Self-adhesive skin electrodes (3M Red Dot Monitoring Electrode 2560; surface 40 × 35 mm) were applied to the non-dominant forearm (2 cm distal to the lateral epicondyle of the humerus, C5 dermatome). A constant current nerve stimulator (MultiStim Vario, Pajunk, Geisingen, Germany) was used to deliver electrical stimuli. These stimuli were applied as 0.3-ms pulses at a frequency of 100 Hz to evoke itch [23]. First, electrical thresholds for perception, unpleasantness and tolerance were determined in a ramping paradigm by continuously increasing the intensity by about 0.2 mA/s until the participant said the respective threshold had been reached (with an upper limit of 15 mA). The perception threshold was defined as "the moment that you experience a sensation for the first time", the unpleasantness threshold was defined as "the moment that the sensation becomes unpleasant for the first time" and the tolerance threshold was defined as "the moment that the sensation becomes unbearable and you want to stop immediately". The definitions of these thresholds were based on the definitions of the thresholds in pain literature [1,7], however without defining the nature of the sensation, i.e., by replacing painful by unpleasant or unbearable. The thresholds were determined twice using a ramping paradigm. Subsequently the mean current intensities of these thresholds were calculated which served as an indicator for the intensity of the short-lasting test stimuli. Definition of acceptable intensities for the test stimuli was based on two considerations. Firstly, previous studies [47,48] showing that the levels of itch and pain evoked by ramping tolerance stimulation are low to moderate. Secondly, the fact that at identical current intensities, electrical test stimuli of short duration are generally perceived as

less itching/painful than stimulation by ramping up to tolerance, probably because energy transmission of short-lasting stimuli is less than that of longer-lasting tolerance stimulation by ramping [25,42]. Taking these considerations into account, electrical test stimuli of 3-s duration were applied, at 100-Hz frequency with 0.3-ms pulse length, at 300% of the intensity of the (ramping) unpleasantness threshold, with a maximum of 150% of the (ramping) tolerance threshold and an upper cut-off limit of 15 mA for safety reasons. Our preparatory pilot study confirmed that electrical test stimuli at the chosen intensity were, firstly, adequate to induce itch and pain, but, secondly, that they were experienced as not inducing more than low to moderate mean itch and pain levels.

2.3.2. Conditioning stimulation

2.3.2.1. Heterotopic pruritic conditioning stimulation (HPCS) by histamine iontophoresis. Histamine was applied by iontophoresis (Chattanooga Group, Hixson, USA). Histamine dihydrochloride (0.5%) was dissolved in a gel of 2% methylcellulose in distilled water and 2.5 ml was placed in an electrode (Chattanooga Ionto Ultra Electrode medium, Hixson, USA) applied to the dominant forearm, 2 cm distal to the lateral epicondyle of the humerus (C5 dermatome). The reference electrode was applied to the skin of the lateral side of the triceps brachial muscle. The current was set at 0.4 mA and histamine was delivered for 2.5 min. Subjects were asked to rate itch levels every 30 s during application and 3 min after histamine application.

2.3.2.2. Heterotopic noxious conditioning stimulation (HNCS) by cold pressor. Subjects were instructed to place their dominant hand in a tank of cold water at about 4 °C (mean temperature 4.1 ± 0.6 °C) "for as long as possible, until the moment that the sensation becomes unbearable and you want to stop directly". The participants were not aware of the maximum time limit of 3 min [6]. The immersion time was recorded and the level of pain during the test was asked at the moment the subjects withdrew their hands. In addition, levels of pain were assessed 3 min after immersion.

2.4. Self-report questionnaires

All self-report questionnaires used in the present study have previously been shown to have satisfactory reliability and validity.

The Anxiety Sensitivity Index (ASI) was used to measure the subjects' fear of bodily sensations that are interpreted as having potentially harmful, physical or psychological consequences. The ASI consists of 16 items, rated on a 5-point Likert scale (1 = very little, 2 = little, 3 = some, 4 = much, 5 = very much). The total score was obtained by summing the scores for the 16 items (range 0–64) [43]. Cronbach's alpha for the ASI in the present study was 0.90 in healthy controls and 0.89 in patients with psoriasis.

Negative affectivity was measured with the neuroticism subscale of the Eysenck Personality Questionnaire (EPQ) [12]. Cronbach's alpha in the present study was 0.89 in healthy controls and 0.85 in patients with psoriasis.

Worrying was measured with the Penn State Worrying Questionnaire (PSWQ) [38]. The PSWQ is a 16-item self-report questionnaire that measures concerns about worries, the extent to which one is bothered by worries, and the extent to which one is engaged in worries. Each item is rated on a 5-point scale (1 = "not at all typical" to 5 = "very typical"), and a total score was obtained by summing the items. Cronbach's alpha for the PSWQ in the present study was 0.84 in healthy controls and 0.91 in patients with psoriasis.

Attentional focus (i.e. the tendency to attend to internal bodily sensations) was measured with the Body Vigilance Scale (BVS) [45], which consists of four items, three of which assess the degree of attentional focus, perceived sensitivity to changes in bodily sensations, and the average amount of time spent attending to sensations. The fourth item contains 13 items concerning anxiety-related bodily sensations (heart palpitations, chest pain, numbness, tingling, shortness of breath, faintness, vision changes, dizziness, hot flash, sweating/clammy hands, upset stomach, nausea, choking/throat closing). Items were rated on a 10-point VAS. The ratings for the bodily sensations of item 4 were averaged to obtain an overall score for item 4. The total score of the BVS is the sum of items 1–4. Cronbach's alpha for the BVS in the present study was 0.85 in healthy subjects and 0.84 in patients with psoriasis.

The severity of skin disease was measured with the skin status scale of the ISDL, which has previously been validated in patients with psoriasis [11]. Items were rated for different body parts (face, hairy scalp, neck, hands, arms, torso, legs, feet and genitals/anus) on a 4-point Likert scale (1 = not at all, 2 = to some extent, 3 = to a great extent, 4 = totally). The sum score reflects the overall severity of the skin condition [11]. At the day of testing, all participants were also asked to indicate the current levels of itch and pain at the start of the experiment as well as the itch and pain levels during the past two weeks on a VAS ranging from 0 (no itch/pain) to 10 (worst itch/pain imaginable).

2.5. Statistics

All analyses were performed with SPSS 16.0 for Windows. Variables were checked for normal distribution. Slightly skewed distributions were only found for electrically evoked itch before and after HPCS. For these variables, square root transformation was performed that resulted in a normal distribution. As measures of DNIC and DPIC, change scores were calculated by subtracting the scores for electrically evoked itch and pain after HPCS and HNCS, respectively, from the scores obtained before HPCS and HNCS. Changes in itch and pain scores before and after applying the conditioning stimuli were analyzed in patients and healthy controls separately, using GLM repeated measures ANOVA. The within-subjects factors were electrically evoked itch/pain scores before and after itch/pain conditioning stimulation.

Pearson correlation coefficients were calculated between change scores for electrically evoked itch and pain, and the following variables: age, body mass index, educational level, menopausal status, itch and pain scores evoked by the conditioning stimuli (histamine and cold pressor, respectively), the cold pressor immersion time and individual characteristics (neuroticism, anxiety sensitivity, worrying and attentional focus on bodily sensations) for both patients and healthy controls, and the current skin disease severity and VAS itch and pain on the day of testing for the patients.

3. Results

3.1. Conditioning stimuli and electrical test stimuli

Histamine evoked itch in 81% of the healthy controls and 88% of the patients, with mean itch scores of 2.5 ± 2.0 for healthy controls and 2.9 ± 2.5 for patients. The cold pressor test caused pain in 87% of the healthy controls and 88% of the patients, with mean pain scores of 4.1 ± 2.9 for healthy controls and 4.1 ± 2.9 for patients. The mean cold pressor immersion time was 51.6 s (±51.6) for healthy controls and was 51.4 s (±60.8) for the patients. There were no significant between-group differences in intensity of itch and pain evoked by the conditioning stimuli or in the duration of cold pressor immersion time for the patients or healthy controls except for a significant correlation between a longer cold pressor immersion time and higher pain levels evoked by cold pressor immersion in the patients ($R = 0.44$, $P < 0.05$), but not in healthy controls.

There were finally no significant correlations between the change scores for electrically evoked itch and pain and the cold pressor immersion time or the intensity of itch and pain evoked by histamine and cold pressor conditioning stimuli, respectively (data not shown).

3.2. HPCS and electrically evoked itch

In healthy controls, the repeated measures ANOVA results for analyzing the effectivity of itch modulation showed that the intensity of electrically evoked itch was significantly lower after than before histamine application (HPCS) ($F_{1,30} = 10.96$, $p = 0.002$) (Fig. 1.). In contrast, the patients with psoriasis had significantly higher levels of electrically evoked itch after than before histamine application ($F_{1,24} = 5.28$, $p = 0.03$). Similar results were obtained when the data were analyzed only for those participants who reported itch elicited by histamine ($F_{1,24} = 7.72$, $p = 0.01$ for healthy controls; $F_{1,21} = 4.61$, $p = 0.04$ for patients).

3.3. HNCS and electrically evoked pain

In healthy subjects, the repeated measures ANOVA results for analyzing the effectivity of pain modulation showed that the intensity of pain evoked by electrical stimulation was significantly lower after the cold pressor test (HNCS) than before ($F_{1,30} = 5.84$, $p = 0.02$) (Fig. 2.). However, no such significant difference was found in the patients with psoriasis, ($F_{1,24} = 0.05$, $p = 0.83$). Similar results were obtained when the analysis was restricted to only those subjects who reported pain evoked by the cold pressor test ($F_{1,26} = 4.62$, $p = 0.04$ for healthy subjects; $F_{1,21} = 0.05$, $p = 0.83$ for patients).

3.4. Role of individual characteristics

The self-report measures of worrying, anxiety sensitivity, neuroticism, and degree of attentional focus on bodily sensations were not significantly correlated with change scores of electrically evoked itch and pain before and after HPCS and HNCS (data not shown). In addition, these change scores were not significantly associated with age, body mass index, educational level and menopausal status in patients and healthy controls, or the current intensity of itch or pain and disease severity of the patients with psoriasis.

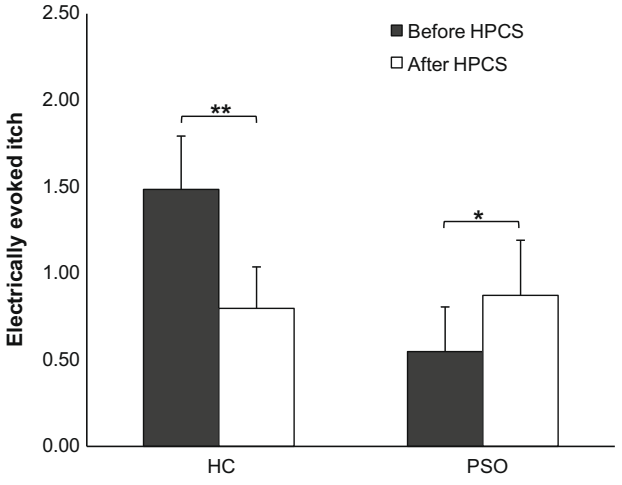

Fig. 1. Electrically evoked itch before and after histamine application. Mean levels of itch evoked by electrical stimulation before and after application of HPCS (heterotopic pruritic conditioning stimulation) by means of a histamine application in both healthy controls (HC, $n = 31$) and patients with psoriasis (PSO, $n = 25$). $^{*}p < 0.05$; $^{**}p < 0.01$; data are means ± S.E.M.

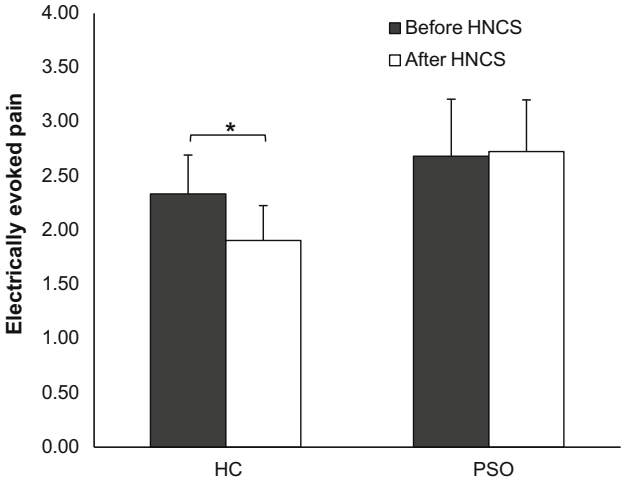

Fig. 2. Electrically evoked pain before and after cold pressor application. Mean levels of pain evoked by electrical stimulation before and after application of HNCS (heterotopic noxious conditioning stimulation) by means of the cold pressor test in both healthy controls (HC, $n = 31$) and patients with psoriasis (PSO, $n = 25$). $^{*}p < 0.05$; $^{**}p < 0.01$; data are means ± S.E.M.

4. Discussion

The present study adds to our knowledge of pain and itch inhibitory processes in healthy subjects and patients with chronic itch. We investigated whether the application of heterotopic pruritic conditioning stimulation would alter levels of induced itch by central mechanisms, analogous to the modulation of pain by heterotopic noxious conditioning stimulation via DNIC. DNIC is a descending endogenous pain-modulatory system activated by excitatory afferent signal from Aδ- or C-fibers, acting on all levels of the spinal cord via processes originating and controlled supraspinally [35,39]. Itch modulation may be based on similar mechanisms involving multireceptive neurons with a "whole-body-receptive-field" [35,37]. Our findings show that in healthy subjects experimentally induced itch can be modulated by a pruritic stimulus such as histamine by a mechanism analogous to DNIC, suggesting DPIC. As expected, HPCS did not result in decreased itch induced after conditioning in patients with psoriasis suffering from chronic itch. This is in line with earlier findings in chronic pain, showing that descending pain control mechanisms are dysregulated in these patients [2,29,30,33].

The conditioning stimuli applied in this study were appropriate pruritic and noxious conditioning stimuli since more than 80% of the subjects experienced itch with histamine application and pain with the cold pressor test. Studies have shown that the effectiveness of endogenous analgesia mediated by DNIC is independent of the conditioning stimulus location or modality, e.g., mechanical, electrical or chemical, as long as the conditioning stimulus is perceived as painful [18,40,41]. We found that both the pruritic and noxious stimuli were able to modulate experimentally evoked itch and pain, respectively, in healthy controls, which shows that the conditioning stimuli were of sufficient intensity and duration [41]. Even healthy individuals who did not report itch (19%) or pain (13%) for the conditioning stimuli showed on average modulation responses (mean decrease 0.9 ± 1.3 for itch; 0.8 ± 1.5 for pain), suggesting that itch and pain may be modulated even when the conditioning stimulation is not perceived as itching of painful. This is congruent with reports showing DNIC-like responses to conditioning stimulation not overtly experienced as painful [34,39]. Nevertheless, descriptive comparison suggested that the modulation responses were less when subjects did not experience the conditioning stimuli in the expected way. Future research should

elucidate whether modulation is more effective when conditioning is overtly perceived as itch or pain.

The lack of the itch and pain modulation in the patients with chronic itch suggests a role of central modulation of itch and pain in chronic physical symptoms. This is supported by earlier studies which showed that less efficacious DNIC was associated with chronic pain [10,39,53], while after surgical relief of pain DNIC responses returned to normal in patients with osteoarthritis [30]. Our results, and specifically the significant increase in itch in the patients with psoriasis after itch conditioning, might be indicative of symptom-specific sensitization and a dysregulated itch and pain modulation in patients with chronic itch. Future research is needed to gain more insight into the underlying mechanisms of sensitization and central modulation, for example, whether the ongoing chronic complaints induce dysregulation of DPIC and DNIC, or whether patients are more predisposed to less efficient DPIC and DNIC modulation mechanisms.

Regarding the quality of sensation perception, patients with chronic pain can perceive itch stimuli as painful [5] and patients with chronic itch can perceive pain stimuli as itchy [22], which are both in contrast to what is observed in healthy subjects. This difference in sensation perception may be related to a dysregulated itch and pain modulation in patients, possibly due to the long-term time course and widespread localization of symptoms. However, in the present study, mean levels of electrically evoked itch and pain did not significantly differ between these groups. Furthermore, as we did not compare patients suffering from chronic itch with patients suffering from chronic pain in the present study, we cannot conclude whether itch and pain modulation are sensation-specific or generic processes. With regard to the specific itch-pain interactions, it is well known that pain can inhibit itch [54], for example by scratching. One could thus expect that pain conditioning (e.g., cold stimulation) might also have a central modulating effect on itch – in addition to its central pain modulating effects. Conversely, we would not expect itch conditioning to affect pain heterotopically, since pain has not been described to be inhibited by itch to date. Future research should elucidate whether DNIC and DPIC are separate processes or (partly) based on the same mechanisms and structures.

The individual characteristics of negative affectivity, anxiety sensitivity, worrying and attentional focus on bodily sensations were not associated with itch and pain modulation. Previous studies also showed negative affectivity and state and trait anxiety not to be associated with the magnitude of DNIC [10,17,18]. In addition, while attentional focus might influence the experience of itch and pain [26,27,48], we found no correlation with the modulation responses. This finding is consistent with earlier findings showing that DNIC-like effects are not dependent on attentional distraction [32]. However, as catastrophizing has recently been found to be associated with less effective DNIC [15,18], we expected worrying may also be related to DNIC or DPIC, since this cognitive strategy has been shown to play a prominent role in itch and pain [9,50]. Future research should further clarify the role of worrying and catastrophizing in itch and pain modulation in experimental and field settings.

While our findings suggest that central inhibitory control mechanisms have a role in modulating itch by heterotopic pruritic stimulation, it is important to take some limitations and directions for future research into consideration. First, test stimuli were applied only once after conditioning stimulation, which meant that we could not study the temporal effects of itch and pain modulation. Second, although results of the HNCS in healthy subjects and patients with chronic itch were completely in line with the previous findings on DNIC in healthy subjects and patients with chronic pain, we cannot exclude that results with regard to the subsequent application of HNCS might be affected by the HPCS applied previously. Third, although we tailored the intensity of the electrical test stimuli based on the individual unpleasantness and tolerance thresholds in a ramping paradigm, the absolute levels of itch and pain evoked by the short electrical test stimuli were still relatively low. Data from earlier studies [47,48] and our preparatory pilot study indicated that the electrical test stimuli applied are perceived as less itching/painful than ramping tolerance stimuli for identical current intensities. This is probably because energy transmission of short-lasting test stimuli is less than that of longer-lasting tolerance stimulation by ramping [25,42]. In future research, it might be preferable to apply test stimuli tailored to subjects' subjective ratings for itch or pain, e.g. determined by a score of 6 of 10 for itch or pain [3,18]. Fourth, the patients' levels of itch (and pain) on the day of testing as well as during the past two weeks were not related to the modulation responses, as might have been expected since worse DNIC responses have been related to more clinical pain [10]. However, itch levels on the day of testing or during the last two weeks may not be representative for disease related itch levels in general. Future research should determine clinical itch and pain over a longer period. Fifth, we studied women only, and so we cannot comment on the inhibitory control mechanisms of itch in men. Besides gender differences in sensitivity to clinical and experimental pain [13], there is inconsistent evidence about the role of gender in pain modulation, while some studies did not find any gender effect [4,31,40], others indicated that DNIC might be less effective in females [18,46]. Future research should investigate the role of gender differences in central itch modulation. Sixth, since itch perception can differ according to type of disease or evoking somatosensory stimuli, e.g., patients with atopic dermatitis have been shown to be generally less sensitive to histamine-induced itch [20,24], investigation of patient groups suffering from chronic itch other than psoriasis, would also provide further insight into itch modulation mechanisms.

To conclude, we showed for the first time that, analogous to DNIC in pain, DPIC mechanisms modulate itch. The combination of histamine as heterotopic pruritic stimulation with electrical test stimuli would appear to be a valid model to investigate the central modulation of itch. In contrast to healthy subjects, itch and pain modulation seemed to be dysregulated in patients with psoriasis suffering from chronic itch. The ability to modulate pain in a pain-free state has been found to be a predictor of postoperative pain [10,53], which suggests that a person's susceptibility to pain disorders might depend on the effectiveness of pain modulation. Our results suggest that similar mechanisms might play a role in itch modulation. In line with a study of patients with osteoarthritis showing that the DNIC response can be normalized by relieving pain [30], future studies can offer a greater insight into whether it is possible to restore dysregulated DPIC and DNIC mechanisms by therapies aimed at rebalancing descending inhibition and facilitation mechanisms of itch and pain.

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References

[1] Arendt-Nielsen L, Bjerring P. Sensory and pain threshold characteristics to laser stimuli. J Neurol Neurosurg Psychiatry 1988;51:35–42.
[2] Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain 2008;140:465–71.
[3] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–72.
[4] Baad-Hansen L, Poulsen HF, Jensen HM, Svensson P. Lack of sex differences in modulation of experimental intraoral pain by diffuse noxious inhibitory controls (DNIC). Pain 2005;116:359–65.

[5] Baron R, Schwarz K, Kleinert A, Schattschneider J, Wasner G. Histamine-induced itch converts into pain in neuropathic hyperalgesia. Neuroreport 2001;12:3475–8.
[6] Birklein F, Depmeier C, Rolke R, Hansen C, Rautenstrauss B, Prawitt D, Magerl W. A family-based investigation of cold pain tolerance. Pain 2008;138:111–8.
[7] Buscher HC, Wilder-Smith OH, van GH. Chronic pancreatitis patients show hyperalgesia of central origin: a pilot study. Eur J Pain 2006;10:363–70.
[8] De Broucker T, Cesaro P, Willer JC, Le Bars D. Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain 1990;113:1223–34.
[9] Eccleston C, Crombez G, Aldrich S, Stannard C. Worry and chronic pain patients: a description and analysis of individual differences. Eur J Pain 2001;5:309–18.
[10] Edwards RR, Ness TJ, Weigent DA, Fillingim RB. Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 2003;106:427–37.
[11] Evers AW, Duller P, van de Kerkhof PC, van der Valk PG, de Jong EM, Gerritsen MJ, Otero E, Verhoeven EW, Verhaak CM, Kraaimaat FW. The Impact of Chronic Skin Disease on Daily Life (ISDL): a generic and dermatology-specific health instrument. Br J Dermatol 2008;158:101–8.
[12] Eysenck HJ, Eysenck SBG. Manual of the Eysenck Personality Scales (EPS Adult). London: Hodder & Stoughton; 1991.
[13] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447–85.
[14] Fortune DG, Richards HL, Corrin A, Taylor RJ, Griffiths CE, Main CJ. Attentional bias for psoriasis-specific and psychosocial threat in patients with psoriasis. J Behav Med 2003;26:211–24.
[15] Goodin BR, McGuire L, Allshouse M, Stapleton L, Haythornthwaite JA, Burns N, Mayes LA, Edwards RR. Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. J Pain 2009;10:180–90.
[16] Goubert L, Crombez G, Van Damme S. The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: a structural equations approach. Pain 2004;107:234–41.
[17] Granot M, Khoury R, Berger G, Krivoy N, Braun E, Aronson D, Azzam ZS. Clinical and experimental pain perception is attenuated in patients with painless myocardial infarction. Pain 2007;133:120–7.
[18] Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, Yarnitsky D. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter. Pain 2008;136:142–9.
[19] Gronroos M, Reunala T, Kartamaa M, Pertovaara A. Altered skin sensitivity in chronic itch: role of peripheral and central mechanisms. Neurosci Lett 1997;228:199–202.
[20] Heyer G, Koppert W, Martus P, Handwerker HO. Histamine and cutaneous nociception: histamine-induced responses in patients with atopic eczema, psoriasis and urticaria. Acta Derm Venereol 1998;78:123–6.
[21] Hosogi M, Schmelz M, Miyachi Y, Ikoma A. Bradykinin is a potent pruritogen in atopic dermatitis: a switch from pain to itch. Pain 2006;126:16–23.
[22] Ikoma A, Fartasch M, Heyer G, Miyachi Y, Handwerker H, Schmelz M. Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. Neurology 2004;62:212–7.
[23] Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically evoked itch in humans. Pain 2005;113:148–54.
[24] Ikoma A, Rukwied R, Stander S, Steinhoff M, Miyachi Y, Schmelz M. Neuronal sensitization for histamine-induced itch in lesional skin of patients with atopic dermatitis. Arch Dermatol 2003;139:1455–8.
[25] Kantor G, Alon G, Ho HS. The effects of selected stimulus waveforms on pulse and phase characteristics at sensory and motor thresholds. Phys Ther 1994;74:951–62.
[26] Keogh E, Dillon C, Georgiou G, Hunt C. Selective attentional biases for physical threat in physical anxiety sensitivity. J Anxiety Disord 2001;15:299–315.
[27] Keogh E, Ellery D, Hunt C, Hannent I. Selective attentional bias for pain-related stimuli amongst pain fearful individuals. Pain 2001;91:91–100.
[28] King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley III JL. Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. Pain 2009;143:172–8.
[29] Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70:41–51.
[30] Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000;88:69–78.
[31] Lautenbacher S, Kunz M, Burkhardt S. The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: Does sex matter? Pain 2008;140:429–35.
[32] Lautenbacher S, Prager M, Rollman GB. Pain additivity, diffuse noxious inhibitory controls, and attention: a functional measurement analysis. Somatosens Mot Res 2007;24:189–201.
[33] Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain 1997;13:189–96.
[34] Lautenbacher S, Roscher S, Strian F. Inhibitory effects do not depend on the subjective experience of pain during heterotopic noxious conditioning stimulation (HNCS): a contribution to the psychophysics of pain inhibition. Eur J Pain 2002;6:365–74.
[35] Le Bars D. The whole body receptive field of dorsal horn multireceptive neurones. Brain Res Rev 2002;40:29–44.
[36] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain 1979;6:283–304.
[37] Le Bars D, Villanueva L, Bouhassira D, Willer JC. Diffuse noxious inhibitory controls (DNIC) in animals and in man. Patol Fiziol Eksp Ter 1992:55–65.
[38] Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther 1990;28:487–95.
[39] Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain 2009;144:16–9.
[40] Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neurosci Lett 2005;380:209–13.
[41] Reinert A, Treede R, Bromm B. The pain inhibiting pain effect: an electrophysiological study in humans. Brain Res 2000;862:103–10.
[42] Prausnitz MR. The effects of electric current applied to skin: A review for transdermal drug delivery. Adv Drug Deliv Rev 1996;18:395–425.
[43] Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther 1986;24:1–8.
[44] Sampogna F, Gisondi P, Melchi CF, Amerio P, Girolomoni G, Abeni D. Prevalence of symptoms experienced by patients with different clinical types of psoriasis. Br J Dermatol 2004;151:594–9.
[45] Schmidt NB, Lerew DR, Trakowski JH. Body vigilance in panic disorder: evaluating attention to bodily perturbations. J Consult Clin Psychol 1997;65:214–20.
[46] Staud R, Robinson ME, Vierck Jr CJ, Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003;101:167–74.
[47] Van Laarhoven AI, Kraaimaat FW, Wilder-Smith OH, van de Kerkhof PC, Cats H, van Riel PL, Evers AW. Generalized and symptom-specific sensitization of chronic itch and pain. J Eur Acad Dermatol Venereol 2007;21:1187–92.
[48] Van Laarhoven AIM, Kraaimaat FW, Wilder-Smith OH, Evers AWM. Role of attentional focus on bodily sensations in sensitivity to itch and pain. Acta Derm Venereol 2010;90:46–51.
[49] Verhoeven EW, Kraaimaat FW, van de Kerkhof PC, van Weel C, Duller P, van der Valk PG, van den Hoogen HJ, Bor JH, Schers HJ, Evers AW. Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. Br J Dermatol 2007;156:1346–9.
[50] Verhoeven EWM, Kraaimaat FW, de Jong EMGJ, Schalkwijk J, van de Kerkhof PCM, Evers AWM. Individual differences in the effect of daily stressors on psoriasis: a prospective study. Br J Dermatol 2009;161:295–9.
[51] Villanueva L. Diffuse Noxious Inhibitory Control (DNIC) as a tool for exploring dysfunction of endogenous pain modulatory systems. Pain 2009;143:161–2.
[52] Villanueva L, Le Bars D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. Biol Res 1995;28:113–25.
[53] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22–8.
[54] Yosipovitch G, Greaves MW, Schmelz M. Itch. Lancet 2003;361:690–4.