Assessment of trigeminal nerve functions by quantitative sensory testing in patients and healthy volunteers

Sareh Said Yekta, DDS,1,2 Ralf Smeets, MD, DDS,3,4 Jamal M Stein, DDS,2 and Jens Ellrich, MD, Dr. med. habil.,1

(1) Medical Physiology & Experimental Pharmacology Group,
Department of Health Science and Technology, Medical Faculty,
Aalborg University, Denmark
(2) Department of Conservative Dentistry, Periodontology and Preventive Dentistry, Aachen University, Germany
(3) Interdisciplinary Center for Clinical Research, Aachen University, Germany
(4) Department of Oral and Maxillofacial Surgery, Aachen University, Germany

Corresponding author:

Jens Ellrich, MD, Dr. med. habil.
Professor of Medical Physiology
Medical Physiology & Experimental Pharmacology Group
Center for Sensory-Motor Interaction
Department of Health Science and Technology
Medical Faculty, Aalborg University
Fredrik Bajers Vej 7D2
DK-9220 Aalborg, Denmark
phone ++45-9940-9896, fax ++45-9815-4008
e-mail jellrich@hst.aau.dk
Abstract

Purpose: Orofacial sensory dysfunction plays an important role in oral and maxillofacial surgery. Quantitative sensory testing (QST) is a psychophysical approach to evaluate thermal and mechanical somatosensation.

Patients and Methods: The present human study (1) collected normative QST data in extraoral and intraoral regions, (2) analyzed effects of age, sex, and anatomical sites on QST, and (3) applied QST in 11 patients with iatrogenic inferior alveolar nerve lesions. Sixty (30 male and 30 female) healthy volunteers were tested bilaterally in the innervation areas of infraorbital, mental, and lingual nerves. Ten patients with sensory disturbances in innervation areas of mental nerve were investigated 1 week, 4 weeks, and 8 weeks after surgery. Another patient with a complete sensory loss after surgery was repetitively tested within 453 days after primary surgery (dental implant) and subsequent surgical reconstruction of the inferior alveolar nerve by autologous graft.

Results: Older subjects were significantly less sensitive than younger subjects for thermal parameters. Thermal detection thresholds in infraorbital and mental regions showed higher sensitivity in women. Sensitivity to thermal stimulation was higher in infraorbital region than in mental and lingual regions. QST monitored somatosensory deficits and recovery of inferior alveolar nerve functions in all patients.

Conclusions: Age, sex, and anatomical region affect various QST parameters. QST might be useful in the diagnosis of inferior alveolar nerve disorders in patients. In dentistry monitoring of afferent nerve fiber functions by QST might support decisions on further interventions.
Temporary and permanent inferior alveolar nerve damages from lower third molar extraction or other maxillofacial interventions are recognized complications of oral surgery\(^1\)\(^-\)\(^4\). Injury varies in severity but often results in loss of sensory function in the lower lip and chin, which may compromise talking, drinking, and eating\(^5\).

Trigeminal nerve damage can lead to chronic pain syndromes\(^6\)\(^,\)\(^7\). An investigation evaluated a population of patients with chronic orofacial pain and found a history of previous oral and maxillofacial surgical procedures in 32% of the patients. Surgical intervention clearly exacerbated pain in 55% of the patients who had undergone surgery\(^6\). The important prerequisite for successful management of nerve injury is an accurate diagnosis. The diagnosis of sensory neuropathy and the evaluation of its recovery are usually based on clinical sensory testing such as sharp-blunt discrimination\(^8\).

Sensory dysfunction in man can be objectively quantified by electrophysiological recordings of trigeminal somatosensory evoked cortical potentials\(^9\)\(^-\)\(^12\) and brainstem reflexes\(^13\)\(^-\)\(^16\) after stimulation of extraoral and intraoral sites. Brain imaging studies such as functional magnetic resonance imaging are able to assess sensory functions as well\(^17\)\(^-\)\(^19\). These methods are complex and very time-consuming and, therefore, seem not be appropriate in clinical routine.

Quantitative sensory testing (QST) is a non-invasive method and has emerged as a useful tool in the assessment of sensory nerve damage in patients\(^20\)\(^-\)\(^24\). Whereas most studies addressed sensory processing in the spinal system only a few focused on the orofacial region\(^25\)\(^-\)\(^28\). Due to different methods of sensory testing, comparison of various results seems to be quite difficult. Recently, a standardized
QST battery has been developed that consists of 13 thermal and mechanical parameters. This QST approach has been used in the face as well.\textsuperscript{23,29,30}

The present study applied and partly adapted the standardized QST battery to extraoral and intraoral orofacial regions. In terms of special requirements in dentistry differences between extraoral and intraoral sites were addressed. Normative data were collected and possible effects of age and sex were analyzed. As an application of normative QST data, the function of different nerve fibers in 11 patients with sensory disturbances after oral surgery was investigated and the sensory recovery was monitored.
Patients and Methods

Healthy volunteers

Orofacial sensory functions were investigated by psychophysical means in 60 healthy volunteers (30 male, 30 female) covering an age range between 19 and 62 yr (female: 38.4±9.1 yr, male: 39.9±10.3 yr; mean±standard deviation). Exclusion criteria were as follows: previous orofacial injuries, neurological or psychiatric history, diabetes, and medication within 48 h. All participants gave their informed consent prior to their inclusion in the study according to the 1964 Declaration of Helsinki (as amended by the 59th General Assembly, 2008; www.wma.net). The protocol was approved by the local ethics committee.

Thermal and mechanical detection and pain thresholds were determined by the quantitative sensory testing protocol (QST) that consisted of 13 parameters: CDT, cold detection threshold; WDT, warm 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; ALL, allodynia; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

Quantitative Sensory Testing, QST

Thermal stimuli were applied by a computer controlled Peltier type thermode with a stimulation area of 16x16 mm² (TSA-II, medoc Ltd., Israel). Starting from a baseline of 32°C, temperature decreased or increased by 1°C/s in order to determine CDT, WDT, CPT, and HPT. Volunteers were asked to press a computer mouse button as soon as they perceive the corresponding cold, warm, cold pain,
or heat pain sensation. After indicating perception, temperature of the thermod returned back to baseline. The range of stimulation temperatures was between 0°C and 50°C. CDT and WDT were specified as difference temperatures (dT) from baseline (32°C), CPT and HPT were defined as absolute temperatures (°C). Due to the common definition of CDT as a temperature difference, CDT values were negative. Thus, increase of absolute value (less negative) corresponded to an arithmetic increase of CDT and vice versa. Therefore, a decrease of CDT (more negative value) corresponded to a decrease of cold sensitivity and vice versa. Arithmetic means of thermal thresholds were calculated from three separate temperature ramps each. Additionally, TSL was determined by alternating warm and cold stimuli. From the 32°C baseline, temperature increased until the indication of warm perception by the subject caused a decrease of temperature down to a cold perception and vice versa. This alternating stimulus series was repeated three times from warm to cold perception and from cold to warm perception. The mean difference between temperatures causing warm and cold perceptions was defined as TSL. In the same test, possible paradoxical heat sensations (PHS, a subjective feeling of heat upon cooling) during cold stimuli were registered.

MDT was measured with modified von Frey filaments with forces of 0.08, 0.2, 0.4, 0.7, 1.6, 4, 6, 10, 14, 20, 40, 60, 80, 100, 150, 260, 600, 1000, 1800, 3000 mN, (Touch-Test Sensory Evaluators, North Coast Medical, CA, U.S.A.). Custom-made weighted pinprick stimulators with forces of 8, 16, 32, 64, 128, and 256 mN and a contact area of about 0.2 mm diameter were applied in order to measure MPT. MDT and MPT were determined by the method of limits starting with a clearly noticeable filament of 16 mN and a usually non painful pinprick stimulator of 8 mN,
respectively\textsuperscript{31}. MDT and MPT were defined as the geometric mean of five series of descending and ascending stimulus intensities. MPS and ALL were acquired by a series of 30 pinprick stimuli and 15 light tactile stimuli in a pseudo-randomized order. Six different pinprick stimuli (8 to 256 mN, see above) were applied five times each. Light tactile stimulations were performed by a cotton wisp (about 5 mN), a cotton wool tip fixed to an elastic strip (about 100 mN), and a brush (about 200 to 400 mN; SENSELab\textsuperscript{TM} Brush 05, SOMEDIC, Sweden). These three light tactile stimuli were applied three times each (single stroke of 1 to 2 cm length) intermingled with pinpricks. Subjects were asked to rate sensory sensations on a numerical scale: 0 defined as “no pain”, 1 to 100 defined as “painful”, 100 defined as “maximum imaginable pain”. Stimulus-response-functions for MPS were calculated as geometric means of individual ratings. The wind-up phenomenon was acquired by applying a single pinprick stimulus (128 mN, see above) and a subsequent series of 10 pinprick stimuli with an interstimulus interval of 1 s within a skin area of about 1 cm\textsuperscript{2}. The subjects gave one pain rating each for the single stimulus and for the complete 1 Hz stimulation series on a numerical rating scale (cf. MPS, see above). This procedure was performed five times. The mean pain rating of trains divided by the mean pain rating to single stimuli was calculated as WUR.

Vibration stimuli were applied by a 64 Hz Rydel-Seifer tuning fork (OF033N, Aesculap, Tuttlingen, Germany) that was placed over maxilla (infraorbital nerve area) or mandible (mental nerve area). Threshold measurement was performed three times on one side starting with maximum vibration amplitude. As soon as the subject indicated disappearance of vibratory sensation the threshold was read on
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a scale ranging from 0/8 to 8/8 (steps of 1/8). VDT was defined as the arithmetic mean of three runs.

As PPT has to be conducted on the masticatory muscles, for the infraorbital and mental region it was determined by stimulation of the masseter muscle with a force gage device (FDN 200, Wagner Instruments, U.S.A.). The stimulator had a circular probe of 1.1 cm diameter that exerted pressures up to 2000 kPa. Pressure was increased with 50 kPa/s until deep muscle pain was evoked. PPT was defined as arithmetic mean of three stimuli.

Healthy subjects were tested bilaterally in innervation areas of infraorbital nerve (hairy skin, upper lip), mental nerve (hairy skin, lower lip), and lingual nerve (glabrous skin, anterior lateral two-thirds of the tongue). In 30 healthy volunteers each, QST started on right or left side.

QST data in all regions on both sides were obtained within one experimental session, which took ~ 2 1/2 h, including a demonstration of each test at a practice area. Subjects were lying on a couch kept their eyes closed throughout the QST procedure. In 20 volunteers QST started in the innervation areas of the infraorbital nerve, in 20 volunteers in the mental and in 20 participants in the lingual region. All investigations were performed by the same trained examiner.

In infraorbital and mental regions all 13 parameters were determined: CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, MPS, ALL, WUR, VDT, PPT. On the tongue QST protocol was adapted to seven parameters: CDT, WDT, TSL, PHS, CPT, HPT and MDT.
Patients

Eleven patients (6 female: 42.8±9.6 yr, 5 male: 39.5±8.4 yr) were tested in innervation areas of mental nerves (hairy skin, lower lip) following different interventions in oral surgery (impacted mandibular third molar surgery, implant insertion, augmentation of the mandible; Tab. 3). All of them were without any medication within 48 h. Other exclusion criteria were diabetes, neurological and psychiatric diseases. Ten patients were examined 1, 4 and 8 weeks after surgery. QST in innervation areas of the affected mental nerves (test areas) was intraindividually compared to the unaffected mental nerve (control area) and interindividually to normative data.

All patients were asked to identify the type of sensory dysfunction in the lower lip (Tab. 3), such as paresthesia (an abnormal sensation that is not unpleasant), dysesthesia (an abnormal sensation that is considered to be unpleasant), hypoesthesia (decreased sensitivity), or anesthesia (complete absence of sensory function) as defined by the International Association for the Study of Pain (IASP; www.iasp-pain.org).

Patient 11 was a 59 years old woman who had been referred to the University hospital by her dentist for surgical treatment of an extremely atrophic mandible. It was decided to perform a bony augmentation of the mandible and additionally to insert dental implants for an over denture on a bar construction. Within the surgery both mental nerves were injured. After surgery the patient reported a complete numbness of the chin on both sides, indicating injury of right and left mental nerves.
QST in innervation areas of left and right mental nerves (test areas) was compared to innervation area of unaffected right infraorbital nerve (control area) and to normative data. QST was repeatedly performed on days 12, 61, 106, 182, 217, 267, 315, 453 postoperatively.

All patients underwent the same QST parameters as the control group (CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, MPS, ALL, WUR, VDT, PPT).

**Statistics**

Data evaluation resembled the standardized protocol of the German Research Network on Neuropathic Pain\textsuperscript{23,30}. According to sex and age (younger and older than the median age of approx. 39 yr) the total group was divided into four equal subgroups and normative data were established for every subgroup. Intraindividual side-to-side comparisons of QST parameters were performed by paired t-test and Wilcoxon signed rank test. Data for right-left comparisons were calculated by subtracting QST data of the one side from the other side for each individual subject and orofacial region. Upper limits of side-to-side calculations were defined as the 95% confidence interval (mean+1.96xSD). As patient 11 suffered from bilateral mental nerve lesions (test areas), intraindividual comparison of QST parameters was performed with the unaffected infraorbital nerve area (control area). Normative data for right-left comparisons could not be used in that patient. For this purpose, data for maximum infraorbital-to-mental differences were calculated by subtracting corresponding QST data from each other for all female healthy volunteers older than 38 years (n=15). Upper limits of infraorbital-to-mental differences were defined as 95% confidence interval (mean+1.96xSD).
Correlations between threshold and age were analyzed by Spearman rank order correlation. Possible differences between different regions were analyzed as well. For all thermal QST parameters and MDT, which were performed in innervation areas of infraorbital, mental and lingual nerves, Friedman Repeated Measures ANOVA (Chisquare=$X^2$, p value) and subsequent Student-Newman-Keuls test (q, p value) were performed. MPT, MPS, VDT, and WUR were assessed in innervation areas of infraorbital and mental nerves, these parameters were compared by Wilcoxon signed rank test (w, p value). T-test and Mann-Whitney rank sum test were applied to analyze differences between male and female. For all QST parameters in patients, varieties between control and test sides and different time points were compared using Friedman Repeated Measures ANOVA (Chisquare= $X^2$, p value) and subsequent Student-Newman-Keuls test (q, p value). Level of significance was set to p<0.05. Statistical analysis was performed by the Software SigmaStat 3.0 (SPSS Inc., U.S.A.).
Results

QST was performed in 60 healthy volunteers on both sides (left, right) on hairy skin of upper and lower lips (extraoral), and on anterior lateral two-thirds of the tongue (intraoral).

Age dependency

Many QST parameters were age-related (Spearman rank order correlation). In infraorbital region, CDT ($r=-0.27$, $p<0.01$) decreased with age (more negative values), demonstrating impairment of cold sensitivity with increasing age. TSL ($r=0.22$, $p<0.05$) and WUR ($r=0.20$, $p<0.05$) increased with age. In the mental region, CDT ($r=-0.31$, $p<0.001$) and VDT ($r=-0.25$, $p<0.01$) negatively correlated and TSL ($r=0.19$, $p<0.05$) positively correlated with age. In the lingual region, CDT ($r=-0.26$, $p<0.01$) negatively correlated, and WDT ($r=0.34$, $p<0.001$) and TSL ($r=0.29$, $p<0.01$) positively correlated with age. In all anatomical regions, parameter correlations demonstrated impairment of sensory function with increasing age.

Differences between test areas (Fig. 1)

Significant differences between test areas were shown for CDT, WDT, TSL ($X^2=142.5$, $p<0.001$), CPT, and HPT. MDT on the tongue differed from mental and infraorbital regions. Thus, thermal sensitivity was higher over upper lip, followed by lower lip and tongue. Differences between test areas could also be assessed for MPT ($w=-1788$, $p<0.01$) (Fig. 1).
Sex related differences (Fig. 2)

Results from 30 female and 30 male healthy volunteers were compared in order to test for sex differences. WDT, TSL, and MPT in the infraorbital region and WDT, and TSL in the mental region were significantly lower in women than in men (at least p<0.05). In both regions, CDT was significantly higher in women than men (at least p<0.05; corresponding to higher cold sensitivity). In the mental nerve area, CPT was higher in female than in male volunteers (p<0.05). In the lingual region, only HPT showed a sex-related difference with a significantly lower value in women (p<0.01). PPT was significantly lower in women than men (p<0.001). In conclusion, sex-related dependency in thermal and mechanical parameters indicated that women tended to be more sensitive than men (Fig. 2).

Side-to-side differences (Tab. 1, 2)

In healthy volunteers left and right sides showed corresponding values in all parameters and in all regions (paired t-test, Wilcoxon signed rank test). Therefore, data from both sides were combined in order to calculate absolute reference data (Tab. 1). Lower and upper limits of QST parameters and corresponding maximum side-to-side differences were calculated as 95% confidence interval. Due to above mentioned influences of sex, age, and anatomical region on QST parameters, normative data were separately calculated for women and men, for age younger than 39 and older than 38, and for infraorbital, mental, and lingual regions (Tab. 1, 2).
**Patient’s data**

Eight patients out of patients 1 to 10 identified paresthesia on week 1 postoperative (Tab. 3). On week 4 postoperative all patients reported complete recovery with normal sensory function. One week postoperative, mean values of the control side were all in normal range as compared to normative data (Tab. 4). Significant differences between control and test side were shown for CDT, WDT, TSL, HPT, MDT and VDT (Fig. 3). Four weeks postoperative, CDT, WDT and MDT on the test side improved, but the differences between the test side and the control side were still significant. TSL, HPT and VDT achieved values within the normal range. Eight weeks postoperative, the mean values for all parameters on the test side were in normal range as interindividually compared to the normative data (Tab. 1, 4). Though, WDT showed significant intraindividual differences between the test side and the control side. Pathological side-to-side differences were not found in all parameters.

Patient 11 was the only patient reporting an anesthesia at the first examination, which was performed 12 days after primary surgery (dental implant) with iatrogenic lesions of both mental nerves (Tab. 3). Except for VDT and PPT, all parameters were incapable of measurement, as even the strongest thermal and mechanical stimulation could not get perceived by the patient. QST showed complete anesthesia 12 days after surgery in right and left mental regions. From day 61 on the strongest thermal and mechanical stimuli started to evoke first sensations in the patient, at least in the left mental nerve area. Affected mental regions were compared to the unaffected right infraorbital region. Every examination took about one our (Fig. 4).
In the left mental nerve area on day 61, QST revealed thermal hypoesthesia to innocuous cold and warm stimuli (CDT, WDT), and a mechanical hypoesthesia (MDT). At this time CPT and HPT normalized according to normative data (cf. Tab. 1). Furthermore, a mechanical hypoalgesia (MPT) established. Subsequent examinations (after 106 days until day 453) showed clear improvement of CDT and final normalization of WDT and MDT. Initial mechanical hypoalgesia (day 61) reverted to hyperalgesia (MPT) on day 106. Even lightest pinprick was classified as unbearably painful. MPT completely normalized 453 days after primary surgery (Fig. 4). Heightened TSL values aroused from elevated WDT and reduced CDT values (more negative). Normalization was achieved on day 267 (TSL: 4.4°C). Sixty one days after surgery the patient also showed pathological differences of MPS in the affected left mental region related to the unaffected infraorbital region (MPS difference: 2.0, upper limit of MPS difference: 1.4). From 106 to 315 days after surgery the performance of MPS and WUR was not possible, since the lightest pinprick was categorized as unbearably painful. These parameters showed normalization on day 453 (MPS: 2.5, WUR: 3.9). There was no allodynia in the left mental area.

In the right mental nerve area, a complete loss of thermal sensory functions and a remarkable mechanical hypoesthesia and hypoalgesia were detected on days 12, 61, and 106 after primary surgery. In contrast to the left side, QST parameters and corresponding sensory functions did not significantly improve within 106 days after surgery. Therefore, a reconstruction of the inferior alveolar nerve by autologous graft (sural nerve) was executed on day 153. Twenty-nine days after transplantation (182 d), CDT and WDT improved and CPT and HPT normalized. Examinations in time course demonstrated further improvement of CDT and WDT.
and final normalization of MDT and MPT within 453 days after primary surgery in
the right mental region (Fig. 4). According to time course of CDT and WDT,
increased TSL normalized within 453 days after primary surgery (TSL: 3.8°C). On
day 106, the patient showed pathological differences of MPS in the affected right
mental region related to the unaffected infraorbital region (MPS difference: 3.0,
upper limit of MPS difference: 1.4). There was no allodynia in the right mental
area. WUR returned to normal on day 106 (WUR: 2.1).

The first investigation on day 12 detected bilateral pallhypoesthesia (VDT left: 5.8,
VDT right: 5.5). On day 61, normalization of this parameter was achieved on left
and right mental regions (VDT left: 6.9, VDT right: 6.6). As PPT was performed on
masseter muscle, this parameter was unaffected (PPT left: 245-317 kPa, PPT
right: 245-284 kPa).

At each examination, this patient was also asked about subjective symptoms
including pain. In the beginning the patient reported numbness. 106 days after
primary surgery she complained of a concomitant feeling of slight swelling of her
chin. Although sensory function of left lower lip gradually improved as tested by
QST the patient reported on pain and dysesthesia (182 days after surgery). On
day 453 sensory functions were clearly improved or even normalized. The patient
indicated only slight paresthesia in the chin region at final QST examination.
Discussion

The applied QST protocol was developed as a comprehensive test battery for somatosensory functions across the full spectrum of primary afferents\textsuperscript{23,30}. The present study translated this standardized QST protocol into the orofacial region, collected and calculated normative data, and applied results from healthy volunteers to patients with sensory deficits.

Decreased sensitivity in the elderly in the present study corresponds to literature\textsuperscript{32-36}. Psychophysical studies revealed impaired thermal and vibration detection thresholds with increasing age due to effects of aging on density and spatial pattern of epidermal innervation\textsuperscript{37-39}. Segmental demyelination with advancing age was shown in animals\textsuperscript{40}. A reduction in number or density of myelinated fibers with aging was reported in peripheral nerves of several animal species, also involving a marked loss of large fibers\textsuperscript{41,42}. Loss of unmyelinated fibers has been denoted in peripheral nerve during the early years of life and in aged humans\textsuperscript{43}, as well as in aged mice\textsuperscript{44}.

Since mechanical thresholds were independent of age, the orofacial region seems to be highly sensitive for mechanical perception also in elderly persons. Except for WUR, there were no age-related changes concerning pain thresholds. This finding is consistent with a study, that showed changes in warmth and cold perception with increased age, but a relatively unaffected pain perception in the facial region\textsuperscript{45}. A recent review emphasizes increase of pain thresholds in elderly\textsuperscript{33}. Noticeable changes in intraoral thermal detection thresholds were shown. These results may depend on age-related atrophic changes that are due to endogenous
factors, as well as to exogenous damage. A previous study described age-related increase of tongue furrows and atrophy of papillae on the tongue\textsuperscript{46}.

Significant differences between test areas were shown for thermal detection and pain thresholds and for MDT. Differences between infraorbital and mental regions were also found for MPT. A previous study reported that mechanical detection threshold for facial skin sites were significantly higher than thresholds for the forefinger\textsuperscript{47}. Another study used an earlier Peltier device to examine orofacial thermal sensibility in subjects with burning mouth syndrome, and reported that the infraorbital area was most thermally sensitive, followed by the tongue tip\textsuperscript{48}. Tactile detection sensitivity, spatial acuity, and sensitivity to warmth were greater on skin sites located on the midface than on the lower face\textsuperscript{49}. Differences within intraoral regions were demonstrated. Sensory innervation of the hard palate of the rhesus monkey was found most richly in the papilla incisiva and first rugae palatinae\textsuperscript{50}. In addition, present results demonstrated highest difference in thermal thresholds between intraoral tongue mucosa and facial hairy skin. These results are possibly due to differences in innervation. Observed differences between various regions could illustrate the variability of tested afferents and their density. Region variation in thermal sensitivity may include differences in the type of orofacial thermal receptors or their localization in tissues\textsuperscript{51}. There are some factors that are known to influence sensitivity, such as medical factors, neurological diseases and injuries. These factors were excluded in this study. In agreement to a prior study, present findings confirm poor lingual temperature processing as compared to orofacial hairy skin in healthy subjects\textsuperscript{25}. 
Differences in thresholds over various orofacial areas indicate that region-specific normative data are necessary for all parameters, and that knowledge of spatial variation pattern is required to select control skin sites for comparison with areas of neurosensory impairment. This is most notably important, if impairments are bilateral and different areas have to be compared.

Differences in methods and QST protocol can cause discrepancies between the different studies. The present study demonstrated that this standardized QST protocol is at least partly qualified for the orofacial region.

Due to missing significant side-to-side differences right–left comparisons in patients seem to be relevant to detect positive or negative sensory signs.

In agreement to prior studies, women were more sensitive than men for many QST parameters\textsuperscript{52-54}. In present data, pronounced sex differences were present on extraoral sites for all thermal detection thresholds corresponding to previous findings\textsuperscript{55}. Female and male skin may vary regarding physical properties, it has been pointed out that female skin appears to have a higher elasticity and extensibility\textsuperscript{56}. In the present study, males showed a significant higher HPT (lingual region), MPT (infraorbital region) and PPT, and a significant lower CPT (mental region) than female, which indicate that women are more sensitive than men in these parameters. Previous studies demonstrated that female subjects rated experimental pain higher than male subjects\textsuperscript{54,57}. These findings may base upon psychosocial sex differences concerning pain perception and expression. Several biological factors may also influence sex differences\textsuperscript{58-60}, hormonal changes during menstrual cycle are supposed to affect sensory and pain perception\textsuperscript{61}.
The results in patients show that a complete sensory recovery of the alveolar inferior nerves was achieved within 8 weeks after surgery. This is in agreement with other studies, which show that the pure demyelinating injuries recover completely in 2 to 4 months\textsuperscript{62,63}, whereas finding of incomplete sensory recovery were presented at 1 year in 73% of the nerves with axonal injury\textsuperscript{63}. However, there is a possibility that postoperative injury such as edema and compression may have occurred in some of the nerves.

The results show that WDT improved slower than other tests, this parameter reflects the function in small unmyelinated C fibers and may indicate that damage to C-fibers is a negative prognostic factor. This is in agreement to a prior study, which showed that the unmyelinated axons in the rat saphenous nerve takes longer to resupply the skin than the myelinated fibers (Lisney SJ, Functional aspects of the regeneration of unmyelinated axons in the rat saphenous nerve, J Neurol Sci. 1987 Sep;80(2-3):289-98.). CDT reflects the function in small myelinated A\textdelta fibers and MDT, the large myelinated A\beta fibres. In contrast to WDT, MDT and CDT recovered quickly. These findings do not correlate with a study, where the improvement of function in small unmyelinated nerve fibres came within 6 weeks, but the improvement of function in small myelinated fibres was not found before 12 months after surgery (Nygaard OP, Kloster R, Meilgren SI, Recovery of sensory nerve fibres after surgical decompression in lumbar radiculopathy: use of quantitative sensory testing in the exploration of different populations of nerve fibres. Journal of Neurology Neurosurgery and Psychiatry 1998;64(1):120-3). These different results may be due to the different testing areas and testing methods.

The results in patients show that QST can offer a possibility for accurate in vivo elucidation of human sensory regeneration after nerve lesions.
In patient 11, application of von Frey filaments in order to assess MDT documented complete anesthesia in both mental nerve areas. At the same time patient’s vibration perception was reduced but not abolished (pallhypoesthesia, see above). This apparent contradiction may be due to mechanical conduction of vibration from mandible to maxilla via the temporomandibular joint. The results show that WDT improved slower than other tests, in contrast to WDT, MDT normalized quickly on the left side. MDT and VDT were able to detect dysfunctions mediated by Aβ fibers, which recovered within 3 to 4 months. The other parameters were able to perceive dysfunctions of Aδ and C fibers, which recovered slower. In short, QST in the patient was able to document the sensory alteration and the recovery up to 453 days after primary surgery. The case report might force future studies in order to assess whether orofacial QST can support diagnosis and monitoring of nerve fiber lesions and regeneration.

QST parameters of the right mental side did not significantly improve within 106 days after surgery. The reconstruction of the inferior alveolar nerve by sural nerve showed a clear improvement, showing that surgery, when indicated, must be based on a specific diagnosis that is amenable to surgical therapy. Regeneration of the right mental nerve was not complete 271 days after surgery. This finding is similar to that of a study on total median nerve transection in monkeys, where only incomplete functional recovery occurred after repair. In the present patient, a complete sensory recovery was achieved 453 days in the left mental region after surgery. The pure demyelinating injuries recover completely in 2 to 4 months, whereas finding of incomplete sensory recovery were presented at 1 year in 73% of the nerves with axonal injury.
In conclusion, somatosensory nerve fiber functions can be assessed in extraoral and intraoral sites by QST. QST parameters depend on age, sex, and innervation area. The presented study applied normative data and hopefully facilitates future studies on the role of QST in diagnosis and monitoring of orofacial nerve fiber dysfunctions. The next step will be using QST in extraoral and intraoral regions following different interventions in oral and maxillofacial surgery. As this QST battery takes 30 minutes of testing (per region, unilaterally), it is still too time-consuming to realize an integration into clinical practice. Therefore, the extent of the testing battery should be reduced without affecting the informative value of the measurement.
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Figure Legends

**FIGURE 1A to F.** Influence of anatomical region on somatosensation.
A) Cold detection threshold (CDT), B) warm detection threshold (WDT), C) cold pain threshold (CPT), D) heat pain threshold (HPT), E) mechanical pain threshold (MPT), and F) mechanical detection threshold (MDT) from 60 experiments in 60 healthy volunteers (30 women, 30 men). CDT and WDT are given as differences from baseline (32°C; dT). CPT and HPT are defined as absolute temperatures (°C). Data on infraorbital region (white), mental region (light gray) and lingual regions (dark gray) are presented as box plots (solid line: median, dashed line: arithmetic mean). Significant spatial differences are indicated by asterisks (*: p<0.05, **: p<0.01; Friedman Repeated Measures ANOVA, followed by Student-Newman-Keuls test). Data for MPT were analyzed for spatial differences by Wilcoxon signed rank test (**: p<0.01).

**FIGURE 2A to F.** Sex differences in orofacial somatosensation.
A) Cold detection threshold (CDT), B) warm detection threshold (WDT), C) cold pain threshold (CPT), D) heat pain threshold (HPT), E) mechanical pain threshold (MPT), and F) pressure pain threshold (PPT) were determined from 60 QST experiments in 60 healthy volunteers (30 women, 30 men). CDT and WDT are given as differences from baseline (32°C; dT). CPT and HPT are defined as absolute temperatures (°C). Data on female (white) and male (gray) are presented as box plots (solid line: median, dashed line: arithmetic mean). Significant sex differences are indicated by asterisks (*: p<0.05, **: p<0.01, ***: p<0.001; t-test and Mann-Whitney rank sum test).
FIGURE 3A to F. Monitoring of sensory thresholds in 10 patients after oral surgery.
A) Cold detection threshold (CDT), B) warm detection threshold (WDT), C) thermal sensory limen (TSL), D) heat pain threshold (HPT), E) mechanical detection threshold (MDT), and F) vibration detection threshold (VDT) were determined from 30 QST experiments in 10 patients (5 women, 5 men). CDT and WDT are given as differences from baseline (32°C; dT), TSL as mean difference between temperatures causing warm and cold perceptions. HPT is defined as absolute temperatures (°C). Data on control area (white, con) and test areas (gray, t-1: one week, t-4: 4 weeks, t-8: 8 weeks after surgery) are presented as box plots (solid line: median, dashed line: arithmetic mean). Significant differences are indicated by asterisks (*: p<0.05; Friedman Repeated Measures ANOVA and subsequent Student-Newman-Keuls test). Asterisk above the box plots show significant differences compared to the control area, n.s: not significant.

FIGURE 4A to F. Long-term monitoring of iatrogenic nerve lesion in patient 11. Recovery of QST parameters in innervation areas of left (A, B, C) and right (D, E, F) mental nerve in one patient after primary surgery (dental implant, day 0) and subsequent surgical reconstruction of the inferior alveolar nerve by autologous graft of the sural nerve (day 153). Eight investigations were performed on days 12, 61, 106, 182 (29 days after sural nerve transplantation as reconstruction of the right inferior alveolar nerve), 217, 267, 315 and 453 after primary surgery in one patient (women, 59 yr). Affected innervation areas of left and right mental nerves (gray bars) were compared to innervation area of the unaffected right infraorbital nerve area (white bars). Dotted lines mark normative data according to Table 1. A, D: Cold detection threshold (CDT), warm detection threshold (WDT). CDT and
WDT are given as differences from baseline (32°C; dT). B, E: Cold pain threshold (CPT), heat pain threshold (HPT). C, F: Mechanical pain threshold (MPT), mechanical detection threshold (MDT).