Pain thresholds and intensities of CRPS type I and neuropathic pain in respect to sex

Running head: Sex-specific pain intensity and thresholds

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Conflicts of interest

All authors declare that they have no conflicts of interest regarding the topic of this publication.

Background and aims

Healthy women have generally been found to have increased experimental pain perception and chronic pain has a higher prevalence in female as compared to male patients. However, no study has investigated whether pain intensity and pain perception thresholds are distinct or similar between sexes within various chronic pain entities. We investigated whether average pain intensities and pain thresholds assessed using quantitative sensory testing (QST) differed between women and men suffering from three distinct chronic pain conditions: Complex Regional Pain Syndrome (CRPS type I), peripheral nerve injury (PNI) or polyneuropathy (PNP), as compared to paired healthy volunteers.

Methods

QST data of 1252 patients (669 female, 583 male) with PNI (n=342), PNP (n=571) or CRPS (n=339), and average pain intensity reports from previously published studies were included. Absolute and z-values (adjusted for age and body region) of cold, heat, pressure (PPT) and pinprick pain thresholds were compared in generalized linear models with aetiology, duration of underlying pain disease and average pain intensity as fixed effects.

Results

Average pain intensity during the past four weeks did not differ between women and men, in both mean and range. In women absolute pain thresholds for cold, heat and pinprick were lower than in males across all diagnoses ($p<.05$). However, after z-transformation these differences disappeared except for PPT in CRPS ($p=.001$).

Discussion

Pain thresholds in patients show only minor sex differences. However, these differences mimic those observed in healthy subjects and do not seem to be linked to specific pathophysiological processes.

Significance

Female healthy participants and female patients with neuropathic pain conditions or CRPS I report lower pain thresholds compared to males, but pain intensity is similar and there is no sex difference in the extent to which the thresholds are altered in neuropathic pain or CRPS. Thus, the sex differences observed in various chronic pain conditions mimic those obtained in healthy participants, indicating that these differences are not linked to specific pathophysiological processes and are of minor clinical relevance.

Introduction

Since decades, gender differences have represented a major topic in pain research, although studies have found conflicting results (Bouhassira et al., 2008; Breivik et al., 2006; Fillingim et al., 2009; Friessem et al., 2009; Lamerato et al., 2016; Moulin et al., 2002; Reitsma et al., 2012; Torrance et al., 2006). The overall consensus is that healthy women appear to be more pain sensitive and demonstrate lower pain thresholds than men (Bartley and Fillingim, 2013; Fillingim et al., 2009; Mogil, 2012). In a recent review of more than 120 studies in healthy volunteers subjected to various experimental pain models, differences in pain thresholds were only minor to moderate (Mogil, 2012), while the majority of studies found female participants to have significantly lower pain tolerance to supra-threshold stimuli (Mogil, 2012; Racine et al., 2012). Within the DFNS (German Research Network on Neuropathic Pain) reference database of healthy controls, women were found to be significantly more pain sensitive using Quantitative Sensory Testing (QST) (Rolke et al., 2006), although the differences were small and could only be seen in group comparison. Consequently, it has been hypothesized that healthy women are more pain sensitive than men. Furthermore, higher prevalence in some chronic pain conditions has been reported in women as compared to men for, e.g., migraine, fibromyalgia, temporomandibular disorders (Bartley and Fillingim, 2013; Breivik et al., 2006; Davis et al., 2011; Fillingim et al., 2009; Friessem et al., 2009; Lamerato et al., 2016; Moulin et al., 2002; Reitsma et al., 2012), to a lesser extent CRPS (Demir et al., 2010; de Mos et al., 2007; Ott and Maihöfner, 2018; Pons et al., 2015; Roh et al., 2014) and some neuropathic pain conditions (Attal et al., 2011; Bouhassira et al., 2008; Torrance et al., 2006). It may therefore be hypothesized that women suffering from various chronic pain conditions have distinct QST-phenotypes in the form of allodynia and hyperalgesia as compared to men. However, while pain tolerance has been extensively studied in healthy volunteers and to some extent in chronic low back pain patients (Meints et al., 2018) and neuropathic pain patients (Arap et al., 2010; Goswami et al., 2016; Krämer et al., 2004; Schäfer et al., 2014; Selim et al., 2010), it has not been attempted to demonstrate if such gender or sex differences are based on variation in pathology or merely mirroring biological differences that can be found in healthy participants.

In the present study, we investigated whether pain thresholds based on QST and self-reported average pain intensity differed between women and men suffering from three distinct chronic pain conditions: Complex Regional Pain Syndrome type I (CRPS I), peripheral nerve injury (PNI), and painful polyneuropathy (PNP) as compared to paired healthy controls. As secondary objectives, we investigated if these potential differences reproduced the results found in healthy participants and whether they were linked to the etiology of the underlying pathology.

Methods

Consortia

Three consortia, which prospectively collected patients using identical study protocols, were involved in this data analysis: The **DFNS** (German Research Network on Neuropathic Pain; http://www.neuropathischer-schmerz.de) founded in 2002 aimed at promoting research on mechanisms and treatments for neuropathic pain, as well as establish a large database for QST-data.

The **IMI EUROPAIN** project (http://www.imieuropain.org), founded in 2009, aims to improve the treatment of patients with long-term pain. It consists of academic study groups working on pain research from Germany, Denmark and the UK. A Spanish SME (small and medium sized enterprises) and researchers from EFPIA (European Federation of Pharmaceutical Industries and Associations) partners active in the pain research are additional contributors. The **NEUROPAIN** project is an investigator-initiated study consisting of several researchers in the field of Neuropathic Pain research within Europe aiming to characterize subgroups of patients with neuropathic pain. IMI EUROPAIN and NEUROPAIN have collected data at the same time and to the same study protocols, including data to the central database from day 1 and are thus homogenous data. To additionally ensure comparability of data collection, an analysis of heterogeneity was conducted, showing that the data of all consortia can be analysed as a homogenous database independently of consortia (Vollert et al., 2016a).

Central database

Patients and healthy participants were assessed between 2002 and 2013. During this time, no changes to the standardized QST-protocol were implemented. Furthermore, all investigators had undergone certification training in the QST-protocol before examining healthy volunteers and patients, and there was a surveillance of maintained data quality during the data collection period [58,61]. The ethics committee of each participating centre approved the assessment protocol and data collection. Each study centre used the computer-assisted program Neuroquast© (Statconsult, Magdeburg, Germany) for local data entry. Study records were imputed monthly into the fully-integrated central database. All centres underwent strict quality control (Magerl et al., 2010; Vollert et al., 2015) and an analysis of heterogeneity showed that the database can be analysed as a homogenous dataset (Vollert et al., 2016a). All patients from the database suffering from CRPS Type I, polyneuropathy or peripheral nerve injury were included in this analysis. All data in this study has been published before, on healthy participants (Rolke et al., 2006) and CRPS (Maier et al., 2010) by the DFNS, polyneuropathy and peripheral nerve injury by all three consortia (Baron et al., 2017; Maier et al., 2010; Vollert et al., 2016b, 2017).

Patients, healthy participants and sex

Sex of the participants was determined using self-report. As it was not part of the initial study planning, no information of cis or trans gender was recorded, to the best of our knowledge and certainly in the vast

majority of the included participants, self-reported gender and biological sex will be identical, as also confirmed during the neurological examination.

Healthy participants were included on condition of an inconspicuous medical history (Rolke et al., 2006). Volunteers suffering from any pain condition were excluded, intake of any medication within the last 24h prior QST lead to exclusion as well (Rolke et al., 2006). A full list of in- and exclusion rules has been defined and agreed upon by the consortia (Gierthmühlen et al., 2015).

Adult patients with neuropathic pain due to PNI (i.e., history of traumatic nerve injury and presence of sensory abnormalities in the innervation and/or abnormal electroneurography), CRPS I (i.e., according to clinical criteria (Harden et al., 2010a)), and PNP (i.e., abnormal electroneurography or abnormally decreased vibration detection threshold at two of four sites less 5/8 at the lower limb, which could not be explained by another disease (England et al., 2005)) were included in the central database. Further details for inclusion of these patient groups can be found e.g., in (Vollert et al., 2016a). All patients gave written informed consent for transfer of their data into the common central database. Exclusion criteria were missing informed consent, insufficient language skills, pain treatment by topical local anaesthetics in the last seven days or by topical capsaicin in the last three months, since this might affect pain thresholds (Baron et al., 2017). Current systemic treatment with pain medication did, in contrast to topical treatment at the site of examination, not lead to exclusion, however, patients with additional secondary painful conditions or neurological or psychiatric conditions treated with opioids, anticonvulsants or antidepressants were excluded. Details on the patients included are presented in *Table* 1.

Assessment of average pain intensity

Before QST, all patients filled out the painDETECT questionnaire (PD-Q) (Freynhagen et al., 2006), which collects information about average pain intensity. Based on this questionnaire, the question "How *severe* was your pain during the past four weeks on average?" with pain intensity rated on a Numerical Rating Scale (NRS; 0: no pain, 10: worst imaginable pain) was taken as “average pain” for this analysis. Here, average pain referred to any type of pain including continuous or paroxysmal pain and pain evoked by daily-life stimuli during the past four weeks.

Quantitative sensory testing (QST)

According to the DFNS protocol, QST consists of seven tests measuring 13 parameters which assess the function of small and large afferent nerve fibers or corresponding CNS pathways: cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical (tactile) detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT) and pressure pain threshold (PPT). Mechanical pain sensitivity was rated on numerical rating scale (NRS, 0 – 100). Rolke et al. provided a detailed description of parameters, protocol, evaluation and database of reference values (Rolke et al., 2006). Testing location was the most

painful area in CRPS and PNI and the dorsolateral aspect of both feet in patients with polyneuropathy. In the original cohort of the DFNS healthy participants all were assessed on the feet (Rolke et al., 2006).

A note on semantics: sensitivity, thresholds, and hyperalgesia

In testing perception thresholds to sensory stimuli, a gain of function, i.e., an increased sensitivity, usually corresponds to a decreased threshold: meaning a less intense stimulus than normally gives rise to the requested percept. A curious exception to this rule is the cold pain threshold, as indeed a perception threshold at a lower temperature than normal would indicate a person being less sensitive to painful cold stimuli. On the other hand, a painful percept below the normal threshold would be higher or further away from starting temperature. To increase readability and accessibility for anyone who is not an expert in the field, for the purpose of this paper, whenever the terms "decreased threshold" or "lower threshold" are used, including cold pain thresholds, they should be read as "lower stimulus intensity needed to give rise to the requested percept" and therefore depict an increased sensitivity. Secondly, in this paper, the term "allodynia" is only used for dynamical mechanical allodynia (DMA), while decreased pain thresholds are generally described as hyperalgesia. While we acknowledge that a strongly decreased pain threshold would fall in the IASP definition under allodynia ("pain due to a stimulus that does not normally provoke pain"), a less pronounced change in threshold might also be labelled hyperalgesia, if it is still within the realm of stimuli that are normally considered painful. Increased sensitivity through decreased thresholds (the *minimum* intensity of a stimulus that is perceived as painful (IASP, 2017)), is not to be confused with increased sensitivity due to decreased pain tolerance (the *maximum* intensity of a pain-producing stimulus that a subject is willing to accept (IASP, 2017)).

Statistical analysis

Sex differences in thermal and mechanical pain thresholds were tested twofold a) as absolute pain thresholds and b) as z-values. According to Rolke et al. (2006a), absolute thermal values (e.g., CPT, HPT) are distributed normally, while assessments of mechanical thresholds, e.g., PPT and MPT are distributed log-normally and were analysed accordingly. To be able to compare QST-parameters independently of their physical dimension and to focus on disease-specific differences, a z-transformation was applied to the DFNS normative material (Magerl et al., 2010; Pfau et al., 2014; Rolke et al., 2006). In this normalization procedure, all values are transformed to a sex, age and body-region adjusted mean = 0 and standard deviation = 1 in healthy participants. To test for sex differences, modified z-scores only adjusted for age and body-region were calculated additionally. Thus, z-scores indicate if a patient has loss of function signs (i.e., hypaesthesia, hypoalgesia, z-values below zero) or gain of function (i.e., hyperaesthesia, hyperalgesia, z-values above zero) as described in (Rolke et al., 2006).

Absolute pain thresholds and z-values of pain and detection thresholds were analysed in general linear models, with sex and aetiology as fixed effect. To control for confounding effects, duration of the underlying disease (under one year, one to five years, over five years), average pain intensity (NRS: 0-10: less than 3, 3 to less than 7, 7-10), and in addition for absolute pain thresholds only, body region (upper limb, lower limb, head, trunk) and age decade were included as fixed effects as well. All p-values presented in this manuscript, except

for the demographic comparisons by chi-squared-test in *Table* 1, result from these corrected models, and p-values less than 0.05 were considered statistically significant after correction for multiple testing using the Benjamini-Hochberg procedure to adjust false discovery rate.

Results

Healthy participants and study population

Demographic data of all patients and healthy participants are shown in *Table* 1. The dataset comprised QST-data of 1252 patients (583 males, 669 (53.4%) females) with PNP (n = 571, 43.4% female), PNI (n = 342, 46.5% female) or CRPS I (n = 339, 77.3% female).

Average pain intensity

In general, duration of painful condition and intensity of average pain within the last four weeks were similar between female and male patients in all aetiologies (see *Table* 1 and *Figure* 1). Compared to females, less male patients with CRPS reported a low pain intensity ($p = 0.005$). Conversely women with PNP more often reported a severe pain intensity as compared to men ($p = 0.011$).

Evoked pain assessed by QST

Healthy female participants showed lower pain thresholds for cold, heat, pinprick and pressure (all $p < 0.01$) in comparison to males, whereas MPS and DMA did not differ (*Figure* 2).

In patients, nearly all absolute pain thresholds were lower (i.e., closer to baseline) in female as compared to male patients for the included painful conditions: CPT ($p = 0.042$), HPT ($p = 0.000$), and MPT ($p = 0.018$) (*Figure* 3, *Table 2*). PPT was lower for female patients only in CRPS ($p = 0.001$). However, z-values of pain thresholds did not differ significantly between male and female patients, except for aetiology-specific sex effects for PPT in CRPS patients ($p < 0.001$). Additional sex effects were found for WUR and MDT. QST-profiles, separately for each aetiology and sex, are displayed in *Figure* 4, p-values resulting from the general linear models can be found in *Table 2.*

Discussion and conclusions

We investigated whether pain intensity and thresholds are distinct or similar between women and men. We found subtly, yet significantly lower pain thresholds for cold, heat, pressure and pinprick for healthy females. Given that in the same cohort, detection thresholds did not differ (shown in (Rolke et al., 2006)), it is unlikely that this difference comes from variations in innervation density, but rather points towards differential central processing (Riley et al., 1998). For patients suffering from CRPS I or painful polyneuropathy or nerve injury, average pain intensity was similar in women and men and there were only minor sex differences in pain thresholds. Female patients reported lower pain thresholds compared to male patients. These sex differences observed in these chronic pain conditions mimic those obtained in healthy participants, indicating that these differences are not linked to specific pathophysiological processes. Interestingly, the variations observed in experimentally evoked pain thresholds within each sex group were much higher than those observed between sexes.

The only exception was CRPS I, where a more pronounced pressure evoked hyperalgesia could be demonstrated in women as compared to men. CRPS I was also significantly more frequent in women in our cohort, corroborated by existing literature (Ott and Maihöfner, 2018), but the reason for this is unknown. It is possible that women are more likely to require CRPS, or that they are more at risk to be suffer from fractures (e.g. for higher rates of osteoporosis) leading to higher incidence of CRPS. Deep pressure pain has been found to have a lower threshold in healthy women as compared to men in prior studies (Chesterton et al., 2003; Pfau et al., 2014; Riley et al., 1998). In contrast to pinprick hyperalgesia, blunt hyperalgesia is considered at least partly due to peripheral sensitization in different pain states (Enax-Krumova et al., 2016; Gierthmühlen et al., 2012; Kilo et al., 1994; Maier et al., 2010; Mainka et al., 2014; Pfau et al., 2009). It is a hallmark sign of CRPS (Gierthmühlen et al., 2012; Harden et al., 2010b; Mainka et al., 2014). Blunt pressure hyperalgesia is more pronounced in CRPS than in peripheral nerve injury, but sex differences have not been reported previously. In our multivariate analyses, the sex difference regarding PPT in CRPS was not related to the duration of pain or average pain intensity, so it cannot be explained by a more severe CRPS.

There is a long lasting debate on whether or not women are more sensitive to pain (Hashmi and Davis, 2014; Mogil, 2012; Racine et al., 2012), with inconclusive results throughout many qualitative and quantitative reviews (Bartley and Fillingim, 2013; Fillingim, 2000; Fillingim et al., 2009; Greenspan et al., 2007; Mogil, 2012; Racine et al., 2012; Riley et al., 1998). Biological factors (hormones, reproductive stage or genetics), psychosocial factors (education and gender roles or sociocultural) and ethnical drivers might influence pain (Bartley and Fillingim, 2013; Rahim-Williams et al., 2012). Varying result interpretations, missing differentiation between pain thresholds, tolerance and pain intensity, lack standardisation of outcome measures (Williamson et al., 2017), different terminology (Greenspan et al., 2007), and the usually ignored influence of the hormone status in females (Pogatzki-Zahn et al., 2019) as well as the investigator provider besides the patient itself

(Kállai et al., 2004; Meyer-Frießem et al., 2019) cause an additional variety of results (Bartley and Fillingim, 2013; Racine et al., 2012). Hence, subtle sex differences might be overestimated.

This study is the first major study focussing on sex differences for pain thresholds (the *minimum* intensity of a stimulus that is perceived as painful (IASP, 2017)), rather than pain tolerance (Mogil, 2012) (the *maximum* intensity of a pain-producing stimulus that a subject is willing to accept (IASP, 2017)). Both relate to the subjective experience of the individual, as they rely on what the individual defines as "painful". In a clinical setting, pain tolerance is more meaningful (as it relates more to the patient's problem), however, pain thresholds have been found to be more experimentally robust (Gelfand, 1964). It has also been reported that gender role expectations affect pain tolerance, but not pain thresholds (Defrin et al., 2009), and that pain tolerance could also be more influenced by cultural components than pain thresholds (Dawson and List, 2009). Subsequently there are more reports of sex effects on pain tolerance (Hashmi and Davis, 2014). Indeed in healthy participants, sex differences have mainly concerned suprathreshold pain responses (Mogil, 2012), although studies did not all clearly differentiate between threshold testing and response to suprathreshold pain stimuli (Racine et al., 2012). Based on a review including more than 120 studies in healthy individuals subjected to different human pain models, pain thresholds were generally similar or only moderately different among males and females (Racine et al., 2012). In contrast, 80% of the studies reported that healthy females have lower pain tolerance (in response to cold, heat , pressure, muscle or electrical stimulations) (Bartley et al., 2016; Bartley and Fillingim, 2013; Fillingim et al., 2009; Mogil, 2012; Racine et al., 2012).

Several limitations of this study should be acknowledged.

As this study is based on a database query, there are limitations to the level of data we could extract. We did not collect information about the menstrual cycle of the female patients (Craft et al., 2004; Iacovides et al., 2015; Pogatzki-Zahn et al., 2019). Neither was the sex of experimenters conducting the QST-protocol in our study systematically recorded and cannot be reconstructed at this point. It has been reported that experimental pain reports may depend on the sex of the experimenter (Aslaksen et al., 2007; Gijsbers and Nicholson, 2005; Levine and De Simone, 1991; Meyer-Frießem et al., 2019; Vigil and Alcock, 2014). As the original focus of this database collection did not lie on sex differences, detailed evaluation of gender identity including gender roles were not performed in addition to collecting data on the sex of the subject.

In addition, we did not take into consideration other potential factors involved in pain, e.g., psychosocial issues, genetics, endogenous hormone levels and social factors. Since our hypothesis was about trait differences between males and females, we preferred to use 4-week average pain scores as retrospective pain ratings instead of current pain intensities for analysis because of day to day variability of pain scores.

It is largely recognized that patients suffering from neuropathic pain or CRPS I vary broadly in sensory phenotypes and underlying mechanisms (Baron et al., 2017; Maier et al., 2010; Üçeyler et al., 2018; Vollert et al., 2017, 2018). It cannot be excluded that distinct sensory phenotypes may be associated with sex differences. While non-painful detection thresholds were not part of the question of this analysis, more pronounced fibre loss could impede pain thresholds, thus influencing pain thresholds. Still, as the QST-profiles

show (*Figure* 4) sensory thresholds do not differ largely between female and male patients and cannot explain the significant difference in pressure pain threshold for CRPS I patients.

Given that this analysis was relying on database data, we could not retrieve information about medication for the study population – neither to assess if and how treatment and gender interact with sensory profiles and pain ratings, nor, more importantly, to look for sex-treatment interactions that could hint towards not only variances in underlying pathology, but also hold the potential for a more nuanced, sex-specified treatment. In the small subset of data of the patient population (not covering CRPS patients) we have medication data on; however, we do not observe any clear pattern of differential prescription (data not shown). In addition, a recent review summarized: "There is a lack of robust evidence to support a gender-specific analgesic management" (Packiasabapathy and Sadhasivam, 2018).

Although our sample is fairly large, it is not epidemiologically representative since it depended on referral to the participating centers, who are highly specialized pain clinics, and will not see patients who have no complaints or are easily adjusted on first-line treatment. Furthermore, we collected information on two neuropathic pain conditions and CRPS I which may not reflect other potential pain conditions including nociceptive pain.

Commonly, female healthy participants and female patients with CRPS I, PNI and PNP demonstrate lower pain thresholds to cold, heat, pressure and pinprick than male patients and healthy participants. However, there is no sex difference in the extent to which these thresholds are altered in CRPS I or peripheral neuropathic pain states, with the only exception of CRPS I in female patients where PPT is significantly lowered. Therefore, from our data, we cannot suggest variance in mechanisms of pain pathophysiology, and gender differences in pain thresholds seem to be of minor clinical relevance and can be adjusted for by sex-specific reference data.

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Author contributions

All authors discussed the results and commented on the manuscript (MS). The specific contribution of each author was: CMF evaluated and interpreted data and drafted the MS. NA contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. RB contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. DB contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. NBF contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. RF contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. JG contributed to patient collection, corrected parts of the MS, added critical literature review of sex and pain aspects, critically reviewed, read and agreed to the final version. MH contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. PH contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. TSJ contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. HK contributed to patient collection, corrected parts of the MS, added critical literature review of sex and pain aspects, critically reviewed, read and agreed to the final version. DK contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. ASL contributed to patient collection, corrected parts of the MS, added critical literature review of sex and pain aspects, critically reviewed, read and agreed to the final version. ASCR contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. MS contributed to study design, contributed to data interpretation, drafted parts of the manuscript, critically reviewed, read and agreed to the final version. JS contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. SS contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. RS contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. TT contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. SSH collected original data, contributed to data evaluation, critically read the manuscript and agreed to the final version. RDT contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. EPZ proof-read the MS, added critical literature review of sex and pain aspects, critically reviewed, read and agreed to the final version. CM contributed to study design and patient collection, corrected parts of the MS, critically reviewed, read and agreed to the final version. JV designed the analyses, performed statistics and interpreted data, created the artwork, drafted and finalized the manuscript.

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Legends of figures

Figure 1:

Sex-specific average pain intensity in patients with CRPS I, peripheral nerve injury and polyneuropathy. A: Pie charts of gender distribution of patients with CRPS I, PNI and PNP in percent. **B**: Average pain intensity on numerical rating scale (NRS, 0 – 10) plotted with mean values and standard deviation in male and female patients with CRPS, PNI and PNP. **C**: Percent of average pain intensity on numerical rating scale (NRS, 0 – 10) classified in mild (NRS ≤ 3), moderate (NRS 4 – 6) and severe (NRS ≥ 7) of male and female patients with CRPS I, PNI and PNP.

CRPS: complex regional pain syndrome, PNI: peripheral nerve injury, PNP: polyneuropathy. Definition of average pain intensity: persistent or paroxysmal spontaneous pain, pain attacks, and pain evoked by daily-life stimuli during the past four weeks on average. None of the differences are significant ($p<0.05$ corrected for multiple testing using the Benjamini-Hochberg procedure).

Figure 2:

Sex-specific QST-evoked pain in healthy participants due to cold, heat, pinprick and pressure stimuli. A: cold pain threshold (CPT), **B**: heat pain threshold (HPT), **C**: mechanical pain threshold (MPT) and **D**: pressure pain threshold (PPT). Data from(Rolke et al., 2006). All differences are significant on a $p <.05$ level, corrected for multiple testing using the Benjamini-Hochberg procedure.

Figure 3:

Sex-specific pain thresholds in patients with CRPS I, peripheral nerve injury and polyneuropathy (z-values adjusted for age and body region, not for sex differences). A: cold pain threshold (CPT), **B**: heat pain threshold (HPT), **C**: mechanical pain threshold (MPT) and **D**: pressure pain threshold (PPT). Presented are mean z-values (gender unspecific – corrected just for age decade and body region) and standard error of mean.

CRPS: complex regional pain syndrome, PNI: peripheral nerve injury, PNP: polyneuropathy. *p=0.001

Figure 4:

Sex-specific somatosensory profiles of patients with CRPS I, peripheral nerve injury and polyneuropathy (z-values adjusted for age and body region, and for sex differences found in healthy participants). Mean of Z-values and standard error of mean (SE). If the resulting z–value exceeds 1.96/ -1.96, it is outside the 95% confidence interval of the standard normal distribution. Cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical (tactile) detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold and pressure pain threshold (PPT). CRPS: complex regional pain syndrome, PNI: peripheral

nerve injury, PNP: polyneuropathy. *p <.05, corrected for multiple testing using the Benjamini-Hochberg procedure.

Table 1: **Clinical data of healthy subjects and patients.**

Characteristic	**Male healthy participants[#] (n = 70, 38.9%)**	**Female healthy participants[#] (n = 110, 61.1%)**	**All (n = 180)**	***p*-value**
Consortia, n/ % DFNS	70 / 100	110 / 100	180 / 100	
Age (years), mean ± SD	37.5 ± 13.0	38.9 ± 13.0	38.4 ± 13.0	0.461
	Male patients (n = 583, 46.6%)	**Female patients (n = 669, 53.4%)**	**All (n = 1252)**	***p*-value**
Consortia, n/ % DFNS	361 / 61.9	475 / 71.0	836 / 66.8	
Age (years), mean ± SD	54.8 ± 13.1	55.7 ± 14.7	55.2 ± 13.9	0.256
CRPS, n/ %	77/ 22.7	262/ 77.3	339	
Age (years), mean ± SD	51.8 ± 12.2	52.1 ± 14.0	52.1 ± 13.6	0.864
Region of pain				
Hand, n	66	242	308	0.075
Foot, n	11	20	31	
Duration of pain disease*				
≤ 1 year, n	41	138	179	0.894
≥ 1 year, n	35	122	157	
Average pain intensity (NRS)				
Mean ± SD (*d*)	4.0 ± 3.3	4.6 ± 3.2	4.5 ± 3.2 (0.19)	0.152
NRS ≤ 3	25	73	98	0.433
NRS ≥ 7	12	49	61	0.531
Peripheral nerve injury, n/ %	183/ 53.5	159/ 46.5	342	
Age (years), mean ± SD	49.2 ± 12.2	50.8 ± 14.1	50.0 ± 13.1	0.280
Region of pain				
Hand or arm, n	86	72	158	0.428
Leg or foot, n	65	49	114	
Dorsal or ventral trunk, n	24	31	55	
Other (e.g. face), n	8	7	14	
Duration of pain disease				
≤ 1 year, n	39	37	76	0.489
≥ 1 year, n	92	72	164	
unknown, n	52	50	102	
Average pain intensity (NRS)				
Mean ± SD (*d*)	5.7 ± 2.4	5.3 ± 2.9	5.5 ± 2.6 (0.15)	0.164
NRS ≤ 3	10	23	33	0.005
NRS ≥ 7	34	32	66	0.718
Polyneuropathy, n/ %	323/ 56.6	248/ 43.3	571	
Age (years), mean ± SD	58.7 ± 12.5	62.7 ± 13.1	60.5 ± 12.9	<0.001
Region of pain**				
Hand, n	5	4	9	0.954

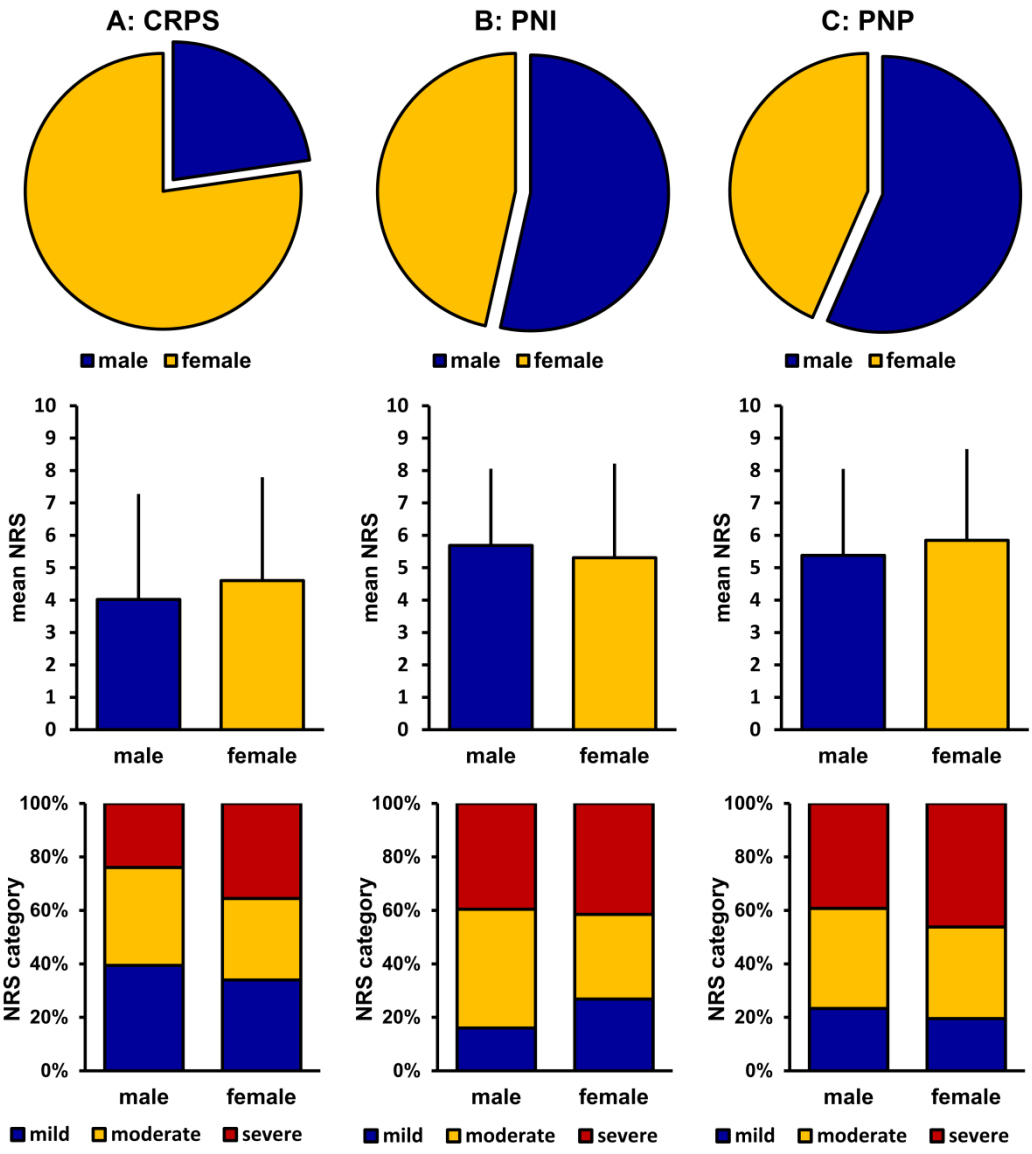
Leg or foot, n	317	244	561	
Duration of pain disease				
≤ 1 year, n	36	30	66	
≥ 1 year, n	216	155	371	0.578
unknown, n	71	63	134	
Aetiology				
diabetic	43	44	87	
fabry	17	8	25	
toxic	10	4	14	0.013
chemo-induced	14	15	29	
HIV-related	12	0	12	
Idiopathic or unknown	227	177	404	
Average pain intensity (NRS)				
Mean ± SD (*d*)	5.4 ± 2.7	5.8 ± 2.8	5.6 ± 2.7 (0.15)	0.085
NRS ≤ 3	38	28	64	0.861
NRS ≥ 7	62	70	132	0.011

Definition of average pain intensity: persistent or paroxysmal spontaneous pain, pain attacks, and pain evoked by daily-life stimuli during the past four weeks on average. SD: standard deviation. NRS: numerical rating scale (0-10; 0: no pain; 10: worst pain imaginable). *d* = Cohen's d (effect size). * unknown n = 3. **others n = 2, [#]Rolke et al. 2006a.

Table 2: **Multivariate general linear models for absolute pain thresholds and z-transformed pain and detection thresholds.**

	Model	Sex	Aetiology	Sex* Aetiology
untransformed, corrected for age decade and test area				
CPT	**<0.001**	**0.042**	0.492	0.509
HPT	**<0.001**	**<0.001**	0.115	0.171
MPT	**<0.001**	**0.018**	0.412	0.094
PPT	**<0.001**	0.926	**0.011**	**0.001**
z-values				
CDT	**<0.001**	0.063	0.219	0.703
WDT	**0.001**	0.467	0.391	0.234
TSL	**<0.001**	0.614	**0.013**	0.090
CPT	**<0.001**	0.189	**<0.001**	0.820
HPT	**<0.001**	0.058	**<0.001**	0.204
PPT	**<0.001**	**0.001**	**<0.001**	**<0.001**
MPT	**0.004**	0.801	**0.002**	0.202
MPS	**<0.001**	0.493	**<0.001**	0.413
WUR	0.220	**0.021**	0.933	0.184
MDT	**<0.001**	**0.001**	0.461	0.189
VDT	0.130	0.131	0.447	0.484

P-values generated in multivariate general linear models for absolute pain and z-transformed pain and detection thresholds in regard to sex and aetiology, corrected for duration of disease, pain intensity, and for absolute pain thresholds additionally body region and age decade. Values in **bold red** indicate significance at $P < .05$ after correction for multiple testing using the Benjamini-Hochberg procedure. CDT: cold detection threshold, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, MPS: mechanical pain sensitivity, MPT: mechanical pain thresholds, PPT: pressure pain threshold, TSL: thermal sensory limen, WDT: warmth detection threshold, WUR: wind-up ratio, VDT: vibration detection threshold.



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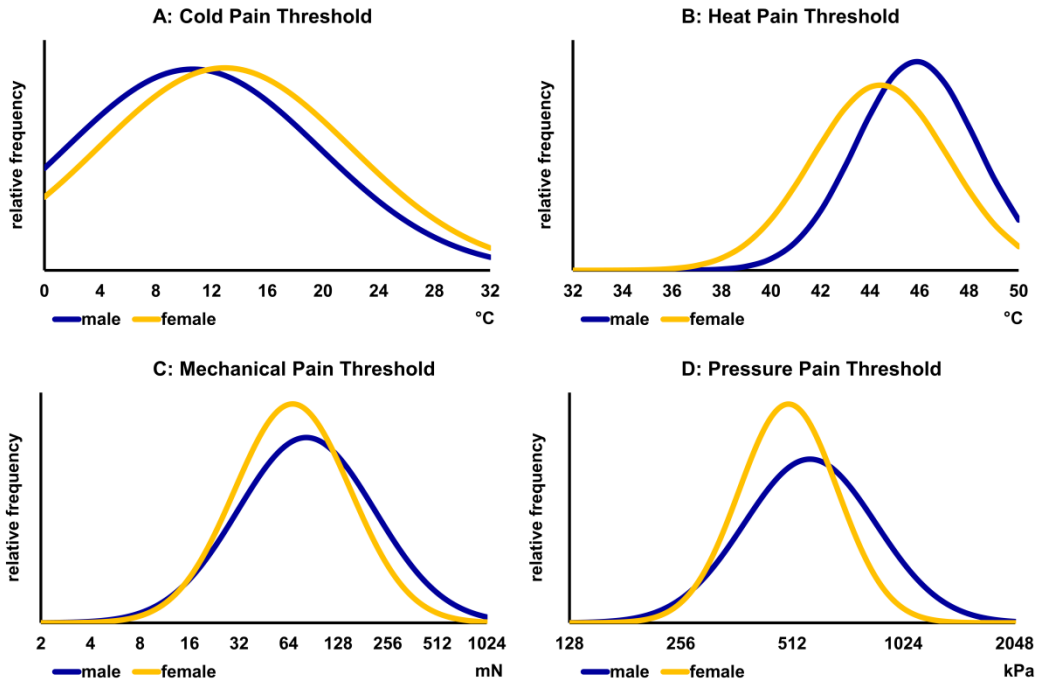

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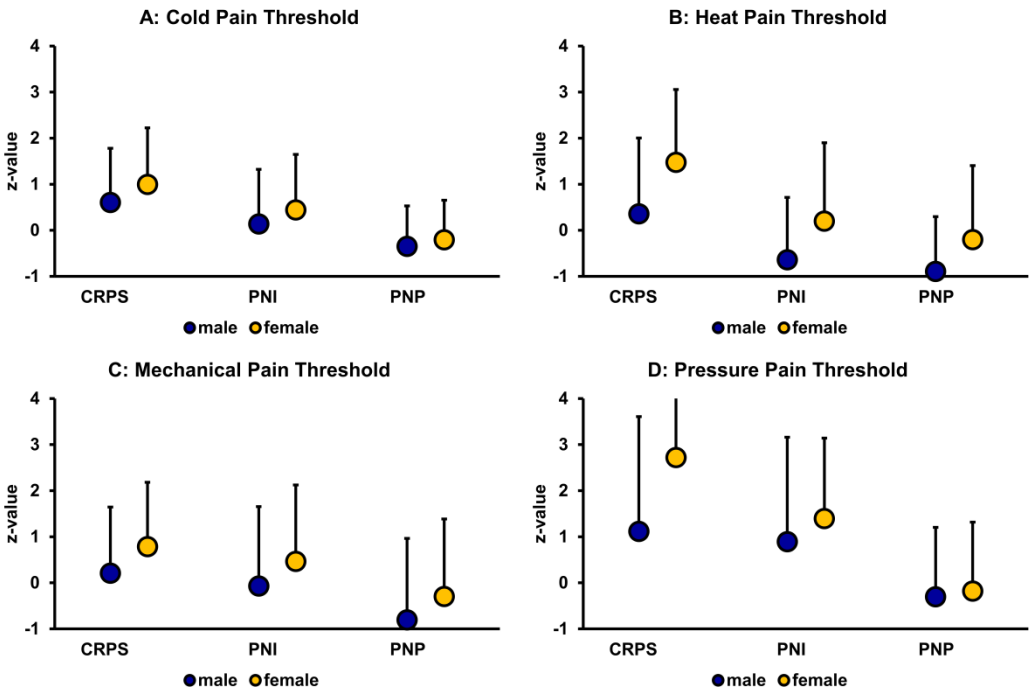
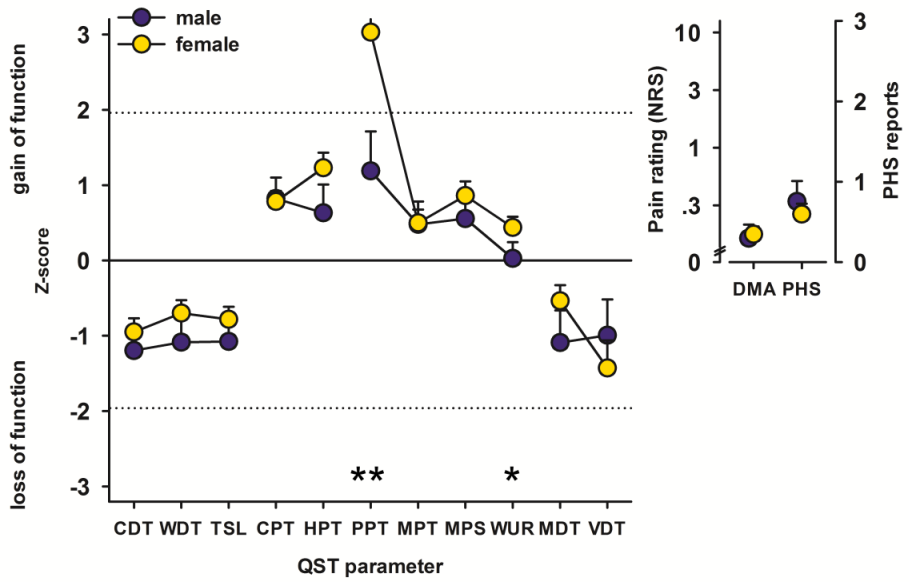
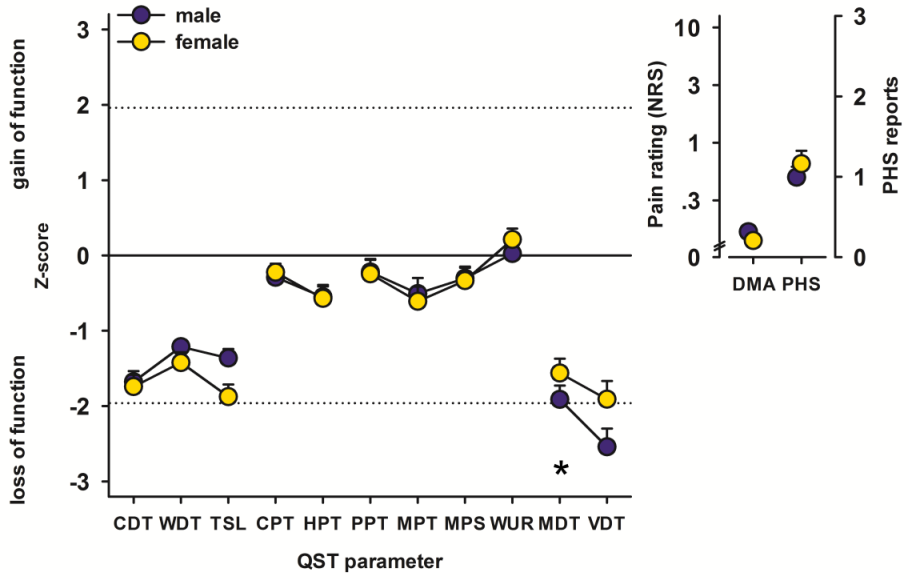


ejp_1550_f3.tif

A: Complex Regional Pain Syndrome



B: Polyneuropathy



C: Peripheral nerve injury