ORIGINAL ARTICLE

Relations between a standardized experimental stressor and cutaneous sensory function in patients with chronic pruritus and healthy controls: an experimental case–control study

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Abstract

Background While chronic pruritus (CP) is a frequent symptom, many aspects of its underlying pathophysiological mechanisms still need elucidation. Research on sensory cutaneous function and on the influence of stress has been conducted mainly in patients with atopic dermatitis but is lacking for patients with CP.

Objective To assess whether a standardized social stressor influences cutaneous sensory function in patients with CP in comparison with healthy controls (HC).

Methods Case–control study; 33 CP and 30 HC were submitted to the standardized quantitative sensory testing protocol before and after the Trier Social Stress Test and 1 h later. Intraepidermal nerve fibre density (IENFD) was determined.

Results Mechanical pain sensitivity and mechanical detection thresholds were significantly higher in CP than in HC, and mechanical detection thresholds increased more in CP than in HC over the three measurements. In both groups, cold pain threshold increased and heat pain threshold decreased from before to after the stress test and remained constant 1 h later. Only in CP, almost all QST tests induced at least a small amount of pruritus, which was not significantly altered by the stress test. IENFD in pruritic skin was significantly reduced in CP when compared to healthy controls.

Conclusion Peripheral thermal sensory function was not altered in CP despite reduced IENFD in lesional skin, but we could demonstrate central sensitization processes specifically in CP and influences of an acute stressor inducing more sensitivity to thermal pain in both groups.

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Conflicts of interest

The authors declare no conflict of interest.

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Introduction

Chronic pruritus (CP) can be a symptom of dermatologic, systemic, neurologic and mental diseases and is frequently of multifactorial origin.[1–7] Its underlying pathophysiological mechanisms have been subject to some research, but many aspects still need elucidation. Next to disease-specific mechanisms, central and peripheral sensitization mechanisms in CP patients have been discussed.[8,9]

Some studies demonstrated that patients with CP are more sensitive to experimentally applied somatosensory stimuli than healthy controls and also to specific itch stimuli such as electrical stimuli, histamine or cowhage.[10–12] Painful stimuli have been shown to evoke itch in patients with atopic dermatitis (AD).[12]

However, most of these studies studied itch exclusively in subjects with AD,[10–13] not in subjects with CP of other origins.

Self-reported pruritus has been associated with self-reportings of stress and stressful life events in population samples[14–17] and in patients with AD[18–20] and psoriasis.[21] Again, most studies focused on healthy participants or population samples or AD, but pruritus pathophysiology in CP patients may differ from

patients with AD and experimentally induced itch in healthy subjects.[9,22,23]

Studies on how stress influences cutaneous sensory function in quantitative sensory testing have been performed in healthy participants and in patients with chronic pain,[24] but research is lacking on patients with CP. We found no studies which investigated relations between experimental stress and cutaneous sensory function in patients with CP.

Altered cutaneous sensory function as assessed by quantitative sensory testing may be also associated with reduced intraepidermal nerve fibre density and both can be related to the diagnosis of small-fibre neuropathy,[25] which has been shown to be associated with pruritus in 68.3%.[26] Therefore, the objective of this study was to study relations between standardized, experimentally induced stress and cutaneous sensory function as assessed by quantitative sensory testing in patients with CP in comparison with healthy controls. As one peripheral mechanism of altered sensory function can be a reduced nerve fibre density, we included intraepidermal nerve fibre density (IENFD) to be able to assess structural changes.

Materials and methods

The local ethics committee approved the study. The study was performed in accordance with the Helsinki declaration of 1975 as revised in 1983. It has been registered in the German Register for Clinical Studies under the number DRKS00013194.

Study participants

A total of 33 patients of the Center for Chronic Pruritus of the University Hospital of Münster with generalized chronic pruritus (19 female, 14 male) and 30 healthy controls (19 female, 11 male) participated in the study. There were no significant differences for the sex distribution (χ^2: 0.22, $P \leq 0.641$) and no significant age differences (patients mean: 51.0 years, SD: 14.53; controls mean: 48.6 years, SD: 14.25; T: 0.66, $P \leq 0.511$) between the two groups. All patients had long-lasting CP of at least 6 weeks (only three patients of less than 1 year, all the others between 1 and 10 years and two patients even longer).

According to the clinical classification of the International Forum for the Study of Itch (IFSI),[22] classification I: 13 patients (39.4%) could be referred to IFSI group I (CP on primary non-lesional skin), nine patients (27.3%) to IFSI group II (CP on primarily lesional skin) and 11 patients (33.3%) to IFSI group III (CP with chronic scratch lesions). According to IFSI classification II, eight patients were classified as having multifactorial pruritus, one patient with lichen planus, four patients with atopic dermatitis, seven with prurigo nodularis, six with inflammatory dermatosis, four with pruritus of unknown origin, two with brachioradial pruritus and one with a previous cutaneous lymphoma.

Inclusion criterion for the patients was that they experienced pruritus of the right forearm.

Exclusion criteria were diabetes mellitus, polyneuropathy, neurologic diseases, chronic pain conditions, excoriations, infections or wounds of the forearm, gravidity, drug addiction, mental diseases, active dermatologic diseases necessitating immediate therapy, lidocaine allergy and marcumar intake. Systemic antihistamines, topic or systemic glucocorticoids, cyclosporine UV radiation, selective serotonin reuptake inhibitors, amitriptyline and gabapentinoids had to be paused 3 days before the examination.

Study design

Figure 1 shows the study design (all procedures and measures are described in detail below).

First, all participants underwent the first quantitative sensory testing session (QST_1). Afterwards, the participants filled in the following measures: visual analogue scales (VAS 0–10) concerning the current itch intensity, current desire to scratch, unpleasantness of itch, subjective strain, mood and subjective stress intensity. Participants were then submitted to a standardized experimental social stress test, the Trier Social Stress Test (TSST).

Directly after the TSST, they filled in the same VAS as before and underwent the second quantitative sensory testing (QST_2). In the hour following QST_2, all participants filled in a set of psychometric self-report questionnaires, followed by the third quantitative sensory testing (QST_3). Their heart rate was recorded continuously with a three canal electrocardiograph from before till 1 h after the TSST.

The whole procedure took 3–4 h.

After that, skin biopsies were taken on another day from the right forearm, in CP from pruritic and non-pruritic skin areas. The biopsy was processed for determination of the IENFD as described previously.[27] For this, an antibody against protein gene product (PGP) 9.5 (polyclonal rabbit, 1 : 2000; Chemicon, Temecula, CA, USA) and, as a secondary antibody, anti-rabbit-fluorescein isothiocyanate (FITC; 1 : 50; pig anti-rabbit immunoglobulin FITC; Dako, Glostrup, Denmark) was used. Three specimens of each 40 µm were used to quantify the intraepidermal nerves per mm.

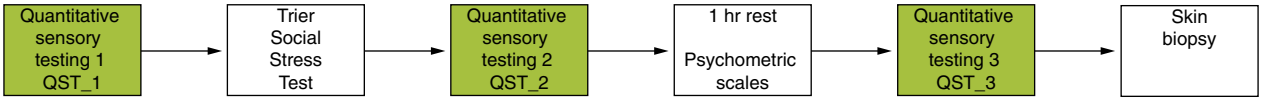

Figure 1 Study design.

The Trier Social Stress Test (TSST)

The Trier Social Stress Test is a standardized experimental stressor, which has been developed and described in detail by Kirschbaum *et al.*[28]

It lasts 15 minutes and consists of the following standardized components:

(i) A stress-provoking preparation phase, in which the participant is informed about the imminent task: a job interview. He receives a paper and pencil for notes, but is not allowed to use them in the interview. (ii) A five-minute job interview, in which the participant presents himself in free speech before an evaluative panel of two people. If he finishes early, he is asked to continue. If he does not proceed, after 20 s of silence he is confronted with standardized questions mostly aiming at weaknesses and problems of the participant. (iii) In the last 5 min, the participant is presented with a mathematical task: to count backwards from 2023 in steps of 17 as quickly and flawless as possible. In case of mistakes, follow the standardized answer 'wrong, 2023', and the participant must start again from 2023.

Quantitative sensory testing (QST)

Quantitative sensory testing was performed according to the protocol of the German Research Network for Neuropathic Pain.[29] Testing stimuli, number of applications and order of stimulus application were the same as described there. The test area was always the right forearm, i.e. a pruritus-afflicted (lesional) skin area in the patients (according to our inclusion criteria).

All participants received standardized instructions on how to rate (thresholds and intensities) and respond to the testing stimuli. Because of the length of the examination, we did not test for the thermal sensory limen, vibration threshold and pressure pain threshold. In addition to the standard protocol, all participants were asked to rate their present pruritus intensity on the right forearm after each QST subtest: 'How strong do you experience itch right now on a scale from 0 (no itch) to 10 (maximum imaginable itch)?' The exact description of the QST tests is provided in the Appendix S1.

Visual analogue scales

Before and after the stress test, the participants filled in six visual analogue scales assessing the current subjective strain, mood, stress intensity, pruritus intensity, desire to scratch and unpleasantness of itch between 0 and 10.

Psychometric scales

Psychometric scales included the Trier Inventory for the Assessment of Chronic Stress (TICS), the Childhood Trauma Questionnaire (CTQ), the Hospital Anxiety and Depression Scale (HADS) and the Dermatologic Life Quality Inventory (DLQI).

From the recorded ECG, parameters of heart rate variability were calculated by Biotrace Software for NeXus-10, version 1.12 (Mind Media B.V., Roermond-Herten, Netherlands).

The results of the VAS, of heart rate variability and the psychometric questionnaires will be presented in other publications.

Data analysis

Statistics were calculated by the Statistical Package for Social Sciences (SPSS), version 25 (IBM, Armonk, New York, US).

According to the recommendations of the QST protocol,[29] the data obtained for the cold detection threshold (CDT), heat detection threshold (HDT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA) and wind-up ratio (WUR – a measure of temporal pain summation) were log-transformed before data analysis.

For the longitudinal detection of significant changes in the QST scores before and after the stress test and 1 h later and to detect differences between CP and HC, we calculated General Linear Models with three measurement repeatings (intrasubject variable = time) for the respective QST scores with the intersubject factor group (CP/HC). Due to the possible violation of data sphericity in studies with small sample sizes, a Greenhouse–Geisser correction was included. We report F values and significance level P for the measurement repeatings (time), for the time × group (CP/HC) interaction and for the test of intersubject effects (group HC or CP). If the time effect resulted significant, post hoc tests were performed to detect between which QST measurements the differences were significant, with Bonferroni correction for multiple testing. We compared IENFD between CP and HC and also IENFD between lesional and non-lesional skin of CP patients by t-tests for independent samples and report T-values and significance level P. As this is a pilot study, P-values of ≤ 0.05 were regarded as significant.

Results

Table 1 shows the results of the different QST thresholds and pain ratings for HC and CP before the Trier Social Stress Test (QST_1), after the Trier Social Stress Test (QST_2) and 1 h later (QST_3), while Table 2 shows the ratings for pruritus induced by the different QST subtests in CP and HC during all three QST tests.

Pruritus patients showed significantly higher mechanical detection thresholds and MPS than HC (effect of group in Table 1). In both groups, from before to after the stress test, mechanical detection thresholds increased from baseline (effect of time). MPS showed a trend to increase (effect of time) and also a trend towards higher increase from baseline to after the stress test in CP (effect of interaction time × group). Also, dynamic mechanic allodynia was marginally higher in CP (effect of group).

Table 1 Longitudinal analyses for changes in the QST scores before (QST_1) and after the stress test (QST_2) and 1 h later (QST_3) in HC vs. CP (effect of time and group and their interaction; General Linear Models with the intersubject factor group and three measurement repeatings)

Quantitative sensory testing QST_1, QST_2 and QST_3	Healthy controls (n = 30)		Chronic pruritus patients (n = 33)		Two-factorial (CP vs. HP) variance analysis with three repeated measurements		
Variable	**Mean**	**SD**	**Mean**	**SD**	**Effect of**	**F**	**$P \leq$**
Cold detection threshold _1†	29.11	3.29	29.38	1.71	Time	1.63	0.208
Cold detection threshold_2†	28.04	5.10	28.62	2.33	Group	0.34	0.561
Cold detection threshold_3†	28.81	3.02	28.25	2.61	Interaction	0.90	0.364
Warmth detection threshold_1†	34.19	0.88	34.60	1.93	Time	0.03	0.955
Warmth detection threshold _2†	34.17	0.89	34.63	1.61	Group	2.01	0.161
Warmth detection threshold_3†	34.27	1.19	34.58	1.22	Interaction	0.07	0.901
Cold pain threshold_1	13.68	10.03	15.61	10.80	**Time***	9.99	**0.001**
Cold pain threshold_2	18.05	9.48	17.20	10.36	Group	0.10	0.756
Cold pain threshold_3	17.27	10.38	18.39	9.07	Interaction	1.60	0.208
Heat pain threshold_1	42.73	4.44	41.44	4.83	**Time****	9.50	**0.001**
Heat pain threshold_2	40.96	4.03	40.60	4.29	Group	0.45	0.506
Heat pain threshold_3	41.13	4.09	40.74	3.90	Interaction	1.30	0.276
Mechanical detection threshold_1†	3.82	5.03	5.61	4.42	**Time*****	5.40	**0.007**
Mechanical detection threshold_2†	4.66	6.67	6.91	7.46	**Group**	6.27	**0.015**
Mechanical detection threshold_3†	5.49	8.31	9.63	18.99	Interaction	0.10	0.888
Mechanical pain threshold_1†	33.48	58.73	19.86	23.43	Time	1.93	0.150
Mechanical pain threshold_2†	20.81	24.20	17.54	23.55	Group	0.14	0.714
Mechanical pain threshold_3†	16.34	22.59	25.75	51.56	Interaction	1.16	0.318
Mechanical pain sensitivity_1†	7.32	9.11	11.34	11.70	Time	2.63	0.087
Mechanical pain sensitivity_2†	5.80	6.11	13.96	13.48	**Group**	4.83	**0.032**
Mechanical pain sensitivity_3†	7.15	6.85	13.51	13.33	Interaction	2.52	0.095
Dynamic mechanical allodynia_1†	0.43	1.38	0.78	1.87	Time	1.07	0.314
Dynamic mechanical allodynia_2†	0.20	0.74	0.77	2.16	Group	2.94	0.092
Dynamic mechanical allodynia_3†	0.24	0.88	0.75	1.97	Interaction	0.03	0.899
Wind-up ratio_1†	3.68	4.93	3.37	4.50	Time	1.24	0.290
Wind-up ratio_2†	3.12	2.38	2.57	2.23	Group	0.003	0.954
Wind-up ratio_3†	3.40	3.03	3.12	2.61	Interaction	0.96	0.376

Post hoc tests with Bonferroni correction: *$P \leq 0.001$ for QST_1 vs. QST_2; $P \leq 0.003$ for QST_1 vs. QST_3; **$P \leq 0.001$ for QST_1 vs. QST_2; $P \leq 0.009$ for QST_1 vs. QST_3; ***$P \leq 0.013$ for QST_1 vs. QST_3.

†Data were log-transformed for analysis.

Significant statistics are printed in bold type.

HC, healthy controls; CP, chronic pruritus patients; QST, quantitative sensory testing; SD, standard deviation; Wind-up ratio, temporal pain summation.

Cold pain thresholds increased and heat pain threshold decreased in CP and HC (with no significant intergroup difference) from before to after the stress test (effect of time) and remained constant 1 h later (as demonstrated by the post hoc tests).

Table 2 shows the participants' pruritus ratings after the different QST subtests before the TSST (QST_1), after the TSST (QST_2) and 1 h later (QST_3).

Almost all QST tests induced at least a small amount of additional pruritus induction in CP and no pruritus sensation in healthy controls, with significant intergroup differences for all tests. Pruritus in CP was most pronounced after the testing of the temporal pain summation (wind-up ratio). However, the QST-induced pruritus was not significantly altered by the stress test: There was no significant effect of time on the pruritus ratings.

Intraepidermal nerve fibre density of non-pruritic skin of the right forearm was not significantly different between CP (mean: 14.54, SD: 8.29) and HC (mean: 15.68, SD: 8.88) (Student t-test: T: 1.31; $P \leq 0.197$). IENFD in pruritic skin was significantly reduced in CP (mean: 9.16, SD: 5.24) when compared to the non-pruritic skin of healthy controls (T: 3.24; $P \leq 0.002$). When comparing pruritic to non-pruritic skin of the CP patients, there was a trend to reduced IENFD in pruritic skin (T: −1.95; $P \leq 0.062$).

Discussion

We investigated relations between a standardized experimental stressor and the reactions to different stimuli of the standardized QST protocol in patients with chronic pruritus and healthy controls and found some interesting differences between CP and HC.

Table 2 Pruritus induced by the different QST subtests in chronic pruritus patients (CP) and healthy controls (HC) before the Trier Social Stress Test (QST_1), after the Trier Social Stress Test (QST_2) and 1 h later (QST_3) in HC vs. CP (effect of time and group and their interaction; General Linear Models with the intersubject factor group and three measurement repeatings)

Pruritus intensity after... Quantitative sensory testing QST_1, QST_2 and QST_3	**Pruritus intensity (VAS 0–10) after the different QST_modalities.**				**Statistics**		
	Healthy controls (n = 30)		**Chronic pruritus patients (n = 33)**		**Two-factorial (CP vs. HP) variance analysis with three repeated measurements**		
Pruritus intensity after...	**Mean**	**SD**	**Mean**	**SD**	**Effect of**	**F**	**$P \leq$**
Cold detection threshold _1	0	0	0.41	1.32	Time	0.54	0.557
Cold detection threshold_2	0	0	0.34	1.07	**Group**	**4.88**	**0.031**
Cold detection threshold_3	0	0	0.17	0.55	Interaction	0.54	0.557
Warmth detection threshold_1	0	0	0.79	1.66	Time	0.97	0.355
Warmth detection threshold _2	0	0	0.54	1.40	**Group**	**8.98**	**0.004**
Warmth detection threshold_3	0	0	0.38	1.01	Interaction	0.97	0.355
Cold pain threshold_1	0	0	0.44	1.22	Time	1.08	0.330
Cold pain threshold_2	0	0	0.65	1.68	**Group**	**9.12**	**0.004**
Cold pain threshold_3	0	0	0.21	0.64	Interaction	1.08	0.330
Heat pain threshold_1	0	0	0.97	1.83	Time	1.00	0.366
Heat pain threshold_2	0	0	1.42	2.54	**Group**	**11.2**	**0.001**
Heat pain threshold_3	0	0	0.68	1.65	Interaction	1.00	0.366
Mechanical detection threshold_1	0.10	0.55	1.10	1.95	Time	1.05	0.331
Mechanical detection threshold_2	0	0	0.84	1.57	**Group**	**11.75**	**0.001**
Mechanical detection threshold_3	0	0	0.72	1.45	Interaction	0.29	0.657
Mechanical pain threshold_1	0.15	0.84	1.43	2.14	Time	2.13	0.135
Mechanical pain threshold_2	0	0	1.35	2.15	**Group**	**11.97**	**0.001**
Mechanical pain threshold_3	0	0	0.94	1.91	Interaction	1.04	0.343
Mechanical pain sensitivity_1	0	0	1.70	2.44	Time	0.36	0.689
Mechanical pain sensitivity_2	0	0	1.89	2.59	**Group**	**19.67**	**0.001**
Mechanical pain sensitivity_3	0	0	1.61	2.39	Interaction	0.36	0.689
Wind-up ratio_1	0	0	2.17	2.77	Time	1.53	0.223
Wind-up ratio_2	0	0	2.33	2.83	**Group**	**19.38**	**0.001**
Wind-up ratio_3	0	0	1.87	2.84	Interaction	1.53	0.223

Significant statistics are printed in bold type.
CP, chronic pruritus patients; HC, healthy controls; QST, quantitative sensory testing; SD, standard deviation; Wind-up ratio, temporal pain summation.

For the thermal detection and thermal pain thresholds, baseline thresholds did not differ between CP and HC. This is in line with the results reported by Pereira *et al.*[30] from a smaller sample of 12 patients with prurigo nodularis and eight healthy controls, who found no differences in the thermal detection and thermal pain thresholds as well. These indicate the function of C and Aδ axons.[29,31]

Significant differences between HC and CP in our sample regarded some mechanical modalities of the QST: CP detected the touch of the von Frey filaments employed for the mechanical detection thresholds (MDT) only at higher stimulus intensities, that is, were less sensitive to touch than HC. This applied to MDT in all three QST testings, before and after the stress test. Alterations in MDT are supposed to represent the function of Aβ axons[29] or central sensitization.[31] Van Laarhoven *et al.*[11] reported that patients with AD (n = 15) perceived the stimulation with the von Frey filaments as unpleasant, stinging at lower stimulus intensities than HC, but they did not report on the detection of the touch (MDT).

The mechanical pain threshold, which is supposed to represent Aδ fibre function (as also is CDT),[29] was not significantly different between CP and HC.

Mechanical pain sensitivity is the geometric mean of all numerical pain ratings for seven standardized pinprick stimuli of seven sizes applied randomly in five runs, which were alternated with three light tactile stimuli used to detect dynamic mechanical allodynia (DMA). In our sample, MPS was significantly higher in CP than in HC, with a trend to increase under stress, not observed in HC (marginal significance of time and interaction time × group). Also DMA (pain ratings induced by light touch) was marginally higher in CP. MPS and DMA are also supposed to represent central sensitization processes.[31]

In contrast to our findings, Pereira *et al.*[30] reported a (not significant) tendency towards reduced MPS in 12 subjects with

prurigo nodularis compared to eight healthy controls. We have no explanation for these contrasting results, except that their sample was composed of one diagnosis group only while we investigated a more representative collective of CP patients. However, because in our sample, there were only seven patients with prurigo nodularis, and we did not perform subgroup analyses; therefore, we cannot compare our results directly to theirs.

In our study, almost all QST subtests induced at least a small amount of additional pruritus sensations in CP patients but no pruritus in HC. That CP experience pruritus in response to mechanical, thermal or pain-inducing stimuli can be interpreted as evidence for sensory sensitization. This is in line with clinical observations, where CP often report that pruritus is evoked by the touch of certain textiles, especially wool or by warmth. Other authors reported that mechanical, electric, thermal or painful stimuli evoked more itch in patients with atopic dermatitis than in healthy controls[10–13] and also explained their findings by central sensitization for itch.[10,11,13]

We also found evidence for sensitization in CP for mechanical painful stimuli (higher MPS and DMA) and also for symptom-specific sensitization (pruritus induced by non-pruritic stimuli or alloknesis). In a review on mechanisms of pruritus, Ikoma *et al.*[32] explain central sensitization for itch and pain by a lowering of neural thresholds for external stimuli. Continuous activation of peripheral nociceptive and pruritogenic afferents in chronic painful or pruritic conditions leads to depolarization of the postsynaptic cells of the spinal cord, which removes the Mg^{2+} blockade from the postsynaptic *N*-methyl-D-aspartate (NMDA) receptor and results in the excitatory postsynaptic potential. Thus, signals from primary afferents for pain or itch cause more intense activation of postsynaptic spinal neurons than they usually do. Moreover, not only signals from pain or itch nerves, but also signals from other nerves, such as Aβ-axons, whose activation usually induces tactile sensation, activate postsynaptic neurons for pain or itch, which is the explanation for allodynia and alloknesis.

Despite reduced IENFD in pruritic skin, we found no indicators for reduced peripheral function in the QST tests indicative of C and Aδ fibre function (CDT, WDT, CPT, HPT and MPT). This finding is in line with Pereira's *et al.*[30] findings of reduced IENFD and intact peripheral sensory function in patients with prurigo nodularis. They concluded that there is no functional small-fibre neuropathy in prurigo nodularis despite neuroanatomical alterations. Schuhknecht *et al.*[27] and Pereira *et al.*[30] discuss that chronic scratching alters skin anatomy and may induce reduced IENFD in CP. Therefore, reduced IENFD must not always be an indicator for small-fibre neuropathy.

We were also interested in the role of stress in cutaneous sensory function. In this study, we applied a standardized experimental stressor – the Trier Social Stress Test – to induce acute stress in the participants. There was a significant increase in the cold pain threshold (CPT) and decrease in the heat pain (HPT) threshold – i.e. more sensitivity to thermally induced pain in both groups. Also, the mechanical detection threshold increased significantly under stress in both groups, but CP started from a higher level. We could identify only one other study which tested the influence of a standardized stressor on QST ratings in healthy controls or other patient groups: Crettaz *et al.*[24] compared stress reactivity in the QST modalities for HC and patients with fibromyalgia. They also reported a significantly lowered heat pain threshold and a tendency towards a higher cold pain threshold after the same stress test (TSST) in 10 healthy subjects, which is in line with our findings.

As we could identify no other study which subjected patients with chronic pruritus to QST before and after a stress test, therefore, we cannot compare our results regarding the stress-induced QST alterations in CP to those of other authors. As in our study reaction to stress influenced the thermal pain thresholds similarly in both groups, this is a further indicator for intact peripheral nerve function in CP, as Pereira *et al.*[30] also reported for prurigo nodularis.

We found no evidence that the standardized acute social stressor employed in our study – the TSST – may increase the pruritus already induced by neutral or painful stimuli in the baseline QST – pruritus ratings did not differ significantly from before to after the stress test. Also, the TSST did not induce pruritus after the QST subtests in healthy subjects.

This finding however does not necessarily mean that stress does not influence pruritus perception in patients with CP and healthy controls. We applied a standardized and acute stressor, which has the advantage that it is always the same for all participants and induces a certain amount of stress in most subjects; its disadvantage is that it cannot be personalized: what a person experiences as stress is highly subjective. Also, the influence of chronic stress cannot be tested by the TSST: this might be quite different, as it is known that acute and chronic stress induce different physiologic reactions.

The mechanisms by which stress may trigger itch have been mainly studied in patients with AD: in the skin, these are mediated by the release of neuropeptides and hormones, which are integrated in the neuroendocrine-immuno-cutaneous system and the hypothalamo-pituitary axis. Stress alters the cutaneous immune response and may thus exacerbate inflammatory conditions. Also, chronic stress-related itch has been hypothesized to induce changes in the hippocampus and subcortical structures and thus in central pruriceptive cycles.[33,34]

A limitation of our study is the small sample size, which was due to the time-consuming and complex procedure with a duration of 3–4 h per subject: 33 patients and 30 healthy controls. Although it is greater than the samples subjected to QST by other authors (10–25 patients or healthy controls),[11,13,24,30] it may still be prone to coincidence and the findings should be confirmed in larger samples.

Another limitation could be the fact that systemic medication and UVB were paused only 3 days before the examination. This time should be sufficient to eliminate most medications, but we cannot exclude that some of these treatments may have influenced the experimental results.

As a conclusion, peripheral thermal sensory function was not altered in CP despite reduced IENFD in lesional skin, but we could demonstrate central sensitization processes specifically in CP and influences of an acute stressor inducing more sensitivity to thermal pain in both groups.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Description of the quantitative sensory testing.