Impairment of pain inhibition in patients with burning mouth syndrome

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Table of Content

This thesis is composed of the following article and additional new data on temporal summation in the spinal nerve innervation in BMS patients. (Fig. 3) Nishihara C, Watanabe K, Ozasa K, Khan J, Eliav E, Imamura Y, Noma N. Altered pain modulation to noxious heat thermal stimuli in burning mouth syndrome. Oral Dis 26, 1777-1782, 2020

ABSTRACT

Objectives: The aim of this study was to examine temporal summation (TS) in the trigeminal innervation and conditioned pain modulation (CPM) in patients with burning mouth syndrome (BMS) and healthy controls using intra-epidermal electrical stimulation (IES). The TS study in the spinal innervation applied a psychophysical test model for TS and aimed to determine whether TS was induced by repeated transcutaneous electrical stimulation of the spinal cord afferents.

Materials and Methods: Twenty-six female BMS patients and 27 healthy female controls participated in this study. The TS study in the spinal innervation included 15 patients with BMS and 15 healthy volunteers as controls. A single stimulus with electrical stimulation followed by a train of 10 successive stimuli was administered to the right chin of participants in both the BMS and control groups. CPM was evaluated with the changes in TS calculated from the difference in numerical pain scale data between these two time points and the following warm (40°C) and hot (47°C) conditioning stimuli applied at the nondominant hand in both the BMS and control groups.

Results: TS was present in both the BMS and control groups. CPM in the BMS group was significantly less efficient at the 47°C condition than that in the control group, while no significant difference was observed in the CPM between the BMS and the control groups at the 40°C condition. The results on additional experiments, showed that TS on the forearm was successfully induced using the IES device in both the controls and patients with BMS. Further, there were no significant differences in the TS between the right chin and the forearm in patients with BMS.

Conclusion: These findings indicate that BMS is associated with a deficit in the CPM

and implicate the involvement of the central nervous system in the pathophysiology of BMS.

INTRODUCTION

Burning mouth syndrome (BMS) is defined as an “intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions.” Recently, the International Headache Society has adopted the term “painful cranial neuropathies” to describe the condition (Vincent and Wang, 2018). BMS is described by moderate to severe pain, whose intensity is similar to that of a toothache, with a distinctive superficial, burning characteristic. The sensations are frequently accompanied by xerostomia and taste alterations (Jääskeläinen, 2017). Peripheral nerve atrophy was reported in small diameter fibers in the epithelium of some patients with BMS, but subepithelial nerve fibers were affected less frequently (Yilmaz *et al*, 2016). Regional anesthetic blocks and topical clonazepam are reportedly ineffective in a proportion of patients with BMS, which suggests that BMS may involve the central nervous system (Yanagisawa *et al*, 1998; Grémeau-Richard *et al*, 2010). Quantitative sensory testing (QST) studies have demonstrated that BMS induces increased sensitivity to warm and cold, thermal pain, as well as heat hyperalgesia (Forssell *et al*, 2002; Yilmaz *et al*, 2016). Previous electrophysiological and imaging studies performed by Jaaskelainen *et al*. and Shinozaki *et al*. demonstrated that habituation of the blink reflex or pain habituation could be suppressed in BMS patients (Jääskeläinen *et al*, 1997; Shinozaki *et al*, 2016). This is indicative of temporal summation (TS) induced by central sensitization. Thus, psychophysical and electrophysiological studies with patients with BMS have revealed disordered pain modulatory system, although, its exact mechanism remains unknown.

Psychophysical testing is useful for assessing pain enhancement or inhibition and for providing modulation-system status information. TS is pain provoked by test

stimulation, when first presented, as well as after successive stimulations (Herrero *et al*, 2000). According to previous studies, TS is assessed using mechanical, thermal, and pressure stimuli (Greenspan *et al*, 2011; Nasri-Heir *et al*, 2015). TS of electrical painful stimulation has been demonstrated (Arendt-Nielsen *et al*, 1995; Staud *et al*, 2007) and intra-epidermal electrical stimulation (IES) has been developed to selectively activate the C fibers (Inui *et al*, 2002). This is relevant as low-frequency, repeated stimulation of C fibers may result in pain enhancement (Eckert *et al,* 2017).

Conditioned pain modulation (CPM) characterizes the pain inhibitory system and represents the ability of the endogenous analgesic mechanism exerted through the inhibitory pain modulation system. CPM can be tested using two remote noxious stimulation: “conditioning pain” stimulation that inhibits “test pain” stimulation (Yarnitsky, 2010). This study aimed to examine these pain modulation profiles in patients with BMS to test the following hypothesis. Patients with BMS presenting with pronociceptive pain profile will demonstrate enhanced response to TS and a less efficient response to CPM, similar to patients with other chronic disorders. CPM was originally investigated in animals as diffuse noxious inhibitory controls (DNIC). DNIC was explained to generate pain inhibition by implicating endogenous opioid system with noxious conditioning stimuli (CS) but not innocuous stimuli applied at a distal area to the receptive field of the test stimulus (Kraus *et al*, 1981). However, recent studies on CPM have reported that not only noxious stimuli but also innocuous stimuli can generate CPM when they are utilized as CS, although CPM magnitude is associated with CS intensity (Nir *et al*, 2011). Contrarily, there have been concerns that this pain inhibition induced by various CS is exerted by distraction. Moont et al. have investigated this point and have concluded that CPM acts independently from

distraction with possible partial overlap (Moont *et al*, 2010). While the innocuous stimulus assessed the potential effect of distraction alone, the noxious stimulus assessed inhibitory pain modulation employing the “pain inhibiting pain” paradigm.

TS is considered to be the psychophysical correlate of the wind-up of the wide-dynamic-range (WDR) neurons in the spinal cord potentially contributing to central sensitization. Wind-up is a progressive, frequency-dependent increase in the excitability of the medullary and spinal dorsal horn WDR neurons evoked by repetitive stimulation of the primary afferent fibers. This study implemented a psychophysical test model for TS and aimed to investigate whether TS was induced by repeated transcutaneous electrical stimulation of the spinal cord afferents.

PARTICIPANTS AND METHODS

Study 1

The protocol of the study was approved by the ethics committee of the Nihon University School of Dentistry (EP16 D024, approval date; Nov. 17. 2016) and all participants signed an informed consent agreement. The study was performed in accordance with the Declaration of Helsinki. Sample size was calculated based on a power analysis using G*Power 3.1.3, which was performed for the within-between interaction in repeated measures ANOVA test with 2 groups, 4 measurements (BMS and controls, TS with and without CPM), an effect size of 0.30, alpha error of 0.05 and a minimum power of 0.95. This analysis led to a sample size of 26 patients. This study included 26 women with BMS and 27 healthy female volunteers. The mean ages of the patients with BMS and controls were 56. 0 ± 10.15 (range, 40–77) years and 52.33 ± 8.04 (range, 41–80) years, respectively. There was no significant difference in the age between BMS and control groups (p = 0.197). The percentage of patients who had attained pre-menopause in the control and the BMS groups was 33.33% (9/27) and 26.92% (7/26), respectively. The control group did not include pregnant women, as well as patients with chronic pain conditions or neurologic diseases. The intra- and extra-oral examination also showed no systemic or local problems. The examiner was blinded to participant status. BMS was diagnosed according to the International Classification of Headache Disorders, Third Edition. The BMS group included patients who complained of superficial intraoral burning pain in the absence of local or systemic conditions/ diseases and no abnormalities in laboratory findings such as nutritional deficiencies, diabetes, oral candidiasis, anemia and hypothyroidism. The laboratory analysis results include hematological assessment of nutritional deficiencies (such as:

serum ferritin, vitamin B12, folic acid and zinc), blood glucose levels, autoimmune markers (such as the antinuclear antibody and anti-SS-A/SS-B antibodies), hypothyroidism that was evaluated by endocrinologist. The swab method, which involves rubbing cotton-tipped swabs over the dorsal surface of the tongue, was used to examine for oral candidiasis.

The included healthy female volunteers were free of oral or dental pathology. No participants had prior history of psychiatric, neurological, or chronic pain disorders or had received dental treatment, with the exception of periodontal maintenance, in the 6 months prior to the experiment. All participants were examined in the laboratory and exposed to two psychophysical test models: TS and CPM. One examiner performed all TS and CPM examinations in this study. IES was administered at the right chin with a stainless steel concentric bipolar electrode (Nihon Kohden, Tokyo, Japan) to test the TS (Inui *et al*, 2002). The electrode consisted of a cylindrical anode (Ø: 1.4 mm) encircling a pushpin-shaped cathode (Ø: 0.2 mm), which was located at the center of the concentric electrode. The pin cathode was designed to protrude 0.1 mm from the outer ring anode and the tip of the pin was inserted in the epidermis without hurting when the electrode was pressed on the skin. The electrode was placed on the chin at the midpoint between the mouth angle and the mid-face. The test amplitude of the stimulation was defined as a single stimulus that evoked pain at least 20–30 in intensity on a numerical pain scale (NPS) with 0 indicating no pain and 100 indicating maximum possible pain. The stimulation for selective activation of the C fibers was defined as overintense of the stimulation (0.125 mA) based on the criteria of the Diabetic Neuropathy Study Group in Japan (Kukidome *et al,* 2016). A single individual stimulus was followed by a 10-consecutive stimulation served at a frequency of 1 Hz. Patients

were requested to rate the pain intensity that she felt on the NPS. NPS scores were evaluated after each of the single stimulation and the 10-consecutive stimulation. For the CPM assessment, warm (40°C) or hot (47°C) stimulation was applied to the non-dominant hand for 10 s with a thermode (Intercross 210, Tokyo, Japan) as CS. The thermode consisted of a Peltier element with a 10 × 10 mm contact area. The participants were asked to rate the pain intensity using the NPS. The difference between the TS without and the warm or hot CS was calculated. In reporting the CPM, negative values indicated a significant reduction in pain. The three TS measures, namely, TS without CS, 40°C CS, and 47°C CS, were assessed in the same order, with a 15-minute interval between each measurement, to allow for a sufficient wash out period. TS without CS was considered the baseline.

Study 2

The study included 15 patients with BMS and 15 healthy volunteers (controls). The mean ages of the patients with BMS and controls were 64.1 ± 10.1(46–77) y and 57.9 ± 8.5 (46–80) y, respectively.

All the participants were examined in a quiet, temperature-controlled room (20–23°C) and exposed to the psychophysical test model, TS test. IES was delivered by a stainless steel concentric bipolar electrode used in the study 1. TS was assessed in the same manner to the study 1 both in the control group and the BMS group.

Data Analysis

Two-way repeated measures analyses of variance (ANOVA) were used to compare two groups (the control and the BMS groups) in the magnitude of TS within-between

groups (3 measures: TS without CS, the 40°C CS, and the 47°C CS). A one-way ANOVA was used to analyze the differences in the magnitude of TS (3 measures: TS without CS, the 40°C CS, and the 47°C CS) in the control and the BMS groups. The Bonferroni test was used for the post-hoc multiple comparisons. A p-value of < 0.05 was considered statistically significant for the ANOVA and the post-hoc test. The SPSS software (version 20.0 for Windows; IBM, Tokyo, Japan) was used for analyses. Data are shown in mean ± SD.

RESULTS

Study 1

The amplitudes of a single stimulus that needed to evoke pain at least 20–30/100 of intensity on the NPS were 0.29 ± 0.14 mA and 0.27 ± 0.15 mA in the BMS and control groups, respectively. In the control group, the mean NPS scores were 26.85 ± 4.57 for a single pulse and 47.66 ± 13.91 for a train of 10 pulses in response to the test stimuli without CS, 17.48 ± 7.32 for a single pulse and 33.48 ± 15.04 for 10 pulses with the 40°C CS, and 17.88 ± 9.27 for a single pulse and 27.81 ± 15.21 for 10 pulses with the 47°C CS in the control group (Table 1).

The difference between two NPS scores (pain intensity after receiving 10 pulses – pain intensity after receiving a single pulse) revealed a TS score: 20.81 ± 13.07 without CS, 16.00 ± 12.99 with the 40°C CS, and 9.93 ± 12.56 with the 47°C CS. TS was induced by repeated painful stimulus (test stimulus) (Fig. 1, $p < 0.001$). TS without CS induced by repeated painful stimulus was significantly inhibited by the 40°C or 47°C CS in control group, respectively (Fig. 2, $p < 0.05$ and $p < 0.01$). In the BMS group, the mean NPS scores were 26.27 ± 9.32 for a single pulse and 44.88 ± 20.78 for a train of 10 pulses in response to the test stimuli without CS, 20.96 ± 11.14 for a single pulse and 34.96 ± 19.99 for 10 pulses with the 40°C CS, and 19.62 ± 10.82 for a single pulse and 38.50 ± 25.99 for 10 pulses with the 47°C CS (Table 1). The mean TS values in the BMS group were 18.62 ± 18.57, 14.00 ± 16.65 and 18.88 ± 23.32 for the TS without CS, with the 40°C CS, and with the 47°C CS, respectively. TS was induced by repeated painful stimulus (Fig. 1, $p < 0.001$), but there was no significant reduction in TS after receiving CS (40°C and 47°C) in BMS patients (Fig. 2). Two-way ANOVA with Group [the control (TS without CS/with the 40°C CS/with the 47°C CS) and the BMS

group (TS without CS/with the 40°C CS/with the 47°C CS)] as a between-subjects factor revealed a significant difference ($F = 3.018$, $p = 0.032$).

In this study, CPM represents a subtracted value of TS without the CS from that with the CS, which indicates suppression of TS in a minus value. The mean CPM with the 40°C and 47°C CS in the control group were -4.81 ± 12.47 and -10.88 ± 16.12 and in the BMS group, -4.61 ± 16.46 and 0.269 ± 23.19, respectively. In the control group, the 47°C CS revealed a significant reduction of TS as compared to the 40°C CS (Fig. 2, $p < 0.05$). On the other hand, CPM with the 47°C CS showed a positive value in the BMS group, meaning no pain reduction. A significant difference was found in the BMS group between CPM with the 40°C and 47°C CS, suggesting that CPM with the 47°C CS was less efficient compared to that with the 40°C CS (Fig. 2).

Study 2

The amplitudes of a single stimulus required to evoke pain of at least 20–30/100 of intensity on the NPS were 0.46 ± 0.30 mA and 0.68 ± 0.32 mA in the BMS and control groups, respectively. In the control group, the mean NPS scores were 17.0 ± 7.06 for a single pulse and 30.26 ± 16.69 for a train of 10 pulses in response to the test stimuli. In the BMS group, the mean NPS scores were 23.93 ± 11.76 for a single pulse and 41.0 ± 19.11 for a train of 10 pulses in response to the test stimuli.

The difference between the two NPS scores (pain intensity after receiving 10 pulses –pain intensity after receiving a single pulse) revealed the TS scores that were 13.26 ± 9.63 in the control group and 17.06 ± 7.35 in the BMS group. There was no significant difference between these two TS scores, which denoted that TS was equally induced by repeated painful stimuli in the both groups (Fig. 3, $p < 0.001$).

DISCUSSION

Previous studies have already demonstrated that repetitive painful electrical stimulation can induce TS (Arendt-Nielsen *et al*, 1995; Staud *et al*, 2007). Repetitive inputs from the long latency nociceptive neurons in peripheral C fibers result in the phenomenon called “wind-up”, which progressively increases the frequency of discharge in WDR dorsal horn neurons (Price *et al*, 1977). Recently, a method of IES was developed for the activation of peripheral C fibers (Inui *et al*, 2002). TS facilitated by nociceptive afferent inputs with IES increases pain intensity (Mouraux *et al*, 2010), and the frequency of IES may be involved in enhancing the amplitude of the event-related brain potentials (Mourauxa *et al*, 2014).

A previous study with patients with BMS demonstrated that the patients exhibited increased intraoral “wind-up” to nociceptive afferent inputs (Nasri-Heir *et al*, 2017). In the present study, TS was induced in patients with BMS, but no significant difference in TS was observed between the patients and controls. As TS presumably reveals overactivity of N-methyl-D-aspartate (NMDA) receptors, the finding that TS was not significantly enhanced in BMS patients relative to controls may indicate that a different mechanism may underlie the persistent pain in patients with BMS; specifically, the “wind-up” and overactivity of NMDA receptors might not be the primary pain mechanism in BMS patients.

CPM is a paradigm based on the concept of “pain inhibits pain” and corresponds to the pain inhibitory system. CPM is typically tested applying different type of painful stimuli to generate the test and the conditioning inputs, which produce inhibitory effects. In respect to this point, CPM may play an essential role in the translational model for assessment of the pain modulating function (Pud *et al*, 2009). The data showed that

the magnitude of pain reduction at 40°C CS in BMS patients was equal to that in healthy controls. Contrarily, the full CPM effect induced by 47°C stimulus was suppressed in patients suffering from BMS but not in healthy controls. These results suggest that the pain signal in BMS patients was processed as usual with non-painful CS, whereas it was processed without inhibition that should be normally emerged with noxious CS. This difference in response may be related to distraction in CPM. The role of distraction in CPM has been discussed in the literature extensively. It has been shown that CPM acts independently from distraction (Moont *et al*, 2010) and CPM magnitude is associated with intensity of CS (Nir *et al*, 2011). When the intensity of the CS is not strong enough, distraction may induce mild but not significant pain inhibition during innocuous CS both in controls and BMS patients, although CPM lacks its inhibitory control during noxious CS in BMS patients.

Impaired CPM has been reported in patients with some chronic pain conditions, such as fibromyalgia, and persistent postendodontic pain (Nasri-Heir *et al*, 2015; Staud *et al*, 2002). Neurophysiological and imaging studies raise a question of whether lesser pain modulation occurs in association with the malfunction of C fibers in BMS condition (Forssell *et al*, 2002, Jääskeläinen *et al*, 1997; Jääskeläinen *et al*, 2001, Jääskeläinen *et al*, 2014, Shinozaki *et al*, 2016). The mechanism of pain habituation observed during the repetition of a noxious stimulus with an interval is explained by C-fiber function, and lack of this phenomenon may be associated with impaired function of C fibers (Shinozaki *et al*, 2016). Peripheral C fiber stimulation induces maladjustment of medullary dorsal horn neurons in cases of orofacial pain (Baad-Hansen *et al*, 2007; Greenspan *et al*, 2011). The data in this study suggested that the pain inhibitory system was impaired when the 47°C CS was applied to the hand in

patients with BMS. It is possible that this pain inhibitory impairment may have developed due to the lack of habituation of pain sensation when applying noxious thermal stimulation to the hand.

The results of study 2 demonstrated that TS was successfully induced using the IES device not only in the trigeminal afferents but also in the cervical spinal afferents both in controls and patients with BMS. No significant difference in TS was observed between the right chin and the forearm in patients with BMS, suggesting that the enhanced pain reaction to noxious stimulation was not site-specific. In addition, the fact that there was no significant difference in TS between the BMS and the control groups suggested that the facilitatory pain modulation that possibly led by the peripheral and the lower central nervous system had not been exaggerated in patients with BMS. Further to the fact that CPM was suppressed in BMS patients, findings may lead us to a hypothesis that BMS has the central rather than the peripheral involvement.

Limitations in this study include association with psychosocial distress and mood conditions, e.g., anxiety and depression. As we have not investigated the relationship between CPM or TS and such mood disorders, additional research is necessary to explore these possible associations.

CONCLUSION

TS was equally induced both in the spinal and the trigeminal innervation in patients with BMS as well as in controls. Contrarily, in the BMS group, CPM was significantly less efficient than in the control group. These findings suggest that the persistent pain of BMS may be associated with the impaired pain modulation in the central rather than the peripheral nervous system.

FIGURES AND TABLE

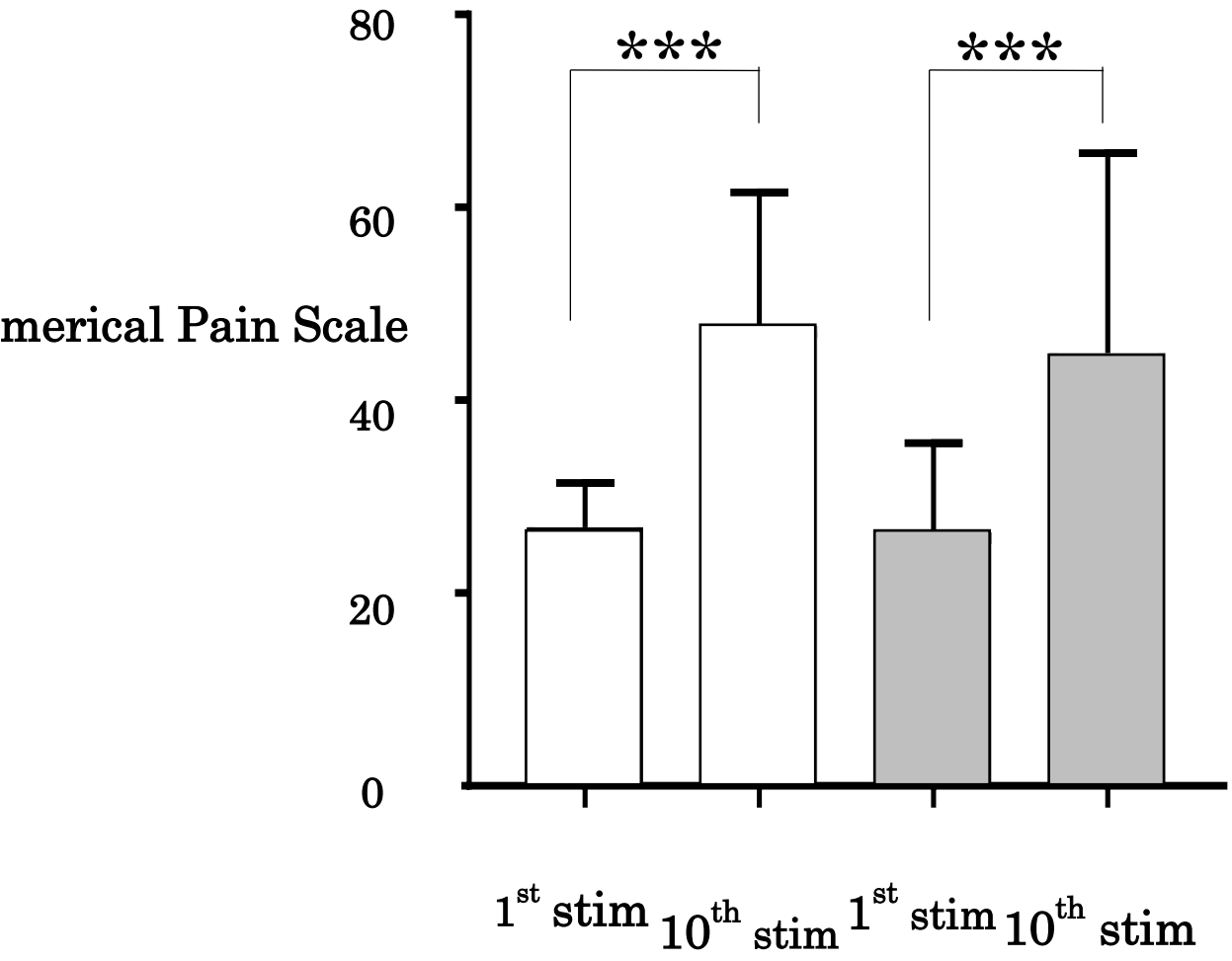

Fig. 1. TS without CS on the chin in both controls and BMS patients

TS was induced by repeated painful stimulus both in controls (white box) and in BMS patients (gray box).

NPS: numerical pain scale, CS: conditioning stimulus

Mean ± SD, ***: $p < 0.001$

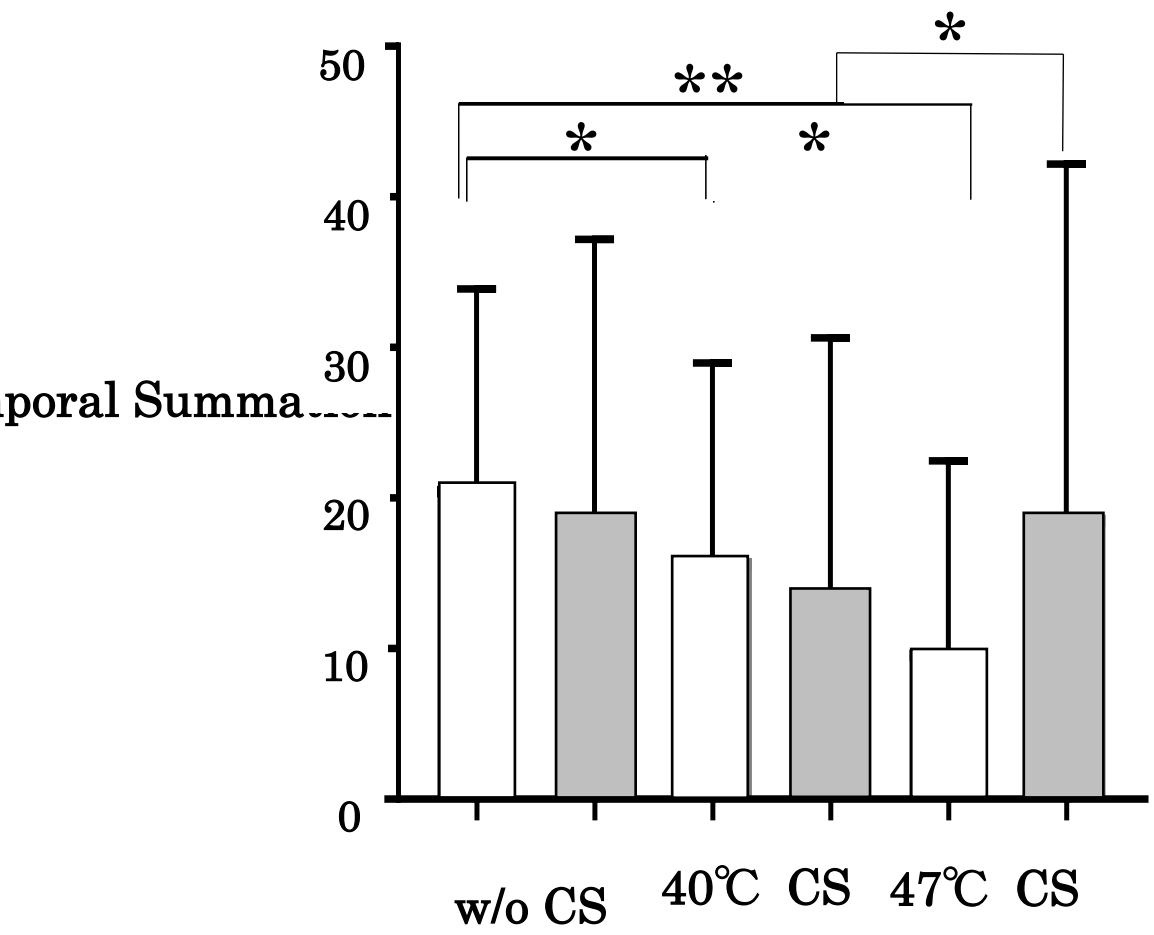

Fig. 2. TS without CS and 40°C CS and 47°C CS on the chin in both in controls and BMS patients

Repeated painful stimulus (test stimulus) induced TS and remote-noxious CS inhibited TS in controls (white box) but less efficient in BMS patients (gray box).

Temporal Summation=Response to the 10^{th} stimulus (NPS) – response to the first stimulus (NPS)

CS: conditioning stimulus, Mean ± SD, *: $p < 0.05$, **: $p < 0.01$

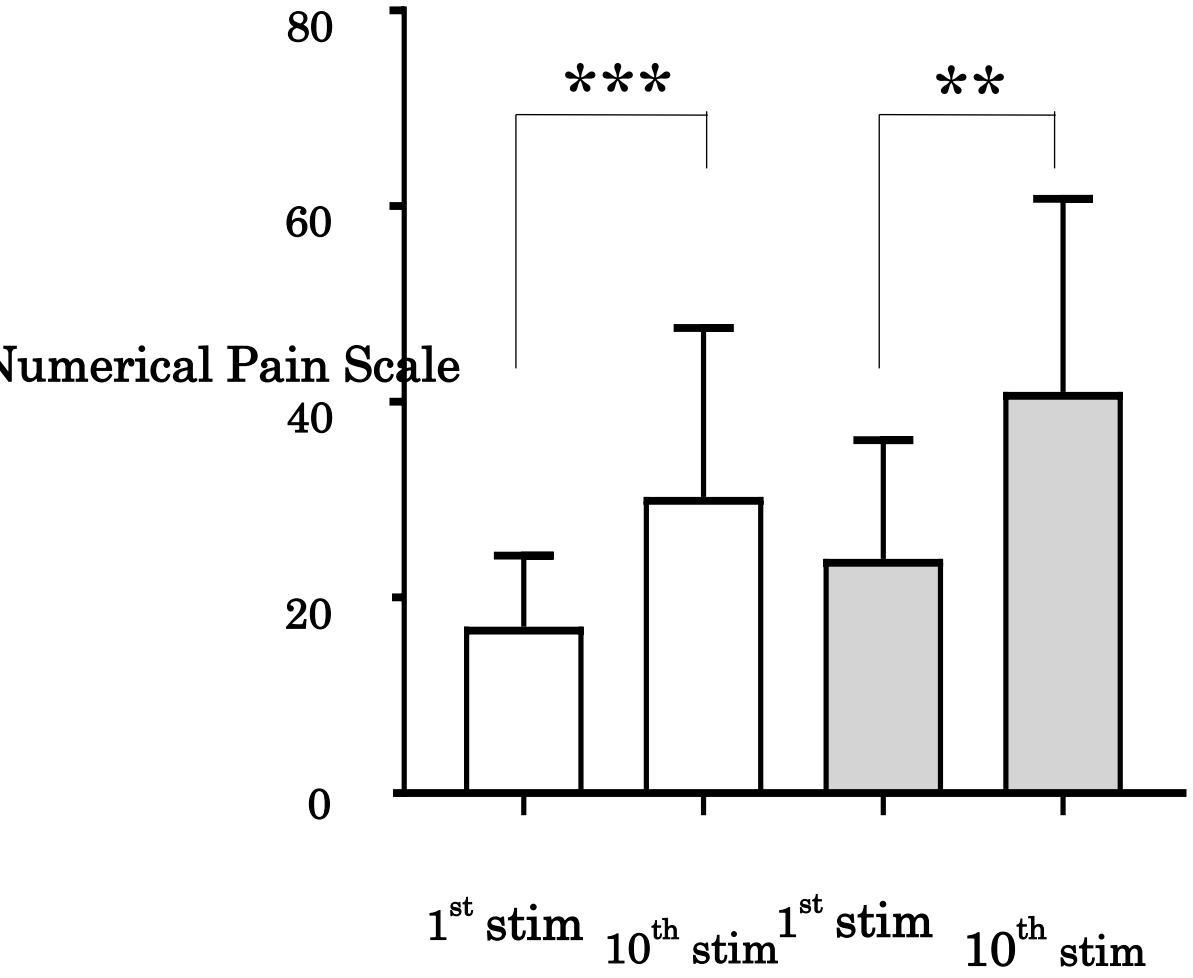

Fig. 3. TS without CS in the forearm in both in controls and in BMS patients

TS was induced by repeated painful stimulus both in controls (white box) and in BMS patients (gray box)

NPS: numerical pain scale, CS: conditioning stimulus

Mean ± SD, **: $p < 0.01$, ***: $p < 0.001$

Table 1. TS and CPM results in BMS patients and controls

A

	Control			
	Single pulse (NPS:0-100)	10 pulses (NPS:0-100)	TS	CPM
Test Stimuli	26.85 ± 4.57	47.66 ± 13.91	20.81 ± 13.07	–
CS (40℃)	17.48 ± 7.32	33.48 ± 15.04	16.00 ± 12.99	-4.81 ± 12.47
CS (47℃)	17.88 ± 9.27	27.81 ± 15.21	9.925 ± 12.56	-10.88 ± 16.12
Intensity (mA)	0.27 ± 0.15			

B

	BMS			
	Single pulse (NPS:0-100)	10 pulses (NPS:0-100)	TS	CPM
Test Stimuli	26.27 ± 9.32	44.88 ± 20.78	18.62 ± 18.57	–
CS (40℃)	20.96 ± 11.14	34.96 ± 19.99	14.00 ± 16.65	-4.61 ± 16.46
CS (47℃)	19.62 ± 10.82	38.50 ± 25.99	18.88 ± 23.32	0.269 ± 23.19
Intensity (mA)	0.29 ± 0.14			

TS: temporal summation, CPM: conditioned pain modulation, CS: conditioning stimulus (BMS, n = 26; control, n = 27)

Mean ± SD, *: $p < 0.05$, **: $p < 0.01$

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