Quantitative Sensory Testing in the Trigeminal Region: Site and Gender Differences

Renata Matos, DDS
PhD Student
Center for Sensory-Motor Interaction (SMI)
Aalborg University, Aalborg, Denmark

Kelun Wang, DDS, PhD
Associate Professor
Center for Sensory-Motor Interaction (SMI)
Aalborg University and
Dept of Oral and Maxillofacial Surgery
Aalborg Hospital, Aalborg, Denmark, and
Stomatological School and Hospital
Nanjing Medical University
Nanjing, PR China

Janek Dalsgaard Jensen, DDS
Consultant

Thomas Jensen, DDS
Consultant

Bjarne Neuman, DDS
Consultant

Department of Oral and Maxillofacial Surgery
Aalborg Hospital, Aalborg, Denmark

Peter Svensson, DDS, Dr Odont, Phd
Professor
Department of Clinical Oral Physiology
University of Aarhus and
Center of Functionally Integrative Neuroscience (CFIN), MindLab
Aarhus University Hospital
Aarhus, Denmark

Lars Arendt-Nielsen, Dr Med Sci, PhD
Professor
Center for Sensory-Motor Interaction (SMI)
Aalborg University, Aalborg, Denmark

Correspondence to:
Kelun Wang
Center for Sensory-Motor Interaction (SMI)
Department of Health Science and Technology
Aalborg University
Fredrik Bajers Vej 7 D2
9220 Aalborg, Denmark
Fax: + 45 9815 4008
Email: kelun@hst.aau.dk

Aims: *To establish a quantitative sensory testing (QST) profile in the trigeminal (V) area and test for site and gender differences in healthy humans.* ***Methods:*** *A standardized QST protocol was applied on 15 healthy men (age range: 18 to 25 years old) and 15 age-matched women, and the sensitivity was examined bilaterally in facial sites supplied by the infraorbital (V2) and mental (V3) nerves. The cold detection threshold (CDT), cold pain threshold (CPT), warm detection threshold (WDT), heat pain threshold (HPT), thermal sensory limen (TSL), mechanical detection threshold (MDT), mechanical pain sensitivity (MPS), mechanical pain threshold (MPT), dynamic mechanical allodynia (ALL), windup ratio (WUR), pressure pain threshold (PPT), and vibration detection threshold (VDT) were determined. Data were tested with ANOVAs for repeated measures and post-hoc comparisons were calculated using Bonferroni tests.* ***Results:*** *There were significant gender differences with lower threshold (higher sensitivity) in women for CDT (P = .030) and PPT (P = .006). A significantly lower threshold (higher sensitivity) was detected for HPT (P < .001), and significantly higher thresholds (lower sensitivity) for VDT (P < .001) and CDT (P < .001) in V2 compared to V3. There were no significant right-to-left side differences for any of the QST parameters.* ***Conclusion:*** *Application of this standardized QST protocol may allow for a better understanding of the underlying mechanisms from somatosensory phenotypes and provide basic information for the study of sensory dysfunctions in the V area.*
J OROFAC PAIN 2011;25:161–169

Key words: craniofacial pain, gender difference, human, quantitative sensory testing (QST), trigeminal system

Orofacial pain represents a diagnostic and treatment challenge for the clinician. Among many pain conditions that affect the face, the masticatory system, the head, and the neck, temporomandibular disorders (TMD) and neuropathic pain (NP) are the most frequent.[1] In the diagnosis and understanding of the underlying pathophysiology of pain, information on the sensory processing is important.[2–5] Since the trigeminal (V) nerve mediates somatosensory impulses, including nociceptive information, from most of the orofacial region, careful assessment is necessary to help diagnosis.[3]

Neurophysiological methods and quantitative sensory testing (QST) offer several tools for diagnostic and etiological investigation of the V somatosensory system.[3,6,7] The modern concept of advanced QST for experimental sensory assessment is a multimodal, multiissue approach where different modalities (thermal, mechanical, electrical, and chemical) are applied to different tissues (skin, muscles, and viscera) and

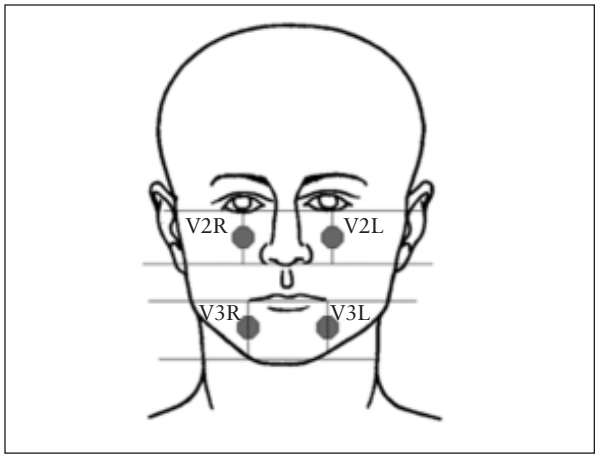

Fig 1 Quantitative sensory testing sites used in this study. V2R: above the right infraorbital foramen; V2L: above the left infraorbital foramen; V3R: above the right mental foramen; V3L: above the left mental foramen.

the responses are assessed by psychophysical methods (thresholds and stimulus-response functions).[8]

A recent study demonstrated the utility of the standardized QST protocol[7] modified for the V region.[5] For instance, Baad-Hansen et al[9] performed a QST battery at six V and one extratrigeminal site and found differences in somatosensory function in the perioral region between patients scheduled for orthognathic surgery and a control group, while Pfau et al[10] obtained a complete somatosensory profile by using the standardized QST protocol[7] in the V region, trapezius, and hand dorsum of patients with TMD and fibromyalgia syndrome. List et al[11] applied a battery of intraoral QST and documented significant abnormalities in intraoral somatesensory function in atypical odontalgia patients, which may reflect peripheral and central sensitization of V pathways. Furthermore, QST has demonstrated diagnostic capabilities in TMD, burning mouth syndrome, oral malignancies, numb chin syndrome, posttraumatic pain, and nerve pathologies,[12] as well as in elucidating mechanisms of central and peripheral sensitization.[13]

As one theoretical possibility of identifying pain mechanisms in patients is to assess the differences in the somatosensory phenotype as precisely as possible, the purpose of this study was to establish a QST profile in the V area and to test for site and gender differences in healthy humans.

Materials and Methods

A standardized QST battery, consisting of seven tests measuring 13 parameters,[5–7] was used to establish a profile of QST bilaterally in facial sites supplied by the maxillary (V2) and mandibular (V3) branches of the V nerve. The tests were applied to the skin overlying the infraorbital foramen and mental foramen. The infraorbital foramen is located bilaterally in the maxilla on the frontal side and, in the inferomedial direction, is located under the infraorbital ridge by about 1 cm. The infraorbital nerve is a major branch of the maxillary nerve, the second division of the V nerve.[14,15] The mental foramen is generally located bilaterally between the first and second premolar teeth in the mandibular bone. The mental nerve is a major branch of the inferior alveolar nerve, which is one of the most important branches of the mandibular nerve, the third division of the V nerve (Fig 1).

The QST methods tested: *(1)* thermal detection thresholds, for the perception of cold, warm, and paradoxical heat sensations; *(2)* thermal pain thresholds, for cold and hot pain sensations; *(3)* mechanical detection thresholds, for touch and vibration; and *(4)* mechanical pain sensitivity, including thresholds for pinprick and blunt pressure, stimulus-response functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (windup-like pain).[6,7]

Subjects

The volunteers for this study were healthy subjects with no signs or symptoms of pain, hyperalgesia, or allodynia in the head, neck, and face region. This was defined as absence of jaw dysfunction and headaches, and absence of subjective pain or soreness of the masticatory muscles. Fifteen men (age range from 18 to 25 years) and 15 age-matched women participated in the experiment, and all the tests were investigated bilaterally over the infraorbital foramen (V2) and the mental foramen (V3). The tests were performed in the same order, and, at the start of each session, the subjects were familiarized with the measurement procedure and the equipment via a demonstration on the right forearm. Declaration and informed consent were obtained from all subjects. The study was approved by the local ethics committee (N-20080057).

Thermal Detection, Thermal Pain Thresholds, and Paradoxical Heat Sensations

The tests for thermal sensation were performed using the thermal sensory device TSA 2001 II (CHEPS-MEDOC). Cold and warm detection thresholds (CDT, WDT) were measured first, followed by thermal sensory limen (TSL, the difference in threshold for alternating cool and warm stimuli), where the subjects

were asked about paradoxal heat sensations (PHS). Then, cold and heat pain thresholds (CPT, HPT) were measured. The mean threshold temperature of three consecutive measurements was calculated. The baseline temperature was 32°C (center of neutral range). The method of limits was used by applying ramp stimuli at a velocity of 1°C/second. The contact area of the thermode was 9 cm^2. The temperature of the thermode increased for WDT and HPT and decreased to determine CDT and CPT. The volunteers were asked to press a button when the respective thermal sensation was perceived. Increasing or decreasing thresholds were established based on the stipulated baseline, ie, the closer a threshold is to the baseline, the lower it will be. In other words, volunteers with lower thresholds will be more sensitive to the stimulus. Cutoff temperatures were –1°C and 51°C, and the verbal instructions given to the subjects were virtually identical to those used by the German Research Network on Neuropathic Pain (DFNS). The subjects were instructed not to look at the computer screen at any time during the testing procedures.[6]

Mechanical Detection Threshold

The mechanical detection threshold (MDT) was measured with a standardized Semmes-Weinstein monofilaments with 20 different diameters (North Coast Medical). The number of each filament (1.65 to 6.65) corresponds to a logarithmic function of the equivalent forces of 0.008 to 300 g. Mechanical detection thresholds were measured using a "method of limits," with five series of ascending and five series of descending stimulus intensities.[15,16] The final threshold was the geometric mean of these five series.

The subjects were instructed to close their eyes during the entire test procedure and to raise their hand as soon as they felt the stimulus in the test site. The filament was applied vertically on the test site and pressure was applied slowly until the filament bowed. Quick applications and bouncing of the filaments against the skin were avoided.[2] At each site, the test started with the number 1.65 filament. If the subject did not raise his/her hand, it was considered a negative response, and the next filament applied was one step higher (number 2.36). This procedure was repeated with increased filament diameters until the subject felt the pressure. This was considered a positive answer. Again, the filament with a lower diameter was applied until the subject no longer felt the pressure. This was considered a negative answer. This procedure continued until five positive and five negative peaks were recorded. If the subject had a positive response while applying the lowest filament (number 1.65), this filament was considered the threshold.

Mechanical Pain Threshold for Pinprick Stimuli

The mechanical pain threshold (MPT) was measured using a set of seven punctuate mechanical stimulators with fixed stimulus intensities (flat contact area of 0.2-mm diameter) that exerted forces of 8 to 512 mN.[17–19] Mechanical pain threshold was measured using a modified "method of limits," with five series of ascending and five series of descending stimulus intensities.[16] The final threshold was the geometric mean of these five series.

The stimuli were applied in the same way as for the MDT, but the subjects were instructed to raise their hand as soon as they felt not only pressure but also pain in the test area.[20] If the subject had no positive response for the force 512 mN, this number was recorded as the threshold.

Stimulus-Response Functions: Mechanical Pain Sensitivity for Pinprick Stimuli and Dynamic Mechanical Allodynia

Mechanical pain sensitivity (MPS) was assessed using the same set of seven punctuate mechanical stimulators as for MPT to obtain a stimulus-response function. These seven pinprick stimuli were applied in a balanced order, five times each, and the subject was asked to give a pain rating for each stimulus on a 0 to 100 numerical rating scale (NRS) (0 indicating "no pain" and 100 indicating "most intense pain imaginable"). This test was applied to detect pinprick hyperalgesia.[6,7] Stimulus-response functions for dynamic mechanical allodynia (ALL) were determined using a set of three light tactile stimulators: cotton wisp exerting a force of ~3 mN; a cotton wool tip, fixed to an elastic strip, exerting a force of ~100 mN; and a standardized brush (Somedic) exerting a force of ~200 to 400 mN. The three tactile stimuli were applied five times each with a single stroke of approximately 1 to 2 cm in length over the skin. They were intermingled with the pinprick stimuli in balanced order, and subjects were asked to give a rating for each stimulus on the same scale as for pinprick stimuli.[5–7] Mechanical pain sensitivity was calculated as the geometric mean of all numerical ratings for pinprick stimuli. ALL was calculated as the geometric mean (compound measure) of all numerical ratings across all three different types of light tactile stimulators.[5–7]

Windup Ratio

This test examined the perceptual correlate of temporal pain summation. The perceived intensity of a single pinprick stimulus (128 mN pinprick) was

compared with that of a series of 10 repetitive pinprick stimuli of the same physical intensity (1/second applied within an area of 1 cm^2) at five different skin sites within the same body region. The subject was asked to give a pain rating representing the single stimulus, and the estimated mean over the whole series of 10 stimuli was obtained by using a 0 to 100 NRS (0 indicating "no pain" and 100 indicating "most intense pain imaginable"). The whole procedure was repeated five times for each point. The windup ratio (WUR) was calculated as the ratio of mean rating of the five series divided by the mean rating of the five single stimuli.[7]

Vibration Detection Threshold

The vibration detection threshold (VDT) was obtained with a vibrameter (100Hz) (Somedic) that was placed over the testing sites. Vibration threshold was determined with three series of ascending stimulus intensities[21,22] for each site. Each subject was instructed to raise his/her hand as soon as he/she felt the stimulus. The mean value of the three measurements was used for further statistical analysis.

Pressure Pain Threshold

The pressure pain threshold (PPT) was obtained with a pressure algometer (Somedic). The algometer probe (1-cm^2 area) was applied with a constant application rate of 30 kPa/second. The subjects pushed a button to stop the pressure stimulation as soon as they felt that the stimulation was painful. The PPT was determined with three series of ascending stimulus intensities for each point. The mean value of the three measurements was used for further statistical analysis.[20]

Statistical Analyses

Descriptive statistics were used to summarize all measurements. The mean values and standard deviation of CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, MPS, ALL, WUR, PPT, and VDT in each gender and each test site were calculated. The design of the experiment corresponded to a repeated measurements framework. Two-way analysis of variance (ANOVA) with repeated measures was performed. The factors in the ANOVA were gender and site/side (V2-left, V2-right, V3-left, and V3-right). Post-hoc comparisons were calculated using Bonferroni tests. All data were normalized with decimal logarithm and added 1 to avoid negative log values.[6,7] The significance level for each test was set at 5%. All statistical calculations were performed by using the Statistical Package for Social Sciences version 15 (SPSS, IBM).

Results

ALL and PHS did not occur in healthy human subjects. For the remaining QST parameters, two-way ANOVAs for repeated measures followed by Bonferroni comparisons were calculated. There were no significant gender and site/side interactions for any of the QST parameters ($P > .05$). Table 1 shows mean and SD of the variables CDT, WDT, TSL, CPT, HPT, MDT, MPT, MPS, WUR, PPT, and VDT.

Gender Difference

The two-way ANOVA showed that there were significant gender differences with higher thresholds in men (lower sensitivity) than in women for CDT ($P = .030$) and higher thresholds in men (lower sensitivity) than in women for PPT ($P = .006$) (Table 1).

Site/Side Difference

There were significant site/side differences for CDT, HPT, and VDT. The multiple comparison test (Bonferroni) revealed differences between sites V2 and V3, as shown in Table 1. The CDT and VDT at V2 were higher (lower sensitivity) than at V3 sites ($P < .001$; $P < .001$). Furthermore, a significant difference between V2 and V3 sites for HPT, with higher (lower sensitivity) values at V3 than at V2 sites, was detected ($P < .001$) (Table 1).

Discussion

The present study revealed significant gender differences detected with lower thresholds (higher sensitivity) in women than in men for CDT and PPT. Significant site differences were also detected with lower threshold (higher sensitivity) for HPT and significantly higher thresholds (lower sensitivity) for VDT and CDT in V2 compared to V3 sites. There was no significant right-to-left side differences for any of the QST parameters.

Gender Differences

The PPT measurements were significantly lower (higher sensitivity) in women than in men, which is in accordance with a series of previous studies[20,23–34] suggesting that there are robust differences between genders, with women exhibiting lower thresholds (higher sensitivity). This difference is reported to be independent of anatomical measurement site, although a trend for greater divergence in more richly innervated anatomical areas has been suggested.[35]

Table 1 Mean and SD of QST Data from Four Different Test Sites in Men (n = 15) and Women (n = 15)

		Site/side				
Variables	Gender	V2-left (mean ± SD)	V2-right (mean ± SD)	V3-left (mean ± SD)	V3-right (mean ± SD)	*P*
CDT (°C)*†	Men	28.83 ± 2.00	29.97 ± 2.07	30.09 ± 1.61	30.32 ± 1.59	A: .030
	Women	30.04 ± 1.40	30.95 ± 0.77	31.24 ± 0.37	31.34 ± 1.17	B: < .001
						C: .886
WDT (°C)	Men	34.12 ± 1.38	33.77 ± 1.56	33.85 ± 1.29	33.54 ± 1.81	A: .109
	Women	33.33 ± 0.64	33.12 ± 0.59	33.14 ± 0.62	33.13 ± 0.72	B: .089
						C: .522
TSL (°C)	Men	3.37 ± 1.60	3.46 ± 2.08	3.46 ± 1.81	3.48 ± 1.99	A: .072
	Women	2.69 ± 1.33	2.38 ± 1.23	2.11 ± 0.81	2.52 ± 1.28	B: .272
						C: .367
CPT (°C)	Men	18.71 ± 7.31	20.96 ± 6.95	19.18 ± 7.34	20.03 ± 7.90	A: .242
	Women	16.11 ± 9.52	17.13 ± 9.49	15.40 ± 10.21	17.08 ± 9.45	B: .206
						C: .487
HPT (°C)†	Men	40.29 ± 3.07	39.71 ± 3.37	41.45 ± 3.17	41.30 ± 3.96	A: .936
	Women	39.75 ± 4.69	39.62 ± 3.45	41.84 ± 3.87	42.22 ± 4.02	B: < .001
						C: .413
MDT (mN)	Men	1.65 ± 0.00	1.65 ± 0.00	1.65 ± 0.00	1.65 ± 0.00	A: .999
	Women	1.65 ± 0.00	1.65 ± 0.00	1.65 ± 0.00	1.65 ± 0.00	B: .999
						C: .999
MPT (mN)	Men	124.08 ± 126.24	122.58 ± 127.92	111.04 ± 143.59	96.59 ± 131.88	A: .368
	Women	74.14 ± 86.80	74.88 ± 93.25	88.15 ± 119.24	81.93 ± 99.59	B: .128
						C: .410
MPS (pain rating-NRS)	Men	1.87 ± 1.49	1.87 ± 1.65	1.95 ± 1.11	2.54 ± 1.75	A: .745
	Women	2.21 ± 2.17	3.49 ± 4.92	3.22 ± 4.31	4.24 ± 6.69	B: .134
						C: .401
WUR (pain rating-NRS)	Men	4.10 ± 2.78	4.13 ± 2.23	3.78 ± 2.48	3.67 ± 2.06	A: .655
	Women	3.87 ± 3.14	3.78 ± 2.56	4.01 ± 3.62	3.16 ± 1.83	B: .127
						C: .716
PPT (kPa)*	Men	153.87 ± 35.03	150.13 ± 33.46	160.27 ± 147.00	160.13 ± 44.44	A: .006
	Women	115.87 ± 36.27	117.93 ± 34.11	125.80 ± 34.33	127.40 ± 43.10	B: .053
						C: .647
VDT (1/1000 mm)†	Men	2.79 ± 2.11	2.61 ± 1.44	1.42 ± 0.78	1.49 ± 0.86	A: .878
	Women	2.77 ± 1.79	2.31 ± 0.98	1.54 ± 0.84	1.42 ± 0.73	B: < .001
						C: .880

A = comparison between gender; B = comparison between site/side; C = interaction between gender and site/side; *indicates significant difference between men and women ($P < .05$); †indicates significant difference between V2 and V3 sites ($P < .05$).

The mechanisms underlying gender differences in experimental pain responses have yet to be elucidated, but prior research suggests that a variety of factors may contribute, including hormonal alterations,[36–40] resting blood pressure,[24] psychological factors,[40,41] endogenous opioid systems, dopaminergic function, and central serotonin function.[40] In addition, other investigators have reported that factors such as sex role expectancies[42] and anxiety[43] may moderate the gender difference. It is also reasonable to assume that gender-specific variation of skin/muscle structural and anatomical characteristics, biochemical composition, mechanical properties, functional differences, and differences in response to exogenous triggers

associated with potential differences in somatosensory innervations may play a role in mechanisms of gender-related influences on pain.[44]

Furthermore, it has been found that glutamate injection into the masseter muscle evokes pain responses that are greater in women than men.[40,45–49] One possible mechanism for this difference may be a greater sensitivity to glutamate of masseter muscle afferents in women and could involve either increased expression of excitatory amino acid receptors or enhancement of receptor function, both of which have been shown to occur secondary to increased levels of the female sex hormone estrogen.[50,51] These gender-related differences in acute experimental masseter muscle pain are particularly interesting given the higher prevalence of many chronic muscle pain conditions in women.[45]

A difference between genders was also observed for CDT. Women had lower (higher sensitivity) CDT than men. The other parameters for thermal assessment did not show significant gender difference. Fillingim et al[35] examined thermal pain thresholds and tolerances applied to the left volar forearm in 209 (117 female, 92 male) healthy young adults. The order of assessments was WDT followed by HPT followed by HPTo (heat pain tolerance). They found that women showed significantly lower WDT, HPT, and HPTo relative to men. The results demonstrating greater sensitivity to warmth and thermal pain among women are consistent with previous research.[26,34] However, gender differences were not reported by Wasner and Brock[52] using measurements of thermal pain thresholds and thermally-induced perceptions. The reasons for the differences in thermal thresholds reported in the present study and other studies may be the anatomical and physiological differences between the tested sites, which would indicate that each body region needs its own QST reference data.[7] In addition to the previously mentioned reasons for gender differences, it seemed plausible that the gender difference in thermal pain responses may be due to generally enhanced somatic sensation rather than a difference in nociceptive processing per se.[35]

Site and Side Differences

Regarding the difference in thresholds between V2 and V3 sites revealed in the present study, it is known that the somatosensory sensibility within the distributions of the mandibular and maxillary nerves is comparable. Van Sickels and colleagues[53] concluded that "comparison of the upper lip (V2) and lower lip (V3) appears to be acceptable for retrospective tests for detection of neurosensory injury of the inferior alveolar nerve." In order to assess the degree of similarity of sites innervated by the infraorbital nerve (V2) and the inferior alveolar nerve (V3), a battery of neurosensory testing consisting of tests for light touch, brush stroke direction, two-point discrimination, and temperature, tested by use of Minnesota thermal disks, was performed. The results showed that temperature sensitivity was not different among the sites tested. The methodological differences, ie, testing instrument or testing sensitivity, could be the reason for the different outcomes between the present study and this study.

On the other hand, Green and Gelhard[54] evaluated subjects' ability to scale the magnitude of warming and cooling stimuli applied to 12 different loci on the face and in the mouth. Significant differences were found among areas for relative sensitivity to both cooling and warming. With the exception of the tongue, facial sites were more sensitive to warming than intraoral sites, the infraorbital region (V2) and nose being the most sensitive. All extraoral and intraoral sites were equally sensitive to cooling. The observed differences between the intraoral and extraoral sites were also reported by Pigg et al,[5] who demonstrated that facial skin is more sensitive for thermal detection and heat pain. The present study showed that HPT was higher and CDT was lower at V3 than at V2. These results suggest that V2 is more sensitive for HPT and less sensitive for CDT.

Another finding was the significant difference between V2 and V3 sites for VDT, with higher values (lower sensitivity) at V2 than at V3 sites. The question about tactile sensitivity differences at the upper lip (V2) versus the lower lip (V3) have consistently shown that identical sensitivities are found for a variety of neurosensory procedures, including spatial resolution,[55–57] cutaneous pressure threshold, and moving two-point discrimination.[58] Conversely, Baad-Hansen et al[9] reported a significant difference between V2 and V3 sites for two-point discrimination thresholds.

Andreatta and Davidow[58] investigated the mediolateral spatial and frequency variations in vibrotactile detection capacity to inputs delivered to the vermilion upper lip and lower lip. The results revealed no significant differences in sensitivity as a function of laterality or between the upper lip and lower lip vermilion sites, but midsagittal vermilion sites were significantly more sensitive to the range of vibrotactile stimuli compared to lateral vermilion locations. The results are fully consistent with previous data.[55,59,60]

Given that microneurographic and histological data clearly indicate variations in peripheral innervation density within the orofacial area,[60–64] it is reasonable to suggest that thresholds may not be uniform along the entire distribution of the maxil-

lary nerve (V2) or mandibular nerve (V3). As such, greater vibrotactile sensitivity at the V3 region may suggest that mechanosensitive receptor densities and/or receptive field characteristics differ at this location compared to the V2 region.

Another interesting finding concerned the lowest force used to elicit tactile response for MDT measurements on healthy humans. There were no significant differences between sides detected in the present study, which is in accordance with previous studies.[6,11,65] However, Komiyama and De Laat[20] measured MDT at multiple points in the orofacial region (cheek skin, maxillary gingiva, and tip of the tongue) of normal subjects. The tongue tip had the lowest MDT value (highest sensitivity), and women showed a significantly lower (more sensitive) MDT at the cheek skin than men.

There are some limitations in this study. First, it is well known that the phases of the menstrual cycle affect sensory and pain perception in females. Some studies reported systematic changes of sensory perception during the menstrual phases.[20] Such factors were not evaluated in this study but could be included in future studies. Secondly, the experimental protocol did not consider the use of an extratrigeminal control site. It should be noted that such a measure was excluded for practical reasons (eg, time consuming), but the inclusion of an extratrigeminal control site is recommended to strengthen the data in future studies.[5] Finally, it should be noted that this study reflected an experimental QST protocol ,and future studies are needed to properly evaluate and recommend the most substantive tests for a shortened research and clinical protocol.[5] In this sense, future studies in the orofacial region may benefit from the use of a compiled standardized QST protocol, which will probably emerge within the next few years.[9]

Conclusions

In the present study, the QST profile in the V area was evaluated. Gender and site differences were observed, which could reflect variability of the biophysical properties of the skin, afferent innervation density, and/or variations in the processing within the central nervous system. The present QST methodology is adequate for further clinical applications, eg, in order to evaluate patients with sensory dysfunctions in the orofacial region.

Acknowledgments

The Det Obelske Familiefond of Denmark supported this study.

References

1. Drobek W, De Laat A, Schoenaers J. Tactile threshold and pressure pain threshold during treatment of orofacial pain: An explorative study. Clin Oral Investig 2001;5:185–193.
2. Jacobs R, Wu CH, Van Loven K, Desnyder M, Kolenaar B, Van Steenberghed D. Methodology of oral sensory tests. J Oral Rehabil 2002;29:720–730.
3. Jääskeläinen SK. Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain 2004;18:85–107.
4. Svensson P, Baad-Hansen L, Thygesen T, Juhl GI, Jensen TS. Overview on tools and methods to assess neuropathic trigeminal pain. J Orofac Pain 2004;18:332–338.
5. Pigg M, Baad-Hansen L, Svensson P, Drangsholt M, List T. Reliability of intraoral quantitative sensory testing (QST). Pain 2010;148:220–226.
6. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
7. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): Standardized protocol and reference values. Pain 2006;123:231–243.
8. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–572.
9. Baad-Hansen L, Arima T, Arendt-Nielsen L, Neumann-Jensen B, Svensson P. Quantitative sensory tests before and 1(1/2) years after orthognathic surgery: A cross-sectional study. J Oral Rehabil 2010;37:313–321.
10. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and fibromyalgia syndrome. Pain 2009;147:72–83.
11. List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: A case-control study. Pain 2009; 139:333–341.
12. Eliav E, Gracely RH, Nahlieli O, Benoliel R. Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain 2004;18:339–344.
13. Juhl GI, Jensen TS, Norholt SE, Svensson P. Central sensitization phenomena after third molar surgery: A quantitative sensory testing study. Eur J Pain 2008;12:116–127.
14. Kazkayasi M, Ergin A, Ersoy M, Bengi O, Tekdemir I, Ethan A. Certain anatomical relations and the precise morphometry of the infraorbital foramen-canal and groove: An anatomic and cephalometric study. Laryngoscope 2001; 111:609–614.
15. Kazkayasi M, Ergin A, Ersoy M, Tekdemir I, Ethan A. Microscopic anatomy of the infraorbital canal, nerve and foramen. Otolaryngol Head Neck Surg 2003;129:692–697.
16. Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede RD. Neurogenic hyperalgesia versus painful hypoalgesia: Two distinct mechanisms of neuropathic pain. Pain 2002;96:141–151.
17. Chan AW, MacFarlane IA, Bowsher D, Campbell JA. Weighted needle pinprick sensory thresholds: A simple test of sensory function in diabetic peripheral neuropathy. J Neurol Neurosurg Psychiatr 1992;55:56–59.
18. Greenspan JD, McGillis SL. Thresholds for the perception of pressure, sharpness, and mechanically evoked cutaneous pain: Effects of laterality and repeated testing. Somatosens Mot Res 1994;11:311–317.

19. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 1999;122:2245–2257.
20. Komiyama O, De Laat A. Tactile and pain thresholds in the intra- and extra-oral regions of symptom-free subjects. Pain 2005;115:308–315.
21. Fagius J, Wahren LK. Variability of sensory threshold determination in clinical use. J Neurol Sci 1981;51:11–27.
22. Goldberg JM, Lindblom U. Standardised method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. J Neurol Neurosurg Psychiatry 1979;42:793–803.
23. Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J. Cephalic muscle tenderness and pressure pain threshold in a general population. Pain 1992;48:197–203.
24. Fillingim RB, Maixner W. The influence of resting blood pressure and gender on pain response. Psychosom Med 1996;58:326–332.
25. Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pain-pressure thresholds and stimulus-response curves. J Orofac Pain 1995;9:347–356.
26. Riley JL III, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: A metaanalysis. Pain 1998;74:181–187.
27. Fillingim RB. Sex, gender, and pain: Women and men really are different. Curr Rev Pain 2000;4:24–30.
28. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259–266.
29. Ayesh EE, Jensen TS, Svensson P. Somatosensory function following painful repetitive electrical stimulation of the human temporomandibular joint and skin. Exp Brain Res 2007;179:415–425.
30. Fillingim RB, Hastie BA, Ness TJ, Glover TL, Campbell CM, Staud R. Sex-related psychological predictors of baseline pain perception and analgesic responses to pentazocine. Biol Psychol 2005;69:97–112.
31. Fillingim RB, Ness TJ, Glover TL, et al. Morphine responses and experimental pain: Sex differences in side effects and cardiovascular responses but not analgesia. J Pain 2005;6:116–124.
32. Komiyama O, Kawara M, De Laat A. Ethnic differences regarding tactile and pain thresholds in the trigeminal region. J Pain 2007;8:363–369.
33. Garcia E, Godoy-Izquierdo D, Godoy JF, Perez M, Lopez-Chicheri I. Gender differences in pressure pain threshold in a repeated measures assessment. Psychol Health Med 2007;12:567–579.
34. Fillingim RB, Maixner W. Gender differences in the response to noxious stimuli. Pain Forum 1995;4:209–221.
35. Fillingim RB, Edwards RR, Powell T. The relationship of sex and clinical pain to experimental pain responses. Pain 1999;83:419–425.
36. Fillingim RB, Maixner W, Girdler SS, et al. Ischemic but not thermal pain sensitivity varies across the menstrual cycle. Psychosom Med 1997;59:512–520.
37. Pfleeger M, Straneva PA, Fillingim RB, Maixner W, Girdler SS. Menstrual cycle, blood pressure and ischemic pain sensitivity in women: A preliminary investigation. Int J Psychophysiol 1997;27:161–166.
38. Isselée H, De Laat A, Bogaerts K, Lysens R. Long-term fluctuations of pressure pain thresholds in healthy men, normally menstruating women and oral contraceptive users. Eur J Pain 2001;5:27–37.
39. Greenspan JD, Craft RM, LeResche L, et al. Consensus Working Group of the Sex, Gender, and Pain SIG of the IASP. Studying sex and gender differences in pain and analgesia: A consensus report. Pain 2007;132:26–45.
40. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, and pain: A review of recent clinical and experimental findings. J Pain 2009;10:447–485.
41. Fillingim RB, Keefe FJ, Light KC, Booker DK, Maixner W. The influence of gender and psychological factors on pain perception. J Gender Cult Health 1996;1:21–36.
42. Otto MW, Dougher MJ. Sex differences and personality factors in responsivity to pain. Percept Mot Skills 1985;61:383–390.
43. Dougher MJ, Crossen JR, Ferraro DP, Garland R. The effects of covert sensitization on preference for sexual stimuli: A preliminary analogue experiment. J Behav Ther Exp Psychiatry 1987;18:337–348.
44. Tur E. Physiology of the skin: Differences between women and men. Clin Dermatol 1997;15:5–16.
45. Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P. Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2001;86:782–791.
46. Cairns BE, Wang K, Hu JW, Sessle BJ, Arendt-Nielsen L, Svensson P. The effect of glutamate-evoked masseter muscle pain on the human jaw-stretch reflex differs in men and women. J Orofac Pain 2003;17:317–325.
47. Gazerani P, Wang K, Cairns BE, Svensson P, Arendt-Nielsen L. Effects of subcutaneous administration of glutamate on pain, sensitization and vasomotor responses in healthy men and women. Pain 2006;124:338–348.
48. Ge HY, Arendt-Nielsen L, Farina D, Madeleine P. Gender-specific differences in electromyographic changes and perceived pain induced by experimental muscle pain during sustained contractions of the upper trapezius muscle. Muscle Nerve 2005;32:726–733.
49. Ge HY, Madeleine P, Arendt-Nielsen L. Gender differences in pain modulation evoked by repeated injections of glutamate into the human trapezius muscle. Pain 2005;113:134–140.
50. Bi R, Broutman G, Foy MR, Thompson RF, Baudry M. The tyrosine kinase and mitogen-activated protein kinase pathways mediate multiple effects of estrogen in hippocampus. Proc Natl Acad Sci 2000;97:3602–3607.
51. Gazzaley AH, Weiland NG, Mcewen BS, Morrison JH. Differential regulation of NMDAR1 mRNA and protein by estradiol in the rat hippocampus. J Neurosci 1996;16:6830–6838.
52. Wasner GL, Brock JA. Determinants of thermal pain thresholds in normal subjects. Clin Neurophysiol 2008;119:2389–2395.
53. Van Sickels JE, Zysset M, Nishioka GJ, Thrash WJ. A comparative study of normal sensibility of the inferior alveolar nerve and the infraorbital nerve. Oral Surg Oral Med Oral Pathol 1989;67:255–257.
54. Green BG, Gelhard B. Perception of temperature on oral and facial skin. Somatosens Res 1987;4:191–200.
55. Chen CC, Essick GK, Kelly DG, Young MG, Nestor JM, Masse B. Gender, side and site dependent variations in human perioral spatial resolution. Arch Oral Biol 1995;40:539–548.
56. Posnick JC, Zimbler AG, Grossman JA. Normal cutaneous sensibility of the face. Plast Reconstr Surg 1990;86:429–433.

57. Wohlert AB. Tactile perception of spatial stimuli on the lip surface by young and older adults. J Speech Hear Res 1996;39:1191–1198.
58. Andreatta RD, Davidow JH. Mechanical frequency and stimulation-site-related differences in vibrotactile detection capacity along the lip vermilion in young adults. Clin Oral Investig 2006;10:17–22.
59. Lee J, Essick GK. Spatial and gender-dependent variations in perioral pinprick sensitivity. J Dent Res 1993;72: 1206–1214.
60. James A, Essick GK, Kelly DG, Tappouni H, McGlone FP. Frequency and site-dependent variations in vibration detection thresholds on the face. Somatosens Mot Res 2000;17:349–360.
61. Edin BB, Essick GK, Trulsson M, Olsson KA. Receptor encoding of moving tactile stimuli in humans. I. Temporal pattern of discharge of individual low-threshold mechanoreceptors. J Neurosci 1995;15:830–847.
62. Halata Z, Munger BL. The sensory innervation of primate facial skin. II. Vermilion border and mucosa of lip. Brain Res 1983;286:81–107.
63. Johansson RS, Trulsson M, Olsson KA, Abbs JH. Mechanoreceptive afferent activity in the infraorbital nerve in man during speech and chewing movements. Exp Brain Res 1988;72:209–214.
64. Nordin M, Thomander L. Intrafascicular multi-unit recordings from the human infra-orbital nerve. Acta Physiol Scand 1989;135:139–148.
65. Kemler MA, Schouten HJ, Gracely RH. Diagnosing sensory abnormalities with either normal values or values from contralateral skin: Comparison of two approaches in complex regional pain syndrome I. Anesthesiology 2000;93:718–727.