# Temporal Summation of Painful Heat Stimulation Is Facilitated in Trigeminal and Extratrigeminal Regions in Painful Myofascial Temporomandibular Disorders: Evidence from a Case-Control Study

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**Aims:** To determine whether patients with painful myofascial temporomandibular disorders (TMD) demonstrate facilitated temporal summation (TS) responses to painful heat stimuli applied to the painful trigeminal and extratrigeminal regions and whether there is a side difference in the trigeminal region for myofascial TMD pain patients compared to healthy controls. **Methods:** Twenty female Chinese myofascial TMD pain patients and 20 age-matched female volunteers participated in this case-control study. Thermal detection thresholds, thermal pain thresholds, and TS of 20 repetitive noxious thermal stimuli were measured on the skin above the masseter muscle on both sides and the thenar eminence of the less painful side/dominant hand. Numeric rating scale (NRS) scores of pain were provided after the 1st, 5th, 10th, 15th, and 20th stimuli, and TS was calculated as the highest NRS score minus the first NRS score in each test. **Results:** Evidence of TS was found in the trigeminal and extratrigeminal regions for both groups, but with facilitated TS responses in myofascial TMD pain patients ($P < .001$). Within the myofascial TMD group and control group, there were no side-to-side differences ($P > .289$). Interestingly, the repetition of the TS test was associated with facilitated responses in myofascial TMD pain patients ($P < .001$). **Conclusion:** The current findings suggest TS of painful heat stimulation is facilitated in myofascial TMD pain patients with no side difference in the trigeminal region. *J Oral Facial Pain Headache 2019;33:174–182. doi: 10.11607/ofph.2248*

**Keywords:** *hyperalgesia, myofascial pain, temporal summation, temporomandibular disorders, thermal detection*

Painful temporomandibular disorders (TMD), which affect approximately 12% of the population,[1] are a group of pathologic conditions involving the temporomandibular joint (TMJ) and masticatory muscles.[2,3] The Diagnostic Criteria for TMD (DC/TMD) groups TMD broadly into myogenous and arthrogenous types.[4,5] Myofascial pain is a subgroup of the myogenous type, which refers to pain of muscle origin and is characterized by pain on palpation and pain in response to jaw movements in the masticatory muscles, with the exceptions of myositis, myospasm, and contracture.[6–8] Despite extensive research in the past few decades, the pathophysiology of TMD-related chronic myofascial pain remains unknown,[8,9] and so the effective management of TMD remains controversial. To explore the mechanisms that may underlie TMD pain, scientists have examined whether TMD patients have altered responses to experimental painful stimuli and whether such aberrations are confined to the painful region or extend to extrasegmental and nonpainful regions as well. Studies examining experimental pain sensitivity in both TMD patients and healthy controls have shown mixed results in terms of finding significant group differences.[8] A few studies showed greater perceptual responses in TMD patients, suggesting that these patients are more sensitive to experimental pain than pain-free individuals.[10–14] The question about region-specific abnormalities in somatosensory function in painful TMD remains unanswered. Some studies have demonstrated that TMD patients are more responsive to

experimental pain not only in the trigeminal region but also in various remote bodily sites,[10–12] while others suggest that altered pain processing is primarily confined to the trigeminal region.[13,14]

Moreover, noxious thermal stimulation may activate different classes of primary afferent fibers and result in two classes of pain: first pain and second pain.[15,16] The former is a well-localized, brief, and sharp pain sensation, while the latter is a diffuse, dull, and burning pain sensation that usually outlasts the stimulus.[17] When peripheral afferent C fibers are activated repetitively at frequencies greater than 0.3 Hz, wide dynamic-range neurons show increasing responses to unchanging or diminishing afferent inputs.[15] This phenomenon is called temporal summation (TS) of pain. TS is regarded as the psychophysical correlate of wind-up, which indicates the increase in the magnitude and frequency of the responses of central nervous system (CNS) nociceptive neurons when repetitive noxious stimuli of constant strength are applied at a frequency greater than 0.33 Hz.[18,19] Several studies have suggested that wind-up and TS of painful afferent inputs share common central mechanisms.[17,20,21] Studies have provided strong evidence of spinal hyperexcitability for mechanically evoked pain, but conclusions for thermal hyperalgesia remain controversial.[4,8]

Throughout the neuroaxis and pain processing pathways, neural signals and conduction can be modulated by peripheral as well as central pathways in the spinal cord and brainstem.[22,23] Irregularities in these modulation processes might be associated with the initiation or maintenance of pain disorders. Therefore, the psychophysical assessment of TS has been suggested as a sensitive experimental tool with high clinical interest for the measurement of pain modulation processes in healthy individuals and for the detection of alterations in pain modulatory mechanisms in pain patients.[24]

Thus, the aims of the present study were to characterize the thermal detection and pain thresholds and the thermal pain intensity during TS in myofascial TMD pain patients and to determine whether region-specific abnormalities of central nociceptive processing exist. It was hypothesized that myofascial TMD patients would demonstrate abnormal thermal processing in both the painful (trigeminal) and extratrigeminal regions as an indication of central sensitization and generalized hyperexcitability.

## Materials and Methods

### Participants

Twenty female patients with myofascial TMD pain (aged 25 to 55 years old, mean age ± standard deviation [SD] = 41.5 ± 13.0 years) and 20 age-matched healthy women as a control group (age 25 to 55 years old, mean age 41.7 ± 13.0 years) participated in this study. Patients were recruited from the TMD Clinic, Stomatology Hospital of Jiangsu Province, China, and were primarily diagnosed with myofascial pain according to the DC/TMD.[5] All healthy participants were volunteers recruited from among trainees and students at Nanjing Medical University through an email/poster campaign. Inclusion criteria for healthy participants consisted of good health status with no history of neck or upper quadrant pain. Patients were given a diagnosis of myofascial TMD pain if they reported pain in the jaw, temples, in the ear, or in front of ear; if the pain was modified with jaw movement, function, or parafunction; if they experienced pain that mimicked their clinical pain in response to palpation of the temporalis or masseter muscles; and if they reported pain spreading beyond the site of palpation but within the boundary of the muscle. Before the experiment, the participants rated their current pain level on a 0- to 10-cm visual analog scale (VAS), where 0 indicated no pain and 10 indicated maximum pain. Inclusion criteria for patients were chronic uni- or bilateral myofascial pain in the last 6 months in the face, exclusion of other face-related pain origins (such as neuropathic pain), and a current VAS score of > 2. The exclusion criteria were neurologic disorders (such as multiple sclerosis or trigeminal neuralgia); current chemotherapy; pregnancy; psychotropic medication; history of treatment of TMD in the past 3 months; or diagnosis of disc displacement without reduction. All participants were tested between the fourth and ninth days of their menstrual cycle to diminish the effect of gonadal steroid hormones on pain perception response.[25]

The study was approved by the local ethical committee of Nanjing Medical University (No: PJ2016-031-001). Informed consent in accordance with the Helsinki II declaration was obtained from all participants prior to inclusion.

### Experimental Design

The participants were comfortably placed in the supine position in a dental chair with their head supported by the headrest. Testing of somatosensory function was conducted in a quiet, isolated room with an ambient temperature between 23°C and 25°C.

The thermode was placed on three sites: both sides of the skin overlying the masseter muscle, and the nonpainful or less painful side of the thenar eminence of the hand for myofascial TMD pain patients/the dominant side for healthy controls. The study was divided into two experiments. The thermal quantitative sensory testing (QST) was performed first, then the TS of painful heat stimulation was randomly tested at each of the three test sites.

### Thermal QST

Thermal QST was performed using a computerized thermal stimulator (MEDOC TSA-2001 apparatus, Medoc). Two different thermodes were used for the assessments. The contact area of the thermode was 30 × 30 mm.

Cold and warm detection thresholds (CDT, WDT, respectively) were measured first, followed by cold and heat pain thresholds (CPT, HPT, respectively). The mean thresholds of three consecutive measurements were calculated. The temperature of the thermode started at a baseline of 32°C and cooled down or heated up at a rate of 1°C/second to the lower limit of 0°C or the upper limit of 50°C.[26,27] Participants were instructed to press a button on the computer mouse as soon as they perceived the thermal sensation of cold, warm, cold pain, or heat pain following the instructions developed by the German Research Network on Neuropathic Pain (DFNS). The procedure then ended, and the temperature returned to baseline. The participants were instructed not to look at the computer screen at any time during the testing procedures.

### TS of Painful Heat Stimuli

The temperature used for the TS experiment was the individually determined HPT + 2°C. This stimulus intensity was determined to assure a mild painful sensation for all participants at the start of the series of 20 stimuli. Using a TS protocol,[12] myofascial TMD pain patients and healthy controls were exposed to 20 painful heat stimuli at a rate of 0.3 Hz, which formed one session. All participants were asked to score pain on an NRS ranging from 0 (no pain) to 100 (most intense pain tolerable) after the 1st, 5th, 10th, 15th, and 20th stimuli, and the NRS scores were recorded as NRS-1, NRS-5, NRS-10, NRS-15, and NRS-20, respectively. TS was calculated as the highest NRS score minus the first NRS score at each site for later analysis.[28] The procedure would be terminated if the participant reported a value of 100. Three sessions were carried out at each site, with an interval of 5 minutes between sessions.

### Statistical Analyses

The necessary logarithmic transformation was performed to secure normal distribution of the data. The mean values and standard deviations (SDs) of CDT, WDT, CPT, HPT, and TS values in the two groups and three test sites were calculated.

Two-way analysis of variance (ANOVA) was used for comparisons between the two groups, with test site (painful trigeminal side, nonpainful trigeminal side, dominant trigeminal side, nondominant trigeminal side, and hand) as the within-subject factor and with group (TMD vs control) as the between-subject factor for thermal detection and thermal pain thresholds, TS, and the effects of repeated TS. A multi-way mixed model ANOVA was used to analyze the NRS scores (NRS-1, NRS-5, NRS-10, NRS-15, and NRS-20) after sequential stimuli (repeated measures) with group (TMD vs control) as the between-subject factor and with stimulus (1st, 5th, 10th, 15th, and 20th) as the within-subject factor both in the trigeminal region (masseter muscle) and the extratrigeminal region (hand). Paired *t* tests were used for investigating differences in thermal detection/thermal pain thresholds and TS between the two sides in the trigeminal region both for myofascial TMD pain patients and healthy controls. A Newman-Keuls test/Bonferroni test was employed for post hoc comparisons. The Pearson correlation test was used to test for associations between current and average clinical pain intensities and TS. All statistical calculations were performed using the Statistical Package for Social Sciences, version 20 (SPSS, IBM). The significance level was set at .05.

## Results

### Clinical Characteristics of Myofascial TMD Pain Patients and Controls

A total of 39 orofacial pain patients were screened for the study. Ten were excluded with a diagnosis of arthralgia, six with a diagnosis of myofascial TMD pain with referral, one due to current VAS pain intensity < 2, and two due to a history of treatment of TMD in the past 3 months. Finally, 20 myofascial TMD pain patients aged 25 to 55 (mean age ± SD = 41.5 ± 13.0 years) participated in the study. There were 8 patients (40%) who reported bilateral pain and 12 (60%) who reported unilateral pain. In patients with either bilateral or unilateral pain, half of them reported that the right side was more affected. As a result, 10 patients had the right side as the most affected side, and 10 patients had the left side as the most affected side. The mean duration of pain for myofascial TMD pain patients was 22.3 ± 6.0 months, and the mean VAS pain score was 3.8 ± 1.0. The maximum unassisted jaw opening was significantly lower in myofascial TMD pain patients (38.1 ± 3.3 mm) than controls (42.9 ± 4.0 mm) ($P < .001$), and the maximum assisted opening was also significantly lower in myofascial TMD pain patients (40.8 ± 2.9 mm) than controls (45.2 ± 4.1 mm) ($P < .001$).

### TMD Patients vs Controls

***Thermal Detection and Pain Thresholds.*** Myofascial TMD pain patients showed higher CDT and CPT values (ie, more sensitive) and lower WDT and HPT

**Table 1 Thermal Detection and Pain Thresholds (°C) in Myofascial TMD Pain Patients and Controls in Trigeminal and Extratrigeminal Regions**

| | TMDs | | | Controls | | |
|---|---|---|---|---|---|---|
| Variables | Painful side | Non-/less painful side | *P* | Dominant side | Nondominant side | *P* |
| CDT | | | | | | |
| Trigeminal | 31.1 ± 0.5 | 31.0 ± 0.4 | .140 | 30.9 ± 0.6 | 30.3 ± 2.6 | .312 |
| Extratrigeminal | 30.9 ± 0.5 | | | 30.4 ± 2.2 | | |
| CPT[a] | | | | | | |
| Trigeminal | 25.5 ± 4.6 | 25.4 ± 4.4 | .957 | 23.2 ± 5.2 | 22.7 ± 6.5 | .562 |
| Extratrigeminal | 23.1 ± 4.6 | | | 21.7 ± 6.4 | | |
| WDT | | | | | | |
| Trigeminal | 33.9 ± 0.8 | 34.1 ± 0.9 | .063 | 34.1 ± 0.8 | 34.1 ± 0.8 | .961 |
| Extratrigeminal | 34.1 ± 1.3 | | | 33.7 ± 0.6 | | |
| HPT[a] | | | | | | |
| Trigeminal | 39.0 ± 3.9 | 39.6 ± 3.2 | .387 | 40.6 ± 2.1 | 40.1 ± 3.0 | .199 |
| Extratrigeminal | 40.5 ± 3.1 | | | 40.7 ± 2.3 | | |

All data are reported as mean ± standard deviation. CDT = cold detection threshold; CPT = cold pain threshold; WDT = warm detection threshold; HPT = heat pain threshold.

**Table 2 Absolute Temporal Summation (TS) Scores (numeric rating scale [NRS]) for TS of Heat Pain and TS of TS in Trigeminal and Extratrigeminal Regions**

| | TMDs | | | Controls | | |
|---|---|---|---|---|---|---|
| Variables | Painful side | Non-/less painful side | *P* | Dominant side | Nondominant side | *P* |
| TS[a] | | | | | | |
| Trigeminal | 63.3 ± 12.2 | 59.5 ± 13.7 | .290 | 46.2 ± 4.3 | 46.1 ± 12.7 | .963 |
| Extratrigeminal | 65.9 ± 14.2 | | | 45.6 ± 14.3 | | |
| TS of TS[a] | | | | | | |
| Trigeminal | 1.0 ± 0.4 | 0.7 ± 0.6 | | 0.4 ± 0.3 | 0.4 ± 0.2 | |
| Extratrigeminal | 0.7 ± 0.6 | | | 0.3 ± 0.2 | | |

All data are reported as mean ± standard deviation. [a]Significant difference between myofascial TMD pain patients and controls ($P < .05$).

values (ie, more sensitive) both in the trigeminal and extratrigeminal regions. The absolute values of all variables for CDT, WDT, CPT, and HPT for the two groups are presented in Table 1. No significant differences were found between the two groups for CDT (group: F = 3.471, $P = .065$; side: F = 0.679, $P = .509$) or WDT (group: F = 0.115, $P = .735$; side: F = 0.679, $P = .509$). Significant differences were found between groups, but not among test sites for CPT (group: F = 4.932, $P = .028$; side: F = 1.504, $P = .227$) and HPT (group: F = 4.027, $P = .047$; side: F = 0.900, $P = .409$). No significant group × side interactions were found for CPT (F = 0.154, $P = .858$) or HPT (F = 0.900, $P = .533$). The post hoc analysis between test sites showed there was no significant difference between test sites.

***Temporal Summation.*** The absolute TS scores for the two groups in the trigeminal and extratrigeminal regions are presented in Table 2. TMD patients showed higher TS scores in both regions. Significant differences were found between groups (F = 56.339, $P < .001$), but not among test sites (F = 0.600, $P = .550$). There was no significant group × site interaction (F = 0.790, $P = .456$). Post hoc analysis showed no significant difference between test sites. The correlation tests between TS scores and mean VAS pain intensity demonstrated no significant associations ($P < .214$, $P > .094$).

In the trigeminal region, the NRS pain scores of the repeated painful heat stimuli increased in both groups after each session of 20 stimuli, with significant differences between groups (F = 21.888, $P < .001$). There was a significant group × stimulus number interaction (F = 17.580, $P < .001$). Multivariate analysis showed there was no significant difference after the 1st (F = 3.398, $P = .069$) or 5th (F = 2.751, $P = .101$) stimuli between the groups, but there were significant differences after the 10th (F = 12.158, $P = .001$), 15th (F = 27.319, $P < .001$), and 20th (F = 42.498, $P < .001$) stimuli between groups. The changes in NRS pain scores after each painful heat stimulus in the trigeminal region for both groups are shown in Fig 1a.

In the extratrigeminal region, the NRS pain scores increased in both groups after a session of 20 painful heat stimuli, and significant differences were found between groups (F = 16.553, $P < .001$). There was a significant group × stimulus number interaction (F = 8.945, $P < .001$). Multivariate analysis showed there was no significant difference after the 5th heat

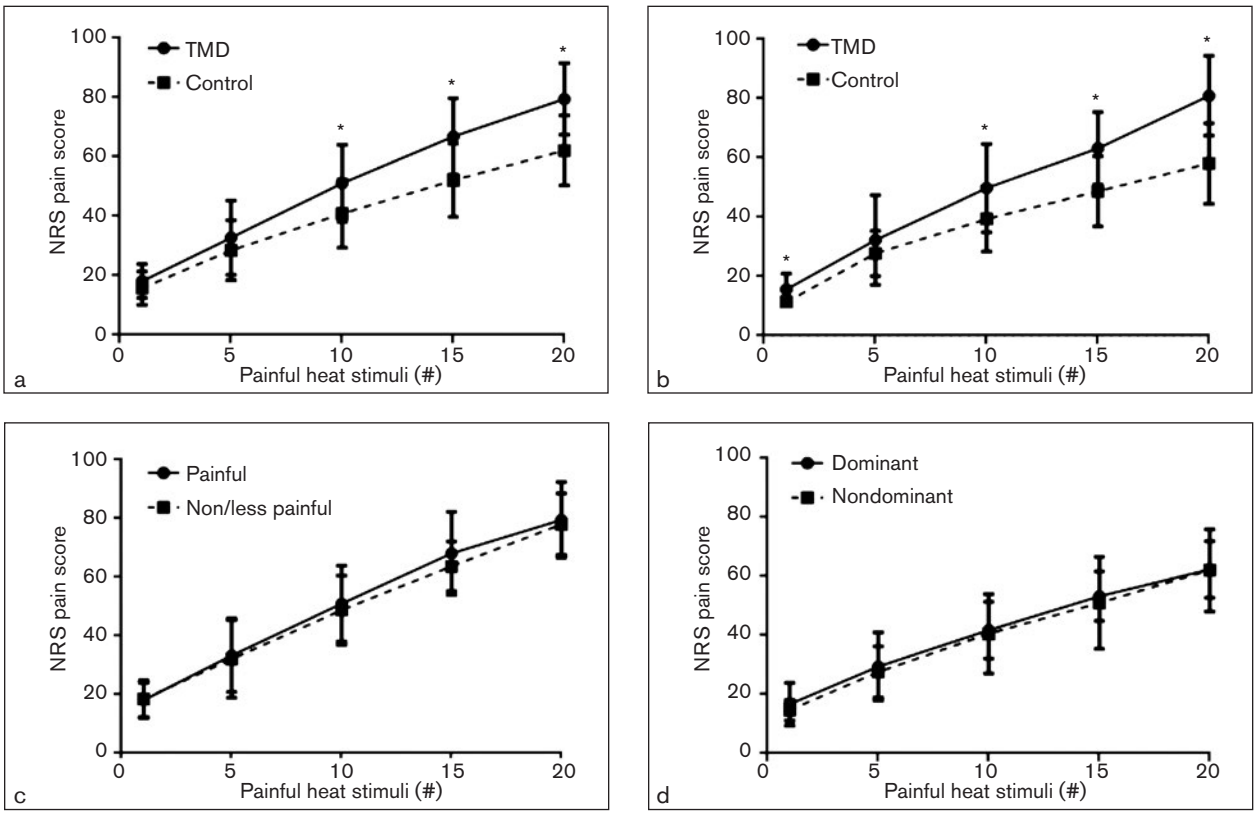


**Fig 1** Hyperalgesia of myofascial TMD pain patients and controls in the trigeminal and extratrigeminal regions in response to painful heat stimuli. Pain scores on a 0–100 numeric rating scale (NRS) after each painful heat stimulus in the **(a)** trigeminal and **(b)** extratrigeminal regions. NRS pain scores after each painful heat stimulus **(c)** on both sides of myofascial TMD pain patients and **(d)** on both sides of healthy controls in the trigeminal region. Mean and standard error of the mean (SEM) are presented. *Significant difference between groups ($P < .05$).

pain stimulus between the two groups (F = 1.388, $P = .246$), but significant differences were found after the 1st (F = 12.839, $P = .001$), 10th (F = 6.453, $P = .015$), 15th (F = 14.365, $P = .001$), and 20th (F = 28.684, $P < .001$) stimuli. The changes in NRS pain scores for both groups in the extratrigeminal region are shown in Fig 1b.

***Effects of Repeated TS.*** The effect of repeated TS tests between myofascial TMD pain patients and healthy controls was analyzed, calculated as the mean TS of the final session minus the mean TS of the first session. The results showed a slight increase of TS from the first session to the last session in both groups, and the myofascial TMD pain patients showed significantly higher TS of TS following repeated stimulation than controls (F = 37.766, $P < .001$), but there was no significant difference among test sites (F = 2.133, $P = .123$) and no significant group × site interaction (F = 0.199, $P = 1.636$).

## Painful vs Nonpainful or Less Painful Side in TMD

***Thermal Detection and Pain Thresholds.*** The absolute values of all QST variables for myofascial TMD pain patients in the trigeminal region are also presented in Table 1. No statistically significant differences were found between the two sides for any of the QST parameters.

***Temporal Summation.*** The absolute values of TS for myofascial TMD pain patients in the trigeminal region are presented in Table 2. The mean TS scores were higher on the painful/more painful masseter side than the nonpainful/less painful side, but no significant difference was found between the test sides ($P = .290$).

The magnitude of NRS pain scores increased on both sides in myofascial TMD pain patients in the trigeminal region, but no significant difference was found between the two sides (F = 2.254, $P = .142$). There was no significant side × stimulus number interaction (F = 0.802, $P = .471$). Multivariate analysis showed there was no significant difference after any heat pain stimulus between the two sides ($P > .140$). The changes in NRS pain scores after each heat pain stimulus on both sides of myofascial TMD pain patients in the trigeminal region are shown in Fig 1c.

The effect of repeated TS tests was also analyzed for side-to-side differences. The results again showed a slight increase of TS from the first session to the last session in both groups, and the myofascial TMD pain

patients showed significantly higher TS in response to repeated stimulation than controls (F = 6.555, *P* = .012). However, post hoc analysis showed there was no significant difference among test sites (F = 0.493, *P* = .612) and no significant group × site interaction (F = 0.158, *P* = .854).

### Dominant Side vs Nondominant Side in Healthy Controls

***Thermal Detection and Pain Thresholds.*** The absolute values of all QST variables for healthy controls in the trigeminal region are presented in Table 1. No statistically significant differences were found between the two sides for any of the QST parameters.

***Temporal Summation.*** The absolute values of TS for healthy controls in the trigeminal region are presented in Table 2. The mean TS score was higher on the dominant side of the masseter than the nondominant side, but no significant difference was found between the test sides (*P* = .963).

The magnitude of NRS pain scores increased on both sides in healthy controls in the trigeminal region, but no significant difference was found between the two sides (F = 0.236, *P* = .628). There was no significant side × stimulus number interaction (F = 0.205, *P* = .817). Multivariate analysis showed there was no significant difference after any heat pain stimulus between the two sides (*P* > .300). The changes in NRS pain scores after each heat pain stimulus on both sides of healthy controls in the trigeminal region are shown in Fig 1d.

## Discussion

The present case-control study explored thermal sensitivity and TS in both trigeminal and extratrigeminal regions in TMD patients with myofascial pain. The most striking findings were the increased thermal sensitivity and facilitated TS responses both in the trigeminal and the extratrigeminal regions. Moreover, there were no side-to-side differences within the myofascial TMD pain patients independent of the side being more or less painful. Finally, there were no significant associations between the intensity of the mean TMD pain and TS scores. The present study suggested a generalized and facilitated thermal sensitivity in patients with myofascial TMD pain.

### TS in Myofascial TMD Pain Patients

In recent years, several psychophysical approaches have been developed to investigate the temporal integrative properties of TMD patients responding to noxious stimuli, among which mechanically evoked pain and thermally evoked pain are the two main procedures.[12,22,28] Surprisingly, most previous studies on TS mechanisms in TMD patients have been limited to extratrigeminal test sites, leaving the question as to whether there would be differences between trigeminal and extratrigeminal test regions. In these studies, TS test sites included the hands, fingers, and forearms in the upper limbs and feet and legs in the lower limbs.[22,24,28–31] TS, a process in which the repetition of a stimulus enhances the induced pain when noxious stimuli of a constant intensity are delivered at a sufficiently high frequency, reflects transient upregulation of the dorsal horn (or brainstem) nociceptive neurons' excitability.[15,24] The TS qualitative analysis has shown strong evidence of spinal hyperexcitability for mechanically evoked pain, while the evidence for thermal hyperalgesia has not reached consensus.[4,22,23,32] Maixner et al[33] evaluated the TS of heat pain on both sides of the masseter muscle and the left forearm and found greater thermal TS in TMD patients than pain-free subjects at either the face or the forearm test site. In another study, Ribeiro-Dasilva et al[28] investigated hyperalgesia and TS at the dorsal forearm, but found no group difference between TMD patients and healthy controls.

For this study, the pain sensitivity measures to be analyzed as statistical outcomes involved data related to all 20 pulses of the suprathreshold painful heat stimuli. Thus, TS was obtained by subtracting the first pain rating from the highest pain rating, reflecting the slope of the maximum amount of TS obtained.[28] A mean pain rating for the 20 heat pulses was used to represent hyperalgesia of nociceptive stimuli.[34]

In the present study, TS was significantly higher for myofascial TMD pain patients both in the trigeminal and extratrigeminal regions, but no side difference was found for myofascial TMD pain patients. Moreover, hyperalgesia was found in both groups in the trigeminal and extratrigeminal regions, and myofascial TMD pain patients showed significantly higher NRS pain scores after painful stimuli than controls, but no significant side difference was found in the trigeminal region. These results indicate that it was possible to elicit TS with suprathreshold thermal stimuli for both groups and that myofascial TMD pain patients were more sensitive to wind-up thermal stimuli. On the other hand, no side or region differences were found in this study, indicating that myofascial TMD pain patients were more likely to generate a time-dependent TS than a spatially dependent TS.

However, several other studies showed no significant differences in hyperalgesia in TMD patients.[12,28] One possible explanation for this inconsistency may lie in the different suprathreshold thermal temperature of the repetitive stimuli. In previous studies, the temperatures were determined as fixed values usually at 46°C, 48°C, and 50°C, while in the present study, the temperature was determined as the individual

HPT + 2°C and most often lower than 46°C. Lower suprathreshold thermal stimuli may have induced lower pain scores at the beginning of the train of 20 repeated stimuli and could therefore have avoided the phenomenon of a ceiling effect.[28] In preliminary experiments, it was found that a sequence of 20 brief painful heat stimuli at approximately this temperature was well tolerated by most individuals and adequate to induce TS in both groups.

Hyperalgesia and allodynia have been described as important features of central sensitization that can be ascribed to increased excitability of spinal (and brainstem) and supraspinal neurons.[12,28] Within minutes to hours after a sustained nociceptive afferent input, there are increases in spontaneous activity, enhanced responsiveness to nociceptive and nonnociceptive stimuli, and enlarged receptive fields of dorsal horn neurons.[15] Dorsal horn neurons in the nociceptive pathways undergo central sensitization during tonic impulse input from C-fiber nociceptive afferent neurons, and this phenomenon is, in turn, closely related to a slow TS of activity termed wind-up. The mechanism for wind-up has been elucidated in electrophysiologic experiments involving microelectrode recordings of neurons of the dorsal horn.[8] Thus, the hyperalgesia and significantly higher TS of myofascial TMD pain patients indicated an upregulated central processing of nociceptive stimuli, which may play a role in the onset or perpetuation of TMD-related myofascial pain. This result could suggest the potential value of pharmaceutical treatment directed toward central sensitization in myofascial TMD pain patients.

### Thermal Somatosensory Characteristics of Myofascial TMD Pain Patients

Thermal pain sensitivity of TMD patients with myofascial pain has been investigated in a number of studies, but differences between TMD pain patients and controls have not been consistent, especially in extratrigeminal regions.[10–14,28] Some studies showed significantly lower HPT for TMD,[12,13] while others found no significant difference in HPT between TMD patients and controls.[14,28] Previous studies showed that TMD pain patients were more sensitive to thermal pain (higher CPT and lower HPT) compared to control individuals both in the trigeminal and extratrigeminal regions.[11–13] In another study, bilateral thermal hyperalgesia (higher CPT and lower HPT) was also found in the trigeminal and extratrigeminal regions.[10] The present study showing hyperalgesia of CPT and HPT in trigeminal and extratrigeminal regions is in accordance with previous studies. These findings may therefore have demonstrated a generalized upregulation of noxious stimuli in myofascial TMD pain patients.

It is well accepted that different thermal parameters in QST assess different types of sensory fibers: CDT represents the function of small myelinated fibers (Aδ) while WDT and HPT represent the function of C fibers, but the relative contribution of C- and Aδ-fiber nociceptors to CPT is less clear.[35,36] In the present study, myofascial TMD pain patients showed lower HPT in trigeminal and extratrigeminal regions, indicating that a functional hyperactivity of C fibers may exist in such patients. With sensitization in terms of HPT and CPT values and almost normal CDT and WDT values in both trigeminal and extratrigeminal regions, it was suggested that generalized upregulation responsiveness and increased responsiveness to thermal stimulation existed in myofascial TMD patients. However, in the trigeminal region, no significant difference for the thermal parameters was found between the painful/more painful side and nonpainful/less painful side in myofascial TMD patients. This phenomenon indicates that sensitization of TMD patients may not only be related to peripheral mechanisms, but is also associated with a significant degree of central processing and may as such constitute a pathophysiologic mechanism contributing to myofascial pain in TMD patients.[33,37] The hypothesis that TMD pain is caused by generalized sensitization of higher-order neurons in the nociceptive pathways combined with a decreased efficacy of endogenous inhibitory systems may account for the results.[14]

### Subject Selection Criteria

Prior to the publication of the DC/TMD, several studies used myofascial pain dysfunction to characterize the patient population.[8,38] Without standardized criteria, these patients could exhibit a combination of signs and symptoms that may make the results incomparable because of the heterogeneity of the subjects.[8] In the present study, the DC/TMD, which represents the most widely accepted classification system for TMD-related research,[5,10,39] was used as the criteria for patient selection. In the criteria, strict operational definitions of terms, including precise specifications for the clinical examination as well as the classification of findings, have been established.[40] Myofascial TMD pain patients were selected excluding patients with a diagnosis of disc displacement without reduction to minimize the influence of possible pain caused by disc displacement. Though consensus has not been reached on the effects of age and gender on thermal sensitivity, a wide range of studies have indicated detectable effects.[17,41–43] Several lines of evidence have indeed suggested that women are more sensitive to noxious stimuli than men, but whether the thermal detection is different between genders is under debate.[41,43–46] Experimental data on age-related changes in pain

perception are also contradictory due to the methodologic differences between studies.[42] Some studies showed sensitivity of the elderly to heat pain decreased,[47,48] while others showed no age-related changes.[42,49] Furthermore, hormonal differences may also be a biologic factor with relevance for TMD-related pain. The sex hormonal level can affect the processing of nociceptive information of the nervous system, modify the perception of pain, and alter sensitivity to noxious stimuli.[8,43,50] Indeed, the perceptual responses to noxious stimuli may vary significantly across the menstrual cycle.[25] In the present study, the authors investigated the thermal sensitivity of women, matched patients and controls by age, and tested participants with a regular menstrual cycle between the fourth and ninth days to diminish the bias of gender, age, and gonadal steroid hormones on thermal pain responses. This particular feature of the present study may be considered a significant methodologic advantage in addition to the strict and updated criteria for myofascial TMD pain.

Moreover, ethnic differences in pain experiences have been demonstrated in a number of studies, which may be caused by variation in endogenous pain modulation systems and differences in skin properties, genetic variables, and culture diversity.[51–53] To avoid the influence of ethnic factors, only Chinese participants were involved in this study, and region-specific changes between healthy controls and TMD patients were compared. The inconsistency of hyperalgesia and TS between controls and TMD patients among different studies may partly be caused by ethnic-related differences, which needs further investigation.

### Study Limitations

Notwithstanding the significant advantages of the present study, a few limitations also must be acknowledged and discussed. The main limitation of the present study could be argued to be the mix of unilateral and bilateral myofascial TMD pain patients not allowing a "clean" comparison of nonpainful vs painful sides. However, the clinical reality is that most myofascial TMD pain patients may have a more or less painful side. This is reflected in the present analyses, as 8 out of 20 patients had pain on both sides.

The sample size in the present study was relatively small, and future studies could consider multi-center collaboration to increase the power and sample size and potentially subgroup the TMD pain patients for an even more detailed investigation. Furthermore, to avoid the effect of gender, only female participants were recruited in this study; however, future studies may also want to address possible gender-related differences in TMD pain patients.

## Conclusions

The present study in Chinese TMD patients with myofascial pain demonstrated a generalized facilitation of thermal pathways compared to healthy controls, which is in accordance with the suggestion of an increased vulnerability of the pain system that may contribute to the pathophysiology of myofascial TMD pain.

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