Temporal Summation of Pain Characterizes Women but not Men with Temporomandibular Disorders

Eleni Sarlani, DDS, PhD
Assistant Professor
Department of Biomedical Sciences

Pauline H. Garrett, DDS
Assistant Professor
Department of Endodontics,
  Prosthodontics, and Operative
  Dentistry

Edward G. Grace, MA, DDS
Associate Professor
Department of Health Promotion and
  Policy

University of Maryland Dental School
Baltimore, Maryland

Joel D. Greenspan, PhD
Professor
Department of Biomedical Sciences

Correspondence to:
Dr Joel D. Greenspan
650 Baltimore Street, 7 South
Baltimore, MD 21201
Fax: +410 706 2027
E-mail: jgreenspan@umaryland.edu

Aims: To examine differences in temporal summation of mechanically evoked pain between women and men suffering from chronic pain associated with temporomandibular disorders (TMD), as well as between male TMD patients and healthy controls. Methods: Series of 10 repetitive, mildly noxious mechanical stimuli were applied to the fingers of 27 female TMD patients, 16 male TMD patients, and 20 healthy men. The subjects rated the pain intensity caused by the 1st, 5th, and 10th stimulus in the series. Pain ratings were analyzed by 3-way repeated-measures analysis of variance. Results: Pain ratings increased significantly with stimulus repetition for the female TMD patients (P < .001). Women with TMD exhibited significantly greater temporal summation of pain than TMD men (P < .001). Neither the healthy men nor the male TMD patients exhibited significant increases in pain perception with repetitive stimulation. In the female TMD patient group, perceptual pain magnitudes were higher with an interstimulus interval of 2 seconds rather than 10 seconds (P < .005). Conclusion: These findings suggest that central nociceptive processing upregulation is likely to contribute to TMD pain for women but is not a factor for men with TMD. J OROFAC PAIN 2007;21:309–317*

Key words: chronic pain, gender differences, temporal summation, temporomandibular disorders

Temporomandibular disorders (TMD) are various pathologic conditions that affect the muscles of mastication and the temporomandibular joint (TMJ). Temporomandibular disorders are characterized by a strong gender predilection, with female to male ratios of 1.5 to 2:1 in the general population[1] and 8 to 9:1 among patients presenting for treatment in tertiary orofacial pain clinics.[2] TMD may be acute and self-limited or may result in chronic pain and dysfunction greatly affecting the patient's quality of life. They are recognized as the most common cause of chronic pain in the orofacial region.[3] Moreover, pain is the predominant symptom that motivates TMD patients to seek treatment.[4] Nevertheless, the cause of TMD pain is often elusive, since pain does not always correspond to observable clinical signs or physical pathology.[5,6]

To explore the mechanisms that underlie TMD pain, a plethora of studies have examined the sensitivity of TMD patients to experimentally evoked pain (for review see Sarlani and Greenspan, 2003).[7] Several of these studies have demonstrated that TMD patients are more responsive to experimental pain not only in the orofacial region but also in various remote bodily sites, suggesting

a generalized upregulation of nociceptive input processing in this patient population. In addition, Maixner et al[8] reported that female TMD patients exhibit more pronounced temporal summation of pain upon repetitive noxious heat stimulation of their hand compared to healthy controls. Similarly, a previous study by the present authors demonstrated that the temporal summation of pain upon repetitive noxious mechanical stimulation on the fingers of the hand was greater among female TMD patients than age-matched healthy women.[9]

Temporal summation of pain is the increase in perceived pain intensity when repetitive noxious stimuli of constant intensity are applied at a frequency greater than 0.2 to 0.3 Hz. Temporal summation is regarded as the psychophysical correlate of wind-up.[10] *Wind-up* is 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.[11,12] Several lines of evidence strongly suggest that wind-up and temporal summation of pain share common central mechanisms.[13–18] Accordingly, greater temporal summation of pain in female TMD patients is likely to indicate a generalized hyperexcitability in central nociceptive processing.

Because of the greater prevalence of TMD among women, all previous studies examining experimental pain sensitivity in TMD patients included either exclusively female patients or only a small number of male patients. Consequently, gender differences in experimental pain sensitivity among TMD patients have not been investigated to date. The presence of such differences may indicate sexually dimorphic TMD pain mechanisms. The aim of this study was to examine differences in temporal summation of mechanically evoked pain between women and men suffering from chronic TMD pain as well as between male patients and healthy controls.

Materials and Methods

Subjects

Twenty-seven female TMD patients (22 right-handed), 16 male TMD patients (13 right-handed), and 20 healthy men (17 right-handed) participated in the present study. The mean age of the female TMD patient group was 36.1 years (age range, 19 to 65 years), the mean age of the male TMD patient group was 35.9 years (age range, 24 to 57 years), and the mean age of the healthy men was 37.8 years

(age range, 19 to 67 years). Twelve female TMD patients were taking oral contraceptives. None of the 5 postmenopausal female TMD patients was receiving hormone replacement therapy.

Twenty-one female patients and 16 male patients were recruited from TMD patients participating in a clinical trial assessing various TMD treatment modalities. These subjects were tested prior to the start of their treatment regimen. Another 6 female patients were recruited from TMD patients seeking treatment at the Brotman Facial Pain Center of the University of Maryland. The healthy male patients were recruited by posted announcements at the university campus. The subjects were naïve regarding the specific aims of the study. All subjects provided informed consent and were paid for their participation. This project was approved by the Institutional Review Board for the Protection of Human Subjects of the University of Maryland, Baltimore.

The exclusion criteria for all subjects included serious injury to the hands at any time; systemic rheumatic diseases, such as systemic lupus erythematosus or rheumatoid arthritis; vascular disorders, such as giant cell arteritis; neurologic disorders, such as multiple sclerosis or trigeminal neuralgia; neoplasia; pregnancy; or self-report of substance abuse. In addition, healthy subjects were excluded if they had masticatory myofascial pain, TMJ arthralgia, degenerative joint disease, and/or disc displacement without reduction, as well as if they complained of frequent and/or persistent pain in any region of the body.

The main inclusion criterion for the patient group in this study was a primary diagnosis of masticatory myofascial pain according to the Research Diagnostic Criteria for Temporomandibular Disorders.[4] Masticatory myofascial pain involves pain originating from the jaw, temples, face, periauricular area, or inside the ear during rest or during function, as well as pain upon palpation of at least 3 of 20 specific masticatory muscle sites. Patients participated in the study only if they reported myofascial pain with a duration of more than 3 months. Patients with painful disc displacement without reduction were excluded from the study. Patients with arthralgia were not excluded from the study, provided that they satisfied the aforementioned inclusion criteria.

Normally cycling female patients who were not taking oral contraceptives were tested between the 4th and 9th days of their menstrual cycle to diminish the fluctuation of the gonadal steroid hormones, which may influence the responses to noxious stimulation.[19,20]

Experimental Design

All subjects participated in 1 experimental session lasting 60 to 90 minutes. Initially, subjects were screened for study inclusion by obtaining a medical/dental history and performing a clinical examination. Next, the subject's mechanical pain threshold was assessed. In addition, the subject was introduced to the temporal summation testing and was trained until (s)he became familiarized with the rating procedures. Prior to data collection, all subjects completed the Beck Depression Inventory, the State-Trait Anxiety Inventory, the Pain Catastrophizing Scale, and the Insomnia Severity and Anxiety Sensitivity Inventories. Next, the temporal summation of mechanically evoked pain was assessed, by delivering repetitive noxious mechanical stimuli to the fingers of the left hand, after interstimulus intervals (ISIs) of 2 and 10 seconds. At the end of the experimental session, the subjects completed the State Pain Catastrophizing Scale, and also rated the anxiety they experienced during the experiment on a 10-cm visual analog scale (VAS) anchored with 0 indicating "no anxiety" and 10 indicating "anxiety as bad as could be." In the same session, the same subjects participated in a test of stimulus conditioning effects upon mechanical pain, the results of which are to be reported separately.

History and Clinical Examination

At the beginning of the experimental session a medical/dental history was obtained from all subjects. All patients rated the average intensity of their facial pain in the past 3 months on a numeric pain rating scale from 0 to 10, where 0 represented "no pain" and 10 "pain as bad as could be." In addition, they completed the Brief Pain Inventory, and they indicated how many days per week on average in the previous 3 months they had experienced TMD-related pain. Moreover, all subjects indicated on a 0-to-5 numeric scale, where 0 represented "not at all" and 5 "extremely," how much they had been distressed by pain in 8 bodily sites in the previous month. A total body pain score was obtained for each subject by summing the pain distress ratings of all bodily sites.

All subjects underwent a clinical examination according to the Research Diagnostic Criteria for Temporomandibular Disorders.[4] The examination included assessment of *(a)* joint function, *(b)* sensitivity of the temporomandibular joints and the masticatory muscles to finger palpation, and *(c)* joint sounds. The following sites were palpated:

temporalis (anterior, middle, posterior, tendon), masseter (origin, body, insertion), posterior mandibular region, submandibular region, lateral pterygoid area, lateral pole of the TMJ, and posterior attachment of the TMJ. Approximately 2 lb of pressure was used for the extraoral muscles and approximately 1 lb for the joints and intraoral muscles. To measure the sensitivity of muscles and joints, the subjects rated the pain evoked by palpation as "none" (0), "mild" (1), "moderate" (2), or "severe" (3). A total palpation pain score for each patient was obtained by summing the pain ratings of all palpation sites.

Mechanical Stimulation

Mechanical stimuli were applied with a computer-controlled linear motor (Neurologic, Bloomington, IN) under force feedback regulation (model 501 motor controller; Biocommunication Electronics, Madison, WI). A computer program sent command signals to the controller in accordance with prescribed timing of specified forces. A force transducer in line with the stimulation probe sent feedback signals to the controller and to an oscilloscope used by the experimenter to verify appropriate stimulus delivery. The system was calibrated every day, after a warm-up period but before the first subject was tested. A stainless-steel probe with a circular contact surface of 0.245 mm^2 was affixed to the tip of the stimulator and used to apply brief mechanical stimuli to the dorsal surface of the middle phalanx of the 2nd, 3rd, or 4th finger. The probe was examined under a light microscope at regular intervals throughout the data collection period to ensure that its shape remained unchanged, as it has been shown that probe shape can have an effect on the perceived pain sensation.[21]

During the sensory testing sessions, the subject was seated comfortably on a chair with his or her left arm resting on a table. The left hand was supported, palmar surface down, by a convex mold, while the finger that was to be stimulated was further supported by polymer clay on top of the mold, which was made to conform to the finger's shape. A curtain prevented the subject from viewing the probe and their left hand during the experiment.

Pain Threshold Estimation and Temporal Summation Training

Each subject's mechanical pain threshold was determined with an ascending method of limits protocol.[21,22] Stimuli consisted of a series of forces ranging from 10 to 250 g (98 mN to 2.45 N). The

stimuli were 0.9 second in duration, consisting of a 0.4-second rise time, a 0.4-second fall time, and a 0.1-second hold time. The ISI in this ascending series of stimuli was 14 seconds. The probe was in contact with the skin throughout each ascending series of stimuli, applying approximately 5 g of resting force. It was retracted and manually moved to another finger between successive series. The subjects were informed that a stimulus would be applied to their fingers every 15 seconds and were asked to report whether the stimulus was painful. They were also told that they should discriminate between sharpness and other sensations and pain and report only the latter.

In the first ascending series, the first stimulus presented was 20 g. The amount of force used for successive stimuli was increased in increments of 20 g to obtain a gross estimation of the subject's pain threshold. For the remaining 3 to 4 series of stimuli, the first stimulus was well below the subject's grossly estimated pain threshold, and subsequent stimuli were applied in 5-g increments. However, the 6th and 10th stimuli in each series were well below the subject's grossly estimated pain threshold to reduce the subject's expectation of ascending forces. The ascending series was terminated when the subject provided 2 or 3 pain reports or when the largest force (250 g) was delivered. The pain threshold was estimated as the midpoint of the last stimulus reported as nonpainful and the first stimulus reported as painful.

Following estimation of the mechanical pain threshold, the subject was trained with 2 random and 2 descending series of 10 stimuli at ISIs of 5 and 2 seconds. The purpose of this training was to familiarize the subject with the shorter ISIs and the rating procedures and to prevent the expectation of progressively increasing stimuli.

Temporal Summation Testing

Temporal summation was tested with a series of 10 repetitive stimuli on the fingers of the left hand at an intensity of $1.5\times$ the individual subject's pain threshold. This stimulus value was chosen to assure a mild but distinctly painful sensation that would be of comparable perceived intensity for all subjects at the start of the series of 10 stimuli. As with the training sessions and threshold determination, each stimulus was 0.9 second in duration, consisting of a 0.4-second rise time, a 0.4-second fall time, and a 0.1-second hold time. The first series was applied at an ISI of 10 seconds and the 2 remaining series at an ISI of 2 seconds. Successive series were applied on different fingers but on the same digits on which

thresholds were based. The stimulation order of the fingers was randomized across subjects. More than 3 minutes elapsed before the same finger was restimulated to allow any residual effects of prior stimulation upon nociceptors to dissipate.[23] Moreover, each stimulation series was delivered on a previously unstimulated site of the skin.

The subjects verbally rated the perceived pain intensity evoked by the 1st, 5th, and 10th stimuli in a train by referring to a numeric pain rating scale visually displayed in front of him or her. This scale was marked along one side with numbers from 0 to 100 in increments of 10; 5 descriptors (not at all painful, slightly, moderately, highly, and extremely painful) indicated the meanings of the numbers. This scale has been used previously.[24] The subject was cued about the initiation of a new train of stimuli 5 seconds before the first stimulus was delivered. Moreover, after they received the 4th or 9th stimulus an auditory cue was given to signal the impending 5th or 10th stimulus, respectively. In this way the subjects were able to focus their attention on their sensations without having to count the stimuli.

Statistical Analysis

Differences between the male and female TMD patients for mechanically evoked pain thresholds and the general group characteristics were determined using Student t test. Differences between the male TMD patients and the healthy male subjects were similarly determined. A 3-way, mixed-model, repeated-measures analysis of variance (ANOVA) was used to assess group differences in the pain intensity ratings of the repetitive noxious stimuli. The post-hoc comparisons were made with Newman-Keuls test. Pearson correlations were calculated to examine the relationship between temporal summation and characteristics of clinical pain. Significance was accepted at $P < .05$.

Results

General Characteristics of the Study Populations

The general characteristics and the psychological variables for the test groups are presented in Table 1. There was no significant age difference between the male and female TMD patients nor between the male TMD patients and the healthy men. The male TMD patients had a significantly smaller painless mouth opening than healthy males ($t = 3.791$; $P < .001$), but a significantly larger painless mouth opening ($t = 2.793$; $P < .01$), as well as sig-

Table 1   Description of the TMD and Control Populations

	Healthy men (n = 20)		Male TMD patients (n = 16)		Female TMD patients (n = 27)	
	Mean	SD	Mean	SD	Mean	SD
Age	37.80	14.81	35.90	9.23	36.10	13.97
Painless opening (mm)	49.00	4.38***	37.94	12.14	28.40	9.76**
Maximum assisted opening (mm)	52.60	4.65	50.88	6.59	45.30	4.91**
Depression	2.80	2.02	5.31	4.25	6.74	4.23
Trait anxiety	32.95	8.56	37.25	9.61	38.74	10.33
State anxiety	31.40	9.73	30.63	8.79	31.22	6.98
Insomnia	4.90	4.51	5.69	3.34	9.17	6.39
PCS	7.85	7.95	13.00	6.62	12.92	6.89
Anxiety sensitivity	11.65	6.47	15.13	12.66	14.63	9.40
State PCS	22.80	26.98	31.56	24.63	30.44	28.98
VAS anxiety	17.25	18.08	13.50	15.07	22.78	21.11

**Significantly different from healthy men ($P < .01$; t test).
***Significantly different from male TMD patients ($P < .001$; t test).
PCS = Pain Catastrophizing Scale; VAS = visual analog scale.

nificantly greater assisted mandibular opening ($t = 2.937$; $P < .01$), compared to the female TMD patients. There were no significant differences in any of the psychological variables between TMD men and healthy controls. There was a trend toward greater insomnia scores among female TMD patients compared to men with TMD ($P = .051$). No significant differences in any of the other psychological variables were detected between male and female TMD patients.

Clinical pain measures for the TMD patients are shown in Table 2. Female patients exhibited significantly greater average pain intensity in the previous 3 months ($t = 2.109$; $P < .05$), a higher total palpation score ($t = 2.79$; $P < .01$), and a greater total body pain score ($t = 2.873$; $P < .01$) than male patients.

Mechanical Pain Thresholds

The mean mechanical pain threshold was 144.8 g (SD = 40.7 g) for healthy men, 118.1 g (SD = 47.3 g) for male TMD patients, and 115.0 g (SD = 49.4 g) for female TMD patients. The difference in the pain threshold between male TMD patients and healthy males did not reach statistical significance ($t = 1.814$; $P = .08$). There was no significant difference between the pain threshold of male TMD patients and that of female TMD patients ($t = 0.204$; $P = .84$).

For safety reasons, the highest force used in the present study was 250 g. One healthy man, 4 TMD males, and 2 TMD females did not perceive 250 g as painful and were eliminated from the study without undergoing temporal summation testing.

Temporal Summation of Pain Intensity Ratings

Stimuli for temporal summation testing were applied at intensities of 1.5× the individual subject's pain threshold. The mean stimulus intensity for temporal summation testing was 206 g (SD = 45.6 g) for healthy males, 182 g (SD = 48.3 g) for male TMD patients, and 173 g (SD = 65.8 g) for female TMD patients.

There was a significant group × trial number interaction (Table 3). Perceptual magnitude of pain increased significantly with stimulus repetition for the female TMD patients ($P < .001$; Figs 1 and 2). TMD women provided significantly higher pain magnitude estimates than TMD men for the 5th and 10th stimuli ($P < .001$; Figs 1 and 2). Neither the healthy men nor the male TMD patients exhibited significant temporal summation of pain (Figs 1 and 2). The pain intensity ratings provided by TMD men for the 1st, 5th, and 10th stimuli in the series were not significantly different than those provided by healthy men.

There was also a significant group × ISI interaction (Table 3). Overall, in the female TMD patient group, perceptual pain magnitudes were higher with an ISI of 2 seconds than an ISI of 10 seconds ($P < .005$), while frequency had no significant effect on the overall pain ratings provided by male TMD patients or healthy men. Examination of the data indicated that for female TMD patients the first rating at 10 seconds was comparable to that at 2 seconds; however, increase in pain with repetitive stimulation was greater at 2 seconds than 10 seconds (Figs 1 and 2).

There were no statistically significant correlations between temporal summation of pain at ISI

Table 2   Clinical Pain Variables for TMD Patients

	Healthy men (n = 20)		Male TMD patients (n = 16)		Female TMD patients (n = 27)	
	Mean	SD	Mean	SD	Mean	SD
Duration of pain (mo)	N/A		94.63	67.78	81.63	95.96
Average pain intensity in previous 3 mo	N/A		4.25	2.21	5.78	2.36*
Average frequency of pain in previous 3 mo	N/A		4.78	1.86	5.28	1.80
Total palpation score (possible range: 0 to 96)	0.75	1.41*	25.38	10.15	38.63	17.26**
Total number of painful body sites	1.60	1.19*	3.56	1.63	4.78	2.06
Total body pain score	2.08	1.64*	7.13	4.59	11.89	5.60**
BPI severity score	N/A		3.39	1.73	3.96	1.87
BPI interference score	N/A		2.47	1.52	2.86	2.23

* Significantly different from male TMD patients ($P < .05$; t test).
** Significantly different from male TMD patients ($P < .01$; t test).
BPI = Brief Pain Inventory.

Table 3   Summary of ANOVA of Pain Intensity Ratings

Factor	F-statistic	P
Main ANOVA results		
Between subjects		
Group	11.24	< .001
Within subjects		
Trial no.	3.84	< .05
ISI	6.04	< .05
Interactions		
Group/trial no.	12.59	< .001
Group/ISI	3.19	< .05

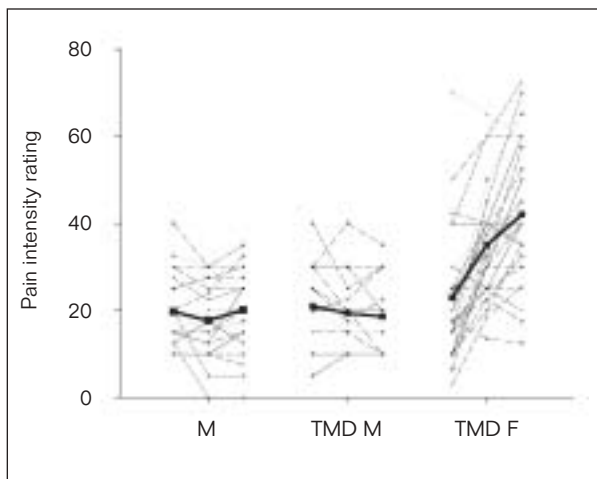No other interactions were statistically significant.

Fig 1 Pain intensity ratings in response to the 1st, 5th, and 10th stimuli in a series of 10 stimuli at an ISI of 2 seconds for healthy men (M), male TMD patients (TMD M), and female TMD patients (TMD F). The thin lines represent individual subject data, while the thick line represents the group mean.
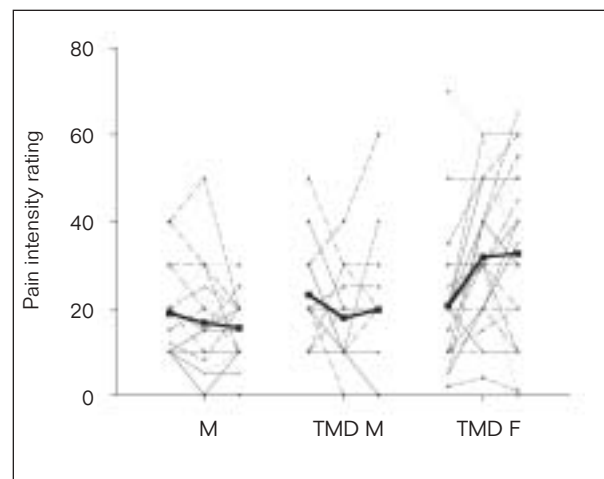
Fig 2 Pain intensity ratings in response to the 1st, 5th, and 10th stimuli in a series of 10 repetitive stimuli at an ISI of 10 seconds for healthy men (M), male TMD patients (TMD M), and female TMD patients (TMD F). The thin lines represent individual subject data, while the thick line represents the group mean.

of 2 seconds and any of the clinical pain variables for either male or female TMD patients.

Discussion

The present study investigated differences in mechanically evoked pain threshold and temporal summation of mechanically evoked pain between male and female TMD patients as well as between male TMD patients and healthy men. The intensity of stimulation for the investigation of temporal summation was set at 1.5 times the individual subject's pain threshold, so that all the subjects perceived the first stimulus in the train of repetitive stimuli as mildly painful. Thus, changes in pain intensity could be measured without concern of a "floor effect" due to an initially nonpainful stimulus. Moreover, this design made feasible the meaningful comparison of temporal summation per se between groups, since the observed differences involved increase in pain, starting from a similar perceptual magnitude.

Gender Differences in Temporal Summation of Pain Among TMD Patients

As a consequence of myalgia, pressure pain thresholds are routinely lower in the masticatory muscles and TMJ of TMD patients compared to healthy controls.[25,26] In addition, several studies have reported that TMD patients exhibit greater sensitivity than healthy controls not only in the craniofacial region but also in remote bodily areas.[27–29] However, this is the first study to explicitly compare experimental pain sensitivity between male TMD patients and healthy men as well as between male and female TMD patients. The present study found that neither healthy men nor TMD male patients exhibited statistically significant temporal summation of mechanically evoked pain. Notably, the lack of temporal summation was very consistent across the male TMD patient group. In contrast, the majority of female TMD patients showed a prominent increase in their pain perception with repetition of the mechanical stimulation. The latter result is consistent with the authors' previous observations[9] and those of others.[8] Temporal summation of pain has a central basis and reflects a transient increase in the excitability of the nociceptive neurons in the CNS.[10] Accordingly, greater temporal summation in response to repetitive noxious stimulation on the hand among female TMD patients provides evidence for a generalized hyperexcitability in the CNS nociceptive processing regions of such patients. Even among people with-

out chronic pain, women show significantly greater temporal summation of pain than men.[30] Yet women with TMD show significantly greater temporal summation of pain than healthy women,[9] suggesting exaggerated temporal integration of nociceptive signals in the CNS of TMD women.[31] Failure of the male TMD patients to exhibit significant temporal summation in the present study suggests that such CNS hyperexcitability is not present among men with TMD and that the CNS mechanisms contributing to chronic TMD pain may be qualitatively different for men and women.

Generalized upregulation of the central nociceptive processing has been implicated in the pathophysiology of TMD, because several lines of evidence suggest that peripheral pathology is not a crucial determinant of TMD pain. First, TMD patients often report pain in the craniofacial region in the absence of any demonstrable peripheral tissue abnormalities. In addition, the level of TMD-related pain does not correlate with clinical measurements of dysfunction, such as range of mandibular motion and number of joint sounds.[5,6] Moreover, a large percentage of TMD patients suffers from widespread pain, which is suggestive of generalized hyperexcitability in CNS nociceptive processing.[32–34] In the present study, female TMD patients exhibited significantly greater total body pain than their male counterparts. In addition, greater pain upon palpation and average facial pain intensity in the previous 3 months indicated a more pronounced severity of TMD among female patients. One could speculate that the enhanced temporal summation in female TMD patients could be related to their greater clinical pain rather than their sex. However, none of the clinical variables correlated significantly with temporal summation with a 2-second ISI for the female TMD patients, indicating that there was not a parametric relationship between temporal summation and any clinical pain measure.

Protocol Differences Affecting Temporal Summation

In the present study, healthy men failed to show a significant increase in their pain perception with repetition of stimulation with either a 10-second or 2-second ISI. This finding contrasts with a previous study by the present authors, in which modest but statistically significant temporal summation of mechanically evoked pain was observed with a 2-second ISI in healthy men.[30] Relatedly, female TMD patients exhibited a smaller magnitude of temporal summation in the present study compared to the previous study.[9] Less pronounced

temporal summation in this report may be due to protocol differences between these studies. One difference is that in the previous studies, subject training and threshold determination were conducted on 1 day and temporal summation testing on another. In the present study, they were conducted within the same 60- to 90-minute session. Many more temporal summation runs were conducted in the previous studies compared to the present study. Also, in the previous study, rating data were collected by having subjects use a pencil-and-paper mechanical VAS, while in the current study subjects gave verbal reports using a visual 0-to-100 scale. However, it is not obvious that these protocol differences are related to the differences in the strength of temporal summation between the current and previous studies. Perhaps more relevant are the specifics of the threshold and training protocols. In all studies, thresholds were estimated using an ascending method of limits protocol. This consists of presenting the subject with progressively increasing intensities of stimuli until the level of stimulation becomes painful. In the previous studies, these ascending series of stimuli were the vast majority of testing and training stimuli that the subject experienced prior to the temporal summation series. In the present investigation, lower-intensity stimuli were interspersed within the ascending series to reduce the subject's expectation of ascending forces. Moreover, in contrast to previous studies by the present authors, the current protocol included both descending series and random intensities during the ratings training period. These modifications were introduced to prevent the expectation of progressively increasing stimuli, which was considered particularly important in the current study, since the temporal summation testing occurred shortly after training. Thus, it is reasonable to suggest that the overall reduction in temporal summation in the current study may be related to the differences in experience before the testing, which should have produced less of an expectation of increasing sensation than the previously used protocol.

Conclusions

The results of the present study support the theory that generalized upregulation of CNS responsiveness to aversive stimulation constitutes a pathophysiological mechanism contributing to TMD pain, but only in women. The extent of temporal summation varies considerably among female TMD patients, so the importance of upregulated central nociceptive processing appears to vary across the female patient population. In contrast, this factor appears to be of no relevance for male TMD patients. Studies investigating the responsiveness of TMD patients to experimental pain should report the sex of the participants and, if the size of their populations allows it, explore gender differences in their outcomes.

References

1. Drangsholt MT, LeResche L. In: Crombie IK (ed). Epidemiology of Pain. Seattle: IASP Press, 1999:203–233.
2. Warren MP, Fried JL. Temporomandibular disorders and hormones in women. Cells Tissues Organs 2001;169:187–192.
3. Dworkin SF. In: Fricton JR, Dubner R (eds). Orofacial Pain and Temporomandibular Disorders. New York: Raven Press, 1995:15–32.
4. Dworkin SF, LeResche L. Research Diagnostic Criteria for Temporomandibular Disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
5. Dworkin SF. Perspectives on the interaction of biological, psychological and social factors in TMD. J Am Dent Assoc 1994;125:856–863.
6. Ohrbach R, Dworkin SF. Five-year outcomes in TMD: Relationship of changes in pain to changes in physical and psychological variables. Pain 1998;74:315–326.
7. Sarlani E, Greenspan JD. Evidence for generalized hyperalgesia in temporomandibular disorders patients. Pain 2003;102:221–226.
8. Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. Pain 1998;76:71–81.
9. Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Evidence for up-regulated central nociceptive processing in patients with masticatory myofascial pain. J Orofac Pain 2004;18:41–55.
10. Ren K. Wind-up and the NMDA receptor: From animal studies to humans. Pain 1994;59:157, 158.
11. Mendell LM, Wall PD. Responses of single dorsal horn cells to peripheral cutaneous unmyelinated fibers. Nature (Lond.) 1965;206:97–99.
12. Mendell LM. Physiology properties of unmyelinated fiber projection to the spinal cord. Exp Neurol 1966;16:316–332.
13. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: A placebo-controlled experimental human study. Anesth Analg 1995;81:63–68.

14. Davies SN, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Res 1987;424: 402–406.

15. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology 1987;26:1235–1238.

16. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain 1977;3:57–68.

17. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. Pain 1994;59:165–174.

18. Vierck CJ, Jr., Cannon RL, Fry G, Maixner W, Whitsel BL. Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. J Neurophysiol 1997;78:992–1002.

19. Riley JL, III, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. Pain 1999;81:225–235.

20. Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? A methodological review. Am J Physiol Regul Integr Comp Physiol 2006;291: R245–R256.

21. Greenspan JD, McGillis SLB. Stimulus features relevant to the perception of sharpness and mechanically evoked cutaneous pain. Somatosensory Motor Res 1991;8:137–147.

22. Gescheider GA. In: Gescheider GA (ed). Psychophysics: The fundamentals. Mahwah, NJ: Lawrence Erlbaum Associates, 1997:45–72.

23. Slugg RM, Meyer RA, Campbell JN. Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. J Neurophysiol 2000;83:2179–2191.

24. Greenspan JD, Roy EA, Caldwell PA, Farooq NS. Thermosensory intensity and affect throughout the perceptible range. Somatosens Mot Res 2003;20:19–26.

25. Ohrbach R, Gale EN. Pressure pain thresholds, clinical assessment, and differential diagnosis: Reliability and validity in patients with myogenic pain. Pain 1989;39: 157–169.

26. Farella M, Michelotti A, Steenks M, Romeo R, Cimino R, Bosman F. The diagnostic value of pressure algometry in myofascial pain of the jaw muscles. J Oral Rehabil 2000;27:9–14.

27. Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. Pain 2001;92:399–409.

28. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. Psychosom Med 1997;59:503–511.

29. Kashima K, Rahman OI, Sakoda S, Shiba R. Increased pain sensitivity of the upper extremities of TMD patients with myalgia to experimentally-evoked noxious stimulation: Possibility of worsened endogenous opioid systems. Cranio 1999;17:241–246.

30. Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Sex differences in temporal summation of pain and aftersensations following repetitive noxious mechanical stimulation. Pain 2004;109:115–123.

31. Sarlani E, Greenspan JD. Why look in the brain for answers to temporomandibular disorder pain? Cells Tissues Organs 2005;180:69–75.

32. Yap A, Tan K, Chua E, Tan H. Depression and somatization in patients with temporomandibular disorders. J Prosthet Dent 2002;88:479–484.

33. Turp JC, Kowalski CJ, Stohler CS. Temporomandibular disorders—Pain outside the head and face is rarely acknowledged in the chief complaint. J Prosthet Dent 1997;78:592–595.

34. Turp JC, Kowalski CJ, O'Leary N, Stohler CS. Pain maps from facial pain patients indicate a broad pain geography. J Dent Res 1998;77:1465–1472.