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

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Abstract
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
1 | INTRODUCTION

Since decades, gender differences have represented a major topic in pain research, although studies have found conflicting results (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008; Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Friessem, Willweber-Strumpf, & Zeng, 2009; Lamerato et al., 2016; Moulin, Clark, Speechley, & Morley-Förster, 2002; Reitsma, Tranmer, Buchanan, & VanDenKerkhof, 2012; Torrance, Smith, Bennett, & Lee, 2006). The overall consensus is that healthy women appear to be more pain sensitive and demonstrate lower pain thresholds than men (Bartley & Fillingim, 2013; Fillingim et al., 2009; Friessem et al., 2009; Friessem, Willweber-Strumpf, & Zeng, 2009; Lamerato et al., 2016; Moulin et al., 2002; Reitsma et al., 2012), to a lesser extent complex regional pain syndrome (CRPS; Demir, Ozaras, Karahmetoğlu, Karacan, & Aytekin, 2010; de Mos et al., 2007; Ott & Maihöfner, 2018; Pons, Shipton, Williman, & Mulder, 2015; Roh et al., 2014) and some neuropathic pain conditions (Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 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, Wang, & Edwards, 2018) and neuropathic pain patients (Arap, Siqueira, Silva, Teixeira, & Siqueira, 2010; Goswami, Anastakis, Katz, & Davis, 2016; Krämer, Rolke, Bickel, & Birklein, 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 this 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: CRPS 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 aetiology of the underlying pathology.

2 MATERIALS AND METHODS

2.1 Consortia

Three consortia, which prospectively collected patients using identical study protocols, were involved in this data analysis: The DFNS (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 homogeneous data. To additionally ensure comparability of data collection, an analysis of heterogeneity showed that the database can be analysed as a homogeneous dataset (Vollert, Attal, et al., 2016). 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 have 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, Kramer, et al., 2016; Vollert et al., 2017).

2.2 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 (Vollert et al., 2015; Vollert, Attal, et al., 2016). The ethics committee of each participating centre approved the assessment protocol and data collection. Each study centre used the computer-assisted program Neuroquast© (Statconsult) 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 homogeneous dataset (Vollert, Attal, et al., 2016). 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 have 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, Kramer, et al., 2016; Vollert et al., 2017).

2.3 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 24 hr 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 electro-neurography), CRPS I (i.e., according to clinical criteria [Harden et al., 2010a]) and PNP (i.e., abnormal electro-neurography 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, Attal, et al., 2016). 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.
| Characteristic | Male healthy participants<sup>a</sup> (n = 70, 38.9%) | Female healthy participants<sup>a</sup> (n = 110, 61.1%) | All (n = 180) | p-value |
|---------------|-----------------------------------------------------|-------------------------------------------------------|---------------|---------|
| Consortia, n% DFNS | 70/100 | 110/100 | 180/100 | .461 |
| Age (years), mean ± SD | 37.5 ± 13.0 | 38.9 ± 13.0 | 38.4 ± 13.0 | .461 |

| Consortia, n% DFNS | 361/61.9 | 475/71.0 | 836/66.8 | .256 |
| Age (years), mean ± SD | 54.8 ± 13.1 | 55.7 ± 14.7 | 55.2 ± 13.9 | .256 |

| CRPS, n% | 77/22.7 | 262/77.3 | 339 | .864 |
| Age (years), mean ± SD | 51.8 ± 12.2 | 52.1 ± 14.0 | 52.1 ± 13.6 | .864 |

| Region of pain | Male patients (n = 583, 46.6%) | Female patients (n = 669, 53.4%) | All (n = 1,252) | p-value |
|---------------|---------------------------------|-----------------------------------|----------------|---------|
| Hand, n | 66 | 242 | 308 | .075 |
| Foot, n | 11 | 20 | 31 | |

| Duration of pain disease<sup>b</sup> | | | | |
|≤1 year, n | 41 | 138 | 179 | .894 |
|≥1 year, n | 35 | 122 | 157 | .894 |

| Average pain intensity (NRS) | Mean ± SD (d) | Mean ± SD (d) | Mean ± SD (d) | |
|-----------------------------|---------------|---------------|---------------|---|
| NRS ≤ 3 | 4.0 ± 3.3 | 4.6 ± 3.2 | 4.5 ± 3.2 (0.19) | .152 |
| NRS ≥ 7 | 25 | 73 | 98 | .433 |
| NRS ≥ 7 | 12 | 49 | 61 | .531 |

| Peripheral nerve injury, n%<sup>c</sup> | 183/53.5 | 159/46.5 | 342 | |
| Age (years), mean ± SD | 49.2 ± 12.2 | 50.8 ± 14.1 | 50.0 ± 13.1 | .280 |

| Region of pain | | | | |
| Hand or arm, n | 86 | 72 | 158 | .428 |
| Leg or foot, n | 65 | 49 | 114 | .428 |
| Dorsal or ventral trunk, n | 24 | 31 | 55 | |
| Other (e.g. face), n | 8 | 7 | 14 | |

| Duration of pain disease<sup>d</sup> | | | | |
|≤1 year, n | 39 | 37 | 76 | .489 |
|≥1 year, n | 92 | 72 | 164 | .489 |
|unknown, n | 52 | 50 | 102 | .489 |

| Average pain intensity (NRS) | Mean ± SD (d) | Mean ± SD (d) | Mean ± SD (d) | |
|-----------------------------|---------------|---------------|---------------|---|
| NRS ≤ 3 | 5.7 ± 2.4 | 5.3 ± 2.9 | 5.5 ± 2.6 (0.15) | .164 |
| NRS ≥ 7 | 10 | 23 | 33 | .005 |
| NRS ≥ 7 | 34 | 32 | 66 | .718 |

| Polyneuropathy, n%<sup>e</sup> | 323/56.6 | 248/43.3 | 571 | |
| Age (years), mean ± SD | 58.7 ± 12.5 | 62.7 ± 13.1 | 60.5 ± 12.9 | <.001 |

| Region of pain | | | | |
| Hand, n | 5 | 4 | 9 | .954 |
| Leg or foot, n | 317 | 244 | 561 | .954 |

| Duration of pain disease<sup>f</sup> | | | | |
|≤1 year, n | 36 | 30 | 66 | .578 |
|≥1 year, n | 216 | 155 | 371 | .578 |
|unknown, n | 71 | 63 | 134 | .578 |

(Continues)
2.4 Assessment of average pain intensity

Before QST, all patients filled out the painDETECT questionnaire (PD-Q; Freynhagen, Baron, Gockel, & Tölle, 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.

2.5 Quantitative sensory testing

According to the DFNS protocol, QST consists of seven tests measuring 13 parameters which assess the function of small and large afferent nerve fibres 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 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).

2.6 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. 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]).

**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 ($p < .05$ corrected for multiple testing using the Benjamini-Hochberg procedure).
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. (2006), 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: <3, 3 to <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 < .05 were considered statistically significant after correction for multiple testing using the Benjamini-Hochberg procedure to adjust false discovery rate.

3 | RESULTS

3.1 | Healthy participants and study population

Demographic data of all patients and healthy participants are shown in Table 1. The dataset comprised QST-data of 1,252 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).
3.2 | 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 ($p = .005$). Conversely women with PNP more often reported a severe pain intensity as compared to men ($p = .011$).

3.3 | Evoked pain assessed by QST

Healthy female participants showed lower pain thresholds for cold, heat, pinprick and pressure (all $p < .01$) 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 ($p = .042$), HPT ($p = .000$), and MPT ($p = .018$) (Figure 3; Table 2). PPT was lower for female patients only in CRPS ($p = .001$). 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 ($p < .001$). 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.

4 | 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, Robinson, Wise, Myers, & Fillingim, 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 & Maihöfner, 2018), but the reason for this is unknown. It is possible that women are more likely to present early in the clinical stage or genetics), psychosocial factors (education and gender roles or sociocultural) and ethnical drivers might influence pain (Bartley & Fillingim, 2013; Rahim-Williams, Riley et al., 2012). Biological factors (hormones, reproductive stage or genetics), psychosocial factors (education and gender roles or sociocultural) and ethnical drivers might influence pain (Bartley & Fillingim, 2013; Rahim-Williams, Riley, Williams, & Fillingim, 2012). Varying result interpretations, missing differentiation between pain thresholds, tolerance and pain intensity, lack standardization 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, Barke, & Voss, 2004; Meyer-Friesem et al., 2012; Rahim-Williams, Riley, Williams, & Fillingim, 2012). Hence, subtle sex differences might be overestimated.

This study is the first major study focusing 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, Shramm, & Eli, 2009), and that pain tolerance could also be more influenced by cultural components than pain thresholds (Dawson & List, 2009). Subsequently there are more reports of sex effects on pain tolerance (Hashmi & Davis, 2014). Indeed in healthy participants, sex differences have mainly concerned supra-threshold 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 & Fillingim, 2013; Bartley et al., 2016; 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, Mogil, & Aloisi, 2004; Iacovides, Avidon, & Baker, 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, Myrbakk, Høifødt, & Flaten, 2007; Gijsbers & Nicholson, 2005; Levine & De Simone, 1991; Meyer-Frießem et al., 2019; Vigil & 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; Üceyler 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.

**FIGURE 4** Sex-specific somatosensory profiles of patients with (a) CRPS I, (b) peripheral nerve injury and (c) 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. CDT, Cold detection threshold; CPT, cold pain threshold; CRPS, complex regional pain syndrome; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical (tactile) detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PHS, paradoxical heat sensation; PNI, peripheral nerve injury; PNP, polyneuropathy; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio. *p < .05, **p < .01, corrected for multiple testing using the Benjamini-Hochberg procedure.
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-specific 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 & Sadhasivam, 2018).

Although our sample is fairly large, it is not epidemiologically representative since it depended on referral to the participating centres, 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.

ACKNOWLEDGEMENTS
The IMI EUROPAIN project is a public-private partnership/EU-Project for understanding chronic pain and improving its treatment. The NEUROPAIN project for the characterization of subgroups of patients with neuropathic pain is an investigator-initiated European multicentre study with Prof. Dr. R. Baron as principle investigator and ten co-investigator sites. Data for these consortia was collected at the following sites: Johannes Gutenberg-University, Mainz, Germany, University of Schleswig-Holstein, Kiel, Germany, Ruhr University Bochum, Germany, Technical University Munich, Germany, Ludwig-Maximilians-University, Munich, Germany, University of Tübingen, Germany, University of Freiburg, Germany, University of Ulm, Germany, University of Erlangen, Germany, Benedictus Hospital Tutzing, Germany, Aarhus University, Denmark, University of Southern Denmark, Odense, Denmark, Karolinska Institute, Stockholm, Sweden, Imperial College London, UK, Neuroscience Technologies, Barcelona, Spain.

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

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. 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. JR 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, 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. 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. RDT 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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**How to cite this article:** Meyer-Frießem CH, Attal N, Baron R, et al. Pain thresholds and intensities of CRPS type I and neuropathic pain in respect to sex. *Eur J Pain*. 2020;24:1058–1071. https://doi.org/10.1002/ejp.1550