Lack of Temporal Summation but Distinct Aftersensations to Thermal Stimulation in Patients with Combined Tension-Type Headache and Myofascial Temporomandibular Disorder

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Aims: *To compare patients with combined tension-type headache and myofascial temporomandibular disorder (TMD) with control subjects on two measures of central processing—ie, temporal summation and aftersensations to heat stimulation in the trigeminal nerve and spinal nerve territories.* ***Methods:*** *A novel heat stimulation protocol was used in which 13 females with tension-type headache/TMD and 20 female controls were exposed to 11 painful heat stimuli at a rate of 0.33 Hz. Two temperature ranges (low, 44°C to 46°C; high, 45°C to 47°C) were tested on the cheek and arm in separate trials. Perceived pain was rated on a 100-mm visual analog scale after the second, sixth, and eleventh stimulus presentation and every 15 seconds after the final stimulus presentation (aftersensations) for up to 3 minutes. The duration of aftersensations was compared using the student unpaired* t *test with Welch correction.* ***Results:*** *Temporal summation was not observed in any of the groups, but aftersensations were consistently reported. The aftersensations lasted longer in tension-type headache/TMD patients (right cheek, 100.4 ± 62.0 seconds; right arm, 115.4 ± 64.0 seconds) than in controls (right cheek, 19.5 ± 2.5 seconds; right arm, 20.3 ± 2.7 seconds) (*$P < .05$*). A cutoff value (right cheek, 44.6 seconds; right arm, 41.5 seconds) provided a sensitivity and specificity of 0.77 and 0.95, respectively, with the high stimulus protocol.* ***Conclusion:*** *The results from this pilot study suggest that aftersensations to painful heat stimulation can appear without temporal summation. Furthermore, the developed test protocol has a good predictive value and may have the potential to discriminate between tension-type headache/TMD patients and control subjects.* J OROFAC PAIN 2012;26:288–295

Key words: aftersensations, central sensitization, myofascial pain, temporal summation, temporomandibular disorder, tension-type headache

Sensitization of nociceptive pathways may be a significant contributing factor that predisposes, perpetuates, and precipitates orofacial pain disorders, including tension-type headache and temporomandibular disorders (TMD).[1–7] Central sensitization is characterized by hypersensitivity to nonpainful stimuli (allodynia), progressive increase in perceived pain to painful stimuli (hyperalgesia), and enlargement of receptive fields (ie, an increased response to stimulation mediated by amplification of signaling and synaptic plasticity in the central nervous system).[8–11] Quantitative sensory testing can assess the clinical manifestations of peripheral and central sensitization,[8,12,13] including the trigeminal area.[14] However, the stimulus modalities applied and perceptual responses assessed vary widely across studies. Temporal summation of painful heat stimuli, a more dynamic form of quantitative sensory testing, occurs when repetitive C-fiber afferent inputs induce enhanced responses in dorsal horn neurons.[15] Temporal summation results in the perception of increased pain, despite constant or even reduced peripheral afferent input,[16] and is therefore considered to be a perceptual manifestation of enhanced central excitability.[17] Temporal summation has been linked to the development and maintenance of chronic pain,[18–20] based on enhancement of pain intensity after repetitive stimulation, increased frequency of aftersensations, and increased occurrence of referred pain.[19,21] In addition, it is commonly used for studies on hyperalgesic mechanisms in chronic pain conditions, such as fibromyalgia[22–24] and TMD.[15,21] However, this relatively simple picture of changes in experimental pain from a repetitive thermal stimulus was made more complex by recent findings that adaptation has both peripheral and central components.[25,26] In particular, with the use of constant suprathreshold thermal stimuli, heat intensity perception that does not increase with time may participate additionally or exclusively in many functions, including the modulation of nociceptive processing during the psychophysical plateau.[27] Such a psychophysical plateau could be accounted for by an early burst of activity followed by a later sustained lower rate of discharge in Aδ and C heat nociceptive afferents [28–32] or by central mechanisms suppressing the heat pain modulatory effects of warm afferents.[33,34] To examine whether orofacial pain patients have a modulation of nociceptive processing, this study aimed to develop a novel repetitive and painful heat stimulation protocol that could discriminate between patients and matched control subjects.

TMD encompasses several conditions that may involve the temporomandibular joint (TMJ) and masticatory muscles. Pain outside the masticatory system (widespread pain) has been shown to be a significant risk factor for the onset of dysfunctional TMD pain among women.[35] Furthermore, Anderson et al have reported a significant association of increased TMD pain intensity and increased frequency of clinical TMD signs with more frequent temple headaches.[36] These findings indicated increased sensitivity in the trigeminal and nontrigeminal sites, as well as larger fields of pain associated with increased headache frequency. Therefore, it has been suggested that a generalized hyperexcitability in the central processing of nociceptive input is implicated in the pathophysiology of TMD[6] and tension-type headaches.[37] Moreover, myofascial TMD is considered as prevalent as tension-type headaches.[38]

Tension-type headache is the most common primary headache disorder and has a large impact on society.[39] Although the pathophysiology of tension-type headache is largely unknown, nociceptive processes in craniofacial muscles are believed to play a role in the development and maintenance of tension-type headaches.[3,40] Sensitization of neurons in the central nervous system may also be of major importance.[1,3–5,7]

The aim of this study was to compare patients with combined tension-type headache and myofascial temporomandibular disorder with control subjects on two measures of central processing—ie, temporal summation and aftersensations to heat stimulation in the trigeminal nerve and spinal nerve territories.

Materials and Methods

Subjects

A total of 24 tension-type headache/TMD female patients were considered for this study. Of those, 13 were eligible for inclusion, and all these subjects (mean age ± standard deviation (SD), 28.8 ± 9.8 years) completed the study. In addition, 20 healthy, age-matched females (mean age ± SD, 22.95 ± 4.6 years) tested in the clinic in the same manner were evaluated as a control population. This study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the local Ethics Committee for Keio University (2010-321). Before each subject signed the consent form, the principal investigator informed the subject of the study procedures.

The main inclusion criteria were complaints of orofacial pain in the masseter and/or temporalis areas for a duration of more than 3 months. All patients underwent a complete medical and dental history, as well as a clinical examination. The history investigated pain, limitation of mandibular motion, and TMJ sounds. The clinical examination included the evaluation of pain and tenderness to palpation of the masticatory muscles and TMJs and the range of mandibular movements. Consecutive patients were examined according to criteria suggested by the Research Diagnostic Criteria for TMD (RDC/TMD)[41] by a single experienced specialist from the TMD/Orofacial Pain Clinic at Keio University Hospital, Tokyo, Japan. The experienced specialist made a clinical judgment that the pain was primarily of muscular origin. Thus, all patients fulfilled criteria for a myofascial subtype of TMD. In addition, if provocation of the pain (joint or muscle) was un-

Fig 1 The thermal stimulator was placed on the right cheek overlying the masseter muscle and on the right arm at the ulnar styloid process in separate trials.

clear in a subject, the examiner identified the origin of pain by palpation and/or jaw movements. Prior to testing, all patients underwent thorough clinical and neurologic examinations to confirm the diagnosis of tension-type headache. These patients fulfilled the criteria associated with pericranial muscle tenderness according to the International Headache Society (code 2.3.1).[42] Exclusion criteria included pregnancy, presence of a score greater than 8 in the Beck Depression Inventory–Second Edition (BDI-2), previous interventions with surgery and/or steroid injections, rheumatoid diseases, neurologic disorders, head or neck surgery, fibromyalgia,[43] and the use of analgesic(s) other than acetaminophen in the 3 days prior to the examination.

Experimental Design

Modulation of nociceptive processing can be investigated using dynamic quantitative sensory testing techniques. In this study, clinical manifestations of the modulation of nociceptive processing were investigated using repetitive suprathreshold (painful) heat stimulation and assessment of aftersensations.[44,45] Modulation of nociceptive processing caused by myofascial pain in the masticatory muscles or tension-type headache was investigated on the right cheek and right arm (Fig 1). Subjects sat in an armchair in a quiet room with an ambient temperature of approximately 25°C throughout the experimental session.

Repetitive Suprathreshold (Painful) Heat Stimulation

Repetitive suprathreshold (painful) heat stimuli were applied to the right cheek and right arm by a thermode with a 1.0-cm^2 surface area by a Thermal Stimulator (Unique Medical). To establish a reliable and low-invasive protocol that would be able to assess the diagnostic value as a test for tension-type headache/TMD, two temperature ranges were examined by a blinded examiner. In the low-stimulus protocol, the temperature gradually increased 2°C per second from the baseline temperature of 44°C to the peak temperature of 46°C. When the temperature reached 46°C, the temperature was gradually decreased at a rate of 2°C per second until the baseline temperature was reached. Sequences of 11 consecutive heat pulses of less than 1-second duration at an interpulse interval of 0.33 Hz were delivered,[46–48] and the thermode was removed as soon as the final stimulus was complete. In the high-stimulus protocol, the baseline temperature was set at 45°C and the peak temperature at 47°C. Pain perception and aftersensations were assessed with a 100-mm visual analog scale (VAS) (0, no pain; 100, most pain imaginable) immediately after the second, sixth, and eleventh stimulus presentation to evaluate temporal summation and every 15 seconds after the final stimulus presentation for up to 3 minutes to evaluate aftersensations. All tests were performed twice for both the right cheek and right arm. The means of the VAS values of 2nd, 6th, and 11th stimuli and the duration of aftersensations were used for further statistical analyses for both the right arm and right cheek.

Statistical Analyses

SPSS 14 (IBM) was utilized for statistical analyses. Modeling of temporal summation development involved two separate repeated-measures three-way analysis of variance (ANOVA). Sustained periods of aftersensations were first analyzed with the Kolmogorov-Smirnov test. Because the hypothesis that the duration of aftersensations was normally distributed could not be rejected, subsequent analysis was performed by means of parametric statistical tests. Group differences in the duration of aftersensations were tested with the Student unpaired t test with Welch correction. Significance indicated that the

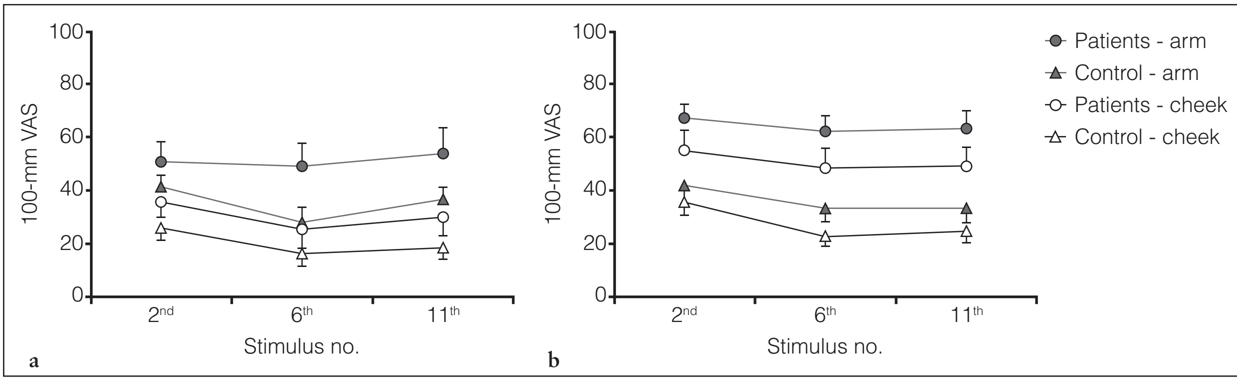

Fig 2 VAS values (0 to 100 mm) after the second, sixth, and eleventh heat stimulus presentation. Each point represents the VAS values averaged across groups and stimulus site; error bars show ± 1 standard error of the mean. *(a)* Low-stimulus protocol. *(b)* High-stimulus protocol.

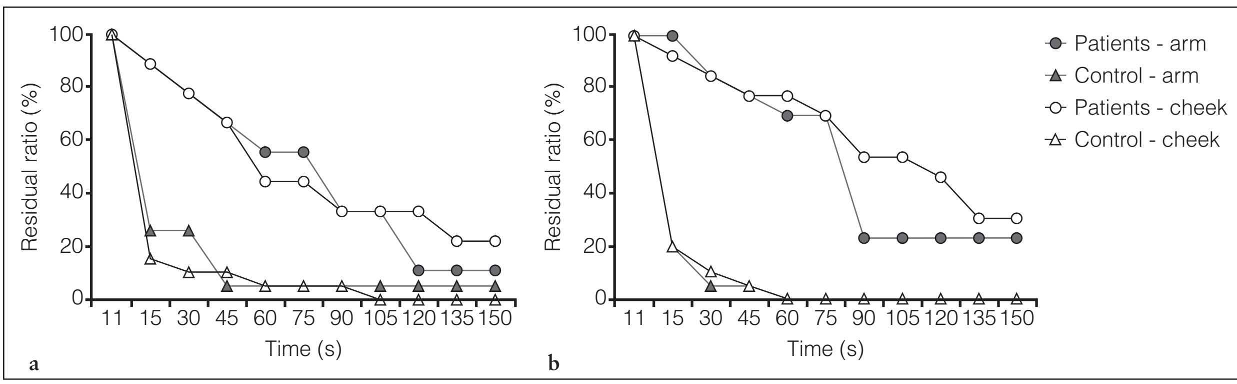

Fig 3 Ratios of subjects who reported aftersensations after completion of the painful heat stimulation. Residual ratio is defined as the ratio of subjects who reported aftersensations on that timing. *(a)* Low-stimulus protocol. *(b)* High-stimulus protocol.

probability of a type I error was no more than 5%. To assess the diagnostic value of aftersensations as a test for tension-type headache/TMD, the sensitivity and specificity were calculated for the low- and high-stimulus protocols. The sensitivity is the fraction of the patients with tension-type headache/TMD who obtained a positive test result, whereas the specificity is the fraction of patients without tension-type headache/TMD who obtained a negative test result.

Results

Tension-type headache/TMD patients and control subjects were similar demographically, including age (*t* test, $P = .058$). All subjects reported pain at 44°C and 45°C, which was the baseline temperature in the low- and high-stimulus protocols. Flare and aftersensations disappeared from all participants, and no adverse effects were observed in this study.

A comparison between the control and tension-type headache/TMD groups for the calculated delta values of evoked pain intensity at each region was used to assess temporal summation. For each stimulus protocol, there were no significant differences between the two groups or between the two stimulus sites in the changes in the VAS pain ratings with increasing number of stimuli (low-stimulus protocol, $F = 0.258$, $P = .773$; high-stimulus protocol, $F = 0.216$, $P = .806$) (Fig 2). Temporal summation was not induced in either group with either of the two stimulus protocols or stimulus sites. The VAS ratings were higher on the arm than on the cheek (low-stimulus protocol, $F = 11.048$, $P = .002$; high-stimulus protocol, $F = 7.237$, $P = .017$), and higher with the high-stimulus protocol than with the low-stimulus protocol (right cheek, $F = 18.746$, $P < .001$; right arm, $F = 35.330$, $P < .001$).

Aftersensations

Participants reported the occurrence of aftersensations to painful heat stimulation. Although all the aftersensations in the control group had disappeared

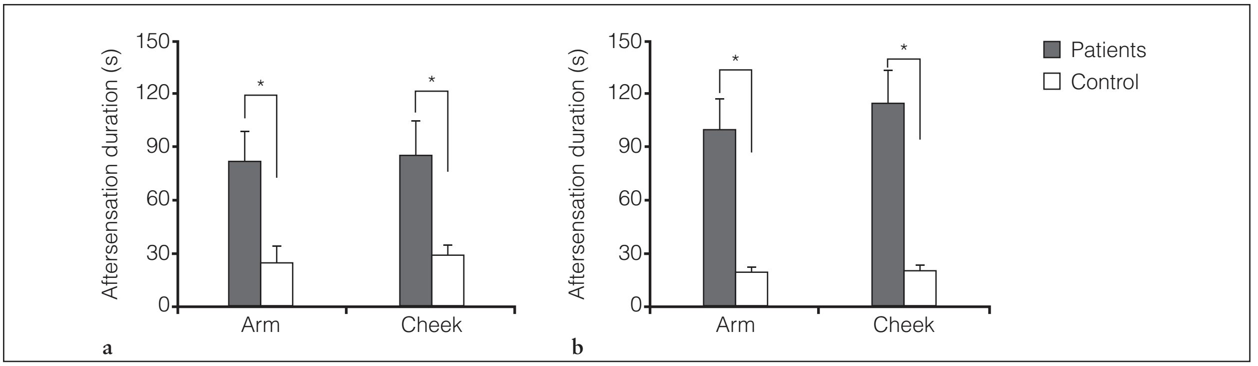

Fig 4 Duration of aftersensations. The mean durations in the tension-type headache/TMD group were significantly longer than in the control group, and there were significant differences between the two groups for the low-stimulus protocol. These differences were more marked for the high-stimulus protocol. $^*P < .05$ by Student unpaired t test with Welch correction. Error bars represent ± 1 standard error of the mean. *(a)* Low-stimulus protocol. *(b)* High-stimulus protocol.

Table 1 Cutoff Values (seconds) Calculated from the Mean Duration of Aftersensations in the Control Group, as well as Specificity and Sensitivity Values Based on the Duration of the Aftersensations

	Cheek			Arm		
	Cutoff (s)	Sensitivity	Specificity	Cutoff (s)	Sensitivity	Specificity
Low-stimulus protocol						
1 SD	49.1	0.56	0.89	68.9	0.44	0.95
2 SD	73.7	0.44	0.95	109.3	0.30	1.00
3 SD	98.3	0.30	1.00	149.7	0.11	1.00
High-stimulus protocol						
1 SD	32.4	0.85	0.90	30.5	0.85	0.95
2 SD	44.6	0.77	0.95	41.5	0.77	0.95
3 SD	56.8	0.77	1.00	52.5	0.77	1.00

SD, standard deviation.

by 60 seconds after the final stimulus in the high-stimulus protocol, some subjects in the control group had aftersensations for more than 60 seconds in the low-stimulus protocol (Fig 3).

The mean duration of aftersensations in the tension-type headache/TMD group were significantly longer than in the control group (Student t test, $P < .01$) for both stimulus protocols (Fig 4).

Cutoff values were set at 3.0 × standard deviation (SD), 2.0 × SD, and 1.0 × SD below the mean duration of the aftersensations in the control subjects (Table 1). The sensitivity and specificity are also presented in Table 1. These cutoff values corresponded to a specificity that ranged from 1.0 to 0.89. Although the specificity of the high-stimulus protocol was similar to that of the low-stimulus protocol, the sensitivity of the high-stimulus protocol was always higher than that of the low-stimulus protocol. The receiver operating characteristic (ROC) curve of the high-stimulus protocol was closer to the (0, 1) point, which is a perfect classification, than that of the low-stimulus protocol (data not shown). These findings were similar on the right cheek and right arm.

Discussion

This study focused on the changes in experimental pain from a repetitive thermal and painful stimulus in patients with both tension-type headache and myofascial TMD. The main finding of this study was that aftersensations to painful heat stimulation appeared without temporal summation in the tension-type headache/TMD group or control group and that the duration of these aftersensations contains important diagnostic information to differentiate between orofacial pain patients and control subjects.

The finding of heat pain hyperalgesia in the trigeminal and extratrigeminal regions are in accordance with some earlier reports[49,50] but disagree with others.[51–55] Hollins et al[26] demonstrated that pain intensity follows a biphasic time course consisting of adaptation followed by sensitization when a series of widely spaced painful thermal stimuli is presented. Moreover, Tran et al[27] suggested that approximately 10 seconds after continuously applying a painful contact heat stimulus to the skin, peripheral or central mechanisms, or a combination of the two, begin to limit perceived pain intensity to create what they refer to as a psychophysic plateau. These results perhaps reflect a gradual sensitization, in addition to temporal summation and adaptation.

The purpose of the present study was to describe and characterize the processes of modulation of nociceptive processing in orofacial pain patients. The study attempted to establish a novel repetitive and painful heat stimulus protocol. Based on the duration of the aftersensations to repetitive and painful heat stimuluation, a cutoff time could be defined with high sensitivity and specificity values. The recommendations from the American Academy of Orofacial Pain (AAOP) indicate that the sensitivity and specificity of any diagnostic test for TMD should be higher than 0.7.[56] In the present study, a high specificity (ie, 1.0 and 0.95) corresponded with a sensitivity of 0.77 with the use of the high-stimulus protocol. Moreover, the obtained sensitivity value was in fact higher than that previously reported for pressure algometry.[57,58]

Although Raphael et al[53] reported differences in the decay of aftersensations in the trigeminal region among TMD patients versus controls, the protocol of this study is easier and faster than that in the study by Raphael et al, which individually determined the threshold.[39] Even though the baseline temperature of this study was higher than that of any other studies,[49–55] flare and aftersensations disappeared from all participants and no adverse effects were observed.

Regarding the psychophysical plateau, it has been demonstrated that the activity of specific thalamic and cortical neural elements increases as stimulus duration, but not perceived intensity, increases.[27] The increase is consistent with the recruitment of a thalamocortical mechanism that participates in the modulation of pain-related cortical responses and the temporal summation of heat pain.[27] In other words, it is suggested that the results of the present study, including the extension of aftersensations, reflected such a modulation of pain-related cortical responses.

Although it is not surprising that the comparison of VAS ratings between the high- and low-stimulus protocols revealed that the VAS ratings were higher with the use of the high-stimulus protocol, the comparison of VAS ratings between the arm and cheek revealed that VAS ratings were higher on the arm. Since the anatomical landmark was the ulnar styloid process for the arm stimulus, one possible explanation for this finding may be that the site of the stimulus was close to nervus cutaneus antebrachii medialis.

The strengths and limitations of this study should also be noted. First, the assessment of aftersensations to repetitive and painful heat stimuli was determined by a blinded examiner, thereby ruling out a chance bias. Second, a specific group of women with strictly myofascial TMD and tension-type headache was included, and patients with other concomitant diseases and other comorbid pain conditions (ie, fibromyalgia and rheumatoid diseases) were excluded. Future studies should investigate the differences in temporal summation and aftersensations between TMD patients with and without frequent episodic tension-type headaches and those with chronic tension-type headaches. In addition, overlapping conditions such as headache attributed to TMD should be tested. Third, the thermal stimulator used in this study can increase and decrease the temperature only by 2°C per second. Because a battery of different test stimuli is needed to obtain comprehensive information about the functional integrity of the various types of afferent nerve fibers,[8] future studies may need to compare the diagnostic value in various temperature ranges or various stimulus modalities. Fourth, although there was no significant difference, the mean age of tension-type headache/TMD patients was higher than that of the control group. Heat pain thresholds have been shown to increase monotonically with age.[59] For example, Rolke et al[60] demonstrated that mean heat pain thresholds in the foot were 45.1°C versus 47.0°C in subjects of a young versus old age cohort. Therefore, the age difference between the two groups may have influenced the present findings. Future studies testing a larger age span may be needed. Another limitation of this study was that it evaluated only women with combined tension-type headache/TMD, which may represent a subset of tension-type headache and TMD patients. However, there is evidence that women have greater susceptibility to the development of temporal summation of thermal pain than men.[47] The study also did not control for variations in the menstrual cycle, which may also have influenced the thermal pain sensitivity to some extent, but should play only a minor role in healthy people (at least for the thermal pain threshold, tolerance, and temporal summation).[18] Future studies should investigate whether the prolonged duration of aftersensations found in this study's sample of women with myofascial tension-tyep headache/TMD are also present in men. Based on these limitations, and the fact that only relatively small groups were tested, the present study should be considered a pilot study. Nonetheless, it provides sufficiently promising results to warrant further investigations of other craniofacial pain conditions to test the ability of the developed test protocol to differentiate between cases and controls.

Conclusions

The main finding of the present pilot study was that the duration of aftersensations in the tension-type headache/TMD group was significantly longer than in the control group in both the trigeminal and extratrigeminal nerve territories. Aftersensations greater than 44.6 seconds with the high-stimulus protocol were associated with a sensitivity of 0.77 and a specificity of 0.95, indicating the potential of the developed test protocol to differentiate between tension-type headache/TMD patients and controls. A prolonged duration of aftersensations in trigeminal and extratrigeminal areas may reflect a dysfunction of thermal channels in tension-type headache/TMD patients as a result of some combination of peripheral sensitization, facilitation of central nociceptive processing, and/or decreased descending inhibition. Further studies in other craniofacial pain conditions are needed to further test the usefulness of the present stimulus protocol.

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