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Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception

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ABSTRACT

The Quantitative Sensory Testing (QST) protocol of the German research network on neuropathic pain (DFNS) encompassing all somatosensory modalities assesses the functioning of different nerve fibers and of central pathways. The aim of our study was: (1) to explore, whether this QST protocol is feasible for children, (2) to detect distribution properties of QST data and the impact of body site, age and gender and (3) to establish reference values for QST in children and adolescents. The QST protocol of the DFNS with modification of instructions and pain rating was used in 176 children aged 6.12–16.12 years for six body sites. QST was feasible for children over 5 years of age. ANOVAs revealed developmental, gender and body site differences of somatosensory functions similar to adults. The face was more sensitive than the hand and/or foot. Younger children (6–8 years) were generally less sensitive to all thermal and mechanical detection stimuli but more sensitive to all pain stimuli than older (9–12 years) children, whereas there were little differences between older children and adolescents (13–17 years). Girls were more sensitive to thermal detection and pain stimuli, but not to mechanical detection and pain stimuli. Reference values differ from adults, but distribution properties (range, variance, and side differences) were similar and plausible for statistical factors. Our results demonstrate that the full QST protocol is feasible and valid for children over 5 years of age with their own reference values.

1. Introduction

We lack knowledge about clinical criteria, classifications and pathophysiology of most chronic pain conditions in children [52]. It is essential to improve classification of chronic pain conditions during their development and to be able to distinguish between nociceptive and/or neuropathic pain [52]. QST was considered an appropriate tool for this purpose in adults although its use is still under debate [67]. With QST it is possible to delineate perceptual functioning of almost all somatosensory modalities corresponding to different types of receptors, peripheral nerve fibers and CNS pathways [33,67,68]. QST examines not only the large fiber function (Aβ) and the lemniscal system like other neurophysiological methods, but also the nociceptive and non-nociceptive small fiber (Aδ, C) function and the spinothalamic pathways, which are involved in peripheral and central pain syndromes [67]. QST is advantageous for the examination of children because it is non-invasive [41]. In contrast to adults, QST has been utilized much less widely in children [93]. Pioneer studies from Hilz, Meier, Meh and Thibault examined cutaneous and proprioceptive sensation [39,40,57,78], thermal and pain sensitivity [41,42,55,57] in healthy children. Peripheral neuropathies were studied in children with diabetes mellitus [1,35,56,58,88], familial dysautonomia [39] and complex regional pain syndrome [74]. Pain sensitivity and somatosensory perception alterations after pain experiences in children were explored within the last years [36,73,86,90,94,95]. These studies established reference values for children in a variety of testing procedures, stimulus

Abbreviations: DMA, dynamic mechanical allodynia; CDT, cold detection thresholds; CI, confidence interval; CPT, cold pain thresholds; HPT, hot pain thresholds; MDT, mechanical detection thresholds; MPS, mechanical pain sensitivity for pinprick stimuli; MPT, mechanical pain threshold; PHS, paradoxical heat sensations; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection thresholds; WUR, wind-up ratio.

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parameters, body sites and age groups for thermal detection thresholds [1,36,39,41,57,74,86,88,90,95], mechanical detection thresholds [36,39,40,57,74,86,88,90,95], thermal pain thresholds [1,36,57,74,83,86,90,94,95] and/or mechanical pain thresholds [36,90,94,95] as shown in Table 6. A major limitation of some studies was the restricted sample size [86] and the failure to separate results for age [1,36,39,56,57,73,74,86,88,90,94,95] and gender [1,35,36,39,41,56,57,73,74,88,90,94,95]. In addition, the protocols differed profoundly limiting the use for clinical routine. Without standard procedures, QST may lead to different results even when using the same instruments [67]. Consequently, the German research network on neuropathic pain (DFNS) established a standard protocol and reference values for adults. This QST battery is feasible within the clinical assessment [67]. The use of the DFNS protocol for QST was also recommended in children for pain classification and diagnosis of underlying mechanisms [52]. However, a comprehensive data base is still lacking. To be able to apply the DFNS protocol for QST in children, reference values are needed to delineate the structure of QST in children and adolescents. Definition of ranges and distributions, as well as the limits of normal values are mandatory to detect pathological deviations of QST profiles. Thus, the aims of our study were: (1) to investigate whether the QST protocol of the DFNS is feasible for children and (2) to explore distribution properties and the impact of age, gender and body site. Based on these assessments, we aimed to provide reference values for children and adolescents as recommended by McGrath and Brown [52].

2. Methods

2.1. Subjects

The study was approved by the Ethics Committee of the Witten/Herdecke University (92/2007). We examined healthy children aged 6.0–12.12 and adolescents aged 13.0–16.12 years. For each year of age, there were 16 subjects, 8 girls and 8 boys. We defined three age groups: young children aged between 6.0 and 8.12 years, older children aged between 9.0 and 12.12 years and adolescents aged between 13.0 and 16.12 years. Subjects were recruited from two primary and secondary schools. With the support of the school principals, all the children and their parents obtained a letter with a short description of the study and test procedure, inviting them for participation in the study. Subjects with acute or chronic pain conditions, other diseases or use of medication within the last month were excluded from the study. Before QST testing, all subjects underwent a short medical history and physical examination. Subjects decided whether their parents stayed in the testing room or outside. All subjects participated voluntarily after information about test procedures. They received 10 Euro as a reimbursement for their participation. All children and their guardians provided written informed consent.

2.2. Qst

While the somatosensory perception battery of the DFNS is excellent [67], QST refers to more than that particular standardized protocol. The DFNS protocol for QST is a standardized Quantitative Sensory Testing battery of seven robust and validated short form tests for the somatosensory perception analysis measuring 13 parameters in the delineated order: cold and warm detection thresholds (CDT and WDT), the difference limen threshold for alternating cold and warm stimuli (TSL) and the number of paradoxical heat sensations (PHS), cold pain and heat pain thresholds (CPT and HPT). Parameters were determined in the method of limits using a TSA 2001II (MEDOC, Israel) thermal sensory testing device [26,92] with a thermode contact area of 9.0 cm^2. All thresholds were obtained with ramped stimuli (1 °C/s), that stopped when the subject pressed a button. The baseline temperature was 32 °C (centre of neutral range) and cut-off temperatures were 0 and 50 °C. The mean threshold temperature of three consecutive measurements was calculated. The difference limens for alternating cold and warm stimuli (TSL) and the number of paradoxical heat sensations (PHS) were determined during three alternating warm and cold stimuli. Cold and heat pain thresholds were obtained when the subject felt 'aching', 'stinging', or 'burning'. The mechanical detection threshold (MDT) was determined with the method of levels using a set of 12 modified von Frey hairs (Optihair2-Set, Marstock Nervtest, Germany). von Frey hairs have fixed stimulus intensity forces of 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 16.0, 32, 64, 128, 256 and 512 mN upon bending on the skin for 1 s with a contact area of 0.5 mm in diameter [25,85,87]. The final threshold was the geometric mean of five series of descending stimuli until no perception was reached and ascending stimuli until the first perception of touch was reached. The mechanical pain threshold (MPT) was determined with the method of levels using a set of seven weighted pinpricks mechanical stimulators with fixed intensity forces of 8, 16. 32. 64. 128. 256, and 512 mN on the skin for 2 s with a contact area of 0.2 mm in diameter [4,7,49]. The final threshold was the geometric mean of five series of ascending stimuli until the first percept of sharpness was reached and descending stimuli until the first perception of blunt touch was reached. The mechanical pain sensitivity for pinprick Stimuli (MPS) was determined using each of the seven pinprick stimuli five times in a pseudorandomised sequence. Within the pinprick stimuli three light tactile stimulators were used five times each to detect dynamic mechanical allodynia (DMA): (1) a cotton wisp exerting a force of −3 mN, (2) a cotton wool tip fixed to an elastic strip exerting a force of ∼100 mN, and (3) a standardized brush (Somedic, Sweden) exerting a force of ∼200–400 mN on the skin for 1–2 s at a single stroke of approximately 2 cm in length [4,47]. Altogether 50 Stimuli (35 pinprick and 15 tactile) were applied in a pseudorandomised sequence with a ∼10 s inter-stimulus interval. Subjects were asked to give a pain rating for each stimulus (see below). 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. Effect of temporal pain summation was determined by the Wind-up ratio (WUR). Wind-up is a frequency-dependent increase in excitability of spinal cord neurons that reaches a plateau after about five stimuli [37]. We defined wind-up as the temporal summation of suprathreshold painful stimuli. The perceived pain intensity from one single pinprick stimulus of the same force (128 mN intensity) was compared to the perceived pain intensity of 10 repetitive pinprick stimuli (1/s frequency), applied within a small area of l cm over face, hand and foot. Subjects were asked to give a pain rating after the single stimulus and the series of 10 stimuli on the numerical rating scale or the facial pain rating scale for children as described above. Wind-up ratio (WUR) was calculated as the mean pain rating of five series of repetitive stimuli divided by the mean pain rating of five single stimuli [67]. The vibration detection threshold (VDT) was determined using a Rydel-Seiffer graded tuning fork (64 H/.8/8 scale) placed on the zygomatic bone, processus styloideus ulnae and malleolus internus until the subject could not feel the vibration any more. Vibration detection threshold represented by the vibration disappearance was calculated as the geometric mean of three stimulus repetitions. This device still proves its usefulness in current clinical trials [89]. The pressure pain threshold was determined using a pressure gauge device (FDN100, Wagner Instruments, USA) with a probe area of l cm^2 (probe diameter 1.1 cm) that exerts forces up to 10 kg/cm^2 or ∼1000 kPa over masseter-, thenar muscle and ball of the foot [46,67]. The pressure pain threshold was calculated

as the geometric mean of three stimulus repetitions of ascending stimulus intensities, each applied as a slowly increasing ramp of 50 kPa/s (~0.5 kg/cm^2 s). All subjects were tested on both sides of the face (cheek), hand and foot (dorsum) in a randomised order. The test sequence for each QST testing was determined in the given order after demonstration of each test at a practice area above the test area. The session lasted 4 h including short breaks if subjects' concentration declined. The verbal instructions of the DFNS for adults were adapted for children by simplifying and shortening the wording (see Appendix 1 of Supplementary material). Subjects were blindfolded during MDT, MFT, MPS, DMA and WUR because it was without discomfort for children in previous studies [78,86,94]. Children below the age of 8 years used the Faces Pain Scale-Revised; (FPS-R) [38] during MPS, DMA and WUR without being able to see the pinprick set. All children were assessed by one of two assessors, who had undergone a 4-week training in an accredited DFNS centre for QST research (Bochum). Skin temperature was measured to ensure skin temperature was >24 °C prior testing as recommend by Hilz et al. [41].

2.3. Pain rating

Pain rating for children from 10 years onward was obtained on a numerical rating scale (NRS) from 0 (no pain) to 100 (very severe pain) identical to the study of Rolke in adults [67]. There is an ongoing debate at which age children are capable of using the NRS for pain rating [5,59,84]. Different to adults, the age of the child has to be taken into account when deciding upon the measurement tool for pain intensity. At present, three pain rating scales are recommended for use in children and adolescents dependent on their age: for children younger than 8 years of age, the Faces Pain Scale-Revised (FPS-R) [38] is recommended [53] and we used the FPS-R in the present study for this particular age group. The scale consists of six faces, from left to right, and show increased pain intensity. A numeric value from 0 to 10 (0–2–4–6–8–10) is assigned to each face, but these numbers are not seen by the child. The scale has been validated from age 4 onwards [3,30] and is the most frequent used pain rating scale in young children. The NRS is one of the recommended measures from the age of 8 years onwards [77] and recent studies into the utility of the NRS in children and adolescents confirmed these recommendations [59,84]. We therefore used the NRS for children aged 8 years and above. However, we screened children capable of numerical reasoning between 8 and 9 years on the basis of Paige's states of cognitive development theory (e.g. [27]]) with the following standard dialog between investigator and child: (investigator) "do you know how much more is 10 compared to 5" and if answered affirmatively "how much more is 6 compared to 2". Children who did not answer correctly (5 or the double for the first question and 4 or the triple for the second question) were intended to rate their pain intensity on the visual analogue scale (VAS) which was converted to a score from 0 (no pain) to 10 (very severe pain) [65]. VAS is the third scale which is recommended for use in children and adolescents [77] although it is not as feasible as the NRS. The FPS-R correlates highly with VAS and NRS without age effects [30,31,38,63]. FAS-R and NRS have a good convergent construct validity so that FPS-R can yield results that are clinically comparable to those obtained with NRS [59,84].

2.4. Data evaluation

Thresholds and average ratings were automatically generated with EXCEL (Microsoft, USA). All ratios following a geometrical distribution were logarithmically transformed (CDT, WDT, MDT, MPT, MPS, DMA, WUR and PPT) (secondary normalization [68]) before statistical analysis. For thermal pain thresholds (CPT, HPT), the numbers of paradoxical heat sensations (PHS) and vibration detection thresholds (VDT) logarithmic transformation were not performed, since the scales are arbitrary and there is no natural zero in the stimulus dimension. Results of CDT were multiplied with −1 and all zero-values were transformed to positive values by a slight shift to allow a log transformation. All statistical calculations were performed with Stata (10.1).

Mean, standard deviation, skewness, kurtosis and Kolmogorov–Smirnov's d were analyzed for their distribution properties in raw and log-transformed data. The product of the geometric mean of skewness and kurtosis combined and the geometric mean of Kolmogorov–Smirnov's d (for continuous test of normality of distribution) was calculated as a compound measure of goodness of normality. Log-transformation was considered to be superior, when the ratio for raw-data to log-transformed data exceeded a factor of 2.5.

Reference data are given as mean ± 1.96 standard deviations of log-transformed data (95% confidence interval) and the corresponding raw-data. For this purpose, data of log transformed QST parameters were re-transformed to values representing the original unit of each test.

Mann–Whitney-*U*-test was computed for each year with the adjacent year (e.g. 6 with 7 and 7 with 8 years of age), separately for girls and boys and both together to define reference data for age groups.

Differences between areas (face, hand, and foot), right and left sides of the body, age and gender were compared using a four-way analysis of variance (ANOVA) for repeated measures. The factor body side was nested under the factor body site to eliminate higher order interactions. Post hoc comparisons were calculated using LSD-post hoc test. To protect against type I error by testing the significance of several main effects and interactions in the ANOVA, a Bonferroni-corrected alpha of 0.006 was used, which was 0.05/number of tests. For the same reason the significance level of the pairwise comparison of age groups was adjusted to 0.017 (Bonferroni adjustment).

To assess intra-individual variability of QST testing, we compared log- and non-log-transformed data for left and right body sides by Bland–Altman-analysis. The deviation range of left and right ratings (limits of agreement) was calculated from the means of the left and right ratings and their differences. Additionally, we calculated mean values and standard deviation of side differences with respect to body site, age and gender. To compare sensitivity of side differences to absolute reference data we averaged the group-specific (body side, age, gender) standard deviations of absolute reference data and of the side differences and calculated ratios of these means. Additionally, confidence intervals were calculated for the side differences.

3. Results

3.1. Descriptive data results

One hundred and ninety children were contacted via mail and asked for participation. Because of their medical history, 10 subjects with chronic headache and two subjects with hyperactivity disorder were excluded from participation. Prior to QST testing two additional subjects were excluded due to psychiatric treatment. All the remaining subjects ($n = 176$) attended the whole QST testing procedure. For all children under the age of 8 their mothers were present. For older subjects mothers were present in nearly half of the subjects (42%) without any difference on results. Only two of the tests were performed with the father attendant. Two third of the subjects were investigated by a female and one third by a male. However, there were no differences between examiners' results. All individuals aged six years and up detected hot pain at a higher temperature than warm and cold pain

at a lower temperature than cold. In addition to evaluating the response to different intensity stimuli this provides a control that children understood the modified verbal instructions of the DFNS protocol (Appendix 1 of Supplementary material) and cooperated satisfactorily. All children between 8 and 9 years and above managed the standard test dialogue to determine children capable of numerical reasoning correctly indicating that they were able to understand the NRS-instructions.

Determination of a complete QST procedure was difficult in children below six years of age due to their limited time span of attention. Nevertheless, the testing procedures were feasible with a mean duration of 32.0 ± 3.5 min in adolescents and of 35.0 ± 6.2 min in children for the full QST protocol over one test area. Thus, assessing six sites in adolescents took about 3 h, while testing in young children was conducted with some breaks between test areas to relax and restore attention, and thus took about 4 h. It was possible to obtain complete QST data in all subjects and at all sites tested. None withdrew from the protocol nor reported severe pain or discomfort during or after testing inclusive blindfolding. The pre-test skin temperature was at a level over 26 °C at all sites and sides previously shown not to influence threshold measurements [41].

3.2. Distribution of QST data

The majority of QST parameters were normally distributed only after logarithmic data transformation (cf. [67]) as shown in Appendix 2 of Supplementary material.

3.3. Analysis of QST data

All QST parameters show a good accordance of left and right side. Mean differences between right and left values were close to zero; confidence intervals and deviation ranges of left and right side were symmetrical, and correlations across the right and left side were highly significant for all QST parameters (for details see Table 1). Accordingly, we combined data from left and right body side for ANOVA and calculation of reference values.

Mean values and standard deviations of QST data are shown in Table 2 for body site, age and gender (usually log-transformed for secondary normal distribution or raw-data). Notably, paradoxical heat sensations (PHS) or dynamic mechanical allodynia (DMA) was not met in any of the young subjects (data not shown) (Fig. 2).

3.4. Analysis of body site, age and gender for QST reference data

Regional differences in sensitivity were encountered in the majority of QST parameters. Generally, the face was more sensitive than the hand and/or the foot dorsum for thermal detection, most mechanical detection and pain stimuli (thresholds decreased CDT, WDT, TSL, MDT, MPT and PPT; $p < 0.001$, for details see Table 3). The hand was more sensitive than the foot for thermal detection and pressure pain stimuli (thresholds decreased CDT, WDT, TSL and PPT; $p < 0.001$, for details see Table 3). In contrast the hand was less sensitive than the foot for mechanical detection and mechanical pain stimuli (thresholds increased MDT, MPT; $p < 0.001$, for details see Table 3). These findings suggest that each body site needs its own QST reference data.

Age effects were strongest and most homogenously present across QST parameters. To analyze age differences we investigated differences between the three age groups: young children (6–8 years; $n = 48$), older children (9–12 years; $n = 64$) and adolescents (13–16 years; $n = 64$). Young children (6–8 years) were less sensitive to all thermal and mechanical detection stimuli (CDT, WDT, TSL and VDT thresholds increased; p values ranged from 0.0059 to 0.001, for details see Table 3) except for the mechanical detection threshold (MDT, $p = 0.058$). No consistent differences were observed for tactile detection (MDT), since all thresholds resided near the lower end of test stimuli (bottom effect). All thermal sensitivities and vibration sensitivity increased with age (p values ranged from 0.0059 to 0.001, for details see Table 3). Young children (6–8 years) were more sensitive to all pain stimuli (HPT, MPS, WUR and PPT thresholds decreased; $p < 0.001$, for details see Table 3) except for the cold pain threshold and mechanical pain threshold (CPT, MPT; for details see Table 3). Pain ratings to pin prick stimuli (MPS) were considerably increased for younger children and the magnitude of pain ratings decreased for any higher age ($p < 0.001$). Pain summation tested by the wind-up ratio (WUR) was marginal for younger children and increased at higher age to reach a plateau at approximately 2.5-fold at age nine and up ($p < 0.001$). Age effects between older children (9–12 years) and adolescents (13–16 years) were marginal. Older children were only more sensitive to thermal pain stimuli (thresholds decreased; p values ranged from 0.053 to 0.002, for details see Table 3). These findings suggest that reference data are needed for younger and older children and adolescents.

Gender effects were less homogenous across QST parameters. Girls tended to be more sensitive than boys for thermal stimuli (CDT, WDT and TSL thresholds decreased; p values ranged from 0.034 to 0.006, for details see Table 3) as well as for thermal and pressure pain stimuli (CPT, HPT and PPT thresholds decreased; p values ranged from 0.005 to 0.003, for details see Table 3). These findings suggest that girls and boys need their own QST reference data. No statistically significant gender differences were found for mechanical detection thresholds (MDT) probably based on bottom

Table 1
Mean difference of left and right side (95%-confidence interval, CI), limits of agreement (Bland–Altman), coefficient of correlation (rho), and proportion of common variance between left and right side.

QST parameter	Mean difference (95%-CI)	Limits of agreement	Correlation coefficient (rho)*	Variance explained (squared rho)
CDT^{log}	0.02 (−0.00 to 0.04)	−0.38 to 0.42	0.72	0.52
WDT^{log}	0.02 (−0.00 to 0.03)	−0.34 to 0.38	0.68	0.46
TSL^{log}	−0.00 (−0.02 to 0.01)	−0.34 to 0.33	0.76	0.58
CPT	0.10 (−0.33 to 0.52)	−9.23 to 9.42	0. 82	0.67
HPT	0.32 (0.06 to 0.59)	−5.43 to 6.08	0.67	0.45
PPT^{log}	0.01 (0.01 to 0.02)	−0.09 to 0.11	0.98	0.97
MPT^{log}	−0.02 (−0.04 to −0.00)	−0.38 to 0.35	0.87	0.76
MPS^{log}	−0.01 (−0.03 to 0.00)	−0.34 to 0.32	0.96	0.93
WUR^{log}	0.02 (0.01 to 0.03)	−0.22 to 0.26	0.88	0.77
MDT^{log}	0.01 (−0.01 to 0.02)	−0.25 to 0.26	0.82	0.68
VDT	0.00 (−0.02 to 0.01)	−0.30 to 0.30	0.87	0.75
Range			0.67–0.98*	0.45–0.97

The deviation range of left and right ratings (limits of agreement) was calculated from the means of left and right ratings and their differences.
* $p < 0.001$ for all QST parameters.

Table 2
Means and standard deviations of log transformed- resp. raw-data for QST parameters.

QST parameter	Body site	Mean ± standard deviation (log-transformed-data^{log} or original results)					
		6–8 years		9–12 years		13–16 years	
Number of subjects		Girls 24	Boys 24	Girls 32	Boys 32	Girls 32	Boys 32
CDT^{log} (°C from baseline)	Face	0.176 ± 0.257	0.279 ± 0.273	−0.021 ± 0.198	0.042 ± 0.200	−0.035 ± 0.221	0.048 ± 0.221
	Hand	0.140 ± 0.239	0.250 ± 0.275	0.025 ± 0.224	−0.007 ± 0.205	−0.054 ± 0.167	0.048 ± 0.226
	Foot	0.239 ± 0.338	0.383 ± 0.261	0.282 ± 0.217	0.285 ± 0.230	0.283 ± 0.282	0.346 ± 0.226
WDT^{log} (°C from baseline)	Face	0.287 ± 0.168	0.319 ± 0.209	0.119 ± 0.160	0.149 ± 0.176	0.086 ± 0.174	0.154 ± 0.160
	Hand	0.273 ± 0.192	0.291 ± 0.185	0.198 ± 0.200	0.149 ± 0.198	0.138 ± 0.154	0.218 ± 0.206
	Foot	0.363 ± 0.185	0.394 ± 0.200	0.334 ± 0.212	0.472 ± 0.170	0.402 ± 0.189	0.512 ± 0.225
TSL^{log} (°C)	Face	0.396 ± 0.222	0.504 ± 0.241	0.235 ± 0.200	0.307 ± 0.212	0.194 ± 0.240	0.252 ± 0.204
	Hand	0.391 ± 0.287	0.492 ± 0.282	0.357 ± 0.258	0.297 ± 0.228	0.240 ± 0.223	0.345 ± 0.224
	Foot	0.585 ± 0.208	0.645 ± 0.183	0.628 ± 0.153	0.655 ± 0.157	0.582 ± 0.246	0.688 ± 0.179
CPT (°C)	Face	21.18 ± 5.69	18.62 ± 5.58	20.72 ± 7.49	17.47 ± 8.50	17.34 ± 8.80	17.38 ± 8.00
	Hand	20.07 ± 6.42	16.74 ± 5.52	22.43 ± 6.65	16.27 ± 8.30	18.59 ± 7.97	17.59 ± 9.15
	Foot	24.11 ± 3.43	18.27 ± 6.16	22.30 ± 6.73	19.42 ± 8.22	17.63 ± 9.23	16.61 ± 8.65
HPT (°C)	Face	39.25 ± 2.79	40.35 ± 3.74	40.32 ± 4.08	41.81 ± 4.25	41.68 ± 3.77	43.14 ± 3.88
	Hand	39.89 ± 3.36	40.86 ± 2.89	40.17 ± 2.93	41.24 ± 3.84	42.13 ± 3.29	42.60 ± 4.10
	Foot	39.78 ± 2.46	40.96 ± 2.91	41.61 ± 3.16	42.06 ± 2.92	42.53 ± 2.93	43.84 ± 3.01
PPT^{log} (kPa)	Face	2.225 ± 0.095	2.212 ± 0.105	2.242 ± 0.105	2.274 ± 0.107	2.250 ± 0.152	2.326 ± 0.150
	Hand	2.407 ± 0.251	2.490 ± 0.194	2.670 ± 0.155	2.672 ± 0.136	2.676 ± 0.096	2.776 ± 0.141
	Foot	2.520 ± 0.250	2.592 ± 0.242	2.890 ± 0.132	2.920 ± 0.180	2.873 ± 0.206	3.017 ± 0.124
MPT^{log} (mN)	Face	1.297 ± 0.328	1.332 ± 0.373	1.219 ± 0.373	1.402 ± 0.332	1.200 ± 0.314	1.283 ± 0.276
	Hand	1.373 ± 0.341	1.411 ± 0.313	1.504 ± 0.364	1.591 ± 0.292	1.534 ± 0.306	1.622 ± 0.260
	Foot	1.334 ± 0.322	1.397 ± 0.386	1.343 ± 0.371	1.511 ± 0.398	1.452 ± 0.363	1.430 ± 0.279
MPS^{log} (NRS 0–100)	Face	0.310 ± 0.723	0.296 ± 0.587	−0.444 ± 0.576	−0.475 ± 0.479	−0.379 ± 0.444	−0.575 ± 0.411
	Hand	0.305 ± 0.573	0.233 ± 0.543	−0.343 ± 0.532	−0.369 ± 0.437	−0.365 ± 0.409	−0.537 ± 0.418
	Foot	0.551 ± 0.455	0.289 ± 0.544	−0.391 ± 0.455	−0.353 ± 0.454	−0.299 ± 0.419	−0.611 ± 0.375
WUR^{log} (ratio)	Face	0.139 ± 0.115	0.176 ± 0.150	0.360 ± 0.199	0.364 ± 0.258	0.307 ± 0.236	0.295 ± 0.187
	Hand	0.183 ± 0.172	0.171 ± 0.218	0.368 ± 0.204	0.329 ± 0.234	0.363 ± 0.236	0.284 ± 0.220
	Foot	0.161 ± 0.158	0.220 ± 0.268	0.469 ± 0.273	0.364 ± 0.208	0.425 ± 0.262	0.406 ± 0.254
MDT^{log} (mN)	Face	−0.591 ± 0.291	−0.665 ± 0.096	−0.730 ± 0.042	−0.708 ± 0.143	−0.743 ± 0.008	−0.741 ± 0.025
	Hand	−0.447 ± 0.311	−0.484 ± 0.254	−0.566 ± 0.248	−0.568 ± 0.275	−0.513 ± 0.280	−0.619 ± 0.185
	Foot	−0.539 ± 0.303	−0.659 ± 0.120	−0.678 ± 0.157	−0.607 ± 0.237	−0.641 ± 0.186	−0.603 ± 0.200
VDT (x/8)	Face	7.743 ± 0.520	7.750 ± 0.394	7.989 ± 0.061	8.000 ± 0.000	7.989 ± 0.061	8.000 ± 0.000
	Hand	7.537 ± 0.557	7.764 ± 0.344	7.889 ± 0.258	7.967 ± 0.181	7.893 ± 0.312	7.959 ± 0.110
	Foot	7.510 ± 0.494	7.723 ± 0.353	7.908 ± 0.196	7.990 ± 0.058	7.951 ± 0.285	7.962 ± 0.150

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, hot pain threshold; PPT, pressure pain threshold (blunt pressure); MPT, mechanical pain threshold (pinprick); MPS, mechanical pain sensitivity (pinprick); WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; PHS, paradoxical heat sensation; and DMA, dynamic mechanical allodynia – *Note*: PHS and DMA never occurred in any of the subject (therefore not listed in the Table).

effects of sensitivity (see above). In addition, no statistically significant gender effect was found for mechanical pain stimuli (MPT, MPS; see Fig. 1 and Table 3).

3.5. QST absolute reference data

Analysis of body site, age and gender lead us to calculate QST reference data for body site (face, hand and foot), age groups and gender. Mean values and 95% confidence intervals of re-transformed log-resp. raw QST data are shown in Table 4. Note that the majority of confidence intervals appear to be asymmetric due to the retransformation of log-normal data into linear graphic representation. The range of confidence intervals was significantly smaller for mechanical and vibration detection thresholds than for thermal detection thresholds ($p < 0.01$). From 13 QST procedures, 8 provide upper and lower reference confidence limits (CDT, WDT, TSL, CPT, HPT, PPT, MPT and MPS), i.e. hypersensitivity as well as hyposensitivity can be diagnosed. The test for cold pain threshold provided only bottom reference confidence limits in older children (9–12) and adolescents (13–16). This was due to large standard deviations particularly for the upper confidence limits. All subjects, however, reported of cold pain at temperatures below 30 °C. The two tests for mechanical detection (MDT, VDT) provide only upper confidence limits because their lower limits were close to the limits of applicable stimulus intensities (bottom effect). Likewise, for pain summation the lower limit of the wind-up ratio (WUR) encompassed a ratio of one, which means that an absence of pain summation is not a pathological finding. However, a suppression below unity (ratios < 0.6) may be formally identified as a pathological wind-down in addition to pathologically excessive wind-up. For the two test of dysesthesia (PHS, DMA), no child demonstrated dysesthesia as was expected for normal skin meaning that any occurrence is pathological in children and adolescents. Thus altogether, there were 22 definable out of 26 formally possible reference confidence limits.

3.6. QST relative reference data

Mean standard deviations of absolute reference data were larger than mean standard deviations of left and right side for individual subjects for all QST parameters (calculated separately for age, gender and body site). As shown in Table 1, mean side differences for individual subjects was close to zero, confidence intervals and deviation ranges of both sides were symmetrical, and correlations across the right and left side were highly significant for all QST parameters. Because systematic inter-individual differences

Table 3
ANOVA and estimated differences comparing body site, age groups and gender for different QST parameters.

ANOVA (main effects)[a]	CDT	WDT	TSL	CPT	HPT	PPT	MPT	MPS	WUR	MDT	VDT
Side laterality	0.842	0.534	0.992	0.886	0.716	0.899	0.959	0.993	0.944	0.979	0.994
Body site	<0.001	<0.001	<0.001	0.596	0.352	<0.001	0.001	0.855	0.149	<0.001	0.193
Age	<0.001	0.003	0.0059	0.104	<0.001	<0.001	0.423	<0.001	<0.001	0.058	<0.001
Gender	0.006	0.015	0.021	0.003	0.004	0.005	0.132	0.151	0.669	0.525	0.034
Pairwise comparison of age groups[b]											
6–8 vs. 9–12	0.000	0.001	0.014	0.938	0.032	0.000	0.202	0.000	0.000	0.032	0.000
6–8 vs. 13–16	0.000	0.006	0.001	0.061	0.000	0.000	0.220	0.000	0.000	0.023	0.000
9–12 vs. 13–16	0.937	0.460	0.356	0.053	0.002	0.051	0.959	0.329	0.383	0.888	0.841
ANOVA (interactions)											
Age × gender	0.001	0.093	0.002	0.000	0.930	0.000	0.000	0.000	0.001	0.000	0.004
Age × body site	0.000	0.000	0.000	0.000	0.244	0.000	0.000	0.063	0.007	0.003	0.089
Gender × body site	0.835	0.015	0.383	0.451	0.114	0.220	0.650	0.830	0.011	0.064	0.001
Age × gender × body site	0.656	0.010	0.147	0.016	0.407	0.105	0.366	0.512	0.099	0.005	0.112
Estimated differences											
Hand vs. face	−0.009	0.029	0.047	−0.084	0.034	0.368	0.223	0.034	−0.000	0.162	−0.072
Hand vs. foot	−0.248	−0.216	−0.284	−1.005	−0.662	−0.202	0.095	−0.014	−0.064	0.089	−0.013
Foot vs. face	0.239	0.245	0.331	0.922	0.696	0.570	0.128	0.048	0.063	0.073	−0.059
9–12 vs. 6–8 years	−0.145	−0.084	−0.082	−0.094	1.032	0.198	0.069	−0.679	0.188	−0.068	0.269
13–16 vs. 6–8 years	−0.143	−0.067	−0.111	−2.246	2.442	0.243	0.067	−0.759	0.159	−0.072	0.277
13–16 vs. 9–12 years	0.002	0.017	−0.029	−2.152	1.411	0.045	−0.003	−0.080	−0.029	−0.004	0.008
Boys vs. Girls	0.065	0.050	0.060	−2.891	1.100	0.057	0.071	−0.106	−0.019	−0.014	0.070

The first part of this table comprises of *p*-values derived from a four-way ANOVA. This analysis was calculated as a repeated-measure ANOVA for the effect of body site and side with factor side nested under factor body site. PHS and ALL did not occur in any subject. A pairwise comprise of age groups (6–8, 9–12 and 13–16) was calculated only in case of significant main effects for age ($p < 0.05$). The second part of this table displays estimated group differences for the main effects body site (hand, face and foot), age (9–12 vs. 6–8 years, 13–16 vs. 9–12 years) and gender (boys and girls). Differences are estimated by linear regression. The reference group is the last group in each case. A significant age effect demonstrates differences between younger (6–8 years) and older (9–12 years) children e. g. older children (9–12 years) and adolescents (13–16 years). A significant gender effect demonstrates differences between boys and girls. The effects refer to log-transformed values beside CPT, HPT and VDT.

[a] Adjusted significance level (Bonferroni): 0.006.

[b] Adjusted significance level (Bonferroni): 0.017.

revealed 45–97% of common variance for individual QST parameters (corresponding to correlation coefficients from $r = 0.67–0.98$) side differences were more sensitive than absolute reference data (on average 1.9 ± 0.8 times; mean ± SD; see Table 5). This was especially pronounced for mechanical testing (improvement of sensitivity: 1.9–3.5-fold) as compared to thermal testing (improvement of sensitivity: 1.1–1.6-fold). Therefore we estimated confidence intervals for side differences as relative reference data. Although QST parameters exhibited similar properties in symmetric body sides, relative QST reference data (side differences) were not normally distributed for many parameters due to an over-representation of data around zero resulting in high kurtosis ranging between 3.8 and 32.6. Table 5 provides means, standard deviations, confidence intervals of side differences and cut-off values, which must be exceeded in case of affected sides to be outside the confidence interval of the absolute reference data. In these cases it is assumed that the control side yields values in the range of reference data.

4. Discussion

This is the first comprehensive study on the implementation of the standardized QST protocol of the DFNS for children and adolescents. This QST protocol was technically feasible in children 6 years and older in accordance with previous studies [57,58,74]. Determination of the QST procedure in younger children was difficult due to their limited time span of attention in accordance with other studies [35,57,58]. The feasibility for VDT and thermal detection may be from age 3, e.g. 4 onward as reported by others [40–42,57]. None of the children had difficulties with the modified verbal instructions of the DFNS protocol comparable to other QST studies [41,42,57,74,95] or with the NRS supporting the results of others [5,59,84]. The time frame needed for assessment was reasonable for one body side and comparable to other QST studies in children [41,42,55,78,90] and adults [67].

4.1. Developmental, gender and body site differences in QST

Body site differences were similar but distinct compared to those of other studies in children and adults [50,66,67] indicating the need of separate sets of QST reference data for each body site. Greater thermal and/or mechanical detection and/or mechanical and blunt pressure pain sensitivity in the face than the hand and/or foot has been shown previously in children [40,55] and adults [12,13,28,44,67,78,83,92]. Difference between hand and foot were less pronounced. Greater thermal detection and blunt pressure pain sensitivity in the hand and greater mechanical detection in the foot was reported in children [40,57] and adults [34,67,76,83]. Contributing factors may include differences in innervation density and overlap of receptor fields, reaction time artifacts related to the distance of the brain and environmental induced thickening of the epidermis [12,45,57]. In contrast to other studies in children [40,57,78] and adults [15,28,51,62,75] we found no differences for VDT probably due to bottom effects.

Age had the greatest effect on reference data. Between younger children on the one hand and older children and adolescents on the other hand there was a gain increase of thermal and mechanical detection in contrast to other studies in children [35,40,41,55,78] and a decrease of heat, blunt pressure and mechanical pain sensitivity supporting the results of others in children [10,22,23,29,48,54,70] and adults [79,91]. There was no difference between older children and adolescents beside hot and blunt pressure pain sensitivity. It is unlikely that differences in the pain assessment (FPS, NRS) may impact on these results because they were only used for mechanical pain ratings, whereas pain increases was most distinct for blunt pressure and temperature pain thresholds. In addition, recent studies have delivered profound evidence for the comparability of the pain scales [59,84]. Little is known about the underlying developmental mechanisms and if there is a critical period for somatosensory perception during childhood [20]. Peripheral factors may only play a minor role because nerve fiber myelination,

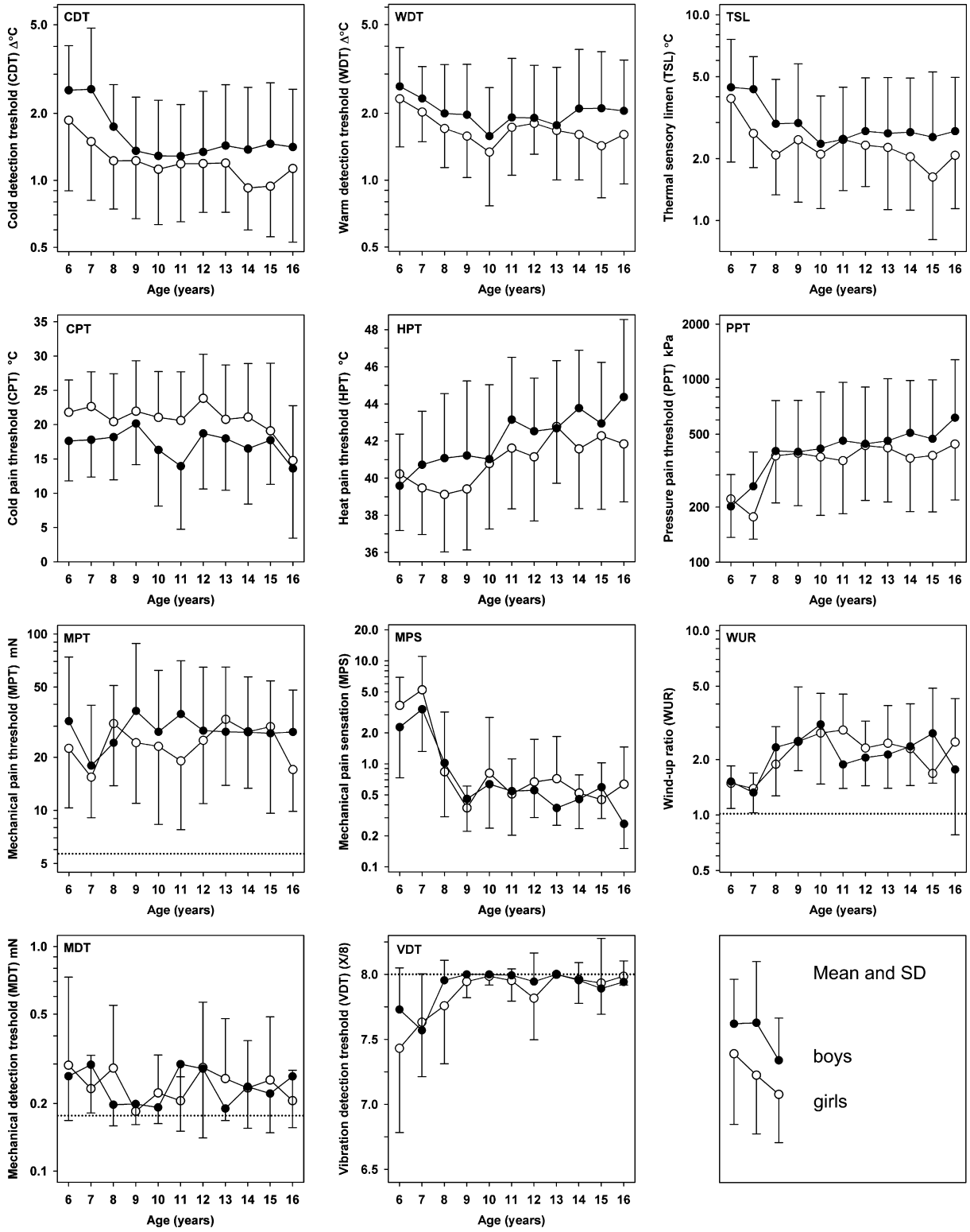

Fig. 1. Means and standard deviation (SD) of QST parameters (original units) for each year of age separated for girls and boys.

innervation density and nociceptive maturation is completed at earlier stages of development [10,22,23,29,48,54,70]. Similar changes in sensory and pain processing during development have been observed in animal studies [20]. They depend on cortical plasticity of neuronal circuitry [9] and on tactile learning processes by NMDA receptor mechanisms in the dorsal horn of the spinal cord where sensory afferents of different modalities are organised [20,21,32]. Presumably, our findings are caused by functional maturation of interneurons in the cortex and the dorsal horn [21]. Other influencing factors may be attention, anxiety, coping strategies and changes in pain reports [31]. Further clinical studies are required to determine factors related to the age effects in children.

Gender differences were more distinct in comparison with other studies in children [78,86], but less compared to adults

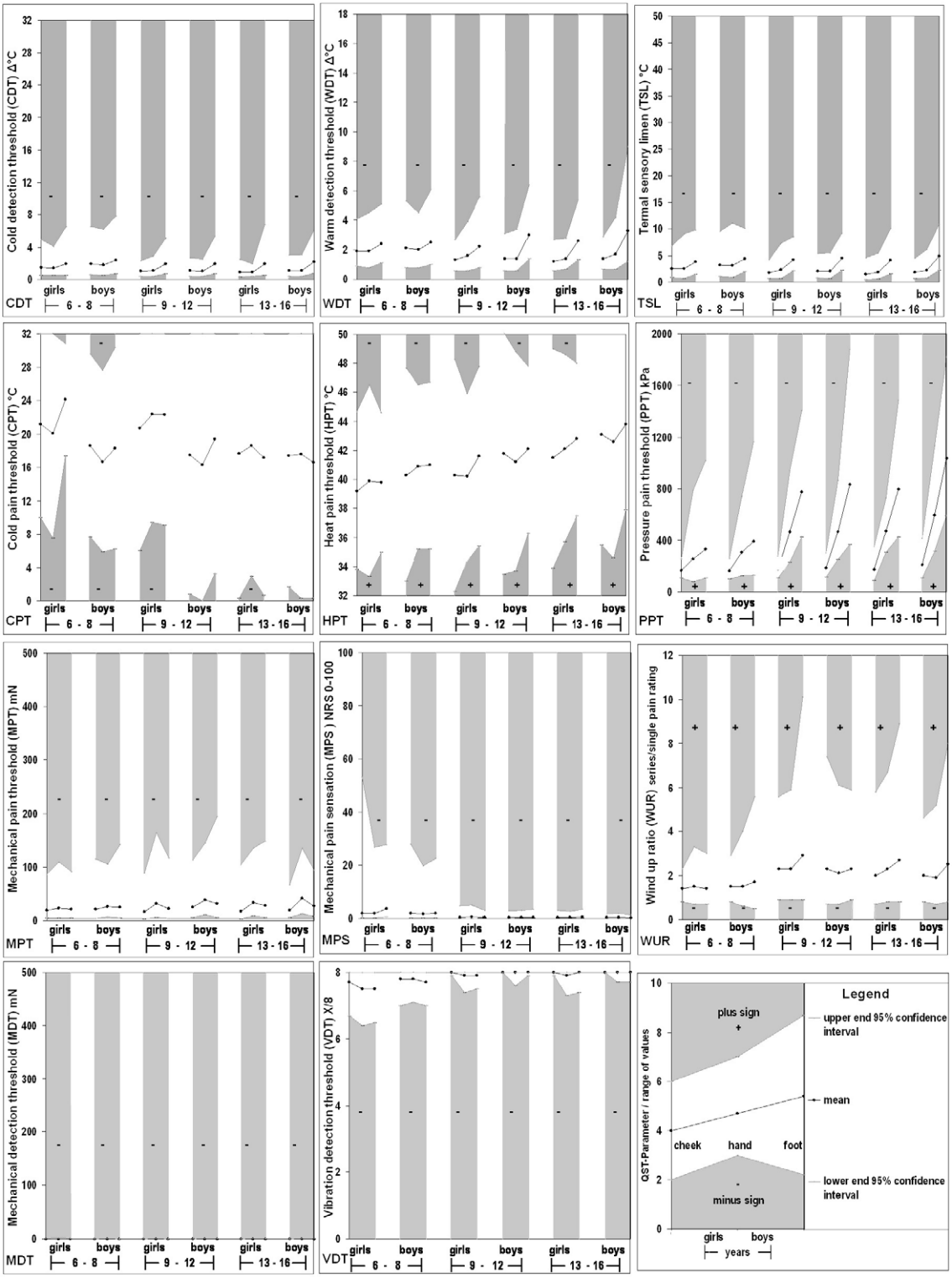

Fig. 2. Means and 95% confidence intervals (original units) for different body sites (first cheek, middle hand and last foot), age groups (6–8, 9–12 and 13–16 years) and gender (boys and girls). Grey-shaded areas depict QST values beyond the 95% confidence intervals allowing the assessment of pathological QST indicating either sensory loss (minus sign, −) or sensory gain (plus sign, +). Note that the majority of confidence intervals appear to be asymmetric due to retransformation of log-normal data into linear graphic representation.

[31]. Greater thermal detection in female than in male have only been shown in adults [50,66,67] but not in children [40,78,86] whereas greater thermal and blunt pressure pain sensitivity has been shown in girls [6,55,60,80,86] and women [60,64]. Surprisingly, we found no gender effects for mechanical pain sensitivity in contrast to other studies in children [16,19,61,66,67,71] and adults [17,22]. The observation of Goodenough and colleagues [8,14,24,66,67,69,72,82] for pain increase in girls with needle pain experience due to gender differences in pain reporting is improbable for our results because they were more pronounced for thermal

Table 4
Absolute QST reference values: means and 95% confidence intervals of re-transformed log- resp. raw-data.

QST parameter	Body site	Lower 95% confidence interal ◄ mean ► upper 95% confidence interval (original results)					
		6–8 years		9–12 years		13–16 years	
Number of subjects		Girls 24	Boys 24	Girls 32	Boys 32	Girls 32	Boys 32
CDT^{log} (°C from baseline)	Face	−4.8◄1.5►−0.5	−6.5◄1.9►−0.6	−2.3◄1.0►−0.4	−2.7◄1.1►−0.4	−2.5◄0.9►−0.3	−3.0◄1.1►−0.4
	Hand	−4.1◄1.4 ►−0.5	−6.2◄1.8 ►−0.5	−2.9◄1.1►−0.4	−2.5◄1.0►−0.4	−1.9◄0.9►−0.4	−3.1◄1.1►−0.4
	Foot	−8.0◄1.7►−0.4	−7.8◄2.4►−0.7	−5.1◄1.9►−0.7	−5.4◄1.9►−0.7	−6.8◄1.9►−0.5	−6.1◄2.2►−0.8
WDT^{log} (°C from baseline)	Face	0.9◄1.9►4.1	0.8◄2.1►5.3	0.6◄1.3►2.7	0.6◄1.4►3.1	0.6◄1.2►2.7	0.7◄1.4►2.9
	Hand	0.8◄1.9►4.5	0.8◄2.0►4.5	0.6◄1.6►3.9	0.6◄1.4►3.4	0.7◄1.4►2.8	0.7◄1.7►4.2
	Foot	1.0◄2.3►5.3	1.0◄2.5►6.1	0.8◄2.2►5.6	1.4◄3.0►6.4	1.1◄2.5►5.9	1.2◄3.3►9.0
TSL^{log} (°C)	Face	0.9◄2.5►6.8	1.1◄3.2►9.5	0.7◄1.7►4.2	0.8◄2.0►5.3	0.5◄1.6►4.6	0.7◄1.8►4.5
	Hand	0.7◄2.5►9.0	0.9◄ 3.1►11.1	0.7◄ 2.3►7.3	0.7◄2.0►5.5	0.6◄1.7►4.8	0.8◄2.2►6.1
	Foot	1.5◄ 3.8►9.8	1.9◄ 4.4►10.1	2.1◄ 4.2►8.5	2.2◄4.5►9.2	1.3◄3.8►11.6	2.2◄4.9►10.9
CPT (°C)	Face	10.0◄21.2►32.0	7.7◄18.6►29.6	6.0◄20.7►32.0	0.8◄17.5►32.0	0.3◄17.3►32.0	1.7◄17.4►32.0
	Hand	7.5◄20.1►32.0	5.9◄16.7►27.6	9.4◄22.4►32.0	0.0◄16.3►32.0	3.0◄18.6►32.0	−0.3◄17.6►32.0
	Foot	17.4◄24.1►30.8	6.2◄18.3►30.3	9.1◄22.3►32.0	3.3◄19.4►32.0	−0.5◄17.6►32.0	−0.3◄16.6►32.0
HPT (°C	Face	33.8◄39.2►44.7	33.0◄40.3►47.7	32.3◄40.3►48.3	33.5◄41.8►50.1	34.3◄41.7►49.0	35.5◄43.1►50.8
	Hand	33.3◄39.9►46.5	35.2◄40.9►46.5	34.4◄40.2►45.9	33.7◄41.2►48.8	35.7◄42.1►48.6	34.6◄42.6►50.6
	Foot	35.0◄39.8►44.6	35.2◄41.0►46.7	35.4◄41.6►47.8	36.3◄42.1►47.8	36.8◄42.5►48.3	37.9◄43.8►49.7
PPT^{log} (kPa)	Face	109◄168►258	102◄163►261	109◄175►280	116◄188►305	90◄178►352	108◄212►417
	Hand	82◄255►790	129◄309►741	232◄468►943	254◄470►866	308◄475►731	316◄597►1130
	Foot	107◄331►1021	131◄391►1165	428◄776►1407	369◄832►1879	430◄799►1890	593◄1039►1820
MPT^{log} (mN)	Face	5◄20►87	4◄22►116	3◄17►89	5◄25►113	4◄16►65.4	6◄19►67
	Hand	5◄24►110	6◄26►106	6◄32►165	10◄39►146	9◄34►136	13◄42►136
	Foot	5◄22►92	4◄25►142	4◄22►118	5◄32►195	5◄28►146	8◄27►95
MPS^{log} (NRS 0–100)	Face	0.1◄2.0►53.3	0.1◄2.0►28.0	0.0◄0.4►4.8	0.0◄0.3►2.9	0.1◄0.4►3.1	0.0◄0.3►1.7
	Hand	0.2◄2.0►26.7	0.1◄1.7►19.9	0.0◄0.5►5.0	0.1◄0.4►3.1	0.1◄0.4►2.7	0.0◄0.3►1.9
	Foot	0.5◄3.6►27.8	0.2◄1.9►22.6	0.1◄0.4►3.2	0.1◄0.4►3.4	0.1◄0.5►3.3	0.0◄0.2►1.3
WUR^{log} (ratio)	Face	0.8◄1.4►2.3	0.8◄1.5►2.9	0.9◄2.3►5.6	0.7◄2.3►7.4	0.7◄2.0►5.9	0.8◄2.0►4.6
	Hand	0.7◄1.5►3.3	0.6◄1.5►4.0	0.9◄2.3►5.9	0.7◄2.1►6.1	0.8◄2.3►6.7	0.7◄1.9►5.2
	Foot	0.7◄1.4►3.0	0.5◄1.7►5.6	0.9◄2.9►10.1	0.9◄2.3►5.9	0.8◄2.7►8.7	0.8◄2.5►8.0
MDT^{log} (mN)	Face	0.1◄0.3►1.0	0.1◄0.2►0.3	0.2◄0.2►0.2	0.1◄0.2►0.4	0.2◄0.2►0.2	0.2◄0.2►0.2
	Hand	0.1◄0.4►1.5	0.1◄0.3►1.0	0.1◄0.3►0.8	0.1◄0.3►0.9	0.1◄0.3►1.1	0.1◄0.2►0.6
	Foot	0.1◄0.3►1.1	0.1◄0.2►0.4	0.1◄0.2►0.4	0.1◄0.2►0.7	0.1◄0.2►0.5	0.1◄0.3►0.6
VDT (x/8)	Face	6.7◄7.7►8.0	7.0◄7.8►8.0	7.9◄8.0►8.0	8.0◄8.0►8.0	7.9◄8.0►8.0	8.0◄8.0►8.0
	Hand	6.4◄7.5►8.0	7.1◄7.8►8.0	7.4◄7.9►8.0	7.6◄8.0►8.0	7.3◄7.9►8.0	7.7◄8.0►8.0
	Foot	6.5◄7.5►8.0	7.0◄7.7►8.0	7.5◄7.9►8.0	7.9◄8.0►8.0	7.4◄8.0►8.0	7.7◄8.0►8.0

CDT cold detection threshold; WDT warm detection threshold; TSL thermal sensory limen; CPT cold pain threshold; HPT hot pain threshold; PPT pressure pain threshold (blunt pressure); MPT mechanical pain threshold (pinprick); MPS mechanical pain sensitivity (pinprick); WUR wind-up ratio; MDT mechanical detection threshold; VDT vibration detection threshold; PHS Paradoxical heat sensation; and DMA dynamic mechanical allodynia – *Note*: PHS and DMA never occurred in any of the subject (therefore not listed in the table).

Table 5
Gain in sensitivity for side differences (relative reference data) over absolute reference data.

QST Parameter	Mean SD of		Gain in sensitivity SD_1/SD_2	Criterion right/left	Mean ± 1.96 × SD	Mean − 1.96 × SD	Relative reference data: 95% CI re-transformed	
	Absolute data (SD_1)	Right–left-difference (SD_2)					Lower cutoff	Upper cutoff
CDT^{log}	0.237	0.199	1.19	Ratio	−0.38	0.41	42%	258%
WDT^{log}	0.184	0.172	1.07	Ratio	−0.34	0.37	46%	233%
TSL^{log}	0.218	0.161	1.35	Ratio	−0.33	0.33	47%	212%
CPT	7.183	4.615	1.56	Difference	−9.04	9.23	−9.04	9.23
HPT	3.311	2.902	1.14	Difference	−5.31	5.96	−5.31	5.96
PPT^{log}	0.172	0.049	3.52	Ratio	−0.09	0.11	81%	129%
MPT^{log}	0.346	0.168	2.06	Ratio	−0.38	0.34	42%	218%
MPS^{log}	0.567	0.163	3.48	Ratio	−0.33	0.31	47%	203%
WUR^{log}	0.226	0.111	2.04	Ratio	−0.21	0.25	61%	179%
MDT^{log}	0.195	0.105	1.86	Ratio	−0.24	0.25	57%	179%
VDT	0.268	0.134	1.99	Difference	−0.29	0.29	−0.29	0.29

Mean and standard deviation of side differences and 95% confidence intervals for ratings (body site, age and gender) together. Confidence intervals of relative reference data are always smaller than CI of absolute reference data, indicating that relative data for side to side contrasts are more sensitive to detect loss or gain of somatosensory function. Gain in sensitivity for side differences (relative reference data) over absolute reference data was calculated from mean standard deviation of absolute data (SD_1) and of side differences (SD_2) from each subject with respect to body site, age and gender as ratios of these means (Ratio/Difference right/left). $Index^{log}$ denotes QST parameters, for which calculations are based on log-transformed data (→ ratios).

Table 6
Means and standard deviations of QST parameters and important influencing factors in healthy children and adolescents from previous QST studies.

Authors	Heimans [35]	Thibault [78]	Meh and Denislic [56]	Hilz et al. [41]	Hilz et al. [40]	Hilz et al. [42]	Meh and DeniÜli [55]	Hilz and Axelrod [39]	Meier et al. [57], Sethna et al. [74]	Abad [1]	Hermannet al. [36]	Zohsel et al. [95]	Schmelzle-Lubiecki et al. [73]	Weintrob et al. [88]	Zohsel [94]	Walker et al. [86]	Wollgarten-Hadamek et al. [90]
Subjects *N* male:female	81	43	150	74	296	225	69	80	101	35	20	28	9	43	23	44	24
		23:20	83:67	41:33	164:132	124:101	35:34	42:38	48:53	19:16	10:10	12:16	5:04	21:22	13:10	16:28	12:12
Age range	6–15	6–12	10–73	5.5 ± 0.9	3–17	7–17 9.5/ 14.8	9–18	10–40	7–17	8–16	10–14	9–15	10.56 ± 0.88	10–38	9–14		9–15
Mean ± SD	10 ± 2.4	9 ± 11	36 ± 17				13.4 ± 2.6	22.9 ± 10.2	11.5 ± 3	12.4 ± 2.6	11.2 ± 1.8	11.0 ± 1.8		10	11.0 ± 1.5	11.1 ± 0.4	11.2 ± 1.9
Feasibility	⩾8 years		⩾4 years	⩾3 years	⩾7 years		⩾6 years CDT ⩾3 years VUR										
Test site	Foot[3]	Hand[2] Foot[3]	Face[1] Hand[2] Foot[3]	Hand[2] Foot[3]	Hand[2] Foot[3]	Face[1] Hand[2] foot[3]	Hand[2] Foot[3]	Face[1] Hand[2] Foot[3]	Hand[2] Foot[3]	Hand[2] Foot[3]	Face[1] Hand[2]	Face[1] Hand[2]	Hand[2]	Foot[3]	Hand[2]	Hand[2]	Face[1] Hand[2]
Detection Thresholds	TSL [3]0.3 ± 0.1	MDT Other method	TSL [1]0.94 ± 0.79♂	CDT [2]2.7 ± 1.2	VUR [2]7,8 ± 0,3	CDT [1]1.5 ± 0.6ch.	TSL [2]1.37 ± 0.71	CDT [1]1.5 ± 0.5	CDT [2]28.5(30.5)31.3	CDT [2]0.6(0.7)0.8			CDT [2]29.49 ± 2.2 le.	CDT [3]28.8 ± 1.4		CDT [2]∼30	
		[2]2.33 ± 0.25	[1]0.80 ± 0.46 ♀	[3]3.5 ± 1.9	[2]7.8 ± 0.2	[2]2.1 ± 0.9ch.	[3]1.81 ± 1.07	[2]1.7 ± 0.7	[3]26.8(30.1)31.1	[3]0.7(0.9)1.3			[2]29.84 ± 1.12 ri.				
		[3]3.51 ± 0.41	[2]1.89 ± 1.12♂ [2]1.53 ± 1.06♀		[2]7.9 ± 0.2 [2]7.8 ± 0.2	[2]2.1 ± 0.9ad [3]2.7 ± 1.1ch.		[3]2.7 ± 1.7					WDT	WDT		WDT	WDT
			[3]4.24 ± 3.19♂		[3]7.7 ± 0.4	[3]3.4 ± 1.6ad.		WDT	WDT	WDT			[2]38.71 ± 1.72 le.	[3]35.5 ± 1.3		[2]∼34	[1]34.2 ± 1.2
			[3]2.98 ± 2.34♀	WDT	[3]7.6 ± 0.3			[1]1.1 ± 0.5	[2]33.0(33.7)36.1	[2]1.1(1.2)1.1			[2]39.2 ± 2.35 ri.				[2]34.4 ± 0.7
				2.0 ± 1.0 [3]2.9 ± 1.2	[3]7.8 ± 0.2 [3]7.6 ± 0.3	WDT [1]1.5 ± 0.9ch.		[2]1.5 ± 0.7 [3]3.1 ± 1.8	[3]33.6(35.1)39.6	[3]1.8(2.1)3.8			MDT	Vibra-meter		PHS: [2]no	
						[2]1.4 ± 0.5ch.							[2]6.55 ± 1.37 le.			MDT	MDT
	Vibra-meter	Vibra-meter				[2]1.3 ± 0.6ad. . [3]2.3 ± 1.0ch [3]2.6 ± 1.1ad.		Vibra-meter	Vibra-meter				[2]6.67 ± 1.37 ri.			[2]∼4.5	[1]∼0.4 [2]∼0.2
Pain thresholds			CPT				CPT		CPT	HPT	HPT	HPT			HPT	CPT 5)	HPT
			[1]24.46 ± 4.88♂ [1]25.15 ± 4.61♀ [2]23.15 ± 4.76♂ [2]24.09 ± 4.87♀ [3]23.63 ± 5.21♂ [3]23.78 ± 5.09♀				[2]20.84 ± 6.0 [3]21.50 ± 6.1		[2]0.0(14.9)28.0 [3]0.0(21.5)28.4	[2]41.4(41.7)43.1 [3]41.5(42.3)43.1	[1]38.08 ± 2.4 [2]41.75 ± 4.1	[1]39.4 ± 3.5♂ [1]38.5 ± 2.5♀ [2]42.8 ± 4.3♂ [2]42.9 ± 4.1♀			[2]43.2 ± 3.5	[2]28.9 ± 0.3♂ [2]26.2 ± 0.7♀ HPT 6) [2]35.6 ± 0.4♂ [2]38.2 ± 0.7♀	[1]38.4 ± 2.4 [2]42.8 ± 4.3
							HPT [2]39.17 ± 4.3 [3]37.63 ± 2.2		HPT [2]35.8(41.7)50.0 [3]37.1(42.3)49.4		MPT [1]104 ± 90 [2]134 ± 106	MPT [1]95.9 ± 103♂ [1]114.3 ± 68 ♀ [2]137.2 ± 109♂			MPT [2]201 ± 118	MPT [2]103.7 ± 90.6♂ [2]134.4 ± 106.2♀	
			HPT [1]37.51 ± 4.13♂ [1]35.95 ± 3.71♀ [2]40.18 ± 4.81♂ [2]37.69 ± 4.21♀ [3]39.59 ± 2.76♂ [3]38.22 ± 3.01♀								WUR [1]9.1 ± 9.4 [2]7.4 ± 7.4	[2]150.1 ± 97♀ WUR [1]5.3 ± 4.9♂ [1]10.4 ± 9.0♀ [2]4.0 ± 5.3♂ [2]7.8 ± 7.3♀			WUR [2]5.8 ± 4.3	WUR [2]9.1 ± 9.4♂ [2]7.4 ± 7.4♀ DMA no	WUR [1]∼8 [2]∼6
Side-diff.		No	No		No								No				
Site-diff. sensitivity		Hand < foot	Face > hand/ foot		Hand > foot				Hand > foot								
Gender-diff. sensitivity		No	♀ < ♂		No											CDT,WDT no CPT,HPT♀ > ♂	
Age diff.	No	No	No	No	No												

Results are shown either as "mean ± standard deviation" or as "upper confidence interval (mean) lower confidence interval". [1]: face, [2]: hand, [3]: foot; Diff.: Differences; ♂: men; ♀ women; ch.: children; ad.: adolescents; le.: left; ri.: right; ∼ exact values not given; CDT cold detection threshold; WDT warm detection threshold; TSL thermal sensory limen; CPT cold pain threshold; HPT hot pain threshold; MPT mechanical pain threshold (pinprick); MPS mechanical pain sensitivity (pinprick); WUR wind-up ratio; MDT mechanical

pain. Hormonal factors accounting for gender differences [31] are also unlikely, because we found no difference between girls before and after puberty. It seems most likely that gender differences in sensory and pain processing reflect underlying central mechanisms that mediate sensory and pain perception due to genetical and psychological factors [2,11,18,66].

4.2. Absolute QST reference data

Until now, a comprehensive set of reference values for the QST protocol of the DFNS in children and adolescents was missing. Mean values and standard deviations at the reference sites of this study are within the published ranges for thermal [41,42,57,73], mechanical [90] and vibration [40] detection and thermal pain thresholds [41,57,73] as shown in Table 6. Other studies with different test instructions and test procedures and/or devices had slightly higher ranges for mechanical detection and mechanical pain thresholds, including temporal summation of the perceived pain [36,73,78,86,94,95]. In the present study, pain summation gradually developed in young children to reach an adult-like plateau in older children and adolescents. However, the pain summation test may be difficult to perform in young children. Our data indicate that the absence of temporal summation of the perceived pain, dynamic mechanical allodynia and paradoxical heat sensation is physiological in line with other studies in children and adults [86]. Reference values in our study differed considerably from adults in the DFNS protocol whereas standard deviations were similar [67]. The range for mechanical and vibration thresholds was higher in adults, especially for the foot, indicating worse innervation density or Aβ-fiber function. In contrast the range for thermal, mechanical and plant pressure pain thresholds was lower compared to that for younger children whereas older children and adolescents differed only for thermal pain [67] (Table 7)).

4.3. Relative QST reference data

Absolute reference data are essential for patients suffering from bilateral pain. Comparison of both body sides within children indicated that right–left differences were more sensitive than absolute reference data, as described previously for adults [67]. For patients with unilateral pain, comparison with the unaffected contra lateral area (relative reference data) are beneficial for increasing the diagnostic sensitivity compared to absolute QST reference data primarily for mechanical testing, but to a much lesser degree for thermal testing.

4.4. Data range of QST reference data

For both, absolute and relative reference data the range of confidence intervals was smaller for mechanical and vibration detection than for thermal detection thresholds ($p < 0.01$) like in adults (69), indicating better discrimination and conduction properties of mechanoreceptors, Aβ-fibers and the lemniscal system than for nociceptors, Aδ-/C-fibers [73]. There were 22 reference confidence limits that could be calculated for all 13 QST tests. Exceeding these limits indicates either loss or gain of sensory functions. Decreased perception thresholds or increased ratings indicate pathological hypersensitivity (plus sign/gain) and increased perception thresholds or decreased ratings indicate loss of sensory function (minus sign/loss). For four additional QST parameters, sensitivity of the testing equipment did allow sufficient sensitivity (bottom effect).

Even though the present confidence intervals are based on only 24–32 children per age and gender group, they provide a profound basis in diagnosing loss or gain of sensory functioning in children and adolescents because of their structure and distribution properties (range, variance, and side differences) were equal for all body sites, similar to other studies in children and adults and plausible for statistical factors.

Table 7
Means and standard deviations of log transformed- resp. raw-data for QST parameters in adults. Modified from [67,68], Appendix 2 of Supplementary material.

QST Parameter	Body site	17–39 years	
		Women	Men
CDT^{log} (°C from baseline)	Face	−0.021 ± 0.197	−0.049 ± 0.226
	Hand	0.054 ± 0.226	0.042 ± 0.231
	Foot	0.284 ± 0.251	0.384 ± 0.255
WDT^{log} (°C from baseline)	Face	0.149 ± 0.193	0.114 ± 0.221
	Hand	0.208 ± 0.211	0.225 ± 0.222
	Foot	0.587 ± 0.195	0.657 ± 0.219
TSL^{log} (°C)	Face	0.273 ± 0.205	0.245 ± 0.274
	Hand	0.378 ± 0.265	0.425 ± 0.258
	Foot	0.761 ± 0.196	0.837 ± 0.205
CPT (°C)	Face	18.44 ± 7.58	14.74 ± 9.71
	Hand	16.16 ± 7.08	12.47 ± 8.67
	Foot	14.52 ± 8.48	11.60 ± 8.19
HPT (°C)	Face	41.52 ± 4.13	43.67 ± 3.57
	Hand	42.61 ± 3.33	44.14 ± 2.77
	Foot	43.81 ± 2.80	45.14 ± 2.37
PPT^{log} (kPa)	Face	2.306 ± 0.090	2.354 ± 0.137
	Hand	2.544 ± 0.108	2.627 ± 0.173
	Foot	2.678 ± 0.118	2.763 ± 0.183
MPT^{log} (mN)	Face	1.608 ± 0.413	1.648 ± 0.428
	Hand	1.889 ± 0.348	1.912 ± 0.431
	Foot	1.831 ± 0.410	1.867 ± 0.409
MPS^{log} (NRS 0–100)	Face	−0.013 ± 0.480	−0.029 ± 0.498
	Hand	−0.082 ± 0.388	−0.120 ± 0.427
	Foot	−0.085 ± 0.389	−0.079 ± 0.478
WUR^{log} (ratio)	Face	0.423 ± 0.247	0.428 ± 0.232
	Hand	0.397 ± 0.250	0.354 ± 0.205
	Foot	0.430 ± 0.257	0.404 ± 0.223
MDT^{log} (mN)	Face	−0.655 ± 0.157	−0.611 ± 0.218
	Hand	−0.182 ± 0.339	−0.140 ± 0.390
	Foot	−0.001 ± 0.458	0.306 ± 0.483
VDT (*x*/8)	Face	7.51 ± 0.57	7.30 ± 0.76.
	Hand	7.84 ± 0.38	7.74 ± 0.42
	Foot	7.57 ± 0.67	7.46 ± 0.64

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, hot pain threshold; PPT, pressure pain threshold (blunt pressure); MPT, mechanical pain threshold (pinprick); MPS, mechanical pain sensitivity (pinprick); WUR, wind-up ratio; MDT, mechanical detection threshold; and VDT, vibration detection threshold.

4.5. Limitations

There are several limitations to our study. Although we found no differences between subjects related to the presence of the mother during tests in older children and adolescents and the sex of the experimenter in line with other results [36,43] further studies are needed to evaluate the impact of parental presence and the sex of the investigation because they can affect children's pain ratings [6,81]. Further the impact of attention and emotional state should be assessed because the testing duration of 4 h may cause fatigue and thresholds can be affected by anxiety and motivation to cooperate. Although the high correlation between body sides indicates high short-term test–retest reliability further studies are needed to evaluate long-term test–retest reliability.

4.6. Conclusions and clinical implications

We conclude that the QST protocol of the DFNS is applicable to children over 5 years of age and valid in comparison with other

studies in children and adults. Our findings demonstrated profound differences between younger children on the one hand and older children and adolescents on the other hand. Further research is needed to detect whether these differences display developmental processes or are related to psychological factors impacting on the QST assessment. In addition, prospective studies are needed to determine the impact of these differences upon pain experiences and pain reactions in the future. Our reference values are baseline data for future studies on children using the DFNS protocol. By means of comprehensive QST as described in this paper, age-dependent differences and sensory phenotypes of neuropathic and other chronic pain conditions in children may be detected more sensitively in the future.

Conflict of interest

The authors declare that they have no conflict of interest, including specific financial interests, relationships or affiliations relevant to the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.01.011.

References

[1] Abad F, Az-Gomez NM, Rodriguez I, Perez R, Delgado JA. Subclinical pain and thermal sensory dysfunction in children and adolescents with Type 1 diabetes mellitus. Diabet Med 2002;19:827.
[2] Aloisi AM. Gonadal hormones and sex differences in pain reactivity. Clin J Pain 2003;19:168–74.
[3] Arts SE, Abu-Saad HH, Champion GD, Crawford MR, Fisher RJ, Juniper KH, Ziegler JB. Age-related response to lidocaine-prilocaine (EMLA) emulsion and effect of music distraction on the pain of intravenous cannulation. Pediatr 1994;93:797–801.
[4] Baumgartner JL, Emslie GJ, Crismo ML. Citalopram in children and adolescents with depression or anxiety. Ann Pharmacother 2002;36:1692–7 (Ref Type: Abstract).
[5] Cepeda MS, Carr DB. Clinical meaning of a decline in pain intensity in children and its implications in care and research. Pecliatr Pain Lett 2008;8:23–7.
[6] Chambers CT, Craig DT, Bennett SM. The impact of maternal behavior on children's pain experiences: an experimental analysis. J Pediatr Psychol 2002;27:293–301.
[7] Chan AW, MacFarlane IA, Bowsher D, Campbell JA. Weighted needle pinprick sensory thresholds: a simple test of sensory function in diabetic peripheral neuropathy. Br Med J 1992;55:56–9.
[8] Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259–66.
[9] Colonnese MT, Phillips MA, Constantine-Paton M, Kaila K, Jasanoff A. Development of hemodynamic responses and functional connectivity in rat somatosensory cortex. Nat Neurosci 2007;11:72–9.
[10] Cooper PJ, Awden HN, Camfield PR, Camfield CS. Anxiety and life events in childhood migraine. Pediatr 1987;79:999–1004.
[11] Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain 2004;8:397–411.
[12] Dyck PJ, Schultz PW, O'Brien PC. Quantitation of touch-pressure sensation. Arch Neurol 1972;26:465–73.
[13] Dyck PJ, Zimmerman I, Gillen DA, Johnson D, Karnes JL, O'Brien PC. Cool, warm, and heat-pain detection thresholds: testing methods and inferences about anatomic distribution of receptors. Neurology 1993;43:1500–8.
[14] Ellermeier W, Westphal W. Gender differences in pain ratings and pupil reactions to painful pressure stimuli. Pain 1995;61:435–9.
[15] Era P, Jokela J, Suominen H, Heikkinen E. Correlates of vibrotactile thresholds in men of different ages. Acta Neurol Scand 1986;74:210–7.
[16] Feine JS, Bushnell MC, Miron D, Duncan GH. Sex differences in the perception of noxious heat stimuli. Pain 1991;44:255–62.
[17] Fernald CD, Corry JJ. Empathic versus directive preparation of children for needles. Child Health Care 1981;10:44–7.
[18] Fillingim R, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. Neurosci Biobehav Rev 2000;24:485–501.
[19] Fillingim RB, Maixner W, Kincaid S, Silva S. Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998;75:121–7.
[20] Fitzgerald M. The development of nociceptive circuits. Nat Rev Neurosci 2005;6:507–20.
[21] Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. Nat Clin Pract Neurol 2009;5:35–50.
[22] Fowler-Kerry S, Lander J. Assessment of sex differences in children's and adolescents' self-reported pain from venipuncture. J Pediatr Psychol 1991;16:783–93.
[23] Fradet C, McGrath PJ, Kay J, Adams S, Luke B. A prospective survey of reactions to blood tests by children and adolescents. Pain 1990;40:53–60.
[24] Frot M, Feine JS, Bushnell MC. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. Pain 2004;108:230–6.
[25] Fruhstorfer H, Gross W, Selbmann O. Von Frey hairs: new materials for a new design. Eur J Pain 2001;5:341–2.
[26] Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. Br Med J 1976;39:1071–5.
[27] Gaffney A, Dunne A. Developmental aspects of childreńs definitions of pain. Pain 1986;26:105–17.
[28] Goldberg JM, Lindblom U. Standardised method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. J Neurol Neurosurg Psychiatr 1979;42:793–803.
[29] Goodenough B, Addicoat L, Champion GD, McInerney M, Young B, Juniper K, Ziegler JB. Pain in 4-to 6-year old children receiving intramuscular injections: a comparison of the faces pain scale with other self-report and behavioral measures. Clin J Pain 1997;13:60–73.
[30] Goodenough B, Kampel L, Champion GD, Laubreaux L, Nicholas MK, Ziegler JB, McInerney M. An investigation of the placebo effect and age-related factors in the report of needle pain from venipuncture in children. Pain 1997;72:383–91.
[31] Goodenough B, Thomas W, Champion GD, Perrott D, Taplin JE, von Baeyer CL, Ziegler JB. Unravelling age effects and sex differences in needle pain: ratings of sensory intensity and unpleasantness of venipuncture pain by children and their parents. Pain 1999;80:179–90.
[32] Granmo M, Petersson P, Schouenborg J. Action-based body maps in the spinal cord emerge from a transitory floating organization. J Neurosci 2008;28:5494.
[33] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain 2007;129:256–9.
[34] Harrison JL, Davis KD. Cold-evoked pain varies with skin type and cooling rate: a psychophysical study in humans. Pain 1999;83:123–35.
[35] Heimans JJ, Bertelsmann FW, de Beaufort CE, de Beaufort AJ, Faber YA, Bruining GJ. Quantitative sensory examination in diabetic children: assessment of thermal discrimination. Diabet Med 1987;4:251–3.
[36] Hermann C, Hohmeister J, Demirakca S, Zohsel K, Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 2006;125:278–85.
[37] Herrero JF, Laird JMA, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol 2000;61:169–203.
[38] Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The faces pain scale – revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173–83.
[39] Hilz MJ, Axelrod FB. Quantitative sensory testing of thermal and vibratory perception in familial dysautonomia. Clin Auton Res 2000;10:177–83.
[40] Hilz MJ, Axelrod FB, Hermann K, Haertl U, Duetsch M, Neundorfer B. Normative values of vibratory perception in 530 children, juveniles and adults aged 3–79 years. J Neurol Sci 1998;159:219–25.
[41] Hilz MJ, Glorius SE, Schweibold G, Neuner I, Stemper B, Axelrod FB. Quantitative thermal perception testing in preschool children. Muscle Nerve 1996;19:381–3.
[42] Hilz MJ, Stemper B, Schweibold G, Neuner I, Grahmann F, Kolodny EH. Quantitative thermal perception testing in 225 children and juveniles. J Clin Neurophysiol 1998;15:529–34.
[43] Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. Eur J Pain 2009;13:94–101.
[44] Jamal GA, Hansen S, Weir AL, Ballantyne JP. An improved automated method for the measurement of thermal thresholds. 1. Normal subjects. J Neurol Neurosurg Psychiat 1985;48:354–60.
[45] Johansson RS, Vallbo AB. Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. J Physiol (Lond) 1979;268:300.
[46] Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region: the influence of skin sensitivity in pressure algometry. J Rehabil Med 1999;31:89–93.
[47] LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190–211.
[48] Lander J, Fowler-Kerry S, Hill A. Comparison of pain perceptions among males and females. Can J Nurs Res 1990;22:39–49.
[49] Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. Pain (Amsterdam) 1998;74:257–68.
[50] Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341–51.

[51] Martina ISJ, Van Koningsveld R, Schmitz PIM, Van der Meche FGA, Van Doorn PA. Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. Br Med J 1998;65:743–7.
[52] McGrath PA, Brown SC. Quantitative sensory testing in children: practical considerations for research and clinical practice. Pain 2006;123:1–2.
[53] McGrath PJ. Behavioral measures of pain. In: Finley GA, McGrath PJ, editors. Measurements of pain in infants and children. Seattle: IASP Press; 1998. p. 83–102.
[54] McGrath PJ, Hsu E, Cappelli M, Luke B, Goodam JT, Dunn-Geier J. Pain from pediatric cancer: a survey of an outpatient oncology clinic. J Psychosoc Oncol 1990;8:109–24.
[55] Meh D, Denislic M. Quantitative assessment of thermal and pain sensitivity. J Neurol Sci 1994;127:164–9.
[56] Meh D, DeniÜli M. Subclinical neuropathy in type I diabetic children. Electroencephalogr Clin Neurophysiol/Electromyogr Motor Control 1998;109:274–80.
[57] Meier PM, Berde CB, DiCanzio J, Zurakowski D, Sethna NF. Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. Muscle Nerve 2001;24.
[58] Meister C, Molinari L, Thun-Hohenstein L, Boltshauser E. Measuring vibration sense in childhood. Normal values and initial experiences in polyneuropathies. Monatsschr Kinderheilkd 1993;141:416–20.
[59] Miró J, Castarlenas E, Huguet A. Evidence for the use of a numerical rating scale to assess the intensity of pediatric pain. Eur J Pain 2009;13:1089–95.
[60] Myers CD, Tsao JC, Glover DA, Kim SC, Turk N, Zeltzer LK. Sex, gender, and age: contributions to laboratory pain responding in children and adolescents. J Pain 2006;7:556–64.
[61] Paulson PE, Satoshi M, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 1998;76:223–9.
[62] Perret E, Regli F. Age and the perceptual threshold for vibratory stimuli. Eur Neurol 1970;4:65–76.
[63] Perrott DA, Goodenough B, Champion GD. Children's ratings of the intensity and unpleasantness of post-operative pain using facial expression scales. Eur J Pain 2004;8:119–27.
[64] Piira T, Taplin JE, Goodenough B, von Baeyer CL. Cognitive-behavioural predictors of children's tolerance of laboratory-induced pain: implications for clinical assessment and future directions. Behav Res Ther 2002;40:571–84.
[65] Price DD, Bush FM, Long SM, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217–26.
[66] Riley JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74:181–7.
[67] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123:231–43.
[68] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
[69] Rollman GB, Lautenbacher S. Sex differences in musculoskeletal pain. Clin J Pain 2001;17:20–4.
[70] Ross DM, Ross SA. Childhood pain. Current issues, research, and management. Baltimore: Urban & Schwarzenberg; 1988.
[71] Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. Pain 2003;106:9–18.
[72] Sarlani E, Greenspan JD. Gender differences in temporal summation of mechanically evoked pain. Pain 2002;97:163–9.
[73] Schmelzle-Lubiecki BM, Campbell KA, Howard RH, Franck L, Fitzgerald M. Long-term consequences of early infant injury and trauma upon somatosensory processing. Eur J Pain 2007;11:799–809.
[74] Sethna NF, Meier PM, Zurakowski D, Berde CB. Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes. Pain 2007;131:153–61.
[75] Sosenko JM, Boulton AJ, Kubrusly DB, Weintraub JK, Skyler JS. The vibratory perception threshold in young diabetic patients: associations with glycemia and puberty. Diab Care 1985;8:605–7.
[76] Stevens JC, Choo KK. Temperature sensitivity of the body surface over the life span. Somatosens Mot Res 1998;15:13–28.
[77] Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. Pain 2006;125:143–57.
[78] Thibault A, Forget R, Lambert J. Evaluation of cutaneous and proprioceptive sensation in children: a reliability study. Dev Med Child Neurol 1994;36:796–812.
[79] Tillman DB, Treede RD, Meyer RA, Campbell JN. Response of C fibre nociceptors in the anaesthetized monkey to heat stimuli: correlation with pain threshold in humans. J Physiol 1995;485:767–74.
[80] Tsao JC, Glover DA, Bursch B, Ifekwunigwe M, Zeltzer K. Laboratory pain reactivity and gender: relationship to school nurse visits and school absences. J Dev Behav Pediatr 2002;23:217–24.
[81] Tsao JC, Lu Q, Myers CD, Kim SC, Turk N, Zeltzer LK. Parent and child anxiety sensitivity: relationship to children's experimental pain responsitivity. J Pain 2006;7:319–26.
[82] Unruh AM. Gender variations in clinical pain experience. Pain 1996;65:123–67.
[83] Verdugo R, Ochoa JL. Quantitative somatosensory thermotest. A key method for functional evaluation of small calibre afferent channels. Brain 1992;115:893–913.
[84] von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the numerical rating scale (NRS-11) for children's self-reports of pain intensity. Pain 2009;143:223–7.
[85] von Frey M, Klasse MP. Untersuchungen über die Sinnesfunctionen der menschlichen Haut. Leipzig, S. Hirzel; 1896.
[86] Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J, Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. Pain 2009;141:79–87 [January].
[87] Weinstein S. Intensive and extensive aspects of tactile sensitivity as a function. In: The skin senses: proceedings. Thomas; 1968. p. 195.
[88] Weintrob N, Amitay I, Lilos P, Shalitin S, Lazar L, Josefsberg Z. Bedside neuropathy disability score compared to quantitative sensory testing for measurement of diabetic neuropathy in children, adolescents, and young adults with type 1 diabetes. J Diabetes Compl 2007;21:13–9.
[89] Whitton TL, Johnson RW, Lovell AT. Use of the RydelûSeiffer graduated tuning fork in the assessment of vibration threshold in postherpetic neuralgia patients and healthy controls. Eur J Pain 2005;9:167–71.
[90] Wollgarten-Hadamek I, Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C. Do burn injuries during infancy affect pain and sensory sensitivity in later childhood? Pain 2009;141:165–72.
[91] Yarnitsky D, Ochoa JL. Warm and cold specific somatosensory systems. Psychophysical thresholds, reaction times and peripheral conduction velocities. Brain 1991;114:1819–26.
[92] Yarnitsky D, Sprecher E. Thermal testing: normative data and repeatability for various test algorithms. J Neurol Sci 1994;125:39–45.
[93] Zaslansky R, Yarnitsky D. Clinical applications of quantitative sensory testing (QST). J Neurol Sci 1998;153:215.
[94] Zohsel K, Hohmeister J, Flor H, Hermann C. Altered pain processing in children with migraine: an evoked potential study. Eur J Pain 2008;12:1090–101.
[95] Zohsel K, Hohmeister J, Oelkers-Ax R, Flor H, Hermann C. Quantitative sensory testing in children with migraine: preliminary evidence for enhanced sensitivity to painful stimuli especially in girls. Pain 2006;123:10–8.