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C-tactile touch perception in patients with chronic pain disorders

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Abstract

Introduction: Slow brushing over the skin activates C-tactile nerve fibers that transmit pleasant tactile experiences in healthy subjects, leading to an inverted U-shaped velocity dependence of ratings: C-tactile optimal stroking stimulations are rated as more pleasant than slower or faster stimulations. Chronic pain diseases such as postherpetic neuralgia (PHN) and complex regional pain syndrome show altered C-fiber innervation density, sensory loss, and pain sensitization.

Objectives: We aimed to investigate whether C-tactile function is affected in painful conditions.

Methods: We assessed psychophysically C-tactile function and sensory perception thresholds in 16 patients with PHN, 19 patients with complex regional pain syndrome, and 22 healthy controls.

Results: Assessment of C-tactile function showed a significantly altered perceived pleasantness of CT stimulation between healthy controls and patients with chronic pain. In specific, tactile stimulation was perceived less pleasant on the affected and contralateral side when compared with controls. In patients with PHN, velocity-dependent pleasantness ratings could not be obtained, suggesting highly impaired C-tactile function with functional loss of pleasant touch perception.

Conclusions: In conclusion, this is the first report of impaired C-tactile function in patients with PHN. Reduced pleasantness resulting from gentle touch can reflect defective C-fiber function or result from central nervous system effects in a chronic pain state.

Keywords: C-tactile fibers, Neuropathic pain, Pleasant touch, Postherpetic neuralgia

1. Introduction

Patients with peripheral neuropathic pain disorders (PNPDs) frequently present with abnormal pain perception.[27] As part of it, nociception is transmitted through thinly myelinated Aδ-nociceptive and unmyelinated C-nociceptive fibers. Another subgroup of C fibers, C-tactile (CT) fibers, is involved in affective touch processing.[29] These slow-conducting (0.9 m/s), unmyelinated fibers, located in the nonglabrous human skin, are reactive to a very low mechanical pressure of 0.3 to 2.5 mN[49] and are highly sensitive to slow stroking stimulation. Human in vivo microneurography recordings show that CT fibers respond optimally to stimulation with a velocity of 1 to 10 cm/s with perception of pleasantness. Stimulations performed with a velocity of ≤0.3 cm/s or ≥30 cm/s are less effective in activating CT fibers.[2,25,36] These characteristics make CT fibers highly sensitive to human interpersonal stroking touch.[25,36]

A coordinate presentation of pleasantness (*y*-axis) and velocities (*x*-axis) shows an inverted u-shaped curve, with intermediate stroking velocities being rated more pleasant than fast or slow stroking. This has been replicated in numerous studies[29] for different body regions[1] and age groups.[8,42] By contrast, firing frequency of myelinated Aβ fibers increases linearly with velocity of stroking.[25]

As patients with PNPD show frequently pathology of C fibers, disturbed tactile pleasantness processing and perception due to CT-fiber involvement is possible. In line, patients with a genetic condition that leads to reduced C-fiber density (hereditary sensory and autonomic neuropathy type V) do exhibit disturbed pain processing and reduced pleasantness when being stroked with CT-optimal stimuli.[30] Similarly, healthy individuals with experimentally induced allodynia experience less pleasant CT-

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targeted stimulation.[24] Hence, we aim to investigate the perception of CT-targeted stimulation in 2 groups of patients with C-fiber damage: postherpetic neuralgia (PHN) and complex regional pain syndrome (CRPS) type I.

Postherpetic neuralgia involves epidermal and dermal neurite loss of small (Aδ and C) and to a lesser degree large (Aβ) sensory nerve fibers[47] in the affected area and contralaterally.[35] Clinically, patients describe burning pain, itching, and dynamic mechanical allodynia. In accordance, quantitative sensory testing (QST) identified thermal and tactile deficits and dynamic mechanical allodynia (DMA) in patients with PHN (PHNP).[37] However, the severity of allodynia does not correlate with epidermal nerve fiber density.[5]

Complex regional pain syndrome I, a peripheral and central nociplastic pain syndrome without large nerve fiber damage, is characterized by persistent distal limb burning pain with swelling, abnormal skin color, temperature, and sweating occurring posttraumatic or without trauma. Evidence points to auto-inflammatory processes in the pathogenesis of CRPS.[7] At disease onset, small-fiber involvement has been suggested.[13,21,33–35] During the chronification, reorganization in somatosensory cortices has been demonstrated.[46] Quantitative sensory testing profiles show heat or pressure hyperalgesia, indicating C-fiber dysfunction, cold hyperalgesia, DMA, and mechanical and thermal hypoesthesia.[14]

We hypothesized that (1) CT-targeted stroking is more painful and less pleasant for patients compared with healthy controls, especially in the affected body region and (2) the typical pleasantness curve is not observed in patients while intensity perception remains unaffected. We furthermore explored the relation between severity of symptoms and the perception of CT-targeted stroking in patients with PNPD.

2. Methods

The study was approved by the Ethics Committee of the University of Dresden (EK346082015), performed between 2018 and 2020, conducted in accordance with the World Medical Association Declaration of Helsinki. Detailed study information was given to all participants, and informed written consent was obtained.

2.1. Participants

In total, 35 patients (PHN: n = 16; CRPS: n = 19) were included (Supplementary Table 1, available at http://links.lww.com/PR9/A113), all outpatients at the University of Dresden Pain Center. Diagnoses were confirmed after medical history and clinical examination by a neurologist specialized in pain management, according to the International Association for the Study of Pain diagnostic criteria for CRPS-I.[16] Patients with PHN were older than patients with CRPS (CRPSP; PHNP: mean 72.9 ± 8.6 years, 7 women; CRPSP: mean 56.5 ± 13.4 years, 15 women). Patients were compared with 22 healthy controls, selected to match the median age and sex distribution of both patient groups (controls: mean 60.8 ± 11.4 years, 16 women). Controls were recruited through public announcements and our participant databases.

The 3 groups differed significantly in age ($F[52,2] = 9.3$, $P < 0.001$) and sex distribution ($\chi^2 = 6.1$, $P = 0.048$). Bonferroni corrected post hoc tests (indicated by "p_{corr}") showed that PHNP were significantly older than CRPSP ($p_{corr} < 0.001$). Controls did not differ significantly in age from CRPSP ($p_{corr} = 0.57$) but differed from PHNP ($p_{corr} = 0.008$).

For all participants, other diseases that may affect somatosensory perception served as exclusion criteria, ie, neurological conditions (Parkinson disease, stroke, and polyneuropathy) or other pain disorders, cancer, and diagnosed mental diseases according to the Diagnostic and Statistical Manual of Mental Disorders-5. We excluded participants younger than 18 years. Good knowledge of the German language was required for comprehension of the instruction and the questionnaires.

2.2. Procedure

2.2.1. Questionnaires

After collection of medical history, participants completed the painDETECT score questionnaire,[11] a screening questionnaire that determines the prevalence of neuropathic pain components (sum score 0–38 points, ≥ 19 indicating >90% likelihood for neuropathic pain). The short version of the Patient Health Questionnaire[44] was used as a screening tool for depression and anxiety disorders (each with cutoff 5).

2.2.2. Standardized quantitative sensory testing

Quantitative sensory testing is a standardized psychophysical test for sensory perception and pain thresholds.

The standardized German QST protocol[40] has been applied to subsamples from both patient groups (PHN: 14 patients, mean age 72.71 ± 9.38 years, 6 women; CRPS: 13 patients, mean age: 52.36 ± 13. years, 10 women) on the most painful body area (affected side) and contralaterally (contralateral side). In brief, calibrated stimuli were applied to test cold detection threshold, warm detection threshold, thermal sensory limen, paradoxical heat sensation, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, mechanical pain sensitivity, DMA, wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT). Using QST, signs of sensory loss or sensory gain, including hyperalgesia by heat, cold, needle pins or pressure, and DMA, are detectable.[31,40] Raw data were collected and transformed as previously described.[40] The results were compared with sex-matched, age-matched, location-matched reference values.[26]

2.2.3. C-tactile–targeted touch perception

C-tactile–targeted touch perception was performed on 3 different body sides: the affected side (individually most painful), the contralateral side, and a reference side. Affected areas were widely distributed for PHNP and CRPSP. For controls, the affected side was chosen to match the distribution of the combined group of patients (Supplementary Table 1, available at http://links.lww.com/PR9/A113).

The left dorsal forearm served as the reference side in all participants because it is rich in CT fibers and was used in multiple studies.[1,24,25,42] However, in healthy individuals, CT perception does not differ between different body areas.[1]

The following procedure was applied. Participants were seated in a comfortable chair with their pronated left forearm on a pillow for the reference side test. Above, we positioned the 70-mm wide soft goat hair brush that was steered by the Rotary Tactile Stimulator (Dancer Design) in half of the patients. This robot enables high-precision control of stroking velocity and force.[10] In the other half of the patients, stimuli were applied manually by an experienced experimenter who had audiovisual support and was trained in delivering stimuli with constant force and velocity.

Stroking by hand of a trained experimenter or robot is comparable.[45] The very same procedure was applied for all locations, if possible. For body sides, which were hard to position in a horizontal direction, curved or small, stroking was manually operated with the same brush. In those cases, the robot was operated simultaneously and served as guidance for the velocity of stroking.

In total, 15 stimuli were delivered in a proximal to distal direction with a force of 0.4 N. The presentation order was randomized within and between participants. Five different velocities were presented CT optimal (1 cm/s, 3 cm/s, and 10 cm/s) and CT suboptimal (0.3 cm/s and 30 cm/s). After each stimulus, participants were asked to rate on 3 visual analogue scales for pleasantness (−10 to 10: very unpleasant to very pleasant), intensity (0–10: not at all intense to very intense), and pain (0–10: not at all painful to very painful).

2.3. Statistical analyses

Data were analysed with the SPSS Statistics for Windows, version 25.0 (IBM, Armonk, NY).

To examine the overall perception of pleasantness, pain, and intensity (hypothesis A), we averaged the 15 ratings each for pleasantness, pain, and intensity per person and test side. Averaged ratings served as a dependent variable in a repeated measures ANOVA with the within-subject factor test side (3) and the between-subject factor group (3). As age and sex distribution differed significantly between groups, both variables were included as covariates in the model. Post hoc tests were calculated between groups with a Bonferroni correction factor of 3 (indicated by p_{corr}). Effect sizes are given for significant results as η^2 for the F-test and as Cohen *d* for post hoc analyses.

To analyse CT-fiber–specific perception (hypothesis B), we examined the effect of velocity on the pleasantness ratings for each group. We first averaged pleasantness ratings over 3 repetitions per velocity and test side and then calculated a repeated measures ANOVA with the within-subject factors of velocity (5) and test side (3) for each group. Pleasantness ratings served as independent variables. As the models were calculated separately for each group, we did not include age and sex as a covariate. The quadratic term of the velocity is reported because we hypothesized a quadratic relation between velocity and pleasantness ratings (compare[25]). Post hoc tests are performed in case of a significant interaction effect for each group and test side as ANOVAs for repeated measurement with the dependent variable of pleasantness rating and the within-group variable of velocity. Again, the quadratic term is inspected.

To test whether the groups differed significantly in their quadratic term of velocity-dependent pleasantness evaluation, an additional repeated measures ANOVA was calculated with the within-subject factors of velocity (5) and test side (3) and the between-subject factor of group (3). To test whether potential group differences are specific for ratings of pleasantness, all statistical analysis for hypothesis B was repeated with the dependent variable of intensity.

We explored the correlation between ratings and QST data using the Pearson correlation coefficient.

3. Results

The painDETECT score questionnaire sum score was significantly different between groups ($F[37,2] = 12.1$, $P < 0.001$). Controls reported significantly less pain than PHNP ($p_{corr} = 0.015$) or CRPSP ($p_{corr} = 0.006$), whereas both patient groups did not differ significantly ($p_{corr} = 0.30$). Reported tactile allodynia differed significantly between groups ($F[31,2] = 9.8$, $P \leq 0.001$) with more allodynia than controls in the PHN ($P = 0.001$) and CRPS group ($P = 0.006$) and no difference between the patient groups ($P = 1$). Reported symptoms of mental disease, measured with the Patient Health Questionnaire, did not differ significantly between groups for anxiety ($F[50,2] = 0.3$, $P = 0.72$, **Table 1**) but differed for depression ($F[49,2] = 3.6$, $P = 0.036$). Here, both patient groups reported more symptoms than controls, but the results differed not significantly after Bonferroni correction.

3.1. Effect of group (hypothesis A)

For pleasantness ratings, there was a significant effect of group ($F[2,45] = 12.1$, $P < 0.001$, $\eta^2 = 0.35$, **Fig. 1**) and group by test side interaction ($F[4,90] = 12.1$, $P < 0.001$, $\eta^2 = 0.35$), but no significant effect of test side ($F[2,90] = 3.0$, $P = 0.063$). Post hoc tests revealed that both patient groups rated touch as significantly less pleasant than controls on the affected (PHNP: $p_{corr} < 0.001$, d = 1.9; CRPSP: $p_{corr} < 0.001$, d = 2.0) and contralateral side (PHNP: $p_{corr} = 0.004$, d = 1.2; CRPSP: $p_{corr} = 0.002$, d = 1.3). Only PHNP rated touch significantly less pleasant on the reference side (PHNP: $p_{corr} = 0.005$, d = 1.1; CRPSP: $p_{corr} = 1$). Furthermore, PHNP rated stroking on the reference side as significantly less pleasant than CRPSP ($p_{corr} = 0.002$, d = 1.3),

Table 1

Descriptive data of the sample.

	PHN (n = 16)		CRPS (n = 19)		Control (n = 22)		Group difference
	M	SD	M	SD	M	SD	
Age	72.88	8.76	56.53	13.40	60.86	11.40	PHN > CRPS, d = 1.5, $p_{corr} < 0.001$ PHN > control, d = 1.5, $p_{corr} < 0.001$
Pain (PD-Q)	23.08	13.70	31.31	17.43	7.77	8.29	PHN > control, d = 1.4; $p_{corr} = 0.015$ CRPS > control, d = 1.9; $p_{corr} = 0.006$
Depression (PHQ)	1.67	2.19	2.29	3.26	0.86	1.46	n.s.
Anxiety (PHQ)	0.07	0.26	0.11	0.32	0.05	0.22	n.s.
Sex	**n**	**%**	**n**	**%**	**n**	**%**	
Female	7	43.8	15	78.9	16	62.5	Female to male imbalanced in CRPS; $P = 0.008$
Male	9	56.2	4	21.1	6	37.5	

Significance tests for group differences are displayed in the last row (*t* test for metric data and χ^2 test for categorical data). The level of significance is set at $P < 0.05$, Bonferroni corrected by factor 3. For significant group differences, the effect size is reported as Cohen d.

CRPS, complex regional pain syndrome; PD-Q, painDETECT score questionnaire; PHN, postherpetic neuralgia; PHQ, Patient Health Questionnaire.

while there was no difference between both groups for the contralateral or affected side (each $P = 1$). Interindividual variability in pleasantness ratings was higher in controls than that in patients on the affected side and contralateral side (affected: controls 5.55 ± 2.90, PHNP 0.21 ± 2.63, CRPSP 0.33 ± 1.71; contralateral: controls 5.63 ± 2.85, PHNP 2.38 ± 2.71, CRPSP 2.36 ± 1.71). On the reference side, interindividual variability in pleasantness ratings was comparable for CRPSP and controls, but was lower for PHNP (controls 5.68 ± 2.85; PHNP 2.71 ± 2.20; CRPSP 5.65 ± 2.72).

For pain ratings, there was no significant effect of test side ($F[2,90] = 3.0$, $P = 0.90$), but there was a significant effect of group ($F[2,45] = 7.1$, $P = 0.002$, $\eta^2 = 0.24$) and a significant group by test side interaction effect ($F[4,90] = 10.9$, $P < 0.001$, $\eta^2 = 0.33$). Post hoc tests revealed that patients and controls did not differ significantly in pain ratings on the reference (PHNP: $p_{corr} = 1$; CRPSP: $p_{corr} = 1$) or on the contralateral side (PHNP: $p_{corr} = 1$; CRPSP: $p_{corr} = 0.54$). Patients with PHN rated stroking on the affected side ($p_{corr} < 0.001$, $d = 1.6$) as significantly more painful than controls, CRPSP did not differ from controls ($p_{corr} = 0.13$) (affected: controls 0.35 ± 0.88, PHNP 3.28 ± 2,73, CRPSP 1.07 ± 1.85; contralateral: controls 0.22 ± 0.60, PHNP 0.26 ± 0.41, CRPSP 0.04 ± 0.08; and reference: controls 0.27 ± 0.65, PHNP 0.24 ± 0.41, CRPSP 0.07 ± 0.14).

For intensity ratings, there was no significant effect of test side, but there was a significant group by test side interaction effect ($F[4,90] = 2.5$, $P = 0.049$). Post hoc tests did not reveal any significant difference after Bonferroni correction. Interindividual variability in intensity ratings was almost similar in controls and patients with pain (Supplementary Material 1, available at http://links.lww.com/PR9/A113).

3.2. Effect of velocity in patients and controls (hypothesis B)

For *healthy participants*, pleasantness ratings followed a quadratic term ($F[1,21] = 14.5$, $P = 0.001$, $\eta^2 = 0.41$, compare **Fig. 2**), and there was no significant side by velocity interaction ($F[8,14] = 0.34$, $P = 0.80$). By contrast, *PHNP* ratings did not follow a quadratic term ($F[1,14] = 2.4$, $P = 0.15$). The absence of a significant side by velocity interaction ($F[8,7] = 1.7$, $P = 0.114$) indicates that PHNP did not show velocity-dependent ratings of pleasantness on any test side. For patients with CRPS, results were test side specific: The quadratic term turned to be significant ($F[1,12] = 10.0$, $P = 0.008$, $\eta^2 = 0.45$), but there was a significant side by velocity interaction ($F[8,5] = 2.3$, $P = 0.027$, $\eta^2 = 0.16$). For the affected side, the quadratic term explained as much variance of pleasantness ratings ($F[1,12] = 8.8$, $P = 0.012$, $\eta^2 = 0.42$) as for the contralateral side ($F[1,12] = 8.1$, $P = 0.015$, $\eta^2 = 0.40$). For the reference side, CRPSP showed no significant quadratic term ($F[1,12] = 0.8$, $P = 0.40$, $\eta^2 = 0.06$).

For comparison of quadratic term between groups, a joint analysis was performed. This revealed a significant side by group interaction ($F[4,13590] = 12.2$, $P < 0.001$, $\eta^2 = 0.35$), but no significant velocity by group interaction ($F[8,180] = 0.6$, $P = 0.70$, $\eta^2 = 0.025$) and no velocity by side and group ($F[16,360] = 1.31$, $P = 0.24$, $\eta^2 = 0.06$) interaction.

Intensity ratings did not differ in relation to velocity and we did not observe a significant main effect of velocity or a significant velocity by side interaction (Supplementary Material 2, Supplementary Fig. 1, available at http://links.lww.com/PR9/A113).

3.3. Quantitative sensory test battery and touch perception

Overall, participants' mean pain ratings on the affected side correlated negatively to the mean pleasantness at the same side ($r = -0.461$, $P < 0.001$) and positively to the mean intensity ($r = 0.349$, $P = 0.014$). The intensity ratings did not relate to the pleasantness ratings ($r = 0.057$, $P = 0.68$). For the reference and contralateral side, no significant correlations were observed.

When comparing z-standardized QST data of both patients groups, sensory abnormalities were observed (compare **Figs. 3 and 4**). In particular, 58.3% of CRPSP and 71.4% of PHNP experienced DMA on the affected side.

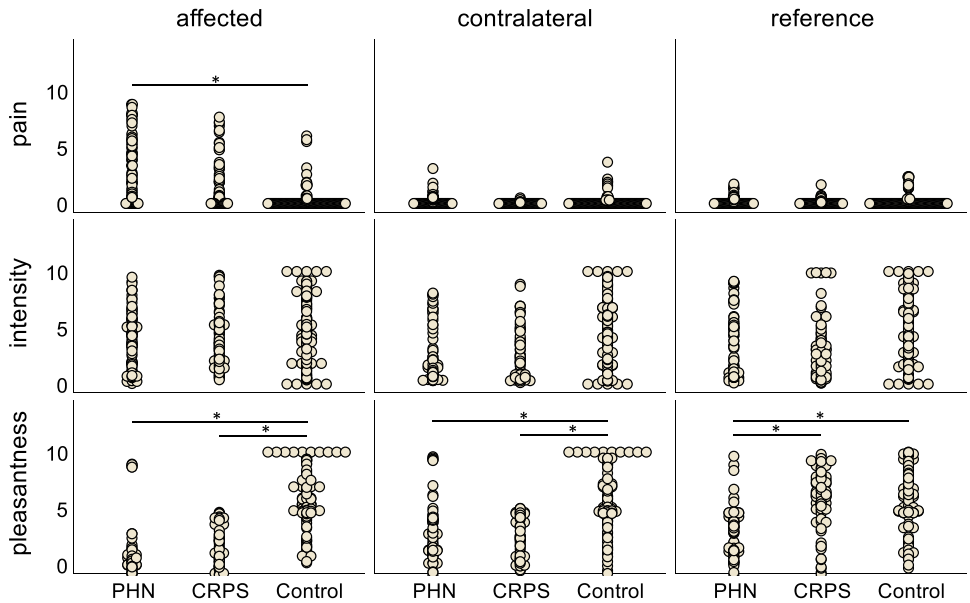

Figure 1. Perceived quality of stroking in dependence of test side and group. One dot represents the rating of one individual per test side and velocity. Ratings are averaged over the 3 repetitions of velocity and rounded for visualization purpose. Significant effects are highlighted by asterisk, *y*-axis shows values of perceived pleasantness, intensity, and pain on visual analogue scales for pleasantness (−10 to 10: very unpleasant to very pleasant), intensity (0–10: not at all intense to very intense), and pain (0–10: not at all painful to very painful).

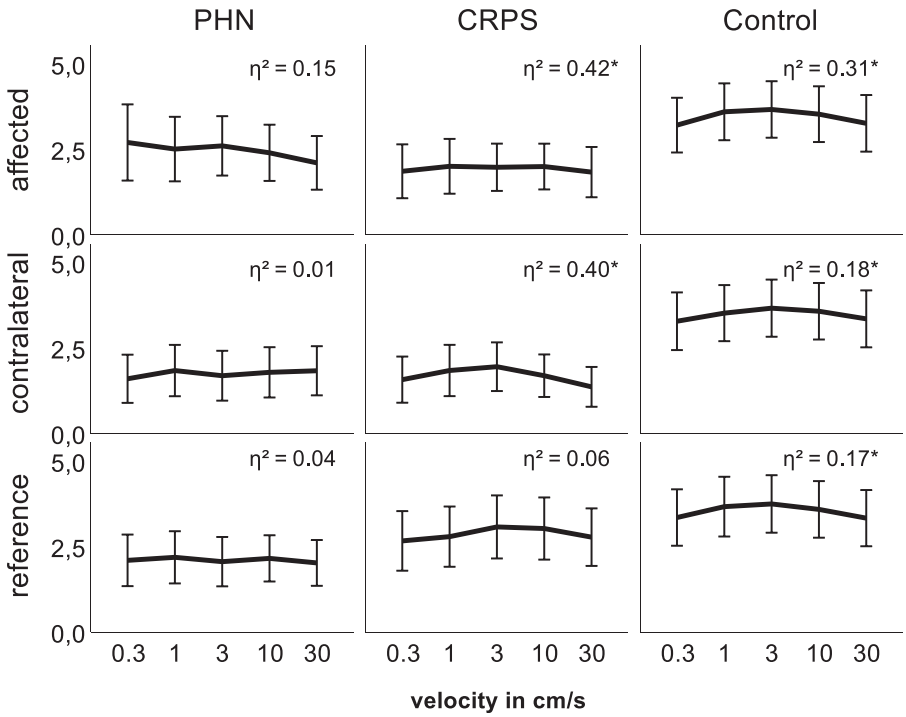

Figure 2. Perceived pleasantness of stroking in relation to the stroking velocity. Group averaged ratings are presented for each test side and group. Effect sizes of the quadratic term are indicated and significant effects are highlighted by asterisk. Error bars indicate the 95% confidence interval, *y*-axis shows values of perceived pleasantness on a visual analogue scale for pleasantness (−10 to 10: very unpleasant to very pleasant). CRPS, complex regional pain syndrome; PHN, postherpetic neuralgia.

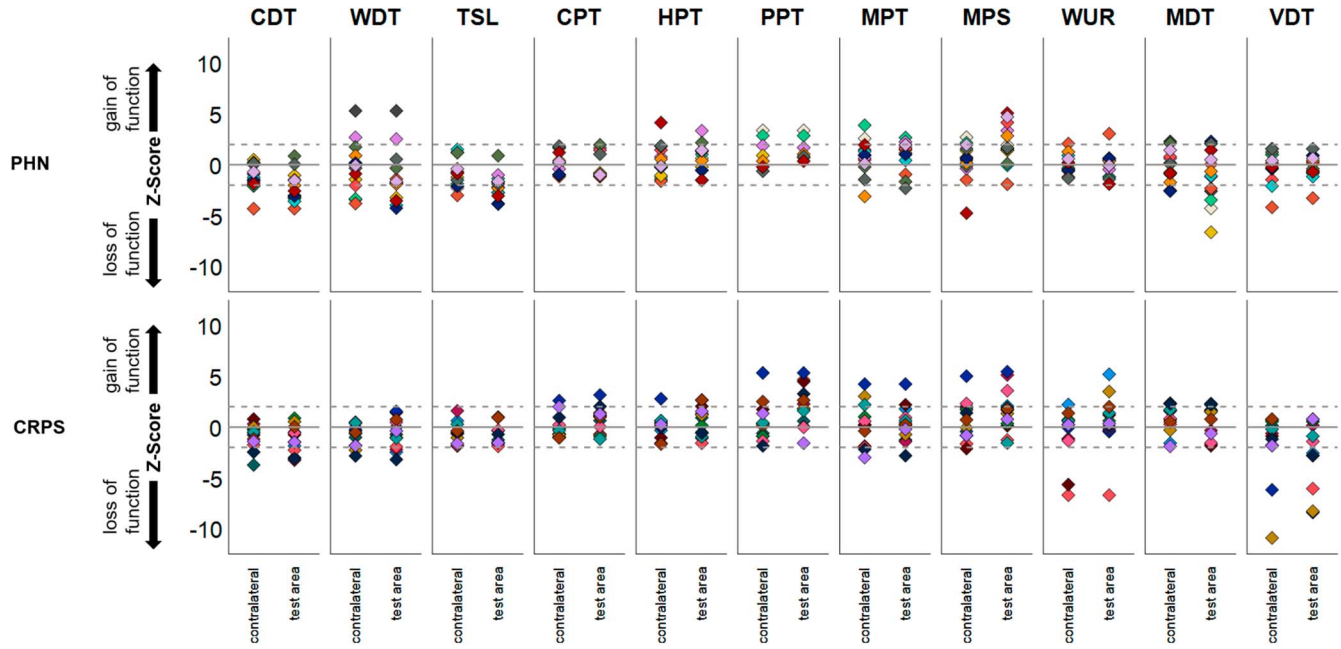

Figure 3. Z-transformed QST data of patients with PHN and CRPS on the contralateral and affected test side. Z-values are displayed on the *y*-axis, the dashed lines indicate the range of 2 SD above/below the mean normative values as indicated in the manual. Each patient is visualized with one color. Z-values were calculated in reference to the individual sex, age, and location. To represent "gain of function" and "loss of function," the Z-scores for CDT, WDT, TSL, HPT, PPT, MPT, and MDT were multiplied by (−1) (Rolke et al. 2006). Reference values were taken from the following studies: Pfau DB et al. (2014). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): reference data for the trunk and application in patients with chronic postherpetic neuralgia. PAIN 155:1002–1015 and Rolke R, et al. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. PAIN 123:231–243.[14,24] CDT, cold detection threshold; CRPS, complex regional pain syndrome; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; PHN, postherpetic neuralgia; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; WDT, warm detection threshold.

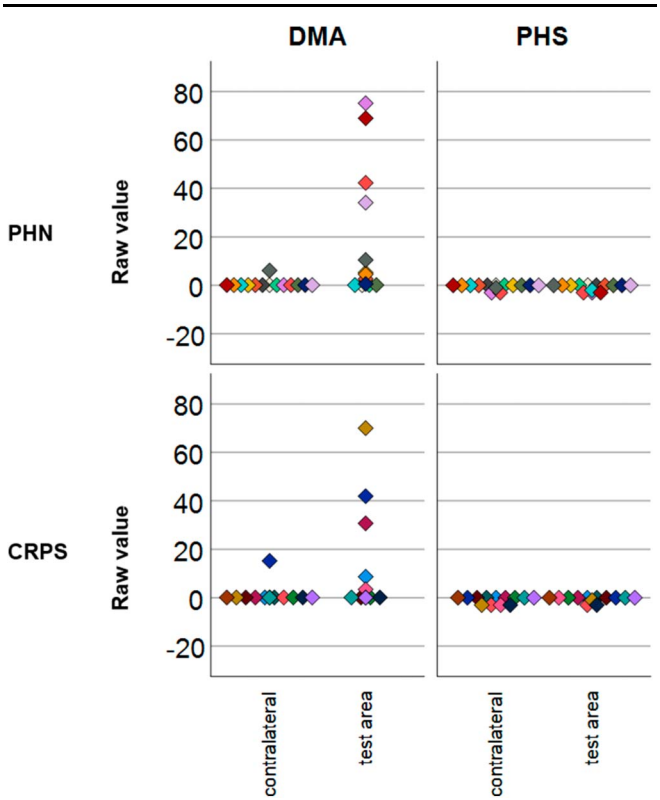

Figure 4. Dynamic mechanical allodynia (DMA) and paradoxical heat sensations (PHSs) of patients with PHN and CRPS on the contralateral and affected test side. Raw values are displayed, PHSs are displayed as occurrence of 3 tests, and PHS is only displayed for patients with pain on the trunk and feet. PHS values were multiplied by (−1) according to the concept that PHS represent a loss of thermodiscriminative function (Rolke et al. 2006). CRPS, complex regional pain syndrome; PHN, postherpetic neuralgia.

Between groups, we found significant differences in z-standardized QST data on the affected side for thermal sensory limen (PHNP −2.08 ± 1.21; CRPSP −0.92 ± 1.44; $P = 0.011$) and VDT (PHNP −0.21 ± 1.12; CRPSP −2.34 ± 3.32 $P = 0.046$) and no significant differences for other parameters or for the contralateral side.

Within groups, CRPSP showed significant side differences for mechanical pain sensitivity (affected 1.64 ± 2.13, contralateral 0.71 ± 1.95, $P = 0.022$), WUR (affected 0.50 ± 2.73, contralateral −0.77 ± 2.61, $P = 0.039$), and PPT (affected 2.08 ± 2.03, contralateral 0.50 ± 1.92, $P = 0.017$).

Patients with PHN showed significantly different cold detection threshold (affected −2.34 ± 1.46, contralateral −1.22 ± –1.26; $P = 0.004$), warm detection threshold (affected −1.24 ± –2.61, contralateral −0.31 ± 2.51; $P = 0.013$), paradoxical heat sensation (affected −0.79 ± 0.35, contralateral −0.50 ± –1.09; $P = 0.009$), cold pain threshold (affected −0.27 ± 1.20, contralateral 0.14 ± 1.10; $P = 0.023$), WUR (affected −0.05 ± 1.22, contralateral 0.01 ± 0.94; $P = 0.018$), VDT (affected −0.21 ± 1.20, contralateral −0.12 ± 1.60; $P = 0.012$), and PPT for the test side and contralateral side (1.55 ± 1.16, contralateral 1.22 ± 1.53, $P = 0.002$). For details see Supplementary Table 2 and 3 (available at http://links.lww.com/PR9/A113).

In patients with pain, there was a significant correlation between overall pleasantness ratings for the reference side and PPT ($r = 0.670$, $P = 0.001$). For the affected side, overall pleasantness ratings correlated inversely to DMA ($r = −0.429$, $P = 0.0326$). Comparing results of QST with perceived touch, PHNP showed an inverse correlation between pleasantness and DMA on the affected side.

4. Discussion

In line with hypothesis A, healthy controls showed significantly higher degrees of pleasantness and less pain than PHNP and CRPSP when gently brushed over the skin. Furthermore, CT function in chronic PHNP seemed reduced in comparison with healthy controls (hypothesis B).

The observation that PHNP present reduced pleasantness ratings on each tested side matches the pathophysiology of PHN, which frequently leads to C-fiber damage.[41] After internal reactivation of hibernating varicella-zoster virus in sensory ganglia cells, neuroimmune–glia interactions modulate the inflammatory process critically and can result in peripheral and consecutively central sensitization for pain.[43] Pain sensitization occurs on the affected side, but during the chronification process, the central nervous involvement leads to contralateral and generalized sensitization phenomena and structural changes because epidermal neurite loss of small nerve fibers has been shown contralaterally.[3,18,35] The observed reduction in interindividual variability in pleasantness ratings as compared to controls may in part be a result of this. Our data support previous findings in patients with fibromyalgia, where a reduced CT function in patients with chronic pain was suggested,[6] although the authors mentioned an altered opioid functioning as a possible underlying mechanism.

In line with hypothesis B, PHNP do not show the typical inverted U-shaped curve of C-tactile–targeted stroking appreciation, which is instead visible in controls. This observation implies a disturbed CT function and demonstrates a dominant injury of C-fiber neurons and less damage to A-fiber neurons in this disease.[41]

Patients with CRPS rated stroking not only on the affected but also on the contralateral side as significantly less pleasant than controls. On the affected side, the reduced pleasant perception of touch can, according to hypothesis A, be attributed to altered morphology and function of C fibers because minimal distal nerve injury affecting C fibers in CRPSP has been reported.[34] In addition, bilaterally reduced intraepidermal nerve fiber density has been shown in unilateral CRPS, supporting our data of bilateral reduction in touch-mediated pleasantness as a result of C-fiber functional deficit.[39]

However, the typical inverted U-shaped curve of pleasantness was preserved in CRPS on the affected side and contralateral side. Therefore, it is probable that reduced pleasant tactile perception is also a result of central nervous system remodeling. Altered tactile localization and spatiotemporal integration have been shown in CRPSP, and evidence for changes in the cortical representation of tactile sensory stimuli support this observation.[38,46] Furthermore, experimental data on peripheral nerve injury show that cortical astrocytes prime the induction of spine plasticity and mirror image pain by synaptic remodeling and cortical reorganization in the primary somatosensory cortex. According to this, we suggest that similar central nervous synaptic restructuring could induce impaired CT function contralaterally in both the PHN and CRPS group and could further alter velocity-dependent pleasantness perception in other body parts, as seen on the reference side in CRPSP.[17]

A direct increase in the firing rate with stroking velocity has been reported for myelinated sensory afferents but not for CT fibers.[25] Replicating this observation, our results do not show velocity-dependent intensity ratings, neither in controls nor in

patients. Overall, intensity perception did not significantly differ between patients and controls. This is in line with a previous study, suggesting a predominant epidermal unmyelinated nerve fiber loss in patients with ophthalmic PHN.[48] The predominant small fiber loss might explain that intensity perception remains mainly unaffected assuming discrete and possibly subclinical Aβ-fiber dysfunction.

In chronic pain conditions such as CRPS or PHN, central maladaptation processes and peripheral hyperexcitability are believed to support and sustain DMA.[4] In our study, DMA correlated negatively with overall pleasantness ratings in patients with pain. A contribution of CT fibers to DMA has been shown in experimental muscle and intradermal pain.[32] This work describes a role of CT fibers in pain processing. By blocking CT input, the authors showed extinction of allodynia, whereas blocking myelinated fibers did not change it. This is in line with the finding that a conduction block of A fibers eliminated only touch-evoked pain and blockade of C-fiber excitation abolished touch-evoked and continuous pain.[20] This supports a central and peripheral component of DMA. In line with previous research, CT fibers seem to lose their ability to transmit pleasant tactile experiences in allodynic conditions such as PHN and CRPS, potentially through the above-mentioned central and peripheral mechanisms.[22]

However, a statistically significant difference for velocity-dependent pleasantness ratings has not been found between the groups of patients with pain and controls. Because a statistical trend is visible, this may be due to low case numbers.

While comparing results of quantitative sensory tests with perceived touch pleasantness, PHNP showed an inverse correlation between pleasantness and dynamic mechanical allodynia on the affected body area.

The inverse correlation between dynamic mechanical allodynia and perceived pleasantness after gentle stroking corresponds to previous results.[23] In addition, a significant correlation between stroking-related pleasantness and PPTs has been shown, and models in which peripheral sensitization maintains altered processing of sensory stimuli have been proposed.[15] These findings combined suggest that peripheral sensitization might support unpleasant tactile sensations during CT-optimal stimulation and that the absence of peripheral sensitization might go along with pleasant CT perception.

Interestingly, the quadratic term of perceived pleasantness did not differ significantly between the groups. We did however find a tendency to a significant group by velocity interaction effect of pleasantness perception ($P = 0.05$) and no quadratic term for both pain groups. As the sample size in this study is relatively small, future studies with more participants might find significant differences. This theory is supported by several participants with altered thermal sensory properties, which are C fiber transmitted (compare **Fig. 3**). It is further underpinned by comparative research of QST properties and epidermal nerve fiber densities.[39]

Besides morphological changes on peripheral and central nervous levels, one must also consider emotional and contextual influences on the perceived pleasantness of touch. There is growing evidence that not only "bottom up" but also "top down" information contributes to affective attributions of touch. Positive expectations towards touch can improve its perceived pleasantness[9,12,28] while experimentally altered perception of the body can decrease its perceived pleasantness.[19] It seems likely that negative expectations and experiences towards touch, such as in allodynia, could negatively affect touch perception.

Overall, we have not obtained typical physiological CT-rating patterns in the PHN group, indicating altered CT function. For CRPSP, CT-rating patterns reflected, at least in part, physiological values. As laid out above, both peripheral and central effects are likely to play a role in the altered touch-mediated pleasantness perception of the chronic pain states investigated here. In PHNP, peripheral C-fiber damage is evident. In PHNP and especially in CRPSP, central sensitisation and neuronal reorganisation could affect C-fiber function and touch sensation.

Our study has several limitations that should be noted. Controls differ significantly in age from PHNP. Confounders cannot be excluded when using QST because some measures of it (eg, WUR) do not lie within the range of previously published data. CT-optimized stroking was delivered by both a human and a robot, and the psychophysiological data are subjective to the participants. Furthermore, the study comprised relatively few test subjects. To address these limitations, further studies enrolling more patients and involving more objective measurements, such as epidermal nerve fiber density, laser-evoked, and contact heat–evoked potentials, are necessary.

Disclosures

The authors declare that there is no conflict of interest.

Because of regulations of the ethics committee, the full data cannot be made available publicly. However, data access will be provided to other researchers on request.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A113.

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