Original article

Time-dependent responses in brain activity to ongoing hot stimulation in burning mouth syndrome

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Abstract: Burning mouth syndrome (BMS) is classified into idiopathic orofacial pain conditions. Although central and peripheral neuropathic mechanisms are believed to be involved, the etiology remains to be fully elucidated. The present study examined temporal brain responses to an ongoing hot stimulus to investigate the pain modulating system in patients with BMS. The thermal stimulation sequence comprised baseline (32°C, 40 s) to warm (40°C, 32 s) to baseline (32°C, 40 s) to hot (49°C, 32 s), which was repeated four times using a Peltier thermometer. These warm and hot stimuli were applied on the right palm and right lower lip in two separate sessions. Functional magnetic resonance imaging data were acquired by recording echo-planar images with a block design. Brain activity induced by pure hot stimulation (49°C vs. 40°C) applied to the palm was more pronounced than that induced by lip stimulation and in patients with BMS compared with controls. Comparison of brain activity between the first 16 s and second 16 s of the stimulus revealed pronounced time-dependent facilitation in patients with BMS during lip stimulation. These findings indicate that the pain modulating system in patients with BMS is dysregulated and that the brain in BMS is highly sensitized to pain information originating from the trigeminal system.

Keywords: burning mouth syndrome, functional MRI, pain matrix, temporal summation

Introduction

Persistent idiopathic orofacial pain can often be disabling for patients. Burning mouth syndrome (BMS) is one of the most typical idiopathic orofacial pain conditions diagnosed following the exclusion of all possible conditions in which continuous pain manifests in intraoral soft tissues [1-2, Headache Classification Subcommittee of the International Headache Society, The International Classification of Headache Disorders: 2nd edition. 9-160, Cephalalgia, 2004]. Although the etiology of BMS is unknown, common characteristic features have been reported. These features include a predilection for postmenopausal women [1,3]; association with psychological conditions including depression, hypochondria, and cancer phobia [4-6]; and taste disturbance [7-9]. Studies have attempted to explain its etiology from immune and endocrine responses [10-12] and neuropathic changes in the peripheral and central nervous systems [13-16].

Recent studies have suggested that there is an alteration in the pain modulating system in the BMS brain [17-21]. In the previous study, it was demonstrated that the perception of pain was more intense in patients with BMS compared with that in controls on administration of a repeated painful hot stimuli to the lower lip, and this increased pain perception was not observed when the same stimulation was repeated on the palm of the hand. During this stimulation, the anterior cingulate cortex (ACC), prefrontal cortex (PFC), and insular cortex (IC), known to be the main components of the medial pain pathway, were highly activated in patients with BMS. It was suggested that one of the reasons for this impairment in the pain modulating system was the loss of the pain habituation in C-fibers that occurs during repetition of a noxious stimulus [21]. The present study investigated whether the same responses were provoked by ongoing painful hot stimulation in patients with BMS.

Materials and Methods

Participants
The participants comprised 15 right-handed female patients (52.6 ± 6.3 years) who were diagnosed with primary BMS and 15 age- and gender-matched, right-handed female controls (49.0 ± 8.4 years). Patients were diagnosed with BMS according to the criteria of the Third Edition of the International Classification of Headache Disorders, beta version (Headache Classification Committee of the International Headache Society, Vol. 38, 1-211, Cephalalgia, 2018). Peripheral and systemic diseases that can manifest a pain and burning sensation in the oral mucous membrane were excluded accordingly [12].

Setting
All participants were enrolled at the Orofacial Pain Clinic at Nihon University Dental Hospital, and imaging data were acquired at Nihon University Itabashi Hospital. Verbal and written consent was obtained from all the participants. The study was conducted in accordance with the Helsinki Declaration. The study was reviewed and approved by the Ethical Board of Nihon University School of Dentistry (EP16D020).

Thermal stimulation
The thermal stimuli sequence that was used in the functional magnetic resonance imaging (fMRI) session had been preliminarily introduced to the participants. They had experience of the protocol prior to the actual test stimuli for MR data acquisition. Thermal stimulation was delivered using a thermal generator (Intercross-210, Intercross, Tokyo, Japan) with an MRI-compatible Peltier thermode (10 × 10 mm). Two sites were selected for the application of thermal stimulation sequence described below: first was to the skin of the right palm and then to the mucosa of the right lower lip. The stimulation sequence started with a 30°C adaptation temperature, followed by warm and hot stimulation sets. A warm stimulation set comprised 40 s of 32°C baseline temperature and 32 s of 40°C warm stimulation. In a hot stimulation set, a 40 s baseline temperature was followed by 32 s of 49°C painful hot stimulation. A pair of warm and hot stimulation sets was repeated four times in a session. The thermode was programmed to return to the adaptation temperature (40 s at 30°C) following the end of the protocol. To avoid the influence of preceding palm stimulation, a 3-min break was scheduled prior to lip stimulation. Following this rest, the same session protocol was repeated on the right lower lip (Fig. 1).

Imaging acquisition
A 1.5-T MRI scanner (Ingenia, Philips, Amsterdam, the Netherlands) with a conventional birdcage head coil was used for collecting anatomical and functional images. The following settings were used in a T2-weighted gradient-echo planar imaging (EPI) sequence (TR: 4,000 ms, TE: 50 ms,
Differences in brain activity were compared between groups (patients with BMS controls and vice versa). ii. Time-dependent facilitation and suppression in brain activity: (Fig. 2, ΔB & ΔC) Differences in brain activity were compared between two time periods (second half periods-first half periods and vice versa). iii. BMS-specific time-dependent facilitation and suppression were further calculated (Fig. 2, ΔG: differences in brain activity were compared between two groups, ΔB-ΔC and vice versa). Differences in brain activity between two groups were further calculated.

In the statistical analyses, analysis of variance followed by a post hoc Bonferroni test was used for multiple comparisons between groups. The comparison of data between two groups was analyzed using a t-test. The threshold for statistical significance was initially set at $P < 0.01$ (uncorrected) for voxel-level analysis, and $P < 0.05$ (family-wise error correction) was set for cluster-level analysis.

**Results**

Pathognomonic brain activation in patients with BMS

Subtraction of the brain activity evoked by painful hot stimulation to the palm of the control group from that of the BMS group revealed significantly activated brain regions during palm stimulation in patients with BMS compared with the controls. These regions included the secondary somatosensory cortex (S2), dorsolateral prefrontal cortex (dIPFC), IC, visual cortex (VC), posterior cingulate cortex (PCC), hippocampus,
parahippocampal gyrus, and cerebellum. Furthermore, statistical analysis of the dataset of brain activity during lower lip stimulation in the two groups showed a significant increase in brain activity during painful hot stimulation to the lower lip of patients with BMS compared with that in the controls. These brain regions included the premotor cortex (PMC), orbitofrontal cortex (OFC), medial PFC (mPFC), dlPFC, ACC, IC, VC, caudate nucleus, and midbrain (Fig. 3).

**Pathognomonic brain suppression in patients with BMS**

Subtraction of the brain activity in patients with BMS from that in controls revealed fewer activated areas in the patients with BMS than in the controls. This revealed that there were few areas showing a significant decrease of brain activation during either palm or lip stimulation in the patients with BMS compared with controls (data not shown).

**Time-dependent facilitation in brain activity**

During painful hot stimulation, brain activation was facilitated in the second half periods compared with the first half periods in both the patients with BMS and the controls. This temporal facilitation of brain activity was more apparent in the patients with BMS than in the controls and during lower lip stimulation than palm stimulation. The BMS brain showed a time-dependent facilitation in the secondary VC (V2), PMC, thalamus, dlPFC, and mPFC during lip stimulation and in the supramarginal gyrus, pons, and cerebellum during palm stimulation (Fig. 4, Table 1).

**BMS-specific time-dependent brain activation**

Subtraction of the brain activity in the first half periods from that in the second half periods revealed brain regions showing time-dependent facilitation. This time-dependent facilitation evoked by sustained lip stimulation was more marked in the patients with BMS than in the controls in the following brain regions: primary motor cortex (PMC, M1), insular cortex (IC), prefrontal cortex (PFC), and anterior cingulate cortex (ACC). However, this BMS-specific time-dependent increase in brain activation was not observed during palm stimulation (Fig. 4).

**Time-dependent suppression in brain activity**

Subtraction of the brain activity in the second half periods from the first half periods revealed no regions showing significant changes.

**Discussion**

The hot pain thresholds in patients with BMS are reported to be higher in the lip than in the hand [22]. In the present study, a fixed-temperature (49°C) stimulus was applied to both the palm and the lower lip, which revealed that the stimulus was perceived to be stronger when it was applied at the palm than the lower lip. Therefore, due to this site-specific difference in pain threshold, the magnitude of the brain response was greater when the stimulation was applied to the palm than the lower lip. No previous studies using quantitative sensory tests have reported significant differences in pain thresholds between patients with BMS and controls. That
indicates the difference in the magnitude of brain activity between patients and controls does not depend on the difference in pain thresholds. Grushka et al. [23] and Ito et al. [24] reported that patients with BMS had a lower pain tolerance compared with controls. These findings suggest that the difference in brain activity between patients with BMS and controls reflects the difference in responses of the central nervous system in the two groups, which was the main focus of the present study.

Subtraction of the magnitude of the brain activity (BMS-patients-controls and vice versa) revealed brain regions of facilitation and suppression in patients with BMS compared with controls, respectively. These changes appeared to be pathognomonic features in BMS. The brain regions that showed higher activation in patients with BMS than in controls during palm stimulation included the somatosensory areas (S2 cortex and supramarginal gyrus), VC, cerebellum limbic system (hippocampus and parahippocampal gyrus), and cerebellum, which are mainly associated with pain perception (Fig. 3A). By contrast, the activated areas in the BMS brain during lip stimulation included the motor-related areas (M1 and PMC), cognito-affective areas (ACC, IC, mPFC, dPFC, and OFC), VC, caudate nucleus, and midbrain (Fig. 3B), which are involved in pain modulation [25-27] and emotions [25,28-30]. These results are consistent with previous reports [21,31]. Changes in gray matter volume or concentration in these regions associated with pain modulation and emotions have been reported in patients with BMS [32,33] and in other chronic pain conditions [28,34], and these changes may reflect the relationship between BMS and the psychological distress induced by chronic pain. Recently, using resting-state fMRI, it was reported that connectivity between these areas exhibit excessive brain activity in the BMS group than in the control group and was associated with the severity of depression [33,35]. These findings suggest that the pathogenesis of BMS is closely associated with depression and anxiety, and these data support this hypothesis.

To examine in detail this difference in brain responses, the present study investigated temporal changes in brain activity during sustained painful hot stimulation in both groups. The results revealed a significant time-dependent facilitation (Fig. 4) with little inhibition (Fig. 5) in both groups. Previous studies have reported that ongoing painful hot stimulation induced temporal summation [36]. This time-dependent facilitation was more apparent in the patients with BMS than in controls, and during lower lip stimulation than palm stimulation, and the brain regions exhibiting time-dependent facilitation were those involved in pain modulation (Fig. 4B). Findings associated with temporal summation may represent the pathognomonic features of BMS pathophysiology. First, time-dependent facilitation may reflect the brain activity to modulate the temporal summation evoked by sustained painful stimulation [37]. In the brain of patients with BMS, the pain modulating function is more active than that of controls, and the brain of patients with BMS facilitated this function without waning over 32 s. Secondly, higher time-dependent facilitation was observed when the stimulation was applied to the lower lip. This finding suggests that there is a site-specific, peripheral mechanism. As shown in Fig. 3, the magnitude of brain response to the fixed temperature was more marked during palm stimulation than lip stimulation. Therefore, the time-dependent facilitation did not affect brain response intensity in a dependent manner. This finding suggests that the brain in patients with BMS is highly sensitized to pain signals originating from the trigeminal system. In patients with BMS, it is known that small nerve fiber atrophy is observed in the oral mucous epithelium [19,38], and such a peripheral pathology may be involved in sensitization of the brain in BMS.

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Conflict of interest
The authors declare that they have no conflict of interest related to the conduct of this study.

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