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ORIGINAL ARTICLE

A study on variability of quantitative sensory testing in healthy participants and painful temporomandibular disorder patients

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Abstract

Objectives: Quantitative sensory testing has mainly used thresholds to evaluate somatosensory sensitivity so far. The variability of different measures from session to session has also been investigated, but the variability of the single individual measures of a threshold or subject-based reports has not been considered. This study aimed to investigate the potential value of threshold variability in one session as a measure of internal consistency in somatosensory function.
Methods: The standardized quantitative sensory testing battery developed by the German Research Network on Neuropathic Pain was performed bilaterally over the infraorbital, mental, and hand regions in 70 healthy and 22 temporomandibular disorder pain participants. Somatosensory variability was investigated by calculating the Coefficient of Variation of three to five repeated measures in one threshold determination. The influences of side, gender, site, age, and presence of pain on the somatosensory variability were evaluated.
Results: In the healthy participants, somatosensory variability was region dependent: hand > mental and/or infraorbital for CDT, WDT, HPT, MDT-N, MPT-Y, MPT-N, WUR, and MPS ($p \leq 0.043$), infraorbital > hand for VDT ($p = 0.001$), mental > infraorbital for HPT and WUR ($p \leq 0.001$); and age dependent for WDT, TSL, CPT, HPT, MDT-Y, MDT-N, MPT-N, and WUR ($p \leq 0.017$). Gender and side had no main effect on variability ($p \geq 0.136$). The pain patients presented higher variability compared with healthy participants for TSL, MDT-N, MPT-Y, WUR, and PPT ($p \leq 0.033$).
Discussion: The somatosensory variability along with the threshold would be a more complete method to investigate the somatosensory disorders and underlying pain mechanisms. The correlation between pain duration and somatosensory variability should be studied further with different pain conditions.

Keywords

Coefficient of Variation, Quantitative sensory testing, somatosensory variability, temporomandibular disorder

History

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Introduction

It has been several decades since the publication of the first study of quantitative sensory testing (QST) (Fruhstorfer et al. 1976), which offered useful tools for diagnostic and etiological investigation of various somatosensory disorders. Subsequently, the German Research Network on Neuropathic Pain (DFNS) developed a standardized QST battery in 2006 (Rolke et al. 2006b), and a reference dataset of healthy subjects and patients with various pain conditions has been established (Rolke et al. 2006a; Maier et al. 2010). QST protocols modified for specific anatomic regions have also been developed (Pigg et al. 2010; Matos et al. 2011). Previous studies have investigated the variability of the different measures from session to session, which related to test reliability (Pigg et al. 2010; Geber et al. 2011), but so far the within-session variability of the single individual measures of a threshold or subject-based reports has not been considered. Normally, the convention is to repeat a single measure 3–5 times and use the average or geometric mean of these measures because of the well-known trial-to-trial variation. However, any judgment based solely on threshold may potentially be incomplete. The variability of the individual values of the three to five measurement repetitions can be considered a measure of the internal consistency of the somatosensory function (Martin and Chapman 1979; Chapman 1980; Chapman et al. 1981, 1982).

Coefficient of Variation (CV) is a normalized measure of dispersion of a probability distribution, which is defined as

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the ratio of the standard deviation to the mean and is a dimensionless number (Araie 2013). A smaller CV indicates a more consistent threshold measure. In fact, the variability of thresholds has been recommended as an important part of diagnosing somatosensory disorders (Yarnitsky et al. 1994). Threshold consistency of psychophysical measures is considered to rely on environmental factors, methodological factors, and the cooperation and attention of the individuals being tested (Svensson et al. 2011). However, other factors, such as the test sides and sites, aging, gender, and ongoing pain, have not been examined yet.

The aim of this study was to evaluate the variability of each single measure in the DFNS QST protocol and compare between sides, genders, sites (infraorbital, mental, hand), age groups, and condition groups (healthy controls vs. pain patients). The following hypotheses were tested: (i) female gender, aging, and presence of pain are associated with larger variability; (ii) there are site-to-site differences but no side-to-side differences in variability.

Materials and methods

Participants

Healthy participants in this study were recruited from Peking University students and staff through flyers distributed around local college campuses. All the potential healthy participants were asked to fill out a questionnaire with a list of the study exclusion criteria before recruitment: (a) Have you participated in any kind of clinical test before? If yes, could you describe the test, is it similar to the current test? (b) Do you have ongoing pain? (c) Did you have chronic pain during the last 6 months? (d) Do you have any systemic diseases (e.g., metabolic diseases, neurogenic diseases, cardiovascular disorders) or previous radiotherapy or chemotherapy? (e) Have you taken any medicine in the last week? If yes, please write down the name of the medicine. (f) Do you have any physical or mental disorders, for example, fibromyalgia syndrome (FMS), bruxism, or psychogenic illnesses? (g) Females only: are you in your menstrual period? Only potential participants, who answered ''no'' to all the questions, or they answered ''no'' to questions (b), (c), (d), (f), (g), and ''yes'' to question (a), but such studies were not similar to the present one, or if they answered ''yes'' to question (e), but the medicine did not affect the nervous system, were involved in tests. Eighty-five people responded to the flyers. Finally, 70 participants between 24 and 69 years old (42.3 ± 12.5 years, mean $\pm$ SD), 36 females (43.1 ± 12.8 years), 34 males (41.5 ± 12.3 years), who met the criteria, were recruited. The 70 healthy participants were divided into five decade groups: 21–30 years, 8 females and 8 males; 31–40 years, 8 females and 8 males; 41–50 years, 8 females and 8 males; 51–60 years, 8 females and 8 males; 61–70 years, 4 females and 2 males.

Temporomandibular disorder (TMD) pain participants were recruited from patients who visited the Center for TMD & Orofacial Pain of Peking University School and Hospital of Stomatology from September 2011 to September 2012. All the potential painful TMD participants were asked to answer one questionnaire with a list of exclusion criteria before recruitment: (a) Do you have any systemic diseases (e.g., metabolic diseases, neurogenic diseases, cardiovascular disorders) or previous radiotherapy or chemotherapy? (b) Have you taken any medicine in the last week? If yes, please write down the name of the medicine. (c) Do you have any physical or mental disorders, for example, fibromyalgia syndrome (FMS), bruxism, or psychogenic illnesses? (d) Females only: are you currently in your menstrual period? (e) Have you received any therapy targeting the jaw joint or muscle pain during the last 2 weeks prior to test? Only potential participants who answered ''no'' to all the questions, or answered ''no'' to questions (a), (c), (d), (e), and ''yes'' to question (b), but the medicine did not affect the nervous system, were recruited for tests. Inclusion criteria: pain intensity in the orofacial region just before the test should be rated by the patients to be >2 cm on a 0–10 cm visual analogue scale (VAS, 10-cm line labeled ''no pain'' at the ''0'' end and ''worst pain imaginable'' at the ''10 cm'' end. Patients were given an explanation of the line and asked to mark a point upon it which corresponded to their pain intensity) (Bond and Pilowsky 1966). The level of education should be high school or higher. Twenty-nine patients met the criteria and agreed to join the study and signed the informed consent form. After excluding participants with missing data, 22 participants (3 males, 19 females) aged 23–67 years (43.3 ± 16.6 years) finally completed the whole test. All patients were investigated and diagnosed using the Research Diagnostic Criteria for TMD by one TMD specialist (Dworkin and LeResche 1992).

The study adhered to the Helsinki Declaration II and was approved by the local ethics committee (PKUSSIRB-2013012).

Quantitative sensory testing (QST) protocols

The standardized QST battery developed by DFNS (Rolke et al. 2006b) and modified for the trigeminal region (Pigg et al. 2010; Matos et al. 2011; Svensson et al. 2011) was used in this study. All QST measures were performed in a quiet room with approximate temperature between 21 and 23 °C. The QST consisted of seven tests measuring a total of 13 different thermal and mechanical parameters (Figure 2): (A) Thermal testing comprised detection and pain thresholds for cold, warm, and hot stimuli (C- and A-delta fiber mediated): cold detection threshold (CDT); warm detection threshold (WDT); number of paradoxical heat sensations (PHS) during the thermal sensory limen procedure (TSL) for alternating warm and cold stimuli; cold pain threshold (CPT); heat pain threshold (HPT). (B) Mechanical detection threshold (MDT) was used as a test for A-beta fiber function using von Frey filaments. (C) Mechanical pain threshold (MPT) was used as a test for A-delta fiber mediated hyper- or hypoalgesia to pinprick stimuli. (D) Stimulus–response functions: mechanical pain sensitivity (MPS) for pinprick stimuli and dynamic mechanical allodynia (DMA) assessed A-delta mediated sensitivity to sharp stimuli (pinprick) and also A-beta fiber mediated pain sensitivity to stroking light touch (CW = cotton wisp; QT = cotton wool tip; BR = brush). (E) Wind-up ratio (WUR) compared the numerical ratings within three trains of a single pinprick stimulus (a) with a series (b) of 10 repetitive pinprick stimuli to calculate WUR

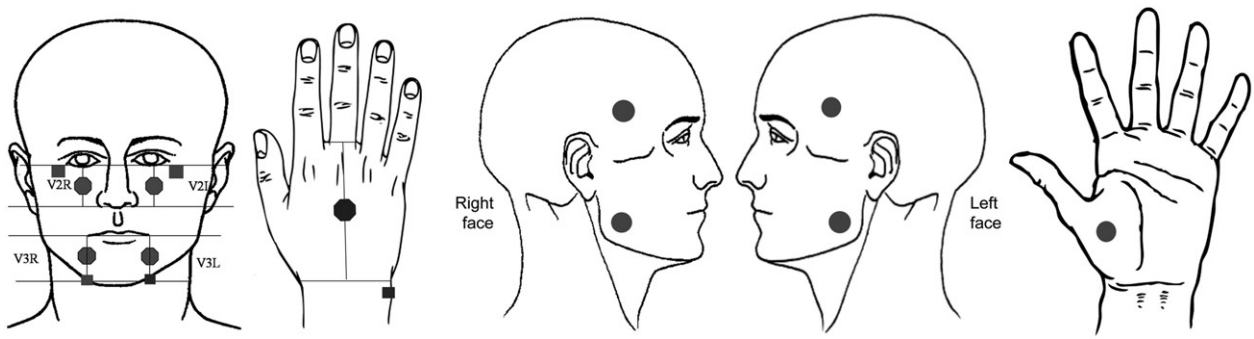

Figure 1. All the tests except for vibration detection threshold (VDT) and pressure pain threshold (PPT) were applied to the skin overlying the infraorbital and mental foramina and the center point of hand dorsum bilaterally ( ). VDT was performed on bony prominences bilaterally: zygomatic process, the lower edge of the mandible beneath the mental foramen and ulnar styloid process ( ). PPT was measured on the most bulky points of temporalis, masseter, and thenar muscles bilaterally ( ).

as the ratio: b/a. (F) Vibration detection threshold (VDT) tested for A-beta fiber function using a Rydel–Seiffer 64 Hz tuning fork. (G) Pressure pain threshold (PPT) was the only test for deep pain sensitivity, most probably mediated by muscle C- and A-delta fibers (Rolke et al. 2006b; Matos et al. 2011). To avoid sequence effects, the seven tests were performed in a random manner produced by Microsoft Excel 2010. The investigator in this study was carefully instructed and trained under supervision according to the latest guidelines (Svensson et al. 2011).

In the present study, all participants were investigated bilaterally on three skin regions: infraorbital region, mental region, and dorsum of the hands. Test sites were identified based on anatomical landmarks to ensure that the same site could be accurately chosen for different participants (Figure 1), and the three regions, test sides (right or left) were tested in random order produced by Microsoft Excel 2010. There were written instruction boards for the participants to read for each different modality just before the beginning of each test (Figure 2) (Rolke et al. 2006b). These instructions were translated into Chinese from those used by the DFNS. The participants were also encouraged to ask questions in case they did not clearly understand the instructions. All participants received a training test and necessary explanation to ensure compliance. The whole trial of seven tests took about 3 h per participant for the six test sites. The participants kept their eyes closed throughout the QST procedure (Rolke et al. 2006b).

Thermal thresholds and thermal sensory limen

Thermal testing was performed using Medoc Pathway (Medoc, Ramat Yishai, Israel) with an ATS thermode (Medoc: 30 mm × 30 mm, square surface). CDT, WDT, CPT, and HPT were measured in triplicate with inter-stimulus interval of 20 s (Figure 2) (Yarnitsky et al. 1995). For the TSL, the temperature first went up and the participants pressed a button when they perceived a change in temperature, then the temperature ramp changed direction immediately and the thermode cooled down and was again reversed when the participants perceived a change in temperature and pressed the button. The number of PHS during this procedure was recorded (Figure 2). Baseline temperature was set at 32 °C; for all thermal testing, ramped stimuli of 1 °C/s were used and the procedure ended when the participants pressed a button. Cut-off temperatures were set at 0 and 50 °C, respectively (Rolke et al. 2006b).

Mechanical detection threshold

Mechanical detection threshold (MDT) was measured with a standard set of von Frey hairs (Semmes–Weinstein monofilaments, Touch-Test™ Sensory Evaluator, North Coast Medical, Morgan Hill, CA, USA) with 20 different diameters. The number of each filament (1.65–6.65) corresponded to a logarithmic function of the equivalent forces of 0.08–3000 mN (Matos et al. 2011). The monofilament was applied perpendicularly to the examination site. Contact time was 1–2 s with inter-stimulus interval around 10 s. The force of the first von Frey hair in increasing order that was perceived by the participants (‘‘yes’’) was noted as the first supra-threshold value. Next, beginning with the force, which had been noted, the von Frey hairs were applied in decreasing order until the participants did not perceive the force anymore (‘‘no’’). This force was noted as the first infra-threshold value. By repeating this process 5 times within the area tested, five infra- and five supra-threshold values were obtained (Figure 2) (Rolke et al. 2006b).

Mechanical pain threshold, mechanical pain sensitivity for pinprick stimuli, dynamic mechanical allodynia, and wind-up ratio for repetitive pinprick stimuli

Weighted pinprick stimuli were delivered with seven custom-made punctate mechanical stimulators with fixed stimulus intensities (flat contact area of 0.2 mm diameter) that exerted forces of 8–512 mN to determine the mechanical pain threshold (MPT) (Rolke et al. 2006b). Contact time was 1–2 s with an inter-stimulus interval of around 10 s (0.1 Hz), which was well below the critical frequency for induction of wind-up (Pfau et al. 2011). All pinprick tests were made with the stimulator perpendicular to the examination sites. The method, which was used to determine the MDT, was also used to determine the MPT, five infra- (‘‘yes’’) and five supra-threshold values (‘‘no’’) were obtained (Figure 2) (Rolke et al. 2006b).

Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA) were evaluated using two sets of instruments in a stimulus–response assessment

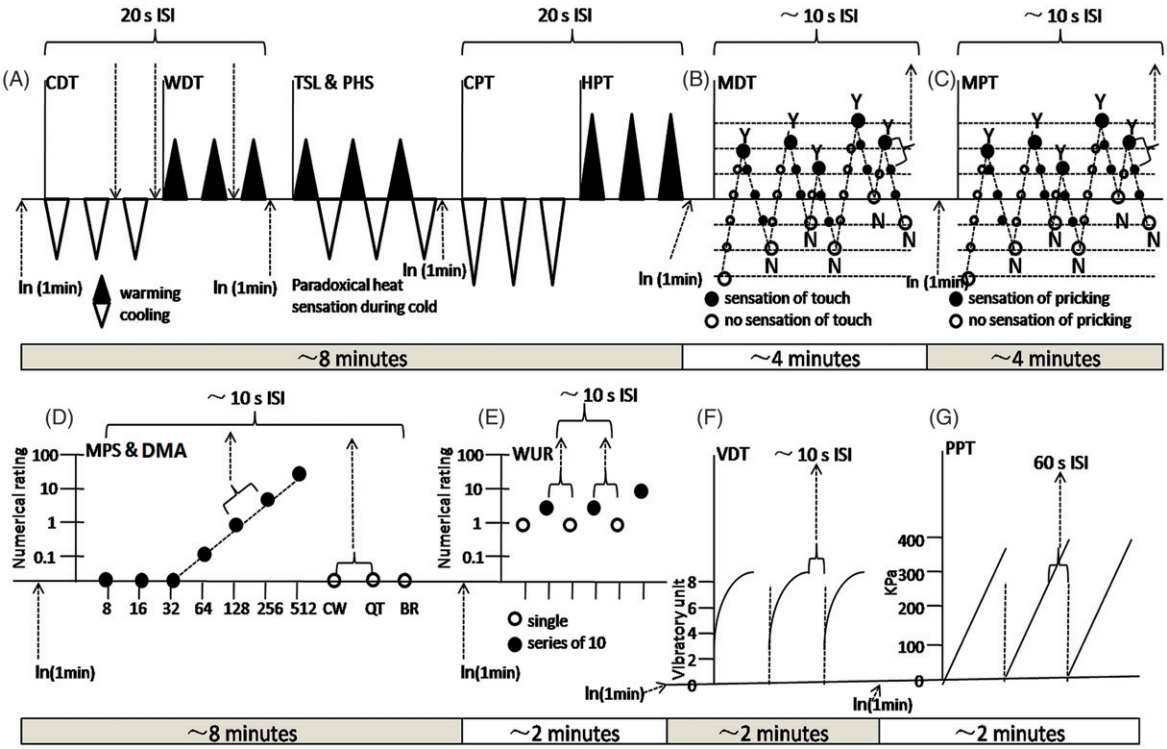

Figure 2. The battery of quantitative sensory testing (QST). The standardized QST protocol consists of seven tests (A–G) to assess the 13 parameters. (A) Thermal testing comprises detection and pain thresholds for cold, warm, and hot stimuli (C- and A-delta fiber mediated): cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), and heat pain threshold (HPT) with inter-stimulus interval of 20 s; number of paradoxical heat sensations (PHS) during the thermal sensory limen procedure (TSL) for alternating warm and cold stimuli. (B) Mechanical detection threshold (MDT) test using von Frey filaments (A-beta fiber mediated) with inter-stimulus interval of ~10 s. (C) Mechanical pain threshold (MPT) for pinprick stimuli (mediated by A-delta fiber) assessing hyper- or hypoalgesia with inter-stimulus interval of ~10 s. (D) Stimulus–response functions: mechanical pain sensitivity (MPS) assess A-delta fiber mediated sensitivity to sharp stimuli (pinprick) and dynamic mechanical allodynia (DMA) assess A-beta fiber mediated pain sensitivity to stroking light touch (CW = cotton wisp; QT = cotton wool tip; BR = brush), with inter-stimulus interval of ~10 s. (E) Wind-up ratio (WUR) compares the numerical ratings within three trains of a single pinprick stimulus (a) with a series (b) of 10 repetitive pinprick stimuli to calculate WUR as the ratio: b/a, with ~10 s intervals between single and series stimulus. (F) Vibration detection threshold (VDT) tests for A-beta fiber function using a Rydel–Seiffer 64 Hz tuning fork with intervals of ~10 s. (G) Pressure pain threshold (PPT) is the only test for deep pain sensitivity, most probably mediated by muscle C- and A-delta fibers, with inter-stimulus interval of 60 s. ISI = inter-stimulus interval; In = instruction.

(Rolke et al. 2006b; Maier et al. 2010). To determine MPS, seven weighted pinprick stimulators (as for MPT) were used. Three tactile stimulators were used to determine DMA: a cotton wisp (~3 mN), a cotton wool tip (Q-tip, ~100 mN) attached to a flexible handle, and a disposable toothbrush (Top Dent®, Meda AB, Solna, Sweden, ~200–400 mN). The tactile stimulator was applied in a single stroke over about 1–2 cm in length of skin for 1–2 s. A series of 10 measurements were made 3 times, each with the 10 stimulators (seven pinpricks and three tactile stimulators) applied in a different order with inter-stimulus interval of 10 s (Rolke et al. 2006b). For each of the resulting 30 stimuli, the participants chose a pain rating on a 0–100 numerical rating scale with the endpoints ''0'' indicating ''no pain'' and ''100'' indicating ''most intense pain imaginable''. Mechanical pain sensitivity was calculated as the geometric mean of one of the three series of numerical ratings for pinprick stimuli. Dynamic mechanical allodynia was calculated as the geometric mean (compound measure) of one of the three series of numerical ratings across all three different types of light touch stimulators (Figure 2) (Rolke et al. 2006b).

To measure the wind-up ratio (WUR) for repetitive pinprick stimuli, the perceived magnitude of a train of 10 pinprick stimuli repeated at a rate of 1 Hz was divided by that of a single pinprick stimulus with the same force (Rolke et al. 2006b). The custom-made pinprick stimulators used in the MPT determinations were used for WUR assessment. The instrument delivered a force which the subject perceived as ''slightly painful'' was chosen and the 128 mN stimulator was tried first. If the response was ''0'' (not painful), the test was repeated with a stronger force. If the subject perceived the stimulus as intolerable, a weaker force was used. If a subject did not perceive the 512 mN stimulator to be painful, the test was abandoned. The WUR test was repeated 3 times with 10 s intervals between the single and train stimulus (Figure 2) (Rolke et al. 2006b).

Vibration detection threshold

The vibration detection threshold (VDT) was measured using a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) (Rolke et al. 2006b; Maier et al. 2010). VDT was performed on bony prominences bilaterally: zygomatic process, the lower edge of the mandible beneath the mental foramen and the ulnar styloid process. The participants indicated when the vibration could no longer be sensed on the 9-point (0–8) scale measuring intensity of vibration; values were recorded to an

accuracy of 0.5 units. The test was repeated 3 times with 10 s intervals (Figure 2) (Rolke et al. 2006b).

Pressure pain threshold

The pressure pain threshold (PPT) was measured with the use of a computerized pressure Algometer (AlgoMed, Medoc) with a probe covered with rubber with surface area of 1 cm^2. PPT was measured on the most bulky points of the temporalis, masseter, and thenar muscles bilaterally with a constant pressure increase rate of 30 kPa/s. At the first painful sensation, the participants pressed a button to interrupt stimulation (Rolke et al. 2006b). The test was repeated 3 times with intervals of 60 s (Figure 2) (Rolke et al. 2005).

Data processing

The Coefficient of Variation (CV) defined as the ratio of the standard deviation to the mean of each individual QST parameter was calculated. Since the TSL was the difference limen for alternating cold and warm stimuli (Rolke et al. 2006b), three limens were calculated based on three alternating cold and warmth detections. Each of the three PHS results was determined during each of the thermal sensory limen procedures. MPS or DMA in the individual test was calculated as the geometric mean of numerical rating for pinprick or light tactile stimuli. Percentage CV values of the three results of CDT, WDT, TSL (limen), PHS, CPT, HPT, MPS, DMA, WUR, VDT, and PPT for each of six sites were calculated for each participant. The five ''Yes'' responses and five ''No'' responses of CV values of MDT and MPT were calculated separately as ''MDT-Y'', ''MDT-N'', ''MPT-Y'', and ''MPT-N''.

All statistical calculations were performed using SPSS 17.0 software for Windows (IBM, Armonk, New York City, USA). The percentage CV data of each parameter was first transformed using $\log_{10}(CV + 1)$. The value ''1'' was added to the CV data to avoid the loss of ''0'' CV values. Assumptions of normal distribution of all original and logarithmic data were investigated with the Kolmogorov–Smirnov method. Differences in CV values between sides, genders, sites, and age groups in healthy participants were analyzed using a four-way ANOVA. The interactions and effect sizes of the factors gender, site, and age group were also calculated. *Post hoc* comparisons were estimated using Bonferroni *post hoc* test with correction for multiple comparisons. The correlations between age (years), pain duration (months), and the logarithmic CV values of each QST parameter were estimated using Spearman's rank correlation coefficient. Both the comparisons of age distribution between females and males and the differences in CVs between 22 TMD pain patients and 22 age- and gender-matched healthy controls were investigated by unpaired *t*-tests. A value of $p < 0.05$ was taken as an indication of a statistically significant difference.

Results

Participants

There was no significant age difference between female and male healthy participants (unpaired *t*-test age: $p = 0.315$). All the recruited TMD patients were suffering from bilateral myofascial pain. The present TMD pain intensity of the included patients on a 0–10 VAS was mean ± SD: 3.1 ± 0.9. The pain duration of the TMD patients varied from 0.5 to 120 months (mean ± SD: 17.3 ± 33.1).

Healthy participants

Influence of side, gender, site, and age

None of the healthy participants reported PHS or DMA in this study. Most of the CV values of different QST parameters were normally distributed only after logarithmic transformation (Kolmogorov–Smirnov, $p > 0.05$) (Rolke et al. 2006b). The results of the four-way ANOVA in healthy participants on the QST CVs with the factors side, gender, site, and age are displayed in Table I. There were significant differences amongst age groups for several of the QST CV measures (age differences, $p \leq 0.017$, Table I) and the different test regions

Table I. Four-way ANOVA analysis and effect size of body side, gender, site, and age on Coefficients of Variation (CVs) of quantitative sensory testing (QST) parameters in 70 healthy participants.

	CDT	WDT	TSL	PHS	CPT	HPT	MDT-Y	MDT-N	MPT-Y	MPT-N	DMA	WUR	VDT	PPT	MPS
Factor															
1 Side	NS	NS	NS	NO	NS	NS	NS	NS	NS	NS	NO	NS	NS	NS	NS
2 Gender	NS	NS	NS	NO	NS	NS	NS	NS	NS	NS	NO	NS	NS	NS	NS
3 Site	<0.001	<0.001	NS	NO	NS	<0.001	NS	<0.001	<0.05	<0.05	NO	<0.01	<0.05	NS	<0.01
4 Age	NS	<0.01	<0.01	NO	<0.001	<0.001	<0.01	<0.001	NS	<0.05	NO	<0.001	NS	NS	NS
2 × 3	<0.01	NS	NS	NO	NS	NS	NS	NS	NS	NS	NO	NS	NS	NS	NS
3 × 4	NS	NS	NS	NO	NS	NS	NS	NS	NS	NS	NO	<0.05	NS	NS	NS
2 × 4	NS	<0.01	NS	NO	NS	<0.05	NS	NS	<0.01	NS	NO	<0.001	<0.001	NS	NS
2 × 3 × 4	NS	<0.05	NS	NO	NS	NS	NS	NS	NS	NS	NO	<0.01	NS	NS	NS
Effect size															
Gender	0.000	0.000	0.003	NO	0.000	0.006	0.009	0.001	0.002	0.004	NO	0.001	0.006	0.000	0.002
Site	**0.129**	**0.115**	0.014	NO	0.009	**0.154**	0.011	0.076	**0.019**	0.025	NO	0.038	**0.023**	**0.009**	**0.035**
Age	0.013	0.047	**0.054**	NO	**0.132**	0.067	**0.059**	**0.110**	0.012	**0.035**	NO	**0.132**	0.000	**0.009**	0.003

The CVs of five ''yes'' and five ''no'' responses were calculated separately, so MDT, MPT were divided into MDT-Y, MDT-N, MPT-Y, MPT-N. The first part of the table shows *p* values of the four-way ANOVA. NS: $p > 0.05$; NO: no occurrence. The second part of the table shows effect sizes for gender, site, and age group differences. CDT: cold detection threshold; WDT: warmth detection threshold; TSL: thermal sensory limen; PHS: paradoxical heat sensation; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; DMA: dynamic mechanical allodynia; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. Bold face numbers are the maximal in effect sizes for one parameter amongst gender, site, and age.

(site differences, $p \leq 0.043$, Table I). The CV values from the dorsum of the hands were higher compared to the mental and/or infraorbital regions for CDT, WDT, HPT, MDT-N, MPT-Y, MPT-N, WUR, and MPS (Table II), while for VDT it was lower than the infraorbital regions (Bonferroni *post hoc* test, $p = 0.001$) (Table II). There were no differences between the CVs of mental and infraorbital region except for HPT and WUR (mental > infraorbital, Bonferroni *post hoc* test, $p \leq 0.001$) (Table II). There was no significant main effect of gender or side on the logarithmic CV values for any of the QST parameters (gender or side differences, $p \geq 0.136$) (Table I).

Correlations

The Spearman's correlations of logarithmic CVs of QST parameters and age (years) were positive (older participants had higher variability) ($\rho \geq 0.128$; $p \leq 0.009$) for WDT, CPT, HPT, MDT-N, MPT-N, and WUR. However, for TSL the correlation was negative (older participants had lower variability) ($\rho = -0.103$; $p = 0.034$) (Table III).

Interactions between factors

There was a significant gender × site interaction for CV of CDT with males having higher CV values than females on the dorsum of hand (Bonferroni *post hoc* test, mean difference for female − male = −0.063, $p = 0.003$) (Table IV). The significant site × age interaction for WUR indicated that the CV values in the mental region were higher compared to the infraorbital region in the 31–40 and 51–60 age groups (Table IV). There were also significant gender × age interactions with higher CV values in young females (21–40 years) for MPT-Y, WUR, VDT; higher CV values for middle- and old-aged males (41–70 years) for HPT, WDT, MPT-Y, VDT (Table IV).

TMD pain patients

Comparisons of TMD pain patients and controls

None of the participants reported PHS or DMA in this study. Interestingly, the 22 TMD pain patients had significantly higher CV values for TSL (unpaired *t*-test, $p = 0.033$), MDT-N ($p < 0.001$), MPT-Y ($p = 0.006$), WUR ($p = 0.023$), and PPT ($p < 0.001$) compared to age- and gender-matched healthy participants (Table V). The Spearman's correlations of logarithmic CVs of QST parameters and pain history (months) of the 22 painful TMD patients were negative ($\rho = -0.237$; $p = 0.026$) for CPT, which indicated longer pain duration had lower variability. However, there were no significant correlations for other parameters ($p > 0.122$) (Table VI).

Discussion

Overall, the main finding of this study was that several factors significantly influenced the within-session variability across

Table III. Correlations between age and Coefficients of Variation (CVs) of quantitative sensory testing (QST) parameters.

CV of parameter	Spearman's rho	*p*
CDT	0.072	NS
WDT	0.128**	<0.01
TSL	−0.103*	<0.05
CPT	0.372**	<0.001
HPT	0.204**	<0.001
MDT-Y	0.017	NS
MDT-N	0.166**	<0.01
MPT-Y	0.094	NS
MPT-N	0.155**	<0.01
WUR	0.355**	<0.001
VDT	−0.011	NS
PPT	0.053	NS
MPS	−0.037	NS

The correlations between the age (years) of the 70 healthy participants and logarithmic Coefficients of Variation (CVs) of QST parameters were evaluated by Spearman's rank correlation analysis. NS: not significant ($p > 0.05$). CDT: cold detection threshold; WDT: warmth detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

**Indicates correlation is significant at the 0.01 level (2-tailed).

*Indicates correlation is significant at the 0.05 level (2-tailed).

Table II. Bonferroni multiple comparisons between different test sites.

Comparisons	CDT	WDT	TSL	CPT	HPT	MDT-Y	MDT-N	MPT-Y	MPT-N	WUR	VDT	PPT	MPS
Hand – infraorbital													
Mean difference	0.103	0.099	−0.078	0.067	0.182	0.143	0.370	0.148	0.199	0.195	−0.156	−0.051	0.038
p	**<0.001**	**<0.001**	NS	NS	**<0.001**	NS	**<0.001**	NS	**0.05**	**<0.01**	**0.001**	NS	NS
Hand – mental													
Mean difference	0.092	0.068	−0.035	0.008	0.086	0.127	0.376	0.274	0.314	−0.031	−0.059	0.020	0.109
p	**<0.001**	**<0.001**	NS	NS	**0.001**	NS	**<0.001**	**<0.01**	**<0.001**	NS	NS	NS	**<0.05**
Infraorbital – mental													
Mean difference	−0.011	−0.031	0.042	−0.059	−0.096	−0.016	0.006	0.126	0.115	−0.225	0.097	0.071	0.071
p	NS	NS	NS	NS	**<0.001**	NS	NS	NS	NS	**0.001**	NS	NS	NS
Standard error	0.015	0.015	0.034	0.049	0.023	0.067	0.073	0.086	0.083	0.063	0.044	0.032	0.039

''Hand – infraorbital'' indicates that the logarithmic Coefficient of Variation (CV) in the hand region was subtracted by that in the infraorbital region, ''Hand – mental'' indicates that the logarithmic CV in the hand region was subtracted by that in the mental region, ''Infraorbital – mental'' indicates that the logarithmic CV in the infraorbital region was subtracted by that in the mental region. CDT: cold detection threshold; WDT: warmth detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. NS: not significant ($p > 0.05$).

Bold values indicate the *P* values ($P < 0.05$) for statistically significant differences among different sites (hand vs. infraorbital, hand vs. mental, infraorbital vs. mental).

Table IV. Detailed analysis of interactions.

Interaction							
Gender × site	Mean difference female – male (p)						
(Log CV of CDT)	Hand	Infraorbital	Mental	Stand. error			
	−0.063 (0.003)	0.038 (NS)	0.025 (NS)	0.021			
		Mean difference female – male (p)					
Gender × age	Log CV of parameter	21–30 (years, $n=16$)	31–40 (years, $n=16$)	41–50 (years, $n=16$)	51–60 (years, $n=16$)	61–70 (years, $n=6$)	Stand. error
	WDT	0.027 (NS)	−0.018 (NS)	0.028 (NS)	**−0.084 (0.002)**	0.035 (NS)	0.027
	HPT	−0.058 (NS)	−0.017 (NS)	**−0.142 (<0.001)**	−0.034 (NS)	0.044 (NS)	0.040
	MPT-Y	**0.439 (0.003)**	0.032 (NS)	0.041 (NS)	**−0.304 (0.039)**	−0.220 (NS)	0.147
	WUR	**0.471 (<0.001)**	0.084 (NS)	0.044 (NS)	−0.094 (NS)	−0.003 (NS)	0.103
	VDT	0.080 (NS)	**0.171 (0.021)**	0.066 (NS)	**−0.277 (<0.001)**	0.024 (NS)	0.074
Site × age		Mean difference (p)					
(Log CV of WUR)	Site comparison	21–30 (years, $n=16$)	31–40 (years, $n=16$)	41–50 (years, $n=16$)	51–60 (years, $n=16$)	61–70 (years, $n=6$)	
	Hand – infraobital	0.254 (NS)	0.239 (NS)	0.282 (NS)	0.099 (NS)	−0.062 (NS)	
	Hand – mental	0.257 (NS)	−0.100 (NS)	0.003 (NS)	−0.291 (NS)	−0.012 (NS)	
	Mental – infraobital	−0.003 (NS)	**0.339 (0.022)**	0.279 (NS)	**0.390 (0.006)**	−0.049 (NS)	
	Stand. error	0.126	0.126	0.126	0.126	0.126	

After four-way ANOVA analysis of the data from healthy participants, the significant interactions were investigated using Bonferroni *post hoc* test. The first part of this table shows the gender × site interaction for CDT; the second part shows gender × age interactions for WDT, HPT, MPT-Y, WUR, and VDT. ''Female – male'' indicates that the logarithmic CV of female subjects was subtracted by that of male subjects; the third part shows the site × age interaction for WUR. ''Hand – infraorbital'' indicates that the logarithmic CV in the hand region was subtracted by that in the infraorbital region; ''Hand – mental'' indicates that the logarithmic CV in the hand region was subtracted by that in the mental region; ''Mental – infraorbital'' indicates that the logarithmic CV in the mental region was subtracted by that in the infraorbital region. CV: Coefficient of Variation; CDT: cold detection threshold; WDT: warmth detection threshold; HPT: heat pain threshold; MPT: mechanical pain threshold; WUR: wind-up ratio; VDT: vibration detection threshold. NS: not significant ($p>0.05$).

Bold values indicate the statistically significant differences and P values ($P<0.05$, in brackets) between two genders (female vs. male) in the first two parts, or among different sites (hand vs. infraorbital, hand vs. mental, infraorbital vs. mental) in the third part.

Table V. The influence of ''presence of pain'' on Coefficients of Variation (CVs) of quantitative sensory testing parameters.

CV of parameter	Healthy controls (mean ± SD)	Patients (mean ± SD)	p
CDT	0.75 ± 0.51	0.79 ± 0.64	NS
WDT	0.68 ± 0.56	0.86 ± 1.4	NS
TSL	**14.0 ± 1.1**	**15.9 ± 9.9**	**<0.05**
CPT	7.9 ± 1.4	6.7 ± 6.9	NS
HPT	2.0 ± 1.3	2.2 ± 1.4	NS
MDT-Y	48.0 ± 2.8	48.0 ± 2.7	NS
MDT-N	**37.1 ± 2.9**	**49.0 ± 2.7**	**<0.001**
MPT-Y	**30.3 ± 2.2**	**39.8 ± 2.9**	**<0.01**
MPT-N	29.1 ± 2.1	34.1 ± 2.5	NS
WUR	**33.7 ± 2.2**	**35.1 ± 1.9**	**<0.05**
VDT	2.4 ± 2.5	1.9 ± 2.3	NS
MPS	30.9 ± 1.7	34.9 ± 2.3	NS
PPT	**13.1 ± 8.1**	**19.0 ± 1.0**	**<0.001**

The differences of CVs between 22 temporomandibular disorder pain patients and age- and gender-matched healthy participants were estimated by unpaired t-tests. The percentage Coefficients of Variation are presented as means ± SDs. CDT: cold detection threshold; WDT: warmth detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. NS: not significant ($p>0.05$). $t(131)=1.9782$ (2-tailed), $\alpha=0$.

Bold values indicate the Coefficients of Variation in healthy controls and patients (Mean ± SD), and P values with statistically significance ($P<0.05$).

Table VI. Correlations between pain duration (months) and Coefficients of Variation (CVs) of quantitative sensory testing (QST) parameters.

CV of parameter	Spearman's rho	p
CDT	−0.166	NS
WDT	−0.160	NS
TSL	0.030	NS
CPT	−0.237*	0.026
HPT	−0.066	NS
MDT-Y	0.101	NS
MDT-N	0.065	NS
MPT-Y	−0.120	NS
MPT-N	−0.159	NS
WUR	−0.034	NS
VDT	−0.087	NS
PPT	−0.048	NS
MPS	−0.072	NS

The correlations between pain duration (months) in 22 painful temporomandibular disorder patients and logarithmic Coefficients of Variation (CVs) of QST parameters were evaluated by Spearman's rank correlation analysis. NS: not significant ($p>0.05$). CDT: cold detection threshold; WDT: warmth detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. The Spearman's correlations were negative for CPT, which indicated longer pain duration had lower variability. However, there were no significant correlations for other parameters.

*Indicates correlation is significant at the 0.05 level (2-tailed).

three to five repetitions of standardized QST measures. Consistency (reliability or reproducibility), the antonym of variability, refers to the repeatability of a measurement across time, patients, or observers, and the extent to which it is error-free (Rommel et al. 2001). Three kinds of consistencies have traditionally been assessed for QST: intra-observer, inter-observers, and center-to-center reliability (Chong and Cros 2004; Heldestad et al. 2010; Geber et al. 2011). These inter-session reliabilities have so far been evaluated for tests separated by hours to months. The consistency evaluated in the present study was calculated using the CV values of three to five repeated measures in the standard thresholds determination within a single session, that is, measures only separated by seconds or minutes. This variability measure can be considered with little influence of time or observer (performed by one investigator) and was different from previous reliability studies (Pigg et al. 2010). Hence, we conducted a study on this novel aspect of variability, which may provide new perspectives to the analysis of QST results (Rolke et al. 2006b). Since the whole QST program lasted about 3 h for six test sites in each participant (Rolke et al. 2006a), attention was a possible factor, which could influence the somatosensory variability for different parameters (Svensson et al. 2011). Thus, the seven QST tests were performed in a randomized order although the original DFNS protocol recommends otherwise (Rolke et al. 2006b). The modified testing order in the present study may be a limitation, as one study had reported preceding thermal testing up to pain thresholds might be followed by mechanical hyperalgesia (Gröne et al. 2012). However, it was not the objective of the present study to evaluate the actual differences in QST measures between groups.

Gender and age

Previous studies have reported higher somatosensory sensitivity in women than men (Rolke et al. 2006a; Matos et al. 2011). Hormonal and neurobiological factors (Greenspan et al. 2007) and several psychological variables (Kröner-Herwig et al. 2012) were assumed to be potential mediators of these gender differences. Contrary to the hypothesis of this study, a gender effect did not emerge on the within-session variability. However, there were significant interactions between gender and other factors for several QST measures (Table IV).

It is well documented that sensory and sensory–motor abilities decline in the course of normal aging (Li and Lindenberger 2002). The observed co-variation or inter-dependence between sensory–motor and cognitive abilities with advancing age may in part explain the increasing variability in elderly participants (Li and Lindenberger 2002). One study has added to this view by demonstrating a relationship between increasing short-term fluctuation in walking ability and short-term verbal and spatial memory in a healthy sample of aged people (Li et al. 2001a). It suggested a possible common factor such as neurological deterioration, which increases with advancing age (Li et al. 2001b). The changes due to aging may also be attributable to the reduction in density of peripheral nerve endings and functions within the central nervous system (McArthur et al. 1998). However, caution needs to be exerted when age effects are evaluated in relatively small groups and when other interaction effects are considered. Nevertheless, the present approach with assessment of CV values in different age groups may be promising to apply in large-scale population studies. Albeit a statistically significant correlation was detected between log CVs and age, which confirmed the hypothesis of this study with older age would be associated with larger variability. However, the low Spearman's rho indicated that age was not strongly associated with within-session somatosensory variability.

Sites

The within-participant site differences may be more reflective of peripheral factors, that is, density of nerve fibers and specific receptors. The within-session variability measured on the dorsum of the hand was higher than in the facial regions, in accordance with other studies (Fruhstorfer et al. 1976; Rolke et al. 2006a, 2006b). This finding can be attributed to the fact that the number of epidermal nerve fibers in the facial areas is significantly higher than on the limbs and trunk; thus epidermal nerve fiber density variation may possibly explain the different within-session variability and sensitivity in different parts of the body (Besné et al. 2002). Interestingly, the lowest variability of the VDT was detected on the hand. This may possibly be explained by anatomical features and the fact that sensation of vibration on the face may be confounded by sounds created due to the close relationship with the ears.

Influence of pain

Chronic pain patients often suffer from more than just pain; depression, anxiety, sleep disturbances, and decision-making disabilities also significantly impact their lives (Apkarian et al. 2004a). One review highlighted brain network activities underlying acute and chronic pain, and identified pain engaged brain regions critical for cognitive/emotion assessments (Apkarian et al. 2005). Another study has demonstrated that chronic pain harms cortical areas unrelated to pain—''default mode network'' (DMN) (Apkarian et al. 2004b). The reduced deactivation in several key DMN regions suggests that the disruptions of the central nervous system may underlie the cognitive and behavioral impairments accompanying chronic pain (Baliki et al. 2008), such as the increase in variability of QST. As expected, the TMD pain patients presented larger within-session variability than healthy participants. A recent study using the same QST protocol has reported that test–retest reliability is significantly higher in painful areas than in pain-free areas (Geber et al. 2011), which is suggested to be caused by attention shifts towards the painful or deafferented body regions (Pfau et al. 2011). An obvious limitation in the present study was the small number of patients, but the preliminary findings indicated that the CV values of the QST parameters may provide additional information about the somatosensory function in TMD pain patients. Another aspect to consider was the impact of pain duration on the variability of somatosensory function but only a weak correlation between the pain history and somatosensory variation was detected in the present study. It has been suggested that the presence of ongoing pain induces increased

variability of somatosensory measures (Curatolo et al. 2001; Rommel et al. 2001). We suggest that the correlation between pain duration and somatosensory variability should be studied further in larger samples and with different kinds of pain conditions.

Conclusions

In this study a novel perspective to the evaluation of the DFNS QST data was put forward, that is, the somatosensory variability within one threshold determination. Investigation of how side, gender, site, age, and presence of pain affected the somatosensory variability was completed. The factors site and age, but not side or gender, significantly influenced the within-session variability in the QST procedures and the variability in TMD pain patients was higher in comparison with healthy controls. Additionally, the present data suggested that the somatosensory variability along with the absolute threshold measures may be a more complete method to investigate the somatosensory disorders and underlying pain mechanisms. Information on the variability, for example, the CV values should be included in reference databases for further studies.

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Declaration of interest

The authors report no conflicts of interest.

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