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Research paper

Method-of-limits; Cold and warm perception thresholds at proximal and distal body regions

Victoria Heldestad Lilliesköld *, Erik Nordh

Dep. of Pharmacology and Clinical Neurosciences, Div. of Clinical Neurophysiology, Umeå University, SE-901 85 Umeå, Sweden

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ABSTRACT

Objective: Thermal quantitative sensory testing with the 'Method-of-Limits' is an established rationale for detection of small nerve fiber dysfunction, but adequate reference values are crucial for such evaluations, regardless of the underlying cause. This study assessed reference data for cold- (CPT) and warm- (WPT) perception thresholds at both proximal and distal sites in eight body regions of the lower and upper extremities, all determined within the same test session for each subject.

Methods: Seventy-five healthy subjects (aged 16–72 years) were tested according to the method-of-limit for CPT and WPT at the dorsum of the foot, the medial and lateral lower leg, the ventral thigh, the thenar eminence, the radial and ulnar part of the lower arm, and the anterior deltoid part of the upper arm.

Results: Overall, thermal perception thresholds (TPT) varied with test location, but were higher in the lower than in the upper part of the body, also WPT were generally higher than CPT. TPT at the dorsum foot highly correlated with age, while inconsistent correlations were noted between TPT and age or height at other tested locations.

Conclusion: This study describes for the first time reference values at eight defined body regions, at both proximal and distal sites.

Significance: The report enables refined evaluations of general small nerve fiber function, as assessed by quantitative thermal sensory testing with the Method-of-Limits.

1. Introduction

Quantitative sensory testing (QST), of cold- (CPT) and warm- (WPT) perception thresholds is a well-established method for detection of small nerve fiber dysfunction, particularly in an early stage of debuting generalised and occasionally painful small fiber neuropathies (Abad et al., 2002; Heldestad and Nordh, 2007; Hendriksen et al., 1993; Hoitsma et al., 2003; Krämer et al., 2004; Løseth et al., 2008), in which patients develop symmetric and distal symptoms of peripheral nerve dysfunction (Hughes, 2002), yet showing normal findings in nerve conduction studies or needle-EMG examinations (Heldestad and Nordh, 2007; Løseth et al., 2008). Neurophysiological studies of C-receptor properties (Weider et al., 1999; Schmidt et al., 1995), have demonstrated that some C-fiber receptors may exhibit hyperactivity, indicating that the pain in patients with proposed 'painful small fiber neuropathy' not necessarily need to be caused by a generalised neuropathic loss of small fibers. Thus, there is a need for a comprehensive rationale for detailed descriptions of the functional state in the thin nerve fibers in diseases with suspected small fibre affection, with or without distal pain. Early assessment of small fibers neuropathy is also of value to prevent from secondary foot ulcerations (Cornblath, 2004) or other types of tissue damage in diabetic patients, and may even be critical in particular diseases like hereditary Amyloidotic transthyretin polyneuropathy, where an early detection of polyneuropathic changes may favour the outcome of symptomatic treatment by liver transplantation (Adams et al., 2000; Jonsén et al., 2001; Suhr et al., 2005), or new emerging pharmaceutical treatment (Berk et al., 2013; Coelho et al., 2012).

The implementation of thermal QST is hampered by that several testing algorithms are being used (Dyck et al., 1993; Fruhstorfer et al, 1976; Lin et al., 2005; Yarnitsky, 1997; Yarnitsky and Sprecher, 1994). For clinical use, the reaction-time inclusive 'Method-of-Limits' can be recommended, as it comprises a quick, reliable and easy-to-use rationale (Heldestad et al., 2010; Krøigård et al., 2015). Regardless of the method used, several factors influence the magnitude of the noted thresholds. Due to spatial summation (Kandel et al., 2012; Schmidt, 1978), the size

* Corresponding author at: Dep. of Clinical Microbiology, Infection and Immunology, Umeå University, SE-901 87 Umeå, Sweden.
E-mail address: victoria.heldestad@umu.se (V. Heldestad Lilliesköld).

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of the stimulation probe is crucial (Dyck et al., 1993; Hilz et al., 1998, 1999), as well as differences in the number of receptors (Guergova and Dufour, 2011; Kandel et al., 2012; Schmidt, 1978) and in the density of nerve terminals between body areas (Chang et al, 2004). Also the velocity of temperature change during stimulation (Palmer et al., 2000; Pertovaara and Kojo, 1985), and the initial skin temperature is of importance (Hagander et al., 2000; Hilz et al., 1995), together with factors such as gender, age and the site of stimulation (Blankenburg et al., 2010; Defrin et al., 2006; Dyck et al., 1993; Hafner et al., 2015; Hagander et al., 2000; Hilz et al., 1999; Huang et al., 2010; Lin et al., 2005; Magerl et al., 2010; Meier et al., 2001; Yarnitsky, 1997; Yarnitsky and Sprecher, 1994).

To enable full evaluation of small fiber dysfunction, thermal QST should provide CPT and WPT reference data for both distal and proximal body regions. Although there are several reports on normative values for QST, both from single centre as well as from multi-centre studies, there is yet no comprehensive study describing full normative data for multiple body regions derived from the same group of healthy subjects. Previously reported reference data mostly assess distal sites in the lower and upper extremities (Blankenburg et al., 2010; González-Duarte et al., 2016; Hafner et al., 2015; Lin et al., 2005; Malmström et al., 2016; Magerl et al., 2010; Meier et al., 2001; Rolke et al., 2006; van den Bosch et al., 2017; Yarnitsky and Sprecher, 1994), although some of the studies also include the face (Blankenburg et al., 2010; Magerl et al., 2010; Rolke et al., 2006).

The purpose of the present study was to estimate cold and warm perception reference thresholds with the Method-of-Limits at different test sites both in the upper and lower extremities and in the same group of subjects. The aim was to define reference values for the cold and warm perception thresholds at distal and proximal parts of the extremities at eight different test sites, assessed from the same population of control subjects.

2. Methods

2.1. Subjects

Seventy-five subjectively healthy subjects initially volunteered for the study (37 men and 38 women (mean age 39 years, median 38, range 16–72 years), divided at 45 years of age into two groups (cf. Table 1 A and B for details). All had given their informed consent according to the World Medical Association's Declaration of Helsinki, and the Regional ethics committee of Northern Sweden approved the study. The immediate exclusion criteria were any sensory symptoms in the extremities, like diffuse numbness, dysesthesias and hyperesthesias, prickling, disturbances in cold- and/or warm perception, or any form of pain. Likewise, any signs, symptoms or diagnosis of diabetes, focal or general neuropathies, cervical spinal injuries excluded subjects from participation. At a further routine neurological status screening none of the initially recruited subjects showed any signs of reduced or asymmetric motor functions or muscular atrophies, nor did they show any signs of abnormalities in tactile or painful stimulus detection. However, during the actual thermal testing procedure a few subjects (n = 7) verbally reported symptoms of locally impaired warmth sense in the feet and/or at the medial or lateral aspects of the lower leg. These comments were taken as a indication of possible small fiber dysfunction, 'subclinical' lumbo-sacral nerve or spinal root affection, or of a localised alteration in central signal processing. These subjects' thermal data in the lower part of the body were therefore rejected in the final analysis. After these exclusions, the final study group consisted of sixty-eight subjects.

2.2. Thermal testing

QST was done with a 2.5 × 5.0 cm^2 computer controlled Peltier element (Thermotest®, Somedic AB, Hörby, Sweden). Totally nine test sessions were performed (including one training session), containing 10 individual cold respective warm stimulations with inter-stimulus intervals randomly varying between 3 and 5 s. During the testing the stimulation probe was manually held with firm contact to the subject's skin over the entire probe stimulating area. The subject was instructed to press an electrical switch as soon as the thermal stimuli were perceived; as soon as a sensation of the probe "becoming cooler" or "becoming warmer", for testing of cold and warm thresholds, respectively. The adapted skin start temperature was 32 °C (baseline temperature), and minimum and maximum temperatures were set to 10 °C and 50 °C, respectively, according to prevailing hospital safety regulations. The rate of change was set to 1 °C/sec during testing, and to 3 °C/s during return to baseline temperature.

2.3. Testing sites

Eight body sites were tested at randomly chosen side and order (cf. Fig. 1); the dorsum of the foot, the medial and the lateral aspect of the lower part of the leg, the ventral thigh, the thenar eminence, the radial and the ulnar part of the lower arm, and the deltoid anterior part of the upper arm.

2.4. Data conditioning and statistical analyses

Thermal data records were manually re-inspected after that each subject had ended the full testing procedure, to ensure data quality, and to remove responses reported by the subject as 'erroneous' or 'unintentional'. The CPT and WPT at each test site were defined as the mean value of the recorded consecutive individual thresholds in the recorded cold and warm sequences, respectively,

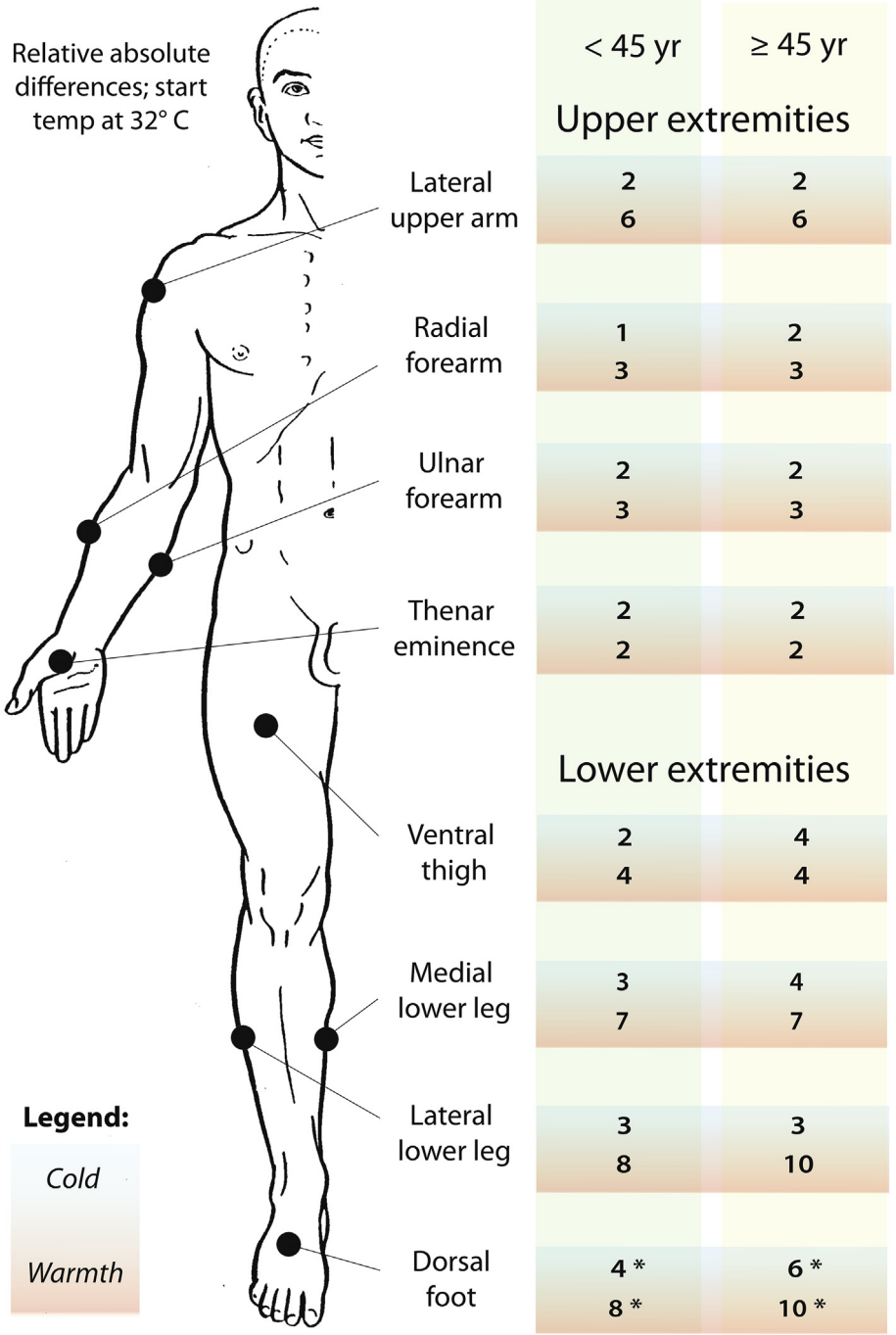
Table 1
Descriptive data of (A) all subjects pooled ($n = 75$); (B) subjects stratified by age (<45 years and ≥45 years) ($n = 75$).

A

Data	Range	Mean (Median)	Female/Male	Sides (Left/Right)
Age (years)	16.0–72.0	39.1 (38.1)		
Height (cm)	150–196	172.4 (172)		
Number			38/37	37/38

B

Age group	Years Range (Median)	Number Female/Men	Number Left/Right	Height (cm) Range (Median)
<45 years	16.0–45.0 (28.6)	22/24	24/22	154–190 (174)
≥45 years	45.0–72.0 (53.0)	16/13	14/15	150–196 (171)



	< 45 yr	≥ 45 yr
Upper extremities		
Lateral upper arm	2 6	2 6
Radial forearm	1 3	2 3
Ulnar forearm	2 3	2 3
Thenar eminence	2 2	2 2
Lower extremities		
Ventral thigh	2 4	4 4
Medial lower leg	3 7	4 7
Lateral lower leg	3 8	3 10
Dorsal foot	4 * 8 *	6 * 10 *

Fig. 1. Proposed thermal cold (CT) and warm (WT) perception upper limit values, rounded to the nearest integers, at eight body sites; the dorsum of the foot (DF); the medial (ML) and lateral (LL) aspects of the lower leg; the ventral thigh (VT); the thenar eminence (TE); the radial (RA) and the ulnar (UA) aspect of the forearm; and the deltoid part of the upper arm (DA). With exception of the DF, the threshold limits given are the 95% percentiles of the thresholds expressed as the absolute relative values (ΔC°). Values for the DF, (marked *), are based on the prediction values; cf. legend to Fig. 2.

and were expressed as the absolute difference in °C from the adapted baseline temperature (Δ°C). Descriptive statistics and statistical analyses were performed with commercially available programs (Microsoft Excel®, Statview® and Graph Pad Prism®). Non-parametric descriptive tests were used; tests of differences between groups (Mann-Whitney *U* test and the Wilcoxon Signed Ranks Test). Correlation analyses (Spearman rank correlation test and multiple regressions) were performed between thermal perception thresholds and both age and height at all tested sites. A significance level of $p < 0.05$ was used throughout.

3. Results

3.1. All subjects pooled

3.1.1. Thermal perception thresholds

In general, the WPT was significantly higher compared to the CPT at all test sites ($p < 0.0001$). Furthermore, the CPT for separate test sites were significantly higher at the lower compared to the upper parts of the body ($p < 0.0001$), except for a lack of difference between the deltoid anterior part of the upper arm and ventral

thigh ($p = 0.0523$). Also, the WPT were significantly higher ($p < 0.0001$) in test sites at the lower compared to the upper parts of the body, except between the ventral thigh and the deltoid anterior part of the upper arm, where WPT at the deltoid anterior part of the upper arm were higher. No significant differences were found between sides.

3.1.2. Gender differences

Significant gender differences were found for CPT at the thenar eminence, ($p = 0.0211$), and for WPT at the ventral thigh ($p = 0.0288$), at the thenar eminence ($p = 0.0093$), and at the radial part of the lower arm ($p = 0.0020$).

3.1.3. Relation to age

No systematic correlations between age and thermal perception thresholds were found for the tested body regions. However, within the distal part of the legs significant correlations were observed at the dorsum of the foot (CPT; r = 0.439, $p = 0.0003$ and WPT; r = 0.546, $p < 0.0001$) (c.f. Fig. 2). Significant correlations were also found between age and CPT at the lateral aspect of the lower leg (r = 0.248, $p = 0.0395$), and the ventral thigh (r = 0.260, $p = 0.0252$), as well as between age and WPT at the lateral aspect of the lower leg (r = 0.268, $p = 0.0258$), the ventral thigh (r = 0.449, $p = 0.0035$), and the radial part of the lower arm (r = 0.230, $p = 0.0395$).

Significant relationship, with age being the most significantly explaining factor, were also noted by multiple regression at all tested sites in the lower part of the body, except at the lateral aspect of the lower leg were both age and height were explaining factors. Significant regressions was found for CPT at the dorsum of the foot ($R^2 = 0.191$, $p = 0.0008$) at the medial part of the leg ($R^2 = 0.085$, $p = 0.0453$), and at the ventral thigh ($R^2 = 0.107$, $p = 0.0169$). For WPT a significant relationship was found at the dorsum of the foot ($R^2 = 0.309$, $p < 0.0001$), at the lateral aspect of the lower part of the leg ($R^2 = 0.113$, $p = 0.0084$), and at the ventral thigh ($R^2 = 0.096$, $p = 0.0268$). No systematic significant relationships was found in the upper part of the body.

3.1.4. Relation to height

Between height and thermal perception thresholds, no systematic correlations were observed with regard to CPT, but significant correlations were seen with regard to WPT at the lateral aspect of the lower part of the leg (r = 0.284, p = 0.0182), at the thenar eminence, (r = 0.280, p = 0.0161), and at the radial part of the lower arm (r = 0.239, $p = 0.039$). Multiple regression did not show any systematic significant relationships where height was the only explaining factor, apart for WT at the radial part of the lower arm ($R^2 = 0.104$, $p = 0.0194$)

3.2. Differences between age groups (<45 and ≥45 years old)

Significantly higher thresholds at the dorsum of the foot were found in the older compared to the younger age group, both for CPT and WPT ($p = 0.002$ and $p < 0.001$), which is illustrated in Fig. 2. Also CPT at the ventral thigh ($p = 0.012$) was significantly higher in the older age group. Fig. 1 summarises the proposed upper limits (mean ± 2 SD) for CPT and WPT at all eight tested body regions, apart from at the dorsum of the foot where linear regression models in combination with a residual variation of 2 SD were used. Table 2 (A and B) show means, medians and SD for all tested sites.

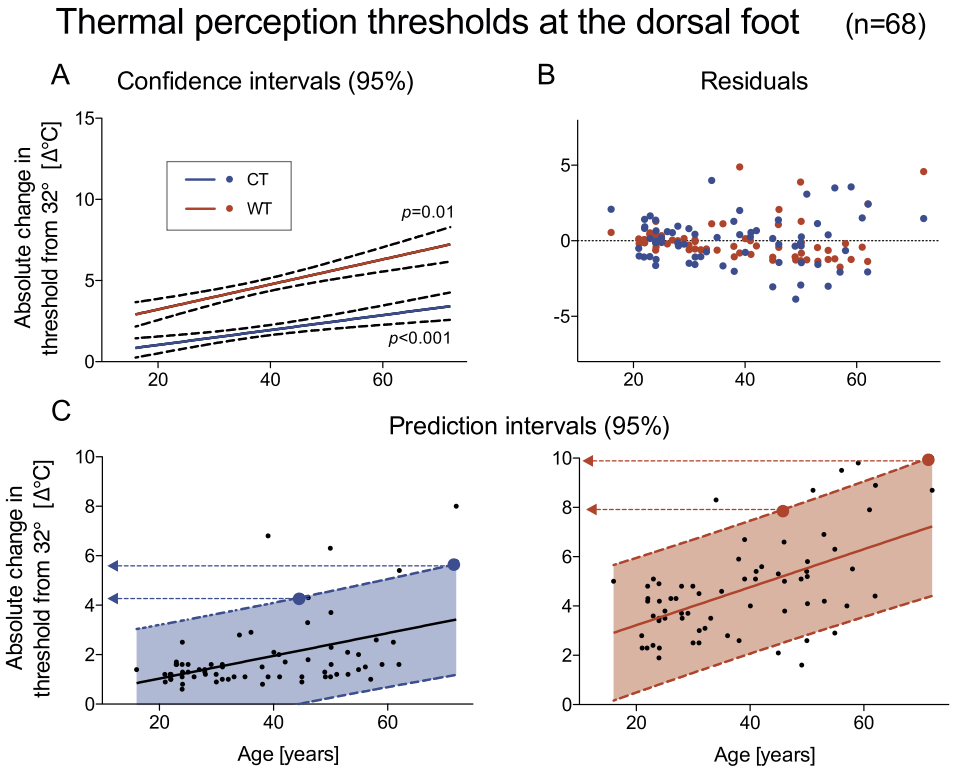


Fig. 2. Graphical overview of selected temperature threshold characteristics at the dorsum of the foot (DF). A/ Linear regressions of absolute values of relative thresholds vs. age, with confidence intervals and significance of the relationships (*CT = 0,1423 + 0,0455 * AGE − 0,0024 * HEIGHT; WT = −5,6819 + 0,0808 * AGE + 4,1993 * HEIGHT*); B/Scatter plot of residuals (the deviations from the regression line of relative threshold values) vs. age; C/and D/Plots of prediction intervals for cold (C) and warm (D). Thin dashed arrows indicate values used in Fig. 1, computed for the upper border ages of 45 and 75 years and a reference height of 175 cm.

Table 2
Mean, median and SD for all tested sites stratified by age ((<45 years (n = 43) and ≥45 years (n = 25)) showing (A) cold thermal perception threshold; (B) warm thermal perception threshold.

A

Tested site	Mean		Median		SD	
	<45	≥45	<45	≥45	<45	≥45
LA	1.1	1.3	1.1	1.1	0.5	0.6
UA	0.9	0.9	0.8	0.9	0.2	0.4
RA	0.9	1.1	0.9	0.9	0.3	0.5
TE	1.0	1.1	0.9	1.0	0.3	0.3
VT	1.3	2.0	1.2	1.6	0.4	1.3
LL	1.6	1.8	1.5	1.6	0.8	0.9
ML	1.7	1.8	1.5	1.6	0.7	0.8
DF	1.4	2.5	1.2	1.9	0.6	1.5

B

Tested site	Mean		Median		SD	
	<45	≥45	<45	≥45	<45	≥45
LA	3.3	3.1	2.8	2.8	1.3	1.7
UA	2.1	2.0	2.1	2.0	0.7	0.6
RA	2.0	2.2	1.9	2.1	0.7	0.6
TE	1.4	1.4	1.3	1.4	0.4	0.3
VT	2.7	2.9	2.6	3.0	0.8	0.7
LL	4.8	5.4	4.3	4.5	1.9	2.3
ML	4.0	4.2	3.8	3.9	1.3	1.3
DF	4.1	6.3	3.9	5.5	1.6	2.7

DF, Dorsal foot; ML, Medial lower leg; LL, Lateral lower leg; VT, Ventral thigh.
TE, Thenar eminence; RA, Radial forearm; UA, Ulnar forearm; LA, Lateral upper arm.
MD. Median; SD, Standard deviation.

4. Discussion

The objective of the present report was to define thermal QST reference data for multiple body regions, at proximal and distal sites, obtained from the same reference population, as such data are lacking for multiple test sites of strategic clinical use. The present report is the first in which such a comprehensive study has been undertaken, and the described data will be useful for more reliable assessments of possible neuropathic changes in small nerve fibers sub-serving temperature detection.

The main findings in our study were that both CPT and WPT were highly significantly correlated with age at the dorsum foot, which are in agreement with earlier studies (Hafner et al., 2015; Hilz et al., 1999; Huang et al., 2010; Lin et al., 2005; Magerl et al., 2010; Rolke et al., 2006). Significant correlations were also noted at the lateral aspect of the lower part of the leg and the ventral thigh, albeit with a weaker degree of strength in the correlation. This clear dependence of age for the dorsum of the foot was also confirmed by multiple regression analyses. Finally, our findings also support the notion of a decreased thermal perception capacity in the elderly, possibly related to a decreased density of intra-epidermal nerve fibers (Lauria et al., 2010; Thomsen et al., 2009). All these findings are concordant with the notions in a review by Guergova and Dufour (2011), which concludes that distal parts of the body are most severely affected by age and especially the warm sense. Furthermore, WPT were overall significantly higher compared to the CPT at all tested body regions, and TPT were in general significantly higher in the lower half of the body than in the upper. These findings are also concordant with earlier studies, in which, however, only distal test locations in the upper and lower part of the body were tested separately in individuals (Hafner et al., 2015; Lin et al., 2005; Magerl et al., 2010; Meier et al., 2001; Rolke et al., 2006; Yarnitsky and Sprecher, 1994).

Earlier reports have presented reference data for subjects of similar ages as in the present study (Lin et al., 2005; Hafner et al., 2015; Hilz et al., 1999; Yarnitsky and Sprecher, 1994), but not for the same eight test locations as in this study. From a clinical perspective, in diagnostic evaluation of patients with putative PNP, it is particularly important to do QST at both distal and proximal sites (Heldestad and Nordh, 2007). As a generalised and length dependent PNP initially manifests itself with a symmetrical distal small fiber impairment, often with early symptoms of pain or impaired thermal sense in the feet, then successively involving more proximal nerves, and eventually the longer abdominal and thoracic peripheral nerves (Hughes, 2002). Thermal QST has in this context been shown to be a very sensitive method for early detection of impaired small nerve function (Heldestad and Nordh, 2007; Hoitsma et al., 2003; Løseth et al., 2008). The use of multiple test sites will also facilitates clinical follow up. However, regardless of the putative cause to a suspected small fiber dysfunction, clinical QST evaluation should be done bilaterally, as potentially unilateral conditions like herniated discs, lumbo-sacral stenosis, peripheral mononeuropathies, or referred musculo-skeletal pain, may unilaterally influence the perceived thermal perception thresholds. This may be of particular importance in the elderly, in which unilateral radiculopathy or herniated discs are common in the lower part of the body (Hsu et al., 1990). In this context, it should be noted that the lateral part of the lower leg as a test site in thermal QST possibly may relates to an increased prevalence of L5/S1 root affection at this segmental level (Kortelainen et al., 1985) and impaired thresholds.

Two factors are likely to primarily explain the observed significantly higher WPT than CPT at all test sites; higher density of cold spots within the human skin (Guergova and Dufour, 2011; Schmidt, 1978), and difference in nerve conduction between A- and C-fibers (Kandel et al., 2012). The general finding of significantly higher thermal perception thresholds at the lower compared to the upper parts of the body is probably related to the finding of a higher density of nerve terminals in the upper part of the body, compared to the lower (Chang et al., 2004). Finally, the unsystematic but significant thermal perception thresholds differences between genders, might be in agreement with a few previous reports of gender differences (Blankenburg et al., 2010;

Lin et al., 2005; Hilz et al., 1999; Yarnitsky and Sprecher, 1994). Higher thresholds for warmth as well as lower epidermal nerve fiber density at the thigh in men compared to women have also been reported earlier (Selim et al., 2010), which might be of relevance for to observed gender differences at the ventral thigh.

It should be kept in mind that for thermal QST in particular, the tested individual's reports of the quality of the subjectively experienced stimuli may give equally important information about the nature of a sensory disturbance. With increasing understanding of the mechanisms for temperature sensation (Mak et al., 2001) it is most likely that the perceived nature of the given stimulus may provide important cues to the underlying sensory system impairment. This has also previously been indicated by Verdugo and Ochoa (1992), who noted that the 'sensation of heat pain' is not merely an extension of the 'sensation of heat', and thus that patients may have selective losses of either one of the two, as well as of both. For this reason, it is crucial that thermal QST is carried out by well trained, informed and instructed personnel, who should be observant of the vigilance of the patient, and who also should make meticulous notes of the patient's reported perception of a given stimuli at each test point.

Finally, as mentioned in the introduction, there are several different strategies for psychophysical assessment of the human sensory perception performance, all with varying pros and cons, and with varying focus on different aspects of the sensory perception testing process. It is thus not feasible to consider one QST rationale as superior to others, but rather to choose a test strategy which is apt for a specific study situation or for a specific group of subjects. In clinical situations, where the QST assessment often is supposed to enlighten putative presence of signs of generalised polyneuropathy in sometimes elderly patients, the overall test duration is a critical factor, as an extended examination might significantly fatigue the subject and hence deteriorate the quality of the assessment. To this end, the M-o-L is advantageous, as the testing is easily comprehended and also comparatively fast. Based on the median values given in Table 2, a complete bilateral test at eight preferred sites (feet, medial lower legs, ventral thighs, and hands) of a hypothetical normal subject performing at the median values would be approx. 30 or 35 min for the lower and higher age groups, respectively. A patient with pronounced polyneuropathy (no thermal perception in the feet or the lower legs, half the capacity of the thighs, and a quarter of the capacity in the hands) might typically complete the test session within about 15–20 min, as the last seven individual tests at each of the foot and lower leg sites may well be aborted after three runs without responses, hence shorting the overall test duration.

The present report will facilitate stringent clinical evaluation of any type of dysfunction of thermal sensation by providing thermal reference data at eight different body regions, at distal and proximal sites in the lower and upper part of the body, and hence improve strategies for, and the quality of, clinical small fiber evaluations.

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Conflict of interest

The authors report no conflicts of interest.

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