The Detection of Small-Fiber Neuropathies in Burning Mouth Syndrome and Iatrogenic Lingual Nerve Injuries: Use of Quantitative Sensory Testing

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Aims: To assess thermal pain perception in patients with burning mouth syndrome (BMS) and lingual nerve injury (LNI) by using a quantitative sensory testing (QST) protocol. **Methods:** QST was used to assess cool, warm, cold pain, and heat pain thresholds in healthy control subjects (n = 17) and in patients with BMS (n = 22) and LNI (n = 47). Capsaicin (10 µg/mL) and ethyl chloride–evoked hypersensitivities at the anterior two-thirds of the tongue were measured using a visual analog scale. Data were analyzed using Microsoft Excel with descriptive statistics, scatter graphs, and two-tailed Student *t* tests with 95% confidence interval and 5% level of significance. **Results:** Patients with BMS significantly reported the most pain at rest ($P < .001$) and capsaicin hypersensitivity ($P < .01$). Despite this increased sensitivity to capsaicin and significantly lower warm threshold than the control subjects ($P < .05$), these patients did not show heat pain hyperalgesia. There was increased sensitivity to ethyl chloride and cold pain hyperalgesia in patients with BMS ($P < .05$) compared with reduced or no sensation of cold or heat pain in patients with LNI. **Conclusions:** This study has demonstrated that the assessment of capsaicin and ethyl chloride–evoked sensitivities as well as the use of QST to assess thermosensitivity are useful approaches for detecting hyperalgesia or hypoalgesia to heat and cold in patients with BMS and LNI. *J Oral Facial Pain Headache 2016;30:87–98. doi: 10.11607/ofph.1531*

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Pain is a subjective, unpleasant but important sensory experience, often indicating that tissue damage has occurred. When pain persists for more than 3 to 6 months after the initial cause or resulting inflammation is no longer present, the pain is classified as being chronic.[1] There are two forms of chronic pain: dysfunctional pain that is a result of altered nerve fibers and/or their activity within the somatosensory system, both centrally and peripherally, and neuropathic pain that persists following surgical procedures, other traumatic event(s), or known neural lesions in the peripheral nerves. Both forms of chronic pain are troublesome for the patient, with many suffering from psychological distress due to the pain.[2,3] This also makes chronic pain more difficult for the clinician to manage.[4] Chronic neuropathic pain within the lingual mucosa is highly evident in burning mouth syndrome (BMS).[5,6] Similar symptoms can also occur in patients with posttraumatic iatrogenic lingual nerve injury (LNI), which is a secondary neuropathy with burning mouth symptoms.[7]

BMS is of unknown pathophysiology; it is characterized by a painful burning sensation predominantly affecting the anterior two-thirds of the tongue that can last at least 4 to 6 months in the absence of any visible lesions or pathology.[6,8–14] BMS can be classified as primary or secondary depending on the etiologic factors, but there is continued debate about the nomenclature. BMS refers to an idiopathic spontaneous condition of unknown cause. Primary BMS is idiopathic and diagnosed if there is burning of the oral mucosa in the absence of a lesion or other cause. Secondary BMS is a neuropathy of the lingual and/or chorda

tympani nerves that is diagnosed if the symptoms can be linked to local, systemic, and/or psychological factors.[15] It is relatively rare, with a prevalence of 12% to 18% amongst postmenopausal women in their fifth to seventh decade.[6,16–18] Patients with BMS frequently report that their burning pain starts spontaneously, is moderate to severe in intensity (may vary throughout the day), and may last several years.[19,20] Additionally, some patients report a subjective dryness of the mouth and dysgeusia in the form of a constant metallic taste or taste phantoms.[12,21,22] It was previously postulated that BMS is a psychogenic condition,[23,24] as these patients often also suffer from distress and anxiety. However, further studies have provided evidence for a multifactorial etiology of BMS and that the anxiety and depression experienced by patients with BMS are more likely to be secondary to the experienced pain.[12,22,25–28]

Patients with posttraumatic LNI may also manifest burning sensations in addition to allodynia, hyperalgesia, dysesthesia, and/or hypoesthesia (numbness) of the tongue, and sometimes dysgeusia.[29] LNI is an unfortunate complication that is relatively common within the United Kingdom following dental procedures (most frequently due to third molar surgery),[29–32] with 0% to 23% experiencing temporary and 0% to 2% experiencing permanent nerve damage.[33–36]

The diagnosis of BMS is by exclusion (International Headache Society [IHS])[37,38] following patients undergoing a thorough clinical examination with a series of screening tools.[38–40] The German Network on Neuropathic Pain (DFNS)[41–43] recently has proposed a standardized psychophysical protocol involving a series of conventional tests with additional psychophysical testing (quantitative sensory testing [QST]) that can measure relative sensory loss or gain in different patient populations. The protocol[42,43] uses 13 different mechanical and thermal stimuli by applying graded von Frey hairs, pressure algometers, several pin-prick stimuli, and QST. These tests (except QST) are restricted to testing perceptual responses evoked by stimulation of the larger Aα and Aβ primary afferent fibers involved in mechanosensation and consequently can detect cases of mechanical allodynia.[33,44]

The QST component of the assessment protocol is a sensitive and accurate method of measuring responses to calibrated, graded innocuous or noxious thermal stimuli with a nonpenetrating probe available in different sizes according to the area being tested.[33,45–50] QST is therefore a noninvasive and reproducible method. Most importantly, it also allows for painful areas to be located. It can be carried out in patients to assess the overall sensory loss or gain, and it allows comparisons of sensation to be made between the injured/neuropathic and uninjured/nonaffected areas.[33] QST is therefore a reliable source of reproducible quantifiable data, which can provide an enhancement to the process of diagnosis and treatment planning and help with the confirmation of physical findings.[47]

Thermal and mechanical pain settings of the QST protocol allow the assessment of perceptual responses evoked by stimulation of the smaller (Aδ and C) fibers involved in thermosensation, as well as the responses evoked by stimulation of Aα and Aβ afferent fibers involved in mechanosensation.[33,51,52] Thus, QST can differentiate various neural mechanisms underlying a neuropathic condition. Cool temperatures between 15°C and 30°C and noxious cold (< 15°C) activate transient receptor potential melastatin-8 (TRPM-8) receptors on the terminals of thinly myelinated Aδ primary afferent fibers (2 to 5 μm in diameter).[53] Pain evoked by noxious cold stimuli, as well as spontaneous and elicited sharp, shooting pain, arise by the firing of action potentials in the Aδ fibers, damaged Aβ fibers, and a small subpopulation of unmyelinated polymodal C fibers; these action potentials are conducted along the fibers to the somatosensory circuits within the central nervous system (CNS). Transient receptor potential Vanilloid-1 (TRPV1) receptors located on the peripheral endings of the smaller (0.3 to 3 μm), slower-conducting unmyelinated C fibers are normally activated by warm stimuli (between 32°C and 42°C) and noxious heat (> 43°C).[33,51,54] Spontaneous activity in nociceptor C fibers is thought to be involved in the production of constant burning-type pain, and the ectopic firing of the larger Aα or Aβ fibers in the generation of mechanical allodynia.

QST has previously been applied to assess patients with chronic pain and a variety of peripheral (limb) neuropathies[55–57]such as diabetic neuropathies,[58–61] multiple sclerosis,[62] and HIV-associated neuropathies.[63] These studies were successful in identifying patients with hypoesthesia and allodynia. A study by Baron et al in 2010 indicated that patients can be clustered into subgroups based on sensory profiles recorded from patients with postdiabetic neuropathy and postherpetic neuropathy.[2] These clusters consequently identified potential neuropathic pain mechanisms.[2] QST studies have also previously reported small-fiber dysfunction in 76% of 46 patients with BMS, thus suggesting that BMS may be associated with a dysfunction related to a small-fiber and/or large-fiber sensory neuropathy.[27] Other evidence supporting this hypothesis comes from studies reporting that patients with BMS show significant alterations in heat pain tolerance[19] and elevated sensory and pain thresholds to argon laser stimulation[64] compared with control subjects. In addition, a previous study[28] reported increased expression of the TRPV1 receptor and its modulator nerve

growth factor (NGF) at the endings of small nerve fibers within the anterior two-thirds of the tongue in patients with BMS, thus providing more evidence that BMS may be associated with a small-fiber trigeminal neuropathy. In order to test this theory further, this study aimed to assess the thermal pain perception of patients with BMS and LNI by using a QST assessment protocol. It was hypothesized that patients with BMS would have increased sensitivity to cold and/or heat pain and the patients with LNI would also have some altered perception of thermal pain.

Materials and Methods

Recruitment of Patients

A total of 105 patients attending tertiary care, specialist oral-facial pain clinics at the Institute of Dentistry of Queen Mary, University of London (QMUL) and King's College London Dental Institute (KCLDI) were assessed in this study. Each patient was given an outline of the study and the option to participate. Patients who wanted to participate in this study then provided their fully informed, written consent before the QST assessment. Patients were not recruited if they had a complex medical history or if they could not speak or understand sufficient English. Ethical permission for the study was obtained from Bart's and The London National Health Service (NHS) Trust, and the London–London Bridge Local NHS Research Ethics Committee (Research Ethics Committee number 06/MRE00/5).

Control Group of Patients

Patients who were scheduled for mandibular third molar extractions under standard local anesthesia were recruited for the control group. None of the control subjects had pain within the tongue at the time of the appointment or a history of any suspected lingual neural dysfunction. Patients with painful pericoronitis, generally existing neuromuscular disease, bleeding problems, or other painful conditions treated with analgesics were excluded from this study. Results from 17 of the 36 control patients (6 men and 11 women; mean age, 46.88 years; range 30 to 79 years) were used in the final data analyses to ensure that the control patients were age-matched as closely as possible to the BMS and LNI patients.

Patients with Lingual Dysfunction

The analyzed population presenting with chronic pain and/or altered sensations within the lingual mucosa comprised 22 and 47 patients diagnosed with BMS and LNI, respectively. The BMS patients were recruited by the same consultants in accordance with the IHS criteria for BMS.[37,38] Such symptoms included a burning sensation of the tongue that started spontaneously with no visible lesions of the oral mucosa or any underlying local or systemic disease. Previous blood test results had revealed normal nutritional levels and thyroid activity. LNI patients were selected on the basis of presentation with symptoms of hypoesthesia, hypoalgesia, allodynia, and/or constant pain within the tongue for more than 4 months as a result of a dental procedure.

Patients with posttraumatic LNI were diagnosed in accordance with the IHS and International Association for the Study of Pain (IASP) guidelines for neuropathy. The majority of LNI cases were caused by third molar surgery (76.9%). Other causes included the administration of an inferior dental block (12.7%), chemical injury due to the local anesthetic (2.6%), and trauma due to endodontic treatment (2.6%), surgery (2.6%), or extraction of teeth other than third molars (2.6%).

Pain Assessment

Prior to any testing, the consultant obtained a detailed history of the patient (medical, social, dental, pain histories, with a focus on events associated with onset of neuropathic symptoms [LNI group]). All patients also completed the McGill Pain Questionnaire to describe their symptoms and rated the degree of their pain at rest by using a visual analog scale (VAS) with 0 being no pain and 10 being worst pain imaginable. Pain levels upon capsaicin (10 µg/mL) and ethyl chloride (EC) stimulation at the site where the patients reported the most pain within the anterior two-thirds of the tongue were also measured using the VAS scoring system. Patients rated their pain levels upon the stimulation with capsaicin (Sigma; ≥ 95% pure extract from *Capsicum* diluted 1:100; final concentration of 10 µg/mL) on a piece of cotton wool three times, for a few seconds each time. Stimulation with EC involved spraying a separate piece of cotton wool with EC and applying this to the tongue three times for a few seconds each time.

Neurologic phenotyping included cranial nerve evaluation (excluding cranial nerves I and VIII) and mapping of any detectable neuropathy (as a percentage area of neuropathy) of the tongue by gently running closed forceps over the tongue surface from the unaffected areas (where relevant) to regions where patients acknowledged changes in sensation. For example, a neuropathic area of 100% was indicated if the whole intraoral lingual nerve dermatome of the injured side was affected.

Mechanosensory subjective function was assessed using a no. 15 von Frey filament (50 g/mm^2). The patient was asked to imagine that being able to feel this filament without any pain was equivalent to 10/10 and that no feeling to touching the area would

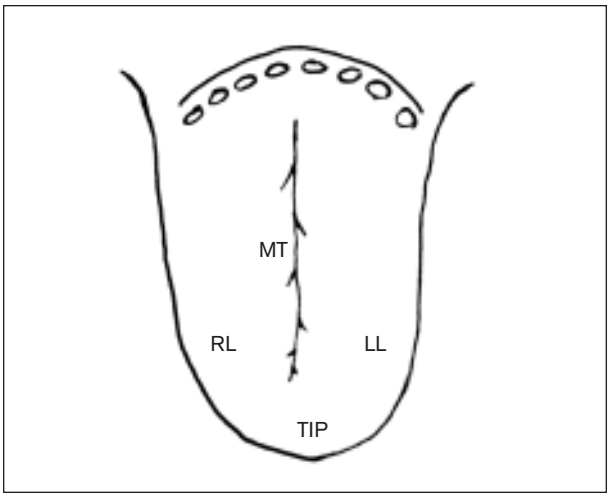


Fig 1 Sites of QST testing within the oral mucosa. Intraoral sites included the middle of tongue (MT), lingual tip (TIP), left lingual (LL) and right lingual (RL) mucosa.

be regarded as 0/10. Both the noninjured and injured sides in the LNI patients were stimulated in the same way, and the patient was asked to score the sensory experience (0 = no sensation to 10 = normal sensation, or above 10 if pain/hypersensitivity was elicited) relative to the uninjured side. Cases of hypersensitivity evoked by the application of the filament to the tongue were indicated by scoring higher than 10.

QST Testing

Choice of assessment site. Control patients had the QST on the laterodorsal surface of the anterior one-third of the tongue, on the same side as the mandibular third molar extraction (Fig 1). This site was chosen for the control patients in order to match the sites tested in the BMS and LNI patients. All BMS patients had the QST at the anterior two-thirds of the tongue, always within the area where patients experienced their maximal discomfort. LNI patients repeated the QST twice; initially on the laterodorsal surface of the anterior one-third of the tongue opposite to the injured side, followed by the anterior one-third of the tongue on the injured side within the neuropathic area where patients experienced their maximal discomfort.

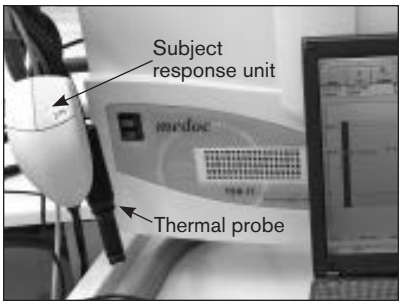
Cool, warm, cold pain, and heat pain perception thresholds were identified by QST using the TSA 2001-II Advanced (MEDOC) neurosensory analyzer (Fig 2) and the Classic Method of Limits.[27,33] This apparatus consisted of a 5 × 5 mm intraoral thermal probe that was held gently in contact with the target area of the lingual mucosa by the patient (after a demonstration and short training session by the same member of staff each time). Patients were also denied visual access to the testing equipment throughout the whole procedure to prevent any bias and influence on their responses. QST for the healthy controls and BMS patients generally took 15 minutes, but it took 30 minutes for the LNI patients since both the side opposite to the injury and the injured side were tested. All thermal tests occurred in a quiet room and patients sat comfortably in a dentist's chair. The same investigator carried out the QST on all of the patients to minimize any risk of inter-investigator error. Baseline temperature of the thermode was set at 32°C, with 0°C and 50°C cutoff limits (Fig 2). The temperature increment was 1°C/second for cool and warm modalities, and 1.5°C/second for the cold and heat pain modalities.

The same investigator instructed the patients to use a subject-response unit as soon as they perceived the target sensation (cool, warm, cold pain, or heat pain); when the target sensation was so noted by the patient, the thermode returned to baseline temperature. Each modality was repeated five times in succession (Fig 2).

A faster response to the cold/warm stimuli, which was indicative of allodynia or hyperalgesia, was evoked by smaller changes from the 32°C baseline temperature. The opposite was true for hypoalgesia, for which there were slower responses to cold or warmth.

Methods of thermal QST data analysis. All data were collated and analyzed using Microsoft Excel.

- *Treatment of individual QST results:* The maximum and minimum values were initially omitted from each of the five values obtained per threshold tested, per patient. Means of the remaining three values for each threshold were calculated and used in further analyses of the results.[65]
- *Treatment of group QST results:* Results were made comparable between the groups by using those in the upper age group in the control group (n = 17). Mean QST results (± standard error of the mean [SEM]) from all patients are presented.
- *Statistical analysis:* F tests for variances were initially carried out in the results, followed by *t* tests assuming equal or unequal variance as appropriate (95% confidence interval [CI]). All results for the *t* tests are expressed as two-tailed values unless otherwise indicated.
- *Further assessment of individual QST results:* Reference values for each threshold tested were deduced by plotting mean values for all control patients on a scatter graph. Obvious outliers were identified and it was concluded that ± 2 from the mean value should be used from the pattern of the plot. Individual thermosensory results for the BMS and LNI patients were then further analyzed with reference to the mean thermosensory results for the control patients.[42]



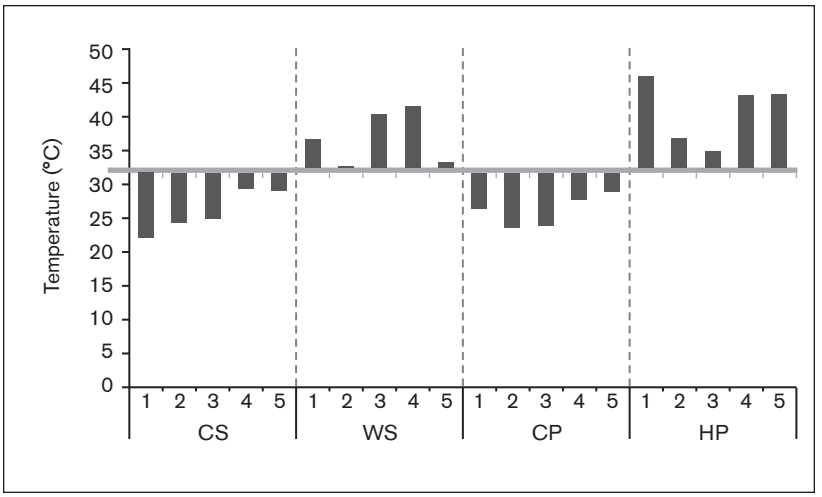


Fig 2 Photograph of the TSA 2001-II Advanced (MEDOC) neurosensory analyzer and graphic representation of how the results were collected via laptop. CS = cool sensation; WS = warm sensation; CP = cold pain threshold; HP = heat pain threshold.

Cases of thermal hyperalgesia were more difficult to identify than hypoalgesia, as there is no widely accepted consensus regarding a specific algorithm[66] for this type of assessment. However, cases of hyperalgesia and hypoesthesia were identified in the same way as outliers by stating that results were abnormal if they fell outside ± 2 SD of the mean control (n = 17) results.

Results

Demographics

Data collected from 86 patients were included in this study; 56 (65%) patients were female (Table 1). The lingual dysfunction group of patients consisted of 22 BMS patients (8 men and 14 women) with a mean age of 57.8 years. The LNI group of patients (n = 47; 16 men and 31 women) was significantly younger than the BMS group, with a mean age of 40.4 years ($P < .001$). The mean duration of symptoms experienced by the BMS patients was significantly longer, at 38.9 months (range 10 to 84 months) compared with the LNI patients, who had their symptoms for a mean duration of 12.0 months (range 1 to 60 months) at the time of their consultation appointment ($P < .001$). Of the LNI group, 26 (55%) had permanent LNI injuries.

Table 1 Summary of the General Demographics of Patients Involved in the Study

	Control (n = 17)	BMS (n = 22)	LNI (n = 47)
Male:Female	6:11	8:14	16:31
Age (y)			
Mean (SE)	46.88 (3.85)	57.8^{+++} (2.85)	40.4 (1.62)
Minimum	30	29	25
Maximum	79	83	63
Duration (mo)			
Mean (SE)	N/A	38.9*** (5.25)	12.0 (2.12)
Minimum		10	1
Maximum		84	60

$^{+++}$Denotes a statistically significant difference in mean age between the LNI group of patients and BMS patients ($P < .001$).
***Denotes a statistically significant difference in mean duration of symptoms between the BMS patients and LNI patients ($P < .001$).

Table 2 VAS Pain Scores Expressed as Means ± SEM (Range) on Scale of 0 (No Pain) to 10 (Worst Pain Imaginable) for the Control, BMS, and LNI Patients at Rest (Baseline Level) and in Response to Ethyl Chloride and Capsaicin Application

Stimulus	Control	BMS	LNI
None (at rest)	0.0 ± 0.0	6.5 ± 0.8* (4–10)	1.6 ± 1.0 (0–4)
Ethyl chloride	0.5 ± 0.2 (0–4)	2.5 ± 0.9 (0–7)	2.9 ± 1.3 (0–7)
Capsaicin (10 µg/mL)	0.8 ± 0.5 (0–5)	6.0 ± 1.2* (0–9)	1.0 ± 1.0 (0–8)

*Denotes a statistically significant difference between the BMS and LNI patients' results (P < .05).

Pain Levels

BMS patients reported moderate to severe pain levels at rest of 6.5 on average, which was statistically significantly greater than the control patients and LNI patients ($P < .05$; Table 2). During the clinical assessments, BMS patients had significantly higher pain levels than the healthy controls and LNI patients upon capsaicin (10 µg/mL) stimulation (Table 2). It was therefore not surprising that all BMS patients also reported that their pain was exacerbated by spicy food, so consequently they avoided such food. Ethyl chloride stimulation conversely did not cause significantly more pain among the BMS or LNI patients.

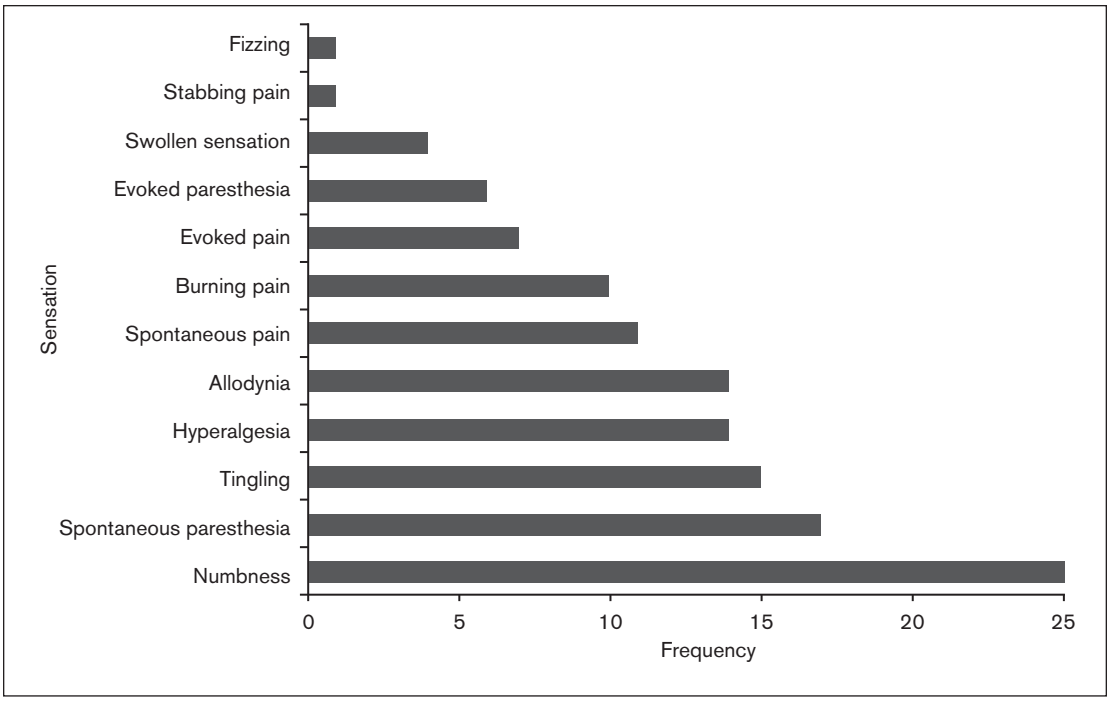


Fig 3 Bar chart demonstrating the symptoms experienced by the LNI patients.

Signs and Symptoms

All BMS patients had symptoms of burning of the tongue and almost half of them also had burning sensations within the gingivae. Mechanical allodynia was indicated in approximately half of the patients (46.2%). Cold and heat allodynia affected a slightly greater proportion (53.8%) of BMS patients.

Equal numbers of LNI patients reported pain and paresthesia (n = 10) or a mixture of numbness, pain, and paresthesia (n = 10). One of these patients specifically described his sensations as "cotton wool in his mouth"-type tingling. Numbness alone affected seven patients, and pain on its own affected three patients. No LNI patients had paresthesia on its own. The most common type of pain reported by the LNI patients was hyperalgesia (n = 14) and allodynia (n = 14), followed by burning types of pain (n = 10) and evoked pain (n = 7; Fig 3). LNI patients who had hot and cold allodynia tended to avoid hot and cold food and drinks.

Overall QST Results

Figure 4 shows some typical QST findings for the control, BMS, and LNI patients, coupled with the indications of allodynia, hyperalgesia, and hypoalgesia.

- *Cool-detection threshold:* BMS patients were significantly more sensitive to cold stimuli than the healthy controls ($P < .05$; Fig 5). Conversely, LNI patients showed significant decreased sensitivity to cool temperature on the injured side ($P < .001$). The difference in cool-detection threshold between the injured side and the opposite side in the LNI patients was significant ($P < .001$; Fig 5).
- *Warm-detection threshold:* Mean QST results showed that BMS patients responded earlier to warm impulses than the control patients, therefore indicating a significantly lower threshold to warm stimuli ($P < .01$; Fig 5). Although the LNI patients showed a similar mean threshold to warmth on the opposite side to the injury compared with the control patients, the LNI patients did show significantly decreased sensitivity to warm stimuli on the injured side compared with the control patients ($P < .001$). Comparison of the injured side of the tongue with the opposite side of the tongue in the LNI patients also indicated significantly less sensitivity to warmth on the injured side ($P < .001$).
- *Cold pain–detection threshold:* BMS patients showed cold hyperalgesia compared with the control patients ($P < .05$; Fig 5). LNI patients conversely showed significant cold hypoalgesia on both the injured side ($P < .001$) and the side opposite to the injury ($P < .01$). There was no significant difference in the cold pain thresholds between the injured and opposite sides ($P > .05$).

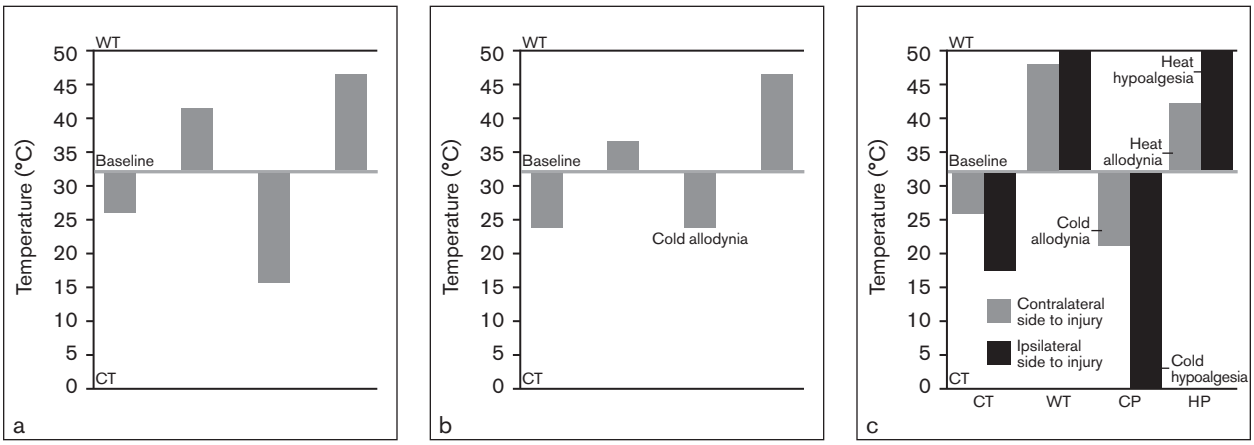


Fig 4 Examples of typical QST findings for the *(a)* control, *(b)* BMS, and *(c)* LNI patients. CT = cool threshold, WT = warm threshold, CP = cool pain threshold, HP = heat pain threshold. Allodynia, hyperalgesia, and hypoalgesia are indicated.

- *Heat pain–detection threshold:* There were no significant differences in the heat pain threshold for the BMS patients compared with the control patients ($P > .05$; Fig 5). However, LNI patients showed heat hypoalgesia on both the injured side of the tongue and the side opposite to the injury in comparison with the control patients ($P < .01$). There were no significant differences in heat pain–detection thresholds on both sides of the tongue in the LNI patients themselves ($P > .05$). The LNI patients often reported that they could not feel the probe getting warmer on the injured side but they could then sense the heat upon removal and replacement of the probe to the same site of the tongue. Furthermore, a patient with LNI reported no feeling of cold or warmth but only increased numbness when the pain thresholds were tested.
- *Individual QST results:* In addition to identifying overall changes in thermal pain amongst the BMS and LNI patients, QST also identified individual patients with allodynia, hyperalgesia, and/or hypoalgesia. BMS patients who were hypersensitive to cold stimuli, for example, were more likely to have cold hyperalgesia. However, those BMS patients who demonstrated heat hyperesthesia did not necessarily suffer from heat hyperalgesia. In contrast to this finding, a greater proportion of LNI patients had cold hypoalgesia on both sides of the tongue following their nerve injury. Similarly, LNI patients who showed hypoesthesia to warm stimuli also demonstrated heat hypoalgesia on both sides of their tongue. No significant relationship was found between the duration of symptoms and the experience of hyperalgesia or hypoalgesia in BMS patients ($P > .05$).

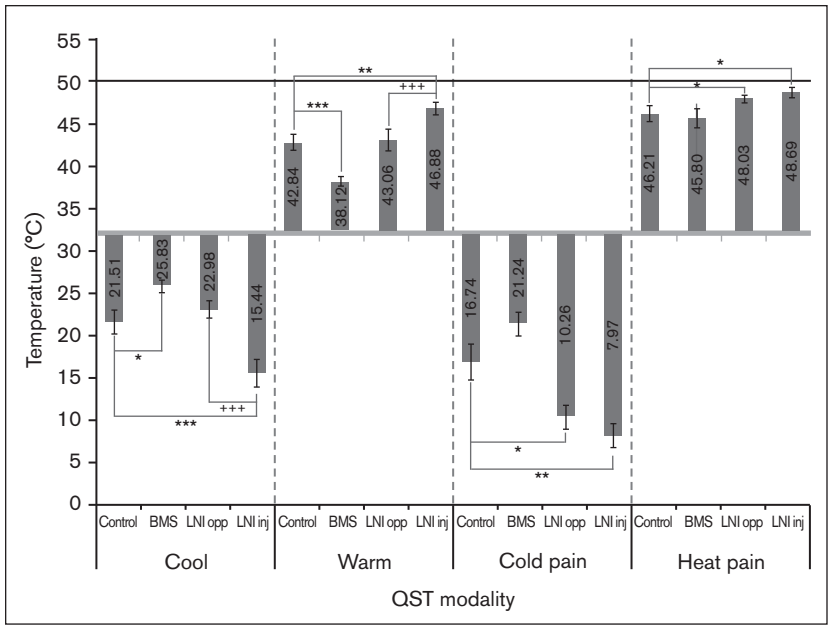


Fig 5 Mean QST test results. *, **, and *** denote statistically significant results ($P < .05$, .01, .001, 2-tailed, respectively, with 95% CI). $^{+++}$ indicates statistically significant results ($P < .001$) when results for the opposite and injured sides amongst the LNI patients were compared.

Discussion

The neurologic changes underlying the symptoms of several relatively common chronic pain conditions affecting the orofacial region, such as BMS and LNI, are poorly understood. A better understanding of peripheral and central neural changes in these conditions will aid the development of novel therapies without the undesirable side effects associated with systemic medications commonly prescribed to manage the pain. QST allows the assessment of perceptual responses evoked by stimulation of the primary afferent fibers that are involved in thermal pain and project to the CNS somatosensory pathways, which process the neural information carried by these peripheral nerve fibers into the CNS. QST is a highly sensitive, noninvasive, and reproducible technique, making it advantageous over other conventional tests.[33,47–52] Previous studies have shown QST to be successful in identifying hypoesthesia, hyperalgesia, and allodynia in patients with a variety of peripheral (limb) neuropathies.[56–63] Although some previous studies have assessed thermal sensation in BMS,[9,19,46,47] there appears to be no evidence in the literature demonstrating, with QST protocols, a direct comparison of thermosensation and pain (including cold pain) in patients with BMS or LNI.

Due to variances seen in the clinical assessment of patients with lingual nerve neuropathy such as BMS or as a result of iatrogenic (surgical) injury, it was hypothesized that BMS patients would have increased sensitivity to cold and/or heat pain and the LNI patients would also have some altered perception of thermal pain. This hypothesis was tested by using QST and the Classic Method of Limits protocol,[27,33] which assessed and compared cases that varied from hypersensitivity and burning-type pain to hypoesthesia amongst BMS and LNI patients. All QST was carried out on each patient by the same investigator. Results from this study have contributed to the baseline data available for lingual pain and quantified examples of thermal hyperalgesia and hypoalgesia amongst BMS and LNI patients compared with controls, indicating the specific sensory deficits that occur in these conditions.

Pain Levels at Rest and After Ethyl Chloride and Capsaicin Application

Consistent with previous studies,[19,67,68] BMS patients who participated in this study reported moderate to severe pain intensity at rest, which was significantly greater than that of the LNI patients and control patients. These patients also characteristically complained of a constant burning sensation of the tongue and hypersensitivity to spicy food, which may have been due to ectopic firing and/or redistribution of deafferented C fibers. Furthermore, central neural changes may also have contributed to the burning sensations in the BMS patients, as previously reported for a functional magnetic resonance imaging (fMRI) study carried out in BMS patients,[69] but this requires further investigation. Since trigeminal nerve injuries are also known to cause changes within the trigeminal brainstem sensory nuclear complex,[70–72] fMRI should be used to assess the central changes in patients with LNI.

It is also plausible to suggest that the baseline constant burning sensation of the tongue could be attributed to the increased expression of TRPV1 receptors at nociceptive C fiber terminals within the oral mucosa (ie, the same terminals that innervate the fungiform papillae within the tongue).[28,73–75] TRPV1 receptors are specifically known to be involved in pain processing and are highly sensitive to capsaicin as well as heat above 43°C and protons. Insensitivity to capsaicin has been shown to be linked to decreased TRPV1 expression in a 50-year-old woman who fortuitously attended the hospital due to her inability to sense hot peppers.[76] Changes in expression and mutation(s) of the TRPV1 receptor should also be explored in a larger sample size of people, as this would further explain these differences in sensitivity to capsaicin.

The occurrence of cold and heat allodynia on the side opposite to the injury in the LNI patients and in comparison with the healthy controls may have been due to contralateral nerve sprouting of peripheral axons and increased density of fascicles distal to the injury.[13,70,77] Also, contralateral changes in the trigeminal brainstem sensory nuclear complex that indicate bilateral effects in the CNS of a unilateral trigeminal nerve injury have also been shown in animal models of trigeminal neuropathic pain.[71,72] Furthermore, morphologic modifications at the central primary afferent endings in the CNS and changes in inhibitory control exerted in the CNS by large-diameter fibers on the small-diameter fibers may also have occurred in the LNI patients who had allodynia.[13]

Studies have reported that patients with BMS have a greater density of taste buds in the fungiform papillae within the anterior two-thirds of the tongue.[78–80] This increased density of taste buds may have a contributory influence on increased pain sensation in BMS patients and possibly in those LNI patients who complained of hyperesthesia or hyperalgesia to warm stimuli and heat pain. Contrary to this finding are reports that LNI patients who experience hypoesthesia tend to have fewer fungiform papillae.[81,82] A previously published study also has strongly supported this phenomenon and provides some insight into the underlying cause of hyperesthesia or hypoesthesia in BMS and LNI patients, whereby

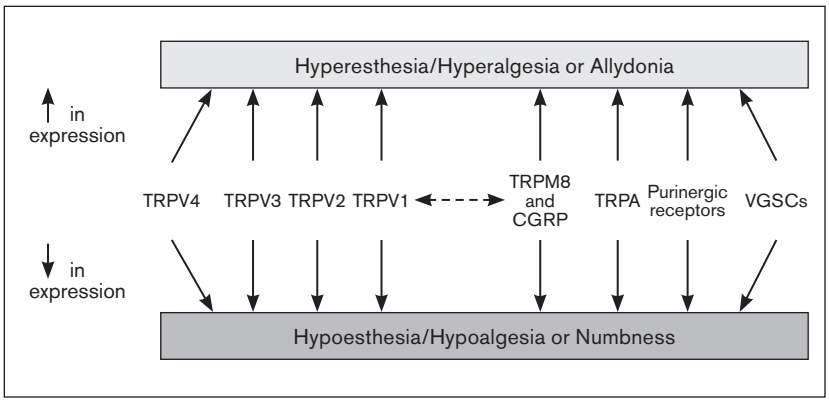


Fig 6 Proposed changes in ion channel expression in hyperesthesia/hyperalgesia or allodynia and hypoesthesia/hypoalgesia or numbness. ◄- - ►indicates association between TRPV1 and TRPM8 and CGRP fibers. CGRP = calcitonin gene-related peptide; TRPA = transient receptor potential ankyrin; TRPV = transient receptor potential vanilloid; TRPM = transient receptor potential melastatin; VGSCs = voltage-gated sodium channels.

there was a significant increase in the expression of TRPV1 and its regulator NGF in tongue biopsy samples from BMS patients.[28] Despite these increases in TRPV1 and NGF, there was a significant decrease in neurofilament expression within the same samples from BMS patients, therefore supporting the view that BMS could be caused by a trigeminal small-fiber sensory neuropathy.[9,21,27]

Cold and Cold Pain Hyperalgesia

QST findings included a trend in increased sensitivity to cold and cold hyperalgesia in the BMS patients. These findings add support to the view that these patients may have an impairment of Aδ fibers.[79] Increased expression or redistribution of the TRPM8 receptors at the endings of the Aδ fibers may be contributing to the cold hypersensitivity (Fig 6). TRPM8 has also been reported to co-localize with TRPV1 and calcitonin gene-related peptide (CGRP) in lingual sensory nerve fibers in rats, within the trigeminal ganglion, but not within the fungiform or filiform taste buds.[83] Other underlying mechanisms for the cold allodynia may include TRPV1 activity on nociceptive C fibers,[74] or increased expression and activity of TRP ankyrin-1 (TRPA1) receptors on trigeminal sensory neurons.[84] These possibilities deserve further exploration by investigating the receptor activity through the use of specific agonists and antagonists during clinical assessments of patients. Since pain is subjective and some of the antagonists act on more than one of the respective ion channels/receptors, it would be advisable to quantify the changes in ion channel/receptor expression within biopsy samples from patients by immunohistochemistry. Future work using animal models should also further assess the central neural changes that occur within the various levels of the ascending trigeminal somatosensory pathways, within the descending modulatory pathways, and within CNS circuits underlying motor and other behaviors.[72,85,86]

Consistent with previous studies,[33,87–89] this study found that responses to cooling were faster than responses to warming, as indicated by the QST results of patients in the control group who did not have a lingual nerve neuropathy (Fig 5). It is therefore not surprising that more increased sensitivity to cooling than to warming was also seen when control patients had to respond to the cold pain and heat pain modalities. This could be due to increased expression and activity of thermal and pain receptors that respond to cold on Aδ nerve fiber terminals in comparison to the C fibers both within the periphery and in the brain, as described above.

Warm and Heat Pain Sensitivity

Adaptation to warming was suggested by some LNI patients in this study who reported that they did not feel the probe getting warmer on the injured side. However, they could then sense the heat upon removal and replacement of the probe to the same site of the tongue. Less sensitivity to heat pain was also shown by BMS patients, which supports a previous study that reported warm allodynia in only 2 of the 52 BMS patients studied.[27] Adaptation to warming and less sensitivity to heat pain most likely occurred due to central sensitization, but this deserves further exploration. These findings were similar to those reported by Harding and Loescher, who also demonstrated that adaptation to warming is more likely to occur than adaptation to cooling.[90]

The lack of response to cold or warmth and only an increased sensation of numbness when the pain thresholds were tested on one of the patients suggests complete impairment of Aδ and C fiber–evoked perceptual responses, perhaps through diminished expression and activity of the respective ion channels involved in cold and heat perception (TRPV1, TRPV2, TRPV3, and TRPV4). This should be investigated further through the use of their respective agonists/antagonists in clinical assessments and

immunohistochemical experiments to allow the quantification of the pain receptor/ion channel expression in patient biopsy samples. It would also be interesting to assess this patient, as well as others who may have similar complaints, further by fMRI for possible CNS changes.

Limitations and Future Studies

Although QST is useful for assessing somatosensation, the results need to be interpreted with consideration given the limitations of this assessment tool. These include the difficulty in identification of cases of heat hyperalgesia/heat pain hyperalgesia compared with hypoalgesia, possibly due to adaptation to warming during the Method of Limits and the 50°C cutoff point. The Method of Limits used through thermal QST relies heavily on the attention and subjective reporting by patients. While the QST of BMS and control patients in the present study took roughly 15 minutes, QST of the LNI patients took approximately 30 minutes since both sides of the tongue were assessed. Consequently, patients may have become distracted or tired during the procedure, causing them to lose their concentration toward the end of the assessment. Although all patients were carefully instructed to gently place the probe without pressing down on the tongue, there may have been variations in the degree of pressure exerted by each patient when holding the probe against the test site and their overall cooperation.

Adaptation to stimuli and loss of concentration during the assessments may be avoided by using *(1)* the Method of Levels in QST, which involves assessing the effects of set temperature levels to determine if they are painful rather than assessing effects of gradually increasing/decreasing temperatures[91] (this would also reduce the amount of time it takes to carry out the tests, thus ensuring patients do not lose interest in the test and maintain a good level of concentration); *(2)* testing faster stimulus ramps to assess responses to warmth and heat pain. This may be achievable by using suprathreshold and incremental stimuli (ie, heat hyperalgesia) and using contact heat-evoked potentials.[92] This may also allow the assessment of heat hyperalgesia by stimulating above the 50°C limit set out by QST. An increase in the temperature above 50°C would involve the activation of the TRPV2 receptor, which is activated by temperatures above 53°C.[93,94] For obvious ethical reasons, the number of stimuli should be kept minimal and the limitations of the technique, such as the inevitable co-activation of mechanosensitive Aβ fibers, should be kept in consideration.[66,95]

Conclusions

This study demonstrated that the assessment of capsaicin and ethyl chloride–evoked sensitivities as well as the use of QST to assess thermosensitivity are useful approaches for detecting hyperalgesia or hypoalgesia to heat and cold in BMS and LNI patients. The Method of Levels in QST assessment deserves exploration among these patients and those with other painful conditions to minimize the risk of adaptation to thermal changes, especially heat. Ion channels in Aδ and C fiber nerve endings deserve further investigation for developing novel diagnostic tests and therapies.

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