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Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes

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ABSTRACT

Neuropathic pain is accompanied by both positive and negative sensory signs. To explore the spectrum of sensory abnormalities, 1236 patients with a clinical diagnosis of neuropathic pain were assessed by quantitative sensory testing (QST) following the protocol of DFNS (German Research Network on Neuropathic Pain), using both thermal and mechanical nociceptive as well as non-nociceptive stimuli.

Data distributions showed a systematic shift to hyperalgesia for nociceptive, and to hypoesthesia for non-nociceptive parameters. Across all parameters, 92% of the patients presented at least one abnormality. Thermosensory or mechanical hypoesthesiac (up to 41%) was more frequent than hypoalgesia (up to 18% for mechanical stimuli). Mechanical hyperalgesias occurred more often (blunt pressure: 36%, pinprick: 29%) than thermal hyperalgesias (cold: 19%, heat: 24%), dynamic mechanical allodynia (20%), paradoxical heat sensations (18%) or enhanced wind-up (13%). Hyperesthesia was less than 5%. Every single sensory abnormality occurred in each neurological syndrome, but with different frequencies: thermal and mechanical hyperalgesias were most frequent in complex regional pain syndrome and peripheral nerve injury, allodynia in postherpetic neuralgia. In postherpetic neuralgia and in central pain, subgroups showed either mechanical hyperalgesia or mechanical hypoalgesia. The most frequent combinations of gain and loss were mixed thermal/mechanical loss without hyperalgesia (central pain and polyneuropathy), mixed loss with mechanical hyperalgesia in peripheral neuropathies, mechanical hyperalgesia without any loss in trigeminal neuralgia.

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DFNS, Deutscher Forschungsverbund Neuropathischer Schmerz = German Research Network on Neuropathic Pain; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

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Thus, somatosensory profiles with different combinations of loss and gain are shared across the major neuropathic pain syndromes. The characterization of underlying mechanisms will be needed to make a mechanism-based classification feasible.

1. Introduction

Neuropathic pain arises after a lesion or disease of the somatosensory system [9,22,55] which leads to spontaneous pain and to multiple positive and negative somatosensory signs such as thermal and mechanical hyperalgesia, allodynia as well as hypoesthesia and hypoalgesia [6,12,20].

It is an open question whether the classification of neuropathic pain syndromes, based solely on the etiology (e.g. nerve lesion induced by virus infection or by diabetes), is the best approach or whether it might be preferable to classify neuropathic pain conditions on the basis of symptoms and signs [27,46,50] or of patterns of somatosensory abnormalities and the likely underlying mechanisms [5,6,12,54]. The individual pattern of somatosensory abnormalities at the affected body area, i.e. the somatosensory profile, likely reflects altered functions in somatosensory processing; this might open a window to understand the underlying mechanisms of pain generation. It might thus be useful to stratify patients based on the somatosensory profile rather than the underlying etiology to approach a mechanism-based classification characteristic [5,23,29].

However, the hypothesis that prototypical combinations of somatosensory abnormalities occur independently of the clinical entity has not yet been proven in a large cohort of patients with neuropathic pain due to a broad spectrum of etiologies. Therefore, it is unknown as to how many patterns with different combinations of abnormal signs exist across different conditions, or if there are specific characteristics for clinical entities such as postherpetic neuralgia or diabetic neuropathy. A better knowledge about the distribution of somatosensory abnormalities within different etiologies may be important also for the future design of clinical trials.

As a first prerequisite for a comprehensive somatosensory characterization of patients, the German Research Network on Neuropathic Pain (DFNS) has developed a standardized quantitative sensory testing (QST) battery [47]. This battery includes the assessment of detection thresholds for thermal and mechanical stimuli, pain thresholds for several stimulus modalities, suprathreshold pinprick tests and wind-up, plus specific assessment for dynamic mechanical allodynia and paradoxical heat sensation and was implemented within the entire DFNS using standardized instructions and investigator training [17,43]. The DFNS reference dataset of healthy volunteers, serving as an age- and gender-matched healthy control reference, allows to determine for each individual patient, which QST findings lie within the 95% confidence range of healthy subjects [46,54].

In this paper we present the frequency of somatosensory abnormalities of a multi-center cohort of 1236 patients with different neuropathic pain syndromes such as polyneuropathy, postherpetic neuralgia, peripheral nerve injury, central pain and other neurological syndromes. The purpose of this study was (i) to describe the somatosensory characteristics of patients with neuropathic pain across the different neurological syndromes, (ii) to analyse the frequency of abnormal somatosensory signs within and across different clinical entities and (iii) to detect syndrome-specific differences in the somatosensory profiles. The concept of a mechanism-based classification of neuropathic pain suggests two hypotheses: (i) similar sensory profiles may occur within different syndromes and (ii) for each syndrome there should be more than one sensory profile.

2. Methods

The German Research Network on Neuropathic Pain (DFNS; http://www.neuropathischer-schmerz.de) was established in 2002 with the aim to foster the research on mechanisms and treatment of neuropathic pain. The central goal of the DFNS was to establish a nationwide database of phenotypically characterized patients with various neuropathic pain states including demographic, psychometric and clinical data as well as results of a standardized quantitative sensory assessment. The study protocol for patient assessment was approved by the ethics committees of all 10 participating centers (leading committee: University Hospital Kiel).

2.1. Central database

The study centers used the computer-assisted program QUAST© (acronym for "Quality Assurance in Pain Treatment") for data entry [18]. QUAST allowed the organization of the central network database including the network communication. For data export into the central data base, a special export data file was created by QUAST automatically (using a specific data collecting matrix and a pseudo-anonymous code number) and sent by e-mail anonymously to the central data base, including the current data set assembly (e.g. QST findings).

2.2. Description of the patient cohort

All subjects participated after written informed consent according to the Declaration of Helsinki. A total of 1487 patients with neuropathic pain syndromes associated with one of the following neurological syndrome were included into the central database: peripheral nerve injury (PNI, which was confirmed if somatosensory signs were present in the innervation territory of the injured nerve according to clinical examination and/or sensory neurography), complex regional pain syndrome types I and II (CRPS, revised criteria [10,25], postherpetic neuralgia (PHN, which was confirmed if neuropathic pain was present for more than 3 months in the affected area after healing of the acute herpes zoster rash), polyneuropathy (PNP, according to clinical criteria [14]), central pain (defined as pain caused by a demonstrable lesion in the central nervous system in an area anatomically attributable to the lesion), trigeminal neuralgia (according to International Headache Classification criteria 2003 [26]) and other neuropathies ($n = 121$) which were low in number (radiculopathy: $n = 15$, phantom limb or stump pain: $n = 27$, atypical facial pain: $n = 36$, regional pain syndrome: $n = 7$, localized neuropathic pain after surgery or trauma: $n = 33$, neuropathic pain due to other neurological diseases: $n = 3$) and fulfilled the corresponding clinical inclusion criteria (e.g. radiculopathy: history of nerve root damage and consistent neurological findings). All diagnoses were made and documented by the local center. Of the 1487 patients, 251 were excluded from the present study either because patients suffered from additional painful diseases or multiple disorders affecting the nervous system, or because records were incomplete (see Fig. 1).

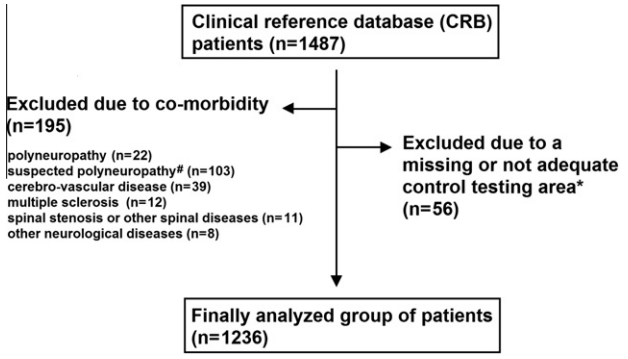

Fig. 1. Flow chart of database analysis (#: patients with unilateral pain syndromes, who showed additionally signs of mostly pain free polyneuropathy; ∗: not applied for patients with bilateral pain (polyneuropathy and central pain due to systemic diseases)).

2.3. Quantitative sensory testing (QST)

In order to assure process quality of QST, all investigators passed a 1 day course of instruction in a central institution (Mainz) and practiced with healthy control subjects [17] using the identical equipment and standardized instructions as described by Rolke et al. [46,47].

The quantitative sensory testing assessed the function of small and large afferent fibers. The standardized assessment contained 13 different thermal and mechanical tests [47]. In brief the following parameters were tested: thermal detection thresholds for the perception of cold (CDT: cold detection threshold) and warmth (WDT: warm detection threshold), paradoxical heat sensations (PHS) during the procedure of alternating warm and cold stimuli (TSL), thermal pain thresholds for cold (CPT: cold pain threshold) and hot stimuli (HPT: heat pain threshold), mechanical detection thresholds for touch (MDT) and vibration (VDT: vibration detection threshold), mechanical pain sensitivity including thresholds for pinprick (MPT: mechanical pain threshold) and blunt pressure (PPT: pressure pain threshold), a stimulus–response–function for pinprick sensitivity (MPS: mechanical pain sensitivity) and dynamic mechanical allodynia (DMA: dynamic mechanical allodynia) as well as pain summation to repetitive pinprick stimuli (WUR: wind-up ratio). For all parameters negative (loss of function) as well as positive (gain of function) phenomena were assessed.

Since pain was the leading complaint, QST was performed at the most painful site within the affected body area (e.g., face, trunk, upper or lower extremity) as well as at the contralateral mirror control area to focus on the pain symptoms and to easily define a standardized testing area for all research centers within DFNS. Thus, the recently published concept of a spatial congruence of pain and sensory signs was directly addressed [55]. In cases of polyneuropathy or other symmetrical neuropathic pain conditions, only the clinically most affected area was evaluated (for details see Table 1).

Currently we do not yet have multi-center reference data for all body regions. We tentatively used hand data as representative for the upper body and foot data for the lower body. Unpublished monocentric data indicate that in spite of mean value differences the 95% confidence intervals overlap vastly for most QST parameters for measurements on the dorsal hand compared to measurements on the palmar hand, in the thoracic areas or in the areas over the trapezius muscle. A prominent exception is VDT being much higher in the thoracic areas or in the areas over the trapezius muscle in healthy subjects, which means that pallhypoesthesia would have been strongly overestimated if data from these regions were compared to reference data from the dorsal hand. Therefore, in cases of QST in the shoulder area ($n = 8$), in the thoracic area ($n = 38$) or in the low back area ($n = 11$) VDT was excluded from the comparison to the reference data base and abnormal values were evaluated only by side-to-side comparison (a side-to-side difference of >0.8/8 was considered abnormal according to Rolke et al. [46]). This way, 93% of the comparisons were for validated reference data. For polyneuropathy, trigeminal neuralgia and CRPS this percentage was even 98–100%. For peripheral nerve injury (83%), central pain (88%) and postherpetic neuralgia (92%) this percentage was lower, since some proximal limb areas were tested (here left–right comparisons are validated but absolute comparisons are not yet). In the category "other neuropathies" we only had 69% standard test sites but this is a rather heterogenous group of patients anyway.

2.4. Data analysis and statistics

2.4.1. Modified QST reference database

For all 13 parameters the recently published reference data (mean values, standard deviation, upper and lower 95% confidence value) for both genders and the three body regions – face, hands and feet were available as reference values per age decade [36].

2.4.2. z-transformation of QST data

In the reference group, cold pain, heat pain thresholds and vibration detection thresholds as well as the numbers of paradoxical heat sensations during the TSL procedure were normally distributed. All other parameters were normally distributed in log-space and were transformed logarithmically before statistical analysis [47]. A z-transformation was performed for each variable, adjusting the data for test site, age and gender. The sign of the resulting z-score was adjusted in such a way that z-values above "0" indicate a gain of function when the patient is more sensitive

Table 1
Clinical data of patients separated for the different etiologies enrolled into the DFNS database.

Neurological syndrome	Poly-neuropathy	Postherpetic neuralgia	Peripheral nerve injury	CRPS	Trigeminal neuralgia	Central pain	Other	All	p
Number of patients (n, %)	343 (27.8%)	72 (5.8%)	154 (12.5%)	403 (32.6%)	92 (7.4%)	51 (4.1%)	121 (9.8%)	1236	
Female (n, %)	143 (42%)	46 (64%)	70 (45%)	312 (77%)	62 (67%)	17 (33%)	61 (50%)	711 (58%)	<0.001
Male (n, %)	200 (58%)	26 (36%)	84 (55%)	91 (23%)	30 (33%)	34 (67%)	60 (50%)	525 (42%)	
Age (mean ± SD, years)	59 ± 12	70 ± 9	47 ± 13	52 ± 13	59 ± 11	55 ± 13	52 ± 15	55 ± 14	
Patients < 50 years (n, %)	79 (23%)	3 (4%)	89 (58%)	155 (38%)	18 (20%)	19 (37%)	55 (45%)	418 (34%)	<0.001
Patients > 69 years (n, %)	73 (21%)	42 (58%)	8 (5%)	29 (7%)	16 (17%)	7 (14%)	17 (14%)	192 (16%)	
Duration of pain ⩽1 year (n, %)	53 (15%)	34 (47%)	37 (24%)	214 (53%)	7 (8%)	11 (22%)	22 (18%)	378 (31%)	<0.001
Duration of pain >1 year (n, %)	290 (85%)	38 (53%)	117 (76%)	189 (47%)	85 (92%)	40 (78%)	99 (82%)	858 (69%)	
Pain intensity (mean ± SD, NRS 0–10)									
Current	5.3 ± 2.8	5.3 ± 2.4	6.7 ± 2.1	5.3 ± 2.7	5.7 ± 3.1	5.9 ± 2.7	6 ± 2.6	5.6 ± 2.7	n.s.
Average (last 4 weeks)	6.3 ± 2.2	5.9 ± 2.2	6.5 ± 2.1	5.8 ± 2.4	6.8 ± 2.6	6.2 ± 2.6	6.6 ± 1.9	6.2 ± 2.3	n.s.
Maximum	7.7 ± 1.9	7 ± 2.1	8.2 ± 1.8	7.5 ± 2.6	8.7 ± 1.5	7.6 ± 2.2	8.2 ± 2.1	7.8 ± 2.1	n.s.

SD, standard deviation; CRPS, complex regional pain syndrome; NRS, numerical rating scale.

to the tested stimuli compared with controls (hyperesthesia, hyperalgesia, and allodynia), while *z*-scores below "0" indicate a loss of function referring to a lower sensitivity of the patient (hypoesthesia, hypoalgesia). A *z*-score of zero represents a value corresponding to the mean of the healthy control subjects. A *z*-score of 0 ± 1.96 represents the range which can be expected to include 95% of healthy control subject data. To compare individual QST data of patients with the mean reference range of the accurately age- and gender-matched healthy controls the patient data were *z*-transformed for each single variable in the same way, using the transformation parameters of the reference group.

2.4.3. Identification of abnormal values

If the individual *z*-values were outside of the 95% confidence interval of the reference group (i.e. *z*-scores >1.96 or <−1.96) the values were designated as absolute abnormalities. To achieve a better sensitivity of QST, we tested for relative abnormalities in the cases, when the QST parameter values in the affected area and the corresponding unaffected control area were both within the normal range. For this purpose, the side-to-side differences of each QST parameter were compared with the 95% confidence interval of the side-to-side differences in healthy controls [46].

2.4.4. A priori interpretation of sensory loss and gain

An isolated loss of small fiber function was diagnosed if the values of CDT or WDT were abnormal on the affected side in comparison with the absolute reference data or if an abnormal side difference was present between the affected and unaffected area in combination with normal MDT and VDT (normal range and no abnormal side differences). Isolated loss of large fiber function was present if values of MDT or VDT were abnormal on the affected side in comparison with the absolute reference data or if an abnormal side difference was present between the affected and unaffected area in combination with unremarkable CDT and WDT (normal range and no abnormal side differences). Mixed loss of function was diagnosed if loss of function was present in both sets of parameters.

Mechanical hyperalgesia was indicated if gain of function (in comparison with the absolute or the relative reference data) was present in case of allodynia (DMA), decreased mechanical or pressure pain threshold (MPT, PPT), or increased mechanical pain sensitivity (MPS). Thermal hyperalgesia was indicated if gain of function (in comparison with the absolute or the relative reference data) was present in CPT or HPT. Mixed hyperalgesia was diagnosed in case of a presence of both mechanical and thermal hyperalgesias.

2.4.5. Statistical analysis

All statistical calculations were performed using the software Statistical Package for the Social Sciences (SPSS, Version 15.0). Distributions of frequencies were analysed by χ^2 tests. As these statistical results only serve for heuristic aims there is no adjustment for multiple comparisons [1], but this issue is discussed in Section 4.5. Patterns of cell frequencies in contingency tables (Appendix A, B and C) are assessed by configuration frequency analysis [33], including adjustment for multiple comparisons, for all abnormal QST values, which occurred in more than 5%. Statistical significance was accepted for $p < 0.05$.

3. Results

3.1. Patients

Demographic data of the patient cohort are shown in Table 1. Gender, duration of pain, and age distribution differed significantly ($p < 0.001$) between the neurological syndromes. The majority of patients were women with the highest female predominance in CRPS and trigeminal neuralgia (77% and 67%, respectively). In central pain, peripheral nerve injury (PNI) and polyneuropathy (PNP) male patients dominated with up to 67%. Age differences between the different syndromes were less pronounced. PNI patients were the youngest with 58% of patients under 50 years, followed by CRPS and central pain. About 20% of the PNP and almost 60% of the postherpetic neuralgia (PHN) patients were older than 70 years. Most of the patients suffered from chronic pain, i.e. in two thirds of the patients the duration was longer than 1 year, whereas only 31% was assessed during the first 12 months after pain onset. Pain intensity generally was severe with ratings of more than 5 on an 11-point numeric scale without relevant differences across entities.

3.2. Distributions of z-transformed QST values

Fig. 2 superimposes distributions of QST data from the 1236 patients with those of 1080 test areas of the DFNS reference data [46]. As shown in the Appendix B the pooled reference data had zero mean and unit variance, as expected for standard normal distributions that result when data are *z*-transformed using their own mean and variance. Across all parameters, 1.8% of the values were below −1.96 (maximum 5.1% for vibration detection threshold (VDT)) and 2.3% above +1.96 (maximum 4.2% for mechanical pain sensitivity (MPS) and wind-up ratio (WUR)); this is slightly less than expected for a 95% confidence interval.

Patients' values displayed similar distribution shapes (Fig. 2) but with larger standard deviations (Appendix B) indicating inhomogeneity of sensory findings. For nociceptive parameters (CPT, HPT, PPT, MPT, MPS, WUR), there were rightward shifts, suggesting the presence of hyperalgesia (positive means in Appendix B), whereas for non-nociceptive parameters (CDT, WDT, TSL, MDT, VDT) there were leftward shifts suggesting hypoesthesia. WUR was the most frequently missing QST parameter (11.1%), mostly infeasible to perform in patients with either hypoalgesia (zero denominator) or more rarely limited by pain tolerance, particularly in patients with pinprick hyperalgesia. Averaged across all single QST parameters, negative sensory signs outside the normal range (16.6%) were more frequent than positive signs (9%).

For CDT, WDT and TSL, only negative sensory signs (thermal hypoesthesia) were detectable within the affected area (Appendix B). Due to the fact that normal variability in healthy subjects already covers the major part of the available data range, negative signs were absent in the affected areas for CPT (0%), and rare for HPT (3.7%). However, positive sensory signs (thermal hyperalgesia) occurred in 10.8% of the patients for CPT and in 17.7% for HPT. For pain to blunt pressure (PPT), positive signs also dominated (26.3%), but a notable proportion of patients (6.2%) exhibited hypoalgesia. MPT and MPS were nearly symmetrically distributed in patients with similar percentages of loss or gain (mechanical hypo- or hyperalgesia for pinprick stimuli). WUR distribution was slightly shifted to the right and there were only a few positive signs of an enhanced wind-up.

MDT and VDT reference data exhibited a skewed distribution, suggesting a floor effect: the test stimuli were not sensitive enough to determine thresholds of the most sensitive subjects. It was not possible to assess a gain of function for VDT, as the maximal value of 8/8 measured by a Rydel–Seiffer 64 Hz tuning fork was within the normal range. The patients' data for MDT and VDT had a broader distribution and clearly showed a leftward shift compared to the reference data. In the affected area, there were mostly negative signs (mechanical hypoesthesia), except for 2.1% of the patients who showed an enhanced tactile sensitivity (hyperesthesia).

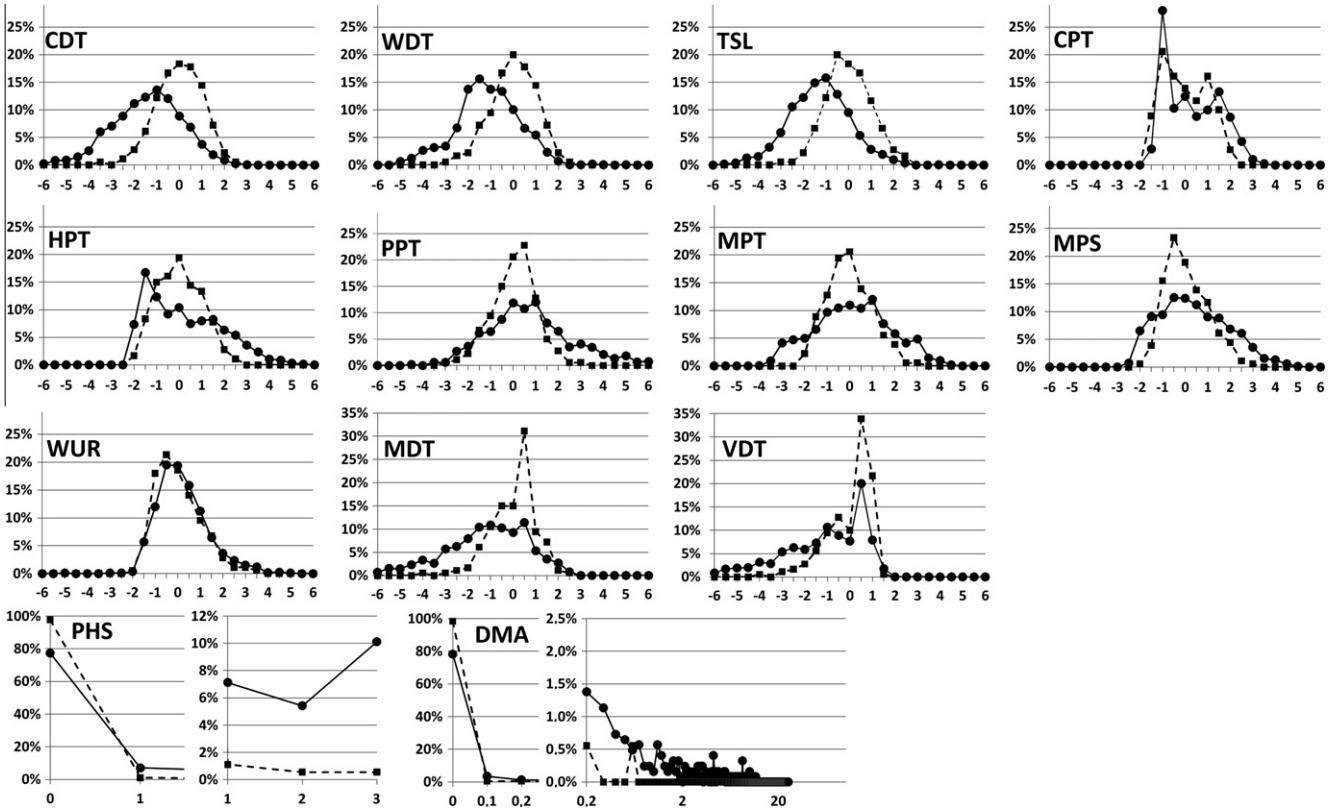

Fig. 2. Distribution of the QST parameters after *z*-transformation. Painful area of all 1236 patients of the DFNS patient database (circles and solid line) in comparison with the reference data base (180 subjects × 6 test sites, squares and broken lines). Note that *z*-transformation [47] eliminates differences due to test site, gender and age. The *y*-axis always indicates the percentage of cases (patients or healthy subjects). For paradoxical heat sensations (PHS) and dynamic mechanical allodynia (DMA) percentages are plotted versus original data: occurrences of PHS (0–3), log numerical ratings scale for DMA (0–100).

PHS and DMA normally do not occur in healthy subjects. Thus, *z*-transformation was not possible for these parameters, because one would divide by zero. Based on raw values, the incidence in our reference data was 2.4% for PHS and 5.1% for DMA. A single report of PHS upon stimulation of the feet was considered normal for older populations [46,36]. When this was taken into account, 18.4% of the patients exhibited an abnormal PHS (see Appendix C), including 10% who presented with this positive sensory sign in all three test repetitions. DMA was present in 19.7% of patients, but mostly of very mild intensity.

3.3. Frequencies of abnormal QST values and of abnormal side-to-side differences

The frequencies of abnormal QST values (outside 95% CI of reference data) for each QST parameter in 1236 patients are shown in Fig. 3. For all non-nociceptive detection thresholds roughly 30% of the patients exhibited sensory loss, virtually no one presented any sensory gain (see also Appendix B). In addition to these absolute sensory abnormalities, Fig. 3 shows the frequency of abnormal side-to-side differences, which identified additionally patients with relative sensory loss (for different parameters between 4.6–8.4% additional patients), but again almost none with relative sensory gain for the non-nociceptive parameters. For the nociceptive parameters, sensory loss (hypoalgesia) was rare (0.3–12.8%) but sensory gain (hyperalgesia) was frequent (7.5–26.3%). The two pinprick tests yielded the largest number of sensory loss (hypoalgesia). Hyperalgesia was most frequently detected for blunt pressure, followed by pinprick, heat and cold. Dynamic mechanical allodynia was about as frequent as heat or pinprick hyperalgesia. The inclusion of abnormal side-to-side differences increased both

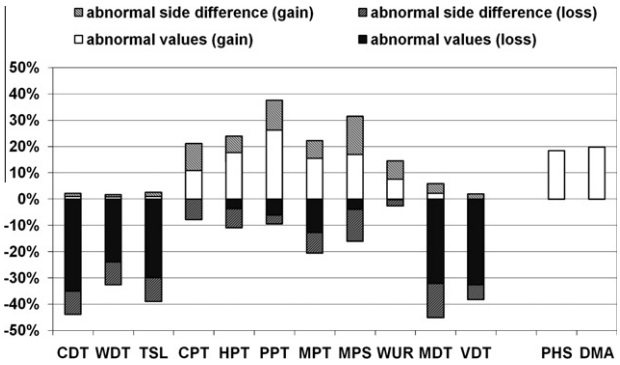

Fig. 3. Absolute and relative sensory abnormalities in the painful area. QST values outside the 95% CI of the reference data base (shaded bars, "absolute abnormalities") and QST differences versus an unaffected control side outside the 95% CI of such differences (hatched bars, "relative abnormalities"). The *y*-axis shows percentage of patients ($n = 1236$), with positive sensory signs plotted upwards and negative sensory signs plotted downwards. Absence of paradoxical heat sensations (PHS) and dynamic mechanical allodynia (DMA) is normal, hence there are no negative signs for PHS nor DMA.

the frequency of patients with loss (1.3–6.7% additional patients with hypoalgesia) and with gain (6.2–12.4% additional patients) in nociceptive function. Notably, cold pain hypoalgesia was only detectable by side-to side comparison. In conclusion, the addition of side-to-side comparisons enhanced the sensitivity to detect sensory abnormality, but did not change the overall pattern of these abnormalities. All subsequent analyses include both absolute and relative abnormalities.

3.4. Sensory phenotypes across neurological syndromes

Across all studied syndromes, 91.9% of all patients had at least one absolute or relative QST-abnormality (Fig. 4), i.e. only 8.1% of the patients had no somatosensory abnormalities with respect to the criteria mentioned above (Section 2.4.3). The percentage of healthy subjects, who did not have any value outside the 95% CI, was 59.4%. This is very close to the expected percentage, considering the performance of 11 tests, each of which has a 95% probability to yield a normal value in healthy subjects ($0.95^{11} = 0.57$; see Section 4: technical considerations). Nearly half of all patients had a mixture of positive and negative sensory signs, 26.1% had only negative signs, fewer (19.7%) had only positive signs (hyperalgesia).

Across the different syndromes, the highest percentage of patients who did not show any abnormalities was found in polyneuropathy (PNP; 16.6%) and the lowest in postherpetic neuralgia (PHN; 0%). Mixtures of positive and negative sensory signs occurred with all syndromes (between 67% in PHN and 21% in PNP). PNP patients presented most frequently (52.2%) only with sensory loss; a similar percentage was shown by patients with central pain (41.2%). In contrast, isolated sensory gain was most prevalent in CRPS (30%) and trigeminal neuralgia (30%).

The Appendix C shows the percentages of sensory abnormalities for each QST parameter and each neurological syndrome (combined absolute and relative abnormalities; in PNP and in some patients with central pain, relative abnormalities could not be assessed, see Methods 2.3). Each of the more common abnormalities occurred in each syndrome, but with some significantly different frequencies (significantly more frequent signs marked in red, significantly less frequent signs marked in blue).

Positive signs were generally overrepresented in CRPS (28.7–66.3%), particularly hyperalgesia to cold, heat, blunt pressure (CPT, HPT and PPT) and also to prinprick, as well as dynamic mechanical allodynia (DMA). Positive signs were also frequent in PNI (24.7–51.1%) and most infrequent in PNP (1.5–11.1%). DMA was much more frequent in postherpetic neuralgia (PHN, 48.6%) than in any other syndrome. The highest rate of paradoxical heat sensation (PHS) was observed in PNP (37.3%) and central pain (26.0%), and the lowest in CRPS and trigeminal neuralgia.

Thermal sensory loss was most frequent in central pain (CDT: 49.1%, WDT: 62.7%) and PHN (52.8–62.5%), relatively frequent in PNP and peripheral nerve injury (PNI), and rare in CRPS. Tactile sensory loss was most frequent in postherpetic neuralgia (40.3–62.5%) as well as in peripheral nerve injury (only MDT) and PNP (only VDT), but significantly less prevalent in trigeminal neuralgia (14.1–16.3%) and in CRPS (MDT).

Cold and heat pain hypoalgesia (CPT; HPT) were most frequent in peripheral nerve injury (14.3–16.2%) and rare in PNP. Heat pain hypoalgesia alone was frequent in PHN and central pain (not significant). Hypoalgesia to blunt pressure (PPT) was revealed at the highest rate in PNP (13.2%). Pinprick hypoalgesia (MPT or MPS) occurred frequently in central pain, PNP, peripheral nerve injury and postherpetic neuralgia.

For some syndromes, the same QST parameter showed either loss or gain in different subpopulations: for example 27.3% of the patients with peripheral nerve injury presented cold hyperalgesia, whereas 14.3% showed cold hypoalgesia. In all patients within the same entity there were comparable percentages showing either pinprick hypoalgesia (for example in PHN 19.5–26.4%) or pinprick hyperalgesia (PHN: 29.2–36.1%).

3.5. Combinations of sensory abnormalities

In order to display relevant combinations of sensory abnormalities, a coding system was applied (Table 2 and Appendix A). For this purpose, signs of hypoesthesia to thermal stimuli (loss of detection in CDT or WDT) were coded as L1 and signs of hypoesthesia to mechanical stimuli (loss of detection in MDT or VDT) as L2. Signs of hyperalgesia to thermal stimuli (gain of function in HPT or CPT) were coded as G1 and signs of hyperalgesia to mechanical stimuli (gain of function in MPT, MPS, DMA or PPT) as G2. When both thermal and mechanical abnormalities were present L3 or G3 were defined, respectively. Normal values were coded as zero (0).

According to the marginal sums, mechanical and thermal test results seem to run mostly in parallel, both being either normal (L0 27.9%, G0 34.1%) or abnormal (L3 34.5%, G3 24.1%). However, thermal tests were less frequently abnormal alone (L1 14.6%, G1 8.9%) than mechanical tests alone (L2 22.9%, G2 32.8%). There

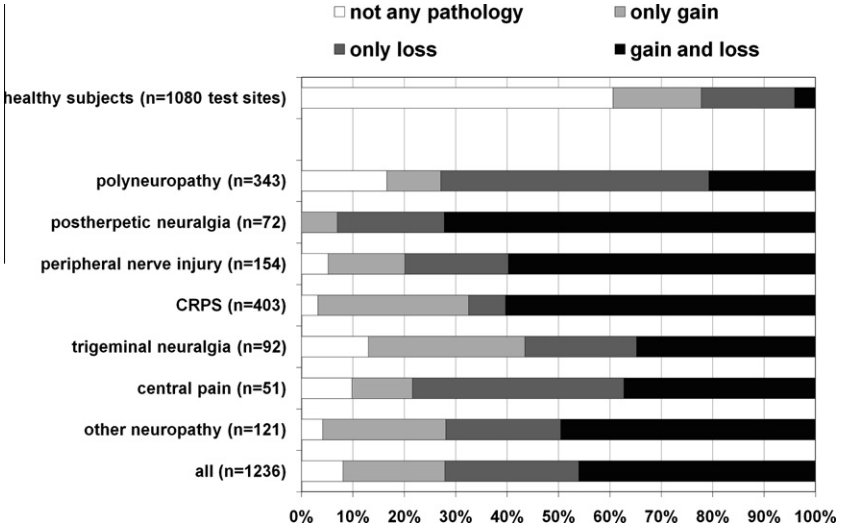

Fig. 4. Sensory findings (gain or loss) according to the neurological syndrome. For each patient ($n = 1236$) QST data of the painful area were scored. For each healthy subject ($n = 180$) all 6 test areas were scored, yielding 1080 areas. "Without any pathology": none of the QST parameters was outside the 95% CI and there was no relative abnormality, "Only loss": at least one abnormally increased thermal or mechanical detection threshold, but neither thermal nor mechanical hyperalgesia. "Only gain": at least one abnormally decreased thermal or mechanical pain threshold, increased mechanical pain sensitivity, decreased pressure pain threshold or DMA, but neither thermal nor tactile hypoesthesia. "Gain and loss": at least one positive sign combined with at least one negative sign.

Table 2
Frequency of different combinations of abnormal values in all patients.

Loss	Gain				
	0 (no)	1 (thermal)	2 (mechanical)	3 (both)	All
All patients					
0	100 (8.1%) **−18**	38 (3.1%) **7**	102 (8.3%) **−11**	105 (8.5%) **22**	**345 (27.9%)**
1	60 (4.9%) **−2**	14 (1.1%) **−2**	66 (5.3%) **6**	42 (3.4%) **−2**	**182 (14.7%)**
2	94 (7.6%) **−3**	29 (2.3%) **4**	82 (6.6%) **−11**	78 (6.3%) **10**	**283 (22.9%)**
3	168 (13.6%) **23**	29 (2.3%) **−9**	156 (12.6%) **16**	73 (5.9%) **−30**	**426 (34.5%)**
All	**422 (34.1%)**	**110 (8.9%)**	**406 (32.8%)**	**298 (24.1%)**	**1236 (100%)**

L0, no loss of detection; L1, only thermal loss; L2, only mechanical loss; L3, mixed loss of detection; G0, no gain (= no hyperalgesia); G1, with only thermal hyperalgesia; G2, with only mechanical hyperalgesia; G3 with both thermal and mechanical hyperalgesia. First row: number of patients (%), percentage of 1236; second row (bold): ± difference from the expected value if independent distribution assumed. Blue cells: significantly lower frequency, red cells: significantly higher by frequency two-sided configuration frequency analysis, without Bonferroni adjustment.

was an inverse relationship between sensory gain and sensory loss: Absence of any abnormality (L0G0) and also the opposite (L3G3) occurred significantly less frequently than expected if independent distribution was assumed, whereas mixed sensory loss without hyperalgesia (L3G0 13.7%) and no loss combined with mixed hyperalgesia (L0G3 8.5%) exceeded significantly the frequency predicted by the marginal sums. Sensory loss with mechanical hyperalgesia (L3G2 12.6%) was also a frequent combination.

There were some differences in the distribution of certain combinations of positive and negative sensory signs between syndromes (Appendix A). L3G0, i.e. mixed loss without any hyperalgesia, was the leading combination of sensory signs in central pain (27.5%) and PNP (24.2%) and the second most frequent in postherpetic neuralgia (13.9%). The combination of thermal and mechanical hyperalgesia without any loss of detection (L0G3) was significantly more frequent in CRPS than in the other syndromes (15.8%, $p < 0.05$). L3G2 (mixed loss combined with only mechanical hyperalgesia) was the leading combination in PHN (29.2%) and PNI (19.5%), and the second most frequent combination in patients with central pain (25.5%) or CRPS (14.1%). Mechanical hyperalgesia without sensory loss (L0G2) was the leading combination in trigeminal neuralgia (17.4%), but was uncommon in all other syndromes.

4. Discussion

This study reports systematic profiling of sensory abnormalities in a large number of patients with different neuropathic pain syndromes. About 92% of the patients presented at least one QST-abnormality. The new grading system for neuropathic pain [55] was not applied formally, because it was not available during the data collection, but the high percentage of somatosensory abnormalities suggests that most enrolled patients would fulfill the criteria for probable or definite neuropathic pain. Every single somatosensory abnormality occurred across all neuropathic pain syndromes studied, whereas the pattern of abnormalities differed across syndromes. About half of the patients had both negative and positive sensory signs, only negative signs were present in 26%, positive sensory signs alone in 20%. Mechanical tests revealed more abnormalities than thermal tests.

4.1. Negative sensory signs

In accordance with other trials [50] negative sensory signs were predominantly found in non-nociceptive parameters, with similar incidence for functions mediated by small fibers and spinothalamic tract neurons (CDT 40.4%, WDT 28.8%) and functions mediated by large fibers and dorsal column tracts (MDT 40.6%, VDT 39.5%). Negative signs in nociceptive parameters occurred in <10% (Appendix C, part B), except for pinprick hypoalgesia (17.8%).

Negative sensory signs are associated with central or peripheral neuronal damage which may lead to ongoing pain via increased ectopic activity [3,32,34,41,42,51,60]. For central pain syndromes, a spinothalamic function loss has been suggested as a necessary prerequisite [8]. This concept is supported by the high incidence of negative signs for CDT, WDT and MPT. But negative signs for MDT and VDT also occurred frequently. The frequent sensory loss in CRPS (Appendix C, part B) indicates either subclinical damage to small nerve branches or pain-induced functional hypoesthesia [2,4,16,37,39,49]. Trigeminal neuralgia is often associated with root damage by vascular compression without leading to clinically obvious sensory deficit [11,53].

4.2. Positive sensory signs

Positive sensory signs for non-nociceptive parameters were as rare as false positive findings in healthy subjects (<5%). In contrast, abnormal positive nociceptive QST parameters ranged from 19.4% (CPT) to 36.4% (PPT). Dynamic mechanical allodynia, (19.7%), paradoxical heat sensations (18.4%) and enhanced wind-up (12.6%) were also observed.

Given the large variability of CPT in healthy subjects, the relatively large percentage of patients with cold hyperalgesia is remarkable. Mechanisms of cold hyperalgesia are poorly understood including both peripheral sensitization and altered central processing [59]. Heat hyperalgesia is thought to be induced by peripheral sensitization of primary afferent C-fibers [56]. It was frequent in postherpetic neuralgia (PHN), peripheral nerve injury and CRPS, but also in central pain (9.8%), the latter suggesting a contribution of central mechanisms [19,35].

Hyperalgesia to pinprick was evident from threshold determination (MPT: 21.7%) as well as from suprathreshold testing (MPS: 29.2%), suggesting a leftward shift of the stimulus–response–function [48,57]. The close association with thermal hyperalgesia supports the hypothesis of central sensitization driven by peripheral input. Pinprick hyperalgesia also occurred together with pronounced sensory loss suggesting a contribution of enhanced neural responsiveness following deafferentation.

DMA is thought to be the consequence of a hyperexcitable state of central nociceptive neurons acquiring responsiveness to tactile input [52]. DMA was present in 19.7% of all patients, most frequently in PHN (48.6%). In other studies 90% of PHN patients presented DMA [28]. One reason for this discrepancy might be the

standardized test procedure of gentle stimuli intermingled with pinprick stimuli. Due to this successive contrast phenomenon unpleasant dysesthesia to brushing may be less frequently reported as pain.

Paradoxical heat sensation, i.e. a cold stimulus perceived as a burning hot painful sensation, is generated hypothetically by impaired central inhibition either by Aδ-cold-fiber loss or by affection of inhibitory thalamic centers [21,59]. In accordance, in our cohort PHS was most common in central pain (26%) and polyneuropathy (37.3%).

Repeated noxious stimuli are associated with a progressive increase in perceived pain intensity, provided that the stimuli are presented no more than three seconds apart [44]. This phenomenon, called temporal summation of pain, is the perceptual correlate of dorsal horn neurons wind-up. In some patients with neuropathic pain this phenomenon is exaggerated [38]. The abnormally enhanced wind-up ratio was most common in PHN (17.4%) and central pain (16.3%). Enhanced wind-up may be more frequent in other conditions such as major depression or pain associated with peripheral arterial disease [30,31].

4.3. Mechanism-based classification approach

Two hypotheses derived from the concept of a mechanism-based classification of neuropathic pain were supported by our data. (i) Despite obvious variation between the neurological syndromes, every single somatosensory sign and many combinations of signs occurred across the neuropathic pain syndromes studied, with about half of the patients exhibiting a combination of sensory loss and gain. (ii) In turn, different patients suffering from the same disease presented different phenotypes, i.e. pinprick hyper- vs. hypoalgesia. This dichotomy had previously been reported for PHN [15,46] and in small case series [7]; it now turned out to be prominent also in peripheral nerve injury and central pain (Appendix C, part B).

4.4. Characteristic patterns of somatosensory abnormalities in different syndromes

There were also notable differences between the somatosensory profiles for different syndromes. The highest rate of sensory abnormalities was found in PHN consistent with intraepidermal nerve fiber density reduction and abnormal neurophysiological responses [40,58]. Thermal and tactile sensory loss were equally frequent. PHN patients also had loss of pinprick sensation (26.4% MPT, 19.5% MPS) but in contrast to all other entities, the incidence of mechanical allodynia (48.6%) was higher than that of pinprick hyperalgesia (29.2% MPT, 36.1% MPS). Therefore, PHN cannot be considered as model for all other types of neuropathic pain.

The trigeminal neuralgia group excluded patients with clinically apparent sensory deficits according to the IHS definition. Therefore, the incidences of sensory loss (e.g. 38.1% CDT) and sensory gain (e.g. 25.0% HPT, 28.7% MPT) suggest that the DFNS QST battery may pick up subclinical abnormalities similarly to laser-evoked potentials [11,53].

Polyneuropathy and central pain were both characterized by low rates of positive and high rates of negative sensory signs (>50% for CDT), similarly to previous results [49]. Paradoxical heat sensation is a notable exception. Its occurrence in 26% of central pain and 37.3% of polyneuropathy patients supports the concept of a deficient inhibition of pain pathways by the thermosensory pathways [13,21,59].

In most of the animal models of neuropathic pain a mechanical peripheral nerve injury is induced and the behavioral hypersensitivity to stimuli such as brushing, cooling or von Frey hairs is assessed [48]. In patients with peripheral nerve injury or CRPS high rates of positive sensory signs were found, most pronounced for blunt pressure pain, followed by dynamic mechanical allodynia and pinprick hyperalgesia.

4.5. Technical considerations

Clinical examination alone does not provide a gold standard for the existence of a neuropathy or CNS lesion. Confirmatory investigations with clinical neurophysiology, radiology, or intraepidermal nerve fiber density measurements would have offered more accurate diagnostic tools for the neuropathy diagnosis and validation of the QST protocol, but were not available for this large group of patients.

In contrast to some authors considering QST primarily for group comparisons [24], the DFNS approach is intended to allow clinical judgments on a single case basis [54]. The dichotomy in pinprick pain sensitivity in PHN, peripheral nerve injury, and central pain (hypo- vs. hyperalgesia) was only detected by assessing each patient individually; group mean values would have appeared false-negatively normal.

Mechanical tests yielded more abnormalities than thermal tests, supporting our view that both stimulus modalities should be tested. Somatosensory profiling combining many QST parameters increases the likelihood to detect an abnormality in any given patient, but also the risk of false positive results. The likelihood in a healthy subject that all 11 QST parameters lie within the normal range can be calculated to be 57% (0.95^{11}), in accordance with our data of 59.4% in healthy subjects. Among patients, that percentage was much lower (8.1%); conservative cut-off values for some parameters may have resulted in false negative results compared to the clinical examination.

In case of unavoidable measurements outside the standard testing areas (face, dorsal hand and dorsal foot), only an approximative comparison to the available reference data was performed, additionally to the side-to-side comparison. Therefore, the syndrome-associated percentage of abnormal values may have to be corrected as soon as multi-center reference values for other body regions become available.

Each formal abnormality must be interpreted for its clinical relevance by an experienced physician, before conveying the findings to the patient. The DFNS has therefore initiated a certification process for QST laboratories for verification of standardized instructions, adequate equipment and training procedures and the correctness of result interpretation using the DFNS reference data [17,54].

5. Conclusions

The analysis of 13 QST parameters in 1236 neuropathic pain patients revealed a remarkable phenotypic heterogeneity across the major neuropathic pain syndromes, and thus confirmed two major predictions of the concept of mechanism-based classification of neuropathic pain. Future work should aim to establish firm links between somatosensory profiles and pathophysiological mechanisms, and to examine whether patients with different somatosensory profiles respond differentially to treatment. The tools developed by DFNS and this databank analysis provide a basis for such studies.

Acknowledgements

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Appendix A

Frequency of different combinations of abnormal values in patients with different neurological syndromes.

Loss	Gain 0 (no)	1 (thermal)	2 (mechanical)	3 (both)	All
Poly-neuropathy					
0	57 (16.6%) **−7**	8 (2.3%) **3**	20 (5.8%) **−1**	8 (2.3%) **6**	**93 (27.1%)**
1	30 (8.7%) **0**	2 (0.6%) **0**	12 (3.5%) **2**	(0%) **−1**	**44 (12.8%)**
2	59 (17.2%) **−6**	5 (1.5%) **0**	30 (8.7%) **8**	1 (0.3%) **−1**	**95 (27.7%)**
3	90 (26.2%) **14**	4 (1.2%) **−2**	17 (5%) **−9**	(0%) **−3**	**111 (32.4%)**
All	**236 (68.8%)**	**19 (5.5%)**	**79 (23%)**	**9 (2.6%)**	**343 (100%)**
Postherpetic neuralgia					
0	(0%) **−1**	1 (1.4%) **1**	(0%) **−2**	4 (5.6%) **3**	**5 (6.9%)**
1	2 (2.8%) **0**	(0%) **−1**	6 (8.3%) **2**	2 (2.8%) **0**	**10 (13.9%)**
2	3 (4.2%) **0**	1 (1.4%) **0**	5 (6.9%) **−2**	6 (8.3%) **2**	**15 (20.8%)**
3	10 (13.9%) **1**	4 (5.6%) **1**	21 (29.2%) **2**	7 (9.7%) **−4**	**42 (58.3%)**
All	**15 (20.8%)**	**6 (8.3%)**	**32 (44.4%)**	**19 (26.4%)**	**72 (100%)**
Peripheral nerve injury					
0	8 (5.2%) **0**	2 (1.3%) **0**	10 (6.5%) **−1**	11 (7.1%) **1**	**31 (20.1%)**
1	2 (1.3%) **−2**	3 (1.9%) **2**	7 (4.5%) **1**	4 (2.6%) **−1**	**16 (10.4%)**
2	11 (7.1%) **2**	2 (1.3%) **−1**	8 (5.2%) **−5**	16 (10.4%) **4**	**37 (24%)**
3	18 (11.7%) **0**	5 (3.2%) **0**	30 (19.5%) **5**	17 (11%) **−5**	**70 (45.5%)**
All	**39 (25.3%)**	**12 (7.8%)**	**55 (35.7%)**	**48 (31.2%)**	**154 (100%)**
CRPS					
0	13 (3.2%) **−1**	12 (3%) **2**	43 (10.7%) **−7**	63 (15.6%) **5**	**131 (32.5%)**
1	6 (1.5%) **0**	2 (0.5%) **−2**	24 (6%) **2**	26 (6.5%) **1**	**58 (14.4%)**
2	9 (2.2%) **−1**	11 (2.7%) **4**	30 (7.4%) **−7**	47 (11.7%) **4**	**97 (24.1%)**
3	14 (3.5%) **2**	5 (1.2%) **−4**	57 (14.1%) **12**	41 (10.2%) **−10**	**117 (29%)**
All	**42 (10.4%)**	**30 (7.4%)**	**154 (38.2%)**	**177 (43.9%)**	**403 (100%)**
Trigeminal neuralgia					
0	12 (13%) **−2**	8 (8.7%) **−1**	16 (17.4%) **3**	4 (4.3%) **−1**	**40 (43.5%)**
1	11 (12%) **2**	4 (4.3%) **−2**	8 (8.7%) **0**	3 (3.3%) **0**	**26 (28.3%)**
2	2 (2.2%) **−1**	4 (4.3%) **2**	2 (2.2%) **−1**	2 (2.2%) **1**	**10 (10.9%)**
3	7 (7.6%) **1**	4 (4.3%) **1**	3 (3.3%) **−2**	2 (2.2%) **0**	**16 (17.4%)**
All	**32 (34.8%)**	**20 (21.7%)**	**29 (31.5%)**	**11 (12%)**	**92 (100%)**

(*continued on next page*)

Appendix A (*continued*)

Loss	Gain 0 (no)	1 (thermal)	2 (mechanical)	3 (both)	All
Central pain					
0	5 (9.8%)	(0%)	3 (5.9%)	2 (3.9%)	**10 (19.6%)**
	0	**0**	**−1**	**1**	
1	3 (5.9%)	(0%)	2 (3.9%)	1 (2%)	**6 (11.8%)**
	0	**0**	**0**	**0**	
2	4 (7.8%)	(0%)	(0%)	1 (2%)	**5 (9.8%)**
	1	**0**	**−2**	**1**	
3	14 (27.5%)	2 (3.9%)	13 (25.5%)	1 (2%)	**30 (58.8%)**
	−1	**1**	**2**	**−2**	
All	**26 (51%)**	**2 (3.9%)**	**18 (35.3%)**	**5 (9.8%)**	**51 (100%)**

L0, no loss of detection; L1, only thermal loss, L2, only mechanical loss; L3, mixed loss of detection; G0, no gain (= no hyperalgesia); G1, with only thermal hyperalgesia; G2, with only mechanical hyperalgesia; G3, with both thermal and mechanical hyperalgesia. First row: number of patients (%), percentage within the same etiology; second row: ± difference from the expected value if independent distribution assumed. Blue cells: significantly lower frequency, red cells: significantly higher by frequency two-sided configuration frequency analysis, without Bonferroni adjustment.

Appendix B

Mean ± standard deviation of the QST parameters after z-transformation in the normal reference data base ([35], modified from [46]) and in patients with neuropathic pain.

	reference data				**patients' data**			
	n	**mean ± SD**	**< −1,96[a]**	**> 1,96[a]**	**n**	**mean ± SD**	**< −1,96[a]**	**> 1,96[a]**
CDT	1080	0.00 ± 1.00	34 3.1%	11 1.0%	1236	−1.42 ± 1.54	434 35.1%	11 0.9%
WDT	1080	0.01 ± 1.00	31 2.9%	16 1.5%	1235	−1.14 ± 1.39	296 24.0%	10 0.8%
TSL	1080	0.01 ± 0.99	18 1.7%	37 3.4%	1233	−1.27 ± 1.33	370 30.0%	11 0.9%
CPT	1080	0.01 ± 0.98	2 0.2%	17 1.6%	1235	0.29 ± 1.21	0 0.0%	133 10.8%
HPT	1080	0.02 ± 0.99	1 0.1%	25 2.3%	1235	0.25 ± 1.67	46 3.7%	218 17.7%
PPT	1078	0.04 ± 0.98	29 2.7%	28 2.6%	1199	1.13 ± 2.57	74 6.2%	315 26.3%
MPT	1080	−0.02 ± 0.99	12 1.1%	37 3.4%	1232	0.13 ± 1.70	158 12.8%	190 15.4%
MPS	1080	0.00 ± 0.99	3 0.2%	40 3.7%	1228	0.37 ± 1.52	49 4.0%	207 16.9%
WUR	1068	0.02 ± 1.00	2 0.2%	45 4.2%	1099	0.21 ± 1.12	3 0.3%	82 7.5%
MDT	1080	0.03 ± 0.99	33 3.1%	12 1.1%	1232	−1.52 ± 3.10	396 32.1%	26 2.1%
VDT*	1078	0.00 ± 0.99	55 5.1%	0 0.0%	1175	−1.59 ± 2.82	402 32.6%	0 0.0%
all			**1.9 ± 1.7%**	**2.3 ± 1.3%**			**16.4 ± 14.4%**	**9.0 ± 8.6%**

a: z-transformed values outside the 95% confidence intervals of the normal range. modified from [45]), CDT: cold detection threshold, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, MPS: mechanical pain sensitivity, MPT: mechanical pain threshold, PPT: pressure pain threshold, SD: standard deviation, TSL: thermal sensory limen, VDT: vibration detection threshold, WDT: warm detection threshold, WUR: wind-up ratio. *: in cases of QST in the shoulder area (n=8), in the thoracic area (n=38) or in the low back area (n=11) VDT was excluded from the comparison to the reference data base and Z-values were not calculated.

Appendix C

Frequency of abnormal values (A: gain; B: loss).

A: GAIN	PNP (n = 343)	PHN (n = 72)	PNI (n = 154)	CRPS (n = 403)	TN (n = 92)	CP (n = 51)	other* (n = 121)	All (n = 1236)
CDT	1 (0.3%) −6	1 (1.4%) 0	3 (2%) 0	11 (2.7%) 3	4 (4.4%) 2	1 (2%) 0	4 (3.3%) 2	**25 (2%)#**
WDT	3 (0.9%) −3	1 (1.4%) 0	1 (0.7%) −1	10 (2.5%) 3	1 (1.1%) 0	2 (3.9%) 1	2 (1.7%) 0	**20 (1.6%)#**
TSL	2 (0.6%) −6	3 (4.2%) 1	2 (1.3%) −1	11 (2.7%) 2	3 (3.3%) 1	2 (3.9%) 1	5 (4.1%) 2	**28 (2.3%)**
CPT	5 (1.5%) −62	15 (20.8%) 1	42 (27.3%) 12	123 (30.5%) 45	16 (17.6%) −2	3 (5.9%) −7	36 (29.8%) 13	**240 (19.4%)**
HPT	24 (7%) −58	15 (20.8%) −2	38 (24.7%) 1	161 (40.1%) 65	23 (25%) 1	5 (9.8%) −7	28 (23.1%) −1	**294 (23.8%)**
PPT	17 (5%) −104	25 (38.5%) 0	75 (51%) 21	262 (66.3%) 120	8 (9.2%) −24	8 (16%) −10	41 (36.3%) −2	**436 (36.4%)**
MPT	38 (11.1%) −36	21 (29.2%) 5	41 (27%) 8	115 (28.7%) 28	14 (15.2%) −6	11 (21.6%) 0	27 (22.3%) 1	**267 (21.7%)**
MPS	29 (8.5%) −71	26 (36.1%) 5	45 (29.6%) 0	187 (46.6%) 70	23 (25.8%) −4	12 (23.5%) −3	37 (30.8%) 2	**359 (29.2%)**
WUR	20 (6.9%) −18	12 (17.9%) 4	23 (17.4%) 6	48 (13.1%) 3	14 (15.7%) 4	7 (16.3%) 1	14 (12.6%) 0	**138 (12.6%)**
MDT	1 (0.3%) −16	4 (5.6%) 0	14 (9.2%) 6	38 (9.5%) 18	– −5	- −3	4 (3.3%) −2	**61 (5%)**
VDT	– −6	4 (2.6%) 3	4 (2.6%) 2	6 (1.5%) −1	4 (4.4%) 3	- −1	5 (4.2%) 3	**23 (1.9%)#**
PHS	128 (37.3%) 65	11 (15.3%) −2	23 (14.9%) −5	38 (9.4%) −36	– −17	13 (26%) 4	14 (11.6%) −8	**227 (18.4%)**
DMA	41 (12%) −26	35 (48.6%) 21	27 (17.5%) −3	97 (24.1%) 18	13 (14.6%) −5	9 (17.7%) −1	21 (17.5%) −3	**243 (19.7%)**

B: Loss	PNP (n = 343)	PHN (n = 72)	PNI (n = 154)	CRPS (n = 403)	TN (n = 92)	CP (n = 51)	other* (n = 121)	All (n = 1236)
CDT	138 (40.2%) 0	45 (62.5%) 16	75 (48.7%) 13	131 (32.5%) −32	35 (38.1%) −2	25 (49%) 4	50 (41.3%) 1	**499 (40.4%)**
WDT	63 (18.4%) −36	38 (52.8%) 17	55 (35.7%) 11	107 (26.6%) −9	23 (25%) −3	28 (54.9%) 13	41 (33.9%) 6	**355 (28.8%)**
TSL	125 (36.7%) 4	40 (55.6%) 15	66 (42.9%) 12	108 (26.9%) −34	22 (23.9%) −11	32 (62.7%) 14	44 (36.4%) 1	**437 (35.5%)**
CPT	– −20	4 (5.6%) 0	22 (14.3%) 13	21 (5.2%) −2	6 (6.6%) 1	5 (9.8%) 2	13 (10.7%) 6	**71 (5.8%)**
HPT	17 (5%) −15	13 (18.1%) 6	25 (16.2%) 11	31 (7.7%) −7	6 (6.5%) −3	9 (17.7%) 4	15 (12.4%) 4	**116 (9.4%)**
PPT	45 (13.2%) 20	4 (6.2%) −1	8 (5.4%) −3	13 (3.3%) −16	5 (5.8%) −2	7 (14%) 3	7 (6.2%) −2	**89 (7.4%)**
MPT	75 (21.9%) 14	19 (26.4%) 6	39 (25.7%) 12	40 (10%) −31	11 (12%) −5	12 (23.5%) 3	23 (19%) 2	**219 (17.8%)**
MPS	17 (5%) −19	14 (19.5%) 6	32 (21.1%) 16	25 (6.2%) −18	9 (10.1%) −1	15 (29.4%) 10	19 (15.8%) 6	**131 (10.7%)**
WUR	1 (0.4%) −6	1 (1.5%) 0	3 (2.3%) 0	10 (2.7%) 2	3 (3.4%) 1	- −1	6 (5.4%) 4	**24 (2.2%)#**
MDT	136 (39.8%) −3	45 (62.5%) 16	88 (57.5%) 26	141 (35.2%) −22	15 (16.3%) −22	25 (49%) 4	50 (41.3%) 1	**500 (40.6%)**
VDT+	157 (45.9%) 26	31 (40.3%) 3	65 (42.2%) 6	142 (35.4%) −12	13 (14.1%) −22	22 (43.1%) 3	43 (35.8%) −3	**473 (38.7%)**

First row: for different diagnosis combined absolute and relative abnormal values (A: gain; B: loss), %: percentages of the number of patients with the same etiology. Second row: ± difference of the observed from the expected value if independent distribution assumed. Blue cells: significantly lower frequency within a QST parameter across etiologies except other (*). Red cells: significantly higher frequency by two-sided configuration frequency analysis, without Bonferroni adjustment. #: no configuration frequency analysis performed because < 5% frequency at all. +: in cases of QST in the shoulder area (n = 8), in the thoracic area (n = 38) or in the low back area (n = 11) abnormal values for VDT were evaluated only by side-to-side comparison.

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