ACTA ODONTOLOGICA SCANDINAVICA, 2018
VOL. 76, NO. 1, 13–20
https://doi.org/10.1080/00016357.2017.1375554

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REVIEW ARTICLE

Quantitative sensory testing for assessment of somatosensory function in human oral mucosa: a review

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ABSTRACT

Objective: This narrative review provides an overview of the quantitative sensory testing (QST) to assess somatosensory function in human oral mucosa.

Material and methods: A literature search was conducted in the PubMed database to identify studies *in vivo* on human oral mucosa using QST methods. A list of 149 articles was obtained and screened. A total of 36 relevant articles remained and were read in full text. Manual search of the reference lists identified eight additional relevant studies. A total of 44 articles were included for final assessment.

Results: The included studies were divided into six categories according to the study content and objective. In each category, there was a great variety of aims, methods, participants and outcome measures. The application of QST has nevertheless helped to monitor somatosensory function in experimental models of intraoral pain, effects of local anesthesia, after oral and maxillofacial surgery and after prosthodontic and orthodontic treatment.

Conclusions: QST has been proved to be sufficiently stable and reliable, and valuable information has been obtained regarding somatosensory function in healthy volunteers, special populations and orofacial pain patients. However, as most of the studies were highly heterogeneous, the results are difficult to compare quantitatively. A standardized intraoral QST protocol is recommended and expected to help advance a mechanism-based assessment of neuropathies and other intraoral pain conditions.

ARTICLE HISTORY
Received 1 September 2016
Revised 14 August 2017
Accepted 24 August 2017

KEYWORDS
Intraoral model; oral mucosa; pressure pain threshold; quantitative sensory testing

Introduction

In humans, several kinds of sensory systems enable perception, for example, vision, audition, proprioception, somatosensation, taste and smell [1]. Just like the cutaneous somatosensory system, the oral mucosa can be regarded as a highly developed and specialized sensory system [2]. Besides gustatory stimuli, the oral mucosa can respond to mechanical, thermal and nociceptive stimuli constituting the somatosensory function [3].

Loss of somatosensory function is often a complication to nerve damages but may be difficult to diagnose if only based on the patient's response and report due to the inherent challenges to precisely describe the extent and magnitude [3]. Several approaches can reveal objective information such as somatosensory evoked potentials (SEPs), functional magnetic resonance imaging (fMRI) and blink reflexes (BR). Though each of them has some merits, there are some problems of their application to the oral mucosa. The SEPs provide information on the transmission of neural impulses and their projection to the cerebral cortex [3] and are routinely used in clinical practice for the assessment of neurological disorders [4]. SEPs can also be recorded with stimulation of the oral tissues and can yield information about the trigeminal somatosensory system; however, SEPs from the trigeminal braches are, in contrast to those recorded from limbs, weak (small amplitude) and difficult to discriminate from the background noise [5]. fMRI can provide a unique image of the pattern of activity within the central nervous system during stimulation of peripheral receptors [3], but the main disadvantage of it includes the relative long imaging time (compromising the temporal resolution), the potential hazard imposed by the presence of ferromagnetic material in the vicinity of the imaging magnet and the potential risk of claustrophobia [6]. Due to costs, practical and technical issues, it is unlikely that SEPs and fMRI will become routine examinations in cases with trigeminal nerve damage and impaired somatosensory function in the oral mucosa [3]. Furthermore, the BR is evoked by electrical stimulation of the trigeminal cutaneous or oral mucosal nerve branches and can be used in the diagnosis of brainstem pathology or peripheral trigeminal neuropathy [7,8]. However, the BR mainly

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Supplemental data for this article can be accessed here.

examines the function of large myelinated nerve fibers and thus does not exclude possible somatosensory dysfunction due to thin fiber pathology [8]. It is still debated if a special electrode configuration can help to more selectively stimulate nociceptive afferent fibers and trigger a 'nociceptive-specific BR' [9–11].

Besides objective approaches, somatosensory function can also be evaluated by psychophysical methods [3]. These methods allow a 'proxy' or indirect measure of the relation between the physiological functions of the receptors and afferent fibers versus the subjective experience of the individual; one useful psychophysical method for the assessment of somatosensory function is known as quantitative sensory testing (QST) [12,13]. QST is considered to represent a useful, noninvasive method to assess both loss and gain of somatosensory function by quantification of the perceptual responses to systematically applied and quantifiable stimuli [14]. It can provide information regarding large myelinated A-beta, thinly myelinated A-delta and small unmyelinated C fiber function, and their corresponding central pathways, complimenting clinical neurophysiological studies (e.g. nerve conduction) that can only assess sensory large fiber function and helping to identify putative mechanisms underlying pathologic pain conditions [13]. In clinical practice, QST is to apply quantitative stimuli (temperature, mechanical, electrical and chemical) to a variety of tissues (e.g. skin, muscle and viscera), and using psychophysical methods such as threshold determination or establishing stimulus-response function to assess the function and integrity of the somatosensory system (Table 1). However, similar to other psychophysical methods, QST requires the active participation of the individual, and so, it lacks the objectivity of traditional approaches [12,13]. Yet, when carried out in a strictly standardized condition, this method is reliable to assess sensory nerve function [13,15,16]. In the last decade, the German Research Network on Neuropathic Pain (DFNS) compiled a comprehensive QST protocol using well-established tests for nearly all aspects of somatosensation to provide parameters for sensory loss and sensory gain. This proposal contains 13 parameters in seven test procedures that encompass thermal and mechanical testing procedures and provides a comprehensive assessment of somatosensory function for both cutaneous and deep pain sensitivity [17].

For completeness, it should also be mentioned that lasers, for example, CO_2 and argon lasers have been applied as sources of noncontact thermal stimulation of the oral mucosa and used to assess sensory and pain thresholds in healthy individuals as well as in patients with burning mouth syndrome [18–21]. In addition to providing a more pure thermal stimulus without simultaneously touching the oral mucosa, the lasers have the distinct advantage that evoked potentials can be recorded in the electroencephalogram due to the short-lasting duration (ms) and high degree of synchronization needed for the analyses of a time-locked biological signal [22,23].

This article is to provide an overview of the studies using QST to assess somatosensory function in the human oral mucosa in order to get a comprehensive understanding of the application of QST. For the limited space, studies using laser stimuli are not covered in detail in the article.

Table 1. Summary of information related to assessment of different peripheral and central somatosensory channels.

Type of stimulus	Peripheral sensory channel	Central pathway	QST
Thermal			
Cold	Aδ	Spinothalamic	Computer-controlled
Warmth	C	Spinothalamic	thermal testing device
Heat pain	C, Aδ	Spinothalamic	
Cold pain	C, Aδ	Spinothalamic	
Mechanical			
Static light touch	Aβ	Lemniscal	Calibrated vFrey hairs
Vibration	Aβ	Lemniscal	Vibrameter
Brushing	Aβ	Lemniscal	Brush
Pinprick	Aδ, C	Spinothalamic	Calibrated pins
Blunt pressure	Aδ, C	Spinothalamic	Algometer

Adapted from Hansson et al. [12].

Material and methods

This review was based on a literature search in PubMed database. The search strategies are shown in Table 2. Inclusion criteria were articles published in English from January 1960 to January 2017; clinical trials and studies *in vivo* on human oral mucosa using QST methods refer to thermal, mechanical, electrical, ischemic and chemical stimulation. Exclusion criteria were reviews, case reports, studies *in vitro* or on animals, studies with nonquantitative testing methods such as questionnaire, inquiry and survey, studies using laser stimuli, articles about QST in oral mucosa diseases, studies using QST on skins, implants or natural teeth rather than on the oral mucosa.

For articles obtained from the database, each title and abstract were screened according to inclusion and exclusion criteria. Relevant articles were read in full text and screened again. The reference lists from each of these articles were then checked manually for additional article.

Result

A list of 149 articles was obtained from the database. After removal of duplicates and screening of the title and abstract, 57 potentially relevant articles were obtained in full text. After applying the selection criteria, 36 articles remained for assessment. Manual search of the reference lists identified eight additional relevant studies. The included studies were divided into six categories according to the study content and objective (Figure 1). Of the 44 studies included for final analysis in the present review, 11 studies were about testing methods and influencing factors of QST in the oral mucosa, five about QST of the oral mucosa in special populations, four about QST used in intraoral pain models, eight about QST applied to the oral mucosa for the assessment of local anesthesia, 13 about QST applied to the oral mucosa after oral and maxillofacial surgery and three about QST in the oral mucosa after prosthodontic or orthodontic treatment.

Table 2. Search strategies for the PubMed database.

((((((("Gingiva"[Mesh]) OR "Mouth Mucosa"[Mesh]) OR "Mouth, Edentulous"[Mesh])) OR oral mucosa)) AND ((((("Evoked Potentials, Somatosensory"[Mesh]) OR ((quantitative sensory test*) OR qst)) OR somatosensory test*) OR somatosensory profile*) and ((((((pain pressure threshold) OR pressure threshold) OR pressure algometer) OR pressure-pain threshold) OR pressure pain threshold)) AND ((((("Gingiva"[Mesh]) OR "Mouth Mucosa"[Mesh]) OR "Mouth, Edentulous"[Mesh])) OR oral mucosa) and ((((((("Hyperesthesia"[Mesh]) OR "Hyperalgesia"[Mesh]) OR "Hypesthesia"[Mesh])) OR vibratory threshold*)) AND ((((("Gingiva"[Mesh]) OR "Mouth Mucosa"[Mesh]) OR "Mouth, Edentulous"[Mesh])) OR oral mucosa)

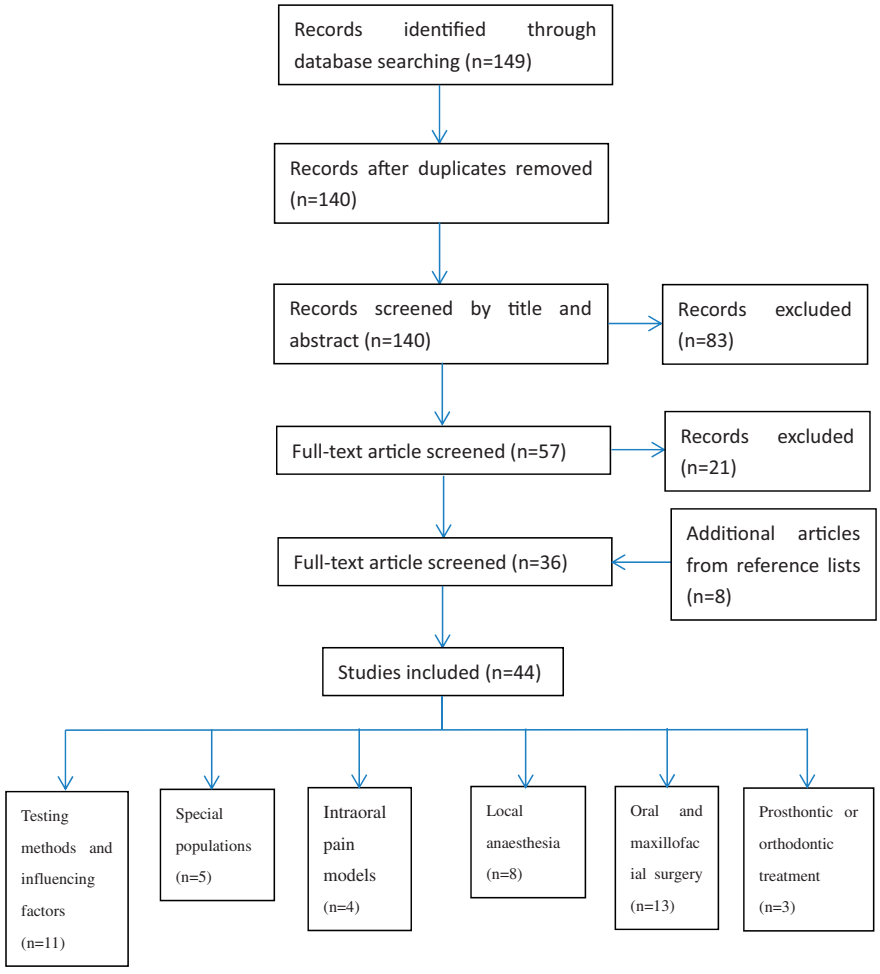

Figure 1. Summary of the study selection process and results.

Discussion

Assessment and influence of factors on QST applied to the oral mucosa

A total of 11 articles studied the testing methods and influence of factors of QST on the oral mucosa (Supplementary Table 1). The aims, materials, methods and testing sites varied widely. Six articles focused on pressure pain thresholds (PPT), one assessed the tactile detection threshold (TDT) and the filament-prick pain detection threshold (FPT), one evaluated the intraoral somatosensory mapping after mechanical stimuli, one studied the reliability of intraoral standard QST, one explored the effect of aging on the sensitivity of the oral mucosa and one compared the variability of measurements of root and mucogingival sensitivity over a 24-h period.

Pain is a common problem in the orofacial area, which poses a challenge for the clinician. One of the differences in function between the oral mucosa and the skin or other mucosal areas is the role of the oral mucosa in withstanding pressure. The oral mucosa needs to resist intermittent but high levels of pressure during functional and parafunctional behaviors, for example, mastication and clenching [24]. According to the studies focusing on PPT, in only one study, PPT was defined as the minimum pressure that induced an unpleasant sensation [25], and in other studies, it was defined as the minimum pressure that induced pain [24,26–29]. Different algometers were used to examine the PPT in the oral mucosa at different test sites, between individuals, after variable pre-loadings and to explore the effect of age, rate of application and properties of the supporting tissues. Early algometers were controlled manually, and later algometers were controlled by computers to provide better control of, for example, the pressure application rate. Though the instruments were different, some similar results were obtained. For dentate volunteers, the PPTs varied significantly between individuals but were stable in the same individual on different occasions [25], it increased linearly with an increase in the rate of applied pressure, and it was higher in

the maxilla than in the mandibular [24–26]. Palatal test sites showed a higher PPT value than the buccal and labial sites [24,27]. After preloading, the PPT of the buccal site did not change, while the PPT of the labial site decreased and the PPT of the palatal site increased [27]. Based on the anatomical landmarks of 20 dentate volunteers, Ogawa et al. [28] elaborated on the PPTs at the edentulous mucosa at 112 sites and found PPT increased from the anterior to posterior alveolus in both the maxilla and mandible but decreased from the anterior palate to the posterior palate.

The distribution feature of PPTs in the oral mucosa is partly due to the type and mechanical property of the mucosa such as thickness, elasticity, keratinization and collagen organization, while the role of the innervation patterns and receptor density has not been sufficiently tested [24,27–29].

In addition to PPTs, some other approaches have been used to investigate somatosensory function of oral mucosa. Komiyama et al. [30] assessed the TDT and the FPT in the intra-oral regions and found both parameters were lowest at the anterior tip of the tongue indicating this area was the most sensitive to tactile and painful stimulation in the orofacial region. With a custom-made silicone-based template, Lu et al. [31] evaluated intraoral somatosensory mapping in the gingivomucosal region and reported the anterior and apical regions were more sensitive than posterior and cervical regions with mechanical stimuli. Furthermore, a standardized QST protocol including 13 test measures was applied to oral mucosa, and the reliability of the comprehensive test battery has been confirmed in healthy volunteers [15]. Most intraoral tests had acceptable to excellent inter-examiner and intra-examiner reliability, and no differences were found between right and left sides [15].

Another factor that affects the mechanosensitivity of the oral mucosa is aging. Due to changes in thickness and hardness of the oral mucosa and the decrease in the number and the sensitivity of mechanoreceptors, the touch thresholds increased while the pain thresholds decreased in the elderly [29,32]. Thermal and vibration sensations may also change intraorally, but the mechanisms are more elusive. Comparison of electrical, pressure and cold stimulation showed calibrated cold stimulation on the root surface was more sensitive than pressure stimulation on the mucogingival junction at root-exposed individuals [33].

QST in patients with orofacial pain or smoking habits

In addition to healthy volunteers, QST has been used in patients with orofacial pain including odontogenic pain and intraoral neuropathic pain to assess the somatosensory disturbance at the oral mucosa. Also, the somatosensory changes in smokers and edentulous orodyskinesia were investigated with QST measures. The summary of related articles is presented in Supplementary Table 2.

Atypical odontalgia (AO) is a kind of intraoral neuropathic pain with no objective signs of pathology [34,35]. A multicenter QST study was performed in patients with AO, and somatosensory abnormalities were commonly detected [36]. Test–retest and interexaminer reliability of the comprehensive standardized QST protocol in patients with AO and healthy controls was examined in another study, and the results showed sufficient reliability for using QST in patients with somatosensory disturbances or neuropathic pain in the trigeminal region [16]. In terms of somatosensory abnormalities, AO is different from acute pulpitis; hence in order to discriminate patients with AO and acute pulpitis, some QST parameters were recommended to assist in the differential diagnosis [37]. Furthermore, higher visual analogue scale (VAS) scores of pain were found in patients with edentulous orodyskinesia in relation to their subjective denture dysfunctional index and sense of inadequate dental occlusion [38].

It has been widely accepted that smoking is an important risk factor for oral diseases and can lead to altered sense of smell and taste [39,40]. As to the effect of somatosensory changes on the tongue in smokers, Yekta et al. [41] used QST and found a reduction of thermal sensitivity by smoking in the lingual nerve distributions.

QST effects of experimental intraoral pain models

Experimental pain models play an important role in studies investigating the mechanisms of neuropathic pain, and the application of QST is hoped to elaborate on the changes in somatosensory sensitivity and underlying mechanisms [42,43]. Topical application of capsaicin is a well-described model of cutaneous pain and has been shown to produce thermal hyperalgesia within the injured zone and various forms of mechanical hyperalgesia in the non-injured surrounding zone. Menthol is an agonist of TRPM8 receptor, and topical application of menthol has been proposed as a surrogate model of cold hyperalgesia [44,45].

A total of four articles studied the experimental intraoral pain models with QST in the oral mucosa (Supplementary Table 3). All studies were performed in healthy participants and investigated the temporal aspects of somatosensory changes after the stimulation (including one on both temporal and special aspects). Different stimulations were used to establish the surrogate orofacial pain model. Topical application of capsaicin, menthol or other agents was used in three studies [42,46,47], and electrical stimulation was used in one study [48]. Outcome measurements were also different such as standardized QST parameters, VAS and numerical rating scale (NRS). Although the sample sizes were relatively small in these studies (less than 20 volunteers), all studies were randomised, placebo-controlled and at least single blinded (two studies were double blinded and two were single blinded).

According to these studies, some results were consistent with the application of capsaicin to the oral mucosa: it caused moderate levels of pain and induced hypersensitivity to warmth, heat pain and cold pain. Moreover, sensitization to heat stimuli adjacent to the application area was found in one study following the application of capsaicin [48]. However, the somatosensory changes after mechanical stimuli have been controversial: one study showed hyposensitivity with the application of capsaicin [46], and another study

found no mechanical changes with capsaicin [48]. The different concentration of capsaicin may account for this disagreement. In terms of the topical use of menthol, Lu et al. [46] reported hypersensitivity to cold and warmth stimuli with a concentration of 40%, while no difference was found in another study with a concentration of 7.5% [48].

In addition to topical application of chemical agents, painful electrical tooth stimulation is also a well-known pain model [49,50]. Baad-Hansen et al. [47] investigated the somatosensory sensitivity of the gingiva adjacent to the stimulated tooth after electrical tooth stimulation and found modest increases in gingival sensitivity to warmth, painful heat and pressure stimuli as well as desensitization to non-painful mechanical stimulation after tooth stimulation and similar thermal threshold changes after tooth stimulation below the sensory threshold.

Intraoral pain models have been used to elaborate on the potential underlying mechanisms of orofacial pain conditions. With different outcome measures, the results were difficult to compare quantitatively. Maybe further studies will be needed to provide specific recommendations on the standardized QST parameters to assist in the investigation of mechanisms of various intraoral pain conditions.

QST effects of local anesthetics and oral drugs

In contrast to experimental oral pain models, local anesthesia is commonly needed in dental practice to reduce acute and chronic pain and facilitate dental procedures [51]. Local anesthetics and oral drugs can be used for oral pain relief and the somatosensory changes after their application can be measured by QST to clarify the underlying pathophysiologic mechanisms. Eight articles involving QST after local anesthesia have been summarized in Supplementary Table 4. All the studies are randomized and double blinded, five of which are placebo-controlled, and three are without placebo. Among the studies investigating the effect of 5% EMLA, Barcohana et al. [52] found that EMLA significantly reduced the pain threshold level with 3-, 5-, and 10-min application times compared with saline. In two other studies, it was also indicated that EMLA had greater and longer anesthetic efficacy than other agents [53,54]. In one study about the effect of an oral medication (Vicodin), no difference was found between the active drug and placebo [55].

The combination of 2% lidocaine with different drugs was compared in three studies.by mechanical or temperature stimulation of the oral mucosa in different nerve distribution areas [51,56,57]. Hyaluronidase and dexmedetomidine increased the duration of the effect of lidocaine [56], and a combination of lidocaine and clonidine were similar to those obtained with lidocaine and epinephrine [51].

As QST is time-consuming, a newly developed device – an electronic von Frey (EVF) device – has been used to compare the effect of topically administered lidocaine gel with placebo gel, and the results showed good to excellent test-retest reliability for all measures – thresholds as well as self-report measures, indicating that the measurement of mechanical pain thresholds and mechanical pain sensitivity with an EvF device can substitute for needle penetration of the oral mucosa [58]. However, there were no significant differences in the effects of lidocaine gel and placebo gel.

QST effects after oral and maxillofacial surgery

After oral and maxillofacial surgery, some patients may suffer from paresthesias or somatosensory loss in the trigeminal region [59–61]. The important prerequisite for successful management of nerve injury is an accurate diagnosis [62]. QST has, indeed, emerged as a widely-used tool in the assessment of somatosensory nerve damage in patients [61]. Whereas most studies have addressed somatosensory processing in the skin and upper/lower lip in the extraoral region, only a few studies have focused on the intraoral region probably due to a previous lack of standardized QST techniques [59–62]. The summary of articles of QST in the oral mucosa after oral and maxillofacial surgery is shown in Supplementary Table 5.

Most studies are prospective with a follow-up from 48 h to 1 year [60,62–70]; two studies are retrospective [59,71], and one is cross sectional [72]. The surgery mode, test sites and measuring parameters vary widely. Different types of interventions in oral and maxillofacial surgery have been investigated including mandibular osteotomy [59,66,67,71,72], fracture fixation [63,64], mobilization of the neurovascular bundle [65], osseointegrated implantation [68], tooth extraction [69], surgical biopsies [70] and other kinds of surgeries [60,62]. Somatosensory alterations and recovery have both been described by means of QST. The degree of somatosensory change and recovery time are dependent on the surgical mode, QST parameter and test site. For patients with fractures, somatosensory change and recovery also correlated with the presence of displacement [63,64]. Zachariades et al. [63] reported that patients with minor displacements or no displacements showed complete recovery.

QST effects after prosthodontic or orthodontic treatment

Prosthodontic and orthodontic treatment may lead to discomfort or pain in patients which is the main reason for complaint and treatment interruption [73,74]. On one hand, denture wearing and the placement of orthodontic appliance induce histological changes and inflammatory reactions in the oral mucosa [75,76]; on the other hand, the condition of the edentulous oral mucosa is different from the normal mucosa which may lead to unique histological reactions when exposed to certain loads [77,78]. The summary of articles on QST after prosthodontic and orthodontic treatment is shown in Supplementary Table 6.

One study showed that the PPT in the palate was 40% lower in complete-denture-wearing patients than dentate subjects, indicating that wearing a denture may make the mucosa more sensitive to painful pressure stimuli [79]. Functional disturbance in the nasopalatine and greater palatine nerves have also been indicated in complete denture wearers [80]. Moreover, a negative correlation between bite

force and PPT was found in the palatal, maxillary and mandibular posterior regions in edentulous patients, which may add another reason for denture pain practice [79].

In patients undergoing orthodontic treatment with fixed appliances, sensitization to blunt-pressure stimuli was found both in the attached gingiva and in the periodontal ligament during a 24 hours observation [81].

Conclusions

In summary, cutaneous QST is a fairly sensitive, simple and relatively inexpensive method for detection of small fiber neuropathy. Recent years have witnessed increased interest in QST methods that contribute to the diagnosis, facilitate staging and long-term follow-up of the natural history of disease and aid in the determination of treatment efficacy. On the oral mucosa, QST has been proved to be stable and reliable, and conclusions have been achieved in the assessment of somatosensory function in healthy volunteers, special pain populations and patients. The application of QST has aided in the standardized assessment of somatosensory changes in experimental models of intraoral pain, effects of local anesthesia, after oral and maxillofacial surgery and after prosthodontic and orthodontic treatment. Sufficient reliability of QST in the oral mucosa has been found both in healthy people and patients with somatosensory disturbances or neuropathic pain, and somatosensory abnormalities were commonly detected in neuropathic pain patients compared with healthy subjects. However, as most of the studies were heterogeneous, regarding stimulation techniques, test sites and outcome parameters, the results are hard to compare quantitatively. A standardized intraoral QST protocol is recommended and expected to continue to help in the mechanism-based assessment of neuropathies and intraoral pain conditions in the oral mucosa. With the advantages and keeping the disadvantages in mind, QST is expected to help in a more mechanism-based diagnosis and characterization of different intraoral pain conditions.

Disclosure statement

The authors have no conflicts of interest to declare.

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