Evidence for Up-regulated Central Nociceptive Processing in Patients with Masticatory Myofascial Pain

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Aims: *Previous work suggests that hyperexcitability of central nociceptive neurons may play a role in the pain of temporomandibular disorders (TMD). The aim of this study was to test this theory by assessing differences, between myalgic TMD patients and pain-free controls, in temporal summation of mechanically evoked pain and aftersensations following repetitive noxious stimulation.* ***Methods:*** *Sixteen series of 10 repetitive, mildly noxious mechanical stimuli were applied to the fingers of 25 female TMD patients with masticatory myofascial pain and 25 age-matched, pain-free female subjects. All subjects rated the pain intensity and unpleasantness evoked by the first, fifth, and tenth stimuli in the series and their aftersensations at 15 seconds and 1 minute following the last stimulus. Data were analyzed by 3-way repeated-measures analysis of variance.* ***Results:*** *Pain and unpleasantness ratings increased with repetition of the stimulation ($P < .0001$). In addition, there was a significant trial number × group interaction for the pain intensity ratings, such that TMD patients provided higher ratings than controls for the tenth stimulus ($P < .001$). The increase in unpleasantness ratings with repetitive stimulation was also higher for the patient group ($P < .0001$). Moreover, TMD patients rated the intensity of aftersensations as higher ($P < .005$) and reported painful aftersensations at significantly greater frequency ($P < .05$).* ***Conclusion:*** *A generalized hyperexcitability of central nociceptive processing in this TMD patient group is indicated by their more pronounced temporal summation of pain and greater aftersensations following repetitive noxious digital stimulation versus controls. Such hyperexcitability may contribute to the pathophysiology of TMD pain.* J OROFAC PAIN 2004;18:41–55.

Key words: myofascial pain syndromes, pain thresholds, temporal summation, temporomandibular disorders, wind-up

Temporomandibular disorders (TMD) constitute the most common cause of chronic pain in the orofacial region.[1] Pain in the masticatory muscles, the temporomandibular joints (TMJs), and the associated structures is the most frequent presenting symptom of TMD[2] as well as the main symptom that motivates patients to seek treatment.[3] TMD-related pain is typically chronic and fluctuating and does not correlate well with specific physical pathology.[4,5] Despite extensive research in the past few decades, the pathophysiology of TMD-related chronic muscle pain remains unknown.

As would be expected, pressure pain thresholds (PPTs) are lower in the masticatory muscles of myogenous TMD patients than in healthy controls.[6–8] Moreover, several studies have

reported that TMD patients exhibit greater sensitivity to experimentally induced pain than pain-free controls, not only in the affected area, but also in various remote bodily sites, suggesting a generalized up-regulation of nociceptive input processing in this patient population (for review, see Sarlani and Greenspan[9]). In addition, Maixner et al[10] reported that TMD patients with a myogenous component exhibit more pronounced temporal summation of pain upon repetitive noxious heat stimulation of their hands than control subjects.

Temporal summation of pain is the augmentation of perceived pain intensity upon repetitive noxious stimulation of constant intensity, at a frequency greater than 0.2 to 0.3 Hz. It is regarded as the psychophysical correlate of wind-up.[11] Wind-up is the increase in the magnitude of the second-order nociceptive neurons' responses when repetitive noxious stimuli of constant strength are applied at a frequency higher than 0.33 Hz.[12,13] Several lines of evidence strongly suggest that wind-up and temporal summation of pain are centrally mediated.[14–19] Accordingly, greater temporal summation of pain in TMD patients would indicate a generalized hyperexcitability in their central nociceptive processing.

The aim of this study was to test this theory by assessing differences between TMD patients with myofascial pain and controls in temporal summation of mechanically evoked pain and aftersensations following repetitive noxious stimulation of the fingers. Both the sensory and the affective dimensions of the painful sensations were measured. Moreover, the frequency-dependent profile of temporal summation of pain was evaluated.

Materials and Methods

Subjects

Twenty-five myalgic TMD female patients and 25 age-matched, pain-free women participated in the present study. Each patient was age-matched with a pain-free woman who was no more than 3 years younger or older. The mean age of the patients was 38.9 years (age range: 21 to 57 years), and the mean age of the pain-free women was 38.8 years (age range: 23 to 58 years). Eight TMD patients and 4 pain-free women were taking oral contraceptives. Three of the 7 postmenopausal patients and 1 of the 9 postmenopausal pain-free controls were receiving hormone replacement therapy. The TMD patients were recruited from the Brotman Facial Pain Center of the University of Maryland, Baltimore, and the pain-free women were recruited from the University of Maryland campus. The subjects were unaware of 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 (IRBPHS) of the University of Maryland.

The exclusion criteria for all subjects included serious injury to the left hand at any time, systemic rheumatic diseases (such as systemic lupus erythematosus or rheumatoid or psoriatic arthritis), vascular disorders (such as giant cell arteritis), neurologic disorders (such as multiple sclerosis or trigeminal neuralgia), neoplasia, pregnancy, and self-report of substance abuse. In addition, pain-free 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 bodily part.

The main inclusion criterion for the TMD patient group in this study was a primary diagnosis of masticatory myofascial pain, according to the Research Diagnostic Criteria for Temporomandibular Disorders.[3] Masticatory myofascial pain involves pain originating from the jaw, temples, face, or around 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. Moreover, patients participated in the study only if they reported a duration of myofascial pain longer than 3 months, a frequency of myofascial pain of at least 2 days per week, and an average pain intensity greater than 2 on a scale of 0 to 10, where 0 was "no pain" and 10 was "pain as bad as could be." TMD patients were excluded if they reported that their pain was the result of acute trauma or infection, or if they were diagnosed with degenerative joint disease and/or disc displacement without reduction.

All subjects agreed to abstain from narcotic analgesics, nonsteroidal anti-inflammatory drugs, acetaminophen, and muscle relaxants for a minimum of 2 days prior to each experimental session. Normally cycling female subjects underwent temporal summation testing between the fifth and ninth day of their menstrual cycle to diminish the fluctuation of the gonadal steroid hormones as a possible influence on the responses to noxious stimulation.[20]

Experimental Design

All subjects participated in 2 experimental sessions, each lasting 60 to 90 minutes. The 2 sessions were separated by at least 1 day. During the first session, a medical/dental history and a clinical examination were carried out to determine whether the subject fulfilled the criteria for inclusion in the study. In addition, the subject's mechanical pain threshold was assessed. Finally, the subject was introduced to the testing procedures to be used in the second session and was trained until she became familiar with these procedures. During the second session, the temporal summation of mechanically evoked pain was assessed by the delivery of repetitive noxious mechanical stimuli at various frequencies. Moreover, aftersensations following the series of repetitive stimuli were evaluated.

History and Clinical Examination

During the first session, each subject underwent a medical/dental history, including current medications, and a clinical examination. The latter assessed: *(1)* joint function, *(2)* sensitivity of the TMJs and the masticatory muscles bilaterally to finger palpation, and *(3)* joint sounds. The following sites were palpated: temporalis muscle (anterior, middle, posterior, tendon); masseter muscle (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 1 kg of pressure for the extraoral muscles and approximately 0.5 kg of pressure 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.

For the TMD patients, the vertical range of motion of the mandible and the sensitivity of the TMJ and the masticatory muscles to palpation were also assessed during the second session, immediately before the temporal summation testing. Moreover, at the beginning of both sessions, TMD patients rated on visual analog scales (VASs) their current facial pain intensity and unpleasantness, as well as the average pain intensity and unpleasantness, the worst pain intensity, and the percentage of waking time that facial pain was present in the previous week. All subject evaluations were performed by the same person.

During the second session, prior to data collection, all subjects completed the Beck Depression Inventory and the State-Trait Anxiety Inventory. Finally, during both sessions, all subjects indicated on a numeric scale (range of 0 to 5, where 0 represented "not at all" and 5 "extremely") how much they had been distressed by pain in various bodily sites in the previous month. A total body pain score was obtained for each subject by summing the pain ratings of all bodily sites.

Mechanical Stimulation

Mechanical stimuli were applied with a computer-controlled linear motor (Neurologic) under force-feedback regulation (model 501 motor controller; Biocommunication Electronics). A stainless steel probe with a circular contact surface of 0.245 mm^2 was affixed to the tip of the stimulator, and brief mechanical stimuli were applied to the dorsal surface of the middle phalanx 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.[21]

During the sensory testing sessions, each subject was seated comfortably on a chair with the left arm resting on a table. The left hand was supported, palm 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 her left hand during the experiment.

Pain Threshold Estimation

During the first experimental session, each subject's mechanical pain threshold was determined with a classic ascending method of limits protocol.[21,22] Stimuli consisted of 23 set forces, ranging from 10 to 150 g (98 mN to 1.47 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 interstimulus interval 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 test site by at least 10 mm 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 or not this stimulus was painful. 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 10 g, and successive stimuli were increased by increments of 20 g. This resulted in a gross estimation of the subject's pain threshold. For the remaining 7 to 8 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 ascending series was terminated when the subject provided 2 or 3 pain reports or when the largest force (150 g) was delivered. The pain threshold was estimated as the midpoint of the last stimulus reported as nonpainful and the first stimulus perceived as painful.

Experimental Protocol for Temporal Summation Testing

During the second experimental session, the subjects were tested with 16 series of 10 repetitive stimuli (10 trials) each at an intensity of 1.25 times the individual subject's pain threshold. As before, 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. To investigate the effect of the stimulation frequency on the temporal summation, the interstimulus interval (ISI) was varied across series of stimuli (2, 5, 10, and 20 seconds). Each ISI was presented to the subject 4 times. The presentation order of the various ISIs was randomized across the session. Successive series of stimulation were applied to different fingers. 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.[23,24] Moreover, each stimulation series was delivered to a previously unstimulated site of the skin. The subjects were told that pain intensity and unpleasantness might increase, decrease, or stay the same with repetition of the stimulation. Visual inspection of the skin following the repetitive noxious stimulation revealed dimpling of the skin but no signs of injury or erythema.

Pain, Unpleasantness, and Aftersensation Ratings

During the second session, the subjects rated the perceived pain intensity evoked by the first, fifth, and tenth stimuli in a series on a 10-cm VAS anchored with "no pain sensation" on the left end and "most intense pain sensation imaginable" on the right end. During other series, they rated the unpleasantness evoked by the first, fifth, and tenth stimuli on a 10-cm VAS anchored with "not at all unpleasant" on the left end and "most unpleasant imaginable" on the right end. The conceptual distinction between pain intensity and unpleasantness was clarified for the subjects by the use of the instructions published by Price et al.[25] Prior to data collection, the subjects were trained until they became familiarized with the rating procedure and reported that they were able to distinguish between pain intensity and unpleasantness.

The subjects were asked to rate the perceived pain intensity during 8 series of stimulation, and the unpleasantness during another 8 series in the session. Each ISI was presented twice in each group of 8 series. The subjects were cued about the initiation of a new series of stimuli 5 seconds before the first stimulus was delivered. Moreover, after the fourth or ninth stimulus, an auditory cue was given to signal that the fifth or tenth stimulus, respectively, would follow. In this way the subjects were able to focus their attention on their sensations without having to count the stimuli. Half the subjects rated the pain intensity first, and half rated the unpleasantness first.

At 15 seconds and 1 minute after the end of each of the stimulation series, the subjects were cued by auditory signals to report any lingering sensations. They provided qualitative verbal descriptors and reported whether or not the sensation was painful. Following the series in which the pain intensity was rated, the subjects rated the intensity of the aftersensations on VAS. If the aftersensation was not painful, they rated its intensity on a VAS that was anchored with "no sensation" on the left end and "the most intense sensation imaginable" on the right end. If the sensation was painful, the subjects rated its intensity on a VAS that was anchored with "no pain sensation" on the left end and "most intense pain sensation imaginable" on the right end. Similarly, following the series during which the pain unpleasantness was rated, the subjects rated the unpleasantness of their aftersensations on a VAS anchored with "not at all unpleasant" on the left end and "most unpleasant imaginable" on the right end.

Statistical Analysis

Group differences in the mechanically evoked pain thresholds, the various psychologic indices, and the general group characteristics were determined by the use of the Student *t* test or the Mann-Whitney rank sum test, where appropriate. A

Table 1 Description of the Populations Studied (Means ± SEMs)

	TMD (n = 25)	Controls (n = 25)
Age	38.90 ± 2.36	38.80 ± 2.29
No. of painful sites	4.81 ± 0.32	1.56 ± 0.21**
Total body pain score	12.56 + 1.44	1.72 ± 0.27**
Painless jaw opening (mm)	40.20 ± 1.07	47.68 ± 1.13**
Maximum assisted jaw opening	48.20 ± 0.91	50.48 ± 1.14
Depression	7.96 ± 1.21	5.08 ± 0.11*
Trait anxiety	38.20 ± 1.97	34.00 ± 1.35*
State anxiety	33.28 ± 1.69	31.76 ± 1.37

*$P < .1$; **$P < .001$ (t test, with the exception of "pain sites," where Mann-Whitney test was used).

Table 2 Characteristics of Patients' Facial Pain (Means ± SEMs)

Characteristics	Value
Duration of pain (mo)	48.18 ± 12.34
Current pain intensity	2.15 ± 0.46
Current pain unpleasantness	2.27 ± 0.55
Average pain intensity previous week	3.82 ± 0.35
Average pain unpleasantness previous week	3.86 ± 0.45
Worst pain intensity previous week	5.58 ± 0.41
Percent of time pain present previous week	37.90 ± 4.90
No. of sensitive palpation sites (possible range: 0–24)	13.08 ± 1.10
Total palpation score (possible range: 0–72)	23.28 ± 2.68

3-way, mixed-model, repeated-measures analysis of variance (ANOVA) was used to assess group differences in various dependent variables, including the pain intensity and unpleasantness ratings of the repetitive noxious stimuli, the intensity and unpleasantness ratings of the aftersensations, and the frequency of painful aftersensations. Post hoc comparisons were made with the Newman-Keuls test. Pearson correlations were carried out to examine the relationship between temporal summation, age, characteristics of clinical pain, and psychologic variables in each of the 2 groups. Significance was accepted at $P < .05$.

Results

General Characteristics of the Study Populations

The general characteristics and the psychologic variables for the test groups are presented in Table 1. There was no age difference between groups. The TMD patients had a significantly smaller painless mandibular opening compared to the control subjects, while no significant difference was detected between the 2 groups in the maximum assisted mandibular opening. TMD patients exhibited a significantly higher number of painful body sites and a significantly greater total body pain score versus control subjects. There was a tendency toward greater depression and trait anxiety scores in patients compared to pain-free subjects, but this trend did not reach statistical significance. No significant differences were detected between the groups in state anxiety measures.

The TMD patients' facial pain characteristics are shown in Table 2. The VAS ratings of average pain intensity and unpleasantness, worst pain intensity, and percentage of time that pain was present in the previous week were averaged across sessions for TMD subjects and then averaged across subjects. The pain intensity and unpleasantness ratings shown in Table 2 represent the VAS scores that were obtained immediately before temporal summation testing.

Mechanical Pain Thresholds

The pain-free subjects' mean mechanical pain threshold was 91.3 g (SD 19.9), while the patients' mean mechanical pain threshold was 76.5 (SD 21.7). The difference between these pain thresholds was statistically significant ($t = 2.513$; $P = .015$).

Temporal Summation of Pain Intensity Ratings

Stimuli for temporal summation testing were administered at intensities of 1.25× each individual subject's pain threshold. More specifically, the mean stimulus intensity for temporal summation testing was 95 g for TMD patients and 114 g for healthy controls. Pain intensity ratings increased significantly with stimulus repetition for both the patient group and the pain-free group (Table 3; Fig 1a). Overall, the averaged pain intensity ratings for the fifth and tenth stimuli were significantly greater than those for the first stimulus when the ISI in the series of repetitive stimulation was 2 or 5 seconds ($P < .0001$). Also, for the same ISIs, the averaged pain responses corresponding to the tenth stimulus were significantly greater than those provided for the fifth stimulus ($P < .0001$).

The stimulation frequency had a significant effect on temporal summation of pain (Table 3). There was a significant trial number × ISI interaction (Table 3). Stimulation frequency had an effect on the pain ratings for the fifth and tenth stimuli

Table 3 Summary of ANOVA of Pain Intensity Ratings

Factor	df	F	*P*
Main ANOVA results*			
Between subjects			
Group	1	1.54	.2204
Within subjects			
Trial no.	2	42.07	< .0001
ISI	3	26.76	< .0001
Interactions			
Group/trial no.	2	3.71	.0280
Trial no./ISI	6	45.03	< .0001
Group/trial no./ISI	6	1.99	.0669

*All other interactions were not statistically significant.

Table 4 Summary of ANOVA of Unpleasantness Ratings

Factor	df	F	*P*
Main ANOVA results*			
Between subjects			
Group	1	1.53	.2223
Within subjects			
Trial no.	2	28.87	< .0001
ISI	3	20.31	< .0001
Interactions			
Trial no./ISI	6	30.80	< .0001
Group/trial no./ISI	6	2.14	.0485

*All other interactions were not statistically significant.

but not for the first stimulus in the series (Fig 1a). Higher average pain ratings were provided for the fifth ($P < .05$) and tenth stimuli ($P < .0001$) at an ISI of 2 seconds as compared to 5 seconds; however, this difference was largely attributable to the patient group (Fig 1a).

The group × trial number interaction was statistically significant, while the 3-way interaction (group × trial number × ISI) fell just short of statistical significance (Table 3). Post hoc tests indicated that patients exhibited significant temporal summation at ISIs of 2, 5, and 10 seconds ($P < .005$), while pain-free controls showed significant increases in their pain intensity ratings at ISIs of 2 and 5 seconds ($P < .0001$; Fig 1a). Patients and pain-free controls provided comparable pain intensity ratings for the first stimulus in the series, for all stimulation frequencies. However, patients provided significantly higher pain intensity ratings than pain-free controls for the tenth stimulus in the series at ISIs of 2, 5, and 10 seconds ($P < .005$; Fig 1a).

Temporal Summation of Unpleasantness Ratings

Unpleasantness ratings also increased significantly with repetition of the stimulation (Table 4; Fig 1b). The same trend appeared here as with pain intensity, but in this case, the 3-way interaction was statistically significant. For the patient group, significant temporal summation of the unpleasantness ratings was observed at ISIs of 2 and 5 seconds ($P < .0001$) as well as 10 seconds ($P < .05$); temporal summation at 2 and 5 seconds was significantly higher than that at 10 seconds ($P < .0001$; Fig 1b). Control subjects provided greater averaged unpleasantness ratings for the fifth ($P < .05$) and tenth ($P < .0001$) stimuli as compared to the first stimulus in the series of repetitive stimulation at ISIs of 2 and 5 seconds (Fig 1b). For both groups, temporal summation for a 2-second ISI was comparable to that seen for a 5-second ISI (Fig 1b).

No significant group difference in the averaged unpleasantness ratings for the first stimulus in the series was detected for any of the stimulation frequencies. However, patients provided greater unpleasantness ratings for the tenth stimulus than pain-free controls at ISIs of 2 and 5 seconds ($P < .0001$) as well as 10 seconds ($P < .05$; Fig 1b).

Aftersensation Intensity Ratings

Patients provided higher aftersensation intensity ratings than healthy controls following repetitive stimulation at all ISIs (Fig 2). There was a significant main effect for sequence—namely, higher intensity ratings were provided at 15 seconds as compared to 1 minute after the end of the repetitive noxious stimulation (Table 5; Fig 2). For the patients, aftersensation intensity ratings were greater following stimulation at higher frequencies as compared to lower frequencies (Fig 2).

Aftersensation Unpleasantness Ratings

No significant group difference was detected for the unpleasantness of aftersensations (Table 6, Fig 3). Higher unpleasantness ratings were provided at 15 seconds as compared to 1 minute after the end of the repetitive noxious stimulation (Table 6; Fig 3). In addition, the aftersensation unpleasantness ratings were greater following stimulation at higher frequencies as compared to lower frequencies (Table 6; Fig 3).

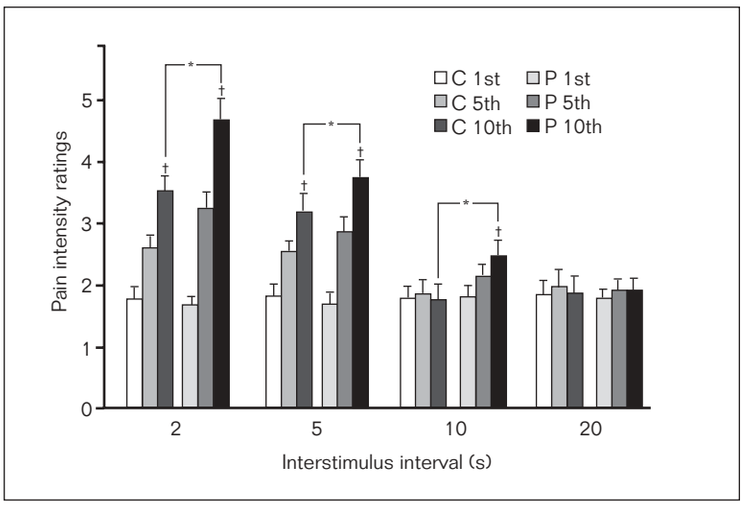


Fig 1a Mean pain intensity ratings in response to the first, fifth, and tenth stimuli in a series of 10 stimuli by healthy controls (C) and TMD patients (P). Error bars indicate standard error of the mean (SEM). Selected significant relationships are depicted on the figure. *Significant group differences ($P < .005$). †Significant temporal summation ($P < .005$).

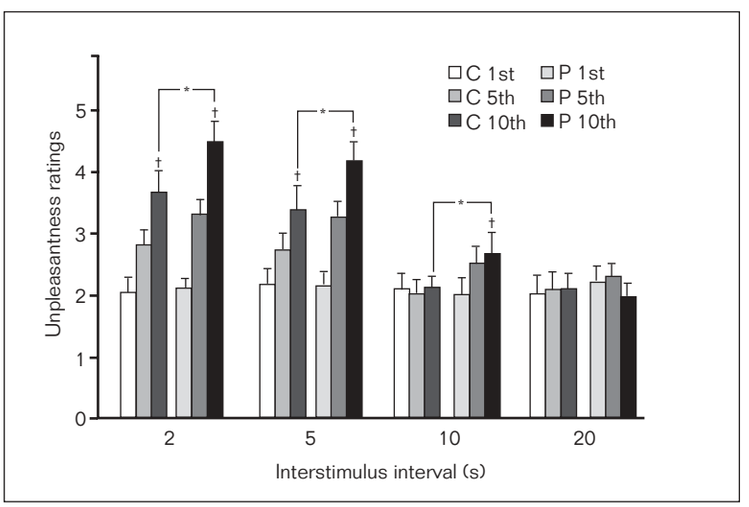


Fig 1b Mean unpleasantness ratings in response to the first, fifth, and tenth stimuli in a series of 10 stimuli by healthy controls (C) and TMD patients (P). Error bars indicate standard error of the mean (SEM). Selected significant relationships are depicted on the figure. *Significant group differences ($P < .05$). †Significant temporal summation ($P < .05$).

Frequency and Quality of Aftersensations

Early aftersensations were reported in 76% of the trials by patients and 67% of the trials by pain-free controls. Late aftersensations were reported in 49% of the trials by patients and 36% of the trials by pain-free controls. There was no significant group difference in the reporting frequency of aftersensations.

The most common words used by the patients to describe their early aftersensations were "tender" (39%), "aching" (21.5%), and "stinging" (21.5%). For the pain-free subjects, the most common words were "tender" (22.3%), "tingle" (17%), and "stinging" (9%). Words closely associated with nociception, such as "tender," "aching," "throbbing," "burning," and "stinging," were used to describe early aftersensations in 23.5% of the trials by the patients and 9.45% of the trials by the pain-free women. TMD patients perceived painful early and late aftersensations in a significantly higher number of trials than pain-free subjects (Table 7; Fig 4).

Relationships Among Temporal Summation, Clinical Pain, and Psychologic Variables

For both groups, depression was significantly correlated with trait anxiety (r = 0.478; $P = .016$) and state anxiety (r = 0.478; $P = .016$), and trait anxiety was significantly correlated with state anxiety (r = 0.478; $P = .016$).

Pain-free Subjects. There were no statistically significant correlations between temporal summation of pain at an ISI of 2 seconds and the number of painful sites or total body pain score among pain-free subjects. In addition, temporal summation did not correlate significantly with age or with any of

Table 5 Summary of ANOVA of Aftersensation Intensity Ratings

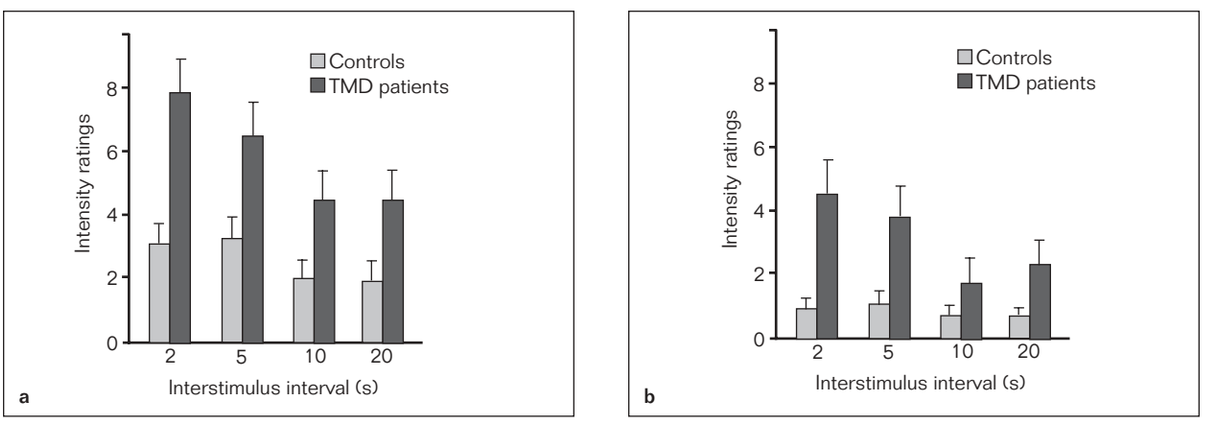
Factor	df	F	*P*
Main ANOVA results*			
Between subjects			
Group	1	8.77	.0047
Within subjects			
Sequence	1	54.55	< .0001
ISI	3	13.13	< .0001
Interactions			
Group/ISI	3	4.69	.0037

*All other interactions were not statistically significant.

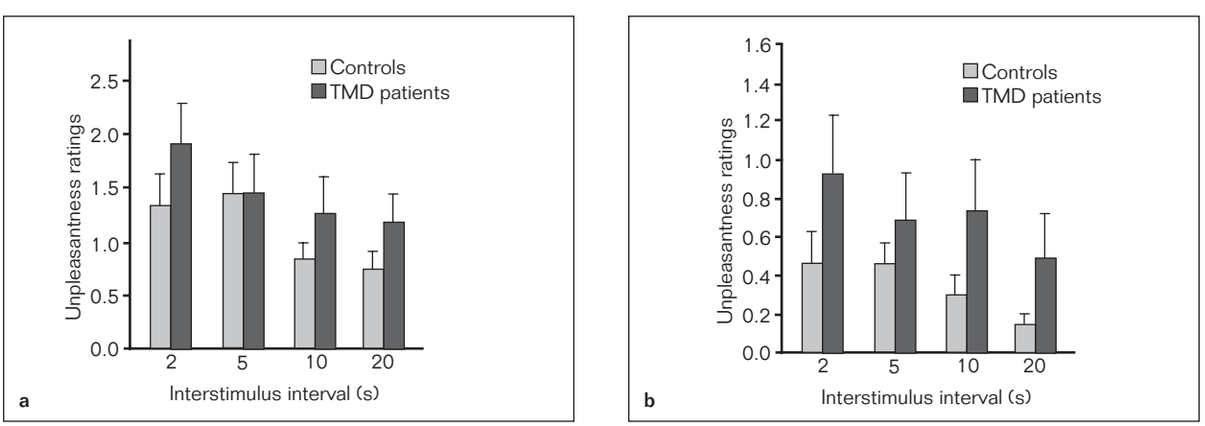
Table 6 Summary of ANOVA of Aftersensation Unpleasantness Ratings

Factor	df	F	*P*
Main ANOVA results*			
Between subjects			
Group	1	1.47	.2309
Within subjects			
Sequence	1	60.16	< .0001
ISI	3	6.75	.0003
Interactions			
ISI/sequence	3	2.88	.0382

*All other interactions were not statistically significant.



Figs 2a and 2b Mean intensity ratings of aftersensations at *(a)* 15 seconds and *(b)* 1 minute after the end of repetitive noxious stimulation at various interstimulus intervals. Error bars indicate standard error of the mean (SEM).



Figs 3a and 3b Mean unpleasantness ratings of aftersensations at *(a)* 15 seconds and *(b)* 1 minute after the end of repetitive noxious stimulation at various interstimulus intervals. Error bars indicate standard error of the mean (SEM).

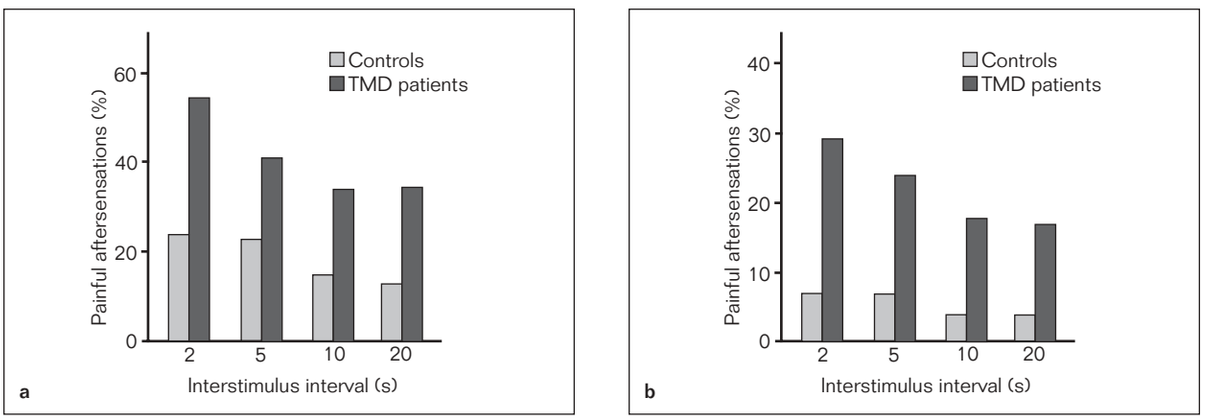
the psychologic variables. The number of painful sites in the previous month correlated significantly with the trait anxiety score (r = 0.532; *P* = .006), while the total body pain score correlated significantly with the depression score (r = 0.567; *P* = .003) and the trait anxiety score (r = 0.494; *P* = .012).

TMD Patients. The temporal summation of pain ratings at an ISI of 2 seconds was not significantly correlated with the number of painful sites in the previous month, the total body pain score, the total palpation pain score, the painless mandibular opening, or the VAS ratings of current pain intensity and average pain intensity in the previous

Table 7 Summary of ANOVA of Frequency of Painful Aftersensations

Factor	df	F	*P*
Main ANOVA results*			
Between subjects			
Group	1	5.47	.0236
Within subjects			
Sequence	1	38.86	< .0001
ISI	3	12.22	< .0001

*No interactions were statistically significant.



Figs 4a and 4b Percentage of painful aftersensations at *(a)* 15 seconds and *(b)* 1 minute after the end of repetitive noxious stimulation at various interstimulus intervals.

week. No significant correlation was detected between temporal summation and age. Temporal summation of pain correlated significantly with state anxiety score (r = 0.478; *P* = .016). The number of painful body sites in the previous month correlated with the average facial pain in the previous week (r = 0.599; *P* = .002). The total body pain score was positively correlated with the average facial pain in the previous week (r = 0.770; *P* < .001) and negatively correlated with the amount of painless opening (r = –0.411; *P* = .041). The average facial pain in the previous week was positively correlated with the total pain palpation score (r = 0.478; *P* = .014) and negatively correlated with the amount of painless opening (r = –0.498; *P* = .011).

Discussion

The present study investigated differences between myalgic TMD patients and pain-free controls in mechanically evoked pain thresholds, temporal summation of mechanically evoked pain, and aftersensations following repetitive noxious mechanical stimulation. The intensity of stimulation for the investigation of temporal summation was set at 1.25× each individual subject's pain threshold, so that all the subjects perceived the first stimulus in the series of repetitive stimuli as mildly painful. Thus, changes in pain intensity could be measured without concern about a "floor effect" following an initially nonpainful stimulus. Moreover, this design made feasible the meaningful comparison of temporal summation per se between groups, since the observed differences involved an increase in pain, starting from a similar perceptual magnitude.

Sensitivity of TMD Patients to Experimental Pain: Implications for the Pathophysiology of TMD

In the TMD group, the unassisted and maximum assisted mouth opening, average and worst pain intensity, pain at multiple body sites, and percentage of time that pain was present in the previous

week were in general comparable to previous reports.[10,26,27] TMD patients consistently exhibit lower PPTs in their masticatory muscles than healthy controls.[6–8] Moreover, the present investigation demonstrated that the mechanical pain threshold of the digits was significantly lower in female TMD patients than pain-free female subjects. This finding is in agreement with several studies reporting that this patient group exhibits lower pain thresholds in bodily areas outside the craniofacial region.[10,26–31] However, a comparable number of studies have failed to detect a significant difference between TMD patients and controls in pain thresholds, in response to noxious stimulation in sites outside the trigeminal region.[32–37] Nevertheless, all but one[38] of the studies that found a significant group difference reported lower pain thresholds among TMD patients, indicating a generalized up-regulation in the processing of nociceptive input among this patient population.

Paradigms that employ tonic or repetitive noxious stimulation may be more efficient in revealing hypersensitivity to laboratory-evoked pain among TMD patients.[27] The present study delivered repetitive noxious mechanical stimulation to the fingers and showed that temporal summation of pain intensity and unpleasantness is significantly more pronounced in myalgic TMD patients compared to pain-free controls. This result is consistent with a previous study, which suggested that temporal summation to repetitive noxious heat stimuli applied to the palm of the hand is significantly greater in TMD patients with a myogenous component than in control subjects.[10] Temporal summation of pain has a central basis and reflects a transient increase in the excitability of the nociceptive neurons in the central nervous system (CNS).[11] Accordingly, greater temporal summation in response to repetitive noxious stimulation on the hand of TMD patients with myofascial pain provides evidence for a generalized hyperexcitability in their CNS nociceptive processing regions. Supporting this theory, the present investigation showed that pain intensity and unpleasantness increased significantly with repetitive stimulation in myalgic TMD patients at a longer ISI (10 seconds) that did not evoke significant temporal summation of pain or unpleasantness in healthy individuals. This finding indicates that in the patient group, the central nociceptive neurons exhibit more prolonged postdischarge responses, which is consistent with augmented excitability. As further evidence for this theory, it was demonstrated that the magnitude of aftersensations that lingered well beyond the last stimulus in the series of repetitive stimuli was significantly higher in the patient group. Moreover, these aftersensations were more frequently painful among the patient population.

Hyperexcitability of the central nociceptive pathways may constitute an etiologic factor accounting for the development and maintenance of various chronic pain conditions.[39,40] In animal studies, sensitization of the central nociceptive neurons, manifesting as a decrease in their thresholds, an expansion of their receptive fields, and augmented responses to suprathreshold stimuli, correlates well with behavioral manifestations of persistent pain, allodynia, and hyperalgesia.[41] Hyperexcitability of these neurons may constitute an underlying pathophysiologic basis of TMD, since up-regulated central processing of nociceptive input might increase the probability of clinical pain when relatively low-level activity from nociceptive afferents enters the CNS. It is suggested that the high-density innervation of the orofacial region and the constant function of the orofacial apparatus could account for the development of pain specifically in the masticatory muscles and the TMJs, in the presence of a generalized hyperexcitability in central nociceptive neurons.[26] Moreover, generalized hyperexcitability could result in amplification of minimal nociceptive input arising from undetectable microscopic peripheral damage or low-level inflammation in the masticatory muscles.

Several lines of evidence suggest that peripheral pathology is not a crucial determinant of pain in TMD patients. First, myogenous TMD patients 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 the range of mandibular motion and number of joint sounds.[4,5] Moreover, there are no gender differences in the predominance of signs of masticatory system dysfunction, despite the greater prevalence of TMD among women.[42] The present study demonstrated that TMD patients reported pain in a significantly greater number of bodily sites compared to controls, which is consistent with the theory that input to central nociceptive pathways is abnormally processed in TMD patients. This finding is in agreement with several studies reporting widespread pain in TMD patients.[27,43–45]

Generalized up-regulation of CNS responsiveness to aversive stimulation may constitute a pathophysiologic mechanism contributing to myofascial pain in only a subset of TMD patients.

Accordingly, it could conceivably constitute a differentiating factor between TMD patients with pain limited to the masticatory system and TMD patients with widespread pain. Differences in patient populations across studies may account for inconsistent results in terms of detecting evidence of generalized hypersensitivity to experimentally induced pain in TMD patients. The present study demonstrated more pronounced temporal summation of pain and greater aftersensations following repetitive noxious stimulation, in an area remote to the face and head, in a group of myalgic TMD patients, many of whom exhibited pain in multiple sites. All patients reported pain in more than 1 site in the previous month, and 19 of 25 patients complained of pain in more than 3 bodily sites. Further studies comparing the generalized sensitivity to noxious experimental stimulation in TMD patients with pain limited to the craniofacial region and in TMD patients with widespread pain would reveal whether central pathophysiologic mechanisms predominantly concern the latter group.

Pathophysiology of TMD as Related to Other Chronic Pain Conditions

The characteristics of TMD pain, including intensity, duration, and temporal pattern, as well as the psychosocial distress measures in TMD patients, are comparable to those in patients with other common chronic pain conditions, including headache and low back pain.[4,46] TMD may also share common central pathophysiologic mechanisms with other chronic pain maladies that lack evidence of peripheral structural abnormalities. Similar to TMD patients, fibromyalgia (FM) patients are characterized by a non–modality-specific increase in experimental pain sensitivity, not only at the designated tender points, but also at various other bodily sites.[47,48] In addition, temporal summation of heat, cold, deep muscular pain, and electrically evoked pain, as well as aftersensations following repetitive noxious heat and mechanical stimulation, are of greater magnitude among FM patients than healthy controls.[49–53] Patients with chronic headache also exhibit a generalized hypersensitivity to noxious experimental stimulation, as well as a greater pain augmentation upon repetitive noxious stimulation than pain-free controls.[54–56] In addition, Kleinbohl et al[57] demonstrated that spine-related musculoskeletal pain patients, as well as patients with chronic headache, exhibited greater sensitization to noxious tonic heat stimulation than controls. Similarly, patients with chronic neck pain following whiplash injury exhibit greater sensitivity to experimental noxious stimulation, not only in the neck but also in remote, unaffected bodily sites.[58] Moreover, Koelbaek Johansen et al[59] reported that infusion of hypertonic saline, both within and outside the traumatized area, induced more severe pain of longer duration as well as larger areas of local and referred pain in this patient group. The fact that various chronic pain conditions have been associated with a generalized hypersensitivity to experimentally induced pain, and an augmentation in temporal summation of pain, supports a role for the central nociceptive system's hyperexcitability in the development and maintenance of chronic pain across many conditions. Alleviation of chronic pain, including TMD-related pain, by centrally acting tricyclic antidepressants in low doses that do not treat depression, further implicates a central pathophysiology as a contributory mechanism to these maladies.[60]

CNS Hyperexcitability and Chronic Pain

Generalized hyperexcitability in the nociceptive regions of the CNS may reflect a predisposing characteristic of TMD patients that preceded and contributed to the onset of chronic facial pain, or it may constitute a consequence of the chronic pain. Animal studies have shown that sustained or intense nociceptive input can lead to sensitization of the second-order nociceptive neurons in the CNS.[39–41,61–64] In addition, these neurons exhibit more pronounced wind-up following peripheral tissue inflammation.[61,62] Hyperexcitability of trigeminal brain stem nociceptive neurons due to increased C-fiber input following inflammation has been implicated in persistent TMD-related pain.[63,64] McMillan and Blasberg[65] reported that injection of local anesthetic at trigger points into the affected muscles of mastication did not alter the reduced PPTs in TMD patients, supporting a role of central nociceptive neuronal hyperexcitability in TMD pain. Macroscopic tissue injury, as well as microtrauma induced by excessive or unaccustomed use of masticatory structures, has been implicated in the etiology of TMD[66] and may trigger the development of central sensitization in TMD patients. Microtrauma, low-level inflammation, or some unrecognized microscopic peripheral pathologic process may generate peripheral nociceptive input and lead to the development and maintenance of central sensitization, in the absence of apparent peripheral pathology. Moreover, sensitization of the brain stem nociceptive neurons may become independent of peripheral nociceptive input, contributing to the persistence of

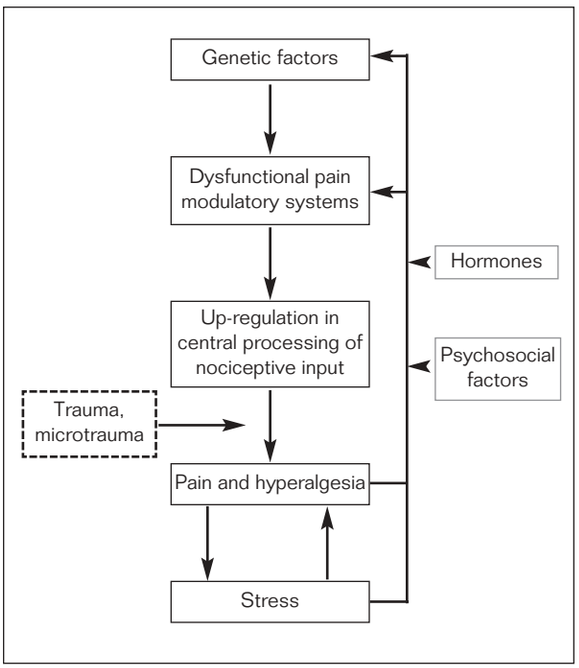


Fig 5 Genetic factors may account for the decreased efficacy of antinociceptive systems in some individuals, predisposing them toward an impairment of endogenous pain modulation. Dysfunctional pain modulatory systems would result in up-regulation in the central processing of nociceptive input. In the presence of such CNS hyperexcitability, trauma or microtrauma due to excessive or unaccustomed muscle use may lead to persistent pain and hyperalgesia. Persistent pain can increase stress levels, and persistent stress may evoke generalized hyperalgesia. Both persistent pain and stress may result in further increase in the hyperexcitability of the CNS nociceptive regions, creating a pain cycle that can conceivably become independent of peripheral noxious input. Additional factors, including hormonal and psychosocial influences, also affect the development and maintenance of chronic TMD pain.

pain even in the absence of peripheral structural abnormalities.

Alternatively, greater excitability in the central nociceptive pathways may precede any painful condition and predispose some individuals toward the development of chronic pain. Supporting this theory, women exhibit more pronounced temporal summation than men.[67,68] Moreover, it was recently shown that the endogenous analgesic systems do not function as effectively in women as in men.[69] These gender differences may be relevant to the higher prevalence of various chronic pain conditions, including TMD, among women.[1,70,71] Large-scale, prospective studies would reveal whether increased responsiveness of the CNS to noxious stimulation represents a result of clinical ongoing pain, or whether it precedes and contributes to the development of chronic TMD pain. These theories are not mutually exclusive; both pre-existing hyperexcitability in the CNS nociceptive region and up-regulation of nociceptive input processing due to chronic pain may play a role in TMD (Fig 5).

Relationship Between Temporal Summation, Clinical Pain, and Psychologic Variables Among TMD Patients

The present investigation demonstrated that in the patient group, the number of painful bodily sites, as well as the total body pain score, correlated significantly with the average facial pain experienced in the previous week. This finding indicates that patients with widespread pain, which is suggestive of a generalized hyperexcitability of the nociceptive regions in the CNS, experience more severe TMD-related pain.

The present study failed to detect an association between temporal summation of pain and characteristics of clinical facial pain and dysfunction, including current facial pain, average pain intensity, total palpation score, and painless mandibular opening. In addition, temporal summation of pain did not correlate with the total body pain score or the number of sites that were painful in the previous month. These results are consistent with another study that did not find a correlation between clinical pain characteristics and sensitivity to experimental pain evoked by hypertonic saline infusion, noxious heat, or pressure stimulation in patients with myogenous TMD pain.[27] In contrast, Fillingim et al[72] found a significant association between ischemic pain sensitivity and clinical pain in TMD patients who represented the upper and lower quartiles in ischemic pain tolerance to a tourniquet procedure. Comparison of extreme groups in this study might have facilitated the detection of a significant relationship between experimentally evoked pain and facial pain in TMD patients. Large-scale, prospective studies examining whether augmented responses to experimental noxious stimulation can predict the future development of a chronic pain condition would provide valuable insights into the clinical relevance of experimental pain.

No correlation was detected between temporal summation of pain and depression or trait anxiety scores. However, there was a significant association between temporal summation of pain and state anxiety measures. This result is in agreement with an

investigation demonstrating that myofascial pain dysfunction patients who exhibited higher scores of anxiety and neuroticism had lower electrical pain tolerance.[29] In contrast, Fillingim et al[72] failed to detect an association between sensitivity to ischemic or thermal pain and trait or state anxiety measures in TMD patients. Similarly, trait and state anxiety scores exhibited no significant relationship with PPTs in myofascial pain dysfunction patients.[28] The different types of pain induction might have contributed to these variable results. Nevertheless, the present findings suggest that among TMD patients, situational anxiety at the time of experimental testing (state anxiety score) may relate more to increased pain ratings than does the overall tendency to experience anxiety (trait anxiety score). Furthermore, studies have shown that experimentally induced anxiety that immediately precedes laboratory testing results in augmented perceptual responses to noxious stimulation.[73,74]

In the present investigation, TMD patients and pain-free individuals provided comparable state anxiety ratings. However, the association between state anxiety and temporal summation magnitude involved only the patient group and not the control group. This finding indicates that state anxiety is a more relevant factor in shaping the responses to noxious stimuli among TMD patients as opposed to controls; this may account in part for the greater temporal summation of pain among patients.

Conclusion

The present study demonstrated that TMD patients exhibit lower mechanically evoked pain thresholds, greater temporal summation of mechanically evoked pain, and stronger aftersensations following repetitive noxious mechanical stimulation of their fingers, in comparison to pain-free controls. These findings indicate a generalized hyperexcitability in the central nociceptive pathways among TMD patients. Such hyperexcitability may contribute to the onset and maintenance of chronic TMD-related pain.

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