Association Between Anxiety and Descending Pain Modulation of Thermal Stimuli in Patients with Burning Mouth Syndrome: A Cross-Sectional Study

Kana Ozasa, DDS
Noboru Noma, DDS, PhD
Momoyo Kobayashi, DDS
Keita Takizawa, DDS
Department of Oral Diagnostic Sciences
Nihon University School of Dentistry, &
Clinical Research Division
Dental Research Institute
Nihon University
Tokyo Japan

Andrew Young, DDS, MSD
Department of Diagnostic Sciences
Arthur Dugoni School of Dentistry
University of the Pacific
San Francisco, California, USA

Eli Eliav, DMD, PhD
Eastman Institute for Oral Health
University of Rochester Medical Center
Rochester, New York, USA

Yoshiki Imamura, DDS, PhD
Nihon University School of Dentistry
Clinical Research Division
Dental Research Institute
Nihon University
Tokyo, Japan

Correspondence to:
Dr Noboru Noma
Department of Oral Diagnostic Sciences
Nihon University School of Dentistry
1-8-13 Kandasurugadai
Chiyoda-ku Tokyo, 101-8310
Tokyo, Japan
Email: noma.noboru@nihon-u.ac.jp

Aims: To investigate the predictive power of depression and anxiety for conditioned pain modulation (CPM) and to examine the relationships of CPM at 40°C and CPM at 47°C with age, disease-related pain, pain duration, and psychosocial factors in burning mouth syndrome (BMS). **Methods:** A total of 22 patients with BMS and 22 healthy female controls participated in this study. Temporal summation was used as the test stimulus for CPM, and subsequent exposure either to a nonpainful (40°C) or a painful (47°C) Peltier thermode was used as the conditioning stimulus. CPM was calculated as the difference in pain perception following the conditioning stimulus. Psychosocial factors were examined using the Profile of Mood States (POMS) and the State-Trait Anxiety Inventory (STAI). **Results:** 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 trait 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 or STAI. A significant positive correlation was found between CPM47°C and trait anxiety, suggesting that trait anxiety negatively affected the endogenous pain modulation system. **Conclusion:** Increases in trait anxiety reduced the CPM effect. These findings suggest that CPM impairments and increases in trait anxiety are involved in the development of BMS. *J Oral Facial Pain Headache 2022;35:67–77. doi: 10.11607/ofph.3050*

Keywords: *anxiety, burning mouth syndrome, conditioned pain modulation, depression, state-trait anxiety inventory*

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 physiologic and psychologic factors have been hypothesized to be involved. Psychologic 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 developing depression and anxiety.[5–7]

The pain modulation system can be assessed using two dynamic psychophysical testing methods: temporal summation 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 (ie, the conditioning stimulus [CS]) is used to inhibit the intensity of another noxious stimulus

(ie, the test stimulus [TS]). CPM can occur when the CS and the TS are remote from each other.[9]

Less efficient CPM responses have been observed in a variety of pain disorders.[10,11] In a previous study, the present authors found an association between deficient inhibitory CPM and the development of BMS[12] and also demonstrated that the magnitude of CPM with a nonpainful 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 temporal summation is induced by a repeated painful stimulus.

Generally, psychologic disorders may be associated with the modulation of pain perception, increased nerve transmission by peripheral pain receptors, and altered pain perception.[13] Psychologic factors include the levels 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 psychologic factors is that serotonin and noradrenaline, as well as anxiety and depression, are involved in CPM responses, and 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 psychologic factors and CPM in patients with BMS.

Although an association between deficient CPM and development of BMS was found in the authors' previous study,[12] the question remains as to how CPM and psychosocial distress such as anxiety and depression are related in patients with BMS. Therefore, the present study aimed to answer two questions: *(1)* Do psychosocial factors predict CPM with nonpainful (40°C/104°F) or painful (47°C/116.6°F) CS applied to the nondominant 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/or psychosocial factors such as depression and anxiety?

Materials and Methods

Participants and Methods

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

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, different from the data that were previously reported.[12] The BMS group inclusion criteria were 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.

A total of 42 individuals initially provided consent to participate in the study and were assessed for eligibility. Six declined to participate during the assessment. An additional 9 were excluded owing to the following assessment findings: 5 for having pain for only 1 month (the ICHD-3 criteria require a minimum pain duration of 3 months); 2 for a positive swab test result that revealed infection with *Candida albicans*; and 2 for having nonburning dysesthesia. BMS examinations were performed at the Department of Oral Diagnostic Sciences, Nihon University School of Dentistry between February 2020 and September 2021. A minimum intraepidermal electrical stimulation (IES) intensity of 0.125 mA is required to selectively stimulate C fibers; five patients reported pain ranging from 3 to 6 on a 0–10 numeric rating scale (NRS) when stimulated at less than 0.125 mA and were therefore excluded from the study. Consequently, a total of 22 patients with BMS were enrolled in the present study (Fig 1). This study also included 22 healthy female volunteers who were free of any oral or dental pathology. No participant had a prior history of psychiatric, neurologic, or chronic pain disorder or had received dental treatment in the 6 months before the experiment, except for periodontal maintenance.

Examinations took place in a quiet, temperature-controlled room (20°C to 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: temporal summation and CPM. The detailed method has been previously described.[12] Briefly, one examiner performed all temporal summation and CPM examinations in this study. To test the temporal summation, IES was administered to the right chin with a concentric bipolar stainless steel electrode (Nihon Kohden)[16] 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 depth; Fig 2a). 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
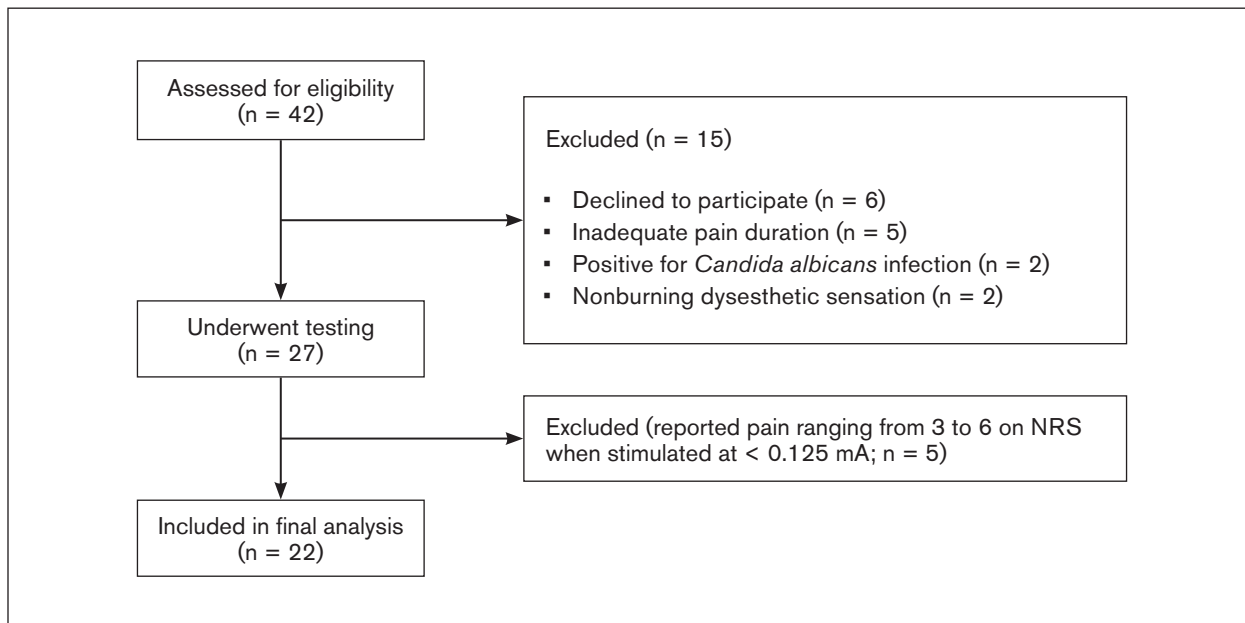
Fig 1 Flowchart describing the patient selection scheme for enrollment in this study.
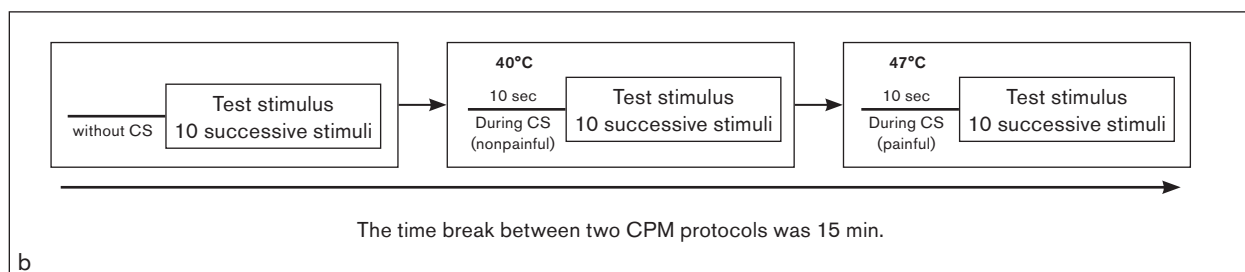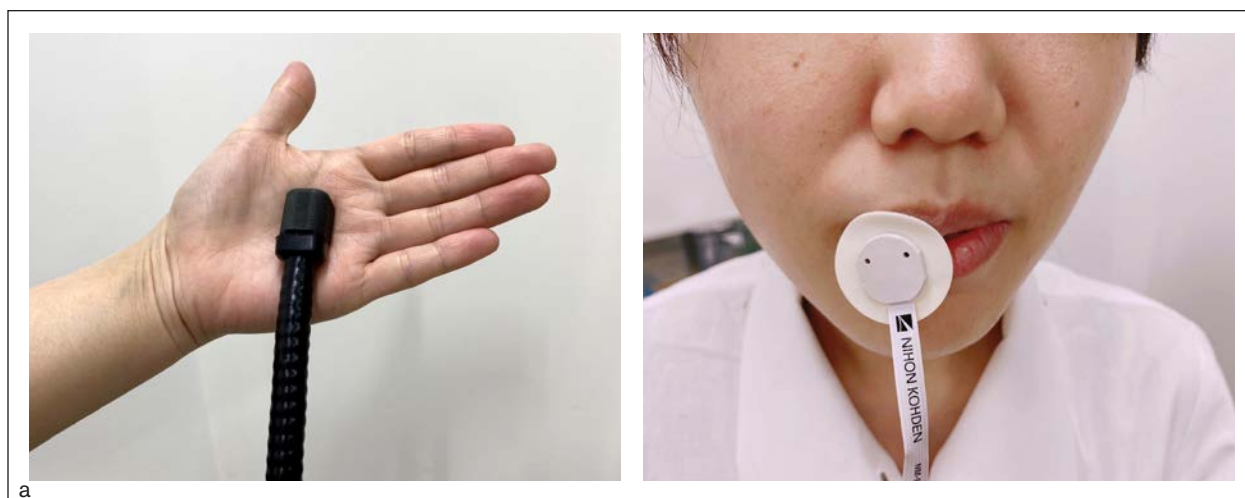

Fig 2 *(a)* Intraepidermal electrical stimulation was performed with a thermode composed of a Peltier element (contact area 10 × 10 mm). *(b)* Conditioned pain modulation protocol schematic.

of the stimulus was defined as a single pain-causing stimulus of at least 20- to 30-mm intensity on an NRS where 0 mm = no pain and 100 mm = 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 1 stimulus and after 10 consecutive stimuli.

For CPM assessment, nonpainful (40°C) or painful (47°C) stimulation was applied to the nondominant hand for 10 seconds with a thermode (Intercross-210, Intercross) as the CS. The thermode constituted a Peltier element with a 10 × 10-mm contact area (Fig 2a). The test stimulus was concurrently applied to the right chin. Participants were asked to rate the pain level of the test stimulus using the NRS. The difference between the test stimulus with nonpainful/painful CS and the test stimulus without CS was calculated. When reporting CPM results, negative values indicate a significant reduction in pain. The three test stimulus measurements (test stimulus without CS; test stimulus with 40°C CS; and test stimulus with 47°C CS) were assessed in that order 15 minutes apart to allow for a sufficient recovery period. Test stimulus without CS was considered as the baseline value (Fig 2b).

Psychologic Testing and Pain Measurement

All participants underwent psychologic 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).[17] Anxiety was measured with the Japanese STAI.[18]

Both state and trait anxiety (the situation-driven transient and the stable personality disposition reflecting the general level of fearfulness, respectively) were evaluated. When answering the State Anxiety Scale, participants chose the number that best described the intensity of their feelings for 13 different items on a 4-point Likert scale, as follows: (1) not at all; (2) somewhat; (3) moderately; and (4) very much so. The State Anxiety Scale score ranges from 13 to 52, and the Trait Anxiety Scale score from 12 to 36. Higher scores denote higher levels of anxiety.

The perception of oral pain in BMS patients was assessed using an NRS for pain intensity where 0 = no pain and 10 = the worst pain possible. Disease-related pain was defined as pain intensity reported by the patient at the first visit.

Sample Size

G*Power version 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. Two-sample means test was used to estimate the sample size per group. CPM values required to run the test (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 .05, and the power was set to 0.8. Based on the selected parameters, the required sample size per group to be able to detect significant differences between groups was estimated at 20.

Data Analysis

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 Shapiro-Wilk W test, a normal distribution of data was confirmed for the variables 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, data did not show a normal distribution (Shapiro-Wilk W = 0.800, $P = .001$; Shapiro-Wilk W = 0.801, $P = .001$). Paired t test was used to compare the two NRS scores (pain intensity after receiving 10 pulses vs pain intensity after receiving a single pulse). Mann-Whitney U test was used to compare CPM40°C and CPM47°C between the BMS and control groups. Unpaired t tests were 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 for the data from BMS patients to define the contribution of independent variables such as psychologic parameters (age, disease-related pain, pain duration [disease duration in 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 R^2 was calculated to determine the percentage of variance that could be explained by each of the potential predictors. Spearman correlation analysis was used to evaluate the possible relationships among age, disease-related 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) was used for statistical analyses. Data are reported as mean ± SD. Differences were considered significant when $P < .05$.

Results

The mean ages of the patients in the BMS and control groups were 57.5 ± 10.9 (range: 41–77) years and 53.6 ± 8.2 (range: 47–80) years, respectively, with no significant difference ($P = .14$).

Temporal Summation

In the control group, the mean NRS scores were 24.63 ± 5.97 for a single pulse and 47.9 ± 14.98 for a train of 10 pulses in response to the test stimulus. In the BMS group, the mean NRS scores were
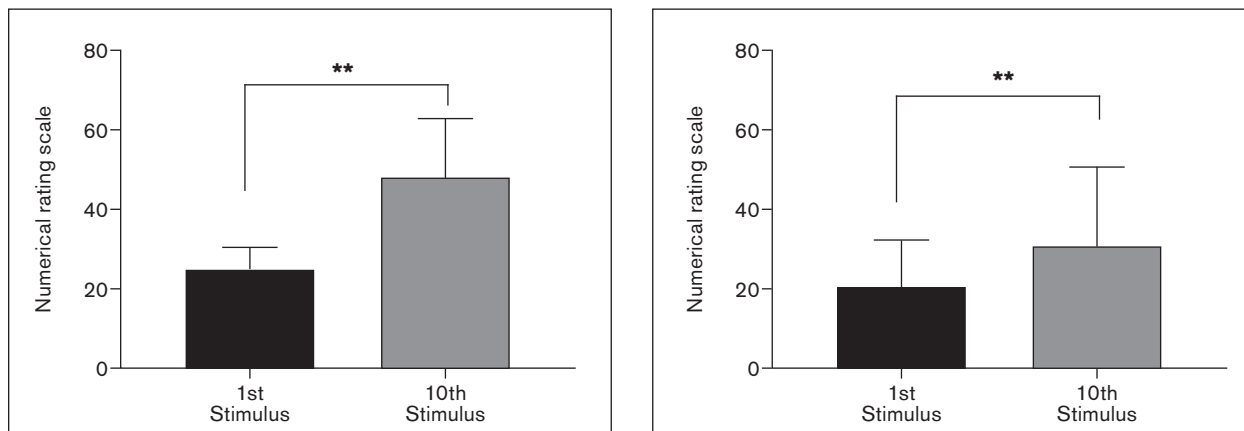
Fig 3 Temporal summation without conditioning stimulus in *(a)* control participants and *(b)* patients with BMS. Data are presented as mean ± SD. **$P < .01$.
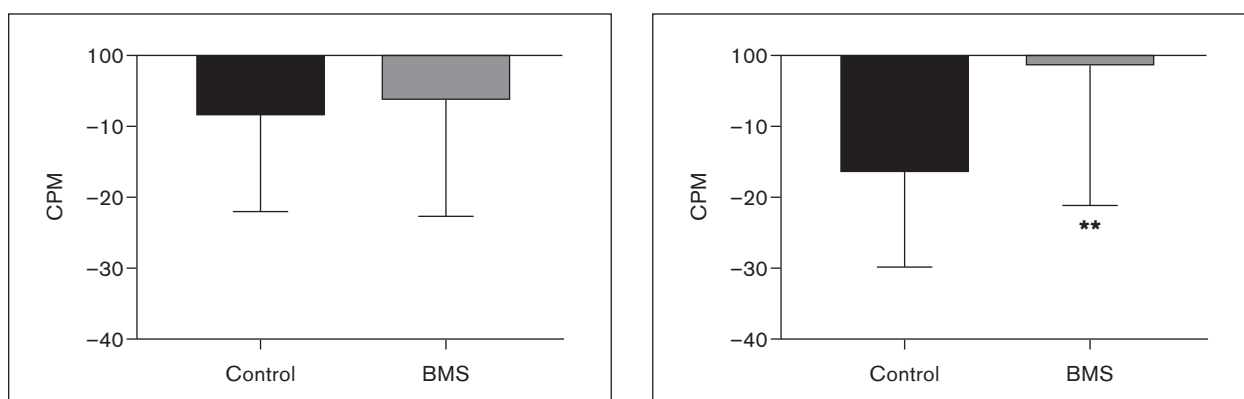

Fig 4 Conditioned pain modulation (CPM; temporal summation with conditioning − temporal summation without conditioning) in control and BMS groups for *(a)* nonnoxious (CPM40°C) and *(b)* noxious (CPM47°C) conditioning stimuli. Data are presented as mean ± SD. **$P < .01$.

20.54 ± 11.40 for a single pulse and 30.5 ± 19.86 for a train of 10 pulses in response to the test stimulus. The temporal summation score; ie, the difference between the two NRS scores (pain intensity after receiving 10 pulses − pain intensity after receiving a single pulse), was 10.00 ± 18.06 and 23.27 ± 14.17 for the BMS and the control groups, respectively. Thus, temporal summation was induced by a repeated painful stimulus (test stimulus) in both the BMS and control groups (Fig 3, $P < .01$ and $P < .01$).

Conditioned Pain Modulation

In the control and BMS groups, the mean NRS scores were 14.72 ± 9.54 and 23.00 ± 24.94 for pain ratings of CS47°C, respectively.

CPM was assessed with the test stimulus as the painful or nonpainful stimulus and with 40°C and 47°C as the CS. CPM signifies the difference between the temporal summation without CS and the temporal summation with CS; a negative value indicates a CS-induced suppression of temporal summation. 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 [CPM40°C and CPM47°C] and BMS group [CPM40°C and CPM47°C]) as a between-subjects factor revealed a significant difference (F = 6.295, $P = .014$). 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 4). However, the BMS group had significantly lower mean CPM with 47°C CS than the control group ($P < .01$, Fig 4).

The STAI state anxiety scores were significantly higher for patients with BMS than for control participants ($P = .015$, Table 1), whereas no significant difference in STAI trait anxiety scores was

Table 1 Comparison of Psychologic Variable Scores Between BMS and Control Groups

	BMS group	Control group
Disease-related pain	3.5 ± 1.8	–
Pain duration (mo)	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

A-H = anger-hostility; BMS = burning mouth syndrome; C = confusion; CPM = conditioned pain modulation; D = depression-dejection; F = fatigue; T-A = tension-anxiety; V = vigor.
Data are presented as mean ± SD. **$P < .01$. *$P < .05$.

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 psychologic 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 pain duration, T-A, V, and F (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 and 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, or trait anxiety (CPM40°C: adjusted $R^2 = 0.12$, F = 1.30, $P = .51$; CPM47°C: adjusted $R^2 = 0.27$, F = 0.51, $P = .76$; Tables 2 and 3).

Spearman correlation analysis was also performed for the 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 was correlated with D, V, and F, whereas state anxiety was correlated with D, A-H, V, and trait anxiety (Table 4). CPM47°C showed statistically significant and positive correlations with trait anxiety (Fig 5a, $P = .016$ and rs =

0.508). By contrast, CPM40°C was not correlated with any of the examined variables. In the control group, Spearman correlation analysis was performed 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 was correlated with T-A, D, A-H, and state anxiety, whereas CPM40°C and CPM47°C were not correlated with state anxiety or trait anxiety.

Discussion

While many studies have already been performed on the role of psychiatric disorders in the pathogenesis of BMS,[19–21] 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 to those of control participants.[22] Matsuoka et al also found that anxiety was significantly higher in patients with BMS than in control participants.[23] 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[5,22–24]; however, some studies did not confirm significant differences in psychologic test scores between patients with BMS and control participants.[25,26] This discrepancy may be owing to differences in age, disease-related pain, pain duration, sample size, psychosocial factors, and/or the type of psychologic tests used.[25]

A previous study demonstrated that patients with BMS exhibit increased intraoral wind-up to repetitive nociceptive afferent inputs.[8] In the present study, TS was induced after 10 consecutive stimuli by IES in

Table 2 Multiple Regression Analyses in the BMS and Control Groups for Effects of Psychologic Parameters on Conditioned Pain Modulation with Noxious Stimulus CPM47°C

Dependent variable	Predictor variable	β	t	P
BMS				
	Constant		1.823	.098
	Age	−0.204	−1.405	.190
	Disease-related pain	−0.134	−0.911	.384
	Pain duration (mo)	0.319	2.147	.057
	T-A	−0.420	−2.200	.052
	D	0.417	1.003	.340
	A-H	0.125	0.415	.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	.091
Control				
	Constant		−0.310	.762
	Age	0.233	0.829	.423
	T-A	−0.028	−0.077	.940
	D	−0.068	−0.135	.895
	A-H	−0.091	−0.210	.837
	V	−0.016	−0.049	.961
	F	−0.169	−0.535	.602
	C	0.091	0.278	.786
	Trait anxiety	−0.280	−0.647	.530
	State anxiety	0.283	0.862	.405

A-H = anger-hostility; C = confusion; CPM = conditioned pain modulation; D = depression-dejection; F = fatigue; T-A = tension-anxiety; V = vigor.
*P < .05.

Table 3 Multiple Regression Analyses in the BMS and Control Groups for Effects of Psychologic Parameters on Conditioned Pain Modulation with Nonnoxious Stimulus CPM40°C

Dependent variable	Predictor variable	β	t	P
BMS				
	Constant		0.263	.798
	Age	−0.342	−1.259	.237
	Disease-related pain	−0.163	−0.594	.566
	Pain duration (mo)	0.377	1.356	.205
	T-A	0.031*	0.088	.932
	D	0.327	0.420	.683
	A-H	−0.257	−0.458	.657
	V	−0.235	−0.485	.638
	F	−0.422	−1.052	.318
	C	0.490	0.966	.357
	Trait anxiety	0.415	1.047	.320
	State anxiety	−0.197	−0.395	.701
Control				
	Constant		0.678	.511
	Age	−0.091	−0.389	.704
	T-A	−0.077	−0.257	.802
	D	0.057	0.136	.894
	A-H	0.208	0.573	.577
	V	0.160	0.593	.564
	F	−0.746	−2.829	.015*
	C	−0.033	−0.119	.907
	Trait anxiety	−0.016	−0.046	.964
	State anxiety	0.009*	0.033*	.974

A-H = anger-hostility; C = confusion; CPM = conditioned pain modulation; D = depression-dejection; F = fatigue; T-A = tension-anxiety; V = vigor.
*Significant (P < .05).

Table 4a Spearman Correlation Analysis for BMS Group

	Age	Disease-related pain	Pain duration	T-A	D	A-H	V	F	C	Trait anxiety	State anxiety	CP-M40°C	CP-M47°C
BMS													
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	–0.310	–0.345	0.531*	0.886**	1	–	–	–	–	–	–	–
V	0.152	–0.365	0.098	–0.260	–0.086	0.064	1	–	–	–	–	–	–
F	–0.030	–0.237	–0.375	0.342	0.635**	0.679**	–0.101	1	–	–	–	–	–
C	0.16	–0.095	0.020	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*	0.280	1	–	–	–
State anxiety	–0.108	0.260	–0.157	0.411	0.522*	0.465*	–0.549*	0.413	0.419	0.666*	1	–	–
CPM40°C	–0.155	0.096	0.46*	–0.248	–0.04	–0.162	–0.073	–0.052	–0.115	0.212	0.187	1	–
CPM47°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

A-H = anger-hostility; C = confusion; CPM = conditioned pain modulation; D = depression-dejection; F = fatigue; T-A = tension-anxiety; V = vigor.
The Spearman correlation coefficient, rs, ranges in value from –1 to +1. *$P < .05$. **$P < .01$.

Table 4b Spearman Correlation Analysis for Control Group

	Age	T-A	D	A-H	V	F	C	Trait anxiety	State anxiety	CP-M40°C	CP-M47°C
Control											
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	0.110	–0.399	0.196	–0.021	0.423*	1	–	–
CPM40°C	0.017	–0.171	0.122	–0.047	–0.027	–0.666**	–0.166	–0.039	–0.046	1	–
CPM47°C	0.006	–0.229	–0.102	–0.268	–0.069	–0.335	–0.056	–0.242	0.047	0.446*	1

A-H = anger-hostility; C = confusion; CPM = conditioned pain modulation; D = depression-dejection; F = fatigue; T-A = tension-anxiety; V = vigor.
The Spearman correlation coefficient, rs, ranges in value from –1 to +1. *$P < .05$. **$P < .01$.
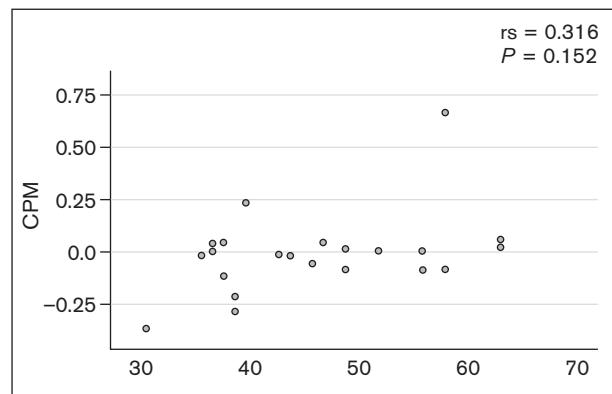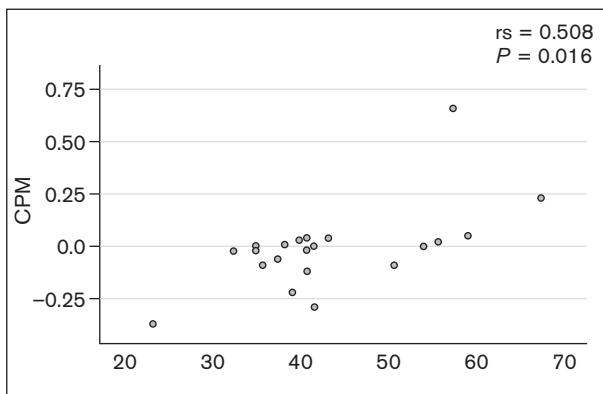

Fig 5 Spearman rank correlation for conditioned pain modulation (CPM; temporal summation with conditioning – temporal summation without conditioning) for (a) trait anxiety and (b) state anxiety. The Spearman correlation coefficient, rs, ranges in value from –1 to +1. $P < .05$ was considered significant.

both the BMS and control groups. As expected, in the control group, the 47°C CS resulted in a significant CPM efficiency when compared to the 40°C CS. By contrast, CPM with 47°C CS was less efficient than that with 40°C CS in patients with BMS.

It was hypothesized that higher average scores on psychologic 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 ($P = .021$, $P = .011$, $P = .013$, and $P = .027$, respectively). However, when the same variables were evaluated for CPM with 40°C CS, none were predictive in the multiple regression analysis (Table 3). Thus, the parameters V, F, C, and trait anxiety predicted an impairment of CPM only when the CS accessed the inhibitory pain modulation mechanism.

To the best of the present authors' knowledge, this is the first study to investigate 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.[27] Vidor et al demonstrated that chronic myofascial pain patients with higher anxiety scores exhibited reduced corticospinal modulation of the pain response.[15] In the partial correlation analysis of the present study, trait anxiety was significantly associated with CPM with 47°C CS, but not CPM with 40°C CS (Table 4). The reason for psychologic factors being associated with noxious (47°C CS) but not with nonnoxious (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 an 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.[27] The magnitude of pain inhibition depends on the intensity of the CS, as only painful,[28,29] but not neutral,[30] 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 (eg, the insula) are associated with stronger CPM inhibition.[31–33] These findings support the observed association of psychologic factors such as V, F, and C with the 47°C noxious CS.

It was also observed that higher levels of trait anxiety were associated with reduced CPM with 47°C CS (Fig 5). 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 increases in state anxiety reduces the CPM effect.[34] The present findings that trait anxiety negatively affected the endogenous modulatory system are in line with Vidor et al.[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 descending pain modulation, which is simultaneously regulated by endogenous opioid activity.[35] Hyperactivation of the amygdala may occur in patients with chronic orofacial pain, but a decrease in opioid activity has also been suggested because the central sensitization induced by the chronic pain condition resulted in attenuated endogenous analgesic responses.[36] Another mechanism to explain these observations involves the anterior cingulated cortex, dorsolateral prefrontal cortex, and insula, which mediate the affective and cognitive components of pain perception.[37] Some studies reported that a lack of anterior cingulated cortex, dorsolateral prefrontal cortex, and insula activity may result in decreased descending activity in patients with chronic low back pain.[38,39] Overall, affective and cognitive areas of inactivation may affect the top-down process, resulting in impaired pain inhibition.[40] Shinozaki et al[41] studied the pain habituation that is normally observed when intermittent noxious stimuli are applied with a long enough recess after every stimulus and reported that BMS patients did not show the reduced pain perception representing the lack of habituation that was observed in healthy controls. Interestingly, the brains of BMS patients, but not of controls, showed a suppressed activation in the anterior and posterior cingulate cortices after the session.[41]

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.[42] In this study, the phase of the menstrual cycle in the healthy volunteers was not determined, and this may have affected the CPM and psychosocial results.

Conclusions

A significant positive correlation was found for CPM47°C with state and trait anxiety in patients with BMS, suggesting that both state and trait anxiety negatively affected the descending pain modulation

system. In other words, higher state anxiety reduced the noxious CS-induced CPM effect. These results imply that for a nonnoxious CS, psychologic test results may not be associated with CPM.

Highlights

Clinical Research

- CPM47°C and trait anxiety were significantly and positively correlated in patients with BMS.
- Trait anxiety negatively affected the descending pain modulation system.
- These results imply that for a nonnoxious CS, psychologic test results may not be associated with CPM.

Acknowledgments

References

1. International Classification of Orofacial Pain, 1st edition (ICOP). Cephalalgia 2020;40:129–221.
2. Eli I, Baht R, Littner MM, Kleinhauz M. Detection of psychopathologic trends in glossodynia patients. Psychosom Med 1994;56:389–394.
3. Sardella A, Lodi G, Demarosi F, Bez C, Cassano S, Carrassi A. Burning mouth syndrome: A retrospective study investigating spontaneous remission and response to treatments. Oral Dis 2006;12:152–155.
4. Galli F, Lodi G, Sardella A, Vegni E. Role of psychological factors in burning mouth syndrome: A systematic review and meta-analysis. Cephalalgia 2017;37:265–277.
5. Schiavone V, Adamo D, Ventrella G, et al. Anxiety, depression, and pain in burning mouth syndrome: First chicken or egg. Headache 2012;52:1019–1025.
6. Malik R, Goel S, Misra D, Panjwani S, Misra A. Assessment of anxiety and depression in patients with burning mouth syndrome: A clinical trial. J Midlife Health 2012;3:36–39.
7. Honda M, Iida T, Kamiyama H, et al. Mechanical sensitivity and psychological factors in patients with burning mouth syndrome. Clin Oral Investig 2019;23:757–762.
8. Nasri-Heir C, Khan J, Benoliel R, et al. Altered pain modulation in patients with persistent postendodontic pain. Pain 2015;156:2032–2041.
9. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611–615.
10. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156(suppl 1):s24–s31.
11. Granovsky Y. Conditioned pain modulation: A predictor for development and treatment of neuropathic pain. Curr Pain Headache Rep 2013;17:361.
12. Nishihara C, Watanabe K, Ozasa K, et al. Altered pain modulation to noxious heat thermal stimuli in burning mouth syndrome. Oral Dis 2020;26:1777–1782.
13. Kim JY, Kim YS, Ko I, Kim DK. Association between burning mouth syndrome and the development of depression, anxiety, dementia, and Parkinson disease. JAMA Otolaryngol Head Neck Surg 2020;146:561–569.
14. Poluha RL, De la Torre Canales G, Bonjardim LR, Conti PCR. Somatosensory and psychosocial profile of patients with painful temporomandibular joint clicking. J Oral Rehabil 2020;47:1346–1357.
15. Vidor LP, Torres IL, Medeiros LF, et al. Association of anxiety with intracortical inhibition and descending pain modulation in chronic myofascial pain syndrome. BMC Neurosci 2014;15:42.
16. Inui K, Tran TD, Qiu Y, Wang X, Hoshiyama M, Kakigi R. Pain-related magnetic fields evoked by intra-epidermal electrical stimulation in humans. Clin Neurophysiol 2002;113:298–304.
17. Koizumi K, Tayama J, Ishioka T, et al. Anxiety, fatigue, and attentional bias toward threat in patients with hematopoietic tumors. PLoS One 2018;13:e0192056.
18. Iwata N, Mishima N, Okabe K, Kobayashi N, Hashiguchi E, Egashira K. Psychometric properties of the State-Trait Anxiety Inventory among Japanese clinical outpatients. J Clin Psychol 2000;56:793–806.
19. Taiminen T, Kuusalo L, Lehtinen L, et al. Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain. Scand J Pain 2011;2:155–160.
20. Jääskeläinen SK, Woda A. Burning mouth syndrome. Cephalalgia 2017;37:627–647.
21. Jääskeläinen SK. Is burning mouth syndrome a neuropathic pain condition. Pain 2018;159:610–613.
22. Sikora M, Verzak Ž, Matijević M, et al. Anxiety and depression scores in patients with burning mouth syndrome. Psychiatr Danub 2018;30:466–470.
23. Matsuoka H, Himachi M, Furukawa H, et al. Cognitive profile of patients with burning mouth syndrome in the Japanese population. Odontology 2010;98:160–164.
24. Adamo D, Pecoraro G, Fortuna G, et al. Assessment of oral health-related quality of life, measured by OHIP-14 and GOHAI, and psychological profiling in burning mouth syndrome: A case-control clinical study. J Oral Rehabil 2020;47:42–52.
25. Sekine N, Okada-Ogawa A, Asano S, et al. Analgesic effect of gum chewing in patients with burning mouth syndrome. J Oral Sci 2020;62:387–392.

26. Davies SJ, Underhill HC, Abdel-Karim A, et al. Individual oral symptoms in burning mouth syndrome may be associated differentially with depression and anxiety. Acta Odontol Scand 2016;74:155–160.

27. Jarrett ME, Shulman RJ, Cain KC, et al. Conditioned pain modulation in women with irritable bowel syndrome. Biol Res Nurs 2014;16:368–377.

28. Razavi M, Hansson PT, Johansson B, Leffler AS. The influence of intensity and duration of a painful conditioning stimulation on conditioned pain modulation in volunteers. Eur J Pain 2014;18:853–861.

29. Granot M, Weissman-Fogel I, Crispel Y, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter. Pain 2008;136:142–149.

30. Albu S, Meagher MW. Divergent effects of conditioned pain modulation on subjective pain and nociceptive-related brain activity. Exp Brain Res 2019;237:1735–1744.

31. Bogdanov VB, Viganò A, Noirhomme Q, et al. Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: An fMRI study in healthy subjects. Behav Brain Res 2015;281:187–198.

32. Youssef AM, Macefield VG, Henderson LA. Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. Hum Brain Mapp 2016;37:2630–2644.

33. Harper DE, Ichesco E, Schrepf A, et al. Resting functional connectivity of the periaqueductal gray is associated with normal inhibition and pathological facilitation in conditioned pain modulation. J Pain 2018;19:635.e1–635.e15.

34. Geva N, Pruessner J, Defrin R. Acute psychosocial stress reduces pain modulation capabilities in healthy men. Pain 2014;155:2418–2425.

35. Le Bars D, Villanueva L, Bouhassira D, Willer JC. Diffuse noxious inhibitory controls (DNIC) in animals and in man. Patol Fiziol Eksp Ter 1992;4:55–65.

36. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. Prog Neurobiol 2008;85:355–375.

37. Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. Pain 1999;79:105–111.

38. Matsuo Y, Kurata J, Sekiguchi M, Yoshida K, Nikaido T, Konno SI. Attenuation of cortical activity triggering descending pain inhibition in chronic low back pain patients: A functional magnetic resonance imaging study. J Anesth 2017;31:523–530.

39. Li T, Zhang S, Kurata J. Suppressed descending pain modulatory and enhanced sensorimotor networks in patients with chronic low back pain. J Anesth 2018;32:831–843.

40. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–391.

41. Shinozaki T, Imamura Y, Kohashi R, et al. Spatial and temporal brain responses to noxious heat thermal stimuli in burning mouth syndrome. J Dent Res 2016;95:1138–1146.

42. Rezaii T, Hirschberg AL, Carlström K, Ernberg M. The influence of menstrual phases on pain modulation in healthy women. J Pain 2012;13:646–655.