Temporal Summation of Heat Pain in Temporomandibular Disorder Patients

Karen G. Raphael, PhD
Professor and Director of Research
Department of Psychiatry
New Jersey Medical School
and Associate Professor
Department of Diagnostic Sciences,
New Jersey Dental School

Malvin N. Janal, PhD
Senior Research Associate
New Jersey Medical School

Sowmya Ananthan, BDS
Candidate
Masters of Science in Dentistry
New Jersey Dental School

Dane B. Cook, PhD
Research Service
William S. Middleton Memorial Veterans Hospital
and Assistant Professor
Department of Kinesiology
University of Wisconsin–Madison

Roland Staud, MD
Professor of Medicine
University of Florida
Gainesville, Florida

Correspondence to:
Dr Karen G. Raphael
Professor and Director of Research
Department of Psychiatry
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
183 S Orange Ave, BHSB F-1555
PO Box 1709
Newark, NJ 07101-1709
Fax: +973 972 8305
Email: raphaekg@umdnj.edu

Aims: *To compare patients with temporomandibular disorders (TMD) to control subjects on two measures of central processing, ie, temporal summation of heat pain and decay of subsequent aftersensations, following thermal stimulation in both a trigeminal and extratrigeminal area.* ***Methods:*** *A "wind-up" protocol was used in which 19 female TMD patients and 17 female controls were exposed to 15 heat stimuli at a rate of 0.3 Hz. Numeric pain ratings were elicited after the 1st, 5th, 10th, and 15th stimulus presentation and every 15 seconds after final presentation (aftersensations) for up to 2 minutes. In separate trials, the thermode was placed on the thenar eminence of the hand and the skin overlying the masseter muscle.* ***Results:*** *Groups did not differ with respect to the slope of wind-up when stimulated at either anatomic site, although asymptotic levels occurred sooner for TMD patients than for controls. In analysis of aftersensations, a significant group × site × time interaction was detected, in which TMD patients experienced more prolonged painful aftersensations than controls when stimulated on the skin overlying the masseter muscles.* ***Conclusion:*** *These results are consistent with the presence of enhanced central sensitivity in TMD and suggest that this sensitivity may be largely confined to the region of clinical pain. This contrasts with conditions such as fibromyalgia, where central sensitivity appears to be widespread.* J OROFAC PAIN 2009;23:54–64

Key words: aftersensations, chronic pain, temporal summation, temporomandibular disorders, wind-up

Temporomandibular disorders (TMD)[1] are a heterogeneous group of conditions affecting the temporomandibular joint and masticatory muscles, in which the predominant subtype[2,3] involves masticatory muscle pain. The cause and appropriate treatment of TMD remain controversial.

As part of the search for an underlying mechanism, research has examined whether TMD patients have altered responses to experimental pain stimuli. Such research has reached mixed conclusions. When measuring pain thresholds, some studies have shown that, compared to pain-free controls, TMD patients have lower thresholds to thermal and pressure stimuli at both masticatory muscle sites[4–6] and remote regions.[7–11] However, some studies[6,9,12–16] found no differences between TMD subjects and controls in perception of heat or pressure stimuli at extratrigeminal sites. For example, a relatively early study[15] found normal thermal nociceptive thresholds in patients with masticatory muscle pain in both the masseter and forearm areas. More recently, Svensson et al[5] found higher responsiveness of masticatory muscle pain patients to deep

phasic stimulation in an extratrigeminal area, but not to tonic stimulation, suggesting that altered pain processing was primarily confined to the trigeminal region. The present investigators are not the first to conclude that the evidence for altered pain processing in TMD patients is mixed.[17]

Wind-up

Wind-up, or its psychophysical correlate, temporal summation of second pain, results from repetitive stimulation of nociceptive C-fibers.[18,19] In humans, wind-up can be measured using standard psychophysical techniques and is characterized by a progressive increase of perceived pain, hyperalgesia, and enlargement of receptive fields in response to repetitive application of a constant pain stimulus.[20,21] Wind-up is dependent on stimulation of N-methyl D-aspartate (NMDA) and neurokinin (NK1) receptors that in turn sensitize wide dynamic range and nociceptive-specific neurons within the dorsal horn of the spinal cord.[19] Therefore, it is a measure of central synaptic plasticity. Wind-up can serve as both an amplification and maintenance mechanism for pain and central sensitization.[19] However, wind-up and central sensitization are not the same phenomenon.[22] Nevertheless, because wind-up is mediated by central (spinal or brainstem) mechanisms, it can be used in human studies to determine the degree of central nervous system (CNS) excitability to nociceptive stimuli.[19,22] This is important because several lines of evidence suggest that chronic musculoskeletal pain conditions may be maintained by CNS dysregulation of endogenous pain control. Specifically, multiple studies (see Price and Staud[23] for review) have found evidence of abnormal wind-up and slower dissipation of painful aftersensations in patients with fibromyalgia, a widespread pain condition that is comorbid with TMD.[24–30]

At least two groups of researchers have found greater wind-up in response to thermal stimuli, when TMD patients were compared to normal controls,[4,31] implying that TMD is associated with sensitization of general pain regulatory systems. Case-control differences in thermal wind-up patterns were found when applying the stimulus to the glabrous surface of the hand[4] or the fingers.[32] The latter study[32] also reported more intense and frequent painful aftersensations, following termination of the thermal pulses. A focus on wind-up aftersensations is important to note, because this response is not dependent on the afferent stimulus and is, therefore, more easily interpretable as an indicator of central sensitivity.

In an intriguing longitudinal study, Maixner et al[33–35] presented early findings from a study of a 3-year cohort of initially TMD-free young women. Baseline C-fiber mediated thermal wind-up was associated with the development of TMD symptoms, but not at a statistically significant level.[35] Since cross-sectional findings cited earlier[4,31] cannot sort out whether elevations in wind-up in TMD patients are a cause or consequence of symptoms, these longitudinal findings are arguably the most provocative findings to date that support wind-up and possibly central sensitization as risk factors for the onset of TMD pain.

To date, no previous research has assessed thermal wind-up that involves applying the thermal stimulus to both the face and an extratrigeminal region such as the hand. The aim of this investigation was to compare TMD patients to control subjects on two measures of central processing, ie, temporal summation of heat pain and decay of subsequent aftersensations, following thermal stimulation in both a trigeminal and extratrigeminal area. It also aims to evaluate the effect of modifying criteria for the definition of a wind-up response on the ability to elicit a wind-up response and to detect difference between clinical groups and anatomic sites over time.

Materials and Methods

Subject Selection

TMD patients (n = 19) were recruited from the orofacial pain clinic at New Jersey Dental School following institutional review board approval at the University of Medicine and Dentistry of New Jersey. For the patient to be included in the study, the treating orofacial pain specialist had to diagnose the patient with a TMD and make a clinical judgment that the pain was primarily of muscle origin. Thus, patients were most likely to fulfill criteria for a myofascial subtype of TMD.[1]

Control volunteers (n = 17) without self-report of chronic facial pain were recruited through flyer postings on the academic campus. Although eligible controls could not have facial pain, they were permitted to have other painful disorders, since selection of pain-free controls can lead to problematic bias and error.[36]

Recruitment was restricted to adult women between the ages of 18 to 65, given that pain threshold and tolerance may differ for women and men. All subjects were English-speaking. Both groups of participants received a $50 honorarium.

Self-Report Questionnaires

Respondents completed several self-report measures. They were asked to place an "X" at each location on an anatomic map of the head and neck and entire body (front and back), to indicate locations in which they had had pain in the past 2 weeks. Time of onset of pain (months) was assessed, and participants rated their current, worst, and average pain (past 6 months) on a numerical 0 to 10 scale, where "0" equaled "no pain" and "10" equaled "pain as bad as it could be." Demographic information, including age, education, and race, was collected.

As an exploratory measure, the State-Trait Anxiety Inventory (STAI) was administered. In the STAI, the most widely used self-report instrument for measuring anxiety in adults,[37] two 20-item self-report scales assess anxiety-proneness (trait) and current anxiety (state) level.

Sensory Testing

Subjective responses to heat pain were measured at the masseter muscle (bilaterally) and the thenar eminence of the nondominant hand, using standardized heat stimuli (Medoc TSA2001 Thermal Sensory analyzer with a 900 mm^2 Peltier thermode; Medoc Advanced Medical Systems). Heat pain was chosen because it can be delivered in a standardized fashion, identical stimuli can be presented to participants, and the rate of perceptual wind-up to heat pain has been shown to be independent of skin temperature changes that accompany repeated contacts of a heated thermode.[38]

Heat pain thresholds were measured using a double random staircase method. The stimuli were applied to each site, starting from a baseline temperature of 32°C. Temperature within each staircase increased at 1°C/s in 2-degree steps until the subject reported that the stimulus increment in that interval was painful. Once pain was indicated, the temperatures were adjusted first downward and then upward in 1-degree and then in 0.3-degree steps, until a consistent threshold could be computed.

The primary psychophysical pain outcome was related to perceptual wind-up. A wind-up paradigm was employed similar to that successfully employed in several investigations of fibromyalgia.[21,39,40] Temporal summation of pain sensations was evaluated by applying a preheated thermode to the thenar eminence of the nondominant hand and to the skin overlying the body of the right and left masseter muscles.

The subject held the thermode assembly against either her face or hand. Contact of the preheated thermode with the skin was controlled by a computer linked to a step motor that physically moved the thermode to and from the skin. The step motor/thermode assembly was mounted in the emptied housing of a 6-volt flashlight. A Plexiglas plate, cut out in the middle to allow passage of the thermode, closed off the open end of the housing. Without power, the thermode sat approximately 1 cm below the level of the plate. When energized, the thermode moved into the opening, level with the outside surface of the plate. The skin tended to fall below the surface of the opening in the plate, so that the energized probe made full contact with the skin surface, if subjects simply kept the plate lightly touching the skin, as they were instructed to do for the entire 45 seconds required to deliver each of the wind-up stimulus trains. The probe was mechanically cycled to contact the skin for 1 second and to dwell away from the skin for 2 seconds (0.3 Hz). A total of 15 stimuli were presented.

The thermode temperature was determined from the method described by Staud et al.[41] Briefly, this temperature was determined separately for each site through an iterative procedure as that which elicited a numerical pain scale (NPS) response of 20 or less to a first stimulus and an NPS response that was at least 25 points greater in response to the 15th stimulus. In this way, a subjectively equal wind-up response was elicited from each subject. This procedure is preferred over a constant stimulus, as it minimizes withdrawal of sensitive subjects[39] and provides clear interpretation of aftersensations, considered the primary indication of central sensitivity.

Subjects rated their experience with an NPS previously validated to measure wind-up in fibromyalgia.[21,39] The scale includes verbal anchors set at 10-point increments, ranging from 10 = warm (no pain) to 100 = intolerable pain (20 = just painful). Subjects were instructed to attend to and report intensity of the peak pain, and that peak pain would be expected to occur 1 to 2 seconds following stimulus presentation. They were also told that the thermal sensations may or may not be painful and to rate each stimulus using the NPS. Subjects were cued to report on the 1st, 5th, 10th, and 15th stimulus presentations and were also cued to rate the intensity of residual sensations at 15-second intervals for 2 minutes after the 15th stimulus (wind-up aftersensations).

Table 1 Demographic, Clinical, and Psychophysical Characteristics of the Sample

Measure	Control (n = 17)	TMD (n = 19)	$\chi 2$ or t	P
Age (y) (mean ± SD)	37.5 ± 13.8	36.2 ± 13.1	0.3	.78
Race			2.97	.23
White	6 (37.5%)	9 (52.9%)		
Black	6 (37.5%)	2 (11.8%)		
Asian	4 (25.0%)	6 (35.3%)		
Hispanic	1 (6.3%)	5 (26.3%)	3.4	.18
Ever married	8 (47.1%)	11 (57.9%)	2.9	.41
State anxiety (mean ± SD)	25.6 ± 9.1	31.4 ± 5.6	2.3	.03
Trait anxiety (mean ± SD)	31.4 ± 6.1	37.5 ± 6.8	2.8	.008
Face pain (left)	1 (5.9%)	18 (94.7%)	28.4	< .001
Face pain (right)	1 (5.9%)	17 (89.5%)	25.1	< .001
Body pain				
Upper extremity (left)	0	2 (10.5%)	1.9	.17
Upper extremity (right)	2 (11.8%)	4 (21.1%)	1.7	.19
Lower extremity (left)	2 (11.8%)	5 (26.3%)	1.2	.27
Lower extremity (right)	3 (17.6%)	4 (21.1%)	.1	.80
Axial	2 (11.8%)	14 (73.7%)	13.9	< .001
Total painful sites (of 5) (mean ± SD)	0.5 ± 0.8	1.5 ± 1.5	2.7	.01
Clinical pain characteristics				
Persistent/recurrent	—	44.4% / 55.6%		
Pain intensity (mean ± SD)				
Present	—	4.3 (2.2)		
Worst last 6 mo	—	6.8 (2.6)		
Average last 6 mo	—	5.1 (2.4)		
Median pain duration (mo)	—	12		
Pain threshold (°C) (mean ± SD)				
Thenar eminence	46.4 ± 3.6	45.8 (2.9)	0.6	.56
Maxillary skin (left)	43.6 ± 4.2	42.5 (4.2)	0.8	.45
Maxillary skin (right)	42.5 ± 4.1	41.8 (4.1)	0.5	.59
Provided at least 1 wind-up trial*	12 (70.6%)	10 (52.6)	1.2	.27

* A wind-up trial is defined as one in which the report to the first stimulus presentation was less than or equal to 20, and the report to the last stimulus presentation was at least 25 points higher than the first.

Statistical Analysis

SPSS version 14 (SPSS, Chicago, IL) was utilized for statistical analysis. Group differences in pain thresholds were tested by use of the Student *t* test. Modeling the development of wind-up and the decay of aftersensations employed an unstructured mixed model approach detailed by Singer and Willett.[42] This analysis is conceptually similar to repeated-measures analysis of variance (ANOVA) but makes no assumptions about compound symmetry, and allows for unbalanced designs. This latter feature was crucial to the analysis of the current data, in which some subjects were missing wind-up data at one or more sites, and some subjects had multiple wind-up trials at some sites. The analysis employed full maximum likelihood (ML) estimation, which produces models that maximize the likelihood of both sampling errors (like restricted maximum likelihood [RML]) and parameters (unlike RML). Inclusion of the latter makes possible the comparison between non-nested models. Significance indicates that the probability of a Type I error was no more than 5%.

Results

Table 1 summarizes the clinical and demographic characteristics of the sample. There was no significant difference between patient and control groups in either demographic characteristics or in heat pain thresholds on either the face or the hand. Patients did, however, report higher levels of both state and trait anxiety, and reported more pain outside the facial region, particularly in the axial region. These reports were focused on neck or shoulder pain (data not shown). About half of the patients reported episodic pain, with an average intensity of 5 out of 10, suggesting moderate pain. The median duration of pain was 12 months.

Table 2 Effect of Varying Criteria for Defining a Wind-up Trial on the Number of Subjects and Trials Eligible for Analysis

Criterion	Included n (%)	Trials with criterion
Stimulus1 ≤ 20 and Δ ≥ 25	22 (61.1)	80
Any Δ ≥ 25	22 (61.1)	103
Stimulus1 ≤ 20 and Δ ≥ 20	25 (69.4)	98
Any Δ ≥ 20	25 (69.4)	133
Stimulus1 ≤ 20 and Δ ≥ 15	27 (.75)	123
Any Δ ≥ 15	28 (77.8)	181
Stimulus1 ≤ 20 and Δ ≥ 10	30 (83.3)	147
Any Δ ≥ 10	33 (91.7)	235

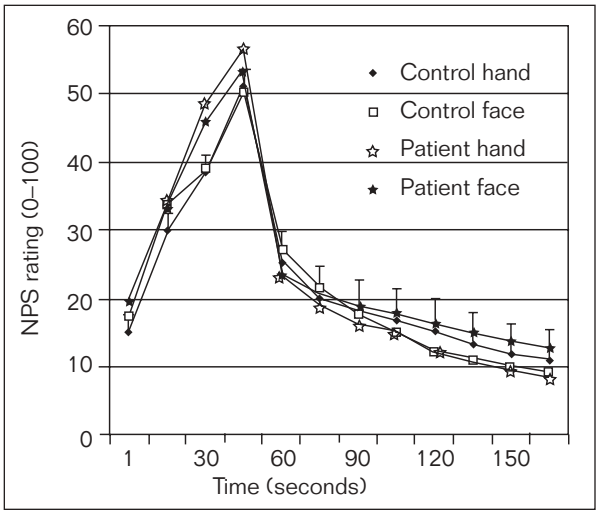

Fig 1 Numeric pain scale (NPS) ratings after 1st, 5th, 10th, and 15th heated thermode presentation and every 15 seconds of aftersensations (no thermode presentation). Error bars shown only for Control subject hands, for purposes of visual presentation. (1 to 45 seconds = wind-up; 60 to 165 seconds = aftersensations.)

A statistically similar proportion of controls and patients, ~50% to 70%, provided at least one valid wind-up trial. That is, a temperature was found which, when repeated every 3 seconds, produced an NPS response to the first stimulus of 20 or less, and a response to the fourth-rated stimulus at least 25 points greater. To find a wind-up stimulus, up to 16 attempts were made on the face and up to 13 attempts were made on the hand, over the course of a testing session lasting a maximum of 2 hours. On average, finding or repeating a wind-up stimulus required 9.8 trials (SD = 3.0) on the face and 5.9 (SD = 2.1) on the hand. Twenty-two of the 36 subjects provided at least one wind-up trial, and 14 provided two or more; 10 subjects provided both a face and hand trial, while another 12 provided only a hand trial. The ability to elicit a wind-up trial on either the hand or the face was statistically similar in patients and controls (details available upon request).

Table 2 details the effect of changing the criterion for defining a trial as one showing wind-up on the number of subjects that could be included in the analysis, and the total number of trials that would have met the criterion. Relaxing criteria, either by reducing the necessary increase in the NPS rating or by allowing the response to the first stimulus to be above the minimum report of pain, had the effect of increasing the number of subjects eligible for analysis as well as the number of trials meeting the criterion. Compared to the most stringent criterion that was employed in analyses below, the most relaxed criteria would have increased the number of eligible subjects by 50% and tripled the number of eligible trials. Nevertheless, principal analyses focus on data produced from the most stringent definition, even at the expense of reduced statistical power, as it was considered most interpretable (ie, change in sensation from nonpainful to painful).

Figure 1 shows the report of wind-up sensation during stimulation (1 to 45 seconds) and following stimulus termination (60 to 165 seconds, aftersensations). Inspection shows similar trajectories during stimulation in patients and controls and in the hand and face during stimulation, although patients appear to give higher ratings at 30 seconds. Similar trajectories were also seen in the slope of aftersensations, but appeared most shallow when patients were stimulated on the face. Comparison of these slopes is presented in analyses below, as Fig 1 does not control for either stimulus temperature or for the presence of multiple wind-up trials in some subjects.

Wind-up Response

As seen in Fig 1, and by definition, responses increased during successive repetitions of the wind-up stimulus (1 to 45 seconds). Mixed models analysis showed an intercept of 18.4 (SEM = 1.2) and a regression coefficient of 12.1 (SEM = 0.6) attributable to time, indicating an average initial response of about 18 NPS units and an increase of

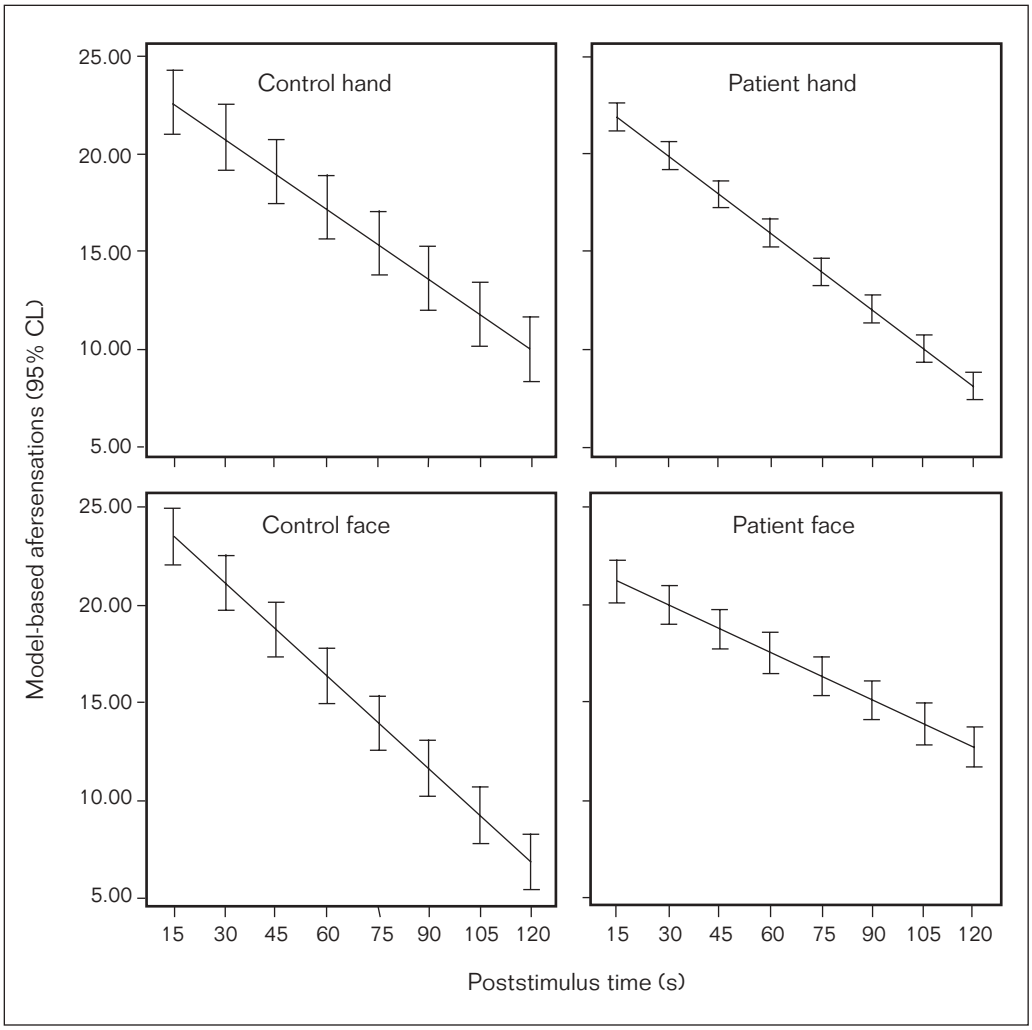

Fig 2 Model-based NPS ratings, adjusted for temperature, broken down by anatomic site and group, CL = confidence limits.

about 12 NPS units in each successive report interval. Subsequent inclusion of temperature, anatomic site, and patient group into the model failed to improve its fit, indicating that this slope was similar for the hand and face, patient and control group, and various wind-up temperatures. While the overall test of the interaction between group and time was not significant ($F[3, 307] = 1.81$, $P = .14$), post-hoc tests showed higher NPS ratings in patients than controls at 30 seconds (mean ± SD = 46.8 ± 9.6 versus 39.7 ± 9.3, $P < .05$), but not at 45 seconds or at earlier time points, supporting the observation in Fig 1 that patients reach asymptomatic levels sooner than controls.

Secondary analyses compared subject groups and anatomic sites on the temperature necessary to elicit a wind-up response. Mixed model analysis showed that, while wind-up on the face required a lower temperature than on the hand (M ± SD = 49.6 ± 2.3 vs 47.8 ± 2.7, $P < .001$), there was no difference between patients and controls and no interaction of group by site. Thus, although there was no difference in wind-up temperature attributable to patient status, temperature required to elicit a wind-up response was lower on the face than on the hands of the average subject.

Modeling of Aftersensations

Model 1, Unconditional Means (UM). Table 3 shows that the intercept (the average initial poststimulation reported sensation) over all persons and all poststimulation intervals was 14.9, indicating that aftersensations were not, on average, painful, but were significantly greater than zero. Inspection of the variance components suggests nonzero levels of both within and between-person variance, justifying the search for variables to which this variance may be attributed. The intraclass correlation coefficient (ICC) was .71, indicating that 71% of the variability among reports of

Table 3 Results of Mixed Model Analysis of Initial Status and Rate of Change of Aftersensations

	Model 1	Model 2	Model 3	Model 4
Initial Status				
Intercept	14.9 (2.75)[a]	21.4 (2.84) [a]	21.9 (2.7) [a]	22.6 (3.8) [b]
Group				–1.7 (5.4)
Site				1.1 (1.6)
Group × site				–.63 (1.93)
Temperature			.96 (.19) [a]	1.26 (.24) [a]
Rate of change				
Time		–1.87 (.32) [a]	–1.87 (.32) [a]	–1.81 (.49) [a]
Group × time				–.16 (.68)
Site × time				–.58 (.36)
Group × site × time				1.33 (.46) [b]
Variance components				
Level 1 (within subject)	67.1 (3.71) [a]	35.9 (2.05) [a]	34.6 (1.98) [a]	33.0 (1.88) [a]
Level 2 (between subjects)				
Initial status	162.3 (50.62) [a]	170.5 (54.3) [b]	152.9 (43.9) [b]	149.0 (47.6) [b]
Rate of change		1.82 (.75) [b]	1.85 (.75) [c]	2.08 (.81) [c]
Covariance		–3.9 (4.6)	–2.36 (4.32)	–2.02 (4.44)
-2 LL***	4762.9	4404.0	4380.1	4350.8
AIC*	4768.9	4416.0	4392.1	4376.8
BIC**	4782.4	4442.0	4419.1	4435.3

Numbers in parentheses indicate the standard error associated with the estimate of that regression parameter.

[a] $P < .001$.
[b] $P < .01$.
[c] $P < .05$.
*Akaike's Information Criterion.
**Bayesian Information Criterion.
***-2^x log likelihood

aftersensations was attributable to differences between persons. The ICC was also interpreted as the autocorrelation among residuals in the repeated observations. Because it was significantly different from zero, this mixed model provides a more appropriate analysis of these data than would be obtained with a repeated measures ANOVA, the results of which are valid only when these errors are uncorrelated.

Model 2, Unconditional Growth (UG). Adding Time to the UM model showed the first poststimulation report to be slightly painful, ie, 21.4. The change in report as a function of poststimulus Time was significantly different from 0, indicating an overall change in the level of aftersensations during the poststimulation interval. The magnitude and sign of the regression coefficient (–1.83) indicates that average report levels decreased by about 2 NPS units for each 15-second period of the poststimulation interval. Inspection of the variance components shows that inclusion of Time reduced both level 1 (within-person variability in true trajectory of change) as well as level 2 variability (between persons). In the first case, a pseudo-R^2 of .465 indicates nearly a 50% reduction in residual variability at level 1, and a 20% reduction at level 2.

Model 3, Adding Temperature Covariate to UG Model. In this model, a measure of the temperature used to elicit wind-up was added as a covariate. In particular, the actual temperature minus the average temperature used in successful wind-up trials (49.5°C) was entered. As a centered measure, the value of the intercept in this model and in model 4 (below) remains interpretable, as the initial NPS report was in models 1 and 2. Addition of this variable significantly reduced unexplained variability at level 2 by about 10% (pseudo-R^2). Inspection of the regression coefficient indicates slightly more than a 1:1 increase in the first report of aftersensations for each degree increase in temperature. Thus, there were significant differences between people in the temperature used to elicit wind-up, and higher temperatures tended to produce greater reports of aftersensations at the first poststimulus interval.

Model 4, Adding Group and Site Variables. The next model added group, site, and their interactions as covariates. Analysis revealed a significant interaction between patient status and site in rate of change. Fig 2 shows reports of aftersensations

over time based on the model's predictions, as a function of patient status and site. Inspection shows a shallower slope when patients were tested in the face (lower right), indicating that the decay of aftersensations was slower for patients when tested in the area of their clinical pain. Computation of individual regression coefficients for each combination of patient group and site showed the shallowest slope (95% confidence limits) over time for the patient face condition [–1.21 (–1.06, –1.36)]. The slope for the patient hand condition was –1.97 (–1.87, –2.07) and the respective values for the control subjects were –2.38 (–2.19, –2.58) and –1.81 (–1.57, –2.04). Relative to Model 3, pseudo-R^2 indicated a 4.3% reduction in level 2 variability (between persons variability in initial status) attributable to the grouping variables, and an 8.1% reduction in level 1 variability (within person variability in true trajectory of change). Neither model 3 nor 4 suggested that initial status was correlated with rate of change. Finally, the presence of nonzero estimates of unexplained variability in Model 4 at both level 1 and level 2 suggests that future research aimed at identifying time varying covariates, as well as additional grouping factors, that might reduce, respectively, these unexplained sources of variation is warranted.

Exploratory Analysis of Changing Wind-up Criteria

As a last analysis, the effect of changing criteria for the definition of wind-up on this analysis was explored. First, reducing the necessary increase from 25 to 20 points (but keeping the requirement that the response to the first stimulus tap be at or below the minimum pain level) had little effect on the statistical results. In particular, analysis of aftersensations using those data, which added three subjects and almost 25% more wind-up trials, showed a three-way interaction of group, site, and time ($P = .02$), and a level of unexplained variance (32.1) that were consistent with the analysis presented in Table 3. Second, however, analysis of aftersensations provided by allowing any 25-point increase in ratings, which added a similar number of wind-up trials to the analysis, failed to show the three-way interaction ($P = .40$) and more than doubled the amount of unexplained variance (67.0). Thus, these analyses suggest that while there was little effect of reducing the necessary increase in report level from 25 to 20 points, there was a strong effect of requiring that initial report levels be nonpainful.

Summary of Main Analyses

To summarize the main analyses, Models 1 and 2 showed, respectively, that there was variability in average report levels, and in decay of aftersensations that could potentially be related to variation in patient and site. In addition, Model 1 showed that the correlation among the residuals made repeated-measures ANOVA an inappropriate model for analyzing these data. Model 3 showed that the level of aftersensations varied directly with the temperature used to elicit wind-up, and that it was valuable to control for these differences in further analyses. Finally, Model 4 showed that the rate of decline in aftersensations was slowest in patients when tested on the face. With regard to the a priori questions, the data suggest that wind-up may be elicited on the face, and while there were no main effects of either site or group on the decay of aftersensations, aftersensations did decay more slowly in the patients, but only when wind-up was elicited from the skin overlying the masseter muscles.

Discussion

This initial investigation of trigeminal versus extratrigeminal wind-up in TMD patients and controls showed that it is possible to elicit thermal wind-up in both the hand and face. It was more likely that wind-up would be elicited from hand than facial stimulation, but it was similarly likely to be elicited from patients and controls. For both anatomic locations, this study failed to demonstrate significant differences in the slope of wind-up for myofascial TMD cases versus control, unlike two prior investigations.[4,31] However, similar to earlier reports by Maixner and colleagues[4] and Sarlani and colleagues,[31] TMD patients were likely to reach wind-up asymptote sooner than controls. Most important, this study showed that decay of painful aftersensations was significantly slower for myofascial TMD patients compared to controls when tested in the trigeminal region (ie, the skin overlying the body of the masseter muscle), but not in an extratrigeminal region (ie, thenar eminence). Thus, these results suggest that enhanced central sensitivity in TMD may be largely confined to the region of clinical pain and not widespread, as generally observed in comorbid conditions such as fibromyalgia.

One possible difference between this study and the two prior studies that found differences in

trajectory of wind-up between TMD cases and controls[4,31] is that controls with other pain conditions were not excluded. Both prior studies explicitly selected "pain free" controls. By violating assumptions on which case-control studies are based, ie, controls representing those who would have been selected as cases had they developed the disease being studied, and using the same exclusion criteria for cases and controls (see Schwartz and Link[43] and Marbach et al[36]), a bias toward finding group differences is more likely in these earlier studies because enhanced general pain perception could be associated with multiple conditions that are allowed in the TMD case group (eg, fibromyalgia, low back pain) but eliminated from the healthy control group. Notably, three studies of experimental pain in TMD patients that correctly selected controls solely on the basis of absence of orofacial pain[5,14,15] did not find significant case-control differences. Our failure to find pain threshold differences between cases and controls in either the trigeminal or extratrigeminal region is, therefore, consistent with other experimental pain studies that employed similar strategies for recruitment of controls. Thus, differences between TMD patients and TMD-free controls in experimental pain response may be even less robust than suggested by some of the earlier studies that most often recruited pain-free controls.

These factors may have led to a conservative group comparison in relation to prior studies on wind-up in TMD. Thus, it is particularly impressive that despite the conservative design, unique differences were documented in decay of aftersensations in the trigeminal region among TMD patients versus controls, despite failure to find case-control differences in decay of aftersensations in an extratrigeminal region. The finding of prolonged aftersensations specific to the trigeminal region in TMD patients deserves further attention. If prolonged aftersensations are confined to the region of clinical pain in TMD patients, it suggests that central synaptic sensitivity is primarily influenced by nociceptive signaling from the temporomandibular joint and/or masticatory muscles and is not a phenomenon of global enhancement of excitability in the CNS.

One might also question whether this study failed to find differences in wind-up slopes between groups or body sites due to its restrictive data inclusion process. In analyses not detailed here, an analysis was conducted that included all trials attempting to elicit a wind-up response which produced at least one report of aftersensations. The effect of this inclusion was to raise the average first report to about NPS = 25 and the 15th report to only about NPS = 35, greatly diluting the magnitude of temporal summation and increasing the magnitude of error variance. Most importantly, these data still did not show any difference between patients and controls in the slope of wind-up. Thus, the failure to show robust differences in wind-up between patients and controls does not appear to be the result of the strict data inclusion process.

One possible criticism of our study is that TMD patients' prolonged painful aftersensations in the trigeminal region might have been a function of deep tissue stimulation rather than wind-up. Most subjects reported that the probe produced a "tap" sensation when energized, particularly on the face. However, the shallow contact seems unlikely to have caused deep tissue stimulation. Nevertheless, to firmly rule out this explanation, it would have been useful to test the response to repetitive contacts of the face at ambient temperatures, using the same stimulus delivery mechanism employed here. It will be important to replicate the current findings using newer technology[44] that avoids the need to cycle thermode contact against the skin.

Another possible criticism of the methods used in the current study is that allowing subjects to hold the thermode assembly themselves may have introduced variation in contact among subjects, introducing error or bias. Note, however, that participants were not holding the thermode but the thermode assembly, with instructions to place their hands or face on the Plexiglas apparatus. Thus, it seems unlikely that there were large differences among participants in the amount of skin stimulated or the amount of force against the thermode. Moreover, even if there were variation in thermode assembly placement, it is hard to imagine how this could account for the very specific finding of group differences in patterns of aftersensations restricted to the face, when the thermode had been removed from the skin.

It is notable that not all patients or controls provided subjective pain ratings that met the strict definition of wind-up used. In fact, although the proportion of cases and controls providing wind-up data (ie, 53% versus 71%) was not significantly different, these data demonstrate a potential difficulty in achieving a subjective wind-up response in human subjects, when defining wind-up according to strict criteria (see Methods). It is suspected that it may have been somewhat more

difficult for a pattern of NPS ratings to meet wind-up criteria when stimulating the face than the hand, because the decreased distance to the CNS when stimulating the face makes it more difficult for subjects to discriminate first from second pain sensations. In results not detailed here, no clinical or demographic characteristics were identified that differentiated individuals who were able to produce a wind-up response from those who were not. Nevertheless, because of the failure to generate a wind-up response in many participants, caution is warranted in interpreting these findings. Replication is essential.

To the authors' knowledge, this is the first study that has explicitly documented problems in achieving a robust wind-up response in the large majority of subjects. Unlike prior studies in which much higher proportions of subjects were reported to achieve wind-up criteria (eg, 55 of 58 subjects[45] or nearly 95%), a notably smaller proportion of subjects in the current study met wind-up criteria. Given the discrepancy in the proportion of subjects achieving wind-up in this study versus prior published literature, possible sources of the discrepancy were considered.

Although subjects were trained during prestudy practice trials to differentiate between pain and sensitivity due to pressure contact, the differentiation may still have been difficult for some subjects. Moreover, a maximum of two hours was spent with each subject; in some prior studies (eg, Staud et al[46]) considerably more time was most likely spent on subject training, including the use of multiple training sessions. In addition, the anatomic sites used, ie, the thenar eminence and the body of the masseter muscle, have limited area. In searching for an adequate wind-up stimulus, if a too-high stimulus intensity was tried (ie, one that elicited a response greater than NPS = 20), this limited surface area may have fostered the development of peripheral sensitization that interfered with later elicitation of a wind-up response. This problem could be avoided in the future by using various areas of the hands or arm, for example. In any case, improvement in technology using a device that can elicit heat pulses with continuous thermode contact[44] may prove to be a more efficient mechanism for eliciting wind-up, particularly in the trigeminal region.

In summary, these novel findings demonstrate the feasibility of generating a wind-up response in the trigeminal region, in both TMD patients and non-TMD controls. The finding of prolonged painful aftersensations in TMD patients, specific to the trigeminal region, deserves replication in larger studies and with newer methods for generating a robust wind-up response.[44] If replicated, additional studies designed to understand better the mechanisms underlying prolonged aftersensations specific to the trigeminal region are warranted.

Acknowledgments

Supported by NIH grant R01 DE018569 and the Foundation of UMDNJ. The authors gratefully acknowledge Dr Eli Eliav for both technical support and helpful comments on an earlier version of this manuscript.

References

1. Dworkin SF, LeResche L. Research Diagnostic Criteria for Temporomandibular Disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
2. LeResche L, Dworkin SF, Sommers EE, Truelove EL. An epidemiologic evaluation of two diagnostic classification schemes for temporomandibular disorders. J Prosthet Dent 1991;65:131–137.
3. Stohler CS. Phenomenology, epidemiology, and natural progression of the muscular temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:77–81.
4. 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.
5. Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. Pain 2001;92:399–409.
6. Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pain-pressure thresholds and stimulus-response curves. J Orofac Pain 1995;9:347–356.
7. Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341–351.
8. 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.
9. Bragdon EE, Light KC, Costello NL, et al. Group differences in pain modulation: Pain-free women compared to pain-free men and to women with TMD. Pain 2002;96:227–237.
10. Malow RM, Grimm L, Olson RE. Differences in pain perception between myofascial pain dysfunction patients and normal subjects: A signal detection analysis. J Psychosom Res 1980;24:303–309.
11. 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.

12. Carlson CR, Reid KI, Curran SL, et al. Psychological and physiological parameters of masticatory muscle pain. Pain 1998;76:297–307.
13. Costello NL, Bragdon EE, Light KC, et al. Temporomandibular disorder and optimism: Relationships to ischemic pain sensitivity and interleukin-6. Pain 2002; 100:99–110.
14. Davidson RM, Gale EN. Cutaneous sensory thresholds from skin overlying masseter and forearm in MPD patients and controls. J Dent Res 1983;62:555–558.
15. Price DD, Harkins SW. Combined use of experimental pain and visual analogue scales in providing standardized measurement of clinical pain. Clin J Pain 1987;3:1–8.
16. Curran SL, Carlson CR, Okeson JP. Emotional and physiologic responses to laboratory challenges: Patients with temporomandibular disorders versus matched control subjects. J Orofac Pain 1996;10:141–150.
17. Sarlani E, Greenspan JD. Evidence for generalized hyperalgesia in temporomandibular disorders patients. Pain 2003;102:221–226.
18. Price DD. Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol 1972;37:371–387.
19. Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: Much ado about something? Progr Neurobiol 2000;61:169–203.
20. 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.
21. 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.
22. Woolf CJ. Wind-up and central sensitization are not equivalent. Pain 1996;66:105–108.
23. Price DD, Staud R. Neurobiology of fibromyalgia syndrome. J Rheumatol 2005;75(suppl):22–28.
24. Wright EF, Des Rosier KF, Clark MK, Bifano SL. Identifying undiagnosed rheumatic disorders among patients with TMD. J Am Dent Assoc 1997;128:738–744.
25. Marbach JJ. Is myofascial face pain a regional expression of fibromyalgia? J Musculoskel Pain 1995;3:93–97.
26. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221–227.
27. Korszun A, Papadopoulos E, Demitrack M, Engleberg C, Crofford L. The relationship between temporomandibular disorders and stress-associated syndromes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:416–420.
28. Plesh O, Wolfe F, Lane N. The relationship between fibromyalgia and temporomandibular disorders: Prevalence and symptom severity. J Rheumatol 1996;23: 1948–1952.
29. Dao TT, Reynolds WJ, Tenenbaum HC. Comorbidity between myofascial pain of the masticatory muscles and fibromyalgia. J Orofac Pain 1997;11:232–241.
30. Raphael KG, Marbach JJ, Klausner J. Myofascial face pain. Clinical characteristics of those with regional vs. widespread pain. J Am Dent Assoc 2000;131:161–171.
31. 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.
32. Sarlani E, Greenspan JD. Why look in the brain for answers to temporomandibular disorder pain? Cells Tissues Organs 2005;180:69–75.
33. Maixner W. Is pain sensitivity a predictive factor for the development of painful temporomandibular disorders? Presented at American Pain Society Annual Meeting. Chicago, IL, 2003.
34. Bhalang K, Slade GD, Sigurdsson A, Maixner W. Pain sensitivity and the development of TMD—Initial outcomes from a three-year prospective study [abstract 1874]. In: Proceedings of the International Association for Dental Research 81st, General Session, Göteborg, Sweden, 2002.
35. Bhalang K, Sigurdsson A, Slade GD, Maixner W. Central sensitization and the development of temporomandibular disorders [abstract]. J Pain 2003;4(suppl 1):12.
36. Marbach JJ, Schwartz S, Link BG. The control group conundrum in chronic pain case/control studies. Clin J Pain 1992;8:39–43.
37. Spielberger C, Gorsuch R, Lushene R. Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
38. Mauderli AP, Vierck CJ Jr, Cannon RL, Rodrigues A, Shen C. Relationships between skin temperature and temporal summation of heat and cold pain. J Neurophysiol 2003;90:100–109.
39. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. Pain 2002;99:49–59.
40. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91:165–175.
41. Staud R, Price DD, Robinson ME, Mauderli AP, Vierck CJ. Maintenance of wind-up of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. Pain 2004;110:689–696.
42. Singer JD, Willett JB. Applied longitudinal data analysis: Modeling change an event occurrence. New York: Oxford University Press, 2003.
43. Schwartz S, Link BG. The 'well control' artefact in case/control studies of specific psychiatric disorders. Psychol Med 1989;19:737–742.
44. Staud R, Price DD, Fillingim RB. Advanced continuous-contact heat pulse design for efficient temporal summation of second pain (wind-up). J Pain 2006;7:575–582.
45. Staud R, Robinson ME, Vierck CJ Jr, Cannon RC, Mauderli AP, Price DD. Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. Pain 2003;105:215–222.
46. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ Jr. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003;102: 87–95.