Involvement of psychological factors and the menstrual status in burning mouth syndrome

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Table of Content

This doctoral thesis consists of the following articles:

1. Ozasa K, Noma N, Kobayashi M, Takizawa K, Young A, Eliav E, Imamura Y: Association between anxiety and descending pain modulation of thermal stimuli in patients with burning mouth syndrome: a cross-sectional study. J Oral Facial Pain Headache. 2021, in press.

2. Ozasa K, Noma N, Young A, Olga A, Eliav E, Imamura Y: Potential differences in somatosensory function during premenopause and early and late postmenopause in patients with burning mouth syndrome: An observational case-control study. J Dent Sci. 2021, in press.

Abstract

Aims: Burning mouth syndrome (BMS) has long been thought to be associated with psychosocial distress and depletion of sex hormones. Previous quantitative sensory testing (QST) studies have revealed abnormal responses that suggest temporal summation induced by central sensitization in BMS patients. However, the role of these psychosocial or menstrual factors in leading to the somatosensory alterations in the chronic pain condition remains elusive. Therefore, I have conducted the following two studies in order to elucidate the pathophysiology of BMS from the neuropathic point of view.

Study 1 aimed to investigate the predictive power of depression and anxiety for conditioned pain modulation (CPM). I also examined the relationships between the magnitude of the CPM with non-painful (40°C) or painful (47°C) conditioning stimulus (CS) and age, pain intensity, pain duration, and the scores of psychosocial inventories in BMS. Study 2 addressed the role of hormonal balance in alteration of the somatosensory function in BMS patients with premenopausal, early postmenopausal, and late postmenopausal statuses.

Methods: Twenty-two patients with BMS and 22 healthy female controls were included in Study 1. For CPM, temporal summation was used as the test stimulus and subsequent exposure either to a non-painful (40°C) or painful (47°C) Peltier thermode was used as the CS. CPM was calculated as the difference in pain perception following the CS. Psychosocial factors were examined using the Profile of Mood States (POMS) and the State-Trait Anxiety Inventory (STAI). Study 2 included 36 women with BMS and 42 age-matched healthy female

volunteers. The QST battery was applied at the tip of the tongue. Data for BMS patients and controls were compared and analyzed.

Results: In Study 1, state anxiety and tension-anxiety scores were significantly higher for patients with BMS than for control participants. Multiple regression analyses showed that CPM47°C was affected by vigor, fatigue, confusion, and state anxiety (adjusted R^2 = 0.685, F = 5.147, *P* = .098). The corresponding analysis for CPM40°C showed that the model was not predictive for the following variables: disease-related pain, pain duration, or components of the POMS and STAI. A significant positive correlation was found between CPM47°C and trait anxiety, suggesting that trait anxiety negatively affected the endogenous pain modulation system. In Study 2, the Z-score in the late postmenopausal BMS group revealed a gain of function for the cold pain threshold and heat pain threshold (Z = 2.08 and 3.38, respectively).

Conclusion: Increases in trait anxiety reduced the CPM effect. My findings suggest that CPM impairments and increases in trait anxiety are involved in the development of BMS. Late postmenopausal patients with BMS showed an increased response of the tongue to noxious thermal stimuli. This supports the theory that changes in sex hormones may affect trigeminal somatosensory function in patients with BMS.

Keywords: burning mouth syndrome, sex hormone, menopause, psychosocial factor, conditioned pain modulation

Introduction

Burning mouth syndrome (BMS) is a chronic condition defined by the International Classification of Orofacial Pain (ICOP) as "an intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without evident causative lesions on clinical examination and investigation."[1] The pathogenesis of BMS remains poorly understood, although both physiological and psychological factors have been hypothesized to be involved. Psychological factors account for BMS symptoms in more than 50% of patients.[2,3] Some studies show psychosocial comorbidities similar to those of other persistent pain conditions. Galli et al. reported anxiety and depression as the most common comorbid disorders among patients with BMS using the State-Trait Anxiety Inventory (STAI) and the Hospital Anxiety and Depression Scale.[4] Psychosocial events are often associated with the onset or exacerbation of symptoms in patients with BMS. Many previous studies have also reported that patients with BMS may be predisposed to develop depression and anxiety.[5–7]

The pain modulation system can be assessed using two dynamic psychophysical testing methods: temporal summation (TS) and conditioned pain modulation (CPM).[8] CPM is a test paradigm used in human beings that potentially

represents the diffuse noxious inhibitory control mechanism. In CPM paradigms, one noxious stimulus (i.e., the conditioning stimulus, or CS) is used to inhibit the intensity of another noxious stimulus (test stimulus, or TS). CPM can occur when the CS and the TS are remote from each other.[9] In a variety of pain disorders, less efficient CPM responses have been observed.[10,11] In a previous study, Nishihara et al. found an association between deficient inhibitory CPM and the development of BMS.[12] I also demonstrated that the magnitude of CPM with a non-painful CS in BMS patients was equal to that in healthy controls, whereas CPM induced by a painful CS was suppressed in BMS patients but not in healthy controls.[12] Another recent study showed that patients with BMS exhibited increased intraoral windup to nociceptive afferent inputs,[8] thus demonstrating that TS is induced by a repeated painful stimulus.

Generally, psychological disorders may be associated with the modulation of pain perception, increased nerve transmission by peripheral pain receptors, and altered pain perception.[13] Psychological factors include the level of anxiety and depression, which may explain some of the interpersonal variability in pain perception and may, therefore, also play a role in CPM. The rationale for suspecting a relationship between CPM and psychological factors is that

serotonin and noradrenaline, as well as anxiety and depression, are involved in CPM responses; previous research reported that chronic pain patients with higher levels of anxiety and depression had less efficient CPM.[14, 15] However, no study has yet investigated the relationship between psychological factors and CPM in patients with BMS.

The predilection of BMS for menopausal and postmenopausal women also suggests that reduced levels of sex hormones,[16] which can influence somatosensory function, may be a factor in BMS pathogenesis, and that intraoral nociception is particularly sensitive to modulation by ovarian hormone levels.[1] A study in ovariectomized female rats showed an increased sensitivity to nociceptive stimulation in the orofacial region.[17] However, clinical behavioral studies have not verified this in premenopausal or early and late postmenopausal patients with BMS.

Although Nishihara et al. previously found an association between a deficient CPM and the development of BMS,[12] the question remains as to how CPM and psychosocial distress such as anxiety and depression are related in patients with BMS. Therefore, I aimed to answer two questions in Study 1: (1) Do psychosocial factors predict CPM with non-painful (40°C) or painful (47°C) CS

applied to the non-dominant hand of patients affected by BMS? And (2) Is CPM

(40°C) or CPM (47°C) correlated with age, disease-related pain, pain duration,

and psychosocial factors such as depression and anxiety? In Study 2, I aimed to

assess somatosensory function in premenopausal, early, and late

postmenopausal patients with BMS, compared with healthy volunteers, and

investigated the association between quantitative sensory testing (QST) data and

the stage of menopause.

Methods

These studies were approved by the Ethics Committee of Nihon University School of Dentistry (EP16 D020-1; February 19, 2020) and was conducted as per the Helsinki Declaration. The study conforms to STROBE guidelines. Informed consent was obtained from all patients and volunteers.

Study 1

Descending pain modulation and psychosocial factors

The study period of recruitment and data collection was between February 2020 and September 2021. This study provides a new set of BMS and control data; the dataset is different from the data Nishihara et al. previously reported.[12] The BMS group inclusion criterion was defined following the diagnostic criteria of BMS in the ICOP, and the exclusion criteria were pregnancy, chronic pain conditions in other body parts, and neurologic diseases, as well as other conditions that elicit intraoral pain.

This study also included 22 healthy female volunteers who were free of any oral or dental pathology. The mean ages of patients in the BMS and control groups were 57.5 ± 10.9 years and 53.6 ± 8.2 years, respectively, with no

significant difference (P = .14). No participant had a prior history of psychiatric, neurological, or chronic pain disorder or had received dental treatment in the six months before the experiment, except for periodontal maintenance.

Examinations took place in a quiet, temperature-controlled room (20–23°C). Although the recruiting researcher (N.N.) was aware of each participant's BMS status, the examiner (K.O.) was blinded to these data. All participants were exposed to two psychophysical test models: TS and CPM. The detailed method has been previously described.[12] Briefly, one examiner performed all TS and CPM examinations in this study. To test the TS, intra-epidermal electrical stimulation (IES) was administered to the right chin with a concentric bipolar stainless-steel electrode (Nihon Kohden, Tokyo, Japan)[18] consisting of a cylindrical anode on the outside (Ø: 1.4 mm) and a needle cathode on the inside (length: 0.1 mm). The tip of a stainless-steel needle electrode was inserted into the epidermis of the skin (0.2 mm deep). By applying the electrode against the skin, the IES needle cathode, which was located between the angle of the mouth and the middle of the chin, was pressed on the epidermis of the right chin, which is innervated by the mental nerve. The test amplitude of the stimuli was defined as a single pain-causing stimulus of at least 20–30-mm intensity on the numerical

rating scale (NRS), where 0 mm indicates no pain and 100 mm indicates the maximum pain possible. The stimulation for selective C-fiber activation was defined as excessive intensity of the stimulation (0.125 mA).[12] A single individual stimulus was followed by 10 consecutive stimuli delivered at a frequency of 1 Hz. The patients were asked to describe the intensity of pain they felt using the NRS. NRS scores were assessed after one stimulus and after 10 consecutive stimuli.

For CPM assessment, non-painful (40°C) or painful (47°C) stimulation was applied to the non-dominant hand for 10 seconds with a thermode (Intercross 210, Tokyo, Japan) as the CS. The thermode constituted a Peltier element with a 10 × 10-mm contact area. The TS was concurrently applied to the right chin. Participants were asked to rate the pain level of the TS using the NRS. The difference between the TS with non-painful or painful CS and the TS without CS was calculated. When reporting CPM results, negative values indicate a significant reduction in pain. The three TS measurements (TS without CS, TS with 40°C CS, and TS with 47°C CS) were assessed in that order 15 minutes apart to allow for a sufficient recovery period. TS without CS was considered as

the baseline value.

Psychological testing and pain measurement

All participants underwent psychological testing. The Japanese version of the

Profile of Mood States (POMS) long form was used, which evaluates tension-

anxiety (T-A), depression-dejection (D), anger-hostility (A-H), vigor (V), fatigue

(F), and confusion (C).[19] Anxiety was measured with the Japanese STAI.[20]

Both state and trait (the situation-driven transient and the stable

personality disposition reflecting the general level of fearfulness, respectively)

anxiety were evaluated. When answering the State Anxiety Scale, participants

chose the number that best described the intensity of their feelings on a four-point

Likert scale, as follows: (1) not at all, (2) somewhat, (3) moderately, and (4) very

much so, for 13 different items. The State Anxiety Scale score ranged from 13 to

52, and the Trait Anxiety Scale score ranged from 12 to 36. Higher scores denote

higher levels of anxiety.

The perception of oral pain in BMS patients was assessed using the NRS

for pain intensity; the scores for pain ranged from 0 (no pain) to 10 (worst pain

possible). "Disease-related pain" was defined as the pain intensity reported by

the patient at the first visit.

Sample size

G*Power 3.1.3 was used to calculate the required number of subjects per group to be able to detect differences between the control and BMS groups. The two-sample means test was used to estimate the per group sample size. CPM values required to run the test (standard deviation [SD] and the "difference to detect") were selected based on previously published data.[12] An SD of 12 and a "difference to detect" of 11 were used. The alpha level was set to 0.05, and power was set to 0.8. Based on the selected parameters, the required per group sample size was estimated to be 20 to be able to detect significant differences between groups.

Study 2

Somatosensory profile with the menstrual status

In Study 2, 36 women with BMS and 42 age-matched healthy female volunteers were included. Patients with BMS were divided into three groups: premenopausal BMS (n = 12; 40.1 ± 6.0 years), early postmenopausal BMS (n = 10; 53.2 ± 2.7 years), and late postmenopausal BMS (n = 14; 70.1 ± 5.0 years). Likewise, the

healthy volunteers were divided into three groups: premenopausal control (n = 21; 45.2 ± 2.4 years), early postmenopausal control (n = 10; 55.6 ± 2.8 years), and late postmenopausal control (n = 11; 64.9 ± 10.8 years). Women whose last menstrual period occurred > 12 months prior were categorized as postmenopausal. Postmenopausal women who reached menopause ≤ 5 years prior were classified as the early postmenopausal group, while those who had reached menopause > 5 years prior were classified as the late postmenopausal group.[21,22]

QST protocol

The QST protocol used in this study was based on that of the German Research Network on Neuropathic Pain[23] and consisted of the thermal and mechanical tests at the tip of the tongue.

Thermal tests

The cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), and heat pain threshold (HPT) were determined with a computer-controlled Peltier-type thermode and the

Classic Method of Limits.

Mechanical tests

The mechanical QST protocol used in this study consisted of tests for the mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT), as described previously.

Data analysis

A two-way repeated measures analysis of variance (ANOVA) was used for a 2 (control vs. BMS groups) × 2 (CS: 40°C vs. 47°C) comparison. Applying the Shapiro–Wilk W test, the data for the following variables were confirmed to be normally distributed: T-A, D, A-H, V, F, C, state anxiety, and trait anxiety (Shapiro–Wilk; $P > .05$). Conversely, for CPM40°C or CPM47°C in the BMS group, the data did not show a normal distribution (Shapiro–Wilk W = 0.800; $P = .001$) (Shapiro–Wilk W = 0.801; $P = .001$). A paired t-test was used to compare two NRS scores (pain intensity after receiving 10 pulses vs. pain intensity after receiving a single pulse). The Mann–Whitney U test was used to compare CPM40°C or CPM47°C

between the BMS and control groups. Unpaired t-tests were also used to determine the significance of any differences between T-A, D, A-H, V, F, C, state anxiety, and trait anxiety between the BMS and healthy control groups. Multiple regression analysis was performed on the data from BMS patients to define the contribution of independent variables such as psychological parameters (age, disease-related pain, pain duration [disease duration; months], T-A, D, A-H, V, F, C, state anxiety, and trait anxiety) to the dependent variable (CPM40°C or CPM47°C) in patients with BMS. Either the corrected or adjusted R2 was calculated to determine the percentage of variance that could be explained by each of the potential predictors. Spearman's correlation analysis was used to evaluate the possible relationships among age, disease-related pain, pain duration of pain, T-A, D, A-H, V, F, C, state -anxiety, trait -anxiety, CPM40°C, and CPM47°C. SPSS software (version 20.0 for Windows; IBM, Tokyo, Japan) was used for statistical analyses. To examine the differences between patients with BMS and healthy controls for the QST variables, a Z-score transformation was performed for all QST variables to provide a somatosensory profile. The detailed Z-score calculation method has been described elsewhere.[24] A positive Z-score indicated sensory gain, and a negative Z-score indicated sensory loss. Z-scores

are presented as means ± standard errors. Other data are shown as the mean ±

SD. Differences were considered significant when *P* was less than .05.

Results

Study 1

Temporal summation

In the control group, the mean NRS scores were 24.6 ± 6.0 for a single pulse and 47.9 ± 15.0 for a train of 10 pulses in response to the test stimuli. In the BMS group, the mean NRS scores were 20.5 ± 11.4 for a single pulse and 30.5 ± 19.9 for a train of 10 pulses in response to the test stimuli. The TS score, i.e., the difference between the two NRS scores (pain intensity after receiving 10 pulses − pain intensity after receiving a single pulse), was 10.0 ± 18.1 and 23.3 ± 14.2 for the BMS and the control groups, respectively. Thus, TS was induced by a repeated painful stimulus (test stimulus) in both the BMS and control groups (Fig. 1, $P < .01$).

Conditioned pain modulation

In the control and BMS groups, the mean NRS scores were 14.7 ± 9.5 and 23.0 ± 24.9 for pain ratings of 47°C CS, respectively.

CPM was assessed with the TS test as the painful or non-painful stimulus and with 40°C and 47°C as the CS. CPM signifies the difference

between TS without CS and TS with CS; a negative value indicates a CS-induced suppression of TS. In the control group, the mean CPM values with 40°C and 47°C CS were -8.5 ± 13.5 and -16.3 ± 13.7, respectively. In the BMS group, the corresponding CPM values with 40°C and 47°C CS were -6.3 ± 16.4 and -1.4 ± 19.6, respectively. Two-way ANOVA with "group" (control group [40°C CPM and 47°C CPM] and the BMS group [40°C CPM and 47°C CPM]) as a between-subjects factor revealed a significant difference (F = 6.295, P = 0.014). However, the main effect for the CS factor revealed no significant difference (F = 0.182, P = .670) between 40°C and 47°C.

The mean CPM values with 40°C CS showed no significant difference between the BMS and control groups (P = .417, Fig. 2). However, the BMS group had a significantly lower mean CPM than the control group (P < .01, Fig. 2).

The state anxiety STAI scores were significantly higher for patients with BMS than for control participants (P = .015, Table 1), whereas no significant difference in trait anxiety STAI scores was detected between the BMS and control groups (P = .12). Regarding POMS results, T-A values were significantly higher in patients with BMS than in control participants (P = .007, Table 1). There was no significant difference in item scores of other POMS components such as D, A-

H, V, F, and C (P = .057, P = .612, P = .176, P = .688 and P = .595) (Table 1).

Next, multiple regression analyses were performed with CPM40°C or CPM47°C as the dependent variable in the BMS group. In the CPM47°C analysis, the model using psychological parameters (age, disease-related pain, pain duration, T-A, D, A-H, V, F, C, state anxiety, and trait anxiety) explained 10.99% of CPM47°C variance in patients with BMS, and CPM47°C was affected by V, F, C and trait anxiety (adjusted R^2 = 0.69, F = 5.15, P = .098; Table 2). When analyzed for CPM40°C, the model was not predictive when the variables were age, disease-related pain, pain duration, T-A, D, A-H, V, F, C, state anxiety, and trait anxiety (adjusted R^2 = 0.100, F = 0.820, P = .80; Table 3). In the control group, multiple regression analysis was performed for CPM40°C or CPM47°C, and the model was not predictive when the variables were age, pain intensity, pain duration, T-A, D, A-H, V, F, C, state anxiety, and trait anxiety (CPM40°C; adjusted R^2 = 0.12, F = 1.30, P = .51; Table 3) (CPM47°C; adjusted R^2 = 0.27, F = 0.51, P = .76; Table 2 and 3).

I also performed Spearman's correlation analysis for the following variables: age, disease-related pain, pain duration, T-A, D, A-H, V, F, C, state anxiety, trait anxiety, CPM40°C, and CPM47°C. The results of the BMS group

showed that trait anxiety correlated with D, V, and F, whereas state anxiety correlated with D, A-H, V, and trait anxiety (Table 4). CPM47°C showed statistically significant and positive correlations with trait anxiety (Fig. 3, $P = 0.027$ and r = 0.51). In contrast, CPM40°C did not correlate with any of the examined variables. In the control group, I performed Spearman's correlation analysis for the following variables: age, T-A, D, A-H, V, F, C, state anxiety, trait anxiety, CPM40°C, and CPM47°C. The results showed that trait anxiety correlated with T-A, D, A-H, and state anxiety, whereas CPM40°C and CPM47°C did not correlate with state anxiety and trait anxiety.

Study 2

Table 5 shows the raw data at the tongue for all QST in the premenopausal, early postmenopausal, and late postmenopausal BMS groups. The pressure pain threshold was significantly decreased in the premenopausal BMS group (0.6 ± 0.4) compared to premenopausal controls (1.1 ± 0.3) ($P < .01$). Among the early postmenopausal groups, the vibration detection threshold was significantly decreased in the BMS group (4.9 ± 0.6) compared with controls (5.7 ± 0.8) ($P < .01$). In the late postmenopausal groups, significant differences were observed

in the comparison of the cold pain threshold (5.8 ± 4.9 °C, controls; 16.1 ± 0.5 °C, BMS) and heat pain threshold (48.1 ± 1.3 °C, controls; 43.7 ± 3.5 °C, BMS) indicating cold and heat hyperalgesia at the tongue ($P < .01$ and $P < .05$, respectively).

Z-score

In the premenopausal and early postmenopausal BMS groups, the means of all the parameters of the tongue remained within the 95% confidence interval of the baseline reference database (Z-scores within ± 1.96; data not shown). On the other hand, in the late postmenopausal BMS group, a mean gain of function in terms of the cold pain threshold and heat pain threshold at the tongue ($Z = 2.08$ and 3.38, respectively) was observed (Fig. 4).

Discussion

Study 1

While many studies have already been performed on the role of psychiatric disorders in the pathogenesis of BMS,[25-27] it remains unknown how anxiety and depression are involved in pain modulation mechanisms in BMS. Sikora et al. found that patients with BMS had increased anxiety, depression, and somatization scores, as well as hostility dimensions, compared with those of control participants.[28] Matsuoka et al. also found that anxiety was significantly higher in patients with BMS than in control participants.[29] There were significant differences in state anxiety and T-A between the BMS and control groups. The increased state anxiety is consistent with results of previous studies[5,28–30]; however, some studies did not confirm significant differences in psychological test scores between patients with BMS and control participants.[31,32] This discrepancy may be due to differences in age, disease-related pain, pain duration, sample size, psychosocial factors, or the type of psychological tests used.[31]

A previous study demonstrated that patients with BMS exhibit increased intraoral windup to repetitive nociceptive afferent inputs.[8] In this study, TS was induced after 10 consecutive stimuli by IES in both patients with BMS and control

participants. As expected, in the control group, the 47°C CS resulted in a significantly higher CPM efficiency when compared with the 40°C CS. By contrast, CPM with 47°C CS was less efficient than that with 40°C CS in patients with BMS.

I hypothesized that higher average scores on psychological tests would predict a reduced CPM efficiency. The multiple regression analysis using age, disease-related pain, pain duration, T-A, D, A-H, V, F, C, state anxiety, and trait anxiety as predictive variables for CPM with 47°C CS explained 10.9% of the variance in patients with BMS; the variables V, F, C, and trait anxiety contributed to reduced CPM efficiency. However, when the same variables were evaluated for CPM with 40°C CS, none were predictive in the multiple regression analysis . Thus, only when the CS accessed the inhibitory pain modulation mechanism, the parameters V, F, C, and trait anxiety predicted an impairment of CPM.

To the best of our knowledge, this is the first study that investigated the predictive clinical value of psychosocial factors for CPM efficiency in patients with BMS. Jarrett et al. demonstrated that patients with irritable bowel syndrome had decreased CPM efficiency when anxiety or fatigue symptoms were present, suggesting that an interaction between pain and anxiety reduced CPM.[33] Vidor et al. demonstrated that chronic myofascial pain patients with higher anxiety scores

exhibited reduced corticospinal modulation of the pain response.[15] In my partial correlation analysis, trait anxiety was significantly associated with CPM with 47°C CS, but not CPM with 40°C CS . The reason for psychological factors only being associated with noxious (47°C CS) but not with non-noxious (40°C CS) stimuli can be found in a previous study that demonstrated a correlation between trait anxiety and CPM when the CS was a noxious temperature stimulus (immersion of the hand in cold water); its participants scored 6/10 on the NRS.[15] Another study also found that impaired CPM efficiency in patients with irritable bowel syndrome was associated with higher anxiety and greater fatigue levels when CPM was assessed by placing the non-dominant hand in a cold-water bath maintained at 12°C as the CS.[33] The magnitude of pain inhibition depends on the intensity of the CS, as only painful,[34, 35] but not neutral,[36] stimuli can trigger effective pain inhibition. Stronger CS-evoked activation of the descending pain-inhibitory network region and higher pain-evoked connectivity between brain regions (e.g., the insula) are associated with stronger CPM inhibition.[37–39] These findings support the observed association of psychological factors such as V, F, and C with the 47°C noxious CS.

I also observed that higher levels of trait anxiety are associated with

reduced CPM with 47°C CS . It is possible that in chronic myofascial pain patients with high trait anxiety and increased disability-related pain, an imbalance occurs between excitatory and inhibitory impulses in the descending systems to the dorsal horn.[15] Geva et al. demonstrated that psychosocial stress leading to the increase in state anxiety reduces the CPM effect.[40] My finding that trait anxiety negatively affected the endogenous modulatory system is in line with Vidor's study.[15,] Changes in amygdala activation may be the neural mechanism underlying this effect. The amygdala is directly or indirectly connected to brainstem structures and influences the descending pain modulation, which is simultaneously regulated by endogenous opioid activity.[41] In patients with chronic orofacial pain, hyperactivation of the amygdala may occur, but a decrease in opioid activity has been suggested because the central sensitization induced by the chronic pain condition resulted in attenuated endogenous analgesic responses.[42] Another mechanism to explain the observations involves the anterior cingulate cortex, dorsolateral prefrontal cortex, and insula, which mediate the affective and cognitive components of pain perception.[43] Some studies reported that a lack of anterior cingulate cortex, dorsolateral prefrontal cortex, and insula activity may result in decreased descending activity in patients with

chronic low back pain.[44,45] Overall, affective and cognitive areas of inactivation

may affect the top-down process, resulting in impaired pain inhibition.[46] Shinozaki

et al. studied the pain habituation that is normally observed when intermittent

noxious stimuli are applied with a long enough break period after every stimulus

and reported that BMS patients did not show reduced pain perception,

representing a lack of habituation that was observed in healthy controls.

Interestingly, the brains of BMS patients but not controls showed suppressed

activation in the anterior and posterior cingulate cortices after the session. [47]

This study has some limitations. Circulating sex hormone quantities,

which vary according to the ovulatory phase of the menstrual cycle, may affect

CPM changes in the masseter muscle in healthy women.[48] In this study, I did not

determine the phase of the menstrual cycle in healthy volunteers; this may have

affected the CPM and psychosocial results.

Study 2

In this study, I found that the cold pain threshold and heat pain threshold at the

tongue were significantly more sensitive in the BMS group than in the control

group at the late postmenopausal stage. In a previous QST study, De Kruijf et

al.[49] found a significant association between years after menopause and cold and warmth sensitivity thresholds. One possible reason for the increased cold pain threshold may be that drastic menopausal changes significantly reduce neuroprotective steroids. This reduction in neuroprotective and neuroregenerative capacities may preferentially put small Aδ fibers at risk.[50] Another possible mechanism is that neuroactive steroids may directly or indirectly affect cold sensitivity in postmenopausal patients with BMS. Yilmaz et al.[51] and Hartmann et al.[52] also reported cold hyperalgesia in patients with BMS, but not in patients with lingual nerve impairment.

According to the Z-scores, postmenopausal patients with BMS also showed an increased response of the tongue to cold pain stimulation (cold pain threshold Z-score = 2.08). Aδ cold afferents seem to be impaired more often than C fibers in patients with BMS, indicating an imbalance in the small fiber input to the central nervous system.[51] Late postmenopausal patients with BMS also showed an increased response of the tongue to heat pain stimulation (heat pain threshold Z-score = 3.38). Grushka et al.[53] demonstrated that patients with BMS were significantly less tolerant of heat pain on the tongue than control subjects. It is well known that the psychophysical responses to noxious thermal stimuli are

dependent not only on stimulus intensity, but also on the duration of the stimulus, interstimulus interval, and characteristics of prior conditioning stimuli. The duration of heat pain tolerance testing may cause sensitization of the C fiber polymodal nociceptors and Aδ heat nociceptors in patients with BMS.[54] This sensitization may account for the decreased heat pain tolerance of patients with BMS.

Conclusions

1. I found a significant positive correlation of CPM47°C with state and trait anxiety in patients with BMS, suggesting that both state and trait anxiety negatively affect the descending pain modulation system.

2. With regard to the central mechanism of BMS, psychological factors and the depletion of sex hormones may alter pain modulation.

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Figures and Tables

a

b
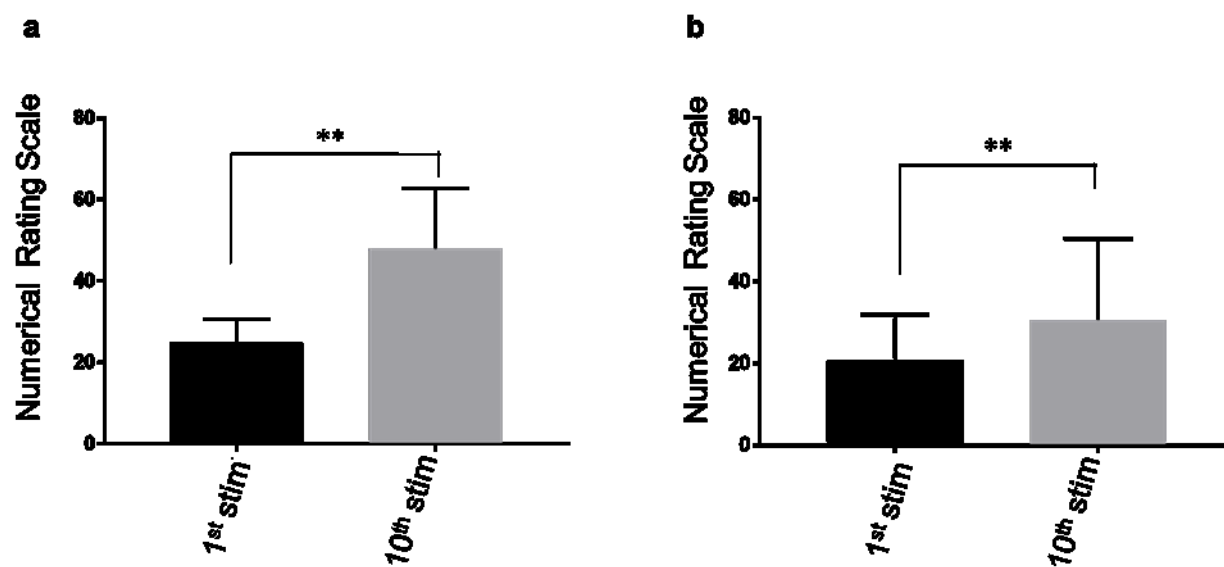
Fig. 1 Temporal summation without the conditioning stimulus in control participants (a) and patients with BMS (b). Data are presented as mean ± SD. **$P < .01$. BMS: burning mouth syndrome.
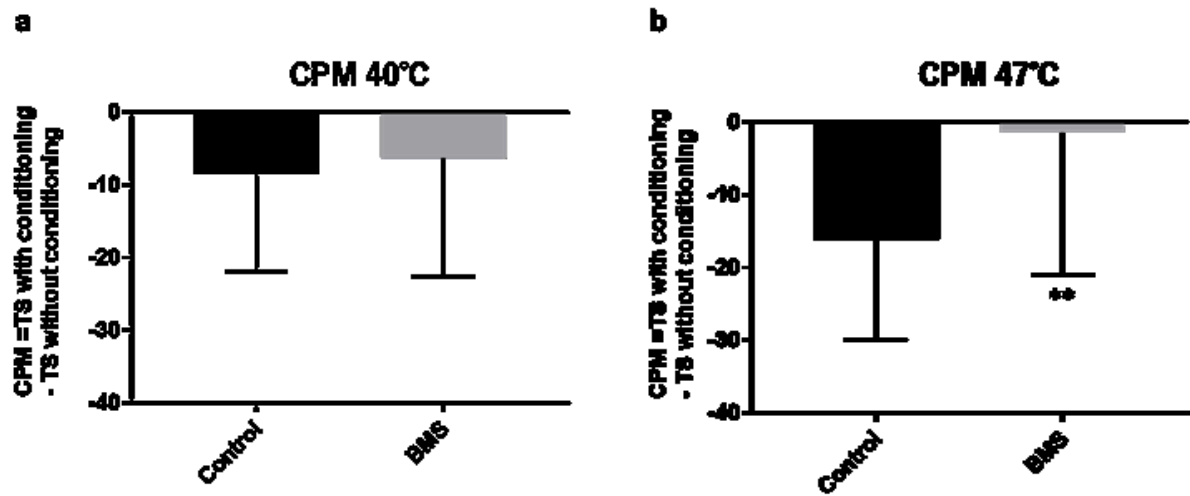
Fig. 2 CPM in control and BMS groups for non-painful (a) and painful (b) conditioning stimuli.

Data are presented as mean ± SD. ** P < .01. BMS: burning mouth syndrome, CPM: conditioned

pain modulation, TS: temporal summation.

Trait anxiety

r = 0.508

P = 0.016

CPM =TS with cc
- TS without con

Trait anxiety score

State anxiety

r = 0.316

P = 0.152

CPM =TS with conditioning
- TS without conditioning

State anxiety score
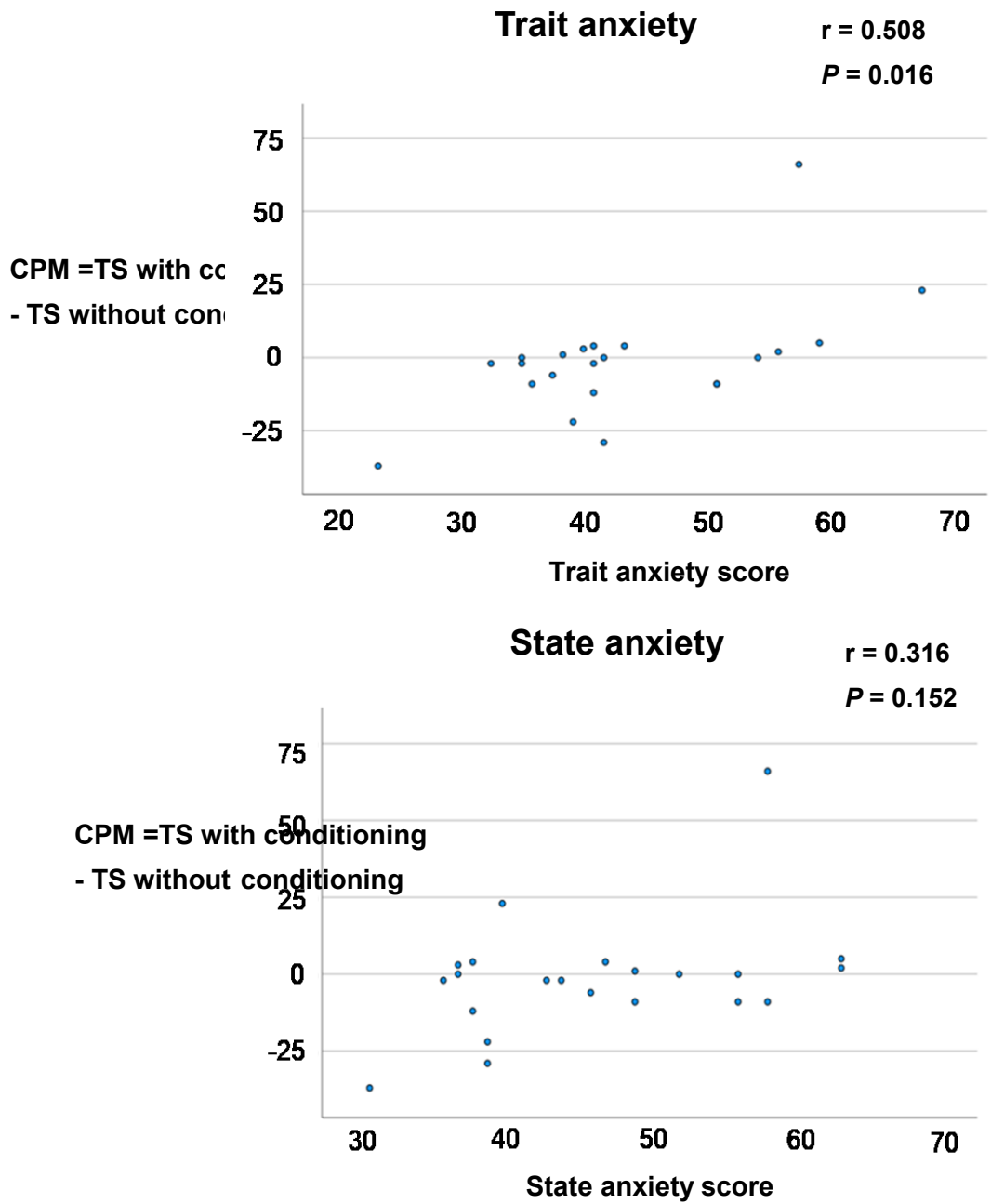
Fig. 3 The Spearman's rank correlation of CPM47°C vs. trait anxiety (a) and state anxiety (b).

The Spearman correlation coefficient, r, ranges in value from +1 to -1. P < .05. CPM: conditioned

pain modulation, TS: temporal summation.
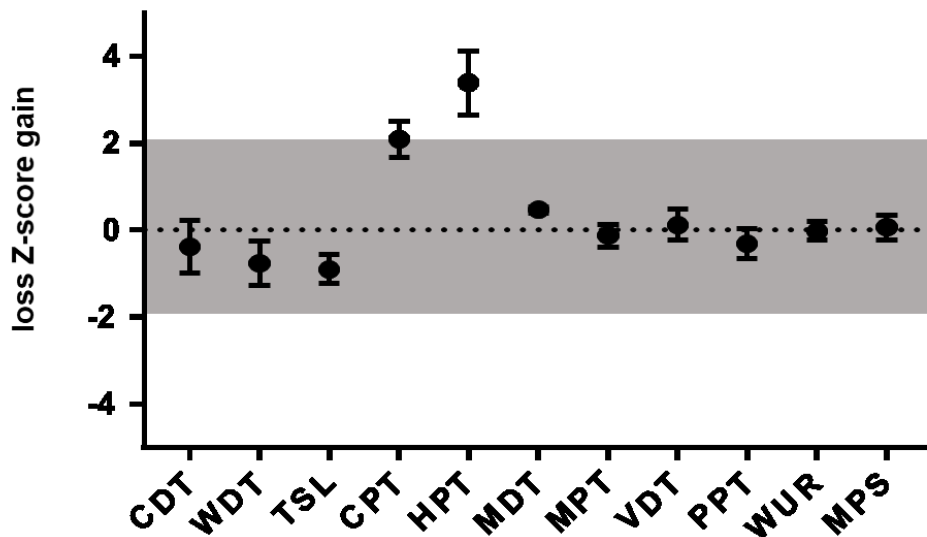
Fig. 4 Z-score QST profiles of the tongue in patients with late postmenopausal BMS. Mean

overall 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 (gray zone indicates Z-scores less than ± 1.96). CDT: cold detection threshold, WDT:

warmth detection threshold, TSL: thermal sensory limen, CPT: cold pain threshold, HPT: heat

pain threshold, MDT: mechanical detection threshold, MPT: mechanical pain threshold, VDT:

vibration detection threshold, PPT: pressure pain threshold, WUR: wind-up ratio, MPS:

mechanical pain sensitivity.

Table 1   Clinical characteristics, psychological and neurophysiological

variables of each group

	BMS	Control
Disease-related pain	3.5 ± 1.8	-
Pain duration (in months)	8.6 ± 12.6	-
T-A	**50.9 ± 8.2****	44.8 ± 4.1
D	52.6 ± 12.5	47.7 ± 6.9
A-H	48.3 ± 9.9	46.7 ± 8.9
V	43.0 ± 11.1	48.2 ± 10.7
F	49.6 ± 11.1	49.3 ± 9.2
C	50.1 ± 12.4	49.9 ± 7.8
Trait anxiety	48.4 ± 12.4	43.8 ± 10.6
State anxiety	**46.3 ± 9.4***	39.4 ± 7.0
TS	10.0 ± 18.0	23.2 ± 14.1
CPM40°C	-6.2 ± 16.3	- 8.5 ± 13.5
CPM47°C	**-1.4 ± 19.5***	- 16.3 ± 13.6

Data are presented as the mean ± SD. **P < 0.01, *P < 0.05

A-H: anger-hostility; BMS: burning mouth syndrome; C: confusion; CPM: conditioned pain modulation; D: depression-dejection; F: fatigue; T-A: tension-anxiety; TS: temporal summation; V: vigor.

Table 2   **Multiple regression analysis to predict CPM47°C**

BMS

Dependent variable	Predictor variable	β	t	P
CPM 47° C	Constant		1.823	0.098
	Age	-0.204	-1.405	0.19
	Disease-related pain	-0.134	-0.911	0.384
	Pain duration (in months)	0.319	2.147	0.057
	T-A	-0.42	-2.2	0.052
	D	0.417	1.003	0.34
	A-H	0.125	0.415	0.687
	V	-0.704	-2.722	.021*
	F	-0.672	-3.133	.011*
	C	0.813	2.999	.013*
	Trait anxiety	0.547	2.583	.027*
	State anxiety	-0.496	-1.867	0.091

Control

Dependent variable	Predictor variable	β	t	P
CPM 47° C	Constant		-0.31	0.762
	Age	0.233	0.829	0.423
	T-A	-0.028	-0.077	0.94
	D	-0.068	-0.135	0.895
	A-H	-0.091	-0.21	0.837
	V	-0.016	-0.049	0.961
	F	-0.169	-0.535	0.602
	C	0.091	0.278	0.786
	Trait anxiety	-0.28	-0.647	0.53
	State anxiety	0.283	0.862	0.405

*$P < 0.05$

A-H: anger-hostility; C: confusion; CPM: conditioned pain modulation; D: depression-dejection; F: fatigue; T-A: tension-anxiety; V: vigor.

Table 3   Multiple regression analysis to predict CPM40°C

BMS

Dependent variable	Predictor variable	β	t	P
CPM 40° C	Constant		0.263	0.798
	Age	-0.342	-1.259	0.237
	Disease-related pain	-0.163	-0.594	0.566
	Pain duration (in months)	0.377	1.356	0.205
	T-A	0.031*	0.088	0.932
	D	0.327	0.42	0.683
	A-H	-0.257	-0.458	0.657
	V	-0.235	-0.485	0.638
	F	-0.422	-1.052	0.318
	C	0.49	0.966	0.357
	Trait anxiety	0.415	1.047	0.32
	State anxiety	-0.197	-0.395	0.701

Control

Dependent variable	Predictor variable	β	t	P
CPM 40° C	Constant		0.678	0.511
	Age	-0.091	-0.389	0.704
	T-A	-0.077	-0.257	0.802
	D	0.057	0.136	0.894
	A-H	0.208	0.573	0.577
	V	0.16	0.593	0.564
	F	-0.746	-2.829	.015*
	C	-0.033	-0.119	0.907
	Trait anxiety	-0.016	-0.046	0.964
	State anxiety	0.009*	0.033*	0.974

A-H: anger-hostility; C: confusion; CPM: conditioned pain modulation; D: depression-dejection; F: fatigue; T-A: tension-anxiety; V: vigor.

Table 4   **The Spearman correlations of clinical characteristics,**

psychological and neurophysiological variables of each group

BMS

	Age	Disease-related pain	Pain duration	T-A	D	A-H	V	F	C	Trait anxiety	State anxiety	CPM 40°C	CPM 47°C
Age	1												
Disease-related pain	-0.142	1											
Pain duration	-0.116	0.216	1										
T-A	-0.042	-0.082	-0.102	1									
D	0.151	-0.237	-0.287	**0.594 ∗ ∗**	1								
A-H	0.165	-0.31	-0.345	**0.531 ∗**	**0.886 ∗ ∗**	1							
V	0.152	-0.365	0.098	-0.26	-0.086	0.064	1						
F	-0.03	-0.237	-0.375	0.342	**0.635 ∗ ∗**	**0.679 ∗ ∗**	-0.101	1					
C	0.16	-0.095	0.02	**0.499 ∗**	**0.807 ∗ ∗**	**0.666 ∗ ∗**	-0.055	**0.491 ∗**	1				
Trait anxiety	0.032	0.132	-0.121	0.264	**0.450 ∗**	0.413	**0.526 ∗**	**0.440 ∗**	0.28	1			
State anxiety	-0.108	0.26	-0.157	0.411	**0.522 ∗**	**0.465 ∗**	**-0.549 ∗**	0.413	0.419	**0.666 ∗**	1		
CPM 40°C	-0.155	0.096	**0.46 ∗**	-0.248	-0.04	-0.162	-0.073	-0.052	-0.115	0.212	0.187	1	
CPM 47°C	-0.028	0.008	0.245	-1,71	0.231	0.03	-0.243	-0.12	0.231	**0.508 ∗**	0.316	**0.521 ∗**	1

Control

	Age	T-A	D	A-H	V	F	C	Trait anxiety	State anxiety	CPM 40°C	CPM 47°C
Age	1										
T-A	-0.381	1									
D	-0.197	**0.592 ∗ ∗**	1								
A-H	-0.362	**0.448 ∗**	**0.618 ∗ ∗**	1							
V	0.188	0.017	-0.285	-0.245	1						
F	-0.327	**0.459 ∗**	0.082	0.408	0.013	1					
C	-0.042	**0.633 ∗ ∗**	**0.481 ∗**	**0.509 ∗**	-0.298	0.359	1				
Trait anxiety	-0.303	**0.472 ∗**	**0.745 ∗ ∗**	**0.564 ∗ ∗**	-0.381	0.332	0.362	1			
State anxiety	-0.286	0.223	0.294	0.11	-0.399	0.196	-0.021	**0.423 ∗**	1		
CPM 40°C	0.017	-0.171	0.122	-0.047	-0.027	**-0.666 ∗ ∗**	-0.166	-0.039	-0.046	1	
CPM 47°C	0.006	-0.229	-0.102	-0.268	-0.069	-0.335	-0.056	-0.242	0.047	**0.446 ∗**	1

$*P < 0.05$, $**P < 0.01$

A-H: anger-hostility; C: confusion; CPM: conditioned pain modulation; D: depression-dejection;

F: fatigue; T-A: tension-anxiety; V: vigor.

Spearman correlation coefficients among pain: Disease-related pain, duration of pain, T-A, D, A-H, V, F, C, state anxiety, trait anxiety, CPM 40°C, and CPM 47°C. The Spearman correlation coefficient, r, ranges in value from +1 to -1.

Table 5   The results of quantitative sensory testing of each group

	BMS		
	Premenopause	**Early postmenopause**	**Late postmenopause**
CDT	-2.63 ± 1.29	-1.84 ± 0.86	-3.91 ± 3.04
WDT	3.52 ± 2.25	2.52 ± 0.94	3.75 ± 3.16
TSL	2.28 ± 2.91	1.37 ± 1.12	2.10 ± 1.46
CPT	12.41 ± 7.38	13.38 ± 6.54	16.10 ± 0.51**
HPT	46.86 ± 2.12	45.06 ± 4.48	43.68 ± 3.46*
MDT(mN)	0.18 ± 0.15	0.16 ± 0.09	0.16 ± 0.06
MPT (mN)	37.84 ± 44.09	60.36 ± 54.0	37.88 ± 20.07
MPS (ratio)	9.05 ± 10.38	13.32 ± 14.35	14.06 ± 16.47
WUR (ratio)	3.46 ± 2.97	2.65 ± 1.51	2.72 ± 1.25
VDT (x/8)	5.89 ± 0.84	4.92 ± 0.64*	5.54 ± 1.07
PPT (kPa)	0.56 ± 0.40**	0.90 ± 0.56	0.55 ± 0.26

MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio, VDT, vibration detection threshold; PPT, pressure pain threshold, DMA, dynamic mechanical allodynia: there is no evidence of the occurrence of DMA

Mean values±SDs

Premenopause control vs. premenopause BMS: **$P < 0.01$, early postmenopause control vs. early postmenopause BMS: *$P < 0.05$, late postmenopause control vs. late postmenopause BMS: **$P < 0.01$.