Alteration of somatosensory profile in patients with burning mouth syndrome

Kosuke Watanabe

Nihon University Graduate School of Dentistry
Major in Oral Diagnostic Sciences

(Directors: Prof. Yoshiki Imamura and Associate Prof. Noboru Noma)

Table of Content

The following article and unpublished data (Figure. 3) are part of this doctoral thesis: Watanabe K, Noma N, Sekine N, Takanezawa D, Hirota C, Eliav E, Imamura Y: Association of somatosensory dysfunction with symptom duration in burning mouth syndrome, Clinical Oral Investigations, in press

ABSTRACT

Objectives: A standardized battery of quantitative sensory tests (QST) developed by the German Research Network on Neuropathic Pain was used to assess the association between somatosensory dysfunction and disease duration in patients with burning mouth syndrome (BMS) in Study1. Study 2 used two psychophysical test models, temporal summation (TS) and conditioned pain modulation (CPM), to study on the function of the pain modulatory system in healthy volunteers.

Materials and methods: In Study 1, 28 female patients with BMS were classified according to disease duration: ≤ 6 months (subchronic BMS, n = 15) and > 6 months (chronic BMS, n = 13). 29 age- and sex-matched healthy volunteers (control group) were recruited from the staff of a dental hospital. The QST battery was applied at the ulnar surface of the right forearm and the tip of the tongue. Data of BMS patients and controls were compared and analyzed.

Study 2 included 25 healthy female volunteers. A single stimulus followed by 10 noxious electrical stimuli at the same intensity was applied at 1 Hz with intra-epidermal electrical stimulation (IES). TS on numerical rating scale (NRS) was obtained after the first stimulus and at the end of the 10 stimuli. For the CPM assessment, stimulation of the non-dominant hand in the 40˚C condition or the 47˚C condition served as the conditioning stimulus (CS), and the TS protocol above served as the test stimulus.

Results: Mechanical pain sensitivity (MPS) at the forearm was significantly higher (i.e., gain of sensation) in the chronic BMS group than in the control group (Z score = 1.99). Multivariate analyses revealed that BMS patients could be discriminated from controls by using pressure pain threshold at the tongue (in the subchronic BMS group) and by MDT and MPS at the tongue tip and MPS at the forearm (in the chronic BMS group).

TS under the 47˚C condition was more significantly suppressed in comparison to TS without the conditioning stimulus under 40˚C. CPM under the 47˚C condition was significantly larger than that under the 40˚C condition.

Conclusions: The augmentation of MPS showed an exaggerated pain response suggesting that the increase of pain sensitivity against accumulated noxious stimuli was probably due to dysregulation of the pain modulation system in the central and the peripheral nervous systems of patients with chronic BMS. CPM utilizing epidermal electrical stimulation as a test stimulus is useful in evaluating the function of the pain modulation system and is expected to be applied in investigating vulnerability of the pain modulation system in chronic pain conditions.

Abbreviation:

burning mouth syndrome (BMS), The German Research Network on Neuropathic Pain (DFNS),quantitative sensory testing(QST),cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), vibration detection threshold (VDT), pressure pain threshold (PPT), wind-up ratio (WUR), mechanical pain sensitivity (MPS), intra-epidermal electrical stimulation (IES), temporal summation (TS), conditioned pain modulation (CPM)

INTRODUCTION

Persons with burning mouth syndrome (BMS) complain of burning pain of the tongue in the absence of abnormal clinical or laboratory findings. The details of the pathophysiology of BMS are an enigma. Recent studies suggest that BMS has a neuropathic component, in which trigeminal somatosensory function is modulated by the chorda tympani and glossopharyngeal nerves and trigeminal reflexes are altered [1–6]. Some reports implicate peripheral neuropathic pathophysiological mechanisms (7–9) while others suggest that central neuropathic mechanisms are primarily involved (2, 3, 10, 11)

Nasri-Heir et al. have reported that the electric taste/tingling detection threshold ratio is higher for persons with chronic BMS than for controls (12). Furthermore, Lauria et al. found that epithelial nerve fibers of the tongue were significantly less dense in BMS patients (6) and that density tended to correlate with duration of symptoms. These studies indicate that somatosensory dysfunction varies in relation to duration of symptoms. Although some quantitative sensory test (QST) studies have evaluated thermal and mechanical sensitivity in BMS patients, none has investigated whether somatosensory function in BMS patients was associated with symptom duration, as assessed by a full QST battery, including pressure pain threshold (PPT), vibration detection threshold (VDT), wind-up ratio (WUR), mechanical pain sensitivity (MPS), and dynamic mechanical allodynia (DMA).

Study 1 used a standardized battery of QSTs that measure cutaneous and deep pain sensitivity to examine somatosensory function in BMS patients and healthy volunteers

and investigate the association between QST data and BMS duration.

There is no gold standard for the definition of chronic pain, however usually pain is regarded as chronic when it lasts or recurs for more than 3 to 6 months (13). Other definition considers chronic pain as pain that persists beyond normal healing time (14). It is recognized that transition from acute pain to chronic pain is completed within 6 months (15). As BMS is defined as the burning pain that recurs daily for >2 hours per day for >3 months in The International Classification of Headache Disorders 3rd Edition (ICHD3) (16), the period between 3 months and 6 months from the onset of pain could be considered as sub-chronic (not totally established chronic). This study focused on the effect of the duration of pain experience on BMS patient's somatosensory function. The cutoff point was set at 6 months when the chronic pain had been established based on literatures.

Study 2 used two psychophysical test models, temporal summation (TS) and conditioned pain modulation (CPM), to measure the pain modulatory system. These dynamic pain paradigms can provide information on the individual's modulation system status by evaluating the modulation processes. The TS test corresponds to the excitatory modulation processes and the CPM test to the inhibitory process. TS is believed to be the psychophysical correlate of wind-up of second-/third-order neurons reflecting central sensitization. The aim of Study 2 was to establish the novel method of cutaneous electrical stimulation to induce the noxious test stimulus. Additionally, I evaluated the noxious test stimulus in CPM in healthy volunteers.

METHODS

Study 1

Participants and Methods

This study was approved by the Ethical Committee of Nihon University School of Dentistry (EP16 D021) and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants. To avoid inter-individual variability in Quantitative Sensory Testing (QST) procedures, I performed all QST measurements.

The study included 28 women with BMS and 29 healthy female volunteers. Patients were divided into 2 groups according to duration of BMS: ≤ 6 months (subchronic BMS, n = 15) and > 6 months (chronic BMS, n = 13). The 29 healthy volunteers were enrolled from the staff of a dental hospital (control group, n = 29). QSTs were performed at the ulnar surface of the right forearm and the tongue tip. BMS was diagnosed according to ICHD3. Inclusion criteria were BMS patients with superficial intraoral pain for longer than 3 months, persistent (> 2 h/day), burning pain, and no visible clinical changes in oral mucosa (redness, swelling, lichen planus, or ulcers). All BMS patients underwent swab testing and blood testing to rule out causative diseases (e.g., oral candidiasis, nutritional deficiencies, anemia, diabetes, and hypothyroidism) for oral pain. In addition, only participants aged 30 through 74 years were enrolled, to avoid the effects of unexplained pathogenesis (< 30 years) and decline in cognitive function (> 74 years). The inclusion criterion for healthy volunteers was self-reported absence of systemic or local conditions that induce any type of orofacial pain or somatosensory changes. Patients were also excluded if they were undergoing dental treatment, had used pain

medication, antidepressants, or non-steroidal anti-inflammatory drugs during the previous 1 month, or had caffeine during the 24 hours before the test. Additionally, BMS patients with hyposalivation (evaluated by salivary flow rate for 5 minutes of gum chewing) were excluded.

All participants were examined in a quiet, temperature-controlled room (20-23°C). The QST protocol used in this study was based on that of the German Research Network on Neuropathic Pain (DFNS) (17) and comprised cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), MPS, DMA, WUR, VDT, and PPT. In patients and controls, QST was performed to evaluate the sensation at 2 sites: the tongue tip and ulnar surface of the right forearm. In total, the measurements required about 90 minutes to complete for all participants.

Thermal thresholds were determined in a method of limits with a baseline temperature of 32°C, followed by 3 sets of increasing and decreasing stimuli with a ramp inclined at 1°C /sec. A thermal sensory testing device (TSA 2001-II, MEDOC, Tel Aviv, Israel) with a thermode made of a Peltier element with a contact surface (size, 16 × 16 mm) was used for this purpose. To determine the detection threshold, the examiner instructed the participant in advance to press the button as soon as she felt a warm, cold, or hot sensation. Participants were told to keep their eyes closing throughout the QST protocol. MDT was assessed by using a standardized set of von Frey filaments (Optihair 2-Set; Marstock Nervtest, Schriesheim, Germany) that exerted forces between 0.25 and 512 mN. MPT was assessed by using a set of custom-made,

weighted, pinprick stimuli needles with fixed stimulus intensities (8, 16, 32, 64, 128, 256, and 512 mN of force with a flat contact surface, 0.2 mm in diameter; PinPrick, MRC Systems GmbH, Heidelberg, Germany). MPS was measured with a set of pinprick stimuli, and pain intensity was reported by using a numerical rating scale for each stimulus. MPS was calculated as the geometric mean of all numerical ratings. To assess DMA, soft stimuli were exerted with a cotton wisp (~5 mN), a cotton wool tip fixed to an elastic strip (~100 mN), and a cotton wool tip fixed to a stiff strip (~400 mN). Stimuli were applied by using a single stroke of approximately 1 cm in length over the tongue at each site, according to the pinprick stimuli in the protocol. WUR was evaluated by applying repeated painful stimuli (a single pinprick stimulus of 128 mN was compared to a series of 10 repetitive pinprick stimuli of the same intensity). Participants were instructed to rate pain for each stimulus on a numerical rating scale of 0–100, and an estimated mean for the 10 stimuli series was calculated. The whole procedure was repeated 5 times. VDT was assessed in 3 series of descending stimuli with a Rydel–Seiffer tuning fork (64 Hz, 8/8 scale; Arno Barthelmes & Co. GmbH, Tuttlingen, Germany) applied at a suprathreshold vibration intensity. Participants were told to give a cue when the vibration had completely stopped. PPT was also assessed by using a pressure gauge device (FDN200; Wagner Instruments, Riverside, USA) with a contacting probe surface of 1 cm2 in three series of ascending stimulus intensities.

Post-hoc comparisons were evaluated by using the Bonferroni test with correction for multiple comparisons. All data in the text and table are presented as mean ± SD. To examine differences between BMS patients and controls in the QST variables, a Z-score transformation was performed for all QST variables, to provide a somatosensory

profile. The detailed method of Z-score calculation has been described elsewhere (18). Briefly, Z-score = (single patient X – control mean) / control SD. A Z-score greater than ± 1.96 (i.e., outside the 95% confidence interval) was considered an abnormal value. A positive Z-score indicated sensory gain, and a negative Z-score indicated sensory loss. To avoid the loss of values of 0, a small constant (0.1) was added to all pain ratings (MPS, DMA). DMA and PHS are normally not present in healthy subjects; thus, Z-score transformation was not performed. Stepwise discriminant analyses (method: minimize Wilks' lambda) were used to identify predictive discriminators among the 13 variables. The Fisher canonical linear discriminant function was used for classification. SPSS software (ver. 20.0 for Windows; IBM, Tokyo, Japan) was used for these analyses, and a p value of < 0.05 was considered to indicate statistical significance.

Study 2

Participants and Methods

This study included 25 healthy female volunteers. All participants were examined in a quiet, temperature-controlled room (20-23°C) and exposed to two psychophysical test models, TS and CPM. the right chin was stimulated with an IES electrode (PNS-7000, Nihon Kohden, Tokyo, Japan), developed by Inui et al.(19) . The electrode consists of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By gently pressing the device against the skin, the needle cathode was inserted into the epidermis of the chin, within the sensory territory of the mental nerve .

TS was assessed with IES. The intensity of the test-stimulus was defined as a single stimulus that evoked pain of at least 20－30/100 on a numerical rating scale (NRS). The stimulation for selective activation of the C fibers was defined as over intensity of

the stimulation (0.125 mA) based on the criteria of the Diabetic Neuropathy Study Group in Japan(20).A single stimulus followed by 10 successive stimuli were applied at a frequency of 1 Hz. Patients were asked to rate the resulting sensation on the NRS (0 to 100, where 100 is the maximum possible pain, and 0 is no pain). NRS scores were obtained after the first stimulus, and at the end of the 10 stimuli. TS was calculated by the difference between these two values. For the CPM assessment, stimulation of the non-dominant hand in the 40˚C condition or the 47˚C condition served as the conditioning stimulus (CS), and the TS protocol above, served as the test stimulus. Warm or hot stimulation was applied to the non-dominant hand for 10 seconds with a thermode (Intercross 210, Intercross, Tokyo, Japan). The thermode consisted of a Peltier element with a 10 × 10 mm contact area. The participants were asked to report on the level of the perceived pain intensity using a NRS as noted above. Data were collected after the first and then at the end of 10 stimuli delivered. The TS with or without applying conditioning stimulus (40 ˚C or 47˚C) was calculated, respectively. The difference between TS values with and without conditioning stimulus represented CPM. In reporting the CPM, negative values indicated pain reduction. The interval between two CPM (40˚C or 47˚C) protocols was 15 minutes.

All data in the text is presented as mean ± SD. The two-tailed t-test was used to detect the differences between BMS patients and controls in the QST test. One-way analysis of variance (ANOVA) followed by Tukey-test was used to analyze the differences in TS values in detecting CPM in healthy volunteer. SPSS software (ver. 20.0 for Windows; IBM, Tokyo, Japan) was used for all analyses. A p value of < 0.05 was considered statistically significant.

RESULTS

No significant difference was found in age between BMS patients (54.8 ± 12.1 years) and controls (49.9 ± 6.9 years) and between subchronic BMS patients (51.9 ± 13.6 years) and chronic BMS patients (58.1 ± 9.6 years). Among all the BMS patients, the proportion of those who had attained menopause was 67.9% (20/28). The percentage of patients who had attained menopause in the subchronic and the chronic groups was 66.7% (10/15) and 76.9% (10/13), respectively. Chi-square test showed no significant difference in the proportion of patients who had attained menopause between the subchronic group and the chronic group ($p = 0.549$). ANOVA revealed that MPS was significantly higher (indicating a gain in sensitivity) at both the tongue and forearm, in the chronic BMS group than in the control group ($p < 0.05$ and $p < 0.01$, respectively).

Z-score

Figures 1 and 2 show Z-scores for all QST variables. Z-scores were calculated for the tongue and forearm in the subchronic and chronic BMS groups. With the exception of MPS and MDT, responses to sensory tests remained within the 95% confidence interval of the baseline reference database (Z-scores within ±1.96; Figures. 1 and 2). Figure 1 illustrates loss of function, as detected by MDT, at the tongue in the chronic BMS group (Z-score = −2.13), despite gain of function by MPS at the forearm (Z = −1.99). In the subchronic BMS group, abnormal Z-scores at the tongue were detected for TSL in 2 patients (13.3%), for CPT in 4 patients (26.7%), for HPT in 2 patients (13.3%), for MDT in 2 patients (13.3%), for MPT in 2 patients (13.3%), for PPT in 5 patients (33.3%), for WUR in 1 patient (6.7%), and for MPS in 1 patient (6.7%).

Similarly, abnormal Z-scores at the forearm were detected for WDT in 1 patient (6.7%), for TSL in 1 patient (6.7%), for VDT in 2 patients (13.3%), for PPT in 4 patients (26.7%), and for WUR in 1 patient (6.7%) (Figure . 2). In the chronic BMS group, abnormal Z-scores at the tongue were detected for CDT in 2 patients (15.4%), for WDT in 2 patients (15.3%), for TSL in 1 patient (7.7%), for CPT in 2 patients (15.4%), for HPT in 1 patient (7.7%), patients for MDT in 3 (23.1%), for MPT in 1 patient (7.7%), for PPT in 6 patients (46.2%), and for MPS in 2 patients (15.4%). Abnormal Z-scores at the forearm were detected for CDT in 1 patient (7.7%), for WDT in 2 patients (15.4%), for TSL in 1 patient (7.7%), for CPT in 1 patient (7.7%), for HPT in 1 patient (7.7%), for PPT in 3 patients (23.1%), and for MPS in 4 patients (30.8%) (Figure. 2).

Multivariate Analysis

The requirements for inclusion of variables in stepwise discriminant analysis (minimize Wilks' lambda) were a firm scientific rationale and differences between the BMS (subchronic or chronic) group and healthy volunteers at the forearm or tongue. In the subchronic BMS group, stepwise discriminant analysis identified PPT at the tongue as a variable sufficient to discriminate BMS patients from controls (Wilks' lambda = 0.607); this was not the case, however, for the forearm (Wilk's lambda = 0.735). In the chronic BMS group, stepwise discriminant analysis identified MDT and MPS at the tongue, and MPS at the forearm, as variables sufficient to discriminate BMS patients from controls (Wilks' lambda = 0.513 and 0.515, respectively). The other variables were not contributory. The Fisher linear discriminant function correctly classified 79.3% of patients with subchronic BMS (using data from the tongue), 96.6% of chronic BMS patients (using data from the tongue), and 89.7% of chronic BMS patients (using data

from the forearm).

Study 2

The mean age of the participants was 48.6 ± 6.7 years (range, 40-61).

TS

TS under the 47˚C condition was significantly smaller when compared to both TS without the conditioning stimulus and TS under the 40˚C condition ($p < 0.01$ and $p < 0.05$, respectively) (Figure.3).

CPM

The mean CPM values under the 40˚C condition and the 47˚C condition were -5.8 ± 12.3 and -13.8 ± 14.8, respectively. The CPM effect during the 47˚C condition was significantly stronger than that during the 40˚C condition ($p < 0.05$)

DISCUSSION

Study 1

Several studies have used QSTs (3, 21–25) and electrophysiological modalities (3, 26–28) to characterize the somatosensory function of BMS patients. However, data on sensation and reflexes have been conflicting. Hartmann et al. (22) reported that BMS patients were significantly less sensitive in cold detection at the tongue, whereas Yilmaz et al. (21) reported that they were significantly more sensitive than healthy volunteers, which suggest cold hypoesthesia and cold hyperesthesia, respectively. Three studies (3, 23, 24) reported decreased sensitivity in warm detection at the tongue in BMS patients as compared with controls. Forssell et al. (3) and Svensson et al. (23) reported decreased pre-pain range, which suggests that the difference between thresholds of warm detection and pain recognition was closer in BMS patients than in controls. Svensson et al. (23) and Mo et al. (24) reported a higher pain threshold in BMS patients than in healthy volunteers, indicating heat hypoalgesia. However, Kaplan et al. found no difference in warm or cold perception between BMS patients and healthy volunteers (25), which is consistent with our results . The frequency of BMS among women increases with age, which may suggest that the hormonal changes due to menopause may play a role in the etiopathogenesis of BMS. In this study, I found no significant difference in the number of patients who had attained menopause between the subchronic and chronic BMS groups ($p = 0.549$). These results revealed the evidence of a lack in the relationship between menopause and chronicity of BMS. However, further research is needed to validate this finding.

Studies of pain response against topical capsaicin application in BMS patients have

also yielded inconsistent results. Just et al. reported an increased pain threshold (loss of sensation) in BMS patients after exposure to graded concentrations of capsaicin solutions (29), while Yilmaz et al. reported that BMS patients exhibited increased pain intensity (response gain) against topical capsaicin at a fixed concentration (21). Grushka, et al. reported decreased heat pain tolerance at the tongue tip in BMS patients (30). This study also showed increased response to pinprick stimuli (MPS Z-score), despite loss of sensation against innocuous mechanical stimuli (MDT Z-score) in women with chronic BMS. Ito et al. reported that duration and intensity of post-stimulus pain were greater in BMS patients than in controls after mechanical stimulation (31). Puhakka et al. reported that BMS patients had higher vibratory detection thresholds and prolonged mental nerve blink reflex latencies (27). This study , MDT Z-score at the tongue was markedly negative in 3 of 13 chronic BMS patients (−8.8, −10.9, and −13.3, respectively), although this hypoesthesia was not observed at the forearm in these patients. In contrast, the remaining 10 patients showed no signs of hypoesthesia at the tongue. Interestingly, only 3 patients exhibited significant hypoesthesia, and the remaining 10 patients exhibited normal tactile sensation, although discriminant analysis revealed that MDT was a critical classifier. Jääskeläinen et al. found that the electrical threshold necessary to elicit the tactile R1 component of blink reflex was higher in primary BMS patients than in controls and that the pain-related R3 component (ultra-late latency) was more frequently observed in BMS patients than in controls (26). This indicates hypofunction of the trigeminal tactile Aβ fiber, despite sensitization of pain-related small fibers. These neurophysiological and electrophysiological studies suggest that BMS is not simply characterized by a decreased pain threshold at the affected site; it may also be associated with decreased sensitivity in detecting innocuous stimuli and increased response to noxious stimuli.

Discriminant analysis allows for identification of predictor variables, mainly those based on metric-independent variables such as Z-scores, as in the present study (28).In this study, MDT at the tongue, and MPS at the tongue and forearm, were identified as critical classifiers in the chronic BMS group, which suggests that MDT and MPS can differentiate BMS patients and healthy volunteers, in relation to pain duration in patients. Some researchers recommend further classifying primary BMS according to the extent to which the condition relies on central or peripheral mechanisms (11, 32). This suggests that BMS patients can be characterized by their capacity for an exaggerated pain response in the absence of lowered pain thresholds. Past and present data (26, 29) show that BMS duration is positively associated with the likelihood of exaggerated pain response. Psychophysical (e.g., Visual Analog Scale and Numerical Rating Scale) and neurophysiological tests (e.g., mechanical thresholds and thermal thresholds) depend on patient attention and compliance. Imaging studies suggest that the pain modulation system in the central and peripheral nervous systems is dysregulated in BMS patients (33–37). Shinozaki et al. noted pain habituation in healthy controls, but not in BMS patients, when the participants were exposed to intervals of repetitive noxious heat stimuli. Further, brain activation in the areas associated with pain modulation (e.g., the anterior cingulate and the prefrontal and insular cortices-areas important in emotion and affection) showed waning activation that corresponded to repetition of noxious stimuli in BMS patients (35). This suggests an increased pain response but not a decreased pain threshold in BMS patients.

This study has limitations. First, I used a 16 × 16 mm thermode to detect thermal

thresholds. Discrepancies in thermal testing results may be attributable to differences in the size of the applied contact thermal probes. The thermode used in this study (16 × 16 mm) was larger than those used in the studies of Hartmann et al. (22) and Mo et al.(24), and this may have required greater intensity for a response. Additional studies will be necessary before a consensus can be reached regarding the optimal size of thermodes for research on trigeminal somatosensory function. Second, I limited participant age to 30 through 74 years, to avoid the effects of unknown hormonal dysfunction and cognitive decline. Furthermore, to exclude secondary BMS I established precise inclusion and exclusion criteria, which decreased the sample size for primary BMS patients, especially those between 40 and 59 years of age. I preferred this to expanding the patient population, however, because I believe it was essential to focus carefully on the pathology of interest. I hope that a future meta-analysis will be able to use QST data from participants with reliable diagnoses.

Study 2

I demonstrated that temporal summation was successfully induced using the IES device which allowed a selective activation of C fibers in healthy volunteers. CPM was induced under the 47˚C condition, but not under the 40˚C condition, suggesting the 47˚C condition resulted in acceleration of the inhibitory pain modulation. This pilot study showed a utility of CPM in observing the effectiveness of the pain modulation, which may be applicable in evaluating the vulnerability of the pain modulation system in chronic pain conditions like BMS as compared to healthy controls.

CONCLUSION

MDT showed loss of sensation, while MPS represented gain of sensation, only in patients with BMS pain longer than 6 months' duration. This exaggerated pain response suggests dysregulation of the pain modulation system in the central and peripheral nervous systems in patients with BMS symptoms persisting longer than 6 months. CPM utilizing epidermal electrical stimulation as a test stimulus is useful in evaluating the function of the pain modulation system and is expected to be applied in investigating vulnerability of the pain modulation system in chronic pain conditions.

REFERENCES

1. Eliav,E., Gracely,R.H., Nahlieli,O. and Benoliel,R. (2004) Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain, 18(4), 339–344.

2. Eliav,E., Kamran,B., Schaham,R., Czerninski,R., Gracely,R.H. and Benoliel,R. (2007) Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. J Am Dent Assoc, 138(5), 628–633.

3. Forssell,H., Jääskeläinen,S., Tenovuo,O. and Hinkka,S. (2002) Sensory dysfunction in burning mouth syndrome. Pain, 99(1-2), 41–47.

4. Grushka,M. and Epstein,J.B. (2002) Burning mouth syndrome. Am Fam Physician, 65(4), 615–620.

5. Jääskeläinen SK (2004) Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain, 18(2), 85–107.

6. Lauria,G., Majorana,A., Borgna,M., Lombardi,R., Penza,P., Padovani,A., et al. (2005) Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain, 115(3), 332–337.

7. Femiano,F., Gombos,F. and Scully,C. (2004) Burning mouth syndrome: The efficacy of lipoic acid on subgroups. J Eur Acad Dermatol Venereol, 18(6), 676–678.

8. Grushka,M., Epstein,J.B. and Gorsky,M. (2003) Burning mouth syndrome and other oral sensory disorders: a unifying hypothesis. Pain Res Manag, 8(3), 133–135.

9. Hershkovich,O. and Nagler,R.M. (2004) Biochemical analysis of saliva and taste acuity evaluation in patients with burning mouth syndrome, xerostomia and/or gustatory disturbances. Arch Oral Biol, 49(7), 515–522.

10. Hagelberg,N., Forssell,H., Rinne,J.O., Scheinin,H., Taiminen,T., Aalto,S., et al.

(2003) Striatal dopamine D1 and D2 receptors in burning mouth syndrome. Pain, 101(1-2), 149–154.

11. Jääskeläinen,S.K. (2012) Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol, 123(1), 71–77.

12. Nasri-Heir,C., Gomes,J., Heir,G.M., Ananthan,S., Benoliel,R., Teich,S., et al. (2011) The role of sensory input of the chorda tympani nerve and the number of fungiform papillae in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 112(1), 65–72.

13. Merskey,H. and Bogduk,N. (1994) Classification of chronic pain descriptions of chronic pain syndrome and definitions of pain terms second edition. Seattle, IASP Press

14. Loeser JD, Butler SH, Chapman CR, Turk DC, eds. (2001) Bonica's management of pain.3rd ed. Philadelphia : Lippincott Williams & Wilkins, 855-866

15. Tighe,P., Buckenmaier,C.C., Boezaart,A.P., Carr,D.B., Clark,L.L., Herring,A.A., et al. (2015) Acute pain medicine in the United States: a status report. Pain Med, 16(9), 1806–1826.

16. Headache Classification Committee of the International Headache and Society (2018) The International Classification of Headache Disorders 3rd edition. Cephalalgia, 38(1), 1–211.

17. Rolke,R., Baron,R., Maier,C., Tölle,T.R., Treede,R.D., Beyer,A., et al. (2006) Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain, 123(3), 231–243.

18. Rolke,R., Magerl,W., Campbell,K.A., Schalber,C., Caspari,S., Birklein,F., et al. (2006) Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain, 10(1), 77–88.

19. Inui,K., Tran,T.D., Qiu,Y., Wang,X., Hoshiyama,M. and Kakigi,R. (2002) Pain-related magnetic fields evoked by intra-epidermal electrical stimulation in humans. Clin Neurophysiol, 113(2), 298–304.

20. Kukidome,D., Nishikawa,T., Sato,M., Igata,M., Kawashima,J., Shimoda,S., et al. (2016) Measurement of small fibre pain threshold values for the early detection of diabetic polyneuropathy. Diabet Med, 33(1), 62–69.

21. Yilmaz,Z., Egbuniwe,O. and Renton,T. (2016) The detection of small-fiber neuropathies in burning mouth syndrome and iatrogenic lingual nerve injuries: Use of quantitative sensory testing. J Oral Facial Pain Headache, 30(2), 87–98.

22. Hartmann,A., Seeberger,R., Bittner,M., Rolke,R., Welte-Jzyk,C. and Daubländer,M. (2017) Profiling intraoral neuropathic disturbances following lingual nerve injury and in burning mouth syndrome. BMC Oral Health, 17(1), 68.

23. Svensson,P., Bjerring,P., Arendt-Nielsen,L. and Kaaber,S. (1993) Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. Clin J Pain, 9(3), 207–215.

24. Mo,X., Zhang,J., Fan,Y., Svensson,P. and Wang,K. (2015) Thermal and mechanical quantitative sensory testing in chinese patients with burning mouth syndrome – a probable neuropathic pain condition? J Headache Pain, 16, 84.

25. Kaplan,I., Levin,T., Papoiu,A.D.P., Patel,N., Patel,T., Calderon,S., et al. (2011) Thermal sensory and pain thresholds in the tongue and chin change with age, but are not altered in burning mouth syndrome. Skin Res Technol, 17(2), 196–200.

26. Jaaskelainen,S.K., Forssell,H. and Tenovuo,O. (1997) Abnormalities of the blink reflex in burning mouth syndrome. Pain, 73(3), 455–460.

27. Puhakka,A., Forssell,H., Soinila,S., Virtanen,A., Röyttä,M., Laine,M., et al. (2016) Peripheral nervous system involvement in primary burning mouth syndrome-results of

a pilot study. Oral Dis, 22(4), 338–344.

28. Escolano-Lozano,F., Barreiros,A.P., Birklein,F. and Geber,C. (2018) Transthyretin familial amyloid polyneuropathy (TTR-FAP): Parameters for early diagnosis. Brain Behav, 8(1), e00889.

29. Just,T., Steiner,S. and Pau,H.W. (2010) Oral pain perception and taste in burning mouth syndrome. J Oral Pathol Med, 39(1), 22–27.

30. Grushka,M., Sessle,B.J. and Howley,T.P. (1987) Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. Pain, 28(2), 169–184.

31. Ito,M., Kurita,K., Ito,T. and Arao,M. (2002) Pain threshold and pain recovery after experimental stimulation in patients with burning mouth syndrome. Psychiatry Clin Neurosci, 56(2), 161–168.

32. Gremeau-Richard,C., Dubray,C., Aublet-Cuvelier,B., Ughetto,S., Woda,A., Grémeau-Richard,C., et al. (2010) Effect of lingual nerve block on burning mouth syndrome (stomatodynia): a randomized crossover trial. Pain, 149(1), 27–32.

33. Albuquerque,R.J.C.C., de Leeuw,R., Carlson,C.R., Okeson,J.P., Miller,C.S. and Andersen,A.H. (2006) Cerebral activation during thermal stimulation of patients who have burning mouth disorder: an fMRI study. Pain, 122(3), 223–234.

34. Khan,S.A., Keaser,M.L., Meiller,T.F., Seminowicz,D.A., Eliav,E., Khan,S.A., et al. (2014) Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain, 155(8), 1472–1480.

35. Shinozaki,T., Imamura,Y., Kohashi,R., Dezawa,K., Nakaya,Y., Sato,Y., et al. (2016) Spatial and temporal brain responses to noxious heat thermal stimuli in burning mouth syndrome. J Dent Res, 95(10), 1138–1146.

36. Sinding,C., Gransjoen,A.M., Schlumberger,G., Grushka,M., Frasnelli,J. and

Singh,P.B. (2016) Grey matter changes of the pain matrix in patients with burning mouth syndrome. Eur J Neurosci, 43(8), 997–1005.

37. Wada,A., Shizukuishi,T., Kikuta,J., Yamada,H., Watanabe,Y., Imamura,Y., et al. (2017) Altered structural connectivity of pain-related brain network in burning mouth syndrome - investigation by graph analysis of probabilistic tractography. Neuroradiology, 59(5), 525–532.

Figure Legends

Figure. 1. Mean overall Z-scores

Results of quantitative sensory testing (QST) (Z-scores)

All QST variables are presented as Z-scores. A Z-score greater than 0 indicates increased sensation, and a Z-score less than 0 indicates loss of sensory function. Z-scores greater than ±1.96 indicate values outside the 95% confidence interval of the baseline values .

Figure. 2. Overall Z-score profiles

Results of quantitative sensory testing (QST) (Z-scores).

All QST variables are presented as Z-scores. A Z-score greater than 0 indicates increased sensation, and a Z-score less than 0 indicates loss of sensory function. Z-scores greater than ±1.96 indicate values outside the 95% confidence interval of the baseline values.

Figure. 3. Essential results of temporal summation

The resulting sensation on NRS of 0 to 100 was recorded after the single and the series (10 stimuli). The data were recorded with and without conditioning stimulus (40˚C or 47˚C). * $p < 0.05$, ** $p < 0.01$

Variable	Control		Subchronic Group (≦ 6m)		Chronic Group (> 6m)	
	tongue	forearm	tongue	forearm	tongue	forearm
CDT (℃)	-2.7 ± 1.5	-4.6 ± 1.9	-2.4 ± 1.2	-4.0 ± 2.5	-3.0 ± 2.4	-4.9 ± 3.5
WDT (℃)	2.5 ± 1.0	4.5 ± 1.3	2.4 ± 0.1	4.5 ± 1.5	2.9 ± 1.7	5.6 ± 2.2
TSL (℃)	1.6 ± 1.3	1.2 ± 1.3	1.1 ± 1.7	2.8 ± 9.3	1.7 ± 1.2	0.5 ± 1.5
CPT (℃)	9.65 ± 5.4	11.1 ± 7.7	13.5 ± 7.7	14.3 ± 8.2	13.0 ± 3.5	13.9 ± 7.6
HPT (℃)	45.9 ± 3.1	44.0 ± 3.4	44.3 ± 4.3	43.6 ± 3.2	44.7 ± 3.5	44.2 ± 3.1
MDT (mN)	0.1 ± 0.0	3.7 ± 3.7	0.1 ± 0.1	3.0 ± 1.9	0.1 ± 0.1	3.2 ± 1.8
MPT (mN)	56.0 ± 35.6	119.2 ± 95.1	45.5 ± 46.1	91.6 ± 93.2	45.4 ± 46.2	125.6 ± 5.1
WUR (ratio)	4.0 ± 3.4	4.6 ± 3.1	3.5 ± 2.7	4.5 ± 5.0	2.5 ± 1.1	3.2 ± 1.9
MPS (ratio)	4.2 ± 6.6	2.4 ± 3.7	9.5 ± 9.0	4.4 ± 6.3	**13.1 ± 14.1***	**9.7 ± 10.9****
DMA (ratio)	0.2 ± 0.2	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	1.5 ± 5.0	0.1 ± 0.0
VDT (x/8)	5.4 ± 0.8	5.4 ± 0.6	5.2 ± 0.7	5.4 ± 0.7	5.3 ± 0.7	5.1 ± 0.6
PPT (kPa)	1.0 ± 0.3	3.2 ± 0.8	0.7 ± 0.4	2.8 ± 1.3	0.7 ± 0.6	3.2 ± 1.7

Table.1 Quantitative sensory testing results

Post-hoc multiple comparisons were performed with the Bonferroni test after one way ANOVA

*$p < 0.05$ **$p < 0.01$ vs. controls

CDT : cold detection threshold, WDT : warm detection threshold, TSL : thermal sensory detection threshold, CPT : cold pain thoreshold, HPT : heat pain threshold, MDT : mechanical detection threshold, MPT : mechanical pain thoreshold, WUR : wind-up ratio, MPS : mechanical pain sensitivity, DMA : dynamic mechanical allodynia, VDT : vibration detection threshold, PPT : pressure pain threshold

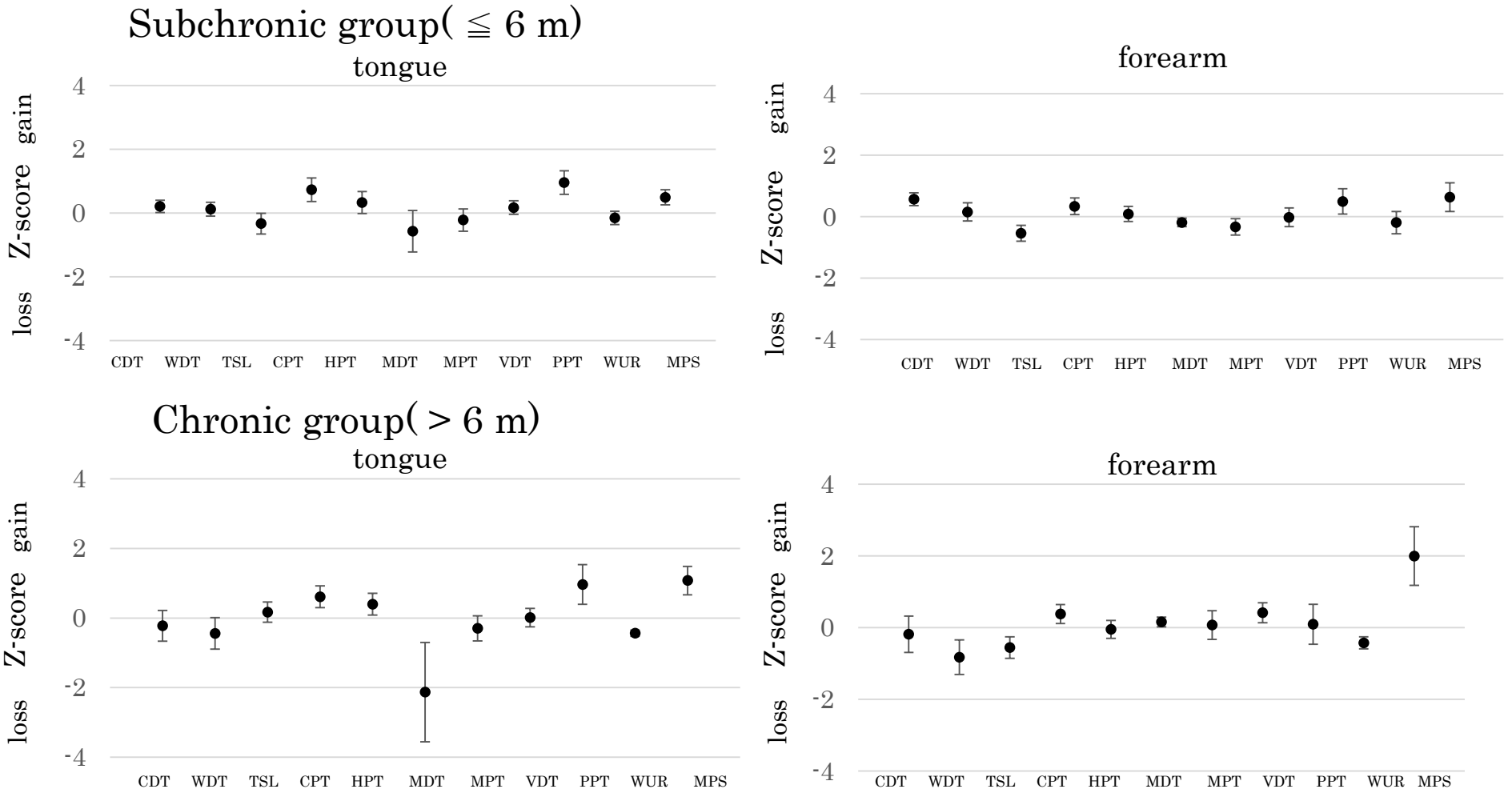

Figure.1　Mean overall Z-scores

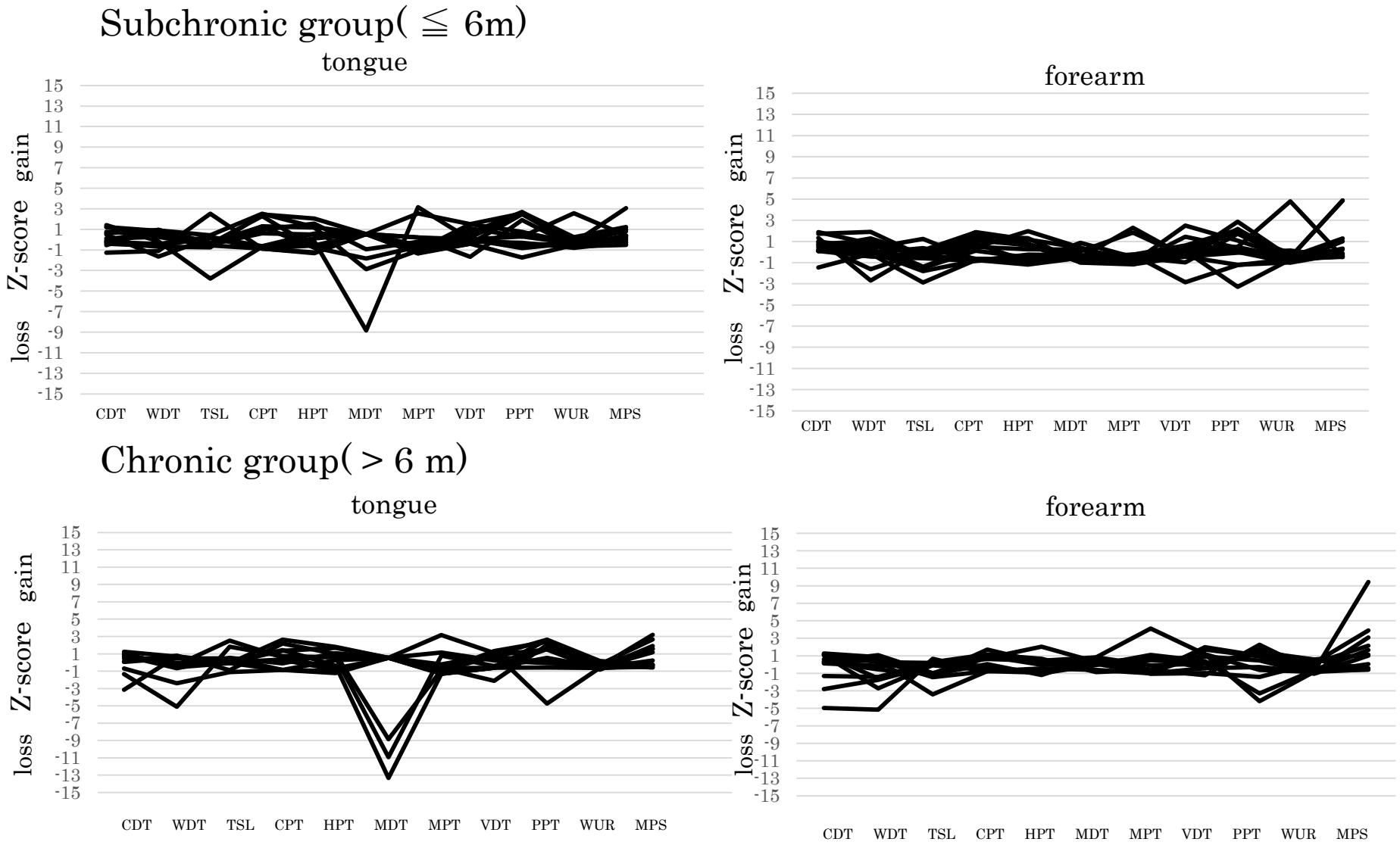

Figure.2 Overall Z-score profiles

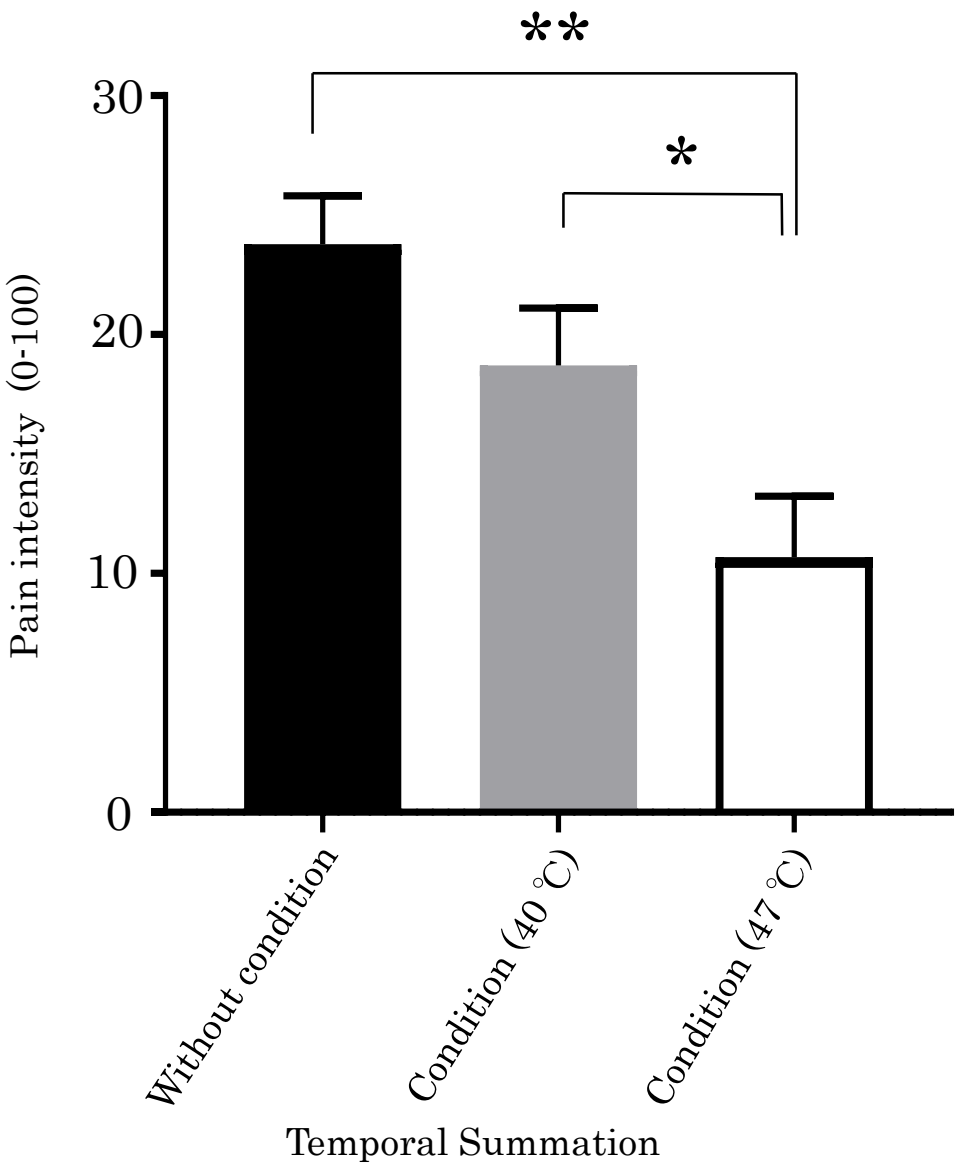

Figure.3 Essential results of temporal summation
* $p < 0.05$, ** $p < 0.01$