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Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values

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Abstract

The nationwide multicenter trials of the German Research Network on Neuropathic Pain (DFNS) aim to characterize the somatosensory phenotype of patients with neuropathic pain. For this purpose, we have implemented a standardized quantitative sensory testing (QST) protocol giving a complete profile for one region within 30 min. To judge plus or minus signs in patients we have now established age- and gender-matched absolute and relative QST reference values from 180 healthy subjects, assessed bilaterally over face, hand and foot. We determined thermal detection and pain thresholds including a test for paradoxical heat sensations, mechanical detection thresholds to von Frey filaments and a 64 Hz tuning fork, mechanical pain thresholds to pinprick stimuli and blunt pressure, stimulus/response-functions for pinprick and dynamic mechanical allodynia, and pain summation (wind-up ratio). QST parameters were region specific and age dependent. Pain thresholds were significantly lower in women than men. Detection thresholds were generally independent of gender. Reference data were normalized to the specific group means and variances (region, age, gender) by calculating *z*-scores. Due to confidence limits close to the respective limits of the possible data range, heat hypoalgesia, cold hypoalgesia, and mechanical hyperesthesia can hardly be diagnosed. Nevertheless, these parameters

Abbreviations: ALL, dynamic mechanical allodynia; CDT, cold detection threshold; CPT, cold pain threshold; DFNS, Deutscher Forschungsverbund Neuropathischer Schmerz = German Research Network on Neuropathic Pain; 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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can be used for group comparisons. Sensitivity is enhanced by side-to-side comparisons by a factor ranging from 1.1 to 2.5. Relative comparisons across body regions do not offer advantages over absolute reference values. Application of this standardized QST protocol in patients and human surrogate models will allow to infer underlying mechanisms from somatosensory phenotypes.

Keywords: QST; Sensory profile; Allodynia; Hyperalgesia; Hypoesthesia; Hypoalgesia; Paradoxical heat sensation; Standardized instructions; Reference data; *z*-score; Sensory profiling

1. Introduction

The modern concept of a mechanism based treatment of pain syndromes is based on the hypothesis that different clinical signs and symptoms reflect different underlying pathophysiological mechanisms of pain generation (Greenspan, 2001; Hansson, 2002; Jensen and Baron, 2003). Extensive animal experimental work suggests that a variety of mechanisms operate alone or in concert that determine a characteristic constellation of sensory signs and symptoms, e.g., burning pain, heat hyperalgesia or mechanical hyperalgesia (Woolf and Salter, 2000).

In order to translate these ideas into the clinical framework of diagnosis and treatment of neuropathic pain and to validate the hypotheses, the most important approach is to characterize the somatosensory phenotype of the patients as precisely as possible. A thorough analysis of each sign and symptom and in particular of the characteristic somatosensory pattern is of utmost importance to identify subgroups of patients and to correlate the specific individual pattern with the likely underlying mechanisms, i.e. to perform a mechanism based diagnosis. The next step would be to perform clinical treatment trials in these subgroups of patients with distinct somatosensory patterns to substantiate the mechanism based treatment concept.

In 2002 the German Research Network on Neuropathic Pain (DFNS) has been founded in order to establish a database of phenotypically characterized patients with various neuropathic pain states and to perform research studies and clinical trials in this cohort of patients (http://www.neuro.med.tu-muenchen.de/dfns/e_index.html). Towards this aim the main focus of the present multicenter study was:

- to implement a standardized quantitative sensory testing protocol for the somatosensory analysis of patients with neuropathic pain,
- to establish age- and gender-matched reference values for these QST parameters.

We extended previous QST protocols such as the CASE IV system (Dyck et al., 1993) by including both thermal and mechanical test stimuli to assess gain and loss of sensory functions, and to determine different types of hyperalgesia, dynamic mechanical allodynia, and hyperpathia. It was our rationale to examine both cutaneous and deep pain sensitivity in order to create profiles of sensory signs related to underlying mechanisms (Price and Dubner, 1977; Devor, 1991; Bennett, 1994; Bendtsen et al., 1996; Fields et al., 1998; Baumgärtner et al., 2002; Hansson, 2002; Treede et al., 2002; Dworkin et al., 2003; Wilder-Smith et al., 2003). The present nationwide DFNS multicenter trial provides complete sensory profiles from 180 healthy human subjects, 18 from each of 10 participating centers. All investigators were centrally trained and adhered to a standardized protocol regarding verbal instructions of the healthy volunteers and technical handling of the QST procedures. Data were analyzed for the influence of age, gender, body side and body region (face, hand and foot). Effect sizes for body region, age and gender differences were calculated for each QST parameter allowing comparisons across parameters. Sensitivity of absolute vs. relative QST reference values was compared for side-to-side contrasts and across body regions. On the basis of absolute QST reference values *z*-score sensory profiles were compiled that ultimately might be used to dissect differences in neurobiological mechanisms in individual neuropathic pain patients.

2. Methods

The German Research Network on Neuropathic Pain (DFNS) has developed a standardized QST battery that consists of 7 tests measuring 13 parameters (Rolke et al., 2006). The tests can be grouped as follows:

- Thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations,
- thermal pain thresholds for cold and hot stimuli,
- mechanical detection thresholds for touch and vibration,
- mechanical pain sensitivity including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (wind-up like pain).

In order not to exceed the time constraints of clinical routine, the protocol was designed to obtain two full sensory profiles within 1 h. The tests were always performed in the same order, as listed in Sections 2.2–2.8. In the present multicenter trial all healthy human subjects were investigated bilaterally over face, hand and foot, which took ~3 h – including a demonstration of each test at a practice area. Subjects looked at a spot on the wall or kept their eyes closed throughout the QST procedure.

In each participating center all QST procedures were performed by trained observers using the same equipment and standardized instructions to the subjects (for standardized

instructions see online supplementary data: Appendix 1, QST videos). All observers were trained by the same instructor (RR) in a 1-day training session.

2.1. Subjects

Each of 10 participating centers of the German Research Network on Neuropathic Pain (DFNS) contributed data from 18 healthy human subjects covering an age range between 17 and 75 years (38.4 ± 12.9 years, mean $\pm$ SD). More women ($n = 110$; 61.1%) than men ($n = 70$; 38.9%) were included. There was no difference in age between women (38.9 ± 13.0) and men (37.5 ± 13.0). Healthy subjects were identified according to medical history. Subjects were specifically questioned about migraine headaches and low back pain. Subjects suffering from any acute or chronic pain condition were excluded. All subjects were without any pain medication for at least 24 h before the investigation. The study was approved by the Ethics Committee of Kiel and local Ethics Committees of the participating centers. All subjects participated after written informed consent.

2.2. Thermal detection and pain thresholds and the number of paradoxical heat sensations

The thermal tests were performed using either a TSA 2001-II (MEDOC, Israel, available in seven centers) or a MSA (SOMEDIC, Sweden, available in three centers). Cold and warm detection thresholds were measured first (CDT, WDT). In addition, subjects were asked about paradoxical heat sensations (PHS) during the thermal sensory limen (TSL) procedure of alternating warm and cold stimuli. Then cold pain and heat pain thresholds were determined (CPT, HPT). The mean threshold temperature of three consecutive measurements was calculated. All thresholds were obtained with ramped stimuli (1 °C/s) that were terminated when the subject pressed a button. For thermal detection thresholds the ramp back to baseline was 1 °C/s, while for thermal pain thresholds this ramp was chosen at maximum device capacity resulting in nominal ~5 °C/s. The baseline temperature was 32 °C and the contact area of the thermode was 9.0 cm^2 for the TSA, and 12.5 cm^2 for the MSA. The small difference in thermode size would at most lead to a 0.5 °C difference in threshold (Defrin and Urca, 1996). Cut-off temperatures were 0, 50 °C for the TSA, and 5, 50 °C for the MSA. There was no difference in reference ranges of CPT between using the 0 or 5 °C lower cut-off.

2.3. Mechanical detection threshold

The mechanical detection threshold (MDT) was measured with a standardized set of modified von Frey hairs (Optihair$_2$-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512 mN graded by a factor of 2 (1–2 s contact time). The contact area of the von Frey hairs with the skin was of uniform size and shape (rounded tip, 0.5 mm in diameter) to avoid sharp edges that would facilitate nociceptor activation. Using the "method of limits", five threshold determinations were made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these five series.

2.4. Mechanical pain threshold

The mechanical pain threshold (MPT) was measured using custom-made weighted pinprick stimuli as a set of seven pinprick mechanical stimulators with fixed stimulus intensities (flat contact area of 0.2 mm diameter) that exerted forces of 8, 16, 32, 64, 128, 256, and 512 mN. The stimulators were applied at a rate of 2 s on, 2 s off in an ascending order until the first percept of sharpness was reached. The final threshold was the geometric mean of five series of ascending and descending stimuli. This test was designed to detect pinprick hypoalgesia.

2.5. Stimulus/response-functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia

Mechanical pain sensitivity (MPS) was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain (the strongest pinprick force was about eight times the mean mechanical pain threshold). Subjects were asked to give a pain rating for each stimulus on a '0–100' numerical rating scale ('0' indicating "no pain", and '100' indicating "most intense pain imaginable"). This test was designed to detect pinprick hyperalgesia.

Dynamic mechanical allodynia (ALL) was assessed as part of the test above, using a set of three light tactile stimulators as moving innocuous stimuli: Cotton wisp exerting a force of ~3 mN, a cotton wool tip fixed to an elastic strip exerting a force of ~100 mN, and a standardized brush (Somedic, Sweden) exerting a force of ~200–400 mN. The tactile stimuli were applied with a single stroke of approximately 2 cm in length over the skin. These stimuli were inserted into the balanced protocol in between the pinprick stimuli.

A total of 50 stimuli, 15 tactile and 35 pinprick, were delivered at each site with the subject giving numerical pain ratings for each stimulus. These stimuli were given in runs of 10 (five runs per test site), and each run consisted of a different pseudo-random sequence of three tactile and seven pinprick stimuli. All stimuli were applied with a ~10 s inter-stimulus interval – well below the critical frequency for wind-up. Mechanical pain sensitivity was calculated as the geometric mean of all numerical ratings for pinprick stimuli. Dynamic mechanical allodynia was calculated as the geometric mean (compound measure) of all numerical ratings across all three different types of light touch stimulators.

2.6. Wind-up ratio representing the perceptual correlate of temporal pain summation

In this test, the perceived intensity of a single pinprick stimulus (128 mN pinprick, when tested over face, and 256 mN pinprick, when tested over hand and foot) was compared with that of a series of 10 repetitive pinprick stimuli of the same physical intensity (1/s applied within an area of 1 cm^2). The subject was asked to give a pain rating representing the single stimulus, and the estimated mean over the whole series of 10 stimuli using a '0–100' numerical rating scale. The whole procedure was repeated five times. Wind-up ratio (WUR) was calculated as the ratio: mean rating of the five series divided by the mean rating of the five single stimuli. Wind-up is a frequency dependent increase in excitability of spinal cord neurons

that reaches a plateau after about five stimuli (Herrero et al., 2000), the perceptual correlate of which can be described by this ratio.

2.7. Vibration detection threshold

The vibration detection threshold (VDT) represents the only disappearance threshold within the proposed QST battery. This test was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed over a bony prominence (cheek, processus styloideus ulnae, malleolus internus) and left there until the subject could not feel vibration any more. Vibration detection threshold was determined as a disappearance threshold with three stimulus repetitions. Though this device has been developed a hundred years ago, it still proves its usefulness in current clinical trials (e.g., Whitton et al., 2005).

2.8. Pressure pain threshold (PPT)

The final test in the protocol was performed over muscle (M. masseter, thenar eminence, instep) with a pressure gauge device (FDN200, Wagner Instruments, USA) with a probe area of 1 cm^2 (probe diameter of 1.1 cm) that exerts forces up to 20 kg/cm^2 corresponding to ~2000 kPa. The pressure pain threshold was determined with three series of ascending stimulus intensities, each applied as a slowly increasing ramp of 50 kPa/s (~0.5 kg/cm^2 s).

2.9. Data evaluation

All data except the numbers of paradoxical heat sensations during the TSL procedure, cold pain thresholds, heat pain thresholds, and vibration detection thresholds were normally distributed in log-space and were transformed logarithmically before statistical analysis (Rolke et al., 2006). All statistical calculations were performed using 'Statistica' software for Windows (StatSoft Inc., USA). Differences between tested regions, right and left sides of the body, age and gender were compared using a four-way analysis of variance (ANOVA) with body region and side as within-subjects factors and age and gender as between-subjects factors. The factor body side was nested under the factor body region to eliminate higher order interactions. Post hoc comparisons were calculated using LSD-post hoc tests.

All data are presented as mean ± SD. Reference data are given as means and 95% confidence intervals (mean ± 1.96SD). For this purpose, data of log transformed QST parameters were retransformed to values representing the original unit of each test. Absolute reference data (specific for body region, age and gender) were used to normalize test results of individual patients by calculating the z-transform: $Z = (\text{value}_{\text{patient}} - \text{mean}_{\text{controls}})/\text{SD}_{\text{controls}}$.

Relative reference data for right–left comparisons were calculated by subtracting the QST data of the left-hand side from the right-hand side of the body for each individual subject and body region. Since the mean right–left differences were zero, the 95% confidence interval of relative reference data was calculated as zero ±1.96SD. For relative reference data across body regions, systematic differences in mean values were taken into account. The relative reference ranges were compared with absolute reference ranges in order to describe which measure is more sensitive to detect sensory plus or minus signs. For this purpose, we averaged the group-specific (body region/side, age, gender = ANOVA factors) standard deviations of absolute reference data. This represents the best case scenario for the use of absolute reference data, since regional and other systematic differences were adequately accounted for.

3. Results

The DFNS reference database consists of 13 parameters obtained for 6 body regions in 180 subjects. In 12 cases, mostly the lower limbs of older men, the wind-up ratio (WUR) could not be calculated, because the denominator (mean rating for the single pinprick stimulus) was zero (12/1080 wind-up ratios = 1.1%). Dynamic mechanical allodynia (ALL) did not occur in healthy human subjects. Paradoxical heat sensations (PHS) significantly occurred only for stimulation of the feet, where up to one PHS in response to three cold stimuli was normal in the age group over 40 years. For the remaining QST parameters, four-way ANOVAs were calculated for the within-subjects factors region and body side (nested under region) and the between-subjects factors age and gender (Table 1).

Mean values of all QST parameters except the wind-up ratio (WUR) were region specific, but there were no significant left–right differences. Therefore, data from left and right body side were combined for absolute reference data. Since WUR is a ratio, region specific differences in pinprick sensitivity were probably eliminated by being similar in both numerator and denominator. For all QST parameters, sensitivity was higher in the face than in the foot (Fig. 1, for precise values see Appendix 2 of online supplementary material). Sensitivity in the hand was usually intermediate, except for the mechanical pain threshold to pinprick stimuli (MPT; lowest sensitivity in the hand) and the vibration detection threshold (VDT; highest sensitivity in the hand). These findings confirm that each body region needs its own QST reference data. This factor had the largest effect size (Table 1, bottom part), much bigger than those for age and gender.

Older subjects (⩾40 years) were significantly less sensitive than younger subjects for all QST parameters (at least, $p < 0.01$) except the three pinprick-evoked measures (MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio). The largest effect sizes for age were found for cold pain threshold (CPT) and vibration detection threshold (VDT; see also Table 1). The significant age × region interactions indicate that age related differences were usually most pronounced for the foot (see Appendix 2 of online supplementary material).

The pain thresholds (CPT: cold pain threshold, HPT: heat pain threshold, MPT: mechanical pain threshold,

Table 1
ANOVA and effect sizes comparing body regions, age groups and gender for different QST parameters

	CDT	WDT	TSL	PHS	CPT	HPT	MDT	MPT	MPS	ALL	WUR	VDT	PPT
ANOVA-factor													
1 region	<0.001	<0.001	<0.001	[a]	<0.001	<0.001	<0.001	<0.001	<0.001	[a]	n.s.	<0.001[c]	<0.001
Side (nested in region)	n.s.	n.s.	n.s.	[a]	n.s.	n.s.	n.s.	n.s.	n.s.	[a]	n.s.	n.s.	n.s.
2 age	<0.001	<0.01	<0.01	[a]	<0.001	<0.001	<0.001	n.s.	n.s.	[a]	n.s.	<0.001	<0.001
3 gender	n.s.	n.s.	n.s.	[a]	<0.01	<0.001	<0.05	<0.01	n.s.[b]	[a]	n.s.	n.s.	<0.001
1 × 2	<0.05	<0.05	<0.01	[a]	n.s.	n.s.	<0.001	<0.01	n.s.	[a]	n.s.	<0.001	<0.01
1 × 3	<0.001	<0.01	<0.01	[a]	n.s.	n.s.	<0.001	n.s.	n.s.	[a]	n.s.	n.s.	n.s.
2 × 3	n.s.	n.s.	n.s.	[a]	n.s.	n.s.	n.s.	<0.05	n.s.	[a]	n.s.	n.s.	n.s.
1 × 2 × 3	n.s.	n.s.	n.s.	[a]	n.s.	n.s.	n.s.	n.s.	n.s.	[a]	n.s.	n.s.	n.s.
Effect size of													
Face vs. foot	1.652	2.391	2.345	[a]	0.296	0.572	2.349	0.724	0.195	[a]	0.017	0.018[c]	2.765
Age differences	0.289	0.192	0.255	[a]	0.516	0.380	0.283	0.070	0.055	[a]	0.130	0.435	0.249
Gender differences	0.052	0.095	0.061	[a]	0.284	0.499	0.139	0.319	0.164[b]	[a]	0.036	0.087	0.283

The first part of this table comprises *p*-values derived from a four-way ANOVA. This analysis was calculated as a repeated measurements ANOVA for the effect of body region and side with factor side nested under factor region. The second part of this table encompasses the effect sizes for body region contrasts (face vs. foot), age and gender differences.

[a] There was no significant occurrence of PHS and ALL in healthy human subjects.

[b] $p = 0.18$ (gender effect on MPS).

[c] Significant effect of region due to hand vs. foot difference.

and PPT: pressure pain threshold) were significantly lower in women than men (at least, $p < 0.01$), whereas the main effect was not significant for the detection thresholds (Table 1). Thermal detection thresholds (CDT: cold detection threshold, WDT: warm detection threshold, and TSL: thermal sensory limen), however, exhibited a significant gender × region interaction, indicating that the higher temperature sensitivity of women was only significant in the lower limbs (see Appendix 2 of online supplementary material). The largest effect sizes for gender differences were found for heat pain (HPT), followed by cold pain (CPT) and pain to blunt pressure (PPT).

3.1. Available data ranges for the detection of sensory plus and minus signs

Region specific mean values and 95% confidence intervals of all QST parameters are shown in Fig. 1. Most confidence intervals were asymmetric, because the majority of measures (CDT, WDT, TSL, MDT, MPT, MPS, ALL, WUR, and PPT) were log-normally distributed (Rolke et al., 2006). The danger of causing tissue damage on one hand, and the resolution of the stimulus devices on the other hand determine the upper and lower limits of available data ranges in sensory testing. All *y*-axes in Fig. 1 display the full available data range per variable, thus enabling us to illustrate the a priori limits of data ranges for sensory plus and minus signs (shaded areas). A plus sign signifies gain of sensory function (reduced threshold or increased rating), a minus sign loss of sensory function.

With 13 QST parameters a total of 26 possible hyper- or hypophenomena might be determined (Table 2). For the number of paradoxical heat sensations (PHS) and dynamic mechanical allodynia (ALL) it is a priori impossible to assess a pathological reduction, since these signs are normally absent. Thus, only 24 of these 26 theoretical abnormalities are observable in principle. As summarized in Table 2, the upper confidence limits of thermal pain thresholds (CPT, HPT) and the lower confidence limits of tactile and vibration detection thresholds (MDT, VDT) were close to the limits of the possible data ranges. Thus, heat and cold hypoalgesia as well as mechanical hyperesthesia can rarely appear in the sensory phenotype obtained with this QST profile. This leaves a total of 20 out of 24 plus or minus signs that are detectable corresponding to 83% of all possible hyper- or hypophenomena.

3.2. Sensory profiles related to absolute reference data

In order to depict individual QST findings in a given patient, either raw data or logarithmically transformed raw data (depending on QST parameter) were *z*-transformed by subtracting the mean value of the corresponding reference group (see Appendix 2 of online supplementary material) followed by a division by the respective standard deviation. If the resulting *z*-value exceeds 1.96, it is outside the 95% confidence interval of the standard normal distribution with zero mean and unit variance, independent of the original units of measurement. Fig. 2 shows two examples of QST profiles in patients with postherpetic neuralgia. Although both patients had similar levels of ongoing pain, one patient exhibited positive sensory signs (heat hyperalgesia, mechanical hyperalgesia to pinprick and blunt stimuli, allodynia to light touch) and the other patient negative sensory signs (thermal and mechanical hypoesthesia).

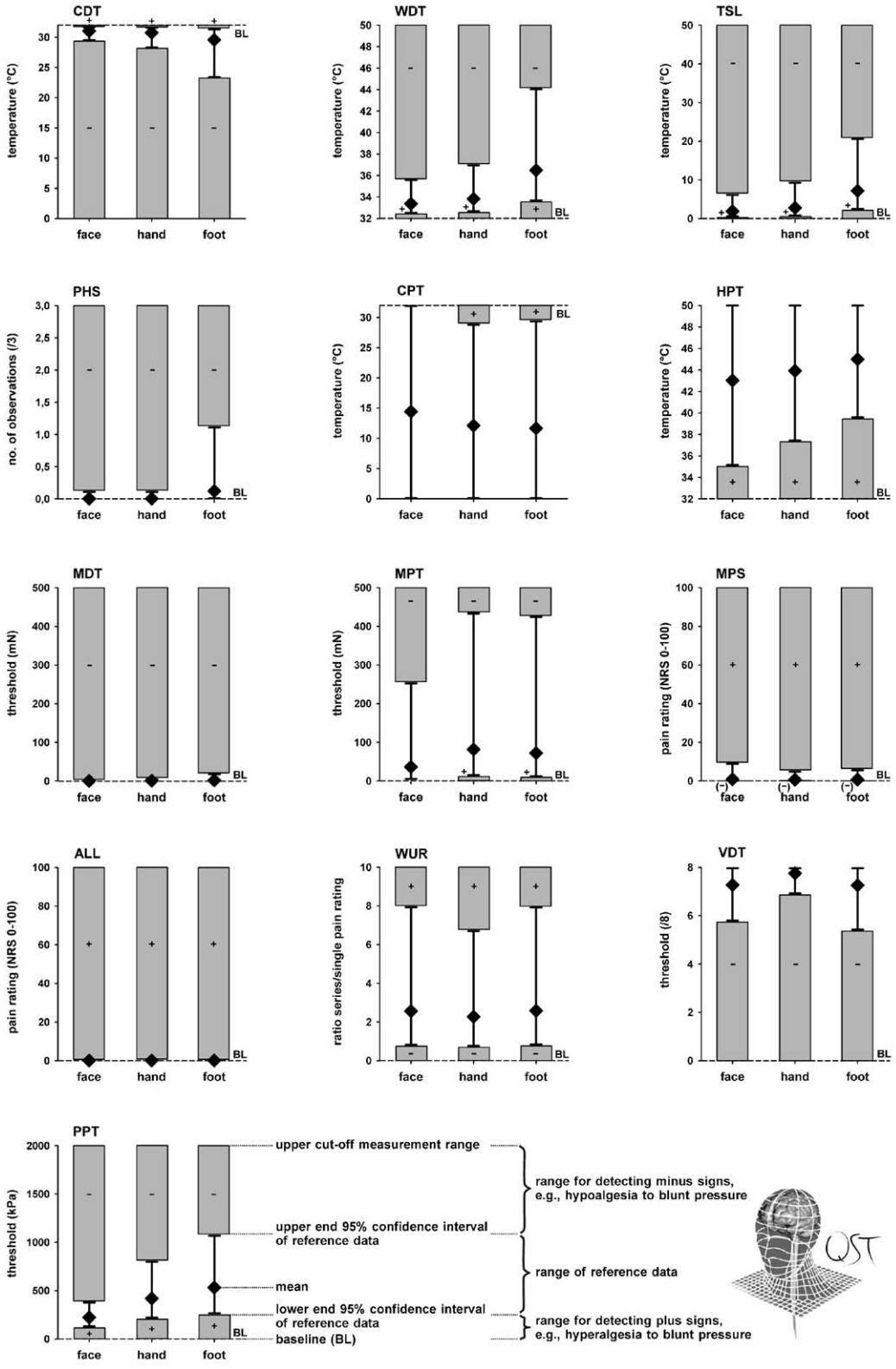

Fig. 1. Ranges of absolute QST reference data allow judgement of plus and minus signs. Absolute QST reference ranges are presented over different body regions across all age groups and gender ($n = 180$ per area). Absolute QST data are presented as means (filled diamonds) ±95% confidence intervals reflecting the reference range in healthy human subjects. Grey bars indicate the measurable range of plus and minus signs for each QST parameter. Most QST parameters allow judgement of clear plus and minus signs. For cold pain hypoalgesia, heat pain hypoalgesia and mechanical hyperesthesia the 95% confidence intervals of the reference data reach the limits of the measurement range. Data from right and left body side combined.

Table 2
Detectability of minus and plus signs for different QST parameters

	CDT	WDT	TSL	PHS	CPT	HPT	MDT	MPT	MPS	ALL	WUR	VDT	PPT
Decreased sensibility (minus signs)													
Face	√	√	√	√	(√)	(√)	√	√	(√)	Ø	√[a]	√	√
Hand	√	√	√	√	(√)	(√)	√	√	(√)	Ø	√[a]	√	√
Foot	√	√	√	√	Ø	(√)	√	√	(√)	Ø	√[a]	√	√
Increased sensibility (plus signs)													
Face	√	√	√	Ø	(√)	√	Ø	√	√	√	√	Ø	√
Hand	√	√	√	Ø	√	√	Ø	√	√	√	√	Ø	√
Foot	√	√	√	Ø	√	√	(√)	√	√	√	√	Ø	√

Data based on 95% confidence intervals of absolute QST reference data reflecting all tested body regions across both age groups and gender.
√, clear minus or plus signs detectable; (√) Minus or plus signs measurable for at least one age or gender group, but for other groups not detectable; Ø, for the detection of sensory abnormality the QST value would have to be outside the measurable data range.
[a] The absence of wind-up is normal. WUR has to show a clear wind-down to be abnormal.

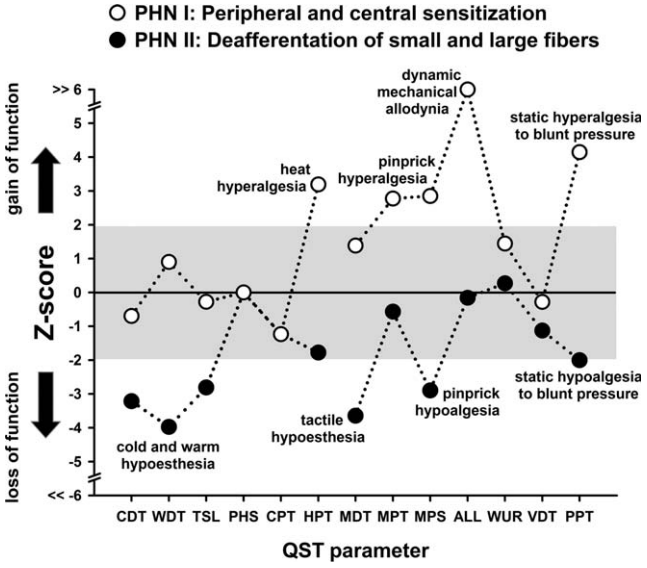

Fig. 2. *z*-score sensory profiles of two patients suffering from postherpetic neuralgia (PHN). *Patient PHN I* (open circles) presents the QST profile of a 70-year-old woman suffering from PHN for 8 years. Ongoing pain was 80 on a 0–100 numerical rating scale. The profile shows a predominant gain of sensory function in terms of heat pain hyperalgesia (HPT), pinprick mechanical hyperalgesia (MPS), dynamic mechanical allodynia (ALL), and static hyperalgesia to blunt pressure (PPT) outside the 95% confidence interval of the distribution of healthy subjects (= grey zone). This profile is consistent with a combination of peripheral and central sensitization. *Patient PHN II* (filled circles) shows the QST profile of a 71-year-old woman with pain for 8 months. Ongoing pain was 70 on a 0–100 numerical rating scale. The QST profile shows predominant loss of sensory function. Note the cold (CDT), warm detection thresholds (WDT), thermal sensory limen (TSL), tactile detection thresholds (MDT), mechanical pain thresholds to pinprick stimuli (MPT), and pressure pain thresholds (PPT) outside the normal range as presented by the grey zone. This profile is consistent with a combined small and large fiber sensory deafferentation. *z*-score: numbers of standard deviations between patient data and group-specific mean value (absolute reference data; see Appendix 2 of online supplementary material).

3.3. Absolute and relative QST reference data

There were no significant differences in QST parameters between the right and left sides of the body, and all correlations across the two body sides were highly significant (all $p < 0.001$). Systematic inter-individual differences accounted for between 61% and 90% of the total variance (squared correlation coefficients r^2 between 0.61 and 0.90). These findings suggest that right–left comparisons (relative reference data) may be more sensitive to detect positive or negative sensory signs than comparisons with absolute reference data.

Distributions of right–left differences are shown in Fig. 3. Compared with fitted normal distributions (drawn lines) there was an over-representation of data around zero values (kurtosis ranged between 1.25 and 6.16), i.e. in a large proportion of subjects the QST parameters were identical in symmetric body regions. Therefore, relative QST reference data were not normally distributed for many parameters. To keep data processing uniform, we nevertheless estimated the 95% confidence intervals from the fitted standard deviations, leading to conservative estimates. Lower and upper cut-off values of these relative reference data are given in Table 3. To allow comparison of sensitivities of absolute and relative reference data, we included two columns showing differences or ratios, which would be needed for an affected side to be outside the 95% confidence interval of the absolute reference data. In these cases it is assumed that the control side yielded values identical to the normal mean. Relative reference data were up to 2.5 times more sensitive than absolute reference data. With the exception of cold and warm detection thresholds relative reference data showed a clinically relevant gain in sensitivity.

In some cases, e.g. distal symmetric polyneuropathies, it may be necessary to use a control area in another region of the body than the affected region (e.g., hand vs. foot). For these comparisons we also calculated

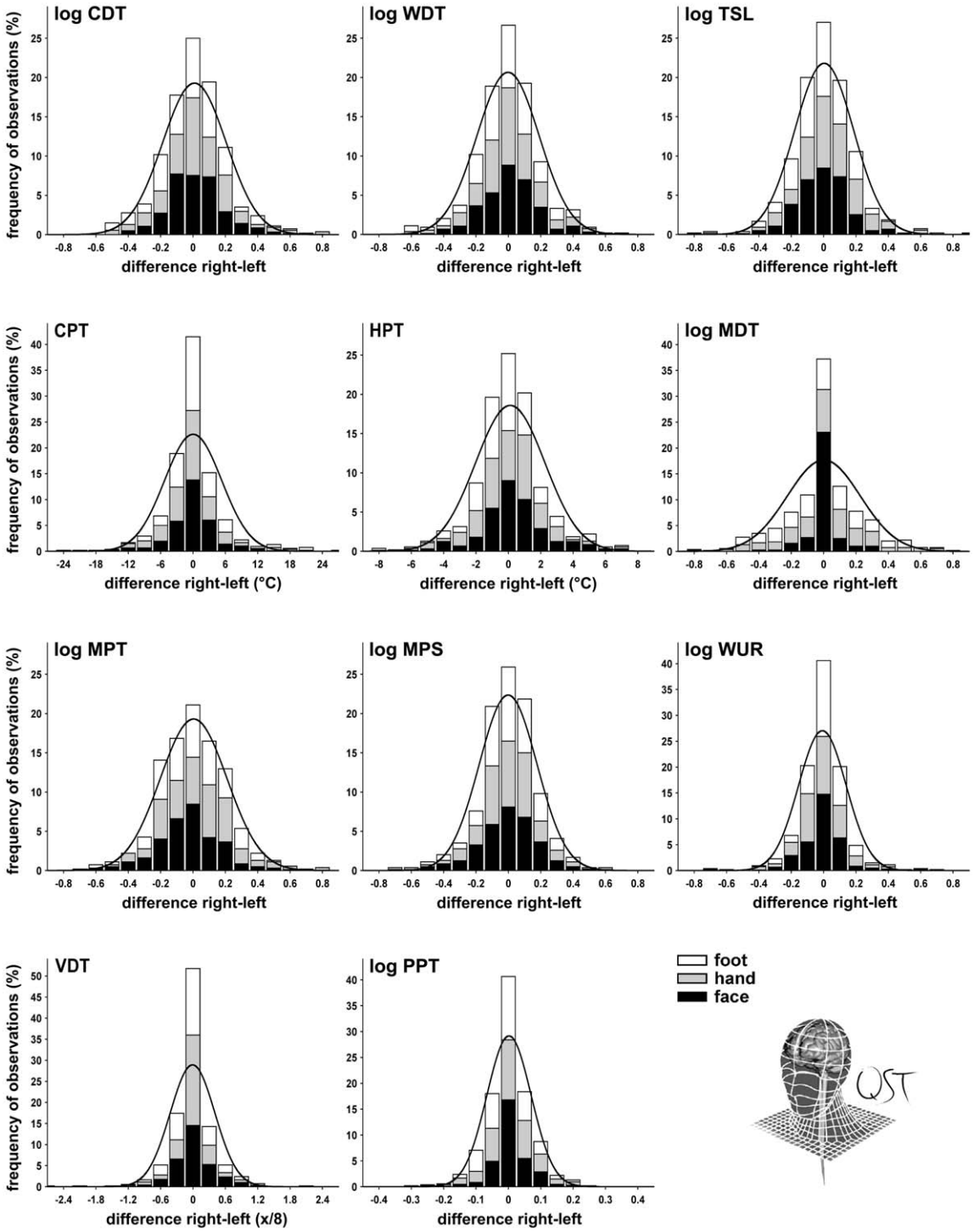

Fig. 3. Distributions of relative QST data. Stacked bar histograms of right–left differences of raw or log data for all QST parameters except paradoxical heat sensations and dynamic mechanical allodynia, which in general were bilaterally absent. Most QST parameters show small side-to-side differences resulting in high kurtosis values of the distributions clustering close to zero. Therefore these ''peaked distributions'' of right–left differences were mostly not normally distributed with the exception of thermal detection thresholds (CDT, WDT, TSL). Note that the right–left difference for log data corresponds to a right–left ratio (exceptions: cold pain, heat pain thresholds, and vibration detection thresholds).

relative reference data (Table 4). These inter-region relative reference data, however, did not generally lead to a higher sensitivity for positive or negative sensory signs when compared with absolute reference data. Since it is commonly preferable to compare the whole battery of sensory tests, for inter-region comparisons we recommend to rely on QST parameters that are z-transformed with respect to absolute reference data. The only useful

Table 3
Sensitivity of absolute vs. relative QST reference data comparing right hand side vs. left hand side of the body

QST parameter	Mean SD of absolute data	Mean SD of right–left-difference	Gain in sensitivity	Criterion	1.96SD de-log	Relative reference data: 95% confidence intervals	
						Lower cutoff	Upper cutoff
CDT	0.238	0.196	1.21	Ratio	× or /2.42	41%	242%
WDT	0.213	0.193	1.10	Ratio	× or /2.39	42%	239%
TSL	0.247	0.182	1.36[b]	Ratio	× or /2.27	44%	227%
PHS	[a]	[a]	[a]	[a]	[a]	[a]	[a]
CPT	8.659	5.254	1.65[b]	Difference	+ or −10.3 °C	−10.3 °C	10.3 °C
HPT	3.185	2.140	1.49[b]	Difference	+ or −4.2 °C	−4.2 °C	4.2 °C
MDT	0.342	0.213	1.60[b]	Ratio	× or /2.62	38%	262%
MPT	0.388	0.206	1.89[b]	Ratio	× or /2.53	40%	253%
MPS	0.441	0.178	2.48[b]	Ratio	× or /2.23	45%	223%
ALL	[a]	[a]	[a]	[a]	[a]	[a]	[a]
WUR	0.246	0.147	1.67[b]	Ratio	× or /1.94	52%	194%
VDT	0.679	0.408	1.67[b]	Difference	+ or −0.8/8	−0.8 /8	0.8 /8
PPT	0.131	0.068	1.93[b]	Ratio	× or /1.36	74%	136%
Mean gain in sensitivity			1.64				

Gain in sensitivity for relative over absolute reference values was calculated as the ratio $SD_{abs.}/SD_{rel.}$. Relative QST reference data ranges are always smaller than absolute ranges, indicating that relative data for side-to-side contrasts are more sensitive to detect plus or minus signs than absolute data. "×" or "/": multiplied or divided by, "+" or " −": added or subtracted.

[a] There was no significant occurrence of PHS and ALL in healthy human subjects.

[b] Clinically relevant gain (>30%).

QST parameters for relative inter-regional comparisons were MPS (contrasts across all tested regions), and WUR (for the contrast hand vs. foot).

4. Discussion

For the first time a standardized QST protocol was implemented on a nationwide basis by the German Research Network on Neuropathic Pain (DFNS). A database of common reference values from 180 subjects collected by 10 centers all over Germany was established. Novel aspects of this project include:

- Determination of a complete somatosensory phenotype in one test session.

Table 4
Sensitivity of absolute vs. relative QST reference data comparing different body regions

QST parameter	Criterion	Foot vs. hand			Foot vs. face			Face vs. hand		
		Mean SD of absolute data	Mean SD of relative data	Gain in sensitivity	Mean SD of absolute data	Mean SD of relative data	Gain in sensitivity	Mean SD of absolute data	Mean SD of relative data	Gain in sensitivity
CDT	Ratio	0.252	0.281	0.90	0.240	0.299	0.80	0.223	0.251	0.89
WDT	Ratio	0.213	0.260	0.82	0.210	0.293	0.72	0.215	0.273	0.79
TSL	Ratio	0.241	0.262	0.92	0.240	0.297	0.81	0.261	0.278	0.94
PHS	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
CPT	Difference	8.391	7.308	1.15	9.009	8.594	1.05	8.613	7.437	1.16
HPT	Difference	2.877	2.641	1.09	3.262	3.609	0.90	3.508	3.256	1.08
MDT	Ratio	0.432	0.449	0.96	0.358	0.502	0.71	0.294	0.427	0.69
MPT	Ratio	0.376	0.335	1.12	0.400	0.391	1.02	0.389	0.368	1.06
MPS	Ratio	0.419	0.283	1.48[b]	0.459	0.318	1.44[b]	0.448	0.333	1.35[b]
ALL	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
WUR	Ratio	0.244	0.184	1.32[b]	0.250	0.216	1.16	0.245	0.215	1.14
VDT	Difference	0.696	0.807	0.86	0.815	0.913	0.89	0.593	0.722	0.82
PPT	Ratio	0.142	0.143	0.99	0.133	0.162	0.82	0.122	0.150	0.81
Mean gain in sensitivity				1.06			0.94			0.98

Gain in sensitivity for relative over absolute reference values was calculated as the ratio $SD_{abs.}/SD_{rel.}$. Relative QST reference data ranges across regions do not increase sensitivity to detect plus or minus signs.

[a] There was no significant occurrence of PHS and ALL in healthy human subjects.

[b] Clinically relevant gain (>30%).

- Clinical feasibility of the QST protocol within 30 min per body region.
- Collection of a joint multicenter reference data set.

4.1. Differences in QST parameters across body regions, age groups and gender

ANOVA showed that differences across body regions had the biggest effect on reference data ranges, much more than age and gender. When this QST protocol is to be used for other body regions (e.g. paraspinal dermatomes in low-back pain) new region-specific reference data are required for all parameters. Age and gender effects were less homogenous across QST parameters.

Most thermal and mechanical thresholds increased with age, consistent with prior studies (e.g., Claus et al., 1990; Yarnitsky and Sprecher, 1994; Hilz et al., 1998; Haanpää et al., 1999; Lautenbacher et al., 2005). Accordingly, reference data graded with age are mandatory. The mean (SD) age for the older subject group was 50.1 ± 7.9 years covering a range up to 75 years. Age dependence, however, was absent for all pinprick evoked measures (mechanical pain threshold, mechanical pain sensitivity, wind-up ratio). Possibly, the decrease in innervation density of intraepidermal nerve fibers is balanced by an improved mechanical coupling of the stimuli to the nerve endings.

Women were more sensitive than men for many QST parameters, consistent with prior studies (e.g., Riley et al., 1998; Rollman and Lautenbacher, 2001; Chesterton et al., 2003). In our data pronounced gender differences were present only for pain thresholds, most remarkable for heat pain. Since detection thresholds were independent of gender, the differences in pain thresholds are unlikely to be due to peripheral factors such as innervation density, and are attributed to different central processing (Rollman and Lautenbacher, 2001; Sarlani et al., 2003).

4.2. Comparison across QST parameters

All thermal or mechanical detection thresholds allowed large ranges for detecting sensory minus signs. In contrast, the detection of significant minus signs in thermal pain thresholds was problematic, since the 95% confidence intervals covered most of the possible data range. The use of right–left comparisons, however, improves the diagnostic sensitivity for heat hypoalgesia by 49% and for cold hypoalgesia by 65%. As an alternative to QST, laser-evoked potentials can be used to assess loss in heat pain sensitivity (Treede et al., 2003; Cruccu et al., 2004). Mechanical pain thresholds were less variable than thermal pain thresholds and hence are sensitive for significant minus signs.

Our QST protocol is relatively insensitive to detect tactile hyperesthesia as a sensory plus sign, since the 95% confidence intervals for these parameters came close to the lowest possible stimulus intensity. This limitation, however, is irrelevant for clinical practice, since true tactile hyperesthesia in the sense of an increased tactile percept is rare. Touch-evoked pain sensation that was formerly called "hyperesthesia" (Noordenbos, 1959; quoted from Loh and Nathan, 1978) has received a new label "allodynia" by IASP (Merskey et al., 1979; Treede et al., 2004) and is assessed by a separate test of our QST protocol (cf. Samuelsson et al., 2005).

Sensory plus signs were assessable for all thermal and mechanical pain thresholds. The mechanical pain sensitivity for pinprick stimuli showed the largest range for the detection of plus signs.

4.3. Relationship between sensory signs, z-score QST profiles, and possible mechanisms

The present QST protocol was developed as a comprehensive test battery for somatosensory functions across the full spectrum of primary afferents: Aβ-fiber function is represented by the mechanical detection thresholds to von Frey hairs (MDT) and vibration (VDT). Aδ-fiber function is represented by the cold detection threshold (CDT) and the mechanical pain threshold (MPT) for pinprick stimuli. The presence of paradoxical heat sensations (PHS) also indicates a disturbance of Aδ-cold fiber function (or central pathways encoding for cold sensation). C-fiber function is represented by the warm detection threshold (WDT) and heat pain threshold (HPT). Whereas these attributions are based on nerve block studies (Fruhstorfer, 1984; Yarnitsky and Ochoa, 1991; Ziegler et al., 1999), the relative contribution of C- and Aδ-fiber nociceptors to cold and pressure pain thresholds (CPT, PPT) is less clear. Nevertheless, these QST parameters also characterize the function of the nociceptive system, which is not possible with standard methods of clinical neurophysiology (Treede et al., 2003; Cruccu et al., 2004). The wind-up ratio using pinprick reflects temporal summation of the perceived pain for this type of stimulus. The large reference range for this parameter indicates that the absence of wind-up is normal.

An advantage of this QST protocol over electrophysiological methods is its sensitivity to the sensory plus signs of hyperalgesia and allodynia. The presence of heat hyperalgesia gives evidence for peripheral sensitization, whereas the isolated presence of static mechanical hyperalgesia or dynamic mechanical allodynia indicates central sensitization (Treede et al., 2004). The relative contributions of peripheral sensitization, central sensitization and disinhibition to cold hyperalgesia and hyperalgesia to blunt pressure are still unknown

(Wasner et al., 2004). Future studies in patients with different diseases and in healthy human subjects undergoing experimental pain models will shed light on these issues (Klein et al., 2005). Previous studies used only subsets of these QST parameters and are biased towards reporting the presence of sensory signs and not their absence.

Clinical interpretation of the raw QST data is difficult, given the multitude of parameters and their variability across region, age and gender. Sensory profiles of a given patient are more conveniently displayed as *z*-scores (Rolke et al., 2006), where each individual parameter is related to its region-, age- and gender-specific reference range and is displayed as the number of standard deviations above or below the normal mean. We verified the sensitivity of this method in two case examples of patients with postherpetic neuralgia that is known to lead to neuropathic pain by at least two distinct mechanisms: sensitization or deafferentation (Fields et al., 1998). Both patients had similar levels of ongoing pain. Patient I exhibited positive sensory signs (heat hyperalgesia, mechanical hyperalgesia to pinprick and blunt stimuli, allodynia to light touch). This pattern perfectly matches the behavioural responses in animals with peripheral and central sensitization as their main pathophysiological mechanisms. Patient II was characterized by negative sensory signs (thermal and mechanical hypoesthesia) without hyperalgesia or allodynia. Animal experiments suggest that hyperactive deafferented neurons in the spinal cord are likely involved in pain generation in this case.

4.4. Absolute vs. relative QST reference data

The mean values of our absolute QST reference data compare well with prior studies for thermal detection and pain thresholds (e.g., Claus et al., 1987; Dyck et al., 1993; Yarnitsky et al., 1995; Hansen et al., 1996; Hagander et al., 2000) as well as mechanical detection and pain thresholds (e.g., Weinstein, 1968; Andrews, 1993; Greenspan and McGillis, 1994; Magerl et al., 1998; Haanpää et al., 1999; Kosek et al., 1999; Ziegler et al., 1999; Baumgärtner et al., 2002). For the thermal detection thresholds, our 95% confidence intervals were larger than in some prior studies. Thermal detection thresholds are recognized to be potentially valuable to assess small-fiber function (Ziegler et al., 1988), but their widespread use has been discouraged because reference values from different studies are inhomogeneous (Perkins and Bril, 2003; Shy et al., 2003). Since our reference data are based on a multicenter study, between-center differences probably contributed to the variance in our data. All other 95% confidence intervals were comparable to prior studies.

For side-to-side comparisons we found a substantially higher sensitivity of relative than absolute QST reference data due to high correlations across body sides and the lack of systematic side differences. Thus, in patients with unilateral pain syndromes relative reference data will yield the most sensitive results in the clinical environment.

For inter-regional comparisons there was in general no advantage of relative over absolute QST reference data. Thus, for the assessment of a patient suffering from a bilateral neuropathic pain state it may be sufficient to assess only the most affected region and to compare the findings with absolute reference data. In this case the total testing time will be reduced from 60 to 30 min. Inter-regional contrasts, however, are important for the distinction between localized and widespread pain. This can be done on the basis of *z*-transformed QST data, because after *z*-transformation any systematic differences across body regions are eliminated.

5. Conclusions and clinical implications

In this study we have established QST reference data for obtaining the full somatosensory phenotype of a patient, including minus and plus signs for all types of primary afferents, cutaneous and deep pain, peripheral and central sensitization. No a priori hypothesis is needed when ordering this profile in clinical practice. Moreover, the reference data of this multicenter trial allow formal identification of sensory plus and minus signs in individual patients by trained observers based on statistical criteria. A training program has already started to share this QST protocol with other laboratories beyond the DFNS. The next steps will be to evaluate test–retest and inter-observer reliabilities of this QST battery, to identify the QST profiles of human surrogate models with known neurobiological mechanisms, and to characterize the somatosensory phenotypes of a variety of neuropathic pain states. This will help to delineate underlying mechanisms of neuropathic pain and other chronic pain entities, to guide more rational treatment algorithms, and to develop and evaluate new analgesic and antihyperalgesic drugs.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2006.01.041.

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