# Warm and cold complex regional pain syndromes: Differences beyond skin temperature?

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## Differences beyond skin temperature?

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### ABSTRACT

**Objective:** To investigate clinical differences in warm and cold complex regional pain syndrome (CRPS) phenotypes.

**Background:** CRPS represents inhomogeneous chronic pain conditions; approximately 70% patients with CRPS have "warm" affected limbs and 30% have "cold" affected limbs.

**Methods:** We examined 50 patients with "cold" and "warm" CRPS (n = 25 in each group). Both groups were matched regarding age, sex, affected limb, duration of CRPS, and CRPS I and II to assure comparability. Detailed medical history and neurologic status were assessed. Moreover, quantitative sensory testing (QST) was performed on the affected ipsilateral and clinically unaffected contralateral limbs.

**Results:** Compared with patients who had warm CRPS, patients who had cold CRPS more often reported a history of serious life events ($p < 0.05$) and chronic pain disorders ($p < 0.05$). In cold CRPS, the incidence of CRPS-related dystonia was increased ($p < 0.05$), and cold-induced pain had a higher prevalence ($p < 0.01$). Furthermore, QST revealed a predominant sensory loss in patients with cold CRPS ($p < 0.05$). In contrast, patients with warm CRPS were characterized by mechanical hyperalgesia ($p < 0.05$) in the QST of affected limbs.

**Conclusion:** Our results indicate that warm and cold complex regional pain syndromes (CRPS) are associated with different clinical findings, beyond skin temperature changes. This might have implications for the understanding of CRPS pathophysiology. *Neurology*® 2009;72:505–512

### GLOSSARY

**A** = anxiety; **ANOVA** = analysis of variance; **CDT** = cold detection threshold; **CPT** = cold pain threshold; **CRPS** = chronic regional pain syndrome; **D** = depression; **DMA** = dynamic mechanical allodynia; **HADS** = Hospital Anxiety and Depression Scale; **HPT** = heat pain threshold; **MDT** = mechanical detection threshold; **MPS** = mechanical pain sensitivity; **MPT** = mechanical pain threshold; **NRS** = numeric rating scale; **NS** = not significant; **PHS** = paradoxical heat sensations; **PPT** = pressure pain threshold; **TSL** = thermal sensory limen; **QST** = quantitative sensory testing; **VDT** = vibration detection threshold; **WDT** = warm detection threshold; **WUR** = windup ratio.

Complex regional pain syndromes (CRPS) might develop after limb trauma.[1] Patients with CRPS show signs of peripheral inflammation and CNS disturbances including movement disorder,[2] body perception disturbances,[3] and sympathetic dysfunction.[4] Considering the diversity of symptoms, it seems unlikely that CRPS is a homogeneous condition. It can be subdivided into CRPS I or II, depending on identification of peripheral nerve lesions.[1]

Another subclassification relies on predominating skin temperature at disease onset.[5] Most CRPS cases are primarily "warm," later turning into "cold" if CRPS becomes chronic. Yet approximately 30% have a decreased skin temperature from the beginning (primarily cold) and usually stay cold in CRPS course.[6] Warm skin fits the hypothesis that CRPS reflects exaggerated post-traumatic inflammation,[7] and cold skin should have a different etiology: alteration of sympathetic outflow[8] or vascular disturbances.[9] This differentiation is supported by the difficult treatment of primarily cold CRPS.[10]

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If pathophysiologies in warm and cold CRPS are different, different clinical symptoms should be present. Such clinical differences have not yet been described. Therefore, in this study patients with primarily warm and cold CRPS were matched for age, sex, presence of CRPS I or II, affected extremity, and duration of symptoms—confounders otherwise responsible for clinical differences. We focused on history, clinical signs, and sensory profiles.

**METHODS** **Subjects.** Patients were recruited from our CRPS outpatient clinic at the Neurological Department of the University Hospital Mainz, Germany. All patients fulfilled the revised diagnostic criteria as proposed by the International Association for the Study of Pain.[1]

Patients were immediately classified as primarily warm or primarily cold if 1) patients firmly stated that the initial skin temperature on the affected side was either increased or decreased and 2) if this statement was consistent with the skin temperature difference at the day of examination. Cases with inconsistent findings were excluded. As a measure of stability of this classification, approximately 80% of the patients were routinely reassessed 6 weeks later, and no switch between warm and cold had been observed. Patients provided written consent, and the study was approved by the local ethics committee.

From all patients investigated in our department within the last years (n = 163), all 25 primarily cold cases were selected. One of the authors (W.M.), who was not involved in patient recruitment, was supplied with a file containing information about age, sex, CRPS type, affected extremity, and duration of symptoms of all patients. Based solely on these data, he selected a matched group (n = 25) from the 98 primarily warm cases for further analysis.

We sought to investigate patients not treated for CRPS. This was not successful in cases with longer CRPS duration. However, for most of treatments before referral proof of efficacy is lacking and was also not reported by the patients. It is unlikely that clinical and quantitative sensory testing (QST; mainly thresholds) data are affected in a systematic manner. For details see table 1 and table e-1 on the *Neurology*® Web site at www.neurology.org.

**Clinical investigation.** All patients underwent a structured interview and detailed neurologic examination. In particular, we assessed the prevalence of other types of chronic pain, social conflicts, and known psychological comorbidities. Then, the patients completed the German versions of the Hospital Anxiety and Depression Scale and McGill Pain Questionnaire (MPQ).[11] The MPQ was chosen for pain assessment because of its frequent use in previous CRPS studies. After environmental adaptation (60 minutes), skin temperature was recorded at the volar aspects of the affected and unaffected extremity by an infrared thermometer.

**Quantitative sensory testing.** QST was performed according to the protocol of the German Research Network on Neuropathic Pain.[12] We examined the affected dorsum of the hand or foot. The corresponding mirror image site of the contralateral extremity served as a control. QST comprised the following detection and pain thresholds.

***Thermal sensation.*** We investigated detection thresholds for cold (CDT) and warm (WDT), a sequence of alternating cold and warm stimuli for the thermal sensory limen (TSL), cold pain threshold (CPT), and heat pain threshold (HPT). We used a thermotester equipped with a 2.8 × 2.8-cm Peltier thermode (TSA 2001-II, Medoc, Israel). Thresholds were assessed at a ramp rate of 1°C/second. During thermal testing, patients were asked to report paradoxical heat sensations (PHS).

***Mechanical sensation.*** Mechanical detection thresholds (MDTs) were investigated using von Frey filaments (Optihair2, Fruhstorfer, Marburg, Germany), and vibration detection thresholds (VDTs) were investigated at the processus styloideus ulnae or the internal malleolus using a 64-Hz Rydel-Seiffer tuning fork (average of three repetitions). Pressure pain thresholds (PPTs) were assessed at the thenar eminence or the instep using a handheld blunt pressure gauge device (1-$cm^2$ contact area; FDN200, Wagner Instruments, Greenwich, CT). Mechanical pain thresholds (MPTs) were obtained by using sets of calibrated pinpricks with a 0.25-mm flat top cylindrical tip and a series of seven forces (8 and 512 mN) geometrically spaced by a factor of 2 (The PinPrick, Department of Physiology, Mainz, Germany). Mechanical pain sensitivity (MPS) was assessed from stimulus response functions (5 repetitions of all pinprick forces). Dynamic mechanical allodynia (DMA) was assessed by moving a cotton swab, Q-Tip, or standardized brush (Somedic, Hörby, Sweden) over the painful skin.

**Statistical analysis.** For comparison with sensitivity of normal subjects, we contrasted the patient data to data from a recently published reference database using the same set of QST methods.[12] First, all data were transformed into standard normal distributions corrected for body region, sex, and age ($Z$ values).[13] $Z$ transformation allows the comparison of values independent of their physical dimensions. Increased sensitivity results in positive $Z$ scores, whereas decreased sensitivity results in negative $Z$ scores, expressed in units of SD of the control group. Statistical comparisons to reference data were made using a Web-based statistics program.[14]

**Table 1** Summary of study patients' characteristics

| | CRPS type | |
|---|---|---|
| | Primarily warm | Primarily cold |
| CRPS I/II | 23/2 | 23/2 |
| Sex, M/F | 8/17 | 6/19 |
| Age, y | 47 ± 8 | 45 ± 12 |
| Familial history of CRPS, positive/negative | 2/23 | 2/23 |
| Duration of CRPS, wk | 21 ± 3 | 22 ± 3 |
| Cause of CRPS | | |
| Limb fracture | 10 | 10 |
| Sprain | 4 | 10 |
| After surgery | 8 | 4 |
| No event identified | 3 | 1 |
| Affected body region, hand/foot | 16/9 | 16/9 |

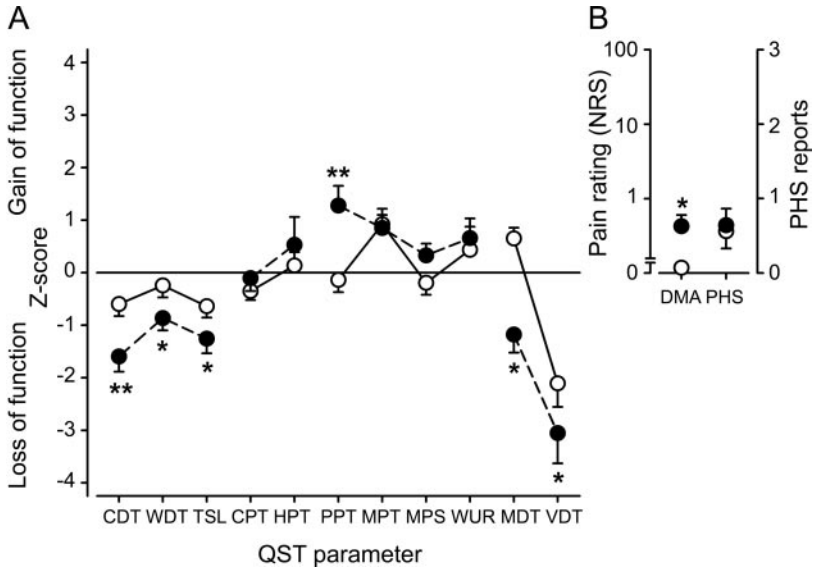
CRPS = complex regional pain syndrome.

**Table 2** Detailed comparison of patients with warm and cold CRPS regarding history, HADS scores, pain characteristics, McGill pain rating index, and motor and autonomic disturbances

| | Warm CRPS, n = 25, no. (%) | Cold CRPS, n = 25, no. (%) | $\chi^2$ | p Value |
|---|---|---|---|---|
| Patient history | | | | |
| Psychosomatic disorders | 4 (16) | 9 (36) | 2.60 | NS |
| Serious life events: family conflict, death of relative, job-related problems | 4 (16) | 10 (40) | 3.57 | <0.05 |
| Chronic pain history* | 8 (32) | 15 (60) | 3.95 | <0.05 |
| Headache | 3 | 3 | | |
| Low back pain | 4 | 8 | | |
| Painful joints | 0 | 3 | | |
| Neuropathic pain: CRPS, neuralgia | 2 | 5 | | |
| HADS-A | 7.4 ± 0.9 | 5.9 ± 0.9 | 0.53 (t value) | NS |
| HADS-D | 6.7 ± 0.9 | 5.3 ± 0.8 | 0.48 (t value) | NS |
| Pain and hyperalgesia | | | | |
| Pain at rest | 22 (88) | 18 (72) | 2.00 | NS |
| McGill PRI | 24.2 ± 3.0 | 22.4 ± 3.9 | 0.30 (t value) | NS |
| Amplification of pain | | | | |
| By lowering | 16 (64) | 10 (40) | 2.89 | NS |
| By striking | 19 (76) | 16 (64) | 0.25 | NS |
| By physical effort | 20 (80) | 17 (68) | 0.94 | NS |
| By night | 13 (52) | 12 (48) | 0.08 | NS |
| By upset | 5 (20) | 6 (24) | 0.12 | NS |
| By temperature | | | | |
| Cold | 4 (16) | 15 (60) | 10.27 | <0.002 |
| Warm | 7 (28) | 6 (24) | 0.10 | NS |
| Allodynia | 12 (48) | 10 (40) | 0.33 | NS |
| Motor disturbances | | | | |
| Weakness | 19 (76) | 12 (48) | 4.16 | <0.05 |
| Movement initiation difficulties | 8 (32) | 10 (40) | 0.35 | NS |
| Dystonia | 0 (0) | 4 (16) | 4.35 | <0.05 |
| Autonomic disturbances | | | | |
| Temperature difference | | | | |
| Warm | 20 (80) | 2 (8) | 26.30 | <0.0001 |
| Cold | 2 (8) | 20 (80) | | |
| Skin temperature, °C | | | | |
| Ipsilateral | 31.1 ± 0.7 | 28.7 ± 1.0 | 1.97 (t value) | (0.056) |
| Contralateral | 30.1 ± 0.5 | 29.7 ± 0.8 | 0.43 (t value) | NS |
| Difference: ipsilateral – contralateral | +1.0 ± 0.4 | −1.0 ± 0.4 | 3.16 (t value) | <0.01 |
| Skin color | | | 13.34 | <0.01 |
| Reddish | 9 (36) | 1 (4) | 8.00 | <0.005 |
| White | 3 (12) | 0 (0) | 3.19 | 0.07 |
| Cyanotic | 8 (32) | 18 (72) | 8.01 | <0.005 |
| No difference | 5 (20) | 6 (24) | 0.12 | NS |
| Edema | 22 (88) | 18 (72) | 2.00 | NS |
| Sweating | 16 (64) | 14 (56) | 0.33 | NS |
| Trophic changes: hair/nail | | | 0.40 | NS |
| Increased | 7 (28) | 9 (36) | 0.37 | NS |
| Decreased | 4 (16) | 4 (16) | 0.00 | NS |

*Chronic pain history: patients may have more than one type of chronic pain.
CRPS = chronic regional pain syndrome; HADS = Hospital Anxiety and Depression Scale; NS = not significant; A = anxiety; D = depression.

**Figure 1** QST profile of primarily warm CRPS: Affected and contralateral side vs controls




(A) Quantitative sensory testing (QST) *Z* profiles from patients with primarily warm complex regional pain syndrome (CRPS). Vertical line (zero) indicates mean of age- and sex-matched healthy controls. Positive *Z* scores indicate gain of function, and negative *Z* scores indicate loss of function. (B) Absolute values of dynamic mechanical allodynia (DMA) and paradoxical heat sensations (PHS). The CRPS side is indicated by filled circles, and the contralateral limbs are indicated by open circles. Asterisks indicate significant differences between affected and unaffected limb: $^{**}p < 0.01$, $^{*}p < 0.05$. NRS = numeric rating scale; CDT = cold detection threshold; WDT = warm detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; PPT = pressure pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = windup ratio; MDT = mechanical detection threshold; VDT = vibration detection threshold.

All further statistical calculations were performed using STATISTICA for Windows (StatSoft Inc., Tulsa, OK). Differences between warm and cold CRPS were analyzed by $\chi^2$ statistics for ordinal data (categorical variables) or by *t* tests for normally distributed variables.

To compare QST in patients with warm and cold CRPS, the affected and unaffected extremity, three-way repeated-measures analyses of variance (ANOVAs) were separately calculated for comparison of sensory (CDT, WDT, TSL, VDT, MDT) and nociceptive QST values (CPT, HPT, PPT, MPT, MPS). Post hoc analysis was performed as planned comparisons (least significant difference tests).

PHS and DMA were analyzed separately by nonparametric statistics. Ipsilateral (according to the affected limb) and contralateral sides of the body were compared using the Wilcoxon matched-pairs signed rank test, and warm and cold CRPS were compared using the Mann–Whitney *U* test.

All data are presented as mean ± SEM, and $p < 0.05$ was considered significant.

## RESULTS

**Patients' history and clinical signs.** At inspection, patients with warm CRPS had predominantly reddish skin (9/25), and patients with cold CRPS had bluish skin (18/25) ($p < 0.01$). Skin temperature difference (ΔT affected − unaffected) was positive (i.e., warmer) in the warm CRPS group (+1.0° ± 0.4°C) and negative (i.e., colder) in the cold group (−1.0° ± 0.4°C) ($p < 0.01$).

There was a trend for more challenging life events (death of a close relative, serious family and work-related problems) associated in time with the trauma in patients with cold CRPS (10/25) vs warm CRPS (4/25) ($p = 0.059$). Furthermore, patients with cold CRPS more often report chronic pain disorders (mostly headache or low back pain) unrelated to CRPS (15/25 vs 8/25, $p < 0.05$). Psychiatric comorbidity (anxiety and depression) was not different between the groups.

Patients with warm and cold CRPS reported different types of temperature-induced pain. Few patients with CRPS (warm: 7/25 vs 6/25, not significant) explicitly stated an increase of pain and symptoms in warm environment, and patients with cold CRPS frequently reported a diminished cold tolerance (15/25), which rarely occurred in warm CRPS (4/25) ($p < 0.01$).

The feeling of "motor weakness" was more prevalent in warm CRPS (19/25 vs 12/25, $p < 0.05$), whereas post-traumatic movement disorder (dystonia) could only be found in cold CRPS (4/25 vs 0/25, $p < 0.05$).

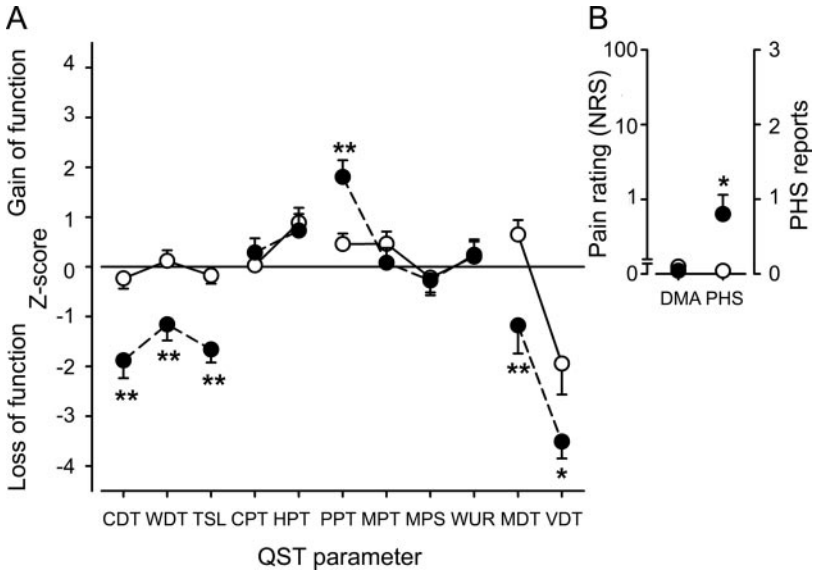
Details of results and statistical values are shown in table 2.

**Quantitative sensory testing.** Patients with warm CRPS were less sensitive in the affected side when nonnociceptive QST was compared with reference data in CDT ($t = -4.54$, $p < 0.001$), WDT ($t = -2.82$, $p < 0.01$), TSL ($t = -3.61$, $p < 0.001$), and VDT ($t = -5.00$, $p < 0.001$). In the nociceptive QST, they were more sensitive (hyperalgesic) for MPT ($t = 2.57$, $p < 0.05$) and PPT ($t = 3.01$, $p < 0.01$). Contralateral changes were less distinct: increased TSL ($t = -2.17$, $p < 0.05$), MDT ($t = -2.57$, $p < 0.01$), and VDT ($t = -4.30$, $p < 0.001$) indicated that loss of sensation also occurred in the apparently unaffected limb, whereas decreased MPT ($t = 3.30$, $p < 0.05$) indicated hyperalgesia (figure 1).

In patients with cold CRPS, sensory changes were also more obvious in the affected limb: negative *Z* scores in CDT ($t = -4.59$, $p < 0.001$), WDT ($t = -3.03$, $p < 0.005$), TSL ($t = -5.02$, $p < 0.001$), and VDT ($t = -4.58$, $p < 0.001$) indicated sensory loss, and positive *Z* scores in PPT ($t = 4.61$, $p < 0.001$) indicated hyperalgesia. On the unaffected side, *Z* scores for VDT were negative ($t = -2.98$, $p < 0.01$), whereas HPT was positive, indicating hyperalgesia ($t = 2.47$, $p < 0.02$). The remaining data were not different from controls (figure 2).

The finding that the ipsilateral (i.e., CRPS) side showed more sensory abnormalities than the contralateral clinically unaffected side was confirmed by direct side-to-side comparisons. Most prominent was

**Figure 2** QST profile of primarily cold CRPS: Affected and contralateral side vs controls




(A) Quantitative sensory testing (QST) *Z* profiles from patients with primarily cold complex regional pain syndrome (CRPS). Vertical line (zero) indicates mean of age- and sex-matched healthy controls. Positive *Z* scores indicate gain of function, and negative *Z* scores loss of function. (B) Absolute values of dynamic mechanical allodynia (DMA) and paradoxical heat sensations (PHS). The CRPS side is indicated by filled circles, and the contralateral limbs are indicated by open circles. Asterisks indicate significant differences between affected and unaffected limb: $^{**}p < 0.01$, $^{*}p < 0.05$. NRS = numeric rating scale; CDT = cold detection threshold; WDT = warm detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; PPT = pressure pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = windup ratio; MDT = mechanical detection threshold; VDT = vibration detection threshold.

a reduction of sensitivity in nonnociceptive sensory modalities (CDT, WDT, TSL, MDT, and VDT) in the affected extremity, and hyperalgesia to blunt pressure. This pattern of sensory differences between affected and unaffected extremities was the same in cold and warm CRPS.

PHS were prevalent in the affected limb (20.7%, $p < 0.001$) but also in the contralateral limb (9.3%, $p < 0.05$) (side difference $p < 0.05$). When stratified for warm or cold CRPS and body side, PHS in the affected hand of cold CRPS (28%) were more frequent than any other combination (i.e., warm CRPS both hands and cold CRPS contralateral: 8.0%–13.3%, $p < 0.05$ each; figure 1).

The incidence of DMA was approximately 45% on the affected side. In warm CRPS, DMA (i.e., the amount of brush-evoked pain) on the CRPS side (0.42 ± 0.25) was increased as compared with the unaffected side (0.06 ± 0.06) ($p < 0.05$). In cold CRPS, neither the affected nor the unaffected side displayed significant DMA (0.01 ± 0.01 vs 0 ± 0). For details, see figures 1 and 2.

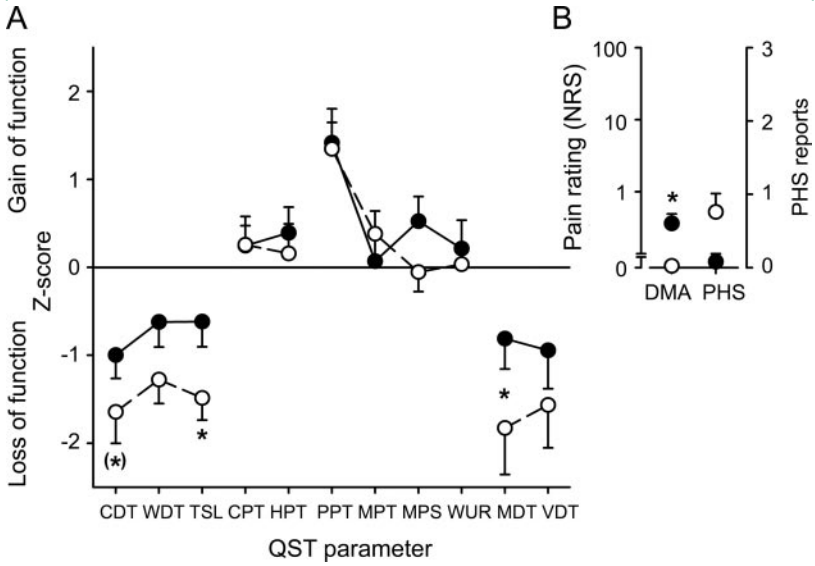
**Overall pattern of differences between warm and cold CRPS.** Three-way mixed-model ANOVA on the set of nonnociceptive QST values revealed no differences between CRPS type [cold vs warm CRPS: $F(1,48) = 0.41$, $p = 0.53$], but significant side differences [affected vs unaffected body side: $F(1,48) = 46.04$, $p << 0.0001$] and differences between the values for CDT, WDT, TSL, MDT, and VDT [$F(1,192) = 24.18$, $p << 0.0001$]. There was also an interaction between CRPS type and affected/contralateral side [$F(1,48) = 4.98$, $p < 0.05$]. Patients with cold CRPS exhibited a greater side difference in nonnociceptive QST values than warm CRPS (average across all tests: −1.56 ± 0.29 vs −0.79 ± 0.19 *z* values, $p < 0.05$). This difference was based on pronounced sensory loss on the ipsilateral side (cold vs warm CRPS across all tests: −1.88 ± 0.31 and −1.32 ± 0.24 *z* values, $p < 0.05$), but not on the contralateral side (−0.31 ± 0.14 vs −0.53 ± 0.16 *z* values, $p = 0.39$). These differences were found in all individual nonnociceptive thresholds and reached significance for MDT ($p < 0.02$) and TSL ($p < 0.05$).

In the mixed-model ANOVA on nociceptive CPT, HPT, PPT, MPT, and MPS, main effects exhibited a similar pattern with no impact of CRPS type [cold vs warm CRPS: $F(1,48) = 0.431$, $p = 0.58$; +0.42 vs + 0.32 *z* values, $p = 0.85$], significant side differences [$F(1,48) = 8.78$, $p < 0.005$], and differences between different nociceptive QST findings [$F(1,240) = 74.64$, $p < 0.001$]. The interaction between CRPS type and body side was not significant [$F(1,48) = 1.59$, $p = 0.214$]. However, there was an interaction between CRPS type and different nociceptive QST values [$F(1,192) = 3.08$, $p < 0.05$] based on hyperalgesia for CPT, HPT, and PPT in cold CRPS but less hyperalgesia to pinprick. Moreover, there was an interaction between body side and nociceptive QST values [$F(1,192) = 9.97$, $p << 0.0001$] based on a pronounced hyperalgesia to blunt pressure in the affected but not in the contralateral hand (+1.54 vs + 0.16 *z* values, $p << 0.0001$). There were no side differences in all other nociceptive QST findings (see figure 3 for details).

Neither on the affected nor on the unaffected side did PHS differ between warm and cold CRPS. In contrast, DMA was significantly higher on the affected side in warm CRPS than in cold CRPS, but no difference was found on the unaffected side.

**DISCUSSION** Warm and cold CRPS are defined according to skin temperature difference between affected and unaffected side at onset of CRPS.[15] In due CRPS course, this differentiation must not be fixed. Cold CRPS most often remains cold, whereas warm CRPS usually turns into cold when the CRPS becomes chronic[16]: regarding latest pathophysiologic findings, CRPS might represent an exaggerated in-

**Figure 3** QST side differences of primarily warm and cold CRPS




(A) *Z* profiles of the differences between affected and unaffected limbs for patients with warm complex regional pain syndrome (CRPS) (filled circles) and cold CRPS (open circles). Vertical (zero) line indicates the contralateral limb as reference. Positive *Z* scores indicate gain of function on affected side, and negative *Z* scores indicate loss of function. Patients with cold CRPS in general had a more pronounced loss of nonpainful sensations (multivariate analysis of variance, $p < 0.02$). (B) Difference between affected and unaffected limbs of absolute values of dynamic mechanical allodynia (DMA) and paradoxical heat sensations (PHS). Asterisks indicate significant differences between warm and cold CRPS side differences in the post hoc least significant difference test and the Mann–Whitney *U* test for DMA: *$p < 0.05$, (*)$p = 0.07$. QST = quantitative sensory testing; NRS = numeric rating scale; CDT = cold detection threshold; WDT = warm detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; PPT = pressure pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = windup ratio; MDT = mechanical detection threshold; VDT = vibration detection threshold.

flammation or an extensive CNS reorganization.[17] However, no conclusive concept for the synergy of these different pathophysiologic mechanisms leading to either warm or cold CRPS exists to date. The present results indicate similarities but also differences between both CRPS subtypes, which go beyond skin temperature. We found disparities regarding individual history, motor function, nociception (pain and hyperalgesia), and finally nonnociceptive sensations. These findings might contribute to a more comprehensive understanding of CRPS.

Trigger events for CRPS usually are limb traumas such as fractures or surgery. After such traumas, signs of inflammation, such as edema, hyperthermia, and pain, are frequently found, usually dwindling within some weeks. Previous studies and the present results suggest that particularly in warm CRPS, this posttraumatic inflammation is exaggerated. Proinflammatory cytokines are up-regulated, and anti-inflammatory cytokines are diminished.[18] This leads to peripheral sensitization, mainly of deeper tissues, and is clinically characterized by hyperalgesia to blunt pressure. Tumor necrosis factor $\alpha$ furthermore contributes to secondary central sensitization indicated by pinprick hyperalgesia and allodynia.[19] Both types of hyperalgesia were more pronounced in patients with warm CRPS. Furthermore, motor weakness in warm CRPS was not a true neurologic paresis, but a "giving-way" weakness due to pain and hyperalgesia during movement and muscle tension. In addition to hyperalgesia, cytokines also amplify neurogenic inflammation.[7,20] The major mediators of neurogenic inflammation are vasoactive neuropeptides responsible for vasodilatation and increased skin temperature,[21] further key features of warm CRPS.

In cold CRPS, obvious signs of exaggerated inflammation are lacking. Our results suggest that in these patients, the most important site of sensory and motor dysfunction might be either the spinal cord or the brain, for the following reasons:

1. Dystonia is part of the posttraumatic movement disorder in CRPS. In our patient cohort, dystonia was exclusively found in cold CRPS. The mechanisms of CRPS-related dystonia have not been fully explored, but recent studies suggest insufficient spinal motor-inhibitory $\gamma$-aminobutyric acid–mediated circuits, which might explain spreading of dystonia to previously unaffected extremities,[2] a fact that can only be explained by central changes.
2. Indications for CNS changes of pain processing in cold CRPS come from PHS and the exaggeration of CRPS pain in cold environments. PHS have been demonstrated in patients with multiple sclerosis[22] due to dysfunction of thermoreceptive projection neurons in the spinal cord. Hyperalgesia to cold has been found in patients with spinal cord injury associated with central neuropathic pain.[23]
3. CRPS I excludes major nerve lesions, and in CRPS II we performed QST outside the respective nerve territory. That is, there should be no or only minor[24] structural damage in the peripheral nervous system. Nevertheless, there was a loss of nonpainful sensitivity, significantly more prevalent in cold CRPS, and not only on the affected but also on the clinically unaffected contralateral side. We have recently been able to show that experimental pain in healthy subjects induces hypesthesia in the vicinity of the painful skin, suggesting presynaptic inhibition of spinal processing of innocuous information.[25] However, such a spinal suppression of nonnoxious processing is spatially restricted and thus contributes only to sensory loss on the CRPS side. Important to notice is that numbness of a painful extremity is not unique to CRPS. It has also been described in chronic myofascial pain, which is also charac-

terized by lacking peripheral skin nerve pathology.[25] However, suppression of spinal sensory processing could not account for the sensory loss in nonpainful limbs in CRPS.[26] Patients with CRPS have difficulties in detecting not only skin sensations, but also visual, auditory, and haptic information, leading to impaired self-perception.[27] All these phenomena must be assigned to altered sensory processing in the brain.[28] Thus, another explanation for the impairment of nonpainful sensations might be the shift of attention toward pain in our patients, which suppresses the perception of stimuli not related to pain and thus reinforcing the negative symptoms.[29]

4. Finally, patients with cold CRPS more often report a history of pain, disorder suggesting an increased risk for chronic pain as compared with warm CRPS. This risk may be genetically or psychologically ("pain proneness") determined or both. Coping with pain could also be determined by biography.[30] This view is supported by the higher incidence of serious life events in relation to the inciting trauma in patients with cold CRPS. Serious life events are stressors and insufficient coping with such a stressor during adolescence might lead to insufficient defense mechanisms in these patients. These insufficient mechanisms could maintain CRPS symptoms.[31]

It is unlikely that a full distinction between cold and warm CRPS can be achieved clinically. All changes "typical" of cold CRPS also apply to some extent to warm CRPS and vice versa. Nevertheless, the present results suggest that warm and cold CRPS might be representatives of peripheral and central CRPS pathophysiology. Future, i.e., longitudinal, studies should focus on how the predominance of one of these mechanisms translates to CRPS symptoms. Ideally, such studies include two further control groups: the first with temperature difference but without pain, and the second with pain but without temperature difference. Thereby the specificity of sensory abnormalities for CRPS can be addressed.

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