

# Sensitivity to itch and pain in patients with psoriasis and rheumatoid arthritis

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**Abstract:** Symptoms of itch and pain in chronic inflammatory conditions of psoriasis (PS) and rheumatoid arthritis (RA) can highly affect patients' quality of life. Studies in other patient groups indicate that sensitivity to itch and pain is altered in line with the patient's main symptom of either chronic itch or pain, as a result of sensitization processes. This study directly compared whether patients with chronic inflammatory conditions associated with chronic itch or pain display a heightened sensitivity to itch and pain, respectively. Sensitivity to itch and pain was measured by applying stimuli of quantitative sensory testing (QST) in female patients with chronic itch due to PS or chronic pain due to RA. Levels of itch and pain evoked by the QST stimuli as well as the tolerance to the stimuli were determined. Patients with PS

reacted to the stimuli with a higher itch response (histamine), while the patients with RA displayed a lowered tolerance to the stimuli (cold pressor test and mechanical stimulation) in comparison with the other patient group. In line with previous studies in other patient groups with chronic itch or pain, further support was found that somatosensory stimuli are processed in line with the patients' main symptom through generic sensitization processes, also in chronic inflammatory conditions such as PS and RA.

**Key words:** itch – pain – pruritus – quantitative sensory testing – sensitization

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## Introduction

Itch is a frequently reported symptom of patients with skin disease, with a prevalence of about 50% of these patients reporting chronic itch, and a prevalence up to 90% in patients with psoriasis (1–4). Alike chronic pain, also in chronic itch, central and peripheral sensitization, next to alterations in immunological factors and skin barrier functions (5), is suggested to play a role in a heightened symptom reporting that does not always completely correspond to the pathophysiology of the condition (6–9). Nociceptive input, for example, by pain or itch, can induce changes in the neural pathways. On the long term, this can lead to central sensitization, inducing functional changes and increased responsiveness to stimuli as a result of increased excitation and reduced inhibition of neural pathways (9). This may lead to enhanced sensitivity, which is frequently not limited to the affected body areas or related to the nociceptive input (9).

Both patients with chronic itch and pain have been shown to be frequently more sensitive to experimentally applied somatosensory stimuli than healthy controls and experience different types of stimuli in line with their main symptom, for example, as itching in patients with chronic itch or as painful in patients with chronic pain (7–9). For example, patients with chronic pain show a tendency to react to stimuli with higher levels of pain than healthy controls; for example, patients with osteoarthritis, fibromyalgia or neuropathic pain show enhanced pain sensitivity towards somatosensory stimuli of various modalities such as mechanical,

pressure, thermal and cold stimuli (9–12). For patients with chronic itch, there is also some evidence for a heightened sensitivity towards itch stimuli, such as histamine, cowhage or electrical stimulation (7,8,11,13). In addition, the tendency for patients with chronic pain to react to stimuli with higher levels of pain than healthy controls and perceive itch stimuli as painful rather than itchy may be indicative of sensitization in the context of the patient's main symptom, that is, itch for chronic itch patients and pain for chronic pain patients (11,13–16). It remains unknown whether this heightened sensitivity might be generalized to other patient groups with chronic itch or pain, especially those with a distinct pathophysiological aetiology of inflammation, such as psoriasis (PS) and rheumatoid arthritis (RA). Investigation of sensitivity in patients with different symptoms, such as itch and pain, adds to our knowledge of specific or general patterns of sensitization that contribute to various chronic symptoms.

In line with previous studies in other patient groups with chronic itch or pain, this study investigated whether somatosensory stimuli are processed in line with the patients' main symptom in patients with chronic inflammatory conditions. This study aimed to investigate whether patients with chronic itch due to PS have a heightened sensitivity to itch and whether patients with chronic pain due to RA have a heightened sensitivity to pain specifically. As sensitization processes are assumed to generally evoke a heightened sensitivity to somatosensory stimuli (9) and sensitivity to stimuli of different modality may reflect different aspects of sensitization

[e.g. enhanced itch perception due to hyperknesis (7,8)], a multi-modal assessment using different stimuli is designated (17). Consequently, different somatosensory stimuli were applied to assess sensitivity to itch and pain. It was expected that patients with PS would overall react with higher levels of itch and that patients with RA are more sensitive to pain with respect to the different stimuli applied.

## Methods

### Patients

Patients were recruited from the outpatient clinics of the Departments of Dermatology and Rheumatology, Radboud University Nijmegen Medical Centre. Patients were screened for the presence of chronic itch (PS) or chronic pain symptoms (RA). Patients were excluded when having physical or psychiatric comorbidity (e.g. multiple sclerosis, diabetes mellitus, psychosis), when using a pacemaker, when they had received a double diagnosis with regard to the conditions investigated, that is, when diagnosed with both PS and RA or when suffering from itch or pain symptoms obviously not related to their inflammatory condition. With regard to the latter point, one patient with PS and one patient with RA had been excluded from the analyses, because of pain due to headache at the moment of testing and itch due to mild eczema, respectively. Twenty-six females diagnosed with psoriasis (PS) and suffering from chronic itch (mean age 47 years, range 20–75 years), and 27 females diagnosed with rheumatoid arthritis (RA) and suffering from chronic pain (mean age 62 years, range 27–77 years) were included in this study. Mean disease duration was 23 years (range 2–57 years) for patients with PS and 15 years (range 3–37 years) for patients with RA [ $F(1,51) = 5.06, P < 0.05$ ]. Clinical levels of itch and pain scored on a visual analogue scale (VAS) were  $M = 2.8, SD = 2.3$  and  $M = 1.3, SD = 2.6$ , respectively, for the patients with PS and  $M = 0.3, SD = 0.7$  and  $M = 2.4, SD = 2.2$  for the patients with RA. Symptoms of itch in patients with RA and pain in patients with PS at the moment of testing were generally associated with their chronic condition, except for one patient with RA reporting itch due to sweating and two patients with PS who self-reported joint pain symptoms. Seventy-three per cent of the patients with PS and 59% of the patients with RA had completed secondary education, and 23% of the patients with PS and 33% of the patients with RA had completed tertiary education. Seventy-three per cent of the patients with PS and 81% of the patients with RA were married or lived with a partner. Educational level did not significantly differ between the two groups, but patients with PS were significantly younger than the patients with RA [ $F(1,51) = 19.91, P < 0.001$ ].

### General procedure

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 regular medication on the test day. Patients were told that the sensory stimuli could provoke any type of sensation, for example itch and pain. All patients with PS and RA received the same stimuli that were applied at the shoulder and arms of the patients (unaffected skin of patients with PS).

### Somatosensory stimuli

Sensitivity to itch and pain was measured by applying mechanical stimuli, electrical stimuli, histamine iontophoresis and the cold pressor test (18). This specific order of the stimuli was the same

for all patients and applied in such a way, in line with previous studies (11,18), that the stimuli with the lowest mean intensity of itch and pain were applied at first (of which patients were unaware). Thresholds were determined for mechanical ( $A\delta$ -fibre threshold), electrical and cold stimuli. Histamine was applied at a fixed intensity for a predetermined time period. For each stimulus, patients were asked to indicate on a 10-point VAS [ranging from no itch/pain (0) to the worst itch/pain imaginable (10)] both the levels of itch and pain they experience, irrespective of the clinical levels of itch or pain. For histamine, only the levels of itch, and for the cold pressor test, only the levels of pain were assessed. As the protocol and part of the data were also used to assess the modulation of itch and pain by conditioning stimulation, electrical stimuli of short duration (3 s) were applied 4 min before and 4 min after histamine iontophoresis and the cold pressor test (19). All stimuli were applied on the same day with intervals in between.

### Mechanical stimulation

Twenty Semmes-Weinstein von Frey calibrated monofilaments were used in a range of 0.00045–447.0 g. Filaments were applied once to the non-dominant forearm (2 cm distal to the lateral epicondyle of the humerus, C5 dermatome) vertically and with increasing force, while avoiding contact with body hair. Patients were asked to report the  $A\delta$ -fibre threshold (defined as 'the moment that the stimulus perception changed into an unpleasant, stinging sensation'), specified by the von Frey hair number. As mechanical stimulation is an ambiguous stimulus, at the  $A\delta$ -fibre threshold, patients reported the levels of itch and pain evoked (11,18). The interval between the filaments was at least 30 s, and the interval between mechanical and electrical stimulation was at least 5 min.

### Electrical stimulation

Self-adhesive skin electrodes (3M Red Dot Monitoring Electrodes 2560, surface  $40 \times 35$  mm, diameter stimulation area ca. 20 mm) were applied to the non-dominant forearm (2-cm distal to the lateral epicondyle of the humerus, C5 dermatome) and the trapezius on the dominant side (at the midpoint of upper trapezius, C4 dermatome). A constant current nerve stimulator (MuliStim Vario, Pajunk, Geisingen, Germany) was used to deliver electrical stimuli, consisting of 0.3-ms pulses at 100-Hz frequency to evoke itch (20), with a continuously increasing intensity of about 0.2 mA/s, applied until the subject reported the respective threshold (with an upper limit of 15 mA). In a pretest trial with the trapezius, three thresholds, that is, the perception threshold defined as 'the moment that you experience a sensation for the first time', the unpleasantness threshold defined as 'the moment that the sensation becomes unpleasant for the first time' and the tolerance threshold defined as 'the moment that the sensation becomes unbearable and you want to stop immediately', were each determined twice. As outcome measure, the tolerance threshold was determined twice on the forearm (18). As the electrical tolerance threshold is an ambiguous stimulus, patients rated the levels of itch and pain evoked. The interval between the threshold measurements was at least 30 s, and the interval between electrical stimulation and histamine iontophoresis was at least 15 min.

### Histamine iontophoresis

Histamine was applied by iontophoresis (Chattanooga Group, Hixson, TN, 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). This electrode was applied to the dominant forearm, 2-cm distal to the lateral epicondyle of the humerus (C5/T1 dermatome). The reference electrode was applied to the skin of the lateral side of the triceps brachial muscle. Current level was set at a fixed current intensity of 0.4 mA, and histamine was delivered for 2.5 min (18,19). As histamine is primarily an itch stimulus, patients were asked to rate itch levels during histamine application every 30 s, of which a mean score was calculated afterwards to be included in the main analysis. The levels of itch were reported up to 3 min after application. In addition, the levels of pain were also reported during application, and, as expected, the mean levels of pain were relatively low and did not differ between the conditions ( $P = 0.98$ ). The interval between the histamine application and the cold pressor test was at least 20 min.

#### Cold pressor test

Patients were instructed to place their dominant hand in a tank of cold water at about 4°C (mean temperature 3.9°C, SD = 0.8) 'for as long as possible, until the moment that the sensation becomes unbearable and you want to stop directly' (18). The participants were not aware of the maximum time limit of 3 min. The immersion time was recorded (tolerance threshold). As the cold pressor test is primarily a pain stimulus, patients were asked about the level of pain during the test at the moment they withdrew their hand. Additionally, also the levels of itch were reported, and, as expected, the mean levels of itch were relatively low and did not differ between the conditions ( $P = 0.30$ ).

#### Statistical analysis

All analyses were performed with SPSS 20.0 for Windows (IBM Corporation, Armonk, NY, USA). Variables were checked for normal distribution. Slightly skewed distributions were only found for itch and pain evoked by mechanical stimulation and itch evoked at the electrical tolerance threshold. Square root transformation was performed for these variables which resulted in a normal distribution.

To test the hypothesis that patients with chronic itch due to PS would display a heightened sensitivity to itch and that patients with chronic pain due to RA would show a heightened sensitivity to pain, GLM multivariate analyses of variance (MANOVAs) were performed, while avoiding multiple testing, with the patient groups (i.e. PS and RA) as between-subjects factor and thresholds of the somatosensory stimuli and VAS itch and pain scores as dependent variables in separate analyses. Finally, for both patient groups separately, Pearson's correlation coefficients were calculated between the tolerance thresholds, levels of itch and pain evoked by the different somatosensory stimuli and the following control variables (possible confounders): age, educational level, clinical levels of itch and pain at the moment of testing, and disease duration. In the case that one of these control variables were significantly correlated with at least one of the outcome measures, the respective main analysis was controlled for this variable in MANCOVA analysis by including all significant control variables separately as covariate.

#### Results

Means and standard deviations of the tolerance and itch and pain evoked by the different stimuli are displayed in Table 1.

The MANOVA test for the tolerance thresholds showed that these thresholds were significantly lower in the patients with RA

**Table 1.** Means, standard deviations (SD) and range of visual analogue scale (VAS) scores for the tolerance thresholds as well as itch and pain evoked by the different somatosensory stimuli of quantitative sensory testing (QST) in patients with psoriasis ( $n = 26$ ) and patients with rheumatoid arthritis ( $n = 27$ )

Somatosensory stimuli	Psoriasis		Rheumatoid arthritis	
	Mean (SD)	Range	Mean (SD)	Range
Mechanical stimulation				
Tolerance <sup>1</sup>	14.4 (5.0)	7–20	11.2 (3.4)	7–20
VAS itch <sup>2</sup>	1.0 (1.9)	0.0–8.0	0.5 (0.9)	0.0–3.0
VAS pain <sup>2</sup>	0.7 (1.2)	0.0–4.0	0.5 (0.9)	0.0–3.0
Electrical stimulation				
Tolerance <sup>3</sup>	7.8 (4.2)	2.5–15.0	8.9 (4.2)	2.9–15.0
VAS itch <sup>2</sup>	1.0 (1.7)	0.0–6.0	0.8 (1.5)	0.0–6.0
VAS pain <sup>2</sup>	2.8 (2.9)	0.0–9.0	3.2 (2.7)	0.0–8.0
Histamine iontophoresis				
VAS itch	3.0 (2.5)	0.0–8.7	1.5 (1.4)	0.0–4.4
Cold stimulation				
Tolerance <sup>4</sup>	49.6 (60.3)	4–180	26.3 (11.4)	5–50
VAS pain <sup>2</sup>	3.9 (3.0)	0.0–9.0	3.6 (2.8)	0.0–8.0

<sup>1</sup>Mechanical A $\delta$ -fibre threshold, specified to hair number.

<sup>2</sup>VAS scores for itch and pain given at the respective threshold.

<sup>3</sup>Electrical tolerance threshold: electrical current in mA.

<sup>4</sup>Cold pressor immersion time in seconds.

than in the patients with PS [ $\Lambda = 0.74$ ,  $F(3,49) = 5.72$ ,  $P < 0.01$ ]. For each stimulus, the mean A $\delta$ -fibre threshold intensity for mechanical stimulation was significantly lower [ $F(1,51) = 7.69$ ,  $P < 0.01$ ] in the patients with RA than in the patients with PS. The mean cold pressor immersion time was also borderline significantly shorter in the patients with RA than in the patients with PS [ $F(1,51) = 3.90$ ,  $P = 0.05$ ]. The electrical tolerance threshold was not significantly different between the two patient groups [ $F(1,51) = 0.82$ ,  $P = 0.37$ ].

The MANOVA test for itch showed that stimuli-evoked itch (mechanical, electrical and histamine together) was higher in the patients with PS than in the patients with RA [MANOVA  $\Lambda = 0.85$ ,  $F(3,49) = 2.89$ ,  $P < 0.05$ ]. For each stimulus separately, univariate analyses showed that levels of itch evoked by histamine were significantly higher in the patients with PS than in the patients with RA [ $F(1,51) = 8.02$ ,  $P < 0.01$ ]. No significant differences were found between the patient groups in itch evoked by mechanical or electrical stimulation [ $F(1,51) = 0.31$ ,  $P = 0.58$  and  $F(1,51) = 0.32$ ,  $P = 0.58$ , respectively]. There were no between-group differences in pain levels evoked by the mechanical, electrical and cold stimuli together [MANOVA  $\Lambda = 0.96$ ,  $F(3,49) = 0.64$ ,  $P = 0.59$ ].

For the control variables, only 11 of 126 correlation coefficients were found to be significant in the two groups, that is, the control variables of age, educational level, clinical levels of itch and pain at the moment of testing, clinical levels of pain the last 2 weeks, and disease duration were significantly correlated with at least one outcome measure for itch and pain sensitivity. The main analyses were generally not affected when including these control variables separately as covariate in the respective MANCOVAs for the tolerance thresholds, evoked itch and evoked pain with the exception that differences in itch sensitivity between the patients with PS and RA became stronger after controlling for disease duration [ $\Lambda = 0.78$ ,  $F(3,48) = 4.66$ ,  $P < 0.01$ ] and diminished after controlling for age [ $\Lambda = 0.97$ ,  $F(3,48) = 0.53$ ,  $P = 0.67$ ]. When excluding the two patients with PS that self-reported joint pain at the

moment of testing, results remained generally the same [VAS itch  $\Lambda = 0.83$ ,  $F(3,47) = 3.27$ ,  $P < 0.05$ ; thresholds  $\Lambda = 0.70$ ,  $F(3,47) = 6.63$ ,  $P \leq 0.001$ ; VAS pain  $\Lambda = 0.97$ ,  $F(3,47) = 0.52$ ,  $P = 0.67$ ].

## Discussion

In the present study, we investigated whether patients with chronic itch due to psoriasis (PS) or chronic pain due to rheumatoid arthritis (RA) with a clear pathophysiological basis of inflammation display heightened sensitivity to itch and pain, respectively. In line with our hypothesis, results indicated that patients may indeed be more sensitive to sensations in line with their main symptom, for example, to itch in patients with chronic itch. More specifically, the patients with chronic itch due to PS were more sensitive to itch regarding stimulation with histamine (possibly partly due to age effects), while the patients with chronic pain due to RA particularly displayed lower tolerance thresholds for mechanical ( $A\delta$ -fibre threshold) and cold stimulation. It has repeatedly been shown that patients with chronic pain display heightened levels of pain and/or lowered tolerance thresholds for experimental mechanical, electrical or thermal stimuli (9–12). This phenomenon of heightened sensitivity is supported by earlier studies in diverse patient groups with chronic pain, for example, in fibromyalgia, osteoarthritis, whiplash pain and musculoskeletal pain (9). Studies showing that patients with chronic pain can perceive itch stimuli as painful (15), and painful stimuli can be perceived as itching in patients with chronic itch (13,14), further support the assumption of an enhanced sensitivity to stimuli in line with the patient's main symptom, for example, as itching in patients with chronic itch. We previously also showed that patients with atopic dermatitis reacted with heightened levels of itch to experimental stimuli, while patients with fibromyalgia reacted with heightened levels of pain (11). This is now the first study demonstrating that this specific heightened sensitivity might also partly be generalized to other patients groups with chronic itch or pain with an inflammatory aetiology, that is, PS and RA, irrespective of the complexity of systemic medication and the presence of other symptoms next to the main symptoms of chronic itch and pain. For example, although the patients with PS or RA predominantly suffered from chronic itch or pain, respectively, also a proportion of patients with PS also suffered from pain, mainly resulting from their skin condition (1,21), but also from comorbid conditions, and some patients with RA also suffer from itch, for example, due to medication intake (22). However, future research should also take into account the mechanisms specifically related to the clinical condition, pathophysiological aetiology and treatment, and the interactions with the sensitivity to itch and pain.

Some limitations and perspectives for future research should be discussed. First, this study investigated the relevance of long-term sensitization to two patient groups with chronic itch or pain by investigating central nervous system responsiveness to peripheral stimulation with stimuli evoking itch and/or pain. As results indicated that between-group differences were most pronounced for the discriminative itch (histamine) and pain (cold pressor test) stimuli, long-term sensitization processes may particularly affect the intensity of the perceived sensation [e.g. by hyperknesis (7,8)] rather than the quality of the sensation, for example, by experiencing ambiguous stimuli as itching. Future research might further eluci-

date to which stimuli patients with chronic itch and pain display a heightened itch and pain sensitivity, respectively. Longitudinal or experimental studies, also combined with measures of central activity such as fMRI, are necessary to further investigate the underlying mechanisms of sensitization (9). Second, the two patient groups were not completely comparable regarding age, educational level, clinical levels of itch and pain, and disease duration. Younger age seemed to affect the sensitivity to itch, possibly also contributing to the difference in itch sensitivity between patients with PS and RA. As a higher age is inherent to the patient group with RA, it is not possible to disentangle the effects of age or condition (RA versus PS) in the present study, and therefore, age effects cannot be ruled out. Little is known about the role of different individual characteristics in sensitivity to itch and pain. However, pain sensitivity varies for different groups of subjects and stimuli (23), and age might be related to the variance in itch and pain sensitivity (24), as, for example, the extent of pain inhibition decreases across the adult lifespan (25). Future research should focus on individual characteristics, such as age, to unravel psychophysiological mechanisms in itch and pain sensitivity. Third, as the clinical condition of the patient may be associated with sensitization processes (9), future research should also include measures of the patient's clinical condition, for example, inflammation level or severity of the condition. Fourth, levels of itch and pain evoked by the stimuli are generally moderate, even when patients were asked to report the tolerance threshold. This may be related to the fact that tolerance to stimuli may be subjected to motivational or cognitive-affective responses, for example retrospective response bias or anticipatory anxiety (26,27). Expectations influencing subsequent stimuli cannot be excluded (27), and the application of multiple stimuli may be subjected to habituation or sensitization effects. Crossover effects were attempted to be minimized by applying stimuli in an order such that the stimuli with the lowest mean intensity of itch and pain were applied at first and stimuli were applied with intervals in between, and pretest trials were conducted with electrical stimulation as previously described (18). In future studies results might be replicated with stimuli inducing higher levels of itch and pain, for example by using stimuli of different modality or intensity (17), and applied both at fixed intensity and by measuring tolerance thresholds. Fifth, in view of the possible sex differences in sensitivity to somatosensory stimuli and the modulation of pain sensations (25,28), comparison of the present data with male patients is desirable.

To conclude, the results of this study showed, although the influence of age effects cannot be ruled out, a specific heightened itch sensitivity in patients with chronic itch due to PS and a specific heightened pain sensitivity in patients with chronic pain due to RA. These findings contribute to our knowledge on sensitization processes in various conditions associated with chronic itch and pain and might further support that generic sensitization processes also play a role for patients with chronic inflammatory conditions. Indicators of heightened sensitivity to itch and pain may be used as tools to identify the complex interaction of psychophysiological factors that play a role in sensitization processes, which may play a role in the course of symptoms in patients with chronic itch and pain. Sensitization processes, which may not only result in a heightened generalized sensitivity, but also in line

with the clinical condition of the patient, for example, towards itch in patients with chronic itch, may be a target to optimize treatment effects in clinical practice to reduce symptoms of itch and pain (9).

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measurements. Dr. van Laarhoven conducted the experiment, and Dr. van Laarhoven and Dr. Evers drafted the manuscript. All authors fully read the article draft and provided their approval. There are no financial or other arrangements that might lead to a conflict of interest for this paper.

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### Conflict of interests

The authors have declared no conflicting interests.

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