Sleep Disorders and their Association with Laboratory Pain Sensitivity in Temporomandibular Joint Disorder

Michael T. Smith, PhD[1]; Emerson M. Wickwire, PhD[1]; Edward G. Grace, DDS[2]; Robert R. Edwards, PhD[3]; Luis F. Buenaver, PhD[1]; Stephen Peterson, BA[1]; Brendan Klick, MS[1]; Jennifer A. Haythornthwaite, PhD[1]

[1]Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, MD; [2]University of Maryland Dental School, Department of Neural and Pain Sciences, Baltimore, MD; [3]Harvard University School of Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Boston, MA

Study Objectives: We characterized sleep disorder rates in temporomandibular joint disorder (TMD) and evaluated possible associations between sleep disorders and laboratory measures of pain sensitivity.
Design: Research diagnostic examinations were conducted, followed by two consecutive overnight polysomnographic studies with morning and evening assessments of pain threshold.
Setting: Orofacial pain clinic and inpatient sleep research facility
Participants: Fifty-three patients meeting research diagnostic criteria for myofascial TMD.
Interventions: N/A
Measurements and Results: We determined sleep disorder diagnostic rates and conducted algometric measures of pressure pain threshold on the masseter and forearm. Heat pain threshold was measured on the forearm; 75% met self-report criteria for sleep bruxism, but only 17% met PSG criteria for active sleep bruxism. Two or more sleep disorders were diagnosed in 43% of patients. Insomnia disorder (36%) and sleep apnea (28.4%) demonstrated the highest frequencies. Primary insomnia (PI) (26%) comprised the largest subcategory of insomnia. Even after controlling for multiple potential confounds, PI was associated with reduced mechanical and thermal pain thresholds at all sites ($P < 0.05$). Conversely, the respiratory disturbance index was associated with increased mechanical pain thresholds on the forearm ($P < 0.05$).
Conclusions: High rates of PI and sleep apnea highlight the need to refer TMD patients complaining of sleep disturbance for polysomnographic evaluation. The association of PI and hyperalgesia at a non-orofacial site suggests that PI may be linked with central sensitivity and could play an etiologic role in idiopathic pain disorders. The association between sleep disordered breathing and hypoalgesia requires further study and may provide novel insight into the complex interactions between sleep and pain-regulatory processes.
Keywords: Temporomandibular joint disorder, insomnia, sleep apnea, sleep bruxism, pain sensitivity, sleep disorders, chronic pain, hyperalgesia
Citation: Smith MT; Wickwire EM; Grace EG; Edwards RR; Buenaver LF; Peterson S; Klick B; Haythornthwaite JA. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *SLEEP* 2009;32(6):779-790.

TEMPOROMANDIBULAR JOINT DISORDER (TMD) HAS BEEN DESCRIBED AS A PROTOTYPIC IDIOPATHIC PAIN SYNDROME CHARACTERIZED BY POORLY understood, episodic, masticatory muscle and/or joint pain. TMD affects an estimated 12% of the population.[1] As in other idiopathic pain disorders such as fibromyalgia and irritable bowel syndrome, patients often present with overlapping signs and symptoms including psychological distress, neuroendocrine abnormalities, and chronic insomnia.[2,3] Recent theoretical perspectives have proposed that these "central sensitivity syndromes" share a common central nervous system substrate characterized by heightened processing of noxious input, which contributes to overlapping daytime sequelae among these disorders.[4]

Several cross-sectional studies have demonstrated that compared to controls, TMD patients exhibit enhanced responsivity to a variety of painful stimuli measured both at facial and extracranial anatomic sites.[5-7] Pain sensitivity at "unaffected" (i.e., non-jaw) sites suggests the involvement of central pain processing mechanisms, beyond peripheral contributions. Recent longitudinal work has reported that enhanced laboratory pain sensitivity in pain free individuals is linked to genetic polymorphisms that predict the development of new onset TMD.[8] This suggests that central processes associated with pain amplification may be critical to understanding the etiopathophysiology of TMD. Clinical factors that contribute to pain amplification in TMD, however, are poorly understood.

Our group has focused on the possibility that sleep disturbance is one such factor that may directly contribute to central sensitization and pain amplification.[9] We recently reported, for example, that sleep onset insomnia symptoms predict the development of chronic pain following serious burn injury.[10] While it is often assumed that insomnia or sleep loss occurring in the context of chronic pain occurs secondarily to the sleep interrupting effects of pain, we and others have demonstrated that insomnias associated with chronic pain are often phenotypically similar to primary insomnia.[11] Shared features include high levels of pre-sleep cognitive rumination and evidence of maladaptive coping strategies that may exist prior to the development of pain and/or independently contribute to insomnia symptoms. It is unknown, however, whether primary insomnia is associated with alterations in laboratory pain sensitivity when it occurs either as a sole condition or as part of a chronic pain disorder such as TMD.

Submitted for publication September, 2008
Submitted in final revised form February, 2009
Accepted for publication March, 2009
Address correspondence to: Michael T. Smith, PhD, Johns Hopkins Hospital, Behavioral Sleep Medicine Program, 600 North Wolfe Street, Meyer 1-108, Baltimore, MD 21287; Tel: (443) 287-2384; Fax: (410) 614-3366; E-mail: msmith62@jhmi.edu

Only a handful of investigations have systematically sought to evaluate the sleep quality of TMD patients. These studies have consistently found that the majority (> 50%) of TMD patients report poor sleep quality, and that subjective ratings of poor sleep are associated with increased clinical pain severity and psychological distress.[12-14] Fundamental descriptive data using polysomnography and standard research diagnostic interviews to quantify the range of sleep disorders in TMD and determine their possible associations with laboratory measures of pain sensitivity are lacking. The extant literature has largely focused on possible relationships between sleep bruxism and TMD.[15,16] Sleep bruxism, however, has not been found to be associated with either poor sleep quality or polysomnographic measures of sleep continuity or architecture disturbances.[17-19]

The objective of this study was to address two critical gaps in the literature: (1) characterize the spectrum of sleep disorders in a well-described sample of myofascial TMD patients, using polysomnography and state-of-the art structured diagnostic interviews; and (2) evaluate possible associations between observed sleep disorder indices and laboratory measures of pain threshold. We hypothesized that rates of primary insomnia would be substantive in TMD and that primary insomnia would be associated with reductions in pain threshold at both masseter and extracranial sites.

METHODS

Participants

We recruited 53 TMD patients from a dental school based, tertiary care, orofacial pain clinic and media advertisements for an ongoing longitudinal study. Eligibility criteria included primary myofascial TMD diagnosis, established by a standard research diagnostic dental exam,[20] typical pain severity ≥ 2 of 10, and minimum symptom duration ≥ 6 months. We excluded patients reporting primary pain conditions or serious medical disorders other than TMD; active alcohol or drug abuse problems; or use of narcotics, antidepressants, anticonvulsants, or muscle relaxants within 2 weeks of participation.

Procedures

The protocol was approved by both Johns Hopkins Univeristy and the University of Maryland institutional review boards in compliance with the declaration of Helsinki. Eligible subjects formally consented and completed panoramic x-rays at the University of Maryland Brotman Facial Pain Research Center. An experienced dentist (EG) performed a standardized and widely used dental exam according to research diagnostic criteria (RDC) for TMD.[20] Interrater reliability studies have found that this examination demonstrates acceptable to excellent reliability (intraclass correlation coefficients, > 0.4 in 87% of cases).[21] The diagnosing dentist completed formal training in RDC procedures and undergoes periodic reliability calibration.

Structured Diagnostic Interviews

After the dental examination, subjects diagnosed with myofascial TMD as a primary diagnosis completed 2 structured diagnostic interviews conducted by a licensed clinical psychologist certified in behavioral sleep medicine (MTS). To diagnose AXIS I psychiatric disorders, subjects completed the computerized Structured Clinical Interview for DSM-IV (SCID)–patient edition. All identified possible diagnoses were then followed up with a clinical interview using the appropriate DSM-IV SCID-I[22] module to confirm diagnosis and clinical course. The SCID-I interview demonstrates excellent interrater reliability (kappa) coefficients, ranging from 0.77 and 0.99 for affective and anxiety spectrum disorders.[23] To diagnose sleep disorders, we administered the Structured Interview for Sleep Disorders (SIS-D).[24] This 30-minute interview for DSM Axis-I and Axis-III sleep disorders is based on DSM-III-R and is the only published interview that demonstrates sound reliability and validity based on PSG and expert interviews. Kappa statistics assessing Inter-rater reliability coefficients for the subclassifications of insomnia and hypersomnias, for example, range between 0.84 and 0.86. In the current study, a modified version of the SIS-D was used to reflect DSM-IV revisions.

Questionnaires

Subjects completed a battery of widely used, psychometrically sound questionnaires, including the Brief Pain Inventory,[25] the Beck Depression Inventory,[26] and Spielberger State –Trait Anxiety Inventories,[27] the Insomnia Severity Index,[28] The Pittsburgh Sleep Quality Index,[29] the Fatigue Severity Scale,[30] and the Epworth Sleepiness Scale.[31] All of these measures are routinely used in sleep research to quantify sleep quality and daytime symptoms associated with sleep disorders.

Dental, Medical, and Psychiatric History Form

This 65-item form was developed by the authors to elicit general medical, dental, and mental health history information, including medication usage, recreational drug use, use of stimulants, and sleep hygiene practices. The form includes a "pain diagram," in which participants mark all areas of pain on multiple views of the human body. Additional items include the initiation and frequency of TMJ problems and associated symptoms, such as daytime clenching, sleep bruxism, and tinnitus. Subjects also indicated the temporal sequencing when sleep problems began relative to TMJ pain. Additional items included rating the frequency in which nighttime awakenings were associated with jaw or facial pain in the past 6 months (0 = never, 1 = in the past, but not in the past 6 months, 2 = occasionally, 3 = often, 4 = very often (almost every night), and the degree to which sleeping on their side aggravated TMJ pain.

Medical History, Physical Examination, and Laboratory Chemistries

After the structured interviews and prior to overnight sleep studies, all subjects completed a standard medical history and physical exam conducted by a study physician as part of the eligibility determination. At this time, we obtained blood and urine samples and conducted laboratory tests, including complete blood count, toxicology testing for recreational drugs, stimulants, opioids, benzodiazepines, and pregnancy testing.

Polysomnography (PSG)

After the screening phase, subjects completed 2 consecutive overnight sleep studies in a sound-attenuated private room located on an inpatient clinical research unit at Johns Hopkins. Signals were recorded using EMBLA N7000 polysomnographs and Somnologica software at a sampling rate of 500 HZ. We provided subjects with an 8-hour period to sleep during their preferred sleep phase. The Night 1 recording montage included recommended placements for EEG, EOG, and EMG according Rechtschaffen & Kales (R&K),[32] with the addition of bilateral masseter EMGs and auditory recordings as described by Lavigne et al.[33] We acquired the following electrophysiologic signals: 4 EEG channels (C4-A1, C3-A2, O1-A2, O2-A1); right and left electroculograms (EOGs) linked to a single mastoid; bilateral masseter EMGs for scoring sleep bruxism, submental EMGs, bilateral anterior tibialis EMGs; and an ECG (single modified ECG lead II, torso placement). Respiratory function was measured via oronasal thermistor, nasal air pressure transducer, pulse oximeter, and abdominal and thoracic strain gauges. On the second recording night, we used an abbreviated montage, removing all respiratory sensors and tibialis EMGs. Sleep continuity and architecture were scored according to R&K criteria[32] by a registered polysomnographic technician, and reviewed and confirmed by a board certified sleep specialist. Clinical sleep indices were scored as defined in the *International Classification of Sleep Disorders*, *2nd Edition* (ICSD-2).[34]

Laboratory Pain Testing Procedures

Subjects completed a standardized quantitative sensory testing protocol frequently used by our lab as fully described elsewhere.[9] Subjects were oriented and familiarized with the procedures in advance. Pain testing was conducted each evening between 15:00 and 17:00 and each morning 30 minutes after waking, following the sleep study. We obtained resting blood pressure before and after pain testing. We focus this report on both thermal and algometric assessments of pain threshold. The order of these procedures was randomized to avoid possible sequence effects. All subjects refrained from any analgesics or centrally acting agents within 24 hours prior to pain testing. Urine toxicology tests confirmed that individuals were not recently/currently using sedatives, opioids, or common recreational drugs.

Pressure Pain Threshold (PPTh)

A Somedic algometer was used to assess PPTh similar to previous studies.[35] The algometer's 1 cm^2 rubber probe was placed over the muscle belly, with the pressure increased steadily at a constant rate (30 kPA/sec), until the subject indicated that s/he "first felt pain." PPTh was assessed 2 times each, bilaterally, at (in a randomized order) the masseter muscle and at the proximal third of the brachioradialis muscle (forearm). The same site was never stimulated consecutively. A period without stimulation $\geq$ 90 sec occurred between successive stimuli. Testing was performed by technicians who were required to maintain and periodically (monthly) demonstrate adequate inter-tester reliability (i.e., pressure pain threshold values are required to be within 1 lb/cm^2 on $\geq$ 80% of reliability trials). Our technicians demonstrate good test-retest reliability, as previously reported[9]

Heat Pain Threshold (HPTh)

Contact heat stimuli, at non–tissue-damaging temperatures, were delivered using a computer controlled, peltier-element-based stimulator (Medoc), with a 9 cm^2 probe. Assessment procedures were similar to those reported previously.[36] HPTh was assessed on the left ventral forearm using an ascending method of limits paradigm; from a non-painful 32°C baseline, the temperature was steadily increased at 0.5°C/sec until the subject reported the first sensation of pain. Three HPTh trials were conducted, separated by $\geq$ 3 minutes between trials. The thermode was affixed snuggly via Velcro straps to ensure even skin contact and repositioned to an adjacent site after each trial to minimize sensitization.

Establishing Sleep Disorder Diagnoses

In order to fully describe the spectrum of sleep disorders in TMD, we utilized both ICSD-2[34] and DSM IV[37] nosologies, as well as available research diagnostic criteria for sleep bruxism,[33] insomnia, and good sleep.[38] Described below are polysomnographic indices and diagnoses warranting specific definition/discussion.

Sleep Disorder Indices

Standard clinical polysomnographic indices defined in the ICSD-2 were utilized. A respiratory disturbance index (RDI [respiratory events events/hour (REM+NREM]) was calculated to diagnose sleep apnea. This index included apneas (> 70% reduction in airflow $\geq$ 10 seconds), hypopneas ($\geq$ 30% reduction of amplitude of thoracoabdominal movement or airflow with > 4% oxygen desaturation), and respiratory effort related arousals (RERAs), i.e., clear drop in inspiratory airflow, increased respiratory effort accompanied by EEG arousal. A periodic limb movement index (PLMI), as defined by ICSD-2, was used to diagnose periodic limb movement disorder. Sleep bruxism events were scored according to RDC criteria developed by Lavigne,[33] using > 10% masseteric EMG amplitude and maximum voluntary contraction threshold. Events were categorized as phasic ($\geq$ 3 EMG bursts of 0.25 to 2.0 sec, separated by 2 interburst intervals), tonic (EMG burst lasting > 2 sec) or mixed. Two primary sleep bruxism Indices were calculated: (1) bruxism bursts/hour sleep (number of phasic or tonic events/hour sleep; and (2) bruxism episodes/hour sleep.

Insomnia Diagnosis

Insomnia diagnoses were determined according to the American Academy of Sleep Medicine Work Group research diagnostic criteria[38] after integrating all available data: PSG data, structured interviews, medical history, and questionnaire data. This system includes psychophysiologic insomnia, primary insomnia, and insomnia due to a medical or psychiatric disorder. It should be noted that psychophysiological insomnia is a subset of primary insomnia, with additional criteria that subjects

report evidence of conditioned sleep difficulty, pre-sleep hyperarousal, etc. To diagnose a subject with primary insomnia in the context of past or present mental or medical disorders, the temporal course of the insomnia symptoms must show some independence from the comorbid condition. Conversely, the diagnosis of insomnia due to a medical / psychiatric condition was made when the onset of the insomnia symptoms coincided with the onset of the mental/ medical disorder, and the temporal course of insomnia symptoms tracked closely with or was primarily attributable to the comorbidity. In the present study, for example, the diagnosis of insomnia due to TMD was made if: (1) the insomnia started at the same time or after the TMD symptoms, and (2) during periods of TMD symptom remission, insomnia was absent and / or subjects reported that TMD symptoms were the primary cause of their sleeping problems.

Sleep Bruxism Diagnosis

We diagnosed subjects with sleep bruxism using ICSD-2 criteria. Since all subjects reported jaw pain (one of the ICSD-2 criteria), the additional self-report of awareness of tooth grinding sounds during sleep was sufficient to make the diagnosis. We also diagnosed subjects based on Lavigne's PSG derived criteria if the subject demonstrated > 4 sleep bruxism episodes/ hr of sleep or > 25 sleep bruxism bursts/hr sleep on either of Night 1 or 2 PSG studies.

Sleep Apnea Diagnosis

Subjects were diagnosed with sleep apnea if their RDI was ≥ 15 or if RDI was 5 to 15 and they complained of sleep-related daytime impairment, including excessive daytime sleepiness, fatigue, or insomnia. It should be noted that according to RDC, we diagnosed patients as having both insomnia and sleep apnea if they met both criteria and the insomnia symptoms were judged to be at least somewhat independent of sleep disordered breathing as described above.

Periodic Limb Movement Disorder Diagnosis

We diagnosed PLMD according to ICSD-2 criteria with a PLM index > 15/h sleep.

Good Sleeper Status

For the purposes of this study, we identified 2 levels of good sleepers: those not meeting criteria for any diagnosable sleep disorder, except self-reported sleep bruxism ("no sleep disorder except self-report bruxism") and those meeting more stringent research diagnostic criteria (RDC) for normal sleepers (controls), established by the American Academy of Sleep Medicine.[38] Because sleep bruxism has not been found to be associated with the complaint of poor sleep and the vast majority of TMD patients self-report sleep bruxism, we did not exclude subjects with self-reported sleep bruxism from either good sleeper category. We did, however exclude subjects demonstrating PSG signs of sleep bruxism who met RDC criteria for sleep bruxism as described above.[33] To satisfy the RDC normal sleeper criteria of no complaints of sleep disturbance or daytime symptoms attributable to unsatisfactory sleep, we required PSQI scores to be < 5 (good sleeper range[29]), in addition to the requirement of no diagnosable sleep disorder, expect self-reported sleep bruxism.

Statistical Plan and Analyses

Since the first aim was to identify rates of ICSD sleep disorders in TMD, we conducted descriptive analyses. Subsequent aims to evaluate potential associations between primary insomnia, sleep disorder indices, and responsivity to noxious stimuli relied in part on these frequency distributions as well as the a priori hypothesis to evaluate whether primary insomnia was associated with hyperalgesia.

Laboratory Pain Testing Data (Data Reduction)

Pain sensitivity indices for AM and PM testing were calculated by averaging across trials each day. Preliminary paired samples *t*-tests revealed no laterality effects; therefore, pressure thresholds for right and left sides were averaged.

We then plotted means with 95% confidence intervals for all 3 pain sensitivity measures (PPTh for masseter and forearm, HPTh for the ventral forearm) by diagnostic groups of interest, averaged over all observations. Since *t*-tests comparing subjects with primary insomnia, sleep apnea, RDC sleep bruxism, against subjects meeting no sleep disorder criteria, demonstrated mean differences on one or more pain sensitivity measures, we then followed these preliminary analyses with 3 multivariate, linear mixed effect models.

Linear Mixed Effects Models (LME)

The overall purpose of the LME analyses was to evaluate the effects of possible confounding and moderating factors, including time of day and determine possible independent effects of primary insomnia and clinical sleep indices on all 3 pain sensitivity measures. LME models have the advantage of including all repeatedly measured pain testing data sampled at all 4 time points (Day 1, PM testing, Day 2 AM and PM testing, and Day 3 AM testing) simultaneously in the model as the dependent variable. This approach to modeling longitudinal data does not make assumptions about equal sample sizes, equally spaced assessment points, or balanced data sets (e.g., subjects need not have the same number of assessment points). In addition, time-varying (e.g., blood pressure prior to pain testing) as well as time-invariant (e.g., gender or age) covariates can be included in the statistical model. We selected model predictors based on previously demonstrated associations with pain sensitivity and on the study hypothesis that primary insomnia would be associated with pain sensitivity. Sleep related variables selected for inclusion were diagnosis of primary insomnia (yes or no), respiratory disturbance index, sleep bruxism bursts/hour (averaged over nights 1 and 2), and the periodic limb movement index. For disorders other than insomnia, which has no defining PSG index, we elected to use continuous PSG indices instead of diagnostic categories to enhance statistical power and accuracy estimation. To select model covariates, we conducted preliminary analyses (2 sample *t*-tests or *t*-tests of Pearson correlation coefficient) to test bivariate associations between the 3 pain sensitivity measures and typical de-

Table 1—Demographic Characteristics (N =53)

Variable	% (n)
Age (mean, SD)	33.6 ± 12.4
Female	81.1% (43)
Ethnicity	
White American	77.4% (41)
African American	9.4% (5)
Asian American	9.4% (5)
Multi-racial	3.8% (2)
Education Level	
High school / some college	22.6% (12)
College graduate	39.6% (21)
Graduate studies	37.7% (20)
Occupational Status	
Full-Time Employment	52.8% (28)
Part-time Employment	13.2% (7)
Student	22.6% (12)
Homemaker	5.7% (3)
Unemployed	3.8% (2)
Marital Status	
Single, divorced, separated	62.2% (33)
Married	34.0%(18)
Living with partner	3.8% (2)
Total Household Income per Annum	
$25,000 or less	22.6% (12)
$25,001–$50,000	26.4% (14)
$50,001–$75,000	13.2% (7)
>$75,000	32.1% (17)

mographic (age, sex, ethnicity [white vs. non-white]) and clinical factors (Spielberger Anxiety Scores, Beck Depression Inventory Scores, body mass index), previously found to be related to pain sensitivity. Of these factors age, sex, and BMI were associated with pain sensitivity ($P < 0.05$) and were therefore selected for inclusion. Similarly, because blood pressure has been robustly associated with pain sensitivity[39] and sleep disorders, particularly apnea,[40] we included an estimate of mean arterial pressure (MAP) derived from resting systolic and diastolic blood pressure taken prior to each pain testing session in the model (MAP = diastolic pressure + 1/3(systolic pressure-diastolic pressure). MAP was inversely associated with pain sensitivity ($P < 0.05$). Finally, to evaluate and control for possible circadian or sequential effects of repeated pain testing (Day 1, 2, or 3), we also included these indicators in the models.

RESULTS

Subject Characteristics

Table 1 reports the general demographics of the 53 participants. Typical of the TMD population, > 80% of the sample was female, with a mean age of 33.6 years. As shown in Table 1, the sample was predominantly white and well-educated. The average duration of TMD symptoms was 9.03 years ± 8.1.

Rates of Sleep Disorders in TMD

Including self-reported sleep bruxism, 89% of participants met ICSD criteria for at least one sleep disorder, and 43.4% were diagnosed with 2 or more sleep disorders. Approximately 19% (n = 10) met American Academy of Sleep Medicine RDC criteria for normal sleeper (control) as developed by Edinger et al. As shown in Table 2, 74% of participants met ICSD self-report criteria for sleep bruxism. However, only 17% of the sample met the PSG derived RDC criteria developed by Lavigne et al.[33] Even after excluding subjects with self-reported sleep bruxism as their only sleep disorder, a large majority of TMD patients 68% (n = 46) were diagnosed with a sleep disorder. Aside from self-reported sleep bruxism, insomnia was the most commonly diagnosed sleep disorder; 36% of the sample met diagnostic criteria for some type of clinically significant insomnia. Primary insomnia comprised 74% of all insomnia cases. Insomnia due to TMD comprised the next highest insomnia subtype (6% of the sample). Surprisingly, 28% of subjects were diagnosed with sleep apnea. The majority of apnea cases (73%) were classified in the mild range (RDI = 5–14.9). Four subjects diagnosed with sleep apnea were also diagnosed with insomnia (primary insomnia [n = 3] and insomnia due to TMD [n = 1]). Rates of all other ICSD sleep disorders, such as periodic limb movement disorder, were less than 5%.

PSG Measures by Diagnostic Category

Because little, if any PSG data has been published to objectively characterize the sleep of TMD patients, we report mean polysomnographic data for the 3 most common sleep related diagnostic categories and the sample overall in Table 3. These data are also presented to provide sleep related detail that will assist in the interpretation of any between-group differences observed in pain sensitivity. As shown in Table 3, we compared PSG data for all patients meeting criteria for each diagnostic category against the subsample of TMD subjects who met RDC criteria for good sleeper controls (n = 10). Sleep continuity and architecture data are detailed for Night 2 (baseline) to avoid the first-night effect confound.

Clinical Characteristics and Symptoms by Sleep Disorder Diagnosis

For similar descriptive purposes, we evaluated whether clinical characteristics, and symptom severity varied by sleep disorder diagnosis relative to TMD patients meeting RDC criteria for good sleepers (Table 4). Independent sample *t*-tests were used to compare good sleepers with subjects in each of the 3 major sleep diagnostic categories. Somewhat surprisingly, there were no statistically significant differences in BMI among the 4 diagnostic categories. BMI averaged 25.4, in the slightly overweight range, for the overall sample. As shown in Table 4, subjects diagnosed with the top 3 most common sleep disorders (primary insomnia, obstructive sleep apnea, and RDC sleep bruxism) reported significant elevations in depression, anxiety, and pain severity symptoms compared to RDC good sleepers ($P < 0.05$) All 3 groups reported poorer subjective sleep quality on the Pittsburgh Sleep Quality Index ($P < 0.05$). Subjects with primary insomnia and sleep apnea also reported increased daytime sleepiness, fatigue, pain-related interference in daily function, and insomnia severity ($P < 0.05$).

Table 2—Rates of International Classification of Sleep Disorders, Second Edition (ICSD-2) Diagnoses of Temporomandibular Joint Disorder (N=53)

Diagnoses	Male (n=10)		Female (n=43)		Total (N=53)	
	n	%	n	%	n	%
INSOMNIAS						
Psychophysiologic	2	20	9	20.9	11	20.8
Idiopathic	0	-	3	7	3	5.7
Primary Insomnia (DSM-IV-TR)						
(Includes psychophysiologic+idiopathic)	2	20	12	27.9	14	26.4
Insomnia due to TMD	0	-	3	7	3	5.7
Insomnia due to Mood Disorder	0	-	2	4.7	2	3.8
Any Insomnia Diagnosis	2	20	17	39.5	19	35.8
OBSTRUCTIVE SLEEP APNEA						
Mild (RDI = 5-14.9)	2	20	9	20.9	11	20.8
Moderate (RDI = 15-29.9)	2	20	0	-	2	3.8
Severe (RDI $\geq$ 30)	1	10	1	2.3	2	3.8
Any Sleep Apnea DX	5	50	10	23.2	15	28.4
MOVEMENT DISORDERS						
Periodic limb movement disorder	1	10	1	2.3	2	3.8
Restless legs syndrome	1	10	1	2.3	2	3.8
Sleep bruxism						
Self-report, ICSD-2 criteria	9	90.0	30	76.9	39	73.6
RDC, PSG derived criteria$^{\delta}$	4	40.0	5	11.9	9	17.3
PARASOMNIAS						
Nightmare disorder	0	0	1	2.3	1	1.9
Circadian Rhythm Disorders						
Delayed sleep phase syndrome	0	0	1	2.3	1	1.9
OTHER – Insufficient Sleep Syndrome	0	0	2	4.7	2	3.8
SUMMARY CATEGORIES						
Subjects with 1 sleep disorder	4	40.0	20	46.5	24	45.3
Subjects with 2 sleep disorders	3	30.0	11	25.6	14	26.4
Subjects with 3 sleep disorders	2	20.0	7	16.3	9	17.0
Any Sleep Disorder Diagnosis	9	90	38	71.2	47	88.7
No sleep disorders (except self-report bruxism)	2	20.0	15	34.9	17	32
RDC Good Sleeper						
(includes SR Brux, excludes RDC Brux)	1	10	9	20.9	10	18.9

RDI = respiratory disturbance index as defined by ICSD-2 (apneas + hypopneas + respiratory related arousals / hour of sleep)
δSleep Bruxism Research Diagnostic Criteria (> 4 bruxism episodes/ hr or > 25 bruxism bursts/hr) (Lavigne et al, 1996[33])
Note: None of the subjects met formal RDC criteria for paradoxical insomnia.

Pain Sensitivity by Sleep Diagnoses

We evaluated whether sleep disorders were associated with pain sensitivity in 2 ways. To provide a preliminary overview, we first conducted LME models comparing pain sensitivity measures for the top 3 diagnostic sleep disorder categories against subjects without any sleep disorder diagnosis (except self-reported sleep bruxism). Since self-reported sleep bruxism was not associated with any alterations in sleep parameters, including the sleep bruxism index, we decided to include these subjects in these preliminary analyses. T-tests from these models revealed that compared to the no sleep disorders group, subjects diagnosed with primary insomnia demonstrated decreased pressure pain threshold (hyperalgesia) at the masseter (t = 2.2, P = 0.03) and decreased heat pain threshold on the ventral forearm (t = 2.54, P = 0.01). Compared to the no sleep disorder diagnosis, subjects diagnosed with sleep apnea demonstrated increased pressure pain threshold (hypoalgesia) on the forearm (t = 2.4, P = 0.02). Subjects diagnosed with sleep apnea also demonstrated a trend toward hypoalgesia at the masseter site (t = 2.0, P = 0.05). Figure 1 depicts mean data for the 4 groups with 95% confidence intervals derived from the LME models.

Because these preliminary analyses suggested multiple group effects on multiple pain sensitivity measures, we next conducted linear mixed effects models to more thoroughly interrogate the independent multivariate associations between sleep disorder indices and hyperalgesia, while controlling for potential confounds and accounting for the possibility of circadian effects and sensitization to the procedures over the course of the 3 testing days.

Multivariate Models Predicting Pain Sensitivity

Table 5 displays the results of our linear mixed effects models examining relationships between sleep disorder indices and the 3 pain sensitivity variables: forearm heat pain threshold, masseter pressure pain threshold, and forearm pressure pain threshold. All 3 overall linear mixed-effects models were statistically significant (P < 0.001). For the dependent variables, there were significant associations between primary insomnia

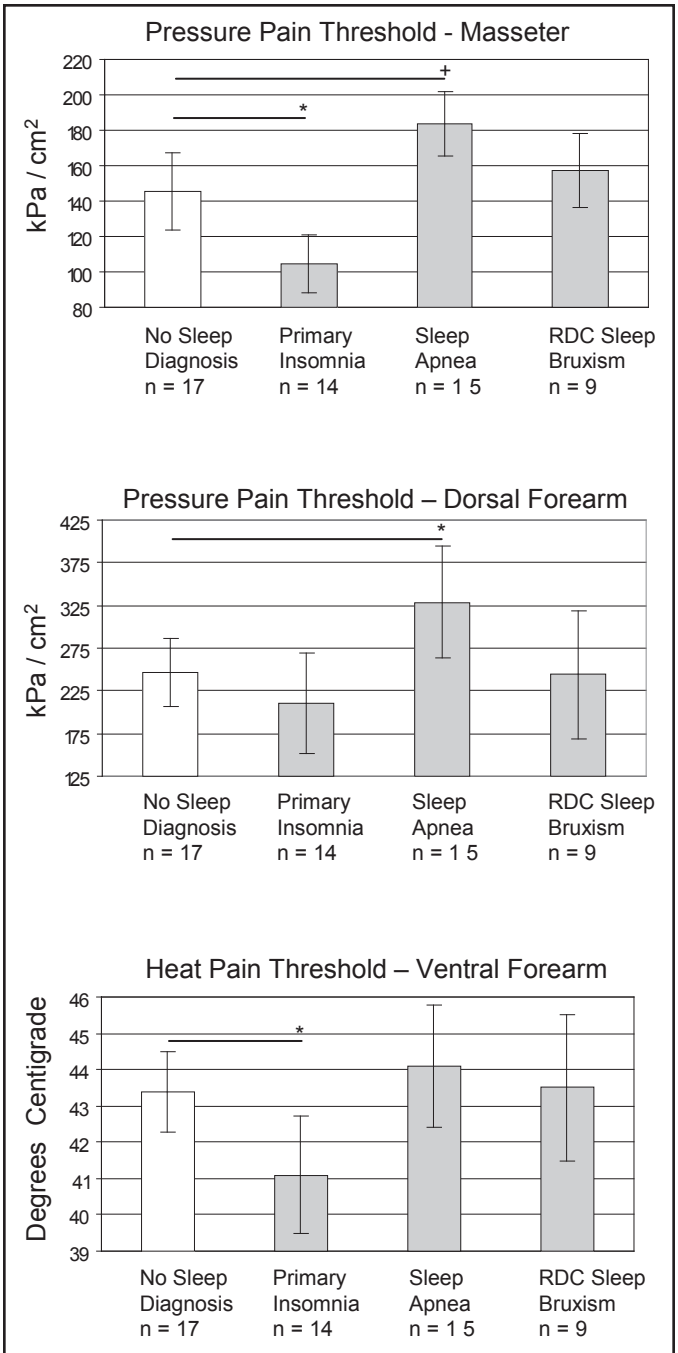

Figure 1—Laboratory Pain Thresholds by Sleep Diagnosis in TMD (Mean with 95% Confidence Intervals, Overall N = 53). Note: No Sleep Diagnosis = No ICSD or DSM sleep disorder diagnosis, except self-reported sleep bruxism in the absence of significant PSG sleep bruxism activity. RDC Sleep Bruxism = subjects met PSG sleep bruxism criteria (Lavigne et al., 1996[33]) on at least one of two study nights. + P = 0.05, *P < 0.05

diagnosis and pain threshold (P < 0.05), controlling for the effects of: the respiratory disturbance index (RDI) during sleep, sleep bruxism bursts/ hr, PLMI, age, sex, BMI, MAP, time of testing (AM vs. PM), and day of testing. The models found that primary insomnia diagnosis was associated with a 2.9°C reduction in heat pain threshold, a 61.3 kPA/cm^2 reduction in masseter pressure pain threshold and 73.4 kPA/cm^2 reduction in forearm pressure pain threshold.

Multivariate analyses also revealed a significant relationship between the RDI during sleep and forearm pressure pain threshold; sleep disordered breathing was associated with increased pressure pain threshold (hypoalgesia). Similarly, when the dichotomous sleep apnea diagnosis variable was substituted for the RDI, patients diagnosed with sleep apnea demonstrated a trend toward increased forearm pressure pain threshold (P = 0.08). We found a "day effect" for pressure pain threshold, such that as the study progressed, subjects became more pain sensitive at both the masseter and forearm sites. None of the other variables demonstrated significant associations with pain sensitivity.

Finally, to determine if the association between hyperalgesia (reduced pain threshold) and primary insomnia was specific to primary insomnia, we conducted secondary LME models substituting "any insomnia diagnosis" (primary insomnia + insomnia due to TMD + insomnia due to mental disorder) for primary insomnia. These models found that "any insomnia diagnosis" was not significantly associated with any of the 3 pain threshold measures (P > 0.05).

DISCUSSION

The overwhelming majority of our sample of TMD patients, who were unselected for sleep disorders, were diagnosed with at least one sleep disorder, most commonly, ICSD self-reported sleep bruxism ([75%]; 17% met RDC PSG criteria for active sleep bruxism). Perhaps more striking, however, we found that 43% of the sample was diagnosed with 2 or more sleep disorders. Insomnia disorder (36%) and obstructive sleep apnea (28.4%) demonstrated the highest frequencies. Primary insomnia comprised the largest subcategory of insomnia (26% of the overall sample). With respect to subjects diagnosed with sleep apnea, 73% were categorized in the mild severity range (RDI = 5–14.9). Compared to subjects meeting RDC criteria for good sleep (19%), subjects diagnosed with any of the three most common sleep disorders, i.e., primary insomnia, sleep apnea, and active sleep bruxism, reported poorer sleep quality, increased anxiety symptoms, increased symptoms of depression, and increased pain severity. As hypothesized, even after controlling for multiple potential confounds and non-insomnia-related PSG sleep disorder indices, the diagnosis of primary insomnia was associated with significant hyperalgesia. Patients with primary insomnia exhibited reduced pain thresholds measured both at an affected TMD-related site (masseter) and a non-TMD related region (arm). Unexpectedly, sleep disordered breathing was associated with mechanical hypoalgesia.

Rates of Sleep Disorders in TMD

To our knowledge, this is the first comprehensive polysomnographic study of sleep in a well characterized sample of myofascial TMD patients. This work will support larger scaled, multisite investigations and prospective cohort studies to better estimate the prevalence and impact of sleep disorders in TMD. Our diagnostic data are consistent with existing self-report studies of TMD, which have found that approximately 50% of patients report poor sleep quality and that self-reported poor sleep is associated with psychological distress and greater clinical pain severity.[12-14] Our finding that 43% of the sample carried

Table 3—Sleep Continuity, Architecture and Clinical Sleep Disorder Indices by Major Diagnostic Categories in TMD

	RDC Good sleeper (n = 10)		Primary Insomnia (n = 14)		Obstructive Sleep Apnea (n = 13)		RDC Sleep Bruxism (n = 9)		Total Sample (N=53)	
PSG Parameters	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Sleep Continuity (Night 2)										
Sleep latency (min)	7.2	4.2	14.1	13.9	8.8	6.0	7.8	5.5	10.5	13.1
Wake after sleep onset (min)	17.6	17.2	42.8+	42.7	38.9	26.7	22.4	17.1	29.6	30.1
Total sleep time (min)	451.7	17.4	416.7*	53.4	433.3	25.4	450.5	19.1	426.8	71.4
Sleep efficiency %	95	0.04	88*	0.09	91	0.05	94	0.03	0.90	15
Sleep Architecture (Night 2)										
NREM stage 1%	5.2	3.1	12.4+	12.0	6.9	7.5	8.6	10.0	7.7	7.8
NREM stage 2%	56.8	8.0	54.5	9.7	58.8	10.4	58.9	7.2	54.3	11.6
Slow wave sleep (NREM 3/4)	25.9	35.8	11.9	9.2	11.9	8.0	12.2	8.7	17.0	19.3
REM %	27.1	12.1	21.2	5.0	23.2	7.0	20.4	4.6	25.0	19.0
REM latency (min, cycle 1)	70.4	21.4	77.4	38.5	69.3	23.2	78.8	36.8	77.7	41.0
Clinical Sleep D/O Indices										
Sleep bruxism (Mean Nights 1& 2)										
Burst/hr	5.6	2.8	5.3	4.5	6.4	4.8	14.0**	7.4	6.4	5.3
Total Episodes/hr	1.9	0.8	2.1	1.3	2.7	2.0	5.3***	1.8	2.4	1.7
Sleep disordered breathing index (events/hour, Night 1)	1.7	1.4	5.8	11.8	13.7*	13.5	5.2	4.9	5.1	8.4
Periodic limb movement index (events/hr, Night 1)	0.07	0.2	2.1	6.1	3.8	12.9	6.0	15.4	1.8	7.3

*Differ from Good Sleeper Reference group, two-tailed t-test (P < 0.05), **P < 0.01, *** < 0.001, + trend > 0.05 < 1.0
RDC Good sleeper is defined by Edinger et al. 2004.[38] RDC Sleep Bruxism is defined by Lavigne et al. 1996.[33]

Table 4—Clinical Characteristics and Symptom Severity by Major Diagnostic Categories in TMD

	RDC Good sleeper (n = 10)		Primary Insomnia (n = 14)		Obstructive Sleep Apnea (n = 13)		RDC Sleep Bruxism (n = 9)		Total Sample (N=53)	
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Body mass index	23.9	4.0	26.1	5.7	26.4	5.4	25.5	3.6	25.4	5.3
Systolic BP, afternoon	118.7	16.2	122.0	11.5	120.2	12.5	115.2	10.5	118.5	12.2
Diastolic BP, afternoon	68.6	10.0	63.9	11.5	69.4	12.2	62.8	7.8	67.0	10.8
Insomnia Severity Index	4.5	3.12	17.5***	4.5	12.6***	5.4	7.6	6.4	10.2	6.6
Pittsburgh Sleep Quality Index	2.7	0.82	9.9***	3.1	7.8***	2.9	6.3*	3.6	6.4	3.5
Epworth Sleepiness Scale	6.0	3.2	7.9*	4.7	10.2*	5.1	10.0+	5.8	8.5	4.6
Fatigue Severity Scale	2.8	1.1	4.6*	1.1	4.0*	1.4	3.3	1.2	3.7	1.3
Beck Depression Inventory	1.6	2.0	10.0***	4.9	8.3***	3.8	9.4*	8.9	7.4	7.0
Speilberger STAI-ST	26.1	4.0	39.9**	9.5	36.3**	10.9	42.8**	12.1	36.3	10.5
Brief Pain Inventory–Severity	1.9	0.85	3.9**	1.4	3.2**	1.5	3.5**	1.5	3.2	1.5
Brief Pain Inventory–Interference	0.96	0.97	3.4**	2.1	2.6**	2.2	2.6+	2.4	2.6	2.2

Independent sample *t*-tests, two-tailed, compare sleep disorder diagnoses against RDC Good Sleeper groups;
+P = 0.051–0.1, *P < 0.05, **P < 0.01, ***P < 0.001

2 or more sleep diagnoses implies that clinicians treating TMD patients should routinely screen patients for sleep disorders and strongly consider referring patients with significant sleep problems for a comprehensive specialty sleep evaluation that includes polysomnography.

Primary Insomnia in TMD

Prior work studying sleep quality in chronic pain disorders has not utilized the recently developed RDC for insomnia; therefore, the rates of primary insomnia, we observed cannot be easily contextualized with findings from the broader chronic pain literature. These data will require replication. It should also be noted that this finding may not generalize to other chronic pain conditions, such as low back pain, in which physical discomfort may play a more prominent role in fragmenting sleep. Our finding of a high rate of primary insomnia versus secondary is consistent, however, with current conceptual models of chronic insomnia, which have highlighted the perspective that as insomnia becomes chronic, even when comorbid with other medical or psychiatric disorders, maladaptive coping factors, and conditioned hyperarousal are likely to develop and contribute to the perpetuation of symptoms.[42] This can blur clean distinctions between primary insomnia versus secondary insomnia

Table 5—Multivariate Mixed Effects Model Coefficients Predicting Heat and Pressure Pain Thresholds

Sleep and Covariate Predictors	Unstandardized β	Std. Error	Standardized β	P-value
Heat Pain Threshold –Volar forearm (Dependent Variable)				
Primary insomnia	−2.9	1.2	−0.37	0.01*
Respiratory disturbance index during sleep	0.08	0.06	0.19	0.17
Sleep bruxism bursts/ hr (M, nights 1 & 2)	−0.02	0.09	−0.03	0.82
Periodic limb movement index	0.01	0.06	0.01	0.93
Age	0.0	0.05	0.0	0.99
Sex	−0.23	1.26	−0.03	0.85
Body mass index	0.10	0.11	0.16	0.32
MAP (prior to testing)	−0.02	0.06	−0.05	0.74
Time	−0.17	0.47	−0.03	0.71
Day	−0.16	0.33	−0.04	0.63
Pressure Pain Threshold – Masseter (Dependent Variable)				
Primary insomnia	−61.3	19.8	−0.42	0.002**
Respiratory disturbance index during sleep	1.4	1.0	0.18	0.19
Sleep bruxism bursts / hr (M, nights 1 & 2)	0.25	1.6	0.02	0.88
Periodic limb movement index	−0.59	1.2	−0.07	0.61
Age	1.2	0.87	0.23	0.16
Sex	−36.2	23.1	−0.22	0.12
Body mass index	3.6	1.9	0.29	0.07
MAP (prior to testing)	−1.1	1.0	−0.17	0.28
Time	2.3	4.7	0.02	0.63
Day	−11.0	3.4	−0.12	0.001***
Pressure Pain Threshold – Dorsal Forearm (Dependent Variable)				
Primary insomnia	−73.4	34.0	−0.26	0.03*
Respiratory disturbance index during sleep	3.7	1.8	0.25	0.04*
Sleep bruxism bursts / hr (M, nights 1 & 2)	−0.58	2.7	−0.02	0.83
Periodic limb movement index	−0.43	2.0	−0.03	0.83
Age	1.8	1.8	0.18	0.22
Sex	−62.5	1.5	−0.20	0.12
Body mass index	−2.4	3.3	0.35	0.02
MAP (prior to testing)	20.3	1.8	−0.20	0.17
Time (AM versus PM)	10.2	12.3	0.04	0.41
Day (1,2,3)	−19.3	8.7	−0.11	0.03*

*P < 0.05, **P ≤ 0.01, ***P ≤ 0.001

diagnoses. Some have argued that endeavoring to make this distinction when chronic insomnia is associated with medical comorbidity may not be tenable.[42] Our data, however, suggest that in TMD, the identification of primary insomnia is possible and it has important implications as discussed below. These data suggest that pure "secondary insomnia" in TMD appears to be infrequent.

Sleep Apnea in TMD

We are not aware of any prior studies in TMD using PSG to determine rates of sleep apnea. A questionnaire-based study, however, comparing TMD patients to well-matched controls reported a 6% prevalence estimate of OSA in TMD.[43] This study based the likelihood of an OSA diagnosis on a self-report symptom cut-off score only. Using PSG, however, we found that approximately one-third of patients had obstructive sleep apnea. This strongly suggests that sole reliance on self-reported symptoms and algorithms based on traditional OSA risk factors, such as BMI, male sex, and complaints of loud snoring, is not likely to be a valid means to screen for OSA in TMD and may substantially underestimate its prevalence. Given the serious cardiovascular consequences of OSA,[40] our data suggest that clinicians treating TMD patients with persistent sleep complaints should strongly consider recommending a PSG study. While we do not have a matched control group to more clearly determine whether our apnea rate of 28% rate is, in fact, elevated, population-based estimates of sleep apnea in middle aged adults are in the range of 4% for men and 2% for women.[44] Even updated estimates accounting for the increasing prevalence of obesity, suggest an overall apnea rate of approximately 17%.[45] Given the young female preponderance and relatively low BMI in our TMD sample, our rate of 28% suggests that sleep apnea is very likely to be well above expected or predicted levels in TMD patients and strongly underscores the need for a large scale definitive study. While it is unknown why sleep apnea rates may be elevated in TMD, a recent epidemiologic survey of the general population reported a strong link between the diagnosis of sleep apnea and self-reported sleep bruxism.[46] Causal relationships between sleep bruxism and TMD remain controversial,[47] however, but it is clear from our data that more research is needed to explore possible interrelationships between sleep bruxism, sleep apnea, and orofacial pain.

Based on similarities in overlapping symptom complexes in primary insomnia and idiopathic pain disorders, and experimental data demonstrating that sleep deprivation induces hyperalgesia in healthy subjects, we hypothesized that insomnia would be associated with hyperalgesia. Our data support this hypothesis and are consistent with a population based study, which found that self-reported poor sleep is associated with reduced pressure pain threshold.[48] We found primary insomnia to be associated with both mechanical and thermal pain sensitivity measured at the masseter (mechanical measurement only) and the arm.

Finding hypersensitivity at unaffected sites has been suggested to implicate aberrant central pain processing deficits that may play a critical role in idiopathic pain disorders such as myofascial TMD.[49,50] Our finding that primary insomnia is associated with hyperalgesia at "unaffected" TMD sites, suggests that primary insomnia may either share a common substrate underlying central sensitivity and/or play a causal role in the development of hyperalgesia. While difficult to gauge the clinical significance of the observed reduction in pain sensitivity, the magnitude of the hyperalgesic effect for primary insomnia is large compared to other clinically meaningful differences found in the pain literature. For example, prior work by our group found a 1.7°C difference in heat pain threshold in men compared to women.[51] Sex differences in pain sensitivity are widely considered to provide physiologic insight into the differential impact of chronic pain disorders among women. In the current study, primary insomnia was associated with a 2.9°C reduction in pain threshold. This effect is well above the just noticeable difference for heat-related stimuli, which is approximately 0.5°C.[52] Our thermal pain threshold values for the primary insomnia group are also consistent with those reported for fibromyalgia, e.g., Geisser et al.[53]

Our findings appear to suggest specificity for a relationship between the construct of primary insomnia and hyperalgesia. Neither sleep bruxism nor sleep apnea was associated with hyperalgesia. While too few subjects were diagnosed with secondary insomnia to draw any firm conclusions, the inclusion of secondary insomnia in the regression models reduced the amount of variance explained by insomnia. This suggests that the relationship between insomnia and hyperalgesia appears to be more robustly tied to the construct of primary and not secondary insomnia. Future work to clarify this issue should focus on conducting quantitative sensory testing in patients with primary insomnia in the absence of clinical pain disorders.

Unexpectedly, we found some evidence that the respiratory disturbance index was associated with higher pain thresholds (hypoalgesia). Because we controlled for blood pressure prior to testing, the possibility that high blood pressure associated with sleep apnea might account for the relationship does not appear viable. It remains possible, however, that sleep-related respiratory events may exert a more subtle impact on the interaction between the cardiovascular system, baroreceptor function (e.g., baroreceptor activation is a known cause of hypoalgesia[39] and pain regulatory systems, than is measured by blood pressure. This finding might have important implications with respect to using quantitative sensory testing to screen patients with TMD who are at risk for sleep apnea and/ or hypertension. It should be noted that while we controlled for BMI, it remains possible that the sleep apnea hypoalgesia finding is confounded by other body habitus measures that were not assessed, such as forearm muscle girth. Body habitus factors are not routinely assessed in quantitative sensory testing studies, and our finding that that BMI was associated with decreased pain sensitivity indicates that body habitus factors should be routinely considered in quantitative sensory testing studies.

We might have expected that sleep apnea, like insomnia, would have been associated with increased pain sensitivity (decreased pain threshold), by virtue of sleep fragmentation, which is often associated with sleep apnea. Sleep apnea related intermittent hypoxia is also linked with elevated inflammatory markers,[54] including proinflammatory cytokines, which are known to sensitize nociceptors and contribute to hyperalgesia. The seeming paradoxical association between sleep apnea and hypoalgesia, might be related to the fact that sleep apnea in our TMD sample, was relatively mild and not associated with either sleep architecture or continuity disturbance. Future planned analysis will utilize power spectral analysis to quantify more subtle sleep microstructure abnormalities linked with both apnea and insomnia in this sample to determine whether they prospectively predict the course of clinical pain.

In our hands, no relationship emerged between the sleep bruxism index and either masseter or forearm pain sensitivity. Although numerous self-report studies have found positive associations between sleep bruxism and orofacial pain severity,[55,56] several PSG studies have failed find a relationship between objective sleep bruxism indices and clinical pain.[19,57] Rompre and colleagues, for example, have recently reported that a subgroup of sleep bruxers who demonstrate reduced bruxism events are at actually at increased risk for reporting pain.[58] This seemingly conflicting data, suggest a complex, perhaps temporally specific relationship between sleep bruxism and clinical pain, and certainly requires more research attention.

Another finding revealed by the LME models was that over the 3 days of quantitative sensory testing and independent of the time of day of the testing, pressure pain thresholds decreased over time at both the masseter and forearm sites. This suggests that patients became sensitized to the mechanical stimulation procedures. This pattern is opposite of what is expected in healthy subjects who tend to habituate to repeated noxious stimulation presented at these intervals.[59] Due to power limitations with this sample, we did not evaluated whether insomnia diagnosis interacted with the effects of repeated testing. Larger scale studies will be required to examine this possibility.

This investigation has a number of limitations which should be considered when interpreting the results. The data are cross-sectional and therefore preclude causal interpretations. The lack of a healthy control group limits firm conclusions about the relative rates of sleep disorders in TMD and the sample size limits power. Moreover, the inclusion of a chronic pain comparison group would be useful in determining whether the observed findings are specific to TMD, or represent some more general phenomena in pain patients. Another potential limitation of this work is that only one clinical researcher conducted the structured diagnostic interviews (MTS: SIS-D, SCID & EG: RDC/TMD). This might limit generalizability. The sound psychometric properties

of these instruments and experience the examiners, however, mitigates this potential issue. Since this is the first study of TMD to incorporate, structured diagnostic interviews to diagnose sleep disorders in TMD, these methods are an advance that await replication. Despite these limitations, this is the first comprehensive investigation of sleep disorders in TMD using polysomnography and structured research diagnostic interviews.

These data are also the first to report a relationship between primary insomnia and hyperalgesia and as such, suggest the possibility that clinical insomnia may indeed play a pathophysiologic role in TMD and other central sensitivity syndromes. These data raise the possibility that targeting factors thought to drive primary insomnia, such as psychophysiologic arousal, in addition to improving sleep continuity may enhance the efficacy of treatments for TMD and other idiopathic pain disorders and possibly have prophylactic benefits.

ACKNOWLEDGMENTS

This work was support by: NIH/NINDS: 5K23NS047168-04 (MTS), Grant Number

R24AT004641 from the National Center for Complimentary & Alternative Medicine (statistical consultation) and by Grant Number UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at www.ncrr.nih.gov. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp."

This work was funded entirely by grants from the National Institutes of Health (MTS).

This study does not describe off-label or investigational use of any product.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Smith has received research support from Sepracor on behalf of Johns Hopkins University, and is on the board of directors and an equity partner in BMED Technologies, Inc., New York. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. LeResche L, Saunders K, Von Korff MR, Barlow W, Dworkin SF. Use of exogenous hormones and risk of temporomandibular disorder pain. Pain 1997;69:153-60.
2. Management of Temporomandibular Joint Disorders. NIH Technol Assess Statement 1996. Report No: Apr 29-May1.
3. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain 2006;123:226-30.
4. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007;36:339-56.
5. 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.
6. Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341-51.
7. 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.
8. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135-43.
9. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep 2007;30:494-505.
10. Smith MT, Klick B, Kozachik S, et al. Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. Pain 2008 March 22.
11. Smith MT, Perlis ML, Smith MS, Giles DE, Carmody TP. Sleep quality and presleep arousal in chronic pain. J Behav Med 2000;23:1-13.
12. Yatani H, Studts J, Cordova M, Carlson CR, Okeson JP. Comparison of sleep quality and clinical and psychologic characteristics in patients with temporomandibular disorders. J Orofac Pain 2002;16:221-8.
13. Harness DM, Donlon WC, Eversole LR. Comparison of clinical characteristics in myogenic, TMJ internal derangement and atypical facial pain patients. [Review]. Clin J Pain 1990;6:4-17.
14. Riley JL, Benson MB, Gremillion HA, et al. Sleep disturbance in orofacial pain patients: pain-related or emotional distress? TMD Sleep 2002;19:106-13.
15. Molina OF, dos Santos J, Nelson SJ, Nowlin T. A clinical study of specific signs and symptoms of CMD in bruxers classified by the degree of severity. Cranio 1999;17:268-79.
16. Trenouth MJ. The relationship between bruxism and temporomandibular joint dysfunction as shown by computer analysis of nocturnal tooth contact patterns. J Oral Rehabil 1979;6:81-7.
17. Goulet JP, Lavigne GJ, Lund JP. Jaw pain prevalence among French-speaking Canadians in Quebec and related symptoms of temporomandibular disorders. J Dent Res 1995;74:1738-44.
18. Lavigne GJ, Manzini C. Bruxism. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. 3rd ed. Philadelphia: WB Saunders; 2000:773-85.
19. Camparis CM, Formigoni G, Teixeira MJ, Bittencourt LR, Tufik S, de Siqueira JT. Sleep bruxism and temporomandibular disorder: Clinical and polysomnographic evaluation. Arch Oral Biol 2006;51:721-8.
20. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301-55.
21. Schmitter M, Ohlmann B, John MT, Hirsch C, Rammelsberg P. Research diagnostic criteria for temporomandibular disorders: a calibration and reliability study. Cranio 2005;23:212-8.
22. Spitzer R, Gibbon R, Williams J. Structured Clinical Interview for DSM-IV Axis 1 Disorders. Version 2. 1997.
23. Skre I, Onstad S, Torgersen S, Kringlen E. High interrater reliability for the Structured Clinical Interview for DSM-III-R Axis I (SCID-I). Acta Psychiatr Scand 1991;84(2):167-73.
24. Schramm E, Hohagen F, Grasshoff U, et al. Test-retest reliability and validity of the Structured Interview for Sleep Disorders According to DSM-III-R. Am J Psychiatry 1993;150:867-72.
25. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. Advances in pain research and therapy: issues in pain management. New York: Raven Press; 1989:391-403.
26. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.

27. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1983.
28. Bastien CH, Vallie'res A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2000;2:297-307.
29. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
30. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. J Psychosom Res 1993;37:753-62.
31. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
32. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: U.S. Government Printing Office; 1968.
33. Lavigne GJ, Rompre PH, Montplaisir JY. Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. J Dent Res 1996;75:546-52.
34. American Academy of Sleep Medicine. International classification of sleep disorders: 2nd ed. Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005.
35. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997 March;70(1):41-51.
36. 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;91:165-75.
37. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4 ed. Washington, DC: American Psychiatric Association; 1994.
38. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep 2004;27:1567-96.
39. Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. Neurosci Biobehav Rev 2004 July;28(4):395-414.
40. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008;52:686-717.
41. Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occuring within the context of medical and psychiatric disorders. Clin Psychol Rev 2005;25:559-92.
42. McCrae CS, Lichstein KL. Secondary insomnia: diagnostic challenges and intervention opportunities. Sleep Med Rev 2001;5:47-61.
43. Collesano V, Segu M, Masseroli C, Manni R. Temporomandibular disorders and sleep disorders: which relationship? Minerva Stomatol 2004;53:661-8.
44. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. New Engl J Med 1993;328:1230-5.
45. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. J Appl Physiol 2005;99:1592-9.
46. Ohayon MM, Li KK, Guilleminault C. Risk factors for sleep bruxism in the general population. Chest 2001;119:53-61.
47. Lobbezoo F, Lavigne GJ. Do bruxism and temporomandibular disorders have a cause-and-effect relationship? J Orofac Pain 1997;11:15-23.
48. Chiu YH, Silman AJ, Macfarlane GJ, et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. Pain 2005;115:316-21.
49. Bradley LA, Kersh BC, DeBerry JJ, Deutsch G, Alarcon GA, McLain DA. Lessons from fibromyalgia: abnormal pain sensitivity in knee osteoarthritis. Novartis Found Symp 2004;260:258-70.
50. Bradley LA, McKendree-Smith NL. Central nervous system mechanisms of pain in fibromyalgia and other musculoskeletal disorders: behavioral and psychologic treatment approaches. Curr Opin Rheumatol 2002;14:45-51.
51. Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB. Catastrophizing as a mediator of sex differences in pain: differential effects for daily pain versus laboratory-induced pain. Pain 2004;111:335-41.
52. Rainville P, Doucet JC, Fortin MC, Duncan GH. Rapid deterioration of pain sensory-discriminative information in short-term memory. Pain 2004;110:605-15.
53. Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. Pain 2003;102:243-50.
54. Ryan S, McNicholas WT. Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS. Arch Physiol Biochem 2008;114:261-6.
55. Macfarlane TV, Gray RJM, Kincey J, Worthington HV. Factors associated with the temporomandibular disorder, pain dysfunction syndrome (PDS): Manchester case-control study. Oral Dis 2001;7:321-30.
56. Velly AM, Gornitsky M, Philippe P. Contributing factors to chronic myofascial pain: a case-control study. Pain 2003;104:491-9.
57. Rossetti LM, Rossetti PH, Conti PC, de Araujo CR. Association between sleep bruxism and temporomandibular disorders: a polysomnographic pilot study. Cranio 2008;26:16-24.
58. Rompre PH, Daigle-Landry D, Guitard F, Montplaisir JY, Lavigne GJ. Identification of a sleep bruxism subgroup with a higher risk of pain. J Dent Res 2007;86:837-42.
59. Prushansky T, Dvir Z, Defrin-Assa R. Reproducibility indices applied to cervical pressure pain threshold measurements in healthy subjects. Clin J Pain 2004;20:341-7.