Chronic Temporomandibular Disorders Are Not Necessarily Associated with a Compromised Endogenous Analgesic System

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Aims: *To test whether temporomandibular disorders (TMD) case-control differences in conditioned pain modulation (CPM) exist, using a mechanically evoked temporal summation (TS) model.* ***Methods:*** *A series of 10 repetitive, mildly noxious, mechanical stimuli were applied to the fingers of 30 women with TMD, who had a primary diagnosis of masticatory myofascial pain, and 30 age-matched healthy women. The subjects rated the pain intensity caused by the 1st, 5th, and 10th stimuli in the series. To evaluate CPM, the same series of mechanical stimulations were applied with concomitant exposure of the other hand to a painfully cold water bath. Statistical inferences were based on* t *tests, chi-square tests, or analysis of variance (ANOVA), as appropriate.* ***Results:*** *Pain ratings increased significantly with stimulus repetition (*$P < .01$*) and CPM significantly reduced TS of pain (*$P < .01$*). Of particular note, both groups showed very similar degrees of CPM, with no significant group difference.* ***Conclusion:*** *Painful TMD is not necessarily associated with a compromised ability to engage the endogenous analgesic system in an experimental setting.* J OROFAC PAIN 2013;27:142–150. doi: 10.11607/jop.943

Key words: chronic pain, conditioned pain modulation, temporal summation, temporomandibular disorders

Temporomandibular disorders (TMD) include an array of pathologic conditions that affect the muscles of mastication and/or the temporomandibular joint (TMJ), and present with pain and dysfunction of the stomatognathic system.[1] Persistent pain that is aggravated with jaw function is common among TMD patients, and has a great impact on their quality of life, since it interferes with daily living activities, such as eating, talking, and laughing. Thus, not surprisingly, pain is the prevalent symptom that motivates patients to seek treatment.[1,2] However, the etiopathogenesis of TMD pain is not fully understood.

TMD-related pain is not predicted by observable clinical signs and does not correlate well with peripheral pathology.[3] Accordingly, dysfunction of the central nervous system processing of nociceptive input has been implicated as a contributing factor to the onset and maintenance of persistent TMD pain.[4] Several studies have demonstrated that TMD patients show greater sensitivity to experimental noxious stimulation than pain-free controls, not only in the orofacial region but also in remote bodily sites, indicating a generalized upregulation of nociceptive input processing in this patient population.[5–8]

Temporal summation (TS) of pain is defined as the increase in perceived pain intensity upon repetitive noxious stimulation of constant intensity at a frequency greater than 0.2 to 0.3 Hz. TS is

regarded as the psychophysical correlate of wind-up,[9] which is the increase in magnitude and frequency of the CNS nociceptive neurons' responses when repetitive noxious stimuli of constant strength are applied at a frequency higher than 0.33 Hz.[10,11] Several lines of evidence strongly suggest that wind-up and temporal summation of pain share common central mechanisms.[12–17] Accordingly, greater TS in TMD female patients suggest a hyperexcitability in their central nociceptive processing, at least in the temporal domain.

Dysfunction of the descending pain inhibitory pathways might play a role in the upregulated central processing of nociceptive input related to TMD. Such impairment of the endogenous analgesic systems has been implicated as a contributing factor in the development and maintenance of multiple chronic pain conditions.[18] The function of the endogenous pain inhibitory systems can be assessed by examining conditioned pain modulation (CPM). CPM refers to the phenomenon where strong tonic painful stimulation (the conditioning stimulation) applied to one body region reduces pain evoked by a phasic noxious stimulus (the test stimulus) in remote body regions.[19]

While a diminished CPM has been reported in fibromyalgia and chronic tension-type headache patients,[20–23] no differences in pain modulation by noxious stimulation were detected between patients with long-term trapezius myalgia and pain-free subjects,[24] or between patients with rheumatoid arthritis and healthy controls.[25] In a study of CPM in TMD patients that used simultaneous delivery of a tonic and a phasic noxious stimulus,[26] it was reported that a submaximal effort tourniquet procedure induced a smaller attenuation in pressure pain sensitivity in the hand of female patients with chronic masticatory myalgia than healthy controls. A study of patients with TMD and irritable bowel syndrome (IBS) by King et al[27] reported increased sensitivity to heat pain but failed to demonstrate CPM using heat as the test stimulus with a concurrent noxious cold bath immersion. The present study further assesses the function of the endogenous analgesic systems in TMD patients. Its aim was to test whether TMD case-control differences in CPM exist, using a mechanically evoked TS model.

Materials and Methods

Subjects

Thirty women with chronic TMD, as described by at least 3 months of persistent pain, and 30 age-matched TMD-free controls participated in the present study. The mean age of the healthy women was 36.7 years (age range, 20 to 63 years; SD, 11.8 years), and the mean age of the female TMD patients group was 36.3 years (age range, 19 to 65 years; SD, 13.4 years). Thirteen TMD female patients and nine healthy women were taking oral contraceptives at the time of the study. None of the six healthy postmenopausal women or five postmenopausal female patients was receiving hormone replacement therapy. The TMD patients were recruited from a larger treatment study, and the healthy controls were recruited from posted advertisements around the University campus.

The subjects were instructed on the protocols to be used but were kept naïve regarding the specific hypotheses to be tested in the study. All subjects provided written informed consent and were paid for their participation. This project was approved by the Institutional Review Board for the Protection of Human Subjects (IRBPHS) of the University of Maryland, Baltimore.

The exclusion criteria for all subjects included serious injury to the hands at any time; systemic arthritic diseases, such as systemic lupus erythematosus or rheumatoid or psoriatic arthritis; irritable bowel disease; potentially confounding vascular disorders, such as giant cell arteritis; potentially confounding neurological disorders, such as multiple sclerosis or trigeminal neuralgia; neoplasia; pregnancy; and self-report of substance abuse. TMD-free control subjects were excluded if they had any of the above criteria as well as masticatory myofascial pain, TMJ arthralgia, degenerative joint disease, and/or disc displacement without reduction.

The main inclusion criterion for the TMD group in this study was a primary diagnosis of masticatory myofascial pain, according to the Research Diagnostic Criteria for TMD.[1,2] 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 3 or more of 20 specific facial muscle sites. Patients participated in the study only if they reported duration of myofascial pain longer than 3 months. Patients with painful disc displacement without reduction were excluded from the study, as the intent was to recruit TMD cases with predominantly myalgic symptoms.

Normally cycling women who were not taking oral contraceptives were tested between the fourth and ninth day of their menstrual cycle, in order to diminish the fluctuation of the gonadal steroid hormones as a factor that may influence the responses to noxious stimulation.[28]

History and Clinical Examination

At the beginning of the experimental session, a medical/dental history specifically relating to facial pain was obtained from all subjects. All subjects rated the average intensity of their facial pain in the past 3 months on a numerical pain rating scale from 0 to 10, where 0 represented no pain and 10 represented pain as bad as it could possibly be. In addition, 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 numerical scale, where 0 represented not at all and 5 extremely, how much they had been distressed by pain in various body sites in the previous month. A total body pain score was obtained for each subject by summing the pain distress ratings of several body sites (see Table 2).

All subjects underwent a clinical examination, assessing: *(a)* joint function, *(b)* sensitivity of the TMJs 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 TMJ, and posterior attachment of TMJ. Palpations were done with approximately 2 lbs of pressure for the extraoral muscles and approximately 1 lb of pressure for the joints and intraoral muscles.[2] 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.

Experimental Design

All subjects participated in two experimental sessions, each lasting 60 to 90 minutes and separated by several weeks. In the initial session, it was determined if the subject fulfilled the criteria for inclusion in the study, by obtaining a medical/dental history and performing a clinical examination. Prior to sensory testing, each subject completed the Beck Depression Inventory (DPI),[29] the State Trait Anxiety Inventory (STA),[30] the Pain Catastrophizing Scale (PCS),[31] the Insomnia Severity Inventory,[32] and the Anxiety Sensitivity Inventory.[33] Next, the subject's mechanical pain threshold and cold pain sensitivity were assessed, as described below. In addition, the subject was introduced to the TS and CPM testing procedures and was trained until she became familiarized with the rating procedures.

In the second experimental session, the TS of mechanically evoked pain was assessed by delivering repetitive noxious mechanical stimuli to the fingers of the left hand, at an interstimulus interval (ISI) of 10 seconds and an ISI of 2 seconds. The shorter ISI produces robust TS, while the longer ISI does not.[34] Moreover, TS at 2-second ISI was assessed while the right hand was immersed either in a neutral-temperature water bath (33°C) or in a painful cold-water bath. Following the data collection, the subjects completed the PCS, and they rated the anxiety they experienced during the experiment on a 10-cm visual analog scale (VAS) anchored with "no anxiety" on the left end and "anxiety as bad as could be" on the right end.

Sequence of Experimental Stimuli

At the beginning of the data collection, TS of pain was tested on the left hand at an ISI of 10 seconds, and 1 minute later TS was tested at an ISI of 2 seconds. One minute later, the CPM protocol was initiated. This consisted of four CPM trials, in which TS was assessed at an ISI of 2 seconds by stimulation of the left-hand digits. Two of the CPM trials involved right-hand immersion in the neutral-temperature water bath, and two involved right-hand immersion in the conditioning cold-water bath. At the beginning of each CPM trial, the subjects were prompted to immerse their right hand in one of the two water baths (neutral or cold temperature). Thirty seconds later, the subjects were asked to provide a pain rating of the right hand. While the subjects maintained the right hand in the water bath, mechanical stimulation at an ISI of 2 seconds was initiated on the left hand. All subjects were instructed to pay attention to the mechanical stimulation during mechanical stimulation testing and to rate the 1st, 5th, and 10th stimulus in the series. At the end of the mechanical stimulation, approximately 1 minute following immersion of the right hand in the water bath, the subjects were prompted to shift their attention to the right hand and give a current pain rating for the hand in the water bath before removing it. The subjects were allowed to rest for 2 minutes following each CPM trial. Half of the subjects underwent a sequence of neutral-cold-cold-neutral water bath and the other half of the subjects experienced a sequence of cold-neutral-neutral-cold water bath CPM trials. Two minutes after the last CPM trial, TS was tested again on the left hand at an ISI of 2 seconds, without a water bath immersion of the right hand. This protocol is depicted in Fig 1.

Mechanical Test Stimulation

Mechanical stimuli were applied with a computer-controlled linear motor (Neurologic Inc) under

force feedback regulation (model 501 motor controller; Biocommunication Electronics). A stainless-steel probe with a circular contact surface of 0.245 mm² was affixed to the tip of the stimulator and applied brief mechanical stimuli to the middle phalanx dorsal surface of the second, third, or fourth fingers. The probe was examined under a light microscope, at regular intervals throughout the data collection period, to ensure its shape remained unchanged, as it has been shown that the probe shape can have an effect on the perceived pain sensation.[35]

During the sensory testing sessions, the subjects were seated comfortably on a chair with their 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 subjects from viewing the probe and their left hand during the testing period.

Pain Threshold Estimation and Temporal Summation Training

Each subject's mechanical pain threshold was determined with an ascending method of limits protocol.[35,36] Stimuli consisted of a range of forces, from 10 to 25g (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, and the probe was moved to another finger between successive series. The subjects were informed that a stimulus would be applied on their fingers every 15 seconds and were asked to report if this stimulus was painful or not. They were also told that they should discriminate between sharpness or other sensations and pain, and report only the latter.

In the first ascending series, the first stimulus presented was 20 g and successive stimuli were incremented by 20 g, resulting in a gross estimation of the subject's pain threshold. For the remaining three to four 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. The exception to progressively increasing forces was that the 6th and 10th stimuli in the series were also well below the subject's grossly estimated pain threshold in order to reduce the subject's expectation of ascending forces. The ascending series was terminated when the subject provided two or three 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.

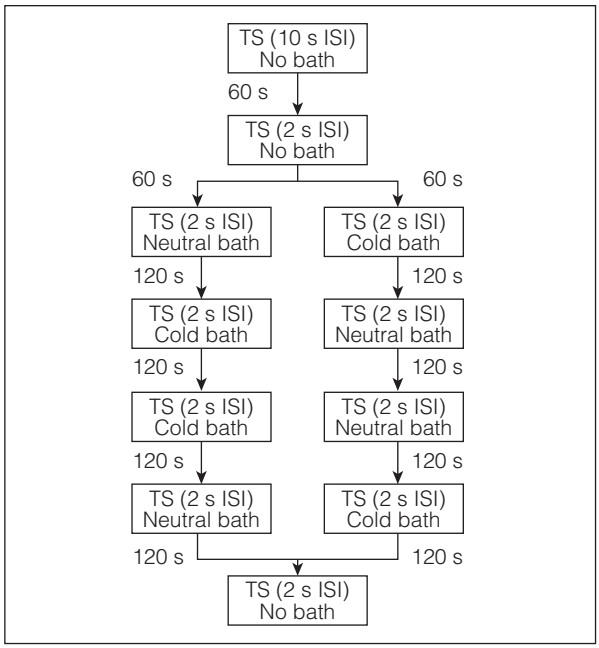


Fig 1 Sequence of the experimental protocol. Half of the subjects started with a cold conditioning bath and the other half started with a neutral conditioning bath to determine CPM.

Following the estimation of mechanical pain threshold, the subject was trained with 2 random and 2 descending series of 10 stimuli at ISIs of 5 and 2 seconds, as well as with a random series of 10 stimuli at an ISI of 2 seconds. The purpose of this training was to familiarize the subject with the shorter ISIs and the rating procedures (described below), and to prevent the consistent expectation of progressively increasing stimulus intensities.

Temporal Summation Testing

TS was tested with 9 series of 10 repetitive stimuli on the fingers of the left hand at an intensity of 1.25 to 1.5× the individual subject's pain threshold. 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 of stimuli was applied at an ISI of 10 seconds and the remaining series at an ISI of 2 seconds. Successive trains of stimulation were applied on the middle phalanx of digits 2, 3, or 4. The stimulation order of the fingers was randomized across subjects. More than 3 minutes elapsed before the same finger was stimulated sequentially, so as to allow any residual effects of prior stimulation upon nociceptors to dissipate.[37] Moreover, each stimulation series was delivered on a previously unstimulated site of the skin.

Table 1 Characteristics of the TMD and Control Populations*

	Healthy women (n = 30)	TMD women (n = 30)
Age (y)	36.7 ± 2.2	36.3 ± 2.5
Painless opening (mm)	43.2 ± 1.7	28.8 ± 1.7*
Maximum assisted opening (mm)	48.1 ± 0.9	43.8 ± 0.9*
Depression	5.4 ± 0.8	6.6 ± 0.8
Trait anxiety	35.5 ± 1.6	36.0 ± 1.7
State anxiety	31.5 ± 1.7	31.1 ± 1.2
Insomnia	4.9 ± 0.7	9.5 ± 1.2*
Pain Catastrophizing Scale	7.8 ± 1.4	12.1 ± 1.2
Anxiety sensitivity	14.5 ± 1.7	13.8 ± 1.7
State Pain Catastrophizing Scale	20.9 ± 5.6	33.6 ± 5.7
VAS anxiety	20.1 ± 3.9	20.8 ± 3.5

*Each value represents the mean ± standard error. *$P < .05$ (t test).

Table 2 Clinical Pain/Distress Ratings of the TMD and Control Populations at Various Body Sites (0 to 5 Scale)*

	Healthy women (n = 30)	TMD women (n = 30)
Face and/or jaws	0.00	3.05 ± 0.2*
Headaches	0.6 ± 0.1	2.4 ± 0.3*
Neck and shoulders	0.3 ± 0.1	2.5 ± 0.3*
Lower back	0.6 ± 0.2	1.6 ± 0.3*
Arms	< 0.1 ± < 0.1	0.5 ± 0.2*
Legs	0.3 ± 0.1	0.7 ± 0.2
Chest	0.00	0.4 ± 0.2*
Other body parts	0.2 ± 0.1	0.7 ± 0.2
Menstrual pain	1.2 ± 0.2	1.6 ± 0.3
No. of subjects with pain outside of the head and neck area	24	28
Total no. of body pain sites outside head and neck area	1.4 ± 0.2	2.6 ± 0.33*
Total body pain score (sum of all body site ratings)	3.1 ± 0.4	13.2 ± 1.1*
Body pain score outside head and neck area	2.3 ± 0.4	5.3 ± 0.7*

*Each value represents the mean ± standard error. *$P < .05$ (t test).

Using a visually displayed numerical pain rating scale with descriptors, subjects rated the perceived pain intensity evoked by the 1st, 5th, and 10th stimuli in a series of test stimuli. This scale was marked with numbers, from 0 to 100 in increments of 10, along one side, while the other side contained 5 descriptors (not at all painful, slightly, moderately, highly, and extremely painful),[38] as described previously.

Each time, the subject was cued about the initiation of a new series of stimuli 5 seconds before the first stimulus was delivered. Moreover, after the subject received the 4th and 9th stimulus, an auditory cue was given to signal that the 5th and 10th stimulus, respectively, would follow. In this way, the subjects were able to focus their attention on their sensations without having to count the stimuli.

Conditioning Stimulus

Immersion of the right hand in painfully cold water served as the conditioning stimulation. To determine the cold pain sensitivity of each subject, evaluation of cold pain sensitivity was conducted approximately 20 minutes before data collection. Subjects were instructed to place their right hand up to the wrist for 60 seconds in a circulating water bath maintained at 13°C. This temperature was chosen as it has been demonstrated to provoke moderate pain, while still being tolerable for most women.[38] Pain intensity ratings were reported on a VAS after 20, 40, and 60 seconds following hand immersion. The VAS was the same one used for the rating of the mechanically evoked pain stimulus. The subjects were instructed that they should differentiate between the sensation of cold and pain and report only the latter. They were also told that in case they found the bath intolerable, they could remove their hand from it. Otherwise, they were cued to remove their hand after the 60-second rating. Depending on the pain ratings provided for the 13°C bath, additional trials were done using different temperatures, in order to determine which temperature would evoke moderate to strong pain (60 to 70 on a 100 VAS) at 60-second immersion for each subject. During the subsequent CPM sessions, the subjects immersed their right hand in a circulating cold-water bath maintained at their predetermined conditioning temperature, or in a circulating water bath maintained at 33°C, which served as the neutral bath control. The change in mechanical pain rating and TS evoked by the cold water reflected the magnitude of inhibitory CPM.

Statistical Analysis

Group differences in continuous variables, including most clinical measures and thresholds, were assessed with t tests. Group differences in proportional metrics were assessed with chi-square statistics. CPM

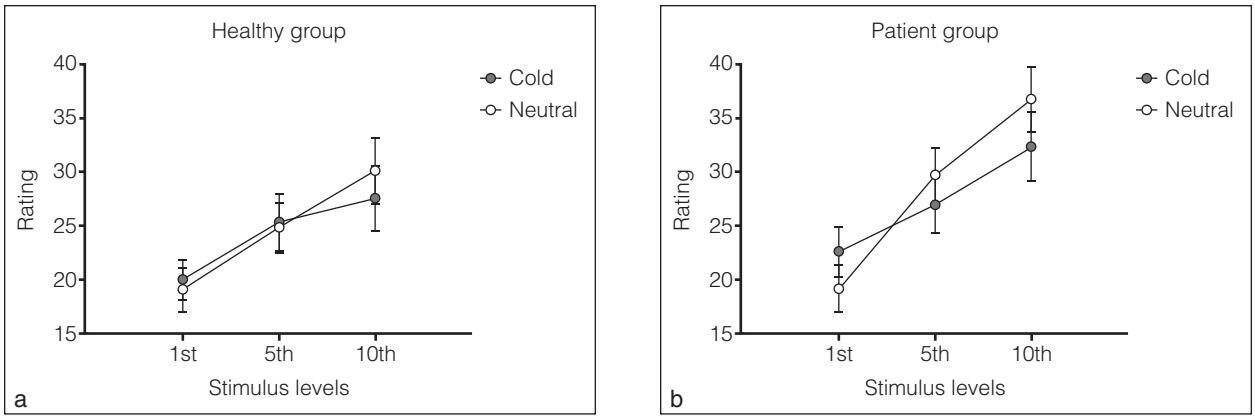
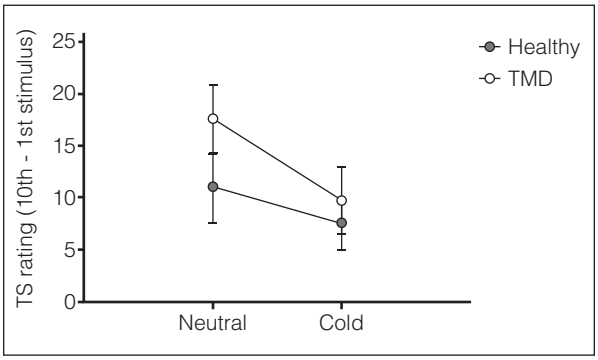


Fig 2 Mean pain intensity ratings of healthy women *(a)* and women with TMD *(b)* to the 1st, 5th, and 10th stimulus in a series of 10 stimuli applied to fingers, while the opposite hand was in either a noxious cold conditioning bath *(filled circles)* or a neutral (33°C) bath *(open circles)*. Error bars = standard error of the mean.

Fig 3 Temporal summation (increase in ratings from the 1st to 10th stimulus in a series of 10 stimuli) for female TMD patients *(open circles)* and healthy women *(filled circles)*, in both the noxious cold conditioning bath and neutral bath. There was a significant main effect for bath, where TS ratings were higher for the neutral bath versus the cold bath (F = 15.2, $P < .01$). Error bars = standard error of the mean.



and TS, requiring multiple measures over time, were assessed by two-way mixed-effect repeated-measures analysis of variance (ANOVA), in which group and time were the two factors. Statistical calculations were conducted using SPSS Version 19. Statistical significance was accepted at $P < .05$.

Results

General Characteristics of the Study Populations

The women with TMD had smaller painless mandibular opening ($t = 5.5$, $P < .01$), as well as smaller maximum mandibular opening ($t = 3.3$, $P < .02$) than the TMD-free control women. In addition, women with TMD had significantly higher insomnia scores ($t = -3.5$, $P < .02$) than TMD-free controls. Body pain was reported by both the TMD and TMD-free women; however, the women with TMD had a significantly higher proportion of painful body sites compared to controls. This was the case when considering all nine body sites ($\chi^2 = 66.1$, $df = 8$, $P < .001$), or when excluding the head, neck, and shoulders ($\chi^2 = 17.1$, $df = 5$, $P < .04$). Considering body sites separately, six of the body sites were significantly more painful for the TMD cases. There was no other statistically significant difference between the two groups in general characteristics or psychological measures (Tables 1 and 2).

Mechanical Pain Thresholds

The mean mechanical pain threshold was 103.6 g (SE = 9.0) for healthy women and 114.2 g (SE = 8.9) for women with TMD. There was no significant group difference in pain threshold ($t = 0.9$, $P = .35$).

Temporal Summation of Pain

The mean stimulus intensity used for temporal summation testing was 174 g for healthy women and 169 g for women with TMD. Significant TS was seen for both groups ($t = 15.2$, $P < .01$). The TMD patients showed greater TS of pain on average (Figs 2 and 3). However, there was not a significant group difference in TS, based on a 2-way ANOVA on rating differences between the 10th and 1st stimulus in the TS series of stimuli ($t = 1.1$, $P = .30$).

Table 3 Clinical Pain Measures for TMD Patients*

	TMD females	Values from Sarlani et al[34]	*t* test	*P* value
Duration of pain (mo)	98.3 ± 22.2	48.2 ± 12.3	–1.87	.07
Average pain intensity in previous 3 mo	5.9 ± .4	5.5 ± 0.3	–0.72	.47
Average frequency of pain in previous 3 mo	5.1 ± .3	4.5 ± .4	–1.31	.20
Painless opening (mm)	28.8 ± 1.7	40.2 ± 1.1	5.47	< .01
Maximum assisted opening	43.8 ± 5.1	48.1 ± 4.2	3.34	< .01
Total palpation score	36.7 ± 3.1	23.3 ± 2.7	–3.21	< .01
Number of total painful body sites (possible sites 0–9)	4.7 ± 2.0	4.8 ± 0.3	0.22	.83
Total body pain score	13.2 ± 1.1	12.6 ± 1.4	–0.36	.72
Insomnia	9.5 ± 1.2	4.9 ± 4.1	–3.26	< .01
Trait anxiety	36.0 ± 1.7	38.2 ± 2.0	0.83	.41
State anxiety	31.1 ± 1.2	31.0 ± 1.4	–0.1	.96
BPI severity	4.0 ± 1.8	n/a	n/a	n/a
BPI interference	3.0 ± 2.2	n/a	n/a	n/a

*Each value represents the mean ± standard error.
BPI, Brief Pain Inventory.

Conditioned Modulation of Pain

The average conditioning bath temperature for healthy subjects was 10°C (range: 5°C to 16.5°C). The average conditioning bath temperature for TMD patients was 11.9°C (range: 8°C to 15.5°C). There was a significant difference in bath temperatures used for healthy controls and TMD patients in the CPM protocol ($t = –2.62$, $P = .01$). However, the pain ratings evoked by the cold baths were comparable for the two groups: TMD group mean = 51, SD = 12.6; control group mean = 49, SD = 11.3; $t = –0.65$, $P = .52$.

Both the women with TMD and healthy women showed reduced TS during exposure to the noxious cold conditioning stimulus, compared to the neutral-temperature conditioning stimulus ($F = 15.2$, $P < .01$). The mean reduction in TS was 3.5 (SE = 1.3) for healthy women and 7.9 (SE = 2.0) for female TMD patients (Fig 3). However, this did not constitute a significant difference in CPM between the two groups, as indicated by the nonsignificant bath x group interaction ($F = 2.2$, $P = .14$). Additionally, there was no significant relationship between cold bath ratings and reduction in TS for either group: $r = –0.16$, $P = .39$ for control group; $r = –0.06$, $P = .78$ for TMD group.

Discussion

This study investigated TMD case-control differences in CPM, and whether they are related to TS. The authors' previous work demonstrated that female TMD patients exhibit enhanced TS of pain upon repetitive mechanical stimulation of the fingers, compared to healthy controls, suggestive of widespread up-regulated central nociceptive processing in this patient population.[7] In contrast, the current study found no significant difference in the magnitude of TS for pain-free controls and TMD patients, and the magnitude of CPM was comparable for healthy and TMD groups.

Temporal Summation of Pain

Previous studies comparing the pain sensitivity of women with and without TMD reported greater pain sensitivity,[7,27,39] and more pronounced TS of pain in TMD patients. This greater sensitivity to experimentally induced pain has been observed in various body sites, not just the symptomatic areas of the cranium.[5,6,8]

However, results of a recent study by Raphael et al failed to demonstrate significant differences in TS between TMD cases and TMD-free controls.[39] Similarly, the results of the present study indicate no significant difference in TS of pain between TMD patients and controls. This result conflicts with the authors' previous study using similar stimuli and protocols, in which statistically significant group differences in TS were observed.[7] One consideration is whether the groups of TMD patients differed in some way between these two studies. One could propose that if the group of TMD patients in the current study were milder cases, they may not differ from healthy control subjects to the same extent as more severe cases. Considering the clinical measures

that were common to the two studies (Table 3), the group of TMD cases for the current study were more severe cases on average than those of the previous study. Therefore, the difference in results cannot easily be attributed to differences in case severity.

There is a protocol difference between the two studies, related to training, which may be relevant to this. In the previous study, nearly all the training prior to the TS testing consisted of stimulus series that were either the same intensity (practice with the TS protocol) or increasing steps of intensity (determining threshold). In the design of the current study, the authors considered that such training could imbue the subject with an expectancy of always experiencing stimulus trains of increasing intensity. This might have been particularly important in the current study, where training and testing were conducted in the same session, in contrast to the earlier study. Thus, in an attempt to lessen potential bias in the expectation of increasing pain with successive stimuli, the current study added series of stimuli intensities in a random sequence during the training session. This difference could explain the decrease in pain ratings for both the TMD patients and the TMD-free controls observed in the current study, and it may be the reason for the failure to replicate significant differences in TS between the two groups. If this post-hoc explanation is correct, it would also suggest that the hypothesized biasing effect was more influential on TMD cases, leading to significant group differences when present (previous study[7]) but failing to show significant differences when not present (current study).

One consideration is whether the current results could have failed to reveal a true difference due to a small sample size. Indeed, a recent large-scale study including 185 TMD cases and 1,633 TMD-free controls found a highly significant group difference in mechanically evoked TS of pain.[8] This is unlikely the reason for the results reported here, as the earlier study[7] found significant group differences in mechanically evoked TS with even fewer subjects.

Conditioned Pain Modulation

King et al have reported that individuals with TMD have a deficit in pain inhibition, in the context of an experimental CPM protocol.[27] In fact, King et al reported that the conditioning stimulus resulted in an increase in pain for the TMD cases, rather than the expected decrease. In contrast, the present study found that both the women with TMD and healthy women exhibited reduced TS in the presence of the noxious cold conditioning stimulus, without a significant difference in CPM between the groups. Indeed, there was not even a trend towards the TMD group showing weaker CPM (Fig 3). The explanation for these disparate results is not apparent. Clearly, more studies of this type are needed to clarify the issue of endogenous analgesic function in chronic TMD. However, at the minimum, the current study indicates that painful TMD is not necessarily associated with a compromised ability to engage the endogenous analgesic system in an experimental setting.

Conclusions

This study failed to find the expected greater TS of pain and reduced CPM in women with TMD relative to groups of healthy controls. In contrast to the authors' previous study, which found significantly greater TS for TMD women,[5] the training period included series of randomly sequenced stimuli intensities, intending to lessen bias in the expectation of ever-increasing pain with successive stimuli. This change in protocol could explain the decrease in TS for both the TMD patients and the TMD-free controls observed in the current study relative to the previous study. Additionally, the finding of a significant CPM effect which was not different for the two groups indicates that painful chronic TMD is not necessarily associated with a compromised ability to engage the endogenous analgesic system in an experimental setting.

Acknowledgments

This study was supported by NIH grant PSO-AR49555 and PHG was partially supported by NIH/NIDCR T32 DE007309 Training Program in Oral and Craniofacial Biology. The authors wish to acknowledge the assistance of Mr Michael Keaser for his assistance in the statistical analysis. The authors reported no conflict of interest related to this study.

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